Individualizing Radiotherapy Using NTCP Models: 17 Years in Ann Arbor

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Introduction

- Phase One clinical trials seek to determine the maximum tolerated dose (MTD) of the investigational treatment.
- Similarly, “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.

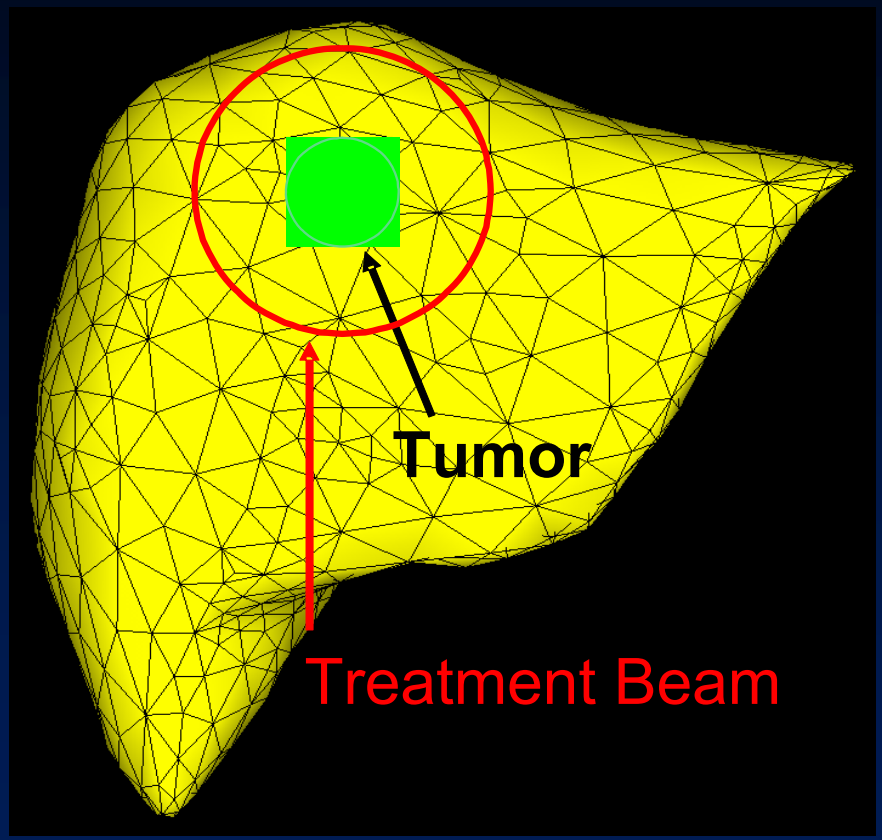
Introduction

- 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.

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

Liver Normal Tissue Studies

- Beginning in 1987, we began a series of studies using 3D conformal therapy based on two fundamental concepts.
  - ✓ First, we had the ability to significantly reduce the dose to the normal liver.
  - ✓ Secondly, conformal treatment planning permitted us to quantify the fraction of normal liver irradiated which can be conveniently expressed for input in a NTCP model.

Partial volume liver irradiation

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

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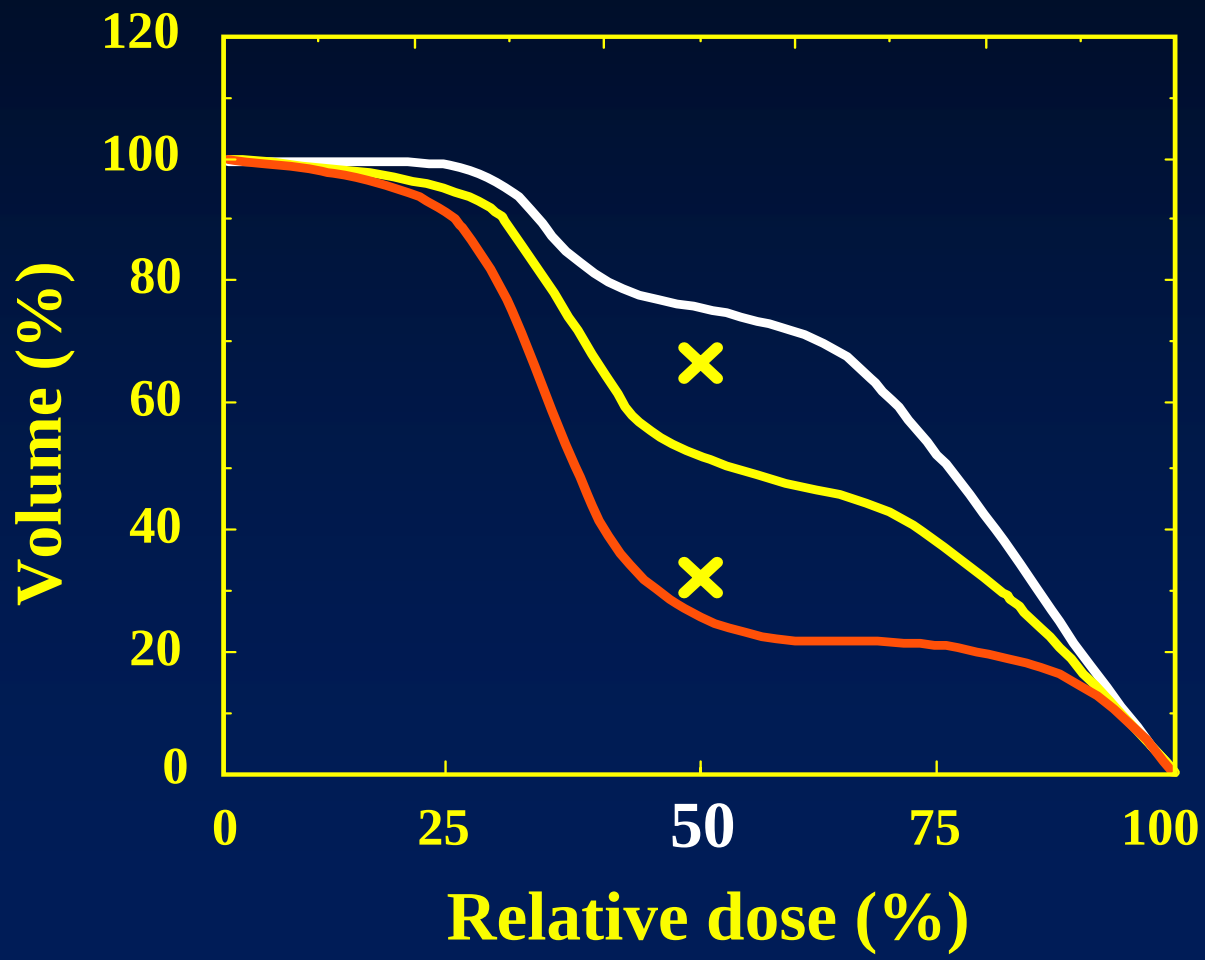
AND RANDALL K. TEN HAKEN, PH.D.

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

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.



Groups of patients

- A-Whole liver alone - 33 Gy
- B-Whole liver alone - 36 Gy
- C-Whole liver plus target boost- 45 and 48 Gy (average 46.4 Gy)
- D-Whole liver plus target boost- 60 and 66 Gy (average 62.0 Gy)
- E-Target only- 48 and 52.8 Gy (average 48.4 Gy)
- F-Target only- 66 and 72.6 Gy (average 67.3 Gy)

Liver NTCP Lyman model parameter adjustment

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

THEODORE S. LAWRENCE, M.D., PH.D.,* RANDALL K. TEN HAKEN, PH.D.,*
MARC L. KESSLER, PH.D.,* JOHN M. ROBERTSON, M.D.,* JOHN T. LYMAN, PH.D.,*,†
MARK L. LAVIGNE, C.M.D.,* MORTON B. BROWN, PH.D.,‡
DANIEL J. DUROSS, M.A.,§ JAMES C. ANDREWS, M.D.,**
WILLIAM D. ENSMINGER, M.D., PH.D.†† AND ALLEN S. LICHTER, M.D.*

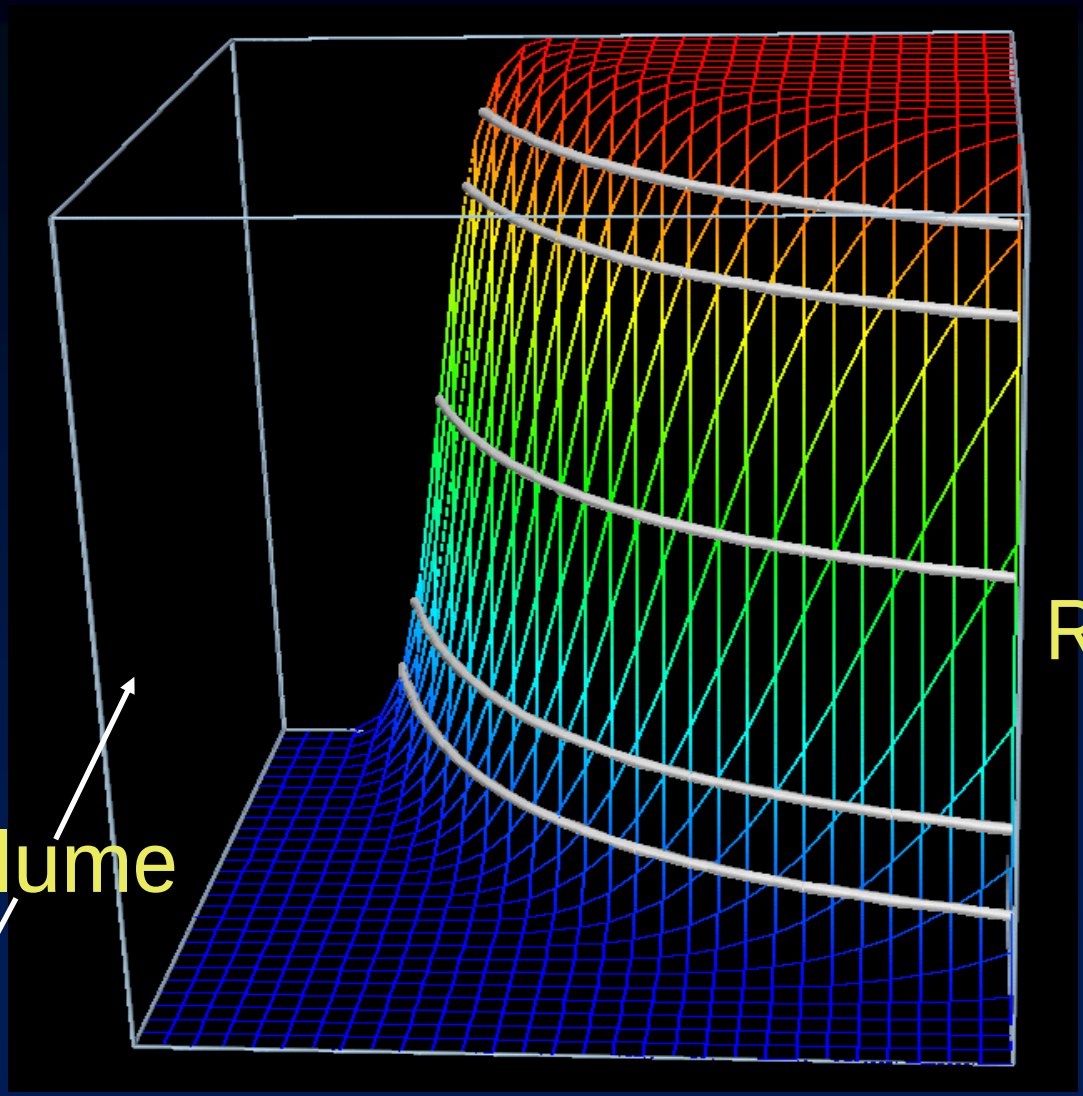
University of Michigan Medical Center, Ann Arbor, MI 48109

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

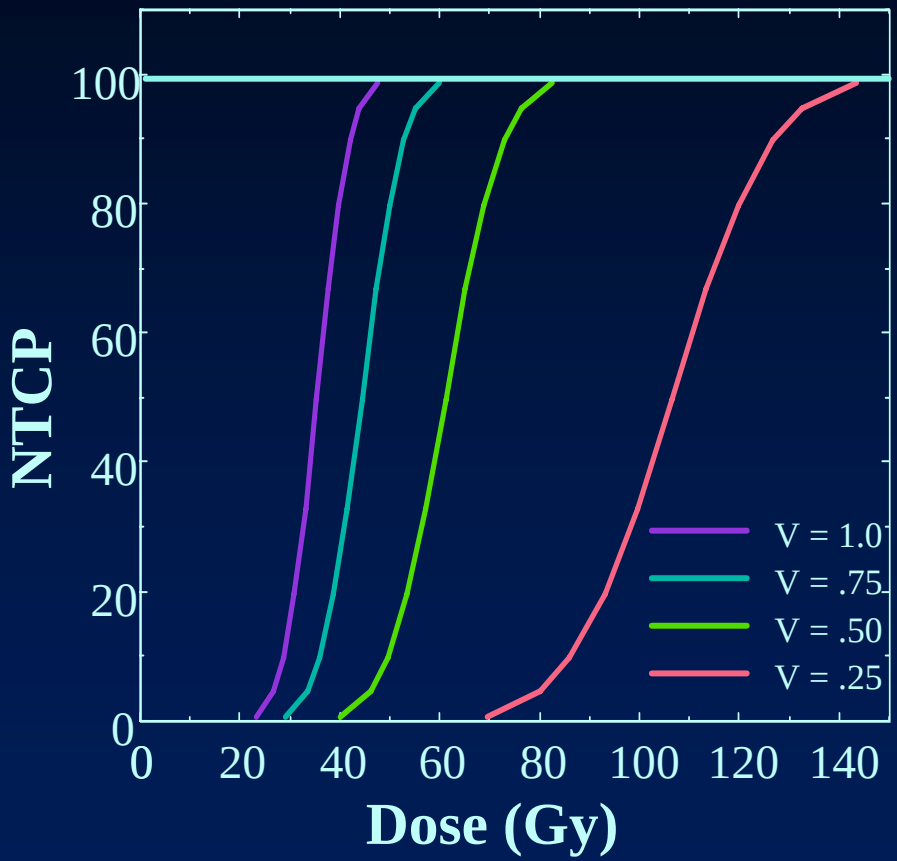
The Lyman NTCP Model

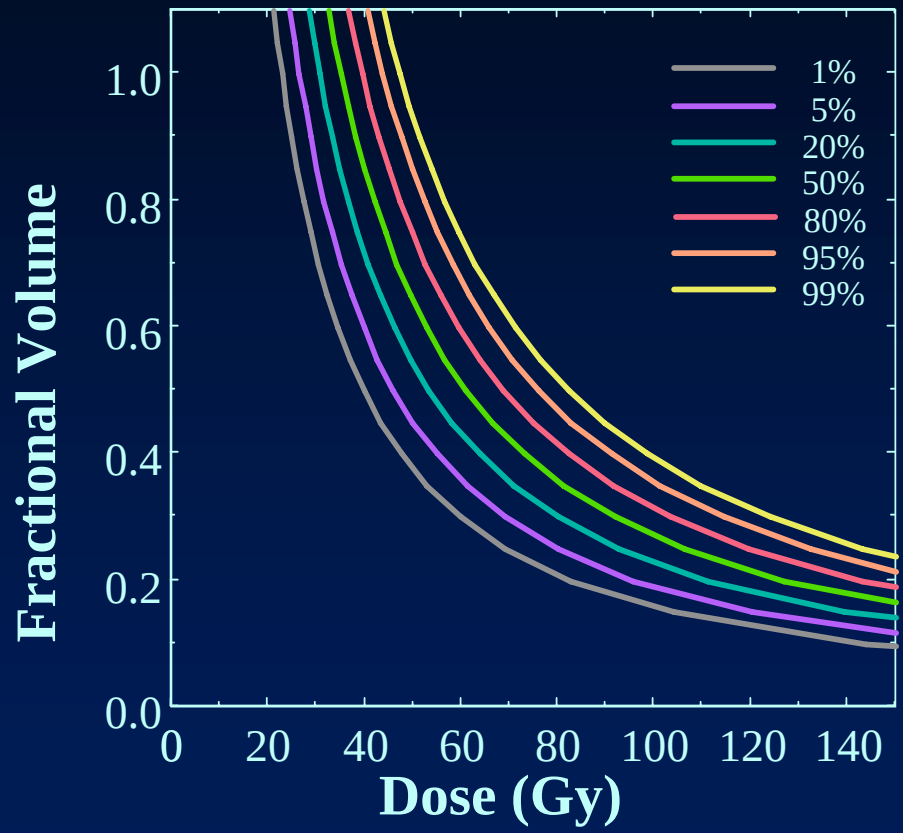
Lyman JT: Complication probability – as assessed from dose-volume histograms. Radiat Res 104:S13-S19, 1985.

Lyman Model Dose-Volume-Response Surface



Dose-Volume-Response contours

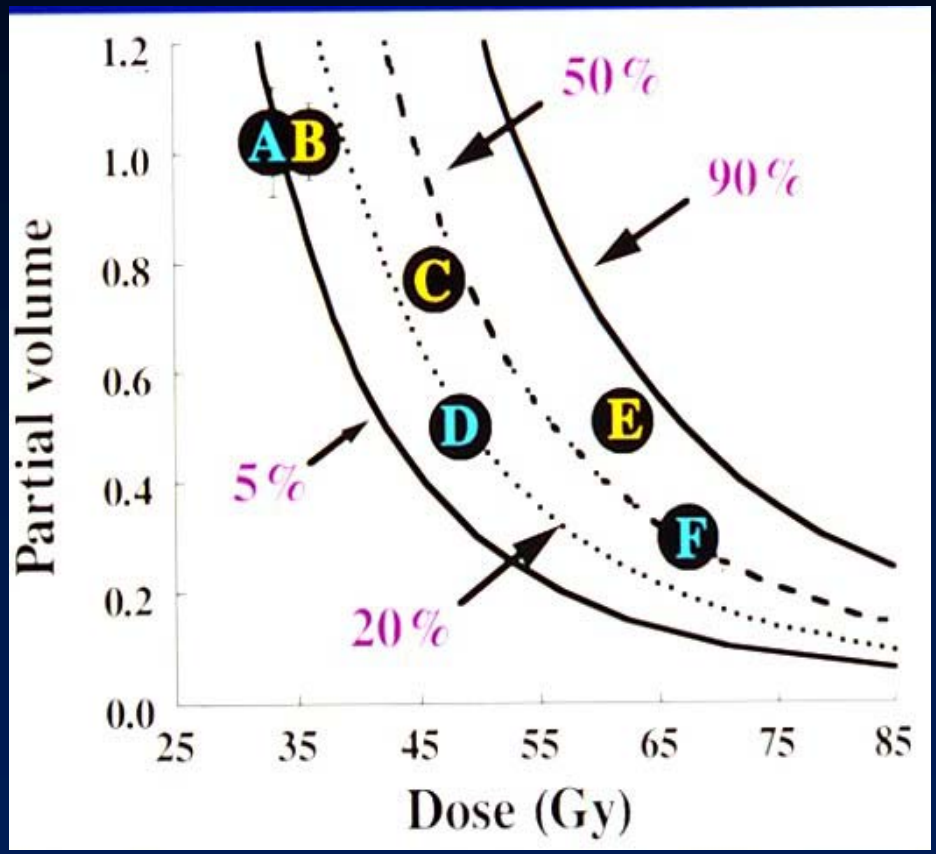


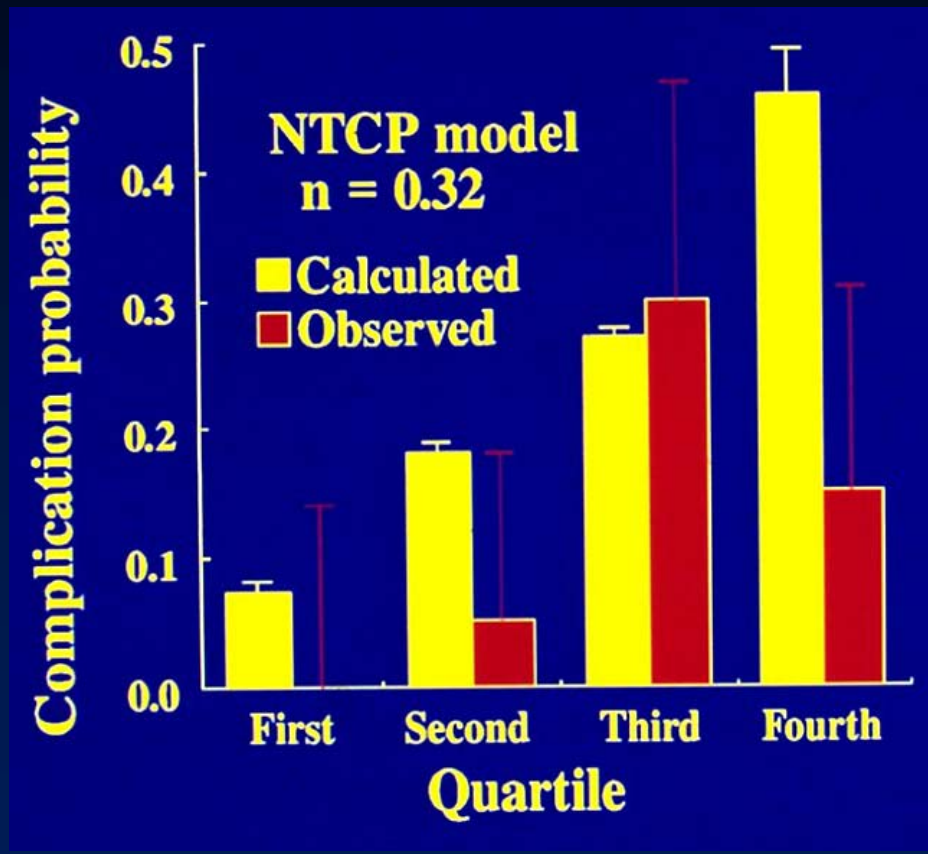


Observed complications

	TREATMENT	DOSE	COMPLICATIONS	
A	Whole liver alone	33 Gy	0 of 19	0 %
D	Target only	48 Gy	0 of 12	
F	Target only	67 Gy	0 of 15	
B	Whole liver alone	36 Gy	3 of 13	27 %
C	Whole liver plus boost	46 Gy	4 of 11	
E	Whole liver plus boost	62 Gy	2 of 9	

Original NTCP parameters





The Lyman NTCP Description

$$NTCP = (2\pi)^{-1/2} \int_{-\infty}^{t} \exp(-x^2 / 2)\, dx,$$

where;

$$t = (D - TD_{50}(v)) / (m \bullet TD_{50}(v)),$$

and;

$$TD_{50}(v) = TD_{50}(1) \bullet v^{-n}$$

“m” determination

$$t = (D - TD_{50}(\nu)) / (m \bullet TD_{50}(\nu))$$

then

$$TD_{50}(\nu) = D / (1 + m \bullet t).$$

Thus, for 2 dose levels D_i (and outcomes t_i) at the same partial volume ν ,

$$TD_{50}(\nu) = D_1 / (1 + m\ t_1) = D_2 / (1 + m\ t_2)$$

and

$$m = (D_1 + D_2) / (D_2\ t_1 + D_1\ t_2)$$

“n” determination

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n}$$

generalizing and rearranging,

$$TD_{XX}(1) = TD_{XX}(v) \cdot v^{n}$$

Thus, for 2 partial volumes v_i (and tolerance doses $TD(v_i)$ for the same complication rate,

$$TD_{XX}(1) = TD_{XX}(v_1)\, v_1^{\,n} = TD_{XX}(v_2)\, v_2^{\,n}$$

and

$$n = \ln\left(TD_{XX}(v_1) / TD_{XX}(v_2)\right) / \ln\left(v_1 / v_2\right)$$

"$TD_{50}(1)$" determination

$$t = (D - TD_{50}(1)) / (m \bullet TD_{50}(1))$$

then

$$TD_{50}(1) = D / (1 + m \bullet t).$$

Thus, for each dose level D_i (and outcome t_i) for whole organ irradiation,

$$TD_{50}(1) = D_i / (1 + m\ t_i)$$

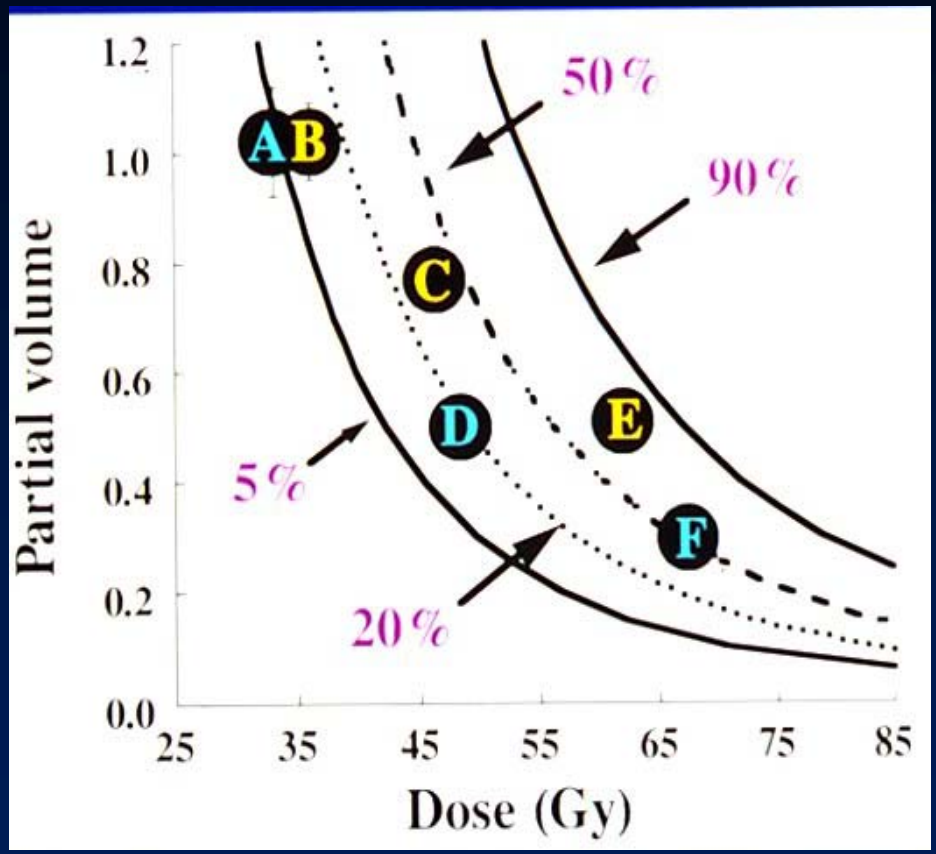
For an known "m" value.

UM Liver Cancer Early Study

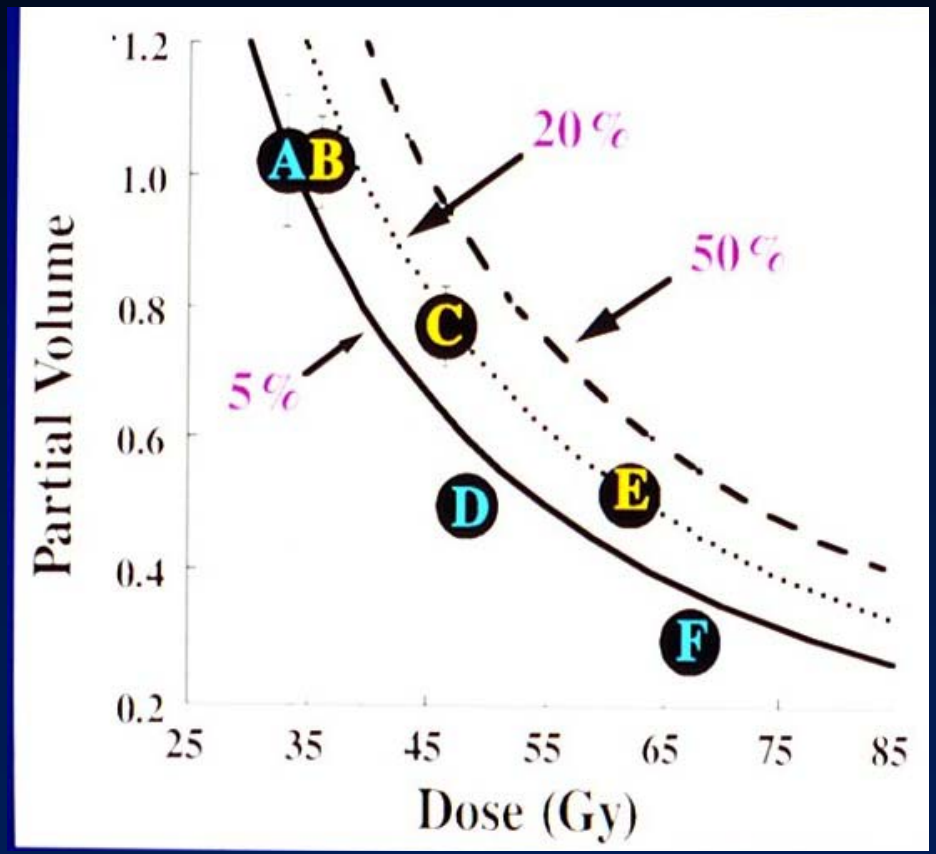
- We were able to estimate parameters of the Lyman mode to describe the probability of causing radiation-induced liver disease, based on both radiation dose and liver volume irradiated.
- Using the parameters n = 0.69, m = 0.15 and TD50 (1) of 45 Gy for 1.5 Gy fx
- “n” differed significantly from the values estimated by literature review

Iso-NTCP curves

Original

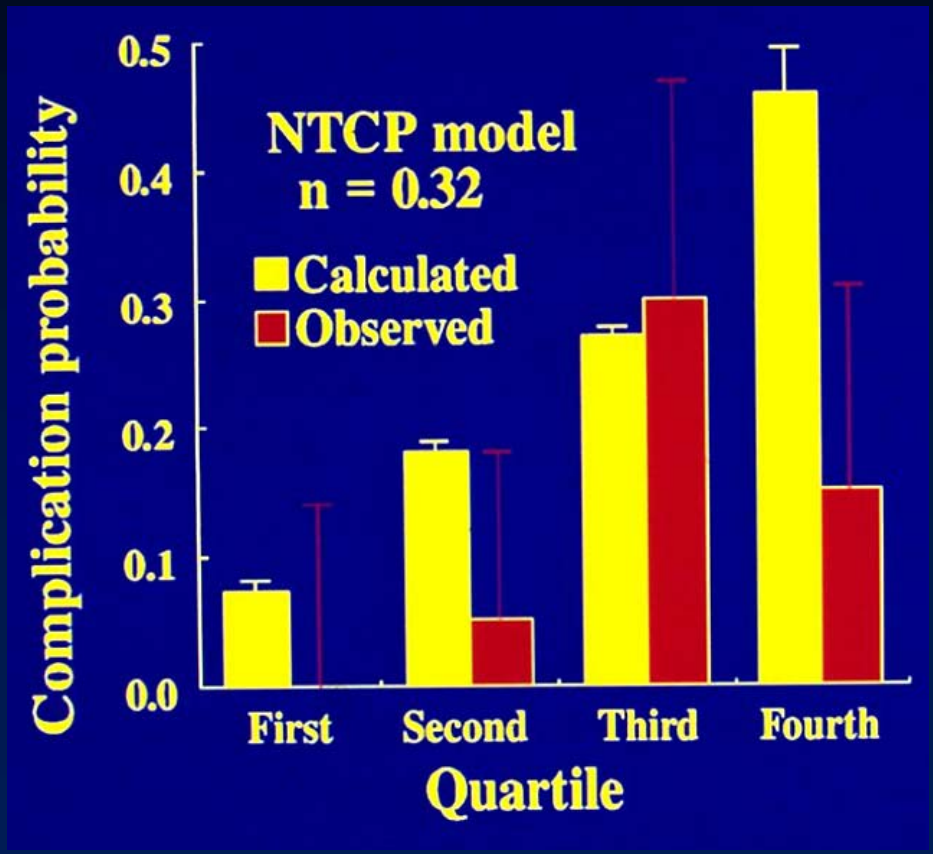


Revised

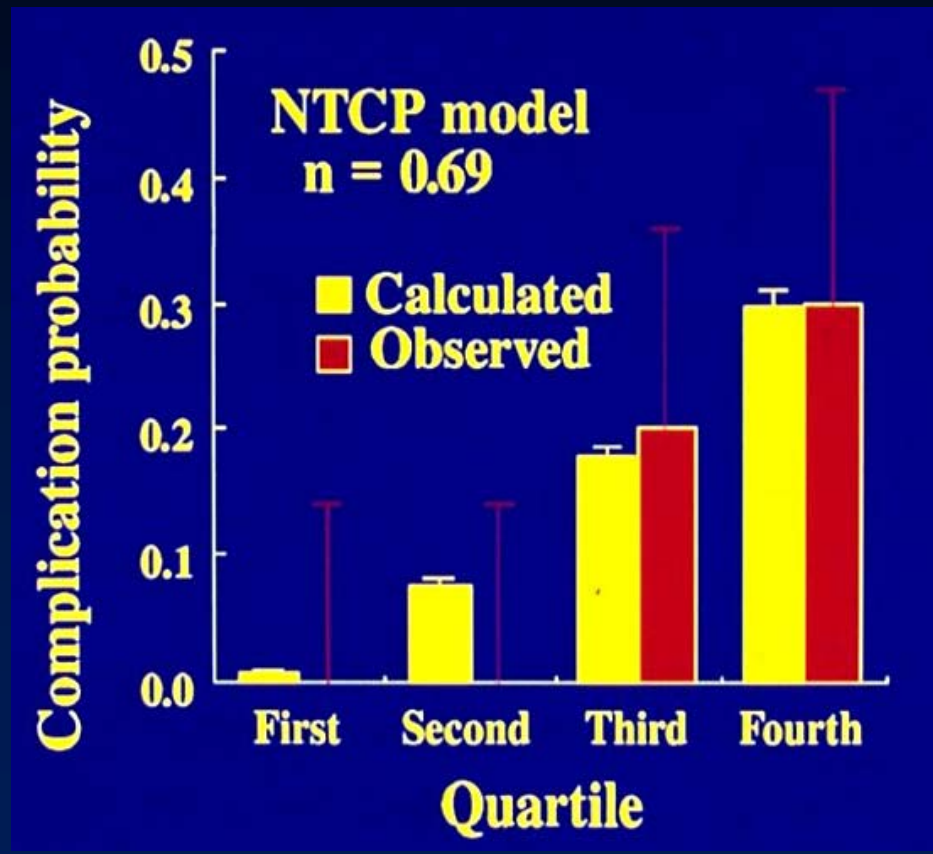


Quartile Plots

Original



Revised



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.

UM Prospective dose escalation studies based on normal tissue tolerance

- Much valuable information can be gained from retrospective studies.
- It was desirable to probe the safe limits of partial organ irradiation in a systematic, prospective manner using modern 3-D RTTP tools to summarize the experience.
  - ✓ **Guidelines for obtaining those tolerance data were not available!**

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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MARK B. HAZUKA, M.D., THEODORE S. LAWRENCE, M.D., PH.D.,
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Int J Radiat Oncol Biol Phys, 27:68-695, 1993

Using the Lyman NTCP description

- The Lyman NTCP description attempts to describe *uniform* partial organ irradiation.
- This implies:
  - ✓ A fractional volume, *V*, of the organ receives a single uniform dose, D.
  - ✓ The rest of the organ, (1 – *V*), receives zero dose.
  - ✓ *i.e.*, a single step DVH, {D , *V*}

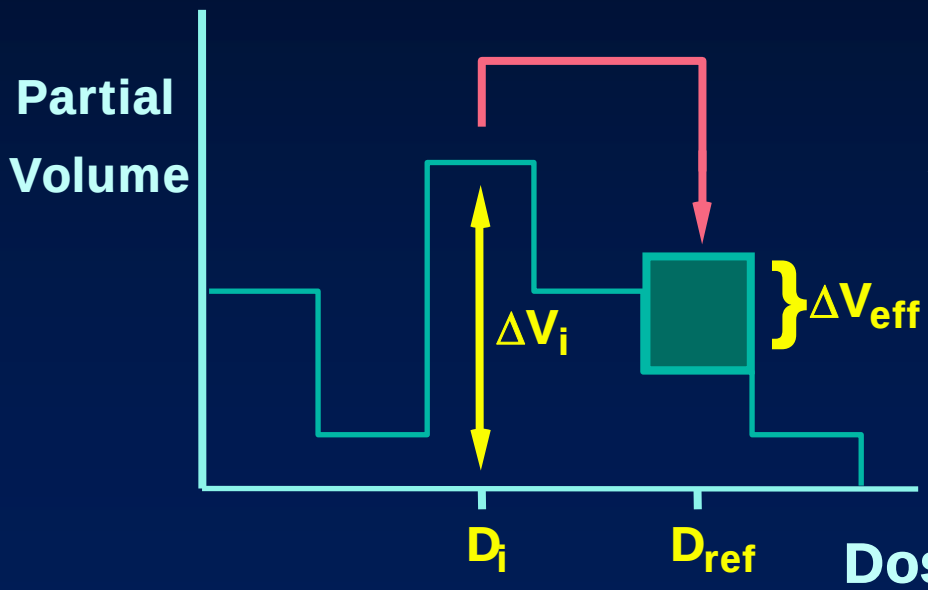
DVH reduction scheme

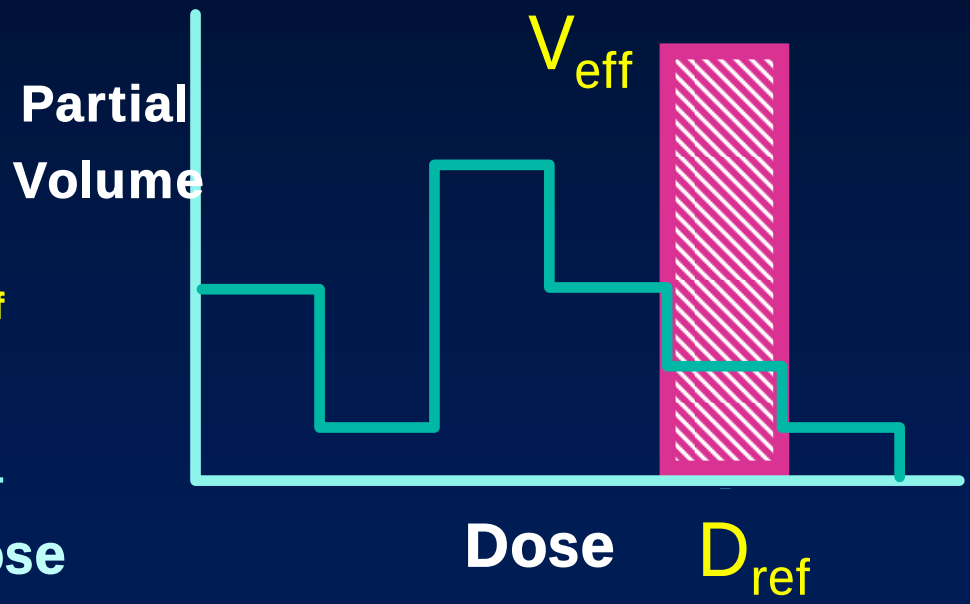
- For non-uniform irradiation, the 3D dose volume distribution (or DVH) must be reduced to a single step DVH that could be expected to produce an identical NTCP.
  - **Kutcher & Burman scheme reduces a DVH to uniform irradiation of an effective fraction of the organ, V_{eff} , to some reference dose, D_{ref}.**

Kutcher GJ, Burman C. Calculation of complication probability factors for non-uniform normal tissue irradiation: the effective volume method. Int J Radiat Oncol Biol Phys 16:1623-1630, 1989.

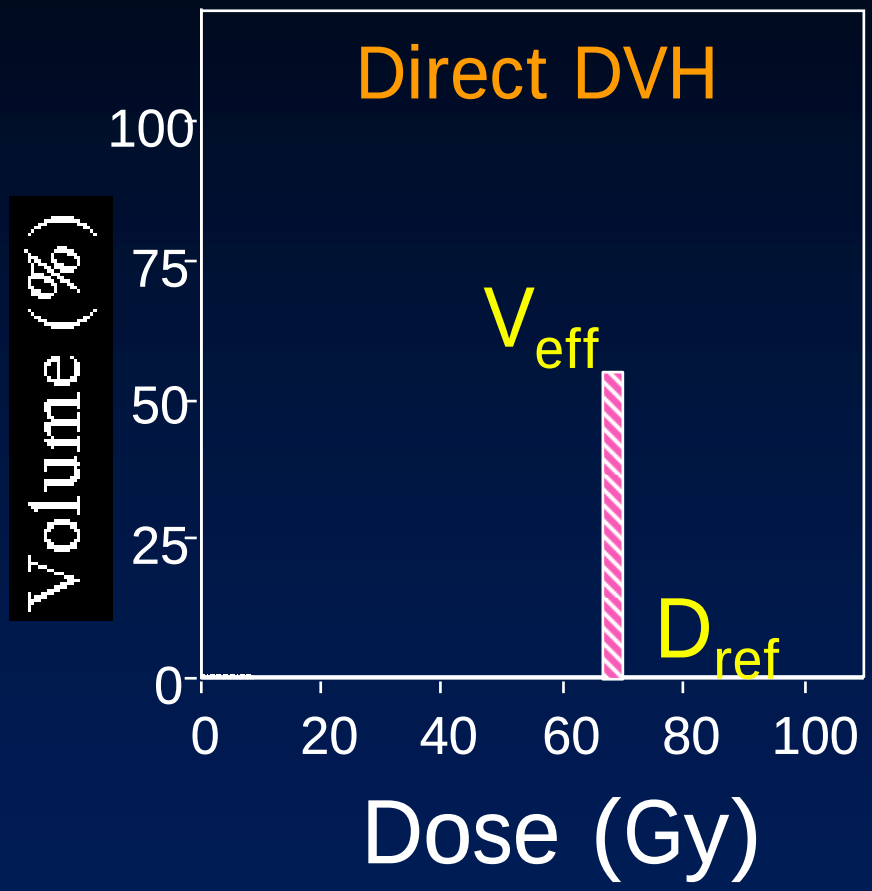
Effective Volume DVH reduction scheme

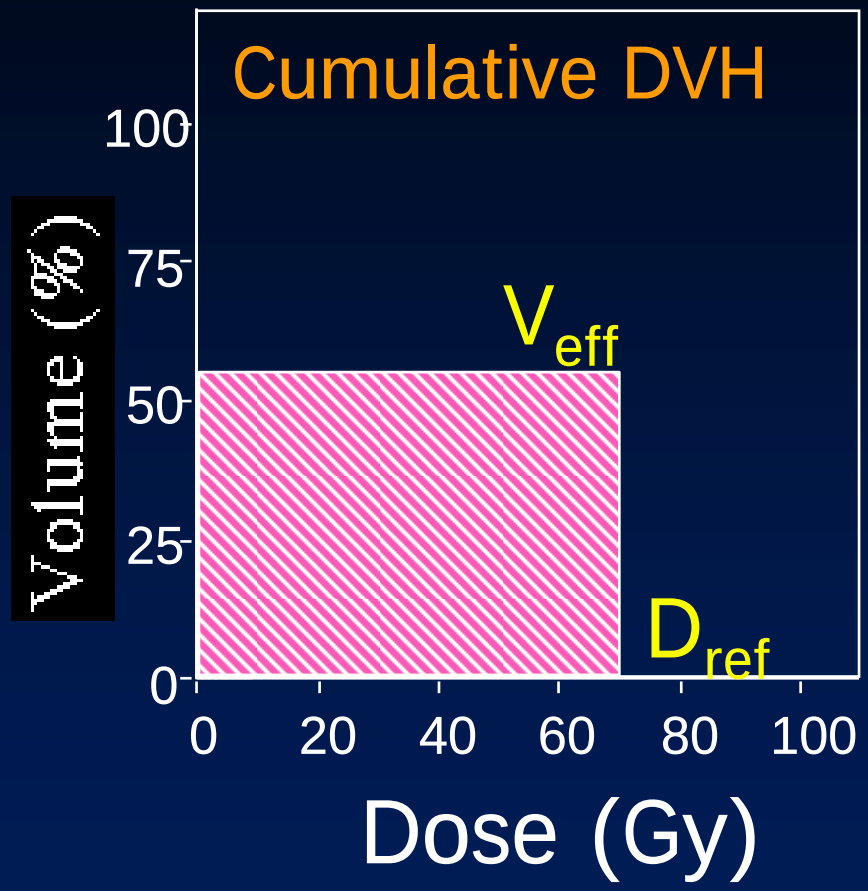
$$V_{eff} = \Sigma \{ v_i \cdot (D_i / D_{ref})^{1/n} \}$$



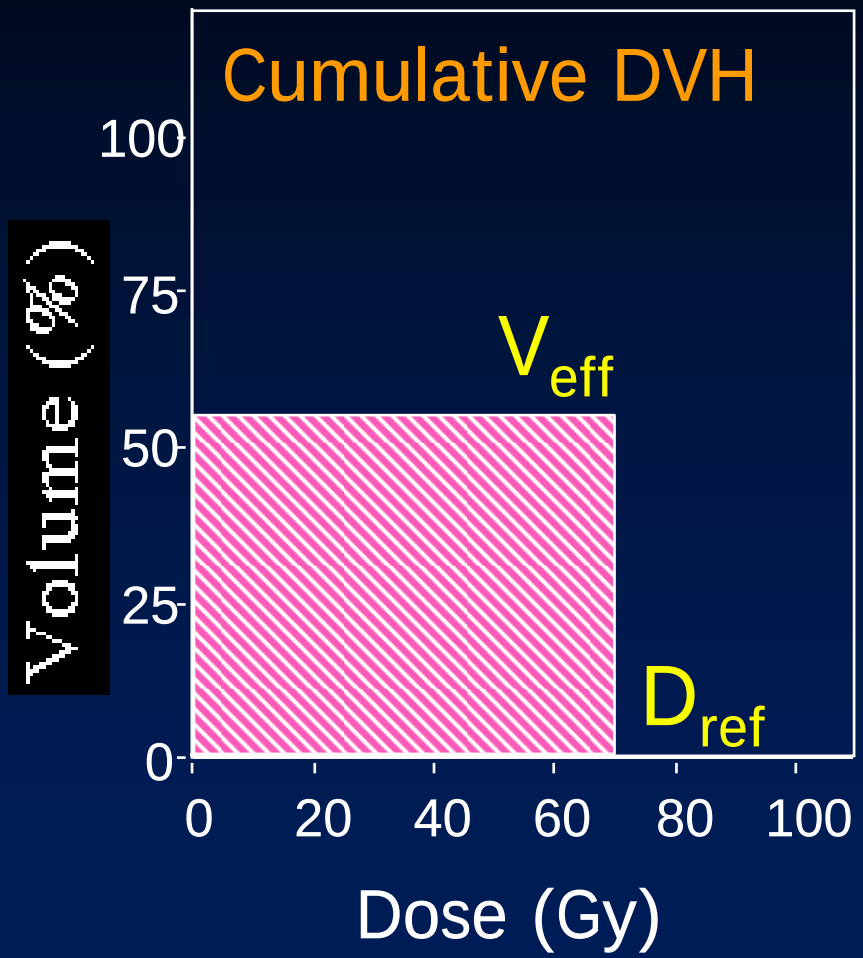


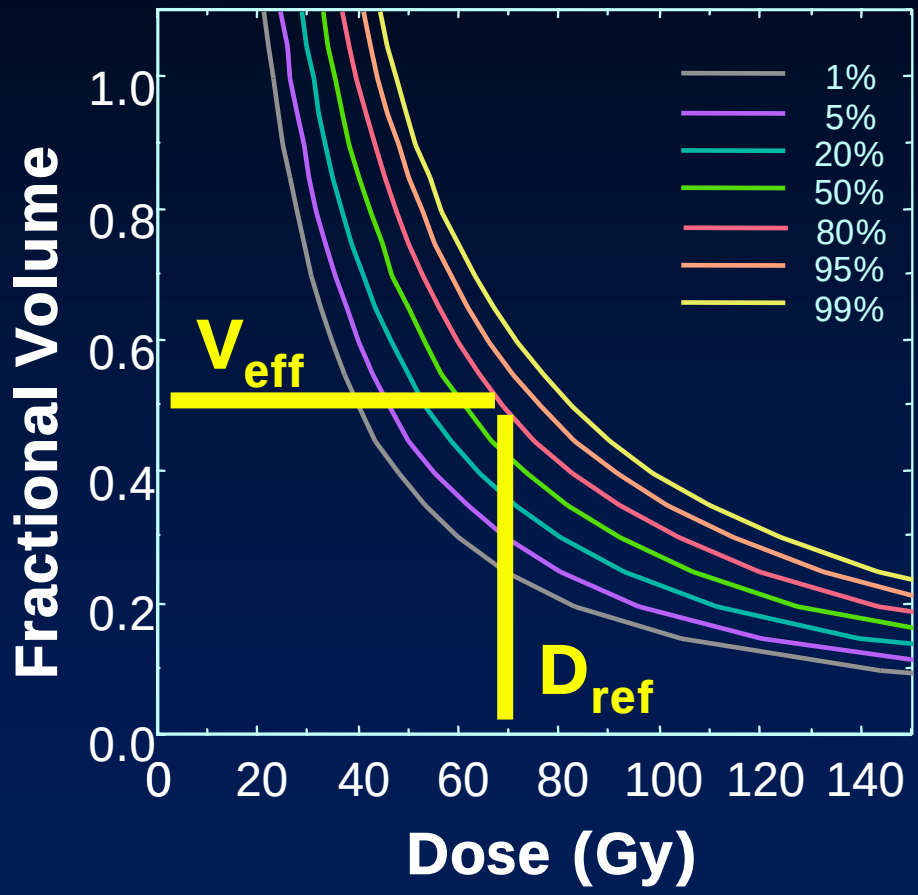
Single step $\{D_{ref}, V_{eff}\}$ DVHs





V_{eff} DVH reduction → *NTCP evaluation*





Key to use of Veff for iso-NTCP dose escalation in the 3DCRT era

Realization that the computation of Veff is independent of dose "units" (Gy, %, ...).

- ✓ The value of Veff depends only on the shape of the DVH and the relative value of Dref.
- ✓ It is convenient to choose Dref = Diso.

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

Key to use of V_{eff} for dose escalation

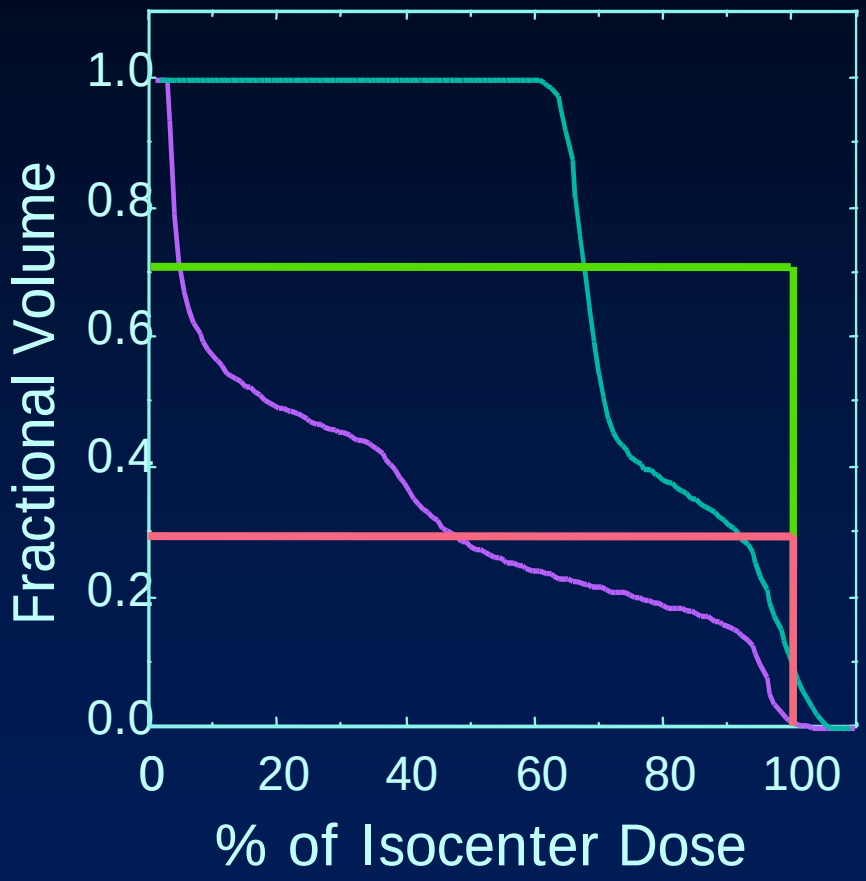
Therefore:

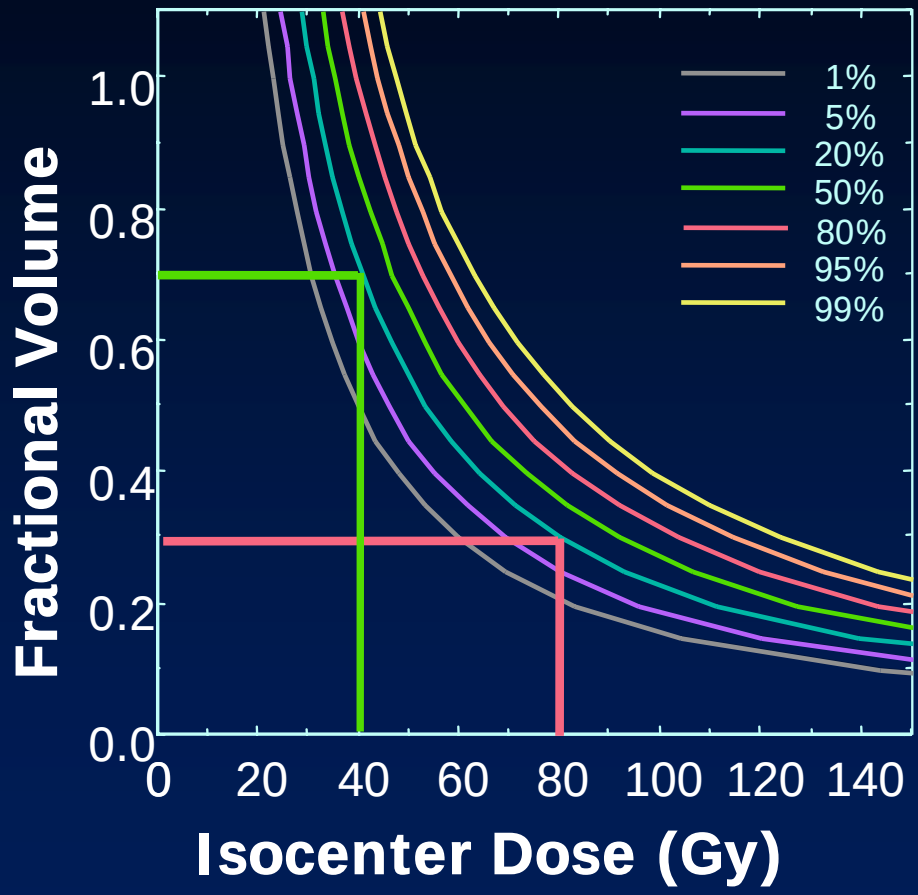
- ✓ A value of Veff may be computed for each patient from a relative isodose distribution (%) before a physical dose (Gy) is prescribed.
- ✓ Was very important in the 3DCRT era

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

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

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

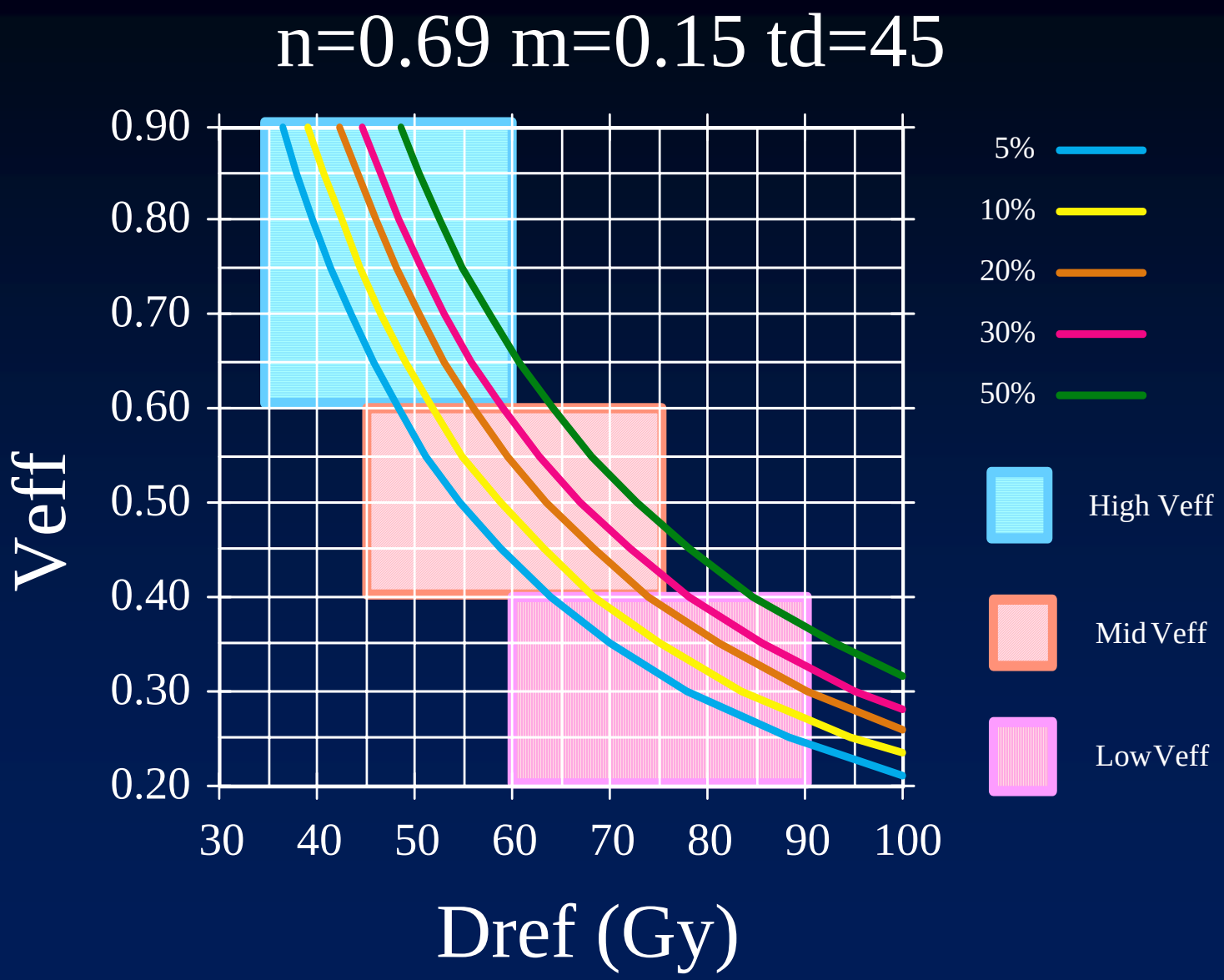




UM liver & lung cancer protocol methods

- 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.

Liver Veff Bins



UM liver cancer protocol considerations

- We first hypothesized that the iso-NTCP dose escalation protocols would permit the safe delivery of higher doses of radiation than we would have prescribed in our previous protocol

Higher tumor doses achieved!

Treatment of Intrahepatic Cancers With Radiation Doses Based on a Normal Tissue Complication Probability Model

By Cornelius J. McGinn, Randall K. Ten Haken, William D. Ensminger, Suzette Walker, Songbai Wang, and Theodore S. Lawrence

J Clin Oncol, 16:2246-2252, 1998

Higher liver tumor doses @ liver iso-NTCP

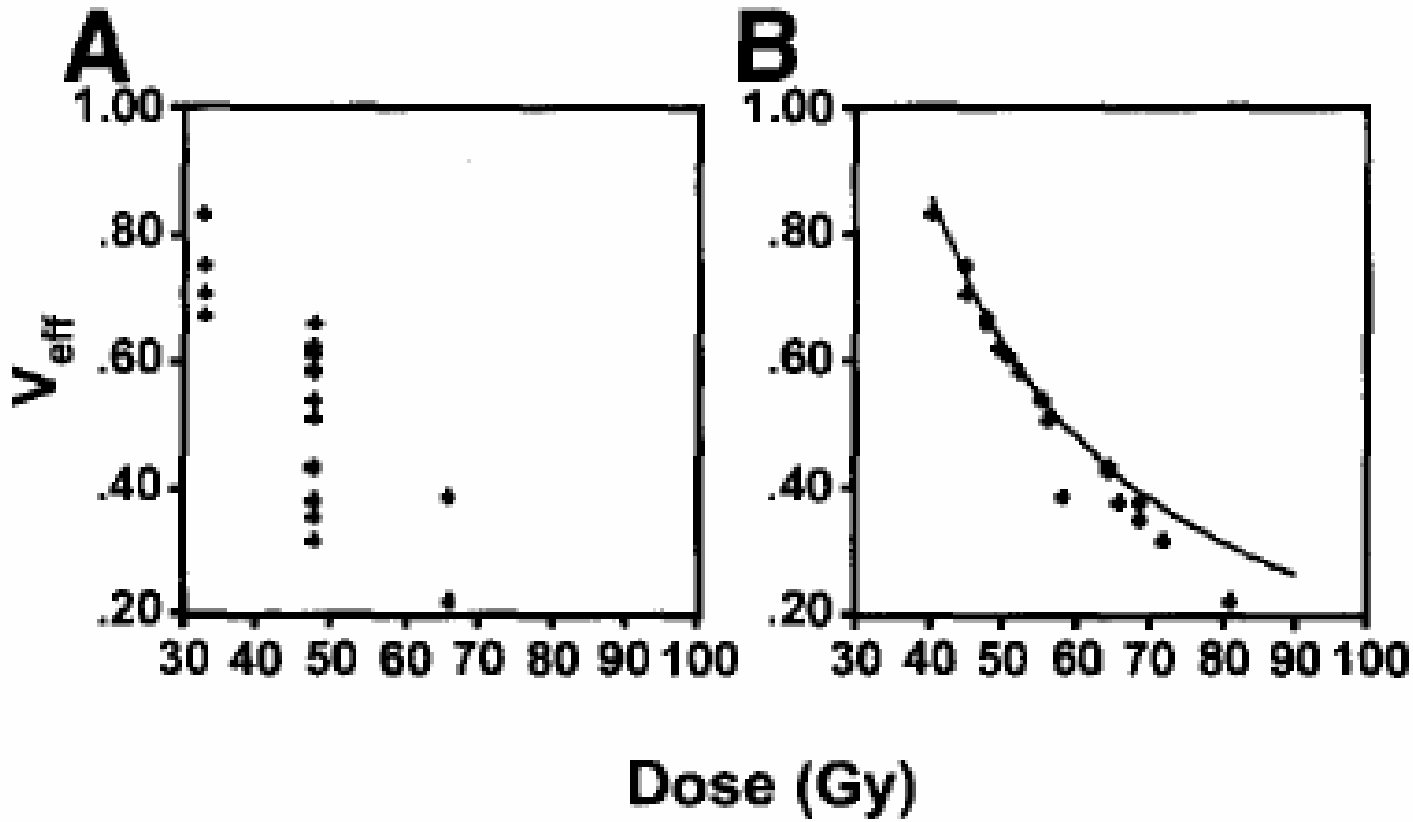


Fig 3. (A) The V_{eff} for each patient is plotted against the dose that would have been prescribed in our previous study (A) or was actually delivered (B). The points in (B) approximate the 10% isocomplication probability contour (solid line), which was the intention of the dose determination method.

General approach at UM for liver and lung dose escalation

- Treat patients and collect data
- Do retrospective analysis to estimate parameters of a descriptive NTCP model
- Start prospective trial.
  - ✓ Escalate nominal isoNTCP's.
  - ✓ Continue to refine parameters.

Iso-NTCP dose escalation

- The methodology presented did not in itself validate the Lyman description, any particular parameterization of that description or the effective volume DVH reduction scheme.
- The user needed only believe in the general dose-volume-NTCP trend generated for the tissue under consideration.

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.

Analysis of radiation-induced liver disease using the Lyman NTCP model (Partial irradiation of the liver)

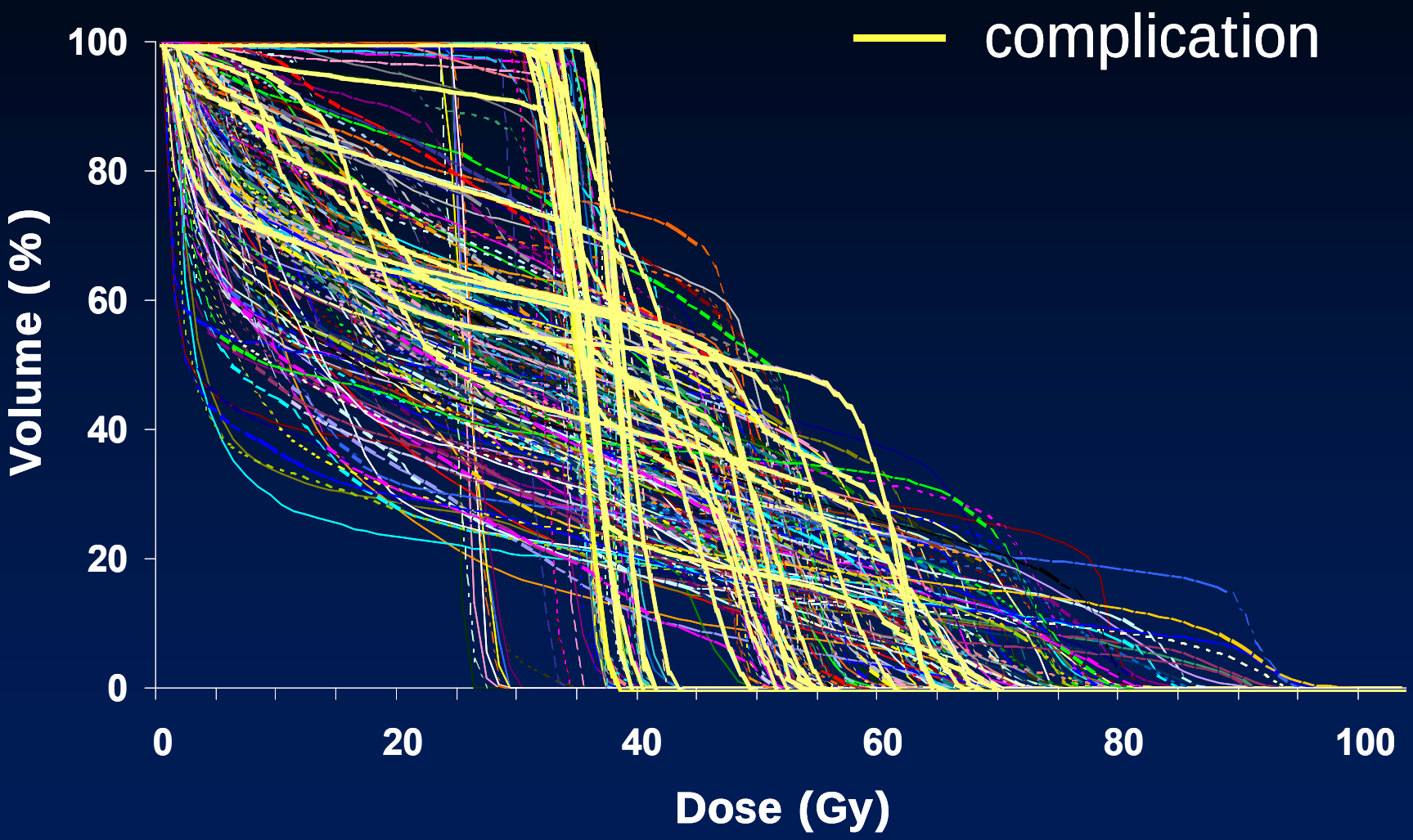
LA Dawson, D Normolle, JM Balter, CJ McGinn,
TS Lawrence, RK Ten Haken
University of Michigan

Int J Radiat Oncol Biol Phys 53:810-21, 2002
(Sem Radiat Oncol 11:240-246, 2001)

Methods

- Normal Liver DVHs and complication data were used in a maximum likelihood analysis to determine best estimates for the NTCP model parameters
- Confidence intervals (CIs) of parameters were determined using profile-likelihood methods

All patients (19/203 complications)



LKB Model parameters

Derived values

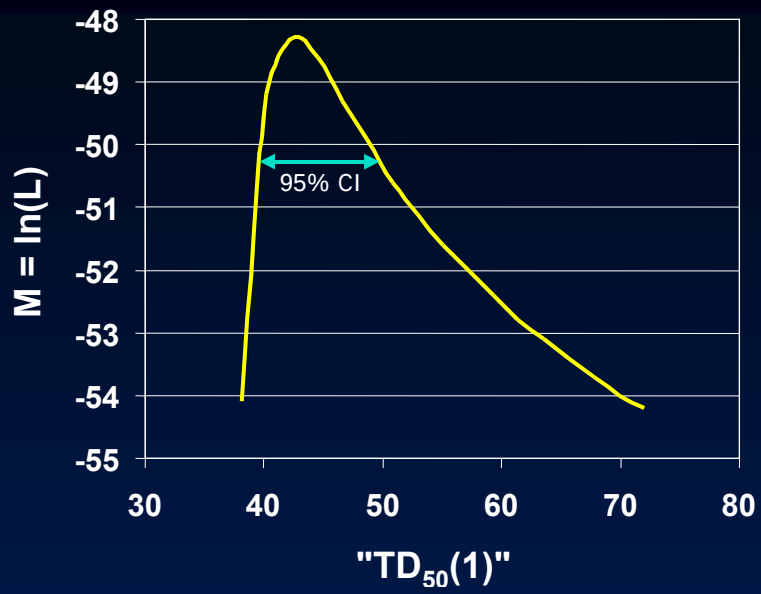
n = 0.94; m = 0.16, TD_{50} = 42 Gy

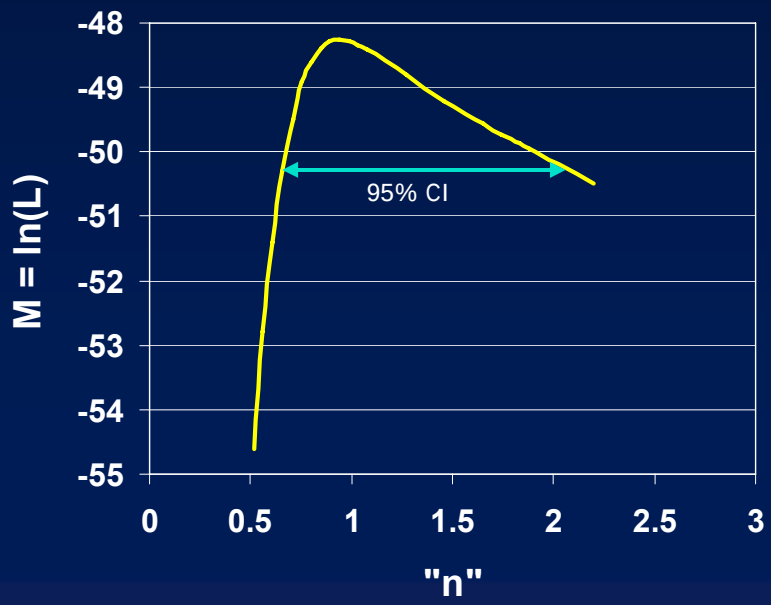
95% Confidence Intervals

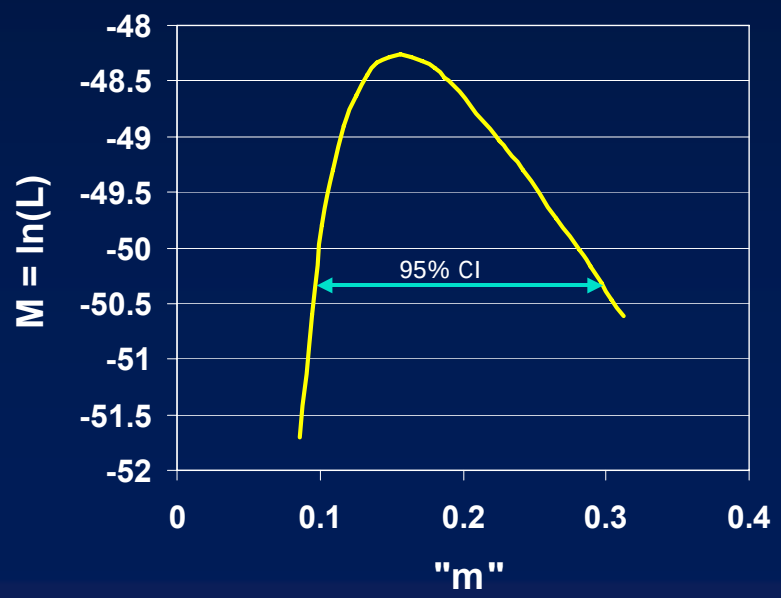
n = [0.67-2.2]

m = [0.10-0.32]

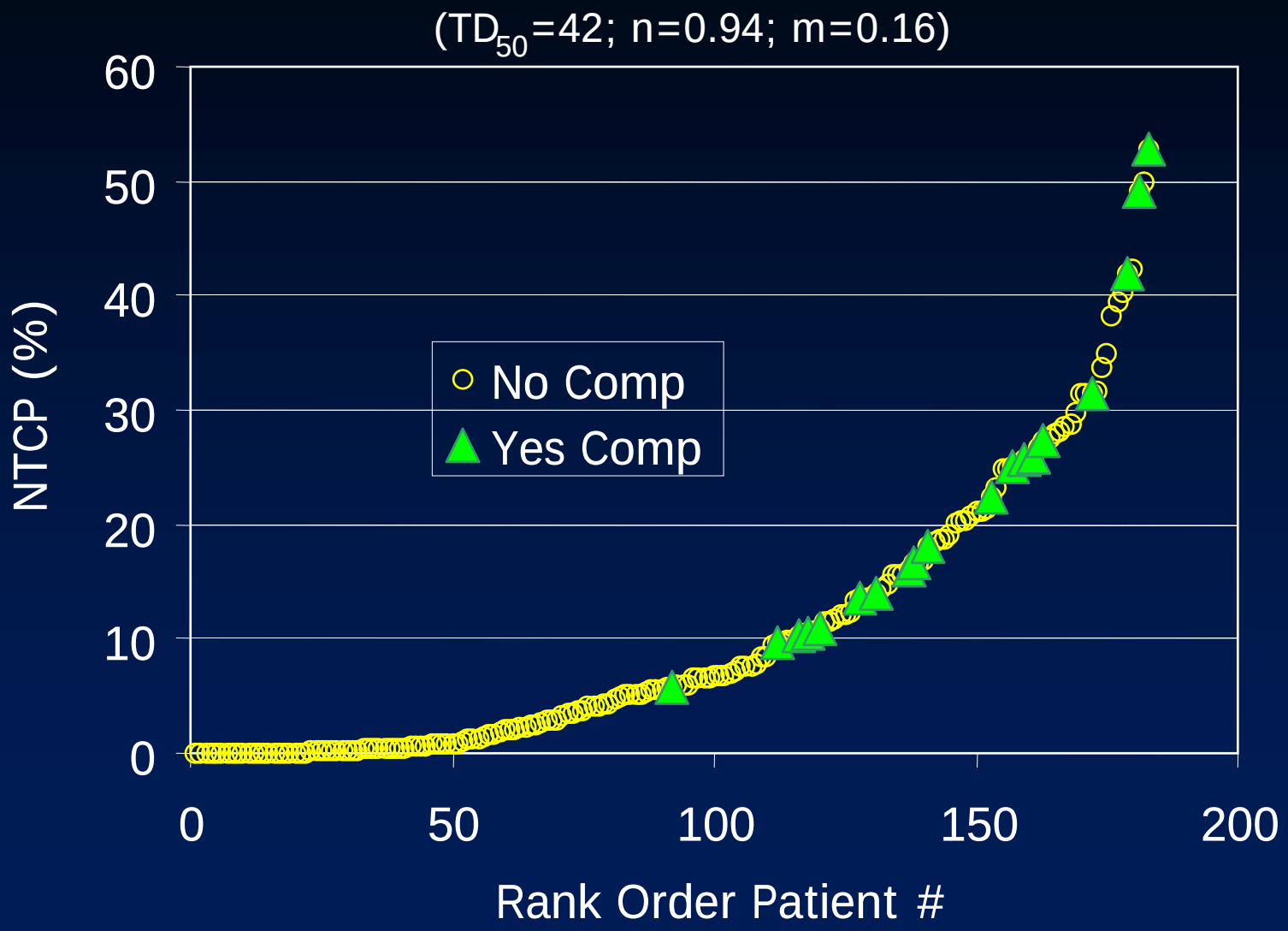
TD_{50} = [40-52]



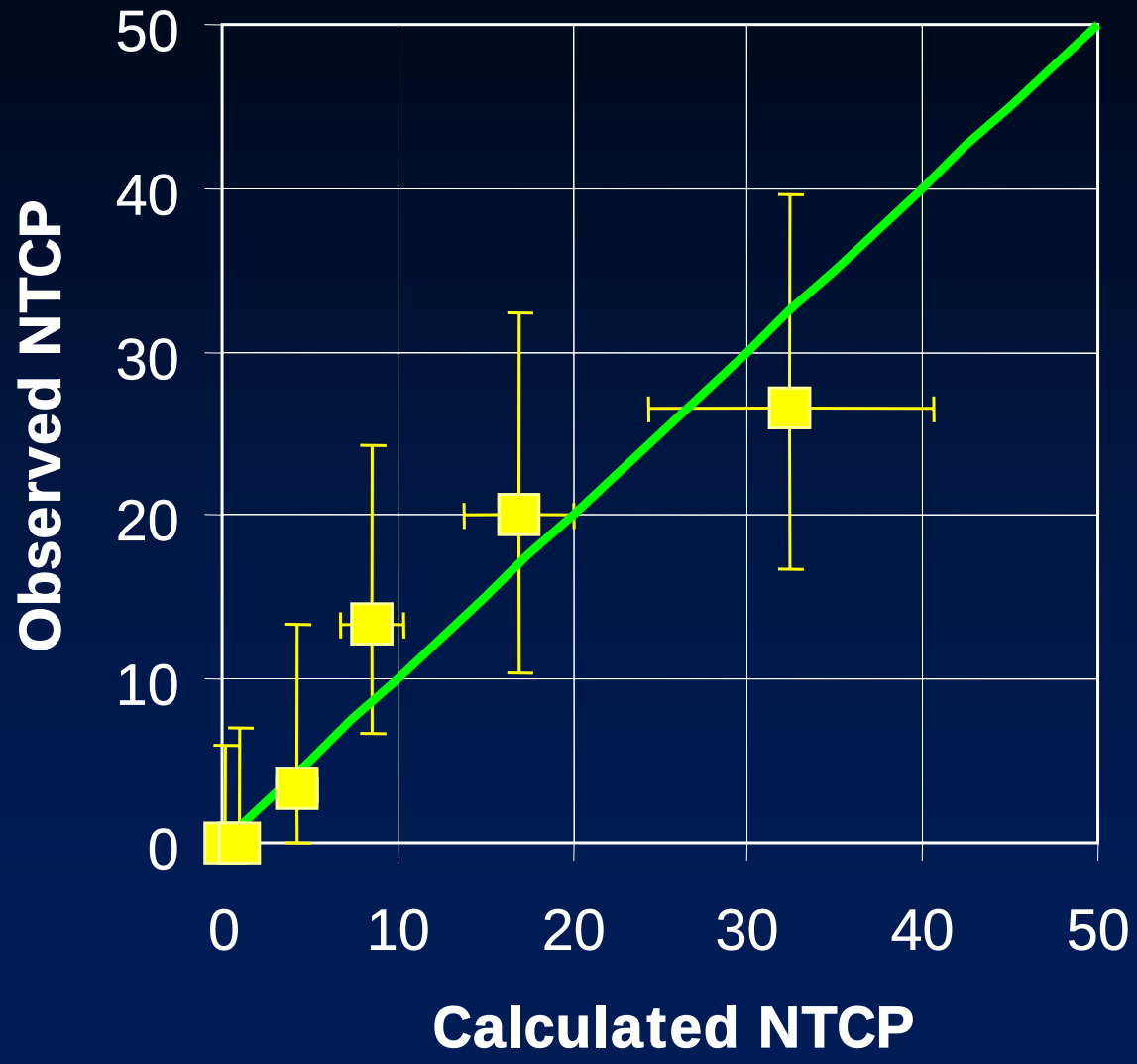




LKB Model (liver NTCP)



LKB Model (liver NTCP)



Damage/injury liver NTCP too.

ANALYSIS OF CLINICAL COMPLICATION DATA FOR RADIATION HEPATITIS USING A PARALLEL ARCHITECTURE MODEL

A. JACKSON, PH.D.,* R. K. TEN HAKEN, PH.D.,† J. M. ROBERTSON, M.D.,† M. L. KESSLER, PH.D.,† G. J. KUTCHER, PH.D.* AND T. S. LAWRENCE, M.D., PH.D.†

* Memorial Sloan-Kettering Cancer Center, New York, NY 10021; and †University of Michigan Medical Center, Anne Arbor, MI 48109

Int J Radiat Oncol Biol Phys, 31:883-891, 1995

Lung NTCP too!

DOSE-VOLUME HISTOGRAM AND 3-D TREATMENT PLANNING EVALUATION OF PATIENTS WITH PNEUMONITIS

MARY KAYE MARTEL, PH.D., RANDALL K. TEN HAKEN, PH.D., MARK B. HAZUKA, M.D., ANDREW T. TURRISI, M.D., BENEDICK A. FRAASS, PH.D. AND ALLEN S. LICHTER, M.D.

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

Int J Radiat Oncol Biol Phys, 28:575-581, 1994

Lung NTCP too!

RADIATION PNEUMONITIS AS A FUNCTION OF MEAN LUNG DOSE: AN ANALYSIS OF POOLED DATA OF 540 PATIENTS

Stefan L. S. Kwa, Ph.D.,* Joos V. Lebesque, M.D., Ph.D.,* Jacqueline C. M. Theuws, M.D.,* Lawrence B. Marks, M.D.,† Mike T. Munley, Ph.D.,† Gunilla Bentel, R.N., R.T.T.,† Dieter Oetzel, Ph.D.,‡ Uwe Spahn, M.D.,‡ Mary V. Graham, M.D.,§ Robert E. Drzymala, Ph.D.,§ James A. Purdy, Ph.D.,§ Allen S. Lichter, M.D.,‖ Mary K. Martel, Ph.D.‖ and Randall K. Ten Haken, Ph.D.‖

*Department of Radiotherapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands; †Department of Radiation Oncology, Duke University Medical Center, Durham, NC, USA; ‡Department of Clinical Radiology, University of Heidelberg, Heidelberg, Germany; §Radiation Oncology Center, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, USA; ‖Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA

Int J Radiat Oncol Biol Phys, 42:1-9, 1998

Lung NTCP too!

COMPARING DIFFERENT NTCP MODELS THAT PREDICT THE INCIDENCE OF RADIATION PNEUMONITIS

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Int J Radiat Oncol Biol Phys, 55:724-735, 2003

Lung NTCP too!

FINAL TOXICITY RESULTS OF A RADIATION-DOSE ESCALATION STUDY IN PATIENTS WITH NON–SMALL-CELL LUNG CANCER (NSCLC): PREDICTORS FOR RADIATION PNEUMONITIS AND FIBROSIS

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The benefit of using biological parameters (gEUD and NTCP) in IMRT optimization for the treatment of intrahepatic tumors

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RK Ten Haken
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Int J Radiat Oncol Biol Phys 62:571-78, 2005

Also

Chapet O, Thomas E, Kessler ML, Fraass BA, Ten Haken RK: Esophagus sparing with IMRT in lung tumor irradiation, an EUD-based optimization technique. Int J Radiat Oncol Biol Phys 63:179-187, 2005

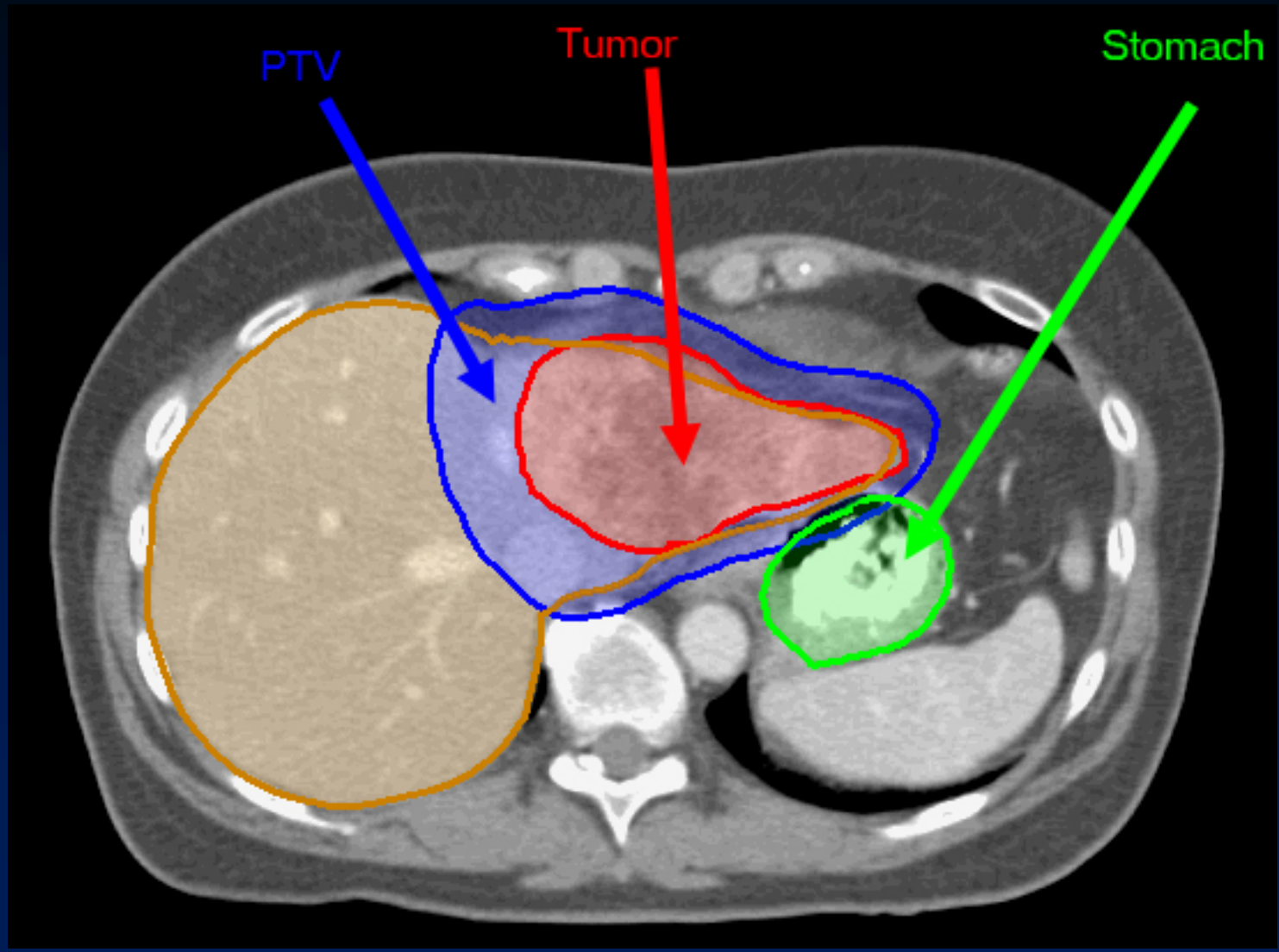
Biological cost functions & IMRT

- Patients at our institution with tumors in the liver have been treated according to IRB approved protocols that seek to escalate *homogeneous* dose (+7%, -5%) to the PTV at a fixed normal liver/lung iso-NTCP.

Difficulties in implementation

- Frequently the risk to other OARs (e.g., stomach-duodenum) limits the tumor dose to below that which could be justified based solely on liver NTCP,
  - ✓ especially when there is an overlap between the PTV and an external (to the liver) OAR.

Liver tumor PTV-OAR overlap



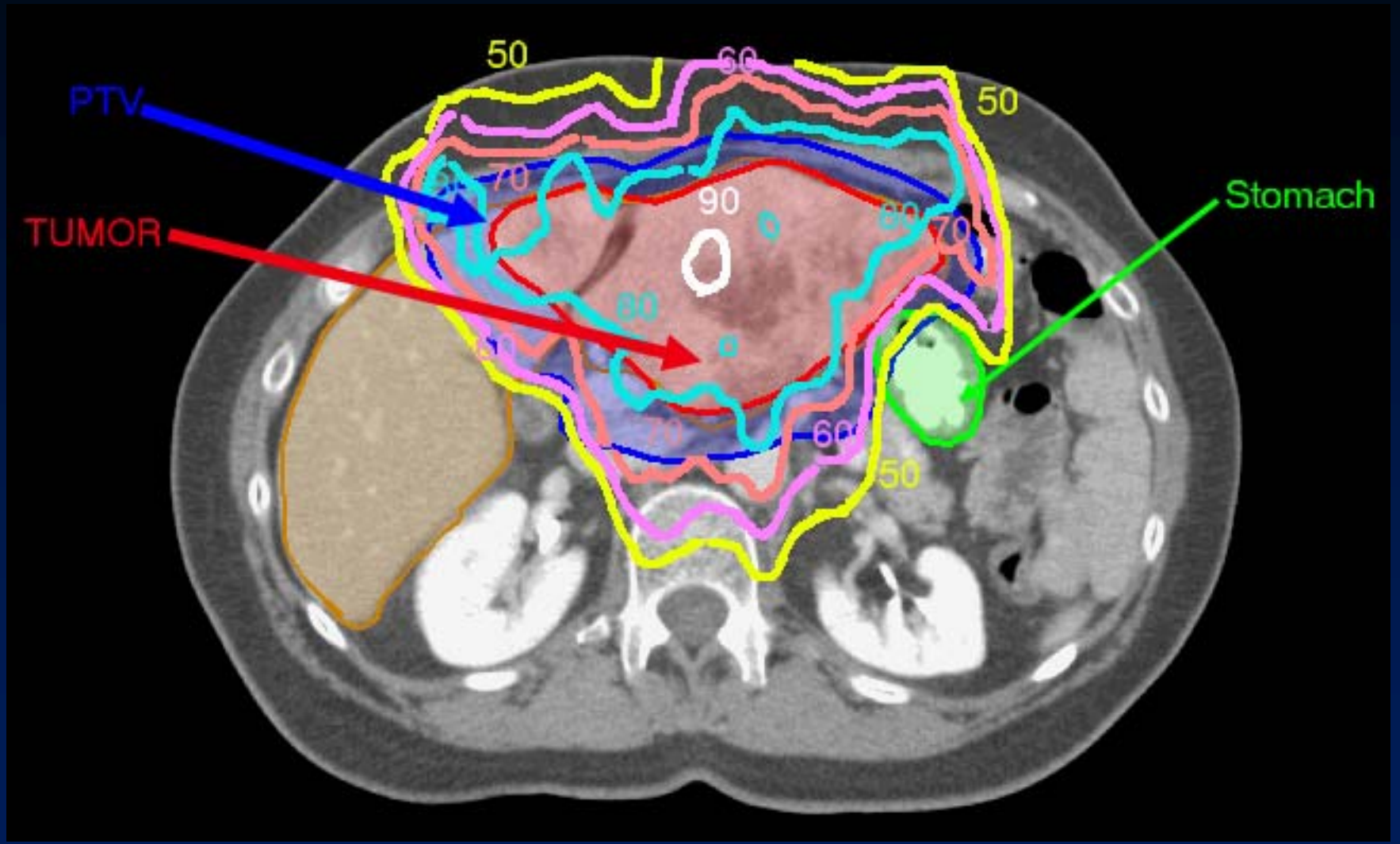
Can we do better?

- Optimized beamlet IMRT may benefit these patients.
- However, even with IMRT, in order to increase the mean PTV dose above the maximum tolerated dose of one of these OARs, it is necessary to relax PTV homogeneity constraints.
- But, how does one do this in a logical – meaningful way?

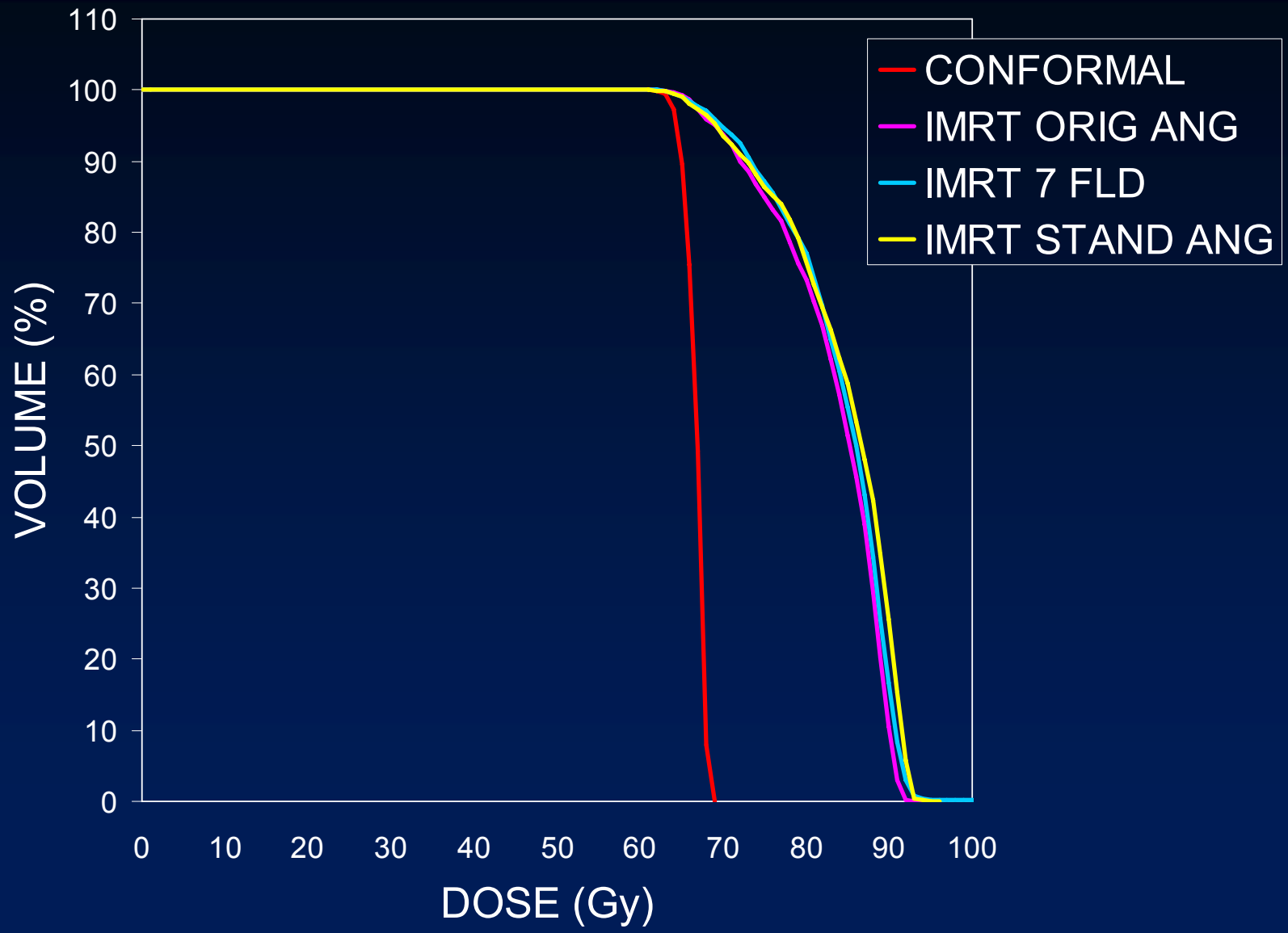
Use of models in optimization

- Models for target and normal tissues could aid in planning, as their use would integrate the contributing effects of all parts of target and normal tissues dose distributions.
- We explored IMRT optimization utilizing:
  - ✓ gEUD costlets for the PTVs to maximize anti-tumor effects,
  - ✓ NTCP costlets to maintain OAR doses within protocol limits.

Non-uniform liver PTV irradiation



PTV DVHs for liver patient



Heterogeneous PTV dose assessment

Patient number	gEUD *a* =-20 CRT (Gy)	gEUD *a* =-20 IMRT (Gy)	gEUD *a* =-5 CRT (Gy)	gEUD *a* =-5 IMRT (Gy)
1	59.2	63.8	60.7	69.3
2	66.5	75.7	66.6	82.0
3	56.0	69.0	57.3	71.1
4	55.5	64.1	57.3	73.7
5	55.6	66.8	58.3	68.6
6	66.6	73.1	67.0	78.1
7	73.9	96.8	75.3	117.7
8	60.5	73.3	66.9	92.7
mean	**61.7**	**72.8**	**63.7**	**81.7**
t test	p=0.001		p=0.003	

IMRT optimization conclusions

- We suggest that the use of biological parameters directly as costlets within the optimizing process should be able to produce IMRT plans that:
  - ✓ utilize heterogeneous PTV coverage to maximize tumor gEUD,
  - ✓ while maintaining NTCP limits for dose limiting normal tissues and other OARs.
  - ✓ in a much more intuitive (and efficient) manner than might be realized using multiple dose/volume based optimization sessions.

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