Outcomes Modeling: NTCP - Normal Tissue Complication Probability

What's Really Changed over the last 20+ years?

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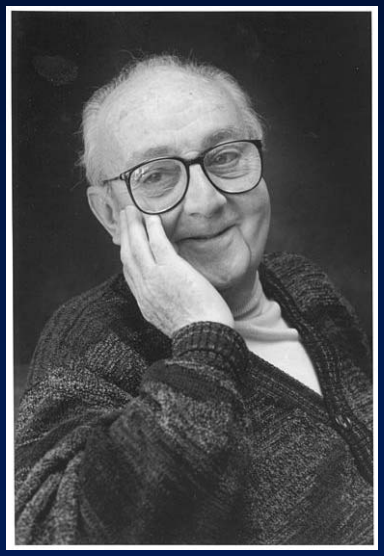
“Essentially, all models are wrong, but some are useful.”

George E.P. Box, 1987*



* Box, G. E. P., and Draper, N. R., (1987), IN: Empirical Model Building and Response Surfaces, p. 424, John Wiley & Sons, New York, NY.

Introduction

- "Traditional" radiation oncology dose escalation trials assign groups of patients to increasing "tumor" dose levels until an unacceptable level of complications appear
- This generally evolves on a sequential basis, regardless of tumor size or the distribution of radiation dose to surrounding normal tissues

Introduction

- This can be a poor strategy for treatments limited primarily by complications to so-called volume-effect normal tissues which encompass the tumors, such as may be the case for tumors located in the liver or lung

Introduction

- A better scheme for Phase I/II dose escalation trials limited by these volume effect organs would attempt to treat sequential groups of patients with dose "distributions" that might be expected to lead to similar anticipated levels of complications
  - (but of course with different tumor doses);
- with sequential escalation of each potential iso-complication level until an MTD profile is realized
  - (which would inherently include the volume effect).

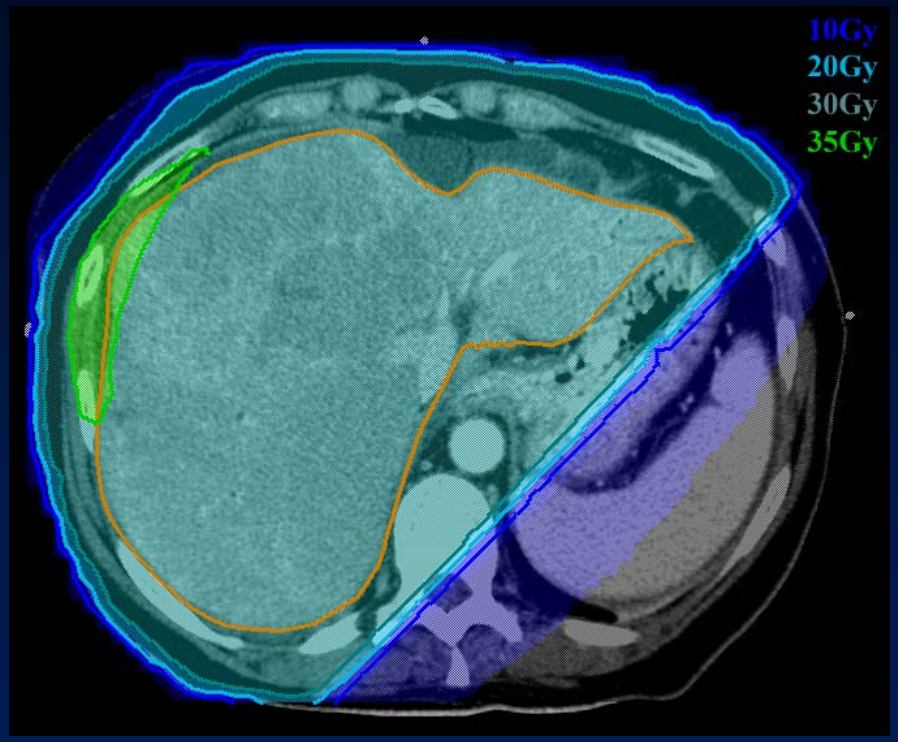
Introduction

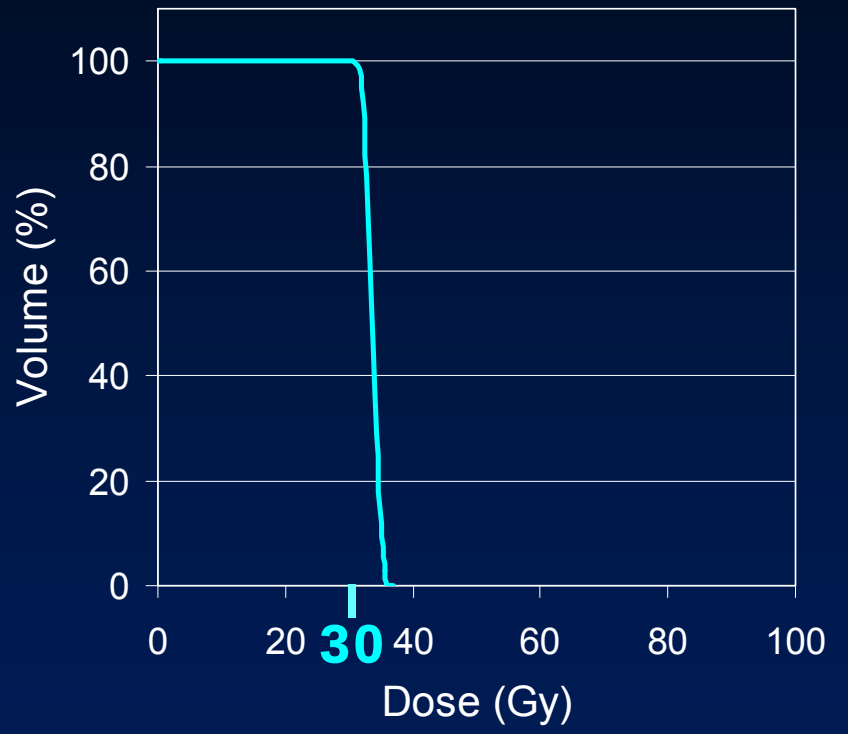
- The use of normal tissue complication probability (NTCP) models prospectively, in the treatment planning process, facilitates this type of normal tissue iso-complication based dose escalation
- This talk will summarize experiences in iso-NTCP dose escalation and planning at the University of Michigan for tumors in the liver and lungs

ca. 1990 *Tolerance Doses simple*

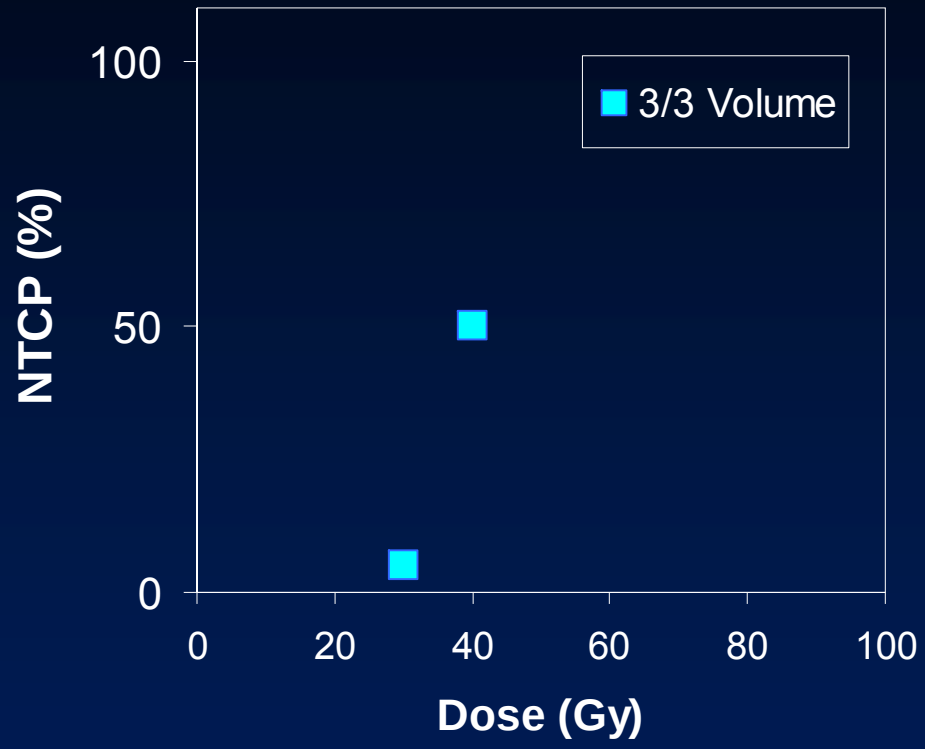
- No Models
- Mostly whole organ irradiation
  - \+ or uniform partial organ irradiation
- Some published complications rates

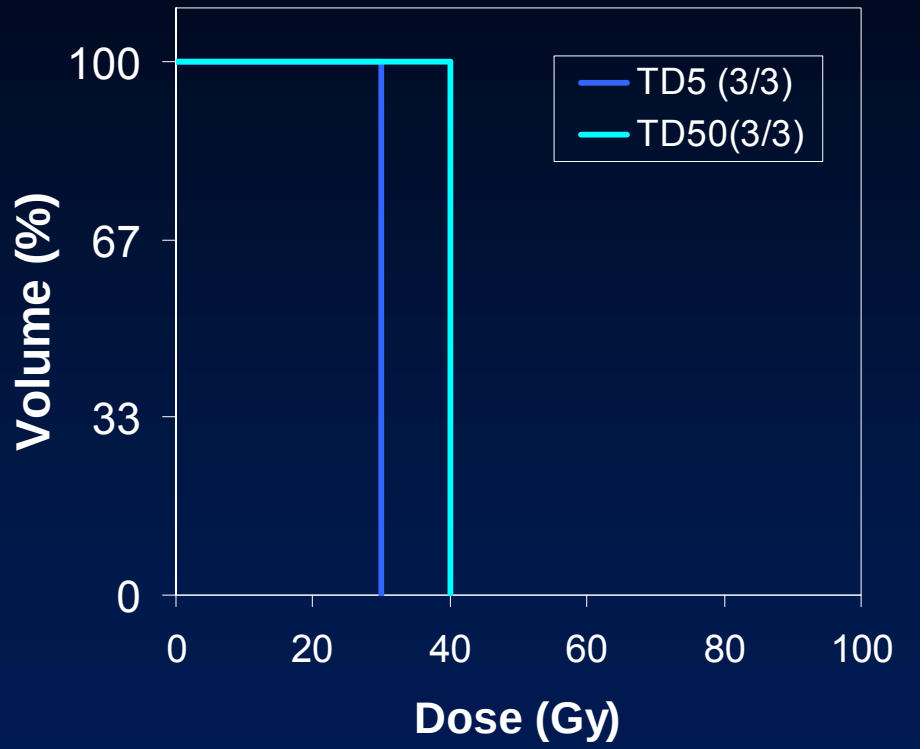
Whole Liver Irradiation



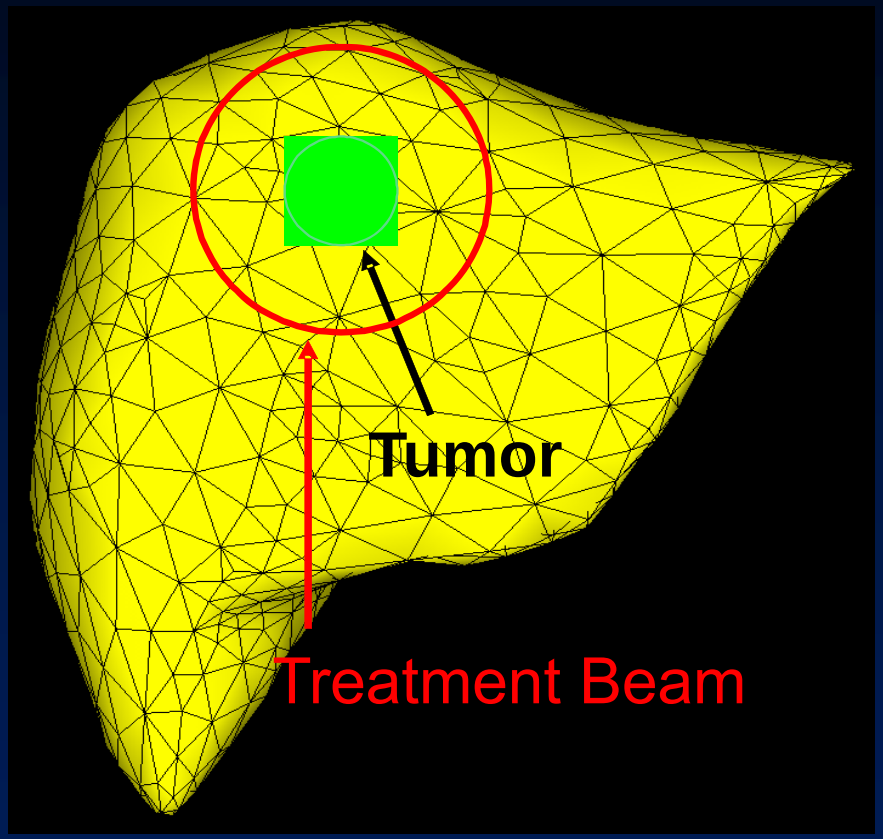


Whole liver tolerance doses ca. 1990





Radiation treatment of liver cancer



- Higher tumor doses appear to be beneficial
- Low tolerance of whole liver to radiation (35 Gy)
- Hope to deliver higher tumor doses through partial liver irradiation
- Need to understand dose/volume relationships of toxicity

ca. 1990 *Modeling was simple*

- No Models
- Some published complications rates
- Get consensus of a group of experts
  - TD5 and TD50
  - For 1/3, 2/3 and 3/3
- A set of ground breaking, useful guidelines for "uniform partial organ irradiation"

The Emami paper

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

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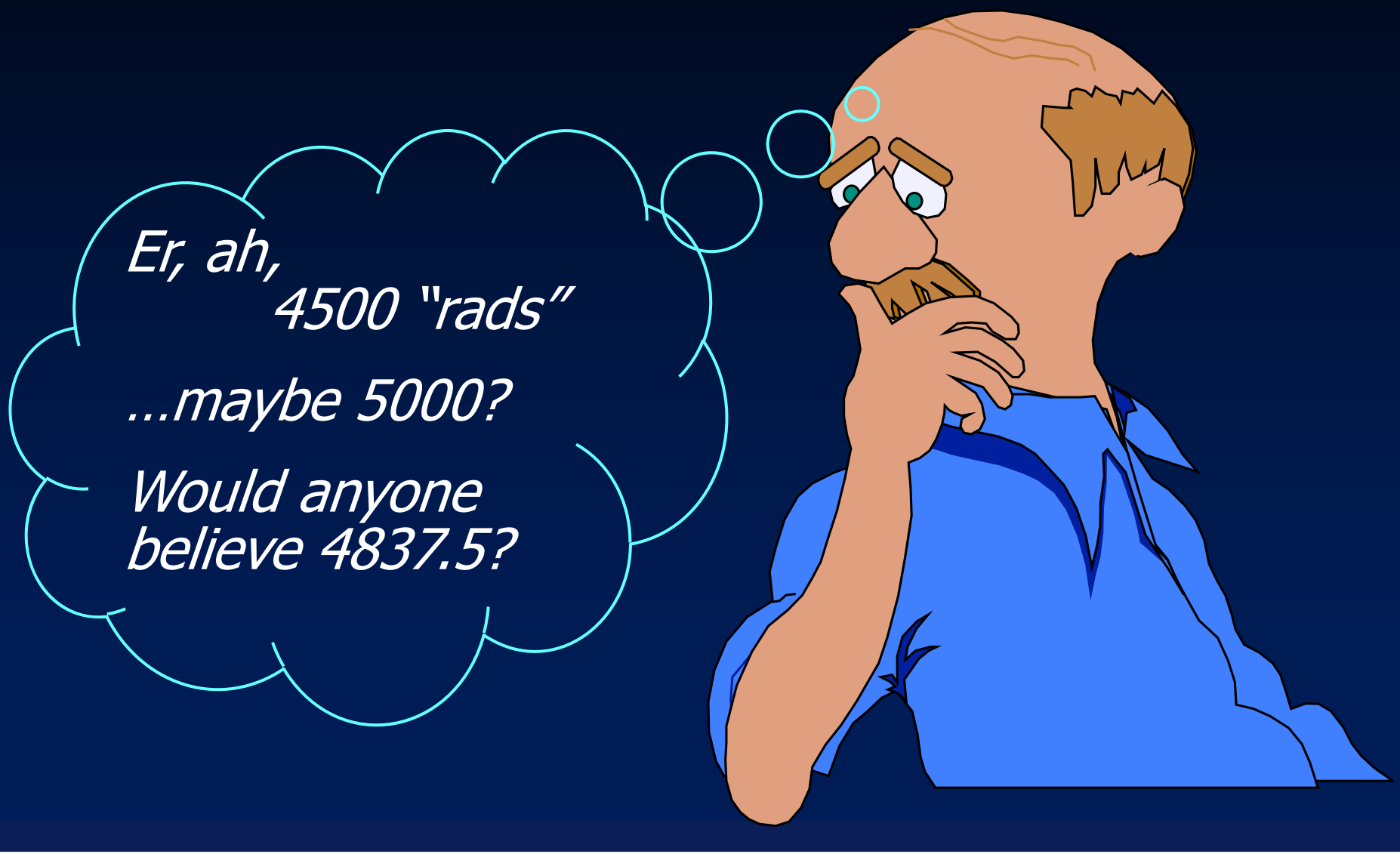
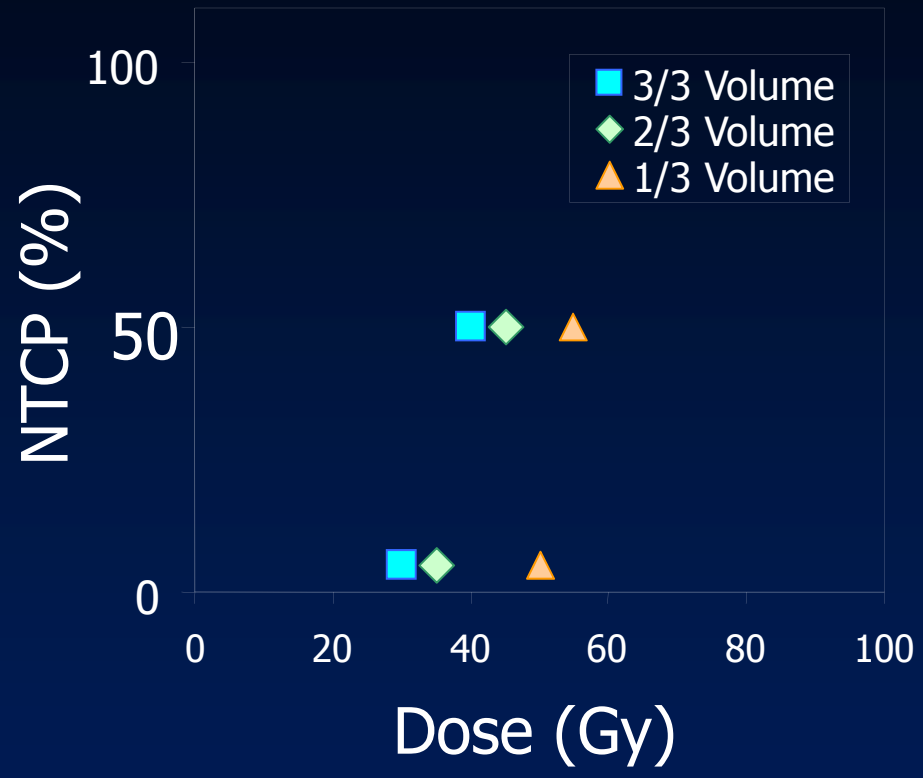
Int J Radiat Oncol Biol Phys, 21:109-122, 1991

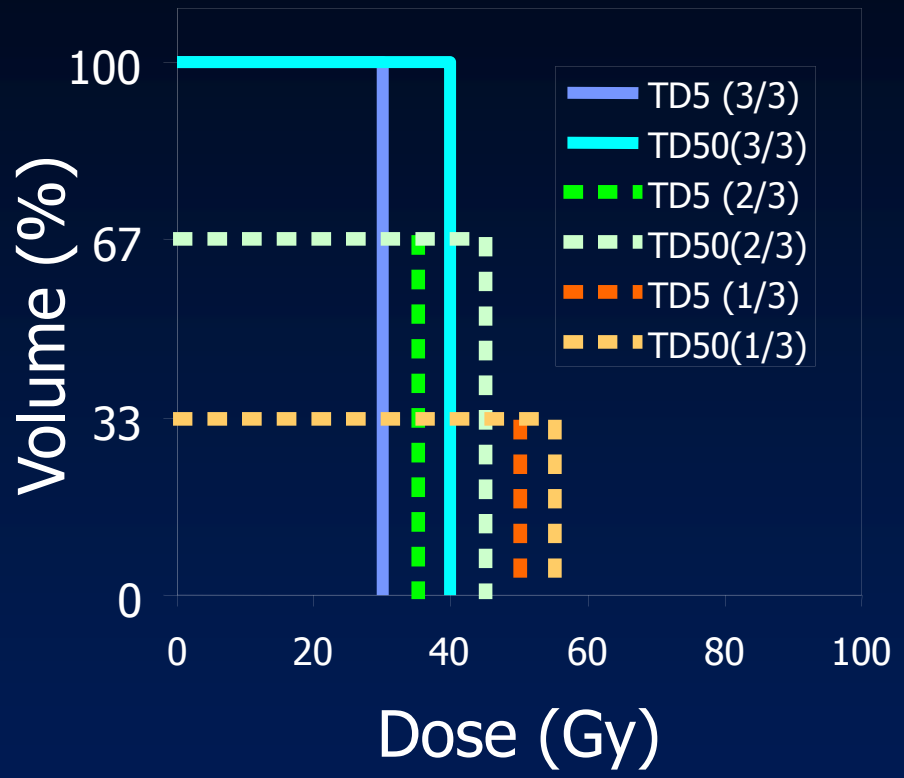
What do you think the TD5 is for uniform irradiation of 1/3 of .....



“Emami” Liver Data

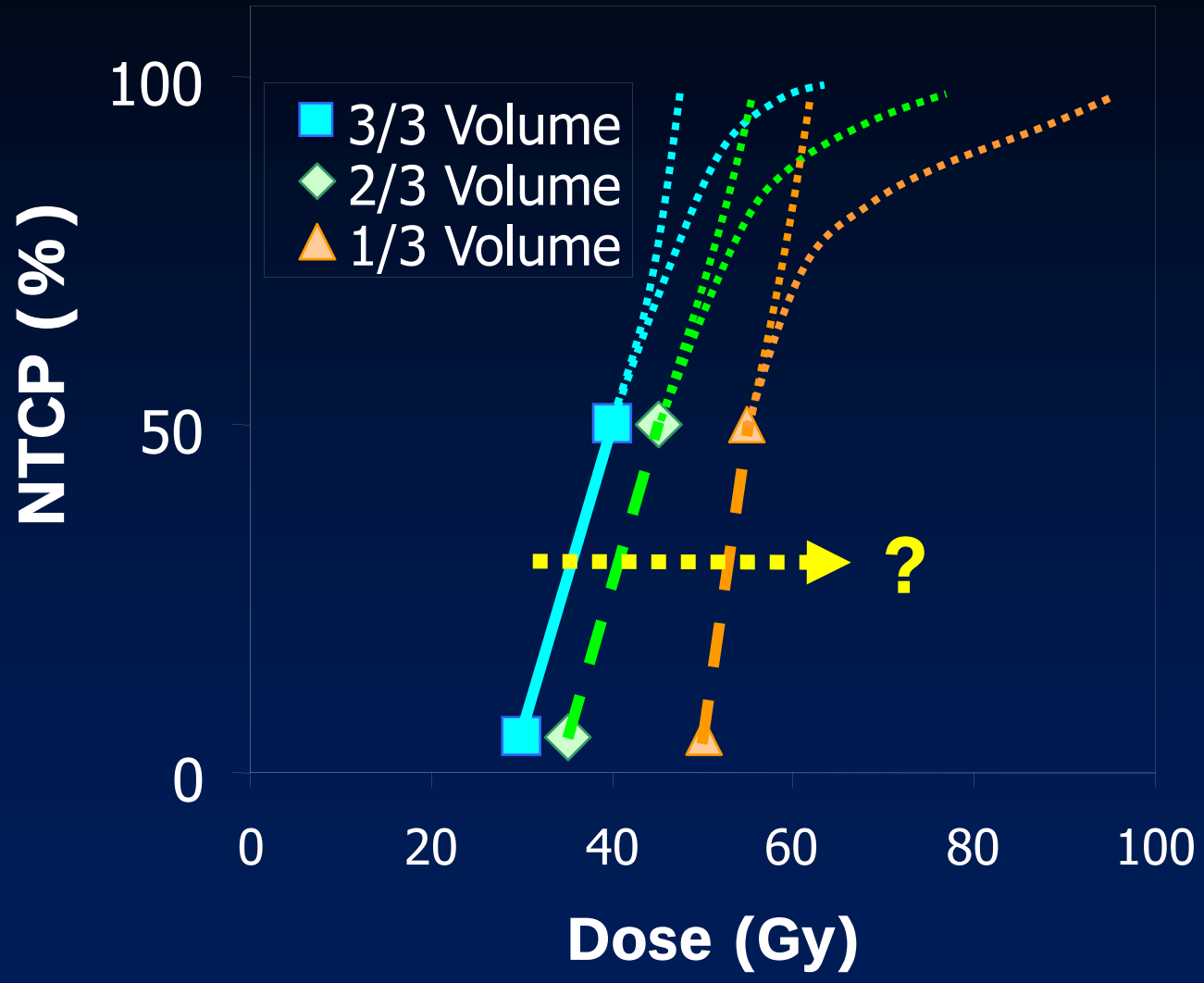
Solid lines: some data
Dashed lines: estimates





Was this sufficient?

Solid lines: some data
Dashed lines: *estimates*



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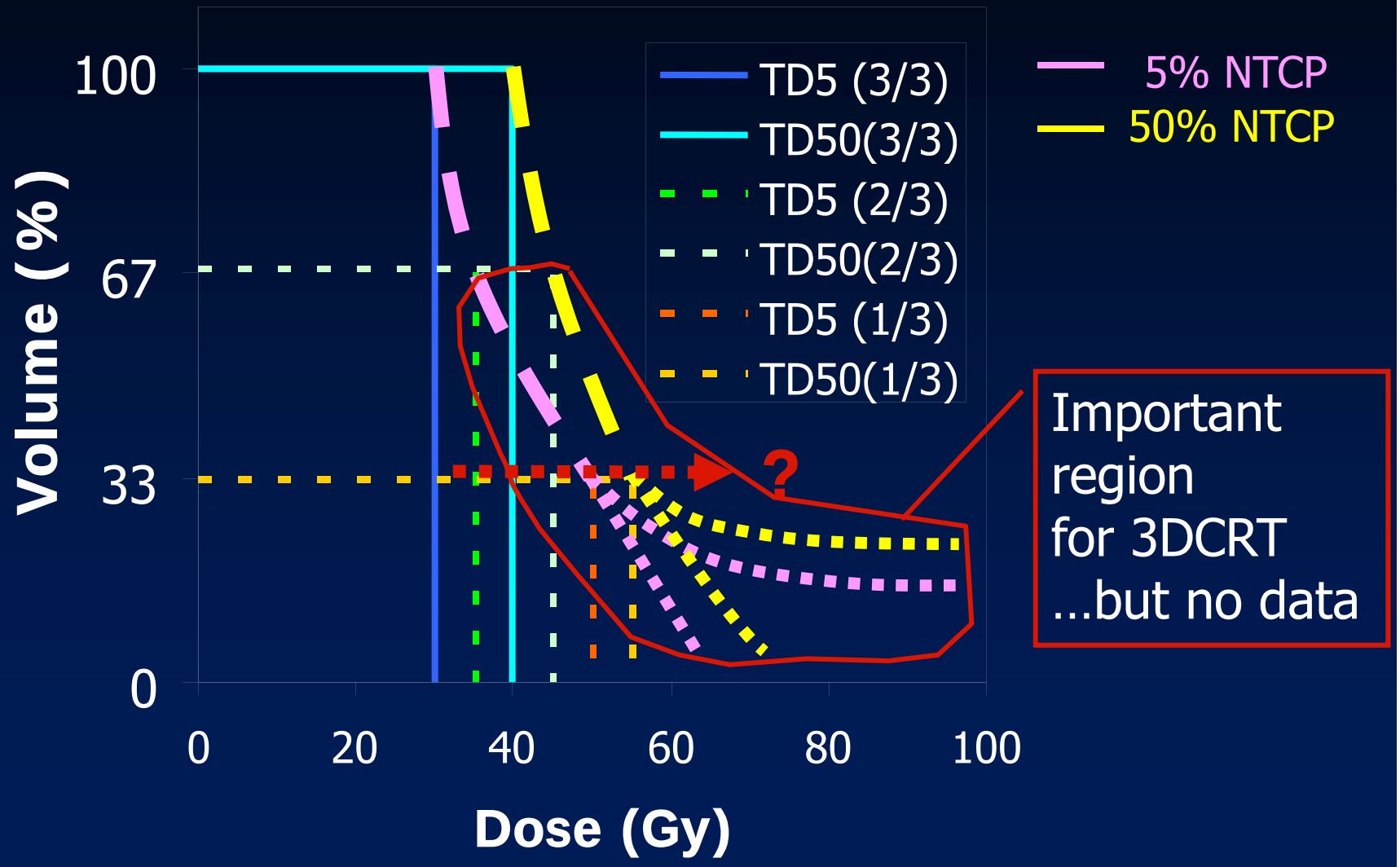

Late 1980s - Early 1990s

- Hint of a model better than no model at all
- Start to probe for signatures of volume effect

Liver Normal Tissue Studies

- In 1987 we began a series of outcomes studies using 3D conformal therapy based on two concepts:
  1. we had the ability to significantly reduce the dose to the normal liver
  2. conformal treatment planning permitted us to quantify the fraction of normal liver irradiated

Partial volume liver irradiation

AN APPLICATION OF DOSE VOLUME HISTOGRAMS TO THE TREATMENT OF INTRAHEPATIC MALIGNANCIES WITH RADIATION THERAPY

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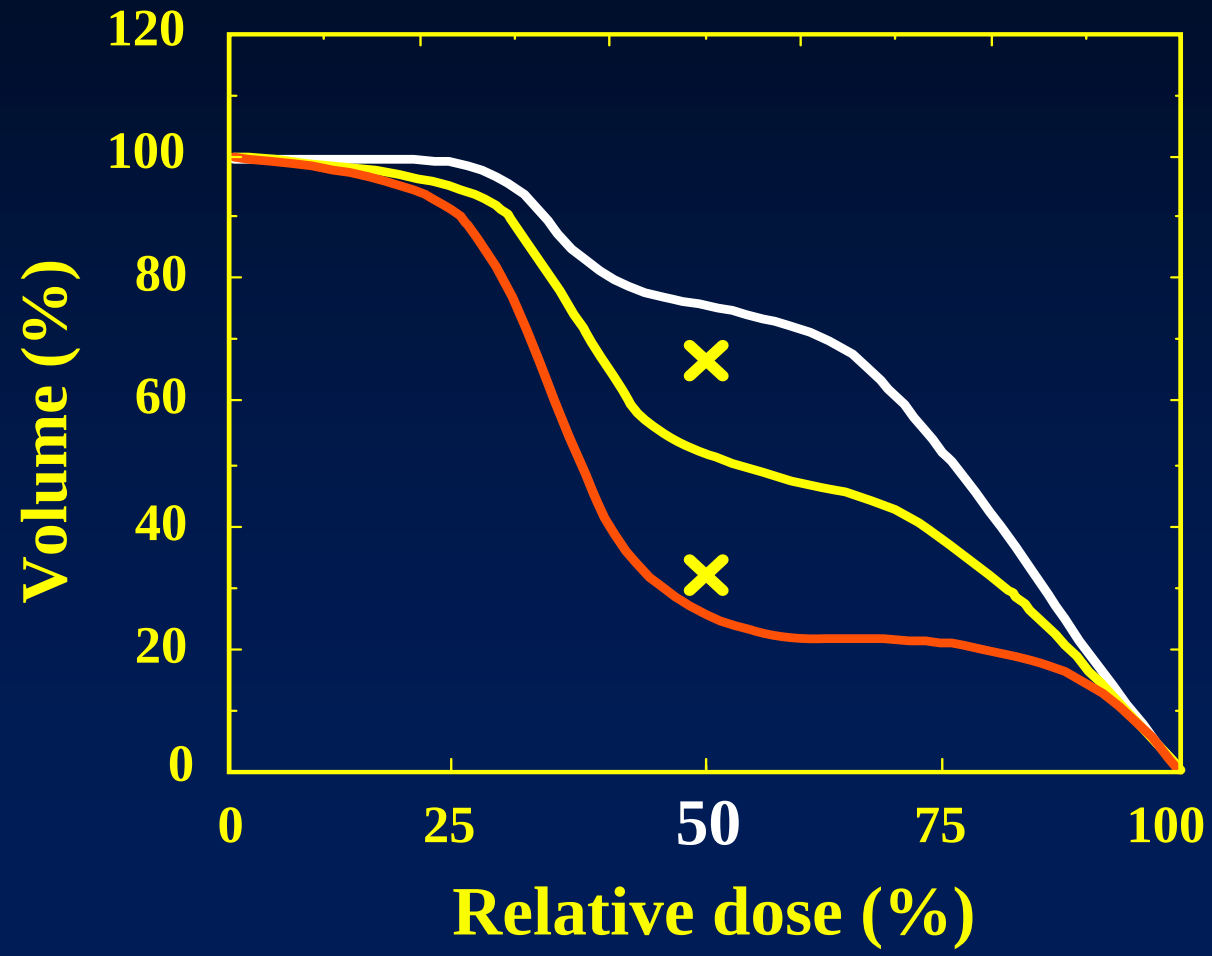
Int J Radiat Oncol Biol Phys, 19:1041-1047, 1990

UM Liver Cancer Early Study

Dose based on the volume of normal liver receiving >50% of the prescription dose.



Liver NTCP Lyman model parameter adjustment

THE USE OF 3-D DOSE VOLUME ANALYSIS TO PREDICT RADIATION HEPATITIS

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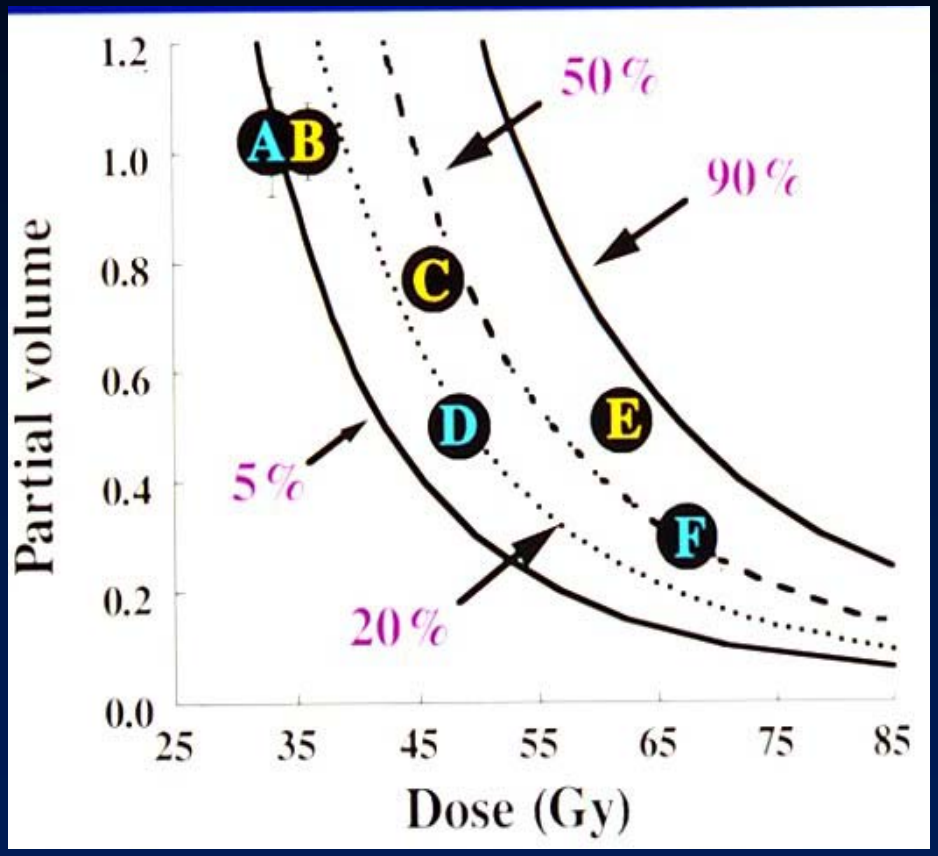
Int J Radiat Oncol Biol Phys, 23:781-788, 1992

Iso-NTCP curves

Original



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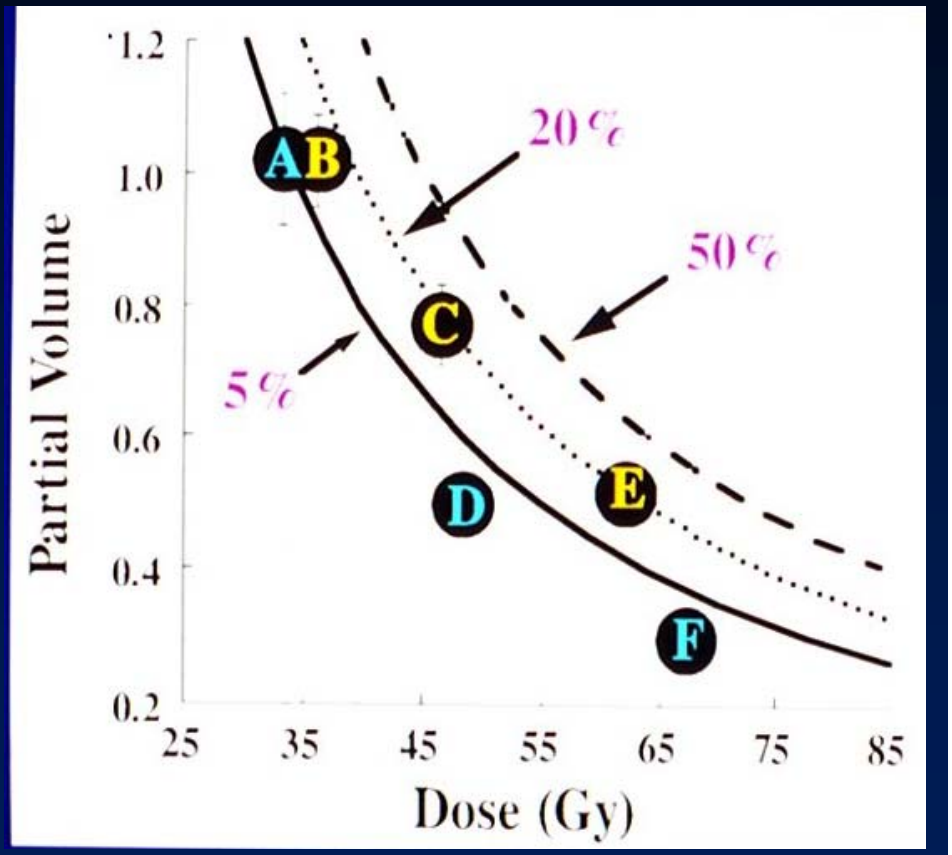

UM Liver Cancer Early Study

- Our results suggested that an NTCP model based on patient data (rather than literature estimates) could be used prospectively to safely deliver far higher doses of radiation with a more consistent risk of complication than would have been previously been considered possible for patients with intrahepatic cancer

Mid 1990s-200x – Using updated models to establish better parameters

- Having established some faith in the existence of the volume effect
- Explore a wider set of the dose-volume space using the model as a guide
- Update parameters when unacceptable complication rates are reached/near

UM Prospective dose escalation studies based on normal tissue tolerance

- We developed a methodology for normal tissue based dose escalation that allowed direct accountability for the effective volume of normal tissue irradiated using:
  - The Lyman NTCP description, and
  - A distinctive property of the effective volume DVH reduction scheme.

Iso-NTCP dose escalation

USE OF V_{eff} AND ISO-NTCP IN THE IMPLEMENTATION OF DOSE ESCALATION PROTOCOLS

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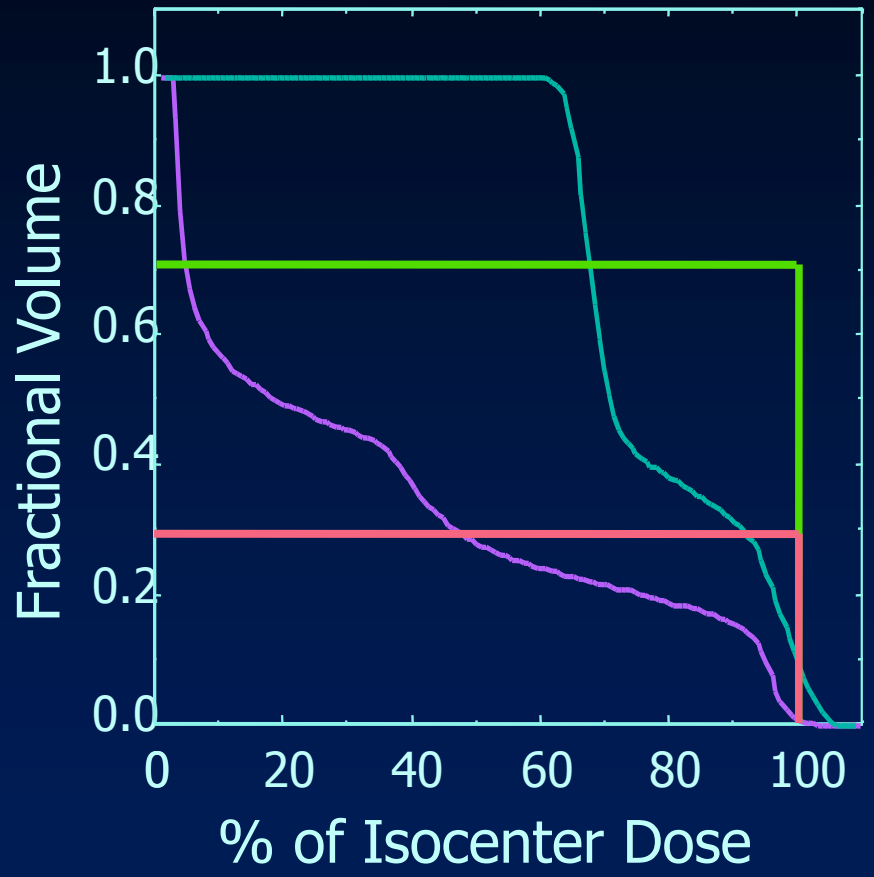
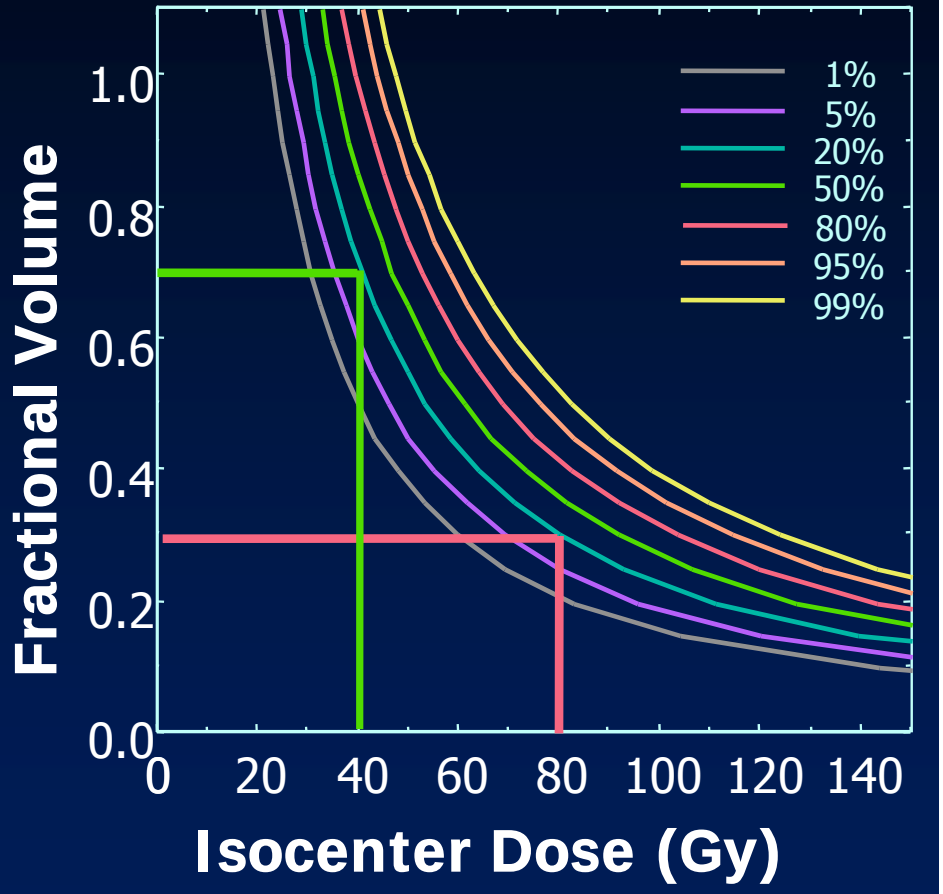
Department of Radiation Oncology, University of Michigan, Ann Arbor, MI 48109-0010

Int J Radiat Oncol Biol Phys, 27:68-695, 1993

V_{eff} *for Iso-NTCP dose prescription*

$$V_{eff} = \Sigma \{ v_i \bullet (D_i / D_{ref})^{1/n} \}$$

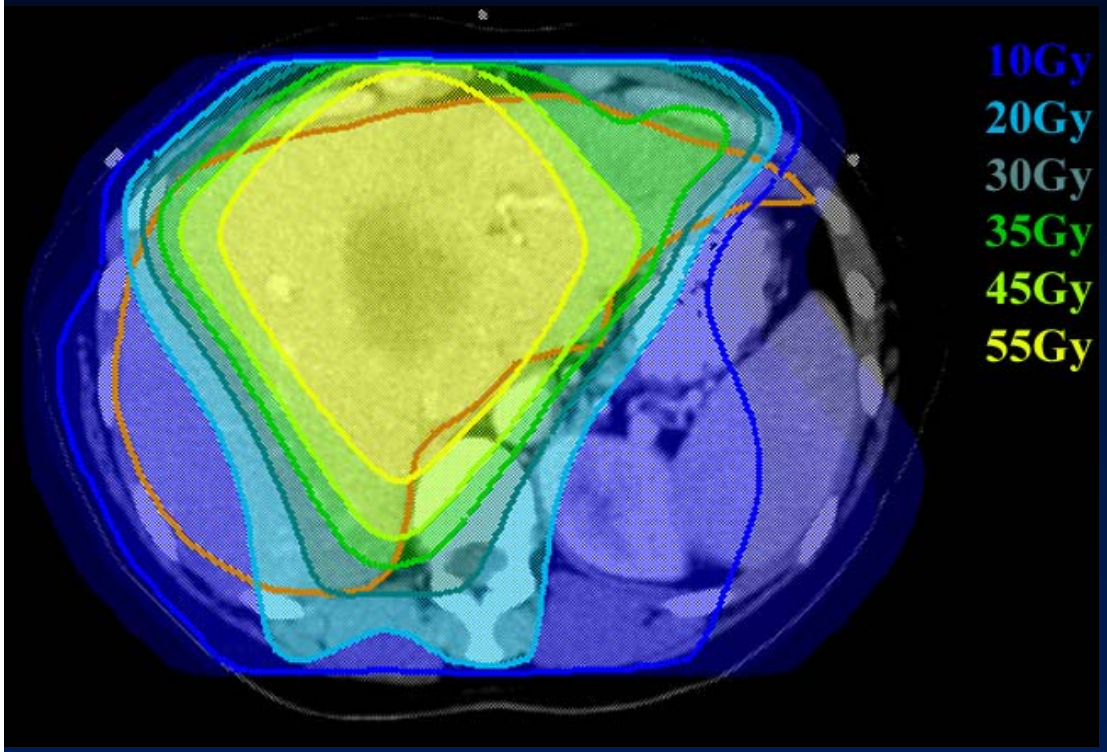


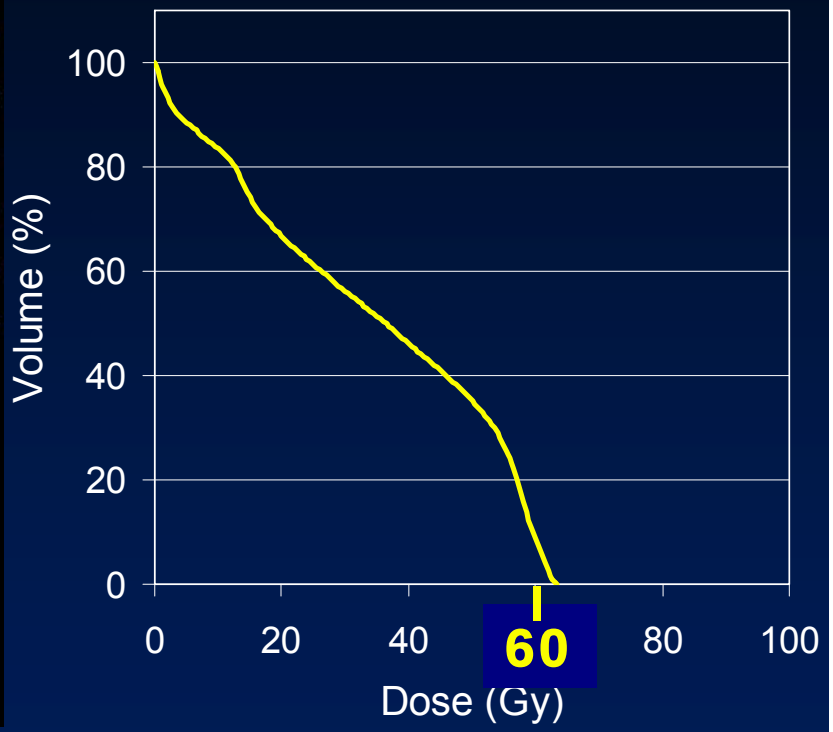


UM liver & lung cancer protocol methods

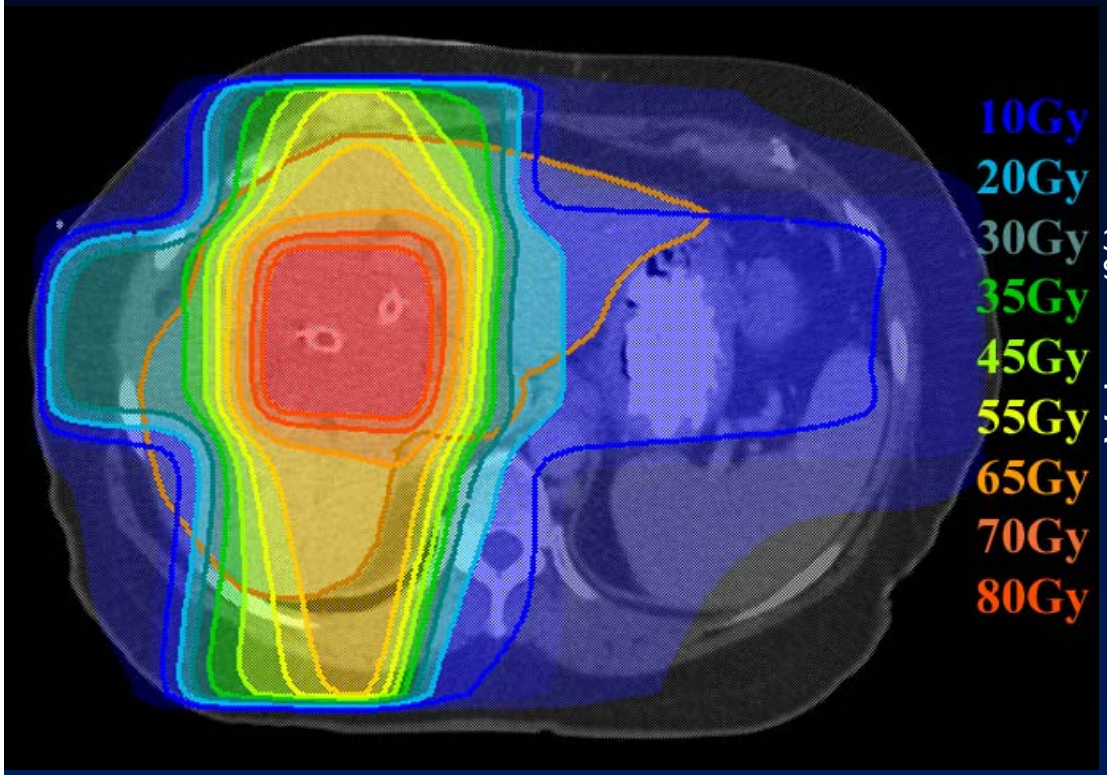
- The goal for the treatment planner was to minimizing the effective volume Veff for the normal liver or lung which in turn allowed for the maximum safe tumor dose to be given at the current iso-NTCP level
- This contrasted with standard dose trials which delivered target dose without regard to the volume of normal tissue

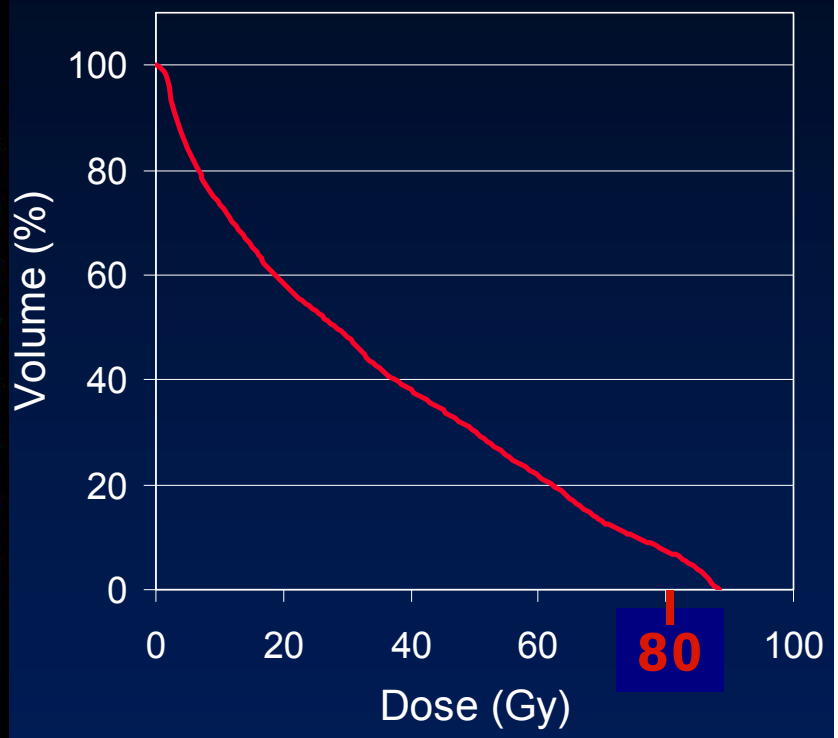
Focal Liver 3DCRT - Larger Target





Focal Liver 3DCRT - Smaller Target





Iso-NTCP dose escalation

- The result was a framework for gathering partial organ tolerance data in a systematic, prospective fashion.
- Moreover, it allowed the introduction of new technologies without alteration of the protocols objectives
  - ✓ More conformal → lower Veff → higher Dref
  - ✓ Same iso-NTCP level

Iso-NTCP dose escalation

- Incorporation of the concepts removed some of the arbitrariness often associated with dose escalation studies that didn't consider the volume of tissue irradiated
- The data resulting from studies which used the methodology were of value for further NTCP model parameterizations

Liver Lyman model NTCP parameters

CLINICAL INVESTIGATION **Normal Tissue**

ANALYSIS OF RADIATION-INDUCED LIVER DISEASE USING THE LYMAN NTCP MODEL

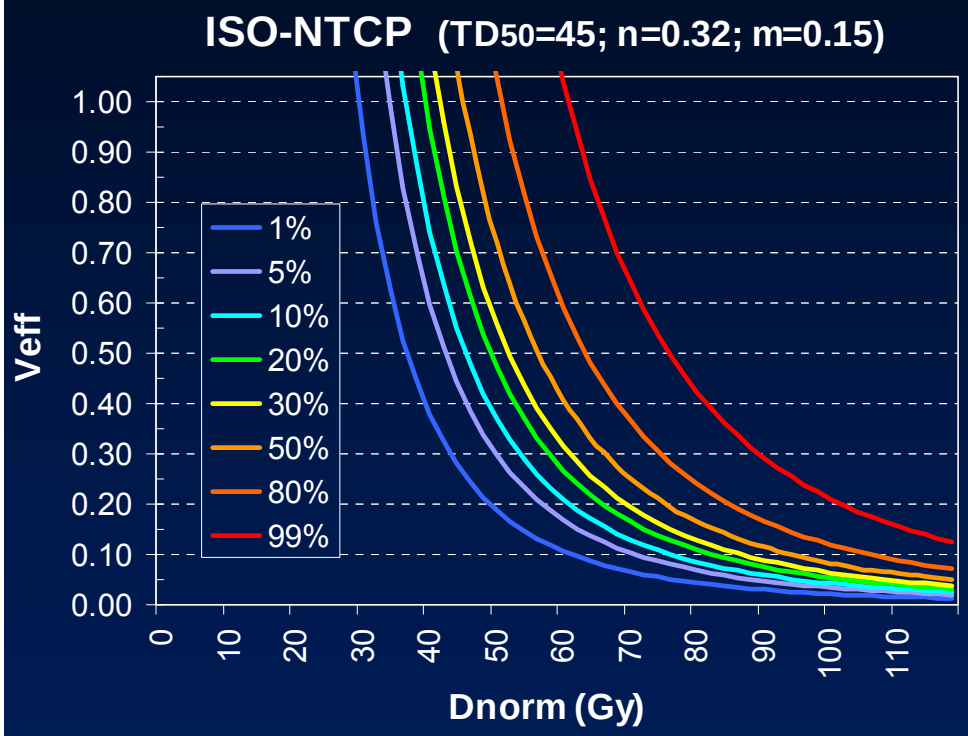
LAURA A. DAWSON, M.D., DANIEL NORMOLLE, PH.D., JAMES M. BALTER, PH.D., CORNELIUS J. MCGINN, M.D., THEODORE S. LAWRENCE, M.D., PH.D., AND RANDALL K. TEN HAKEN, PH.D.

Department of Radiation Oncology, University of Michigan, Ann Arbor, MI

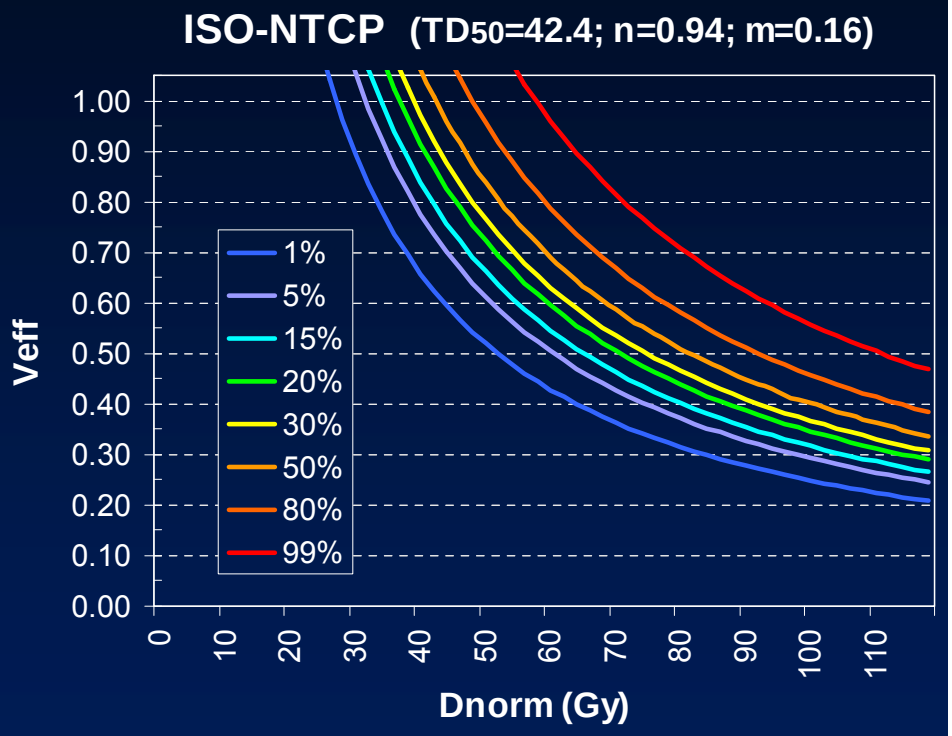
Int J Radiat Oncol Biol Phys, 53:810-821, 2002

LKB Model Parameters (early 2000s)

Original Emami-Burman Parameters



Derived Parameters



QUANTEC Liver Paper

RADIATION-ASSOCIATED LIVER INJURY

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Int J Radiat Oncol Biol Phys, 76:S94-S100, **2010**

QUANTEC Liver Summary Table

Organ	Volume segmented	Irradiation type (Partial organ or as stated)*	Endpoint	Dose (Gy), or dose/volume parameters*		Rate (%)	Notes on dose/volume parameters
Liver	Whole liver – GTV	3D-CRT or Whole organ	Classical RILD[b]	Mean dose	< 30-32	< 5	Excluding patients with preexisting liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
	Whole liver – GTV	3D-CRT	Classical RILD	Mean dose	< 42	< 50	
	Whole liver – GTV	3D-CRT or Whole organ	Classical RILD	Mean dose	< 28	< 5	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding Hepatitis B reactivation as an endpoint
	Whole liver – GTV	3D-CRT	Classical RILD	Mean dose	< 36	< 50	
	Whole liver – GTV	SBRT (hypofraction)	Classical RILD	Mean dose	< 13 < 18	< 5 < 5	3 fractions, primary liver cancer 6 fractions, primary liver cancer
	Whole liver – GTV	SBRT (hypofraction)	Classical RILD	Mean dose	< 15 < 20	< 5 < 5	3 fractions, for liver metastases 6 fractions, for liver metastases
	> 700 cc of normal liver	SBRT (hypofraction)	Classical RILD		< 15	< 5	Critical volume based, in 3-5 fractions

L. Marks, et al., IJROBP, 76:S10-S19, 2010

20+ years of outcomes modeling

- There are many more data in different dose/volume regions than in 1990
- This situation will continue to improve
- Outcomes models continue to play a role in iso-toxicity RT protocols,
  - especially for tumors in so-called volume effect organs

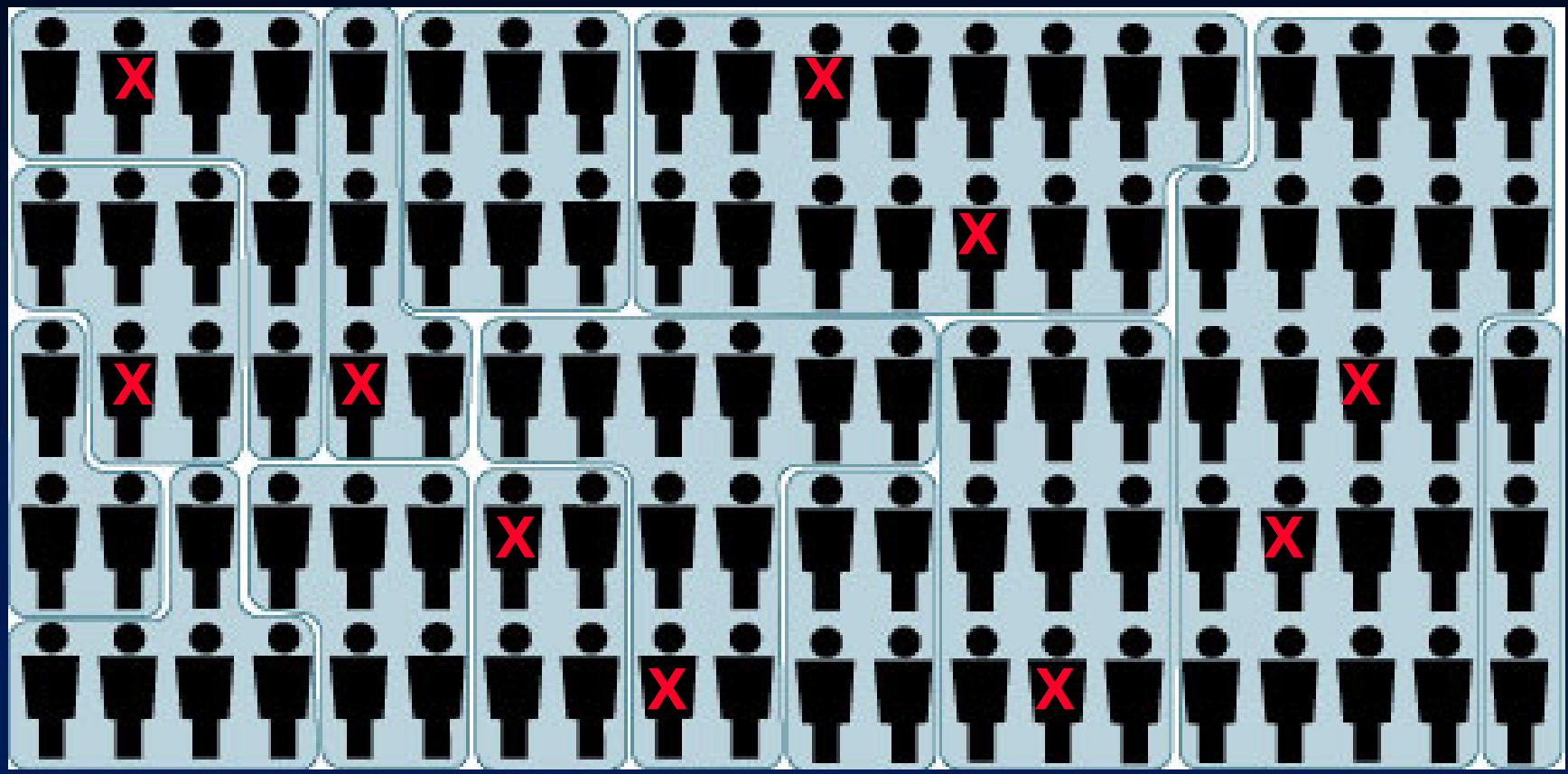
20+ years of outcomes modeling

- (overly?) simple mathematical models where nearly everything seems to be related to mean dose
- Assumes all patients are representative of a uniform cohort
- Assumes homogeneously responding tumors and normal tissues
- Assumes previous experience still applies to modern therapeutic approaches

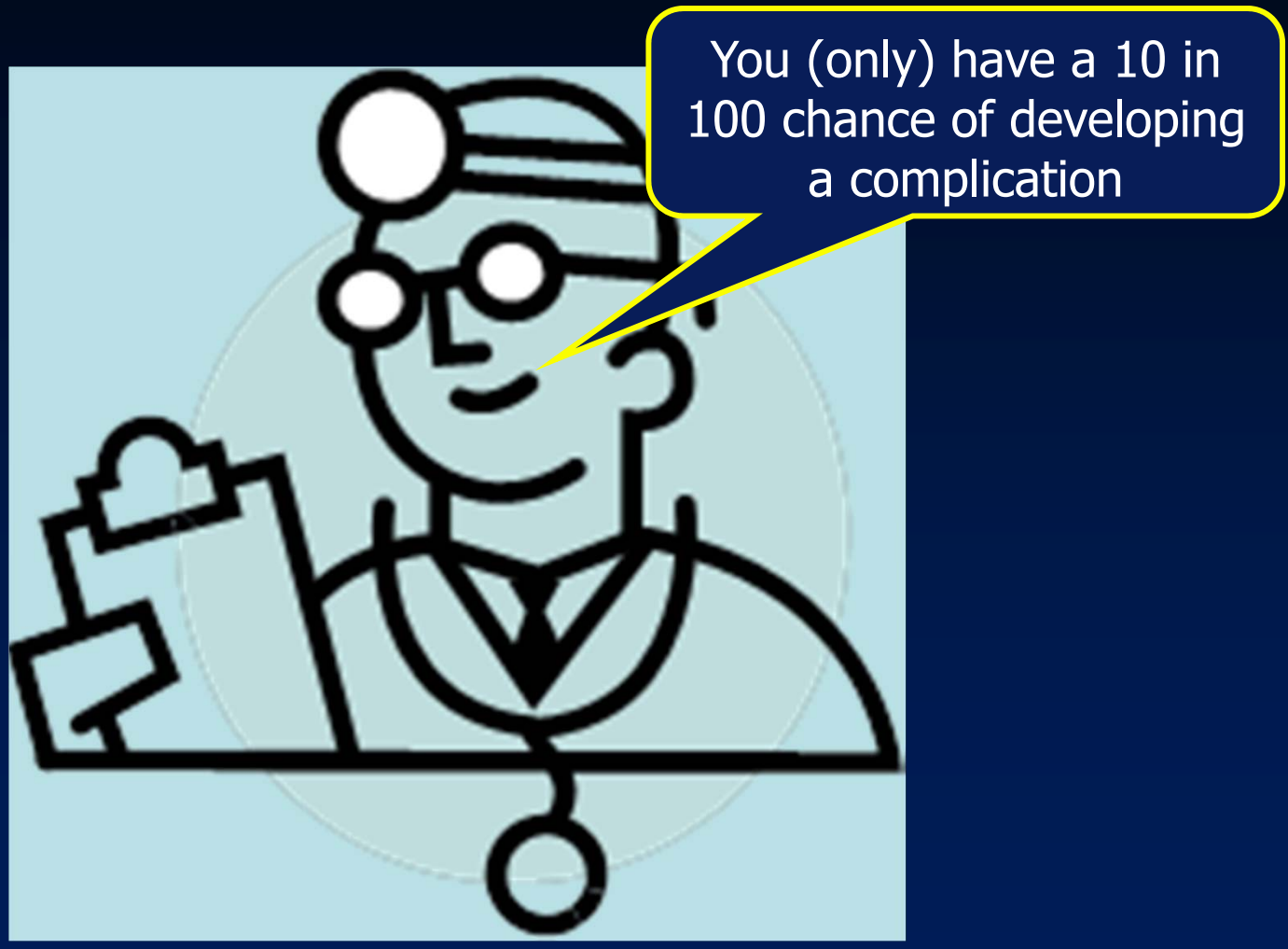
Does iso-NTCP individualize therapy?

- Population based NTCP parameters
  - Permit design of protocols that can maximize target dose for each patient at a equal level of risk (e.g., 10% NTCP)
- Therefore, as the patients, their tumors and geometries are all different:
  - each will get their own individualized maximum tolerated dose treatment,
  - ***but, as a member of the population!***
    - i.e., each patient will have a 10 in 100 chance of getting the dose limiting complication

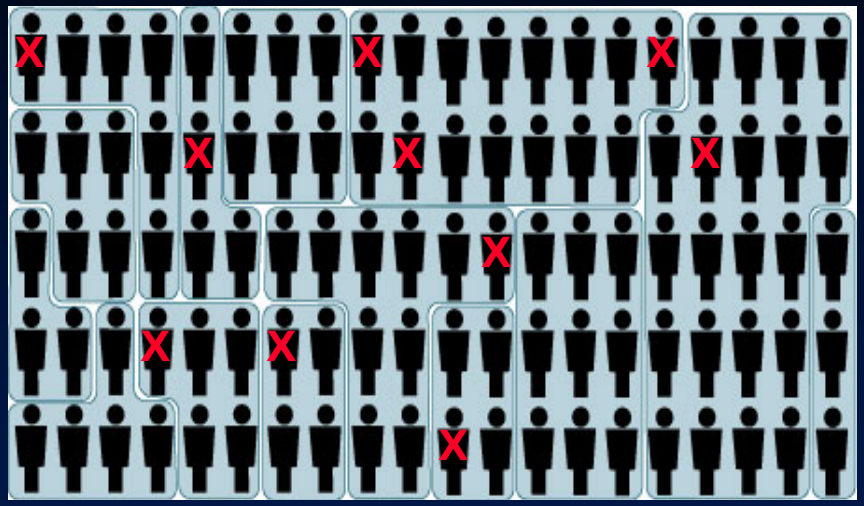
10 of 100 patients will have a complication

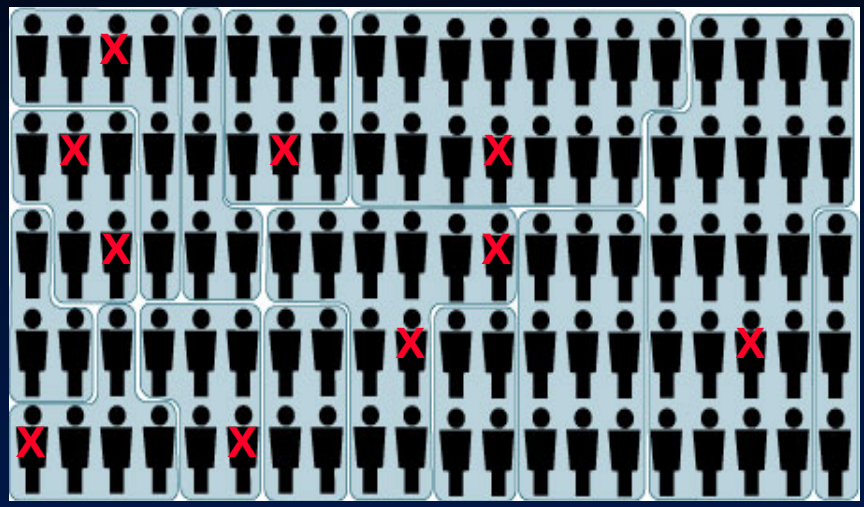


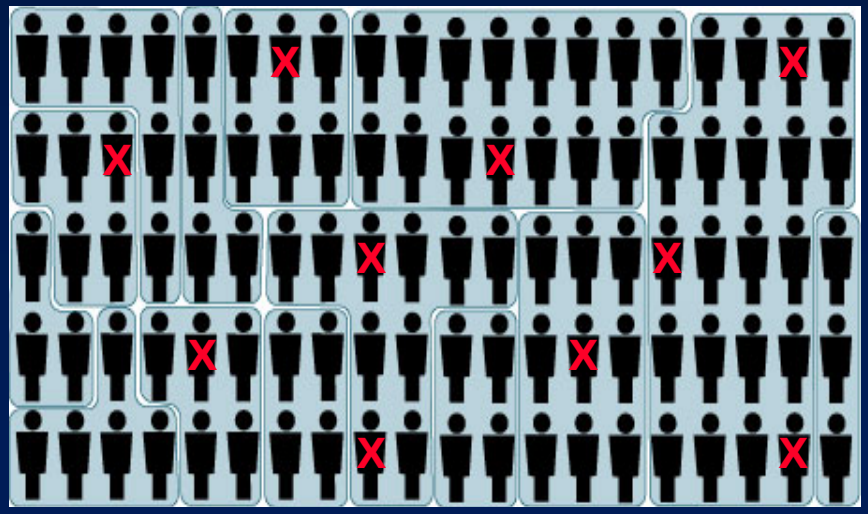
However, we can't tell which 10 of 100 they will be!

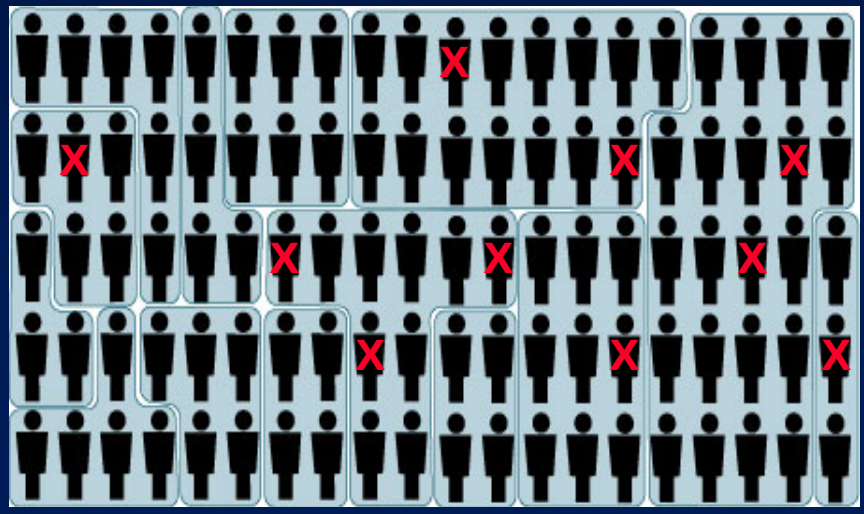


10 of 100 patients will have a complication (which 10?)

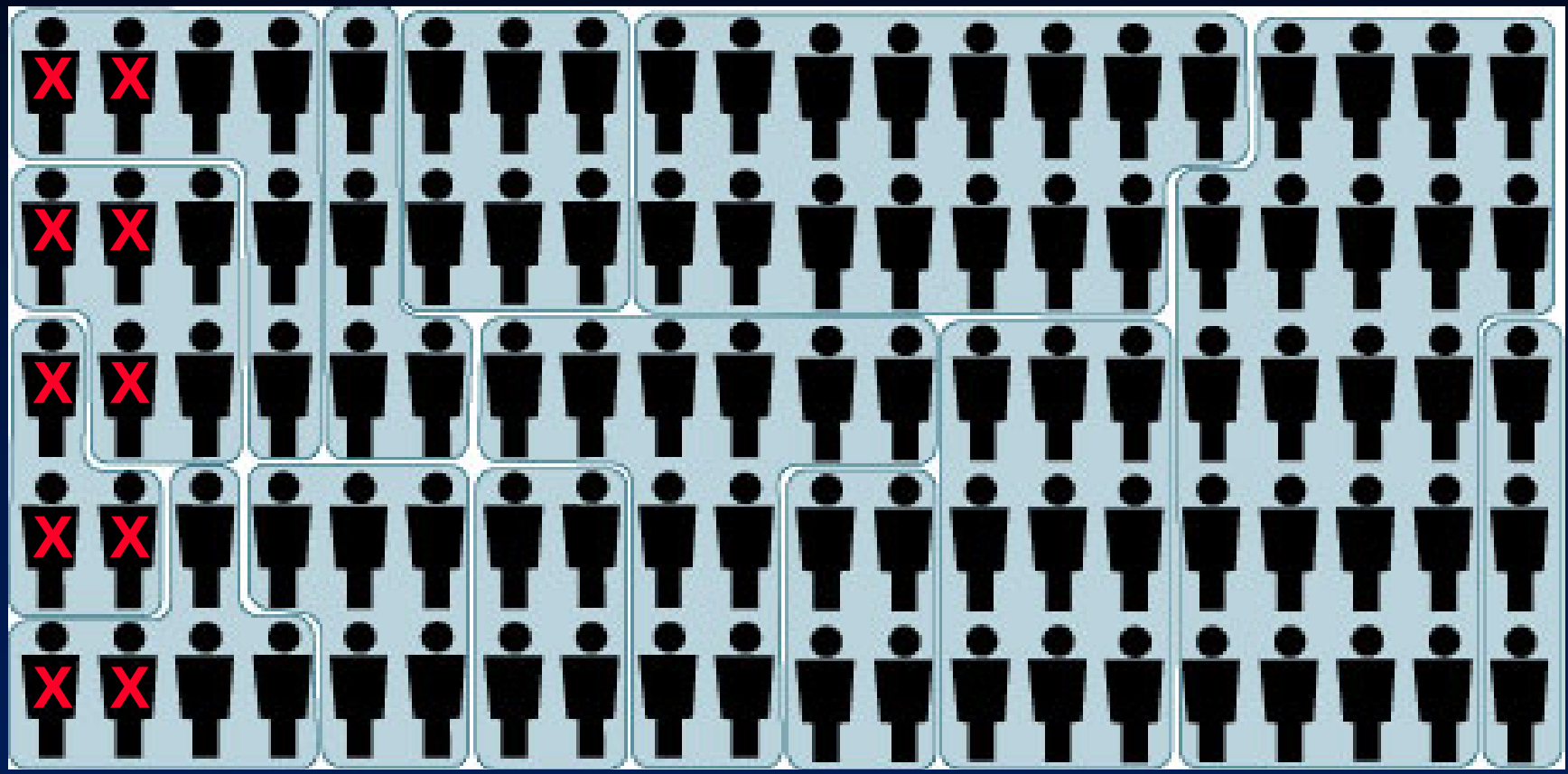








What if we could identify which 10 of 100?



What if we could identify the sensitive subgroup?

- We could decrease the risk of complication if we could determine during therapy the 10% of patients who are at greatest risk for toxicity
- Moreover, we could potentially increase dose for the 90% of those who would experience no severe toxicity using the current population-based approach.

How can we identify subgroups?

- Requires additional patient specific information
- Validated, efficient means of obtaining equivalent (or inferred) data
- With recognition that the patient model changes over the course of treatment

How can we identify subgroups?

- Subgroup characteristics
  - Anatomic
  - Biological
  - Functional
- Tools to identify
  - Physiological imaging
  - Cytokines and other biomarkers
  - Other predictive assays or characteristics

Standard Radiation Therapy

- Treatment based on a population estimate of what might control a tumor
- Estimated risk of normal tissue damage based on the most sensitive 5-10% of the population
- Treatment delivered to the initially prescribed dose
  - Stop only for unacceptable acute toxicity

Response-based adaptive therapy

- Assess pretreatment the patient's tumor and normal tissues
  - Genetically
  - With functional and molecular imaging
  - With plasma cytokines
- Determine during treatment:
  - If, *and what parts of*, the tumor are responding
  - If, *and what parts of*, the normal tissues are being injured

Response-based adaptive therapy

- Adapt therapy to the individual patient's response
  - redistribute dose to the resistant part of the tumor
  - while sparing the functioning normal tissues

Examples – Preliminary Data

- Poster 20: Optimization of Response-Based, Adaptive Therapy

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