Biological / Clinical Outcome Models in RT Planning

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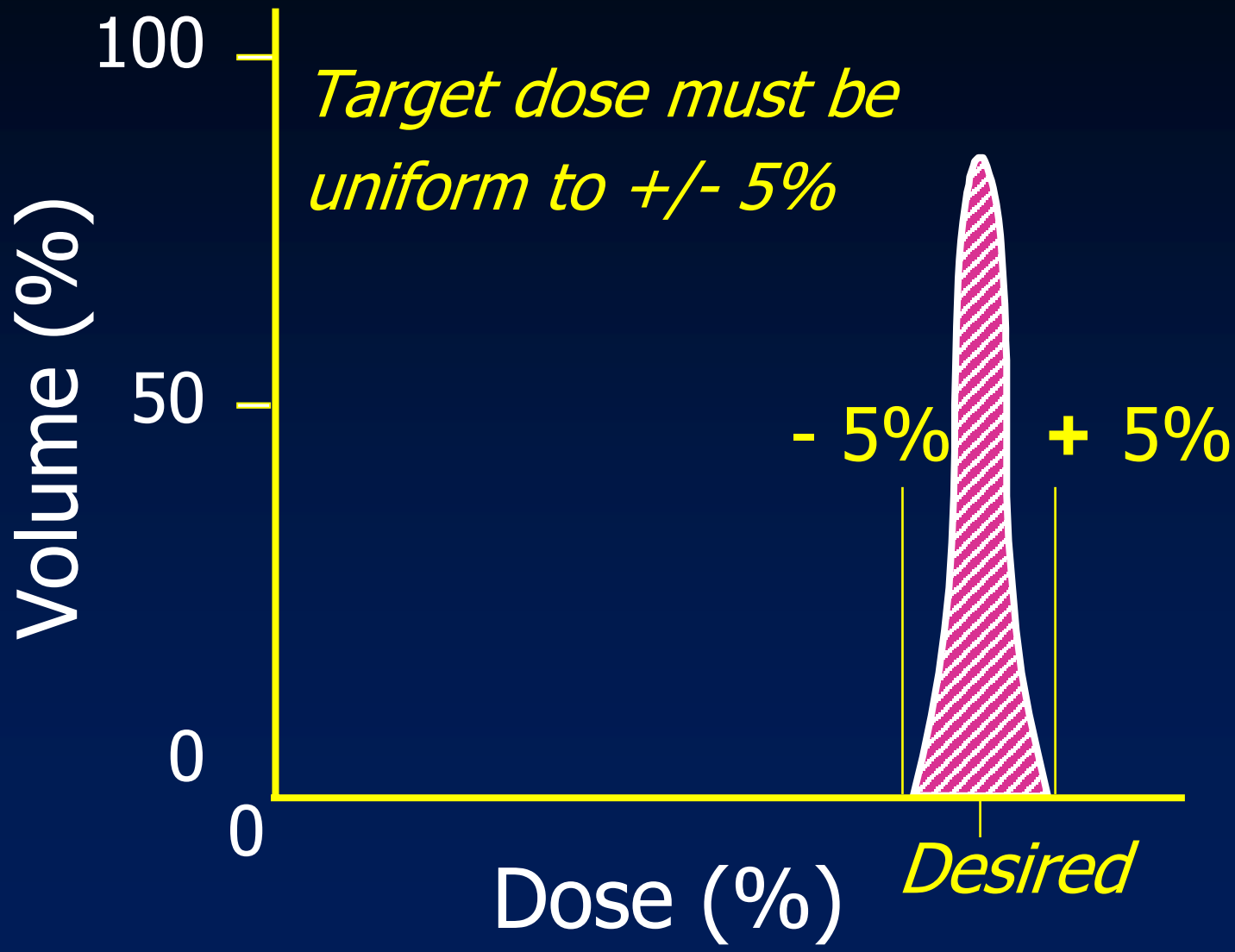
Why consider use of models?

- Are there problems that use of outcomes models could help resolve?
- Would their use make things easier or more consistent?
- Is this relevant today?

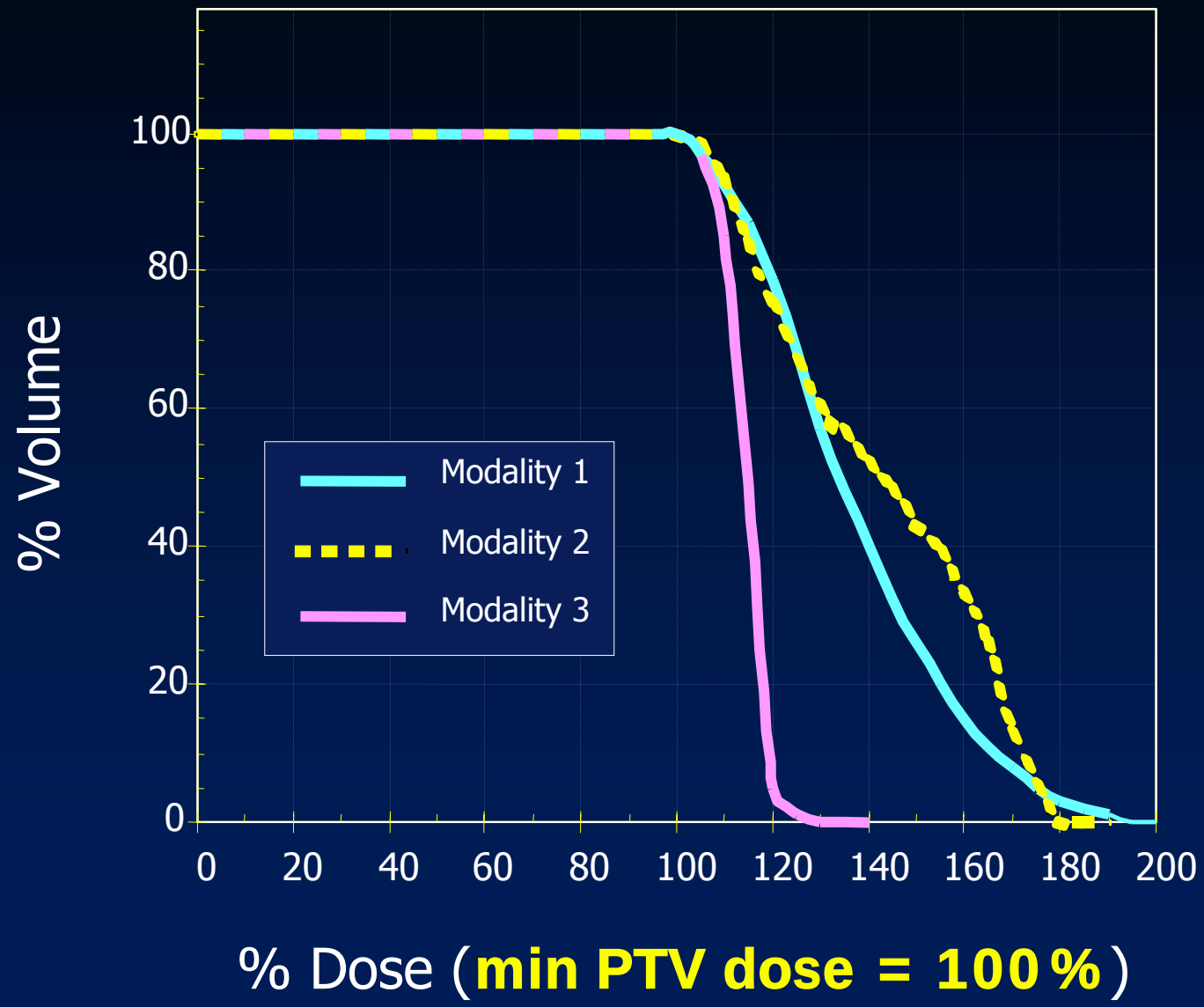
3D CRT – PTV covered!



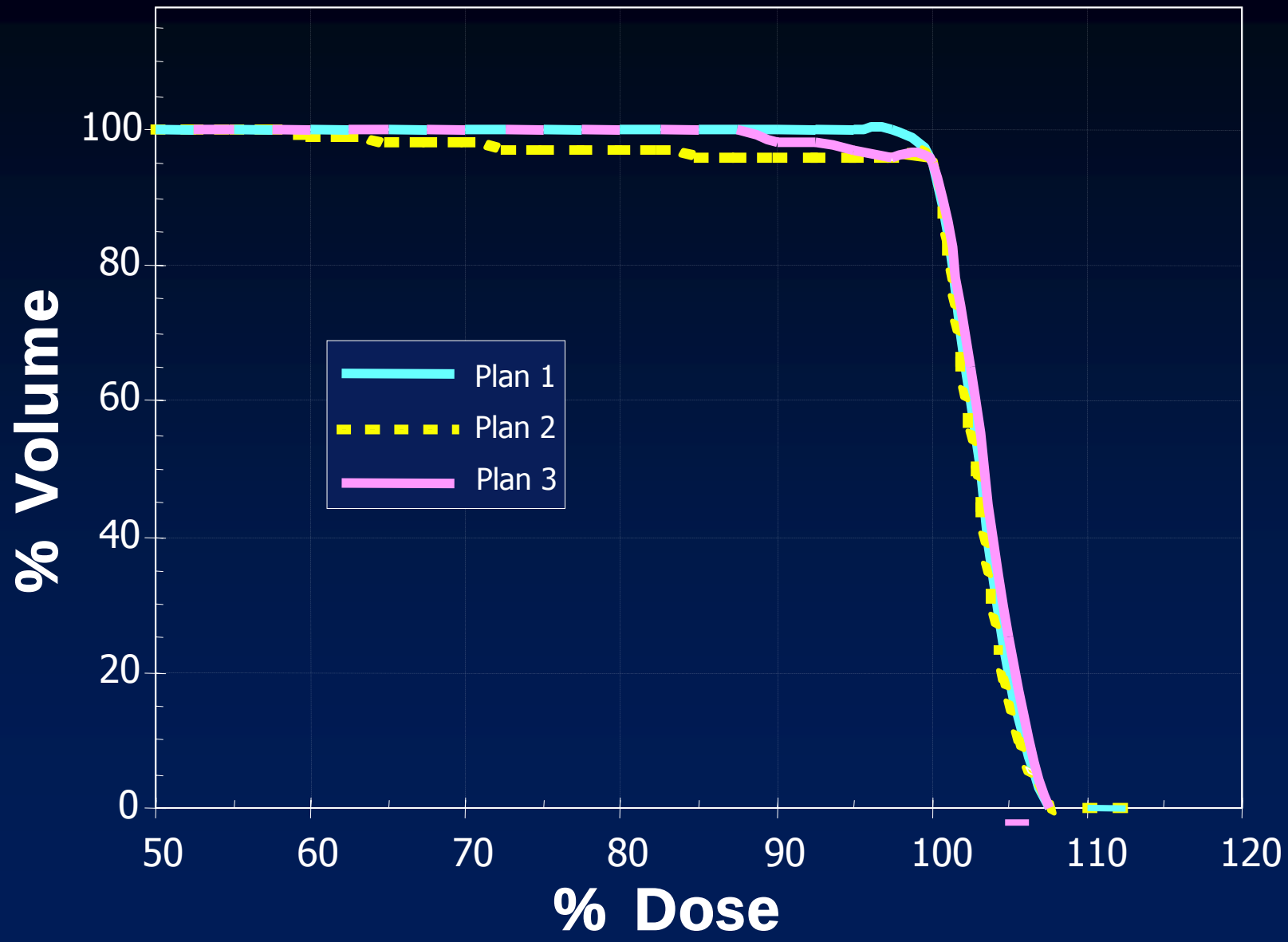
RTOG IMRT target criteria

- The prescription dose is the isodose which encompasses at least 95% of the PTV.
- No more than 20% of any PTV will receive >110% of its prescribed dose.
- No more than 1% of any PTV will receive <93% of its prescribed dose.

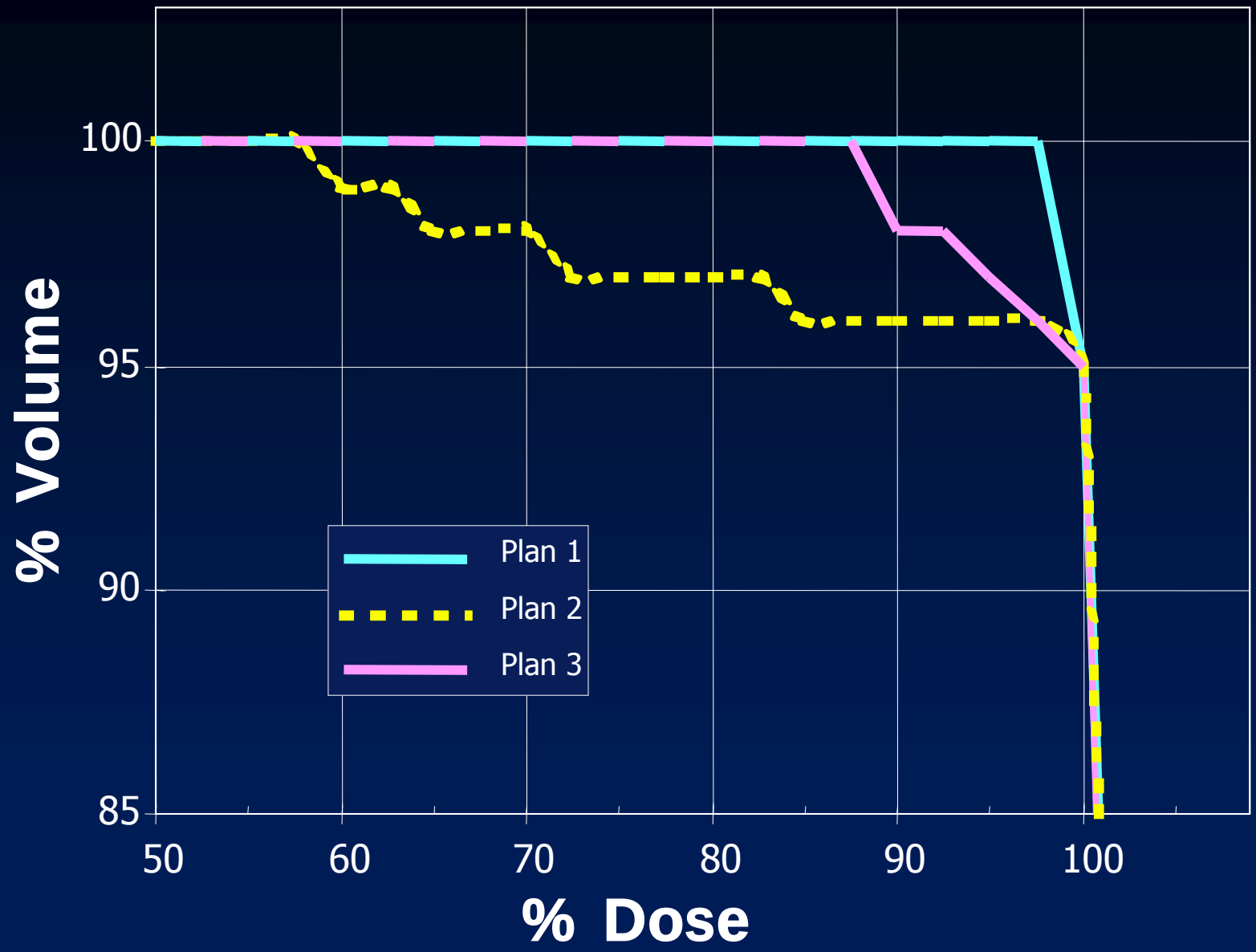
Irregular Target Volume DVHs



Dose normalized to 95% of PTV



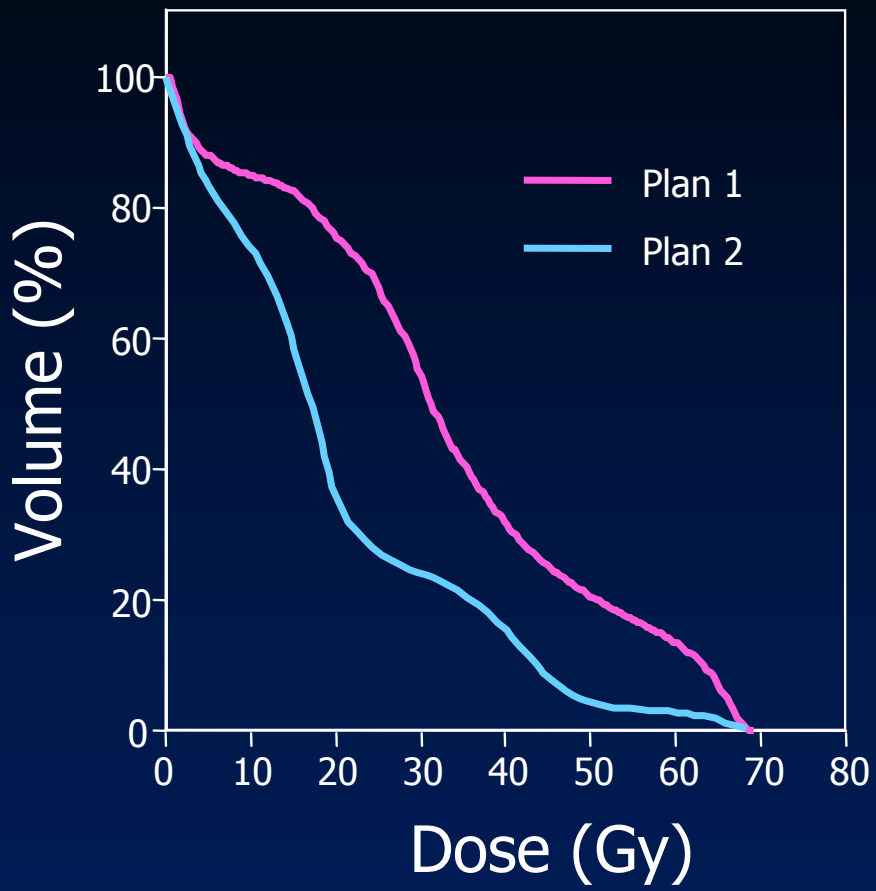
Dose normalized to 95% of PTV



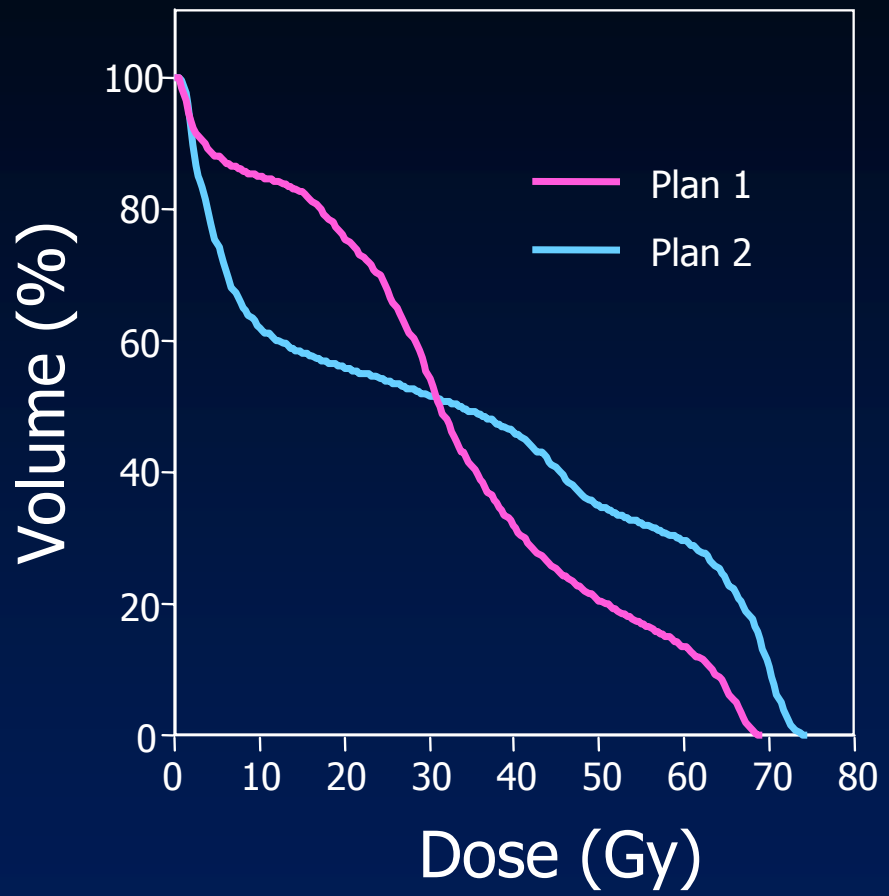
Target volume issues

- Are target volume hot spots beneficial?
- Are target volume cold spots detrimental?
- How do cold spots and hot spots play off against each other?
- **Use of TCP or EUD models could help us make rational decisions**

DVH Comparison - normal tissue



Easy!
Plan 2 is less toxic

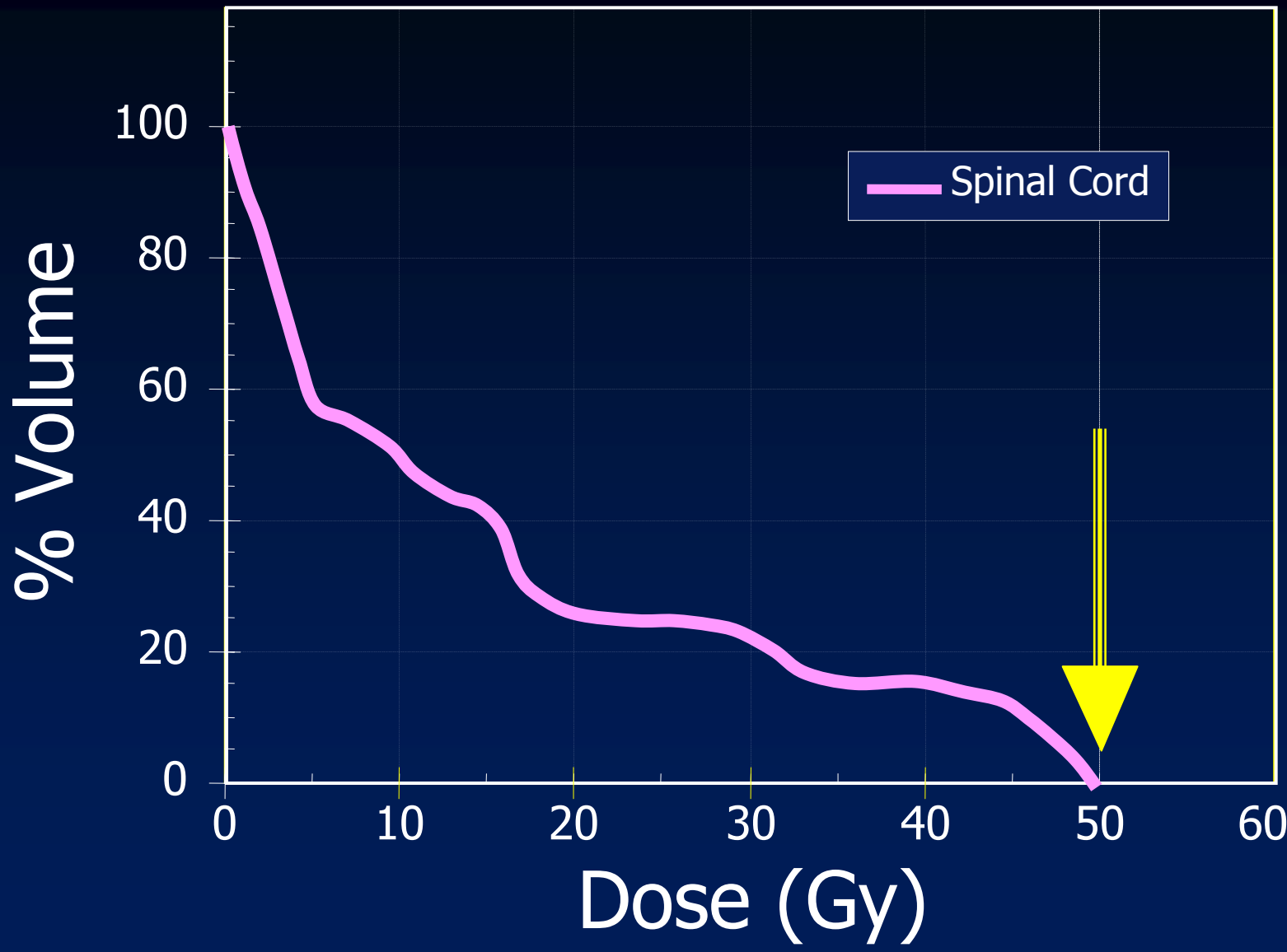


Who knows?
Depends on tissue type

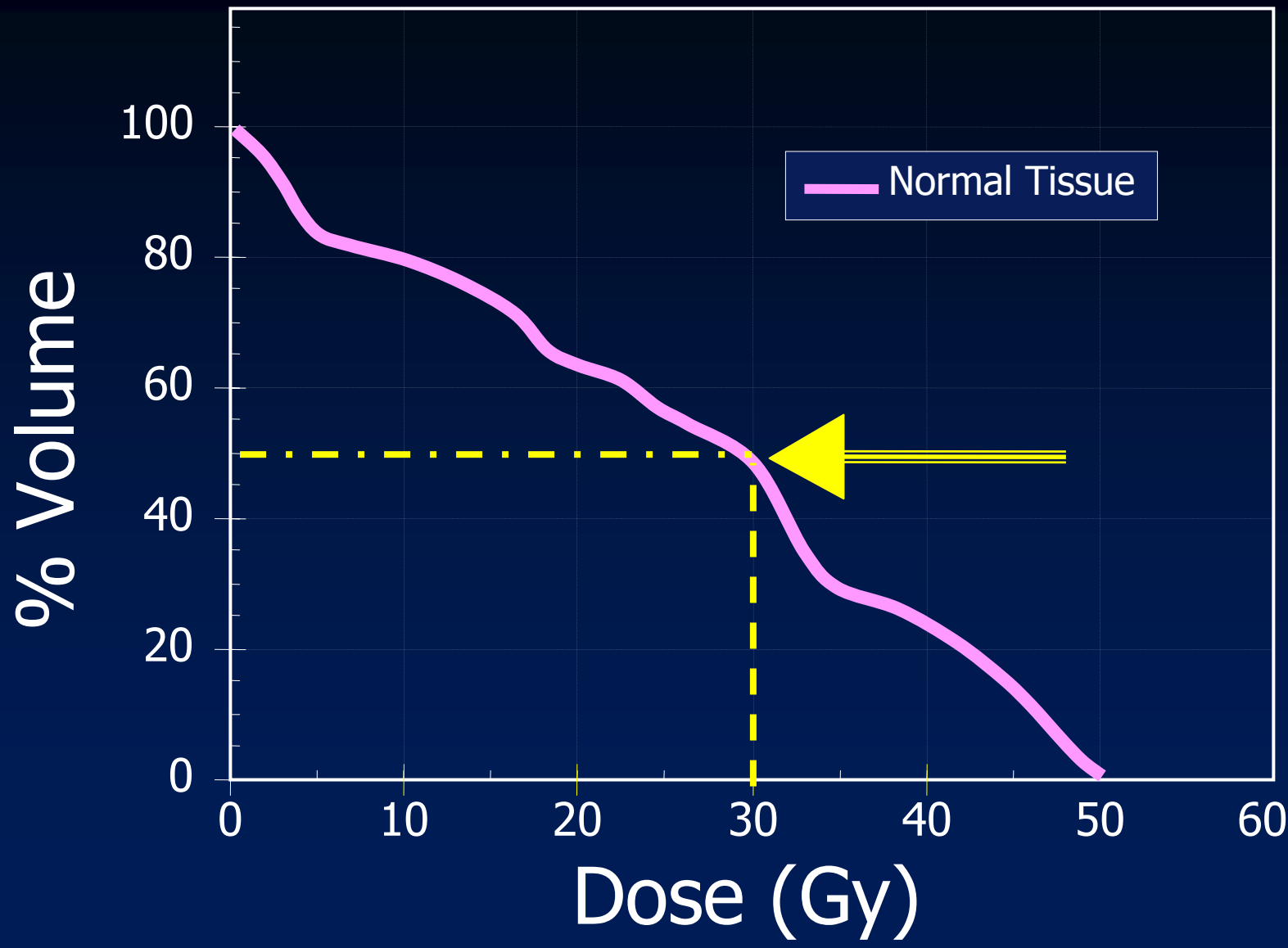
RTOG normal tissue dose criteria

- Small bowel < 30% to receive ≥ 40 Gy
  - **minor deviation 30% to 40 Gy**
- Rectum < 60% to receive ≥ 30 Gy
  - **minor deviation 35% to 50 Gy**
- Bladder < 35% to receive ≥ 45 Gy
  - **minor deviation 35% to 50 Gy**
- Femoral head ≤ 15% to receive ≥ 30 Gy
  - **minor deviation 20% to 30 Gy**

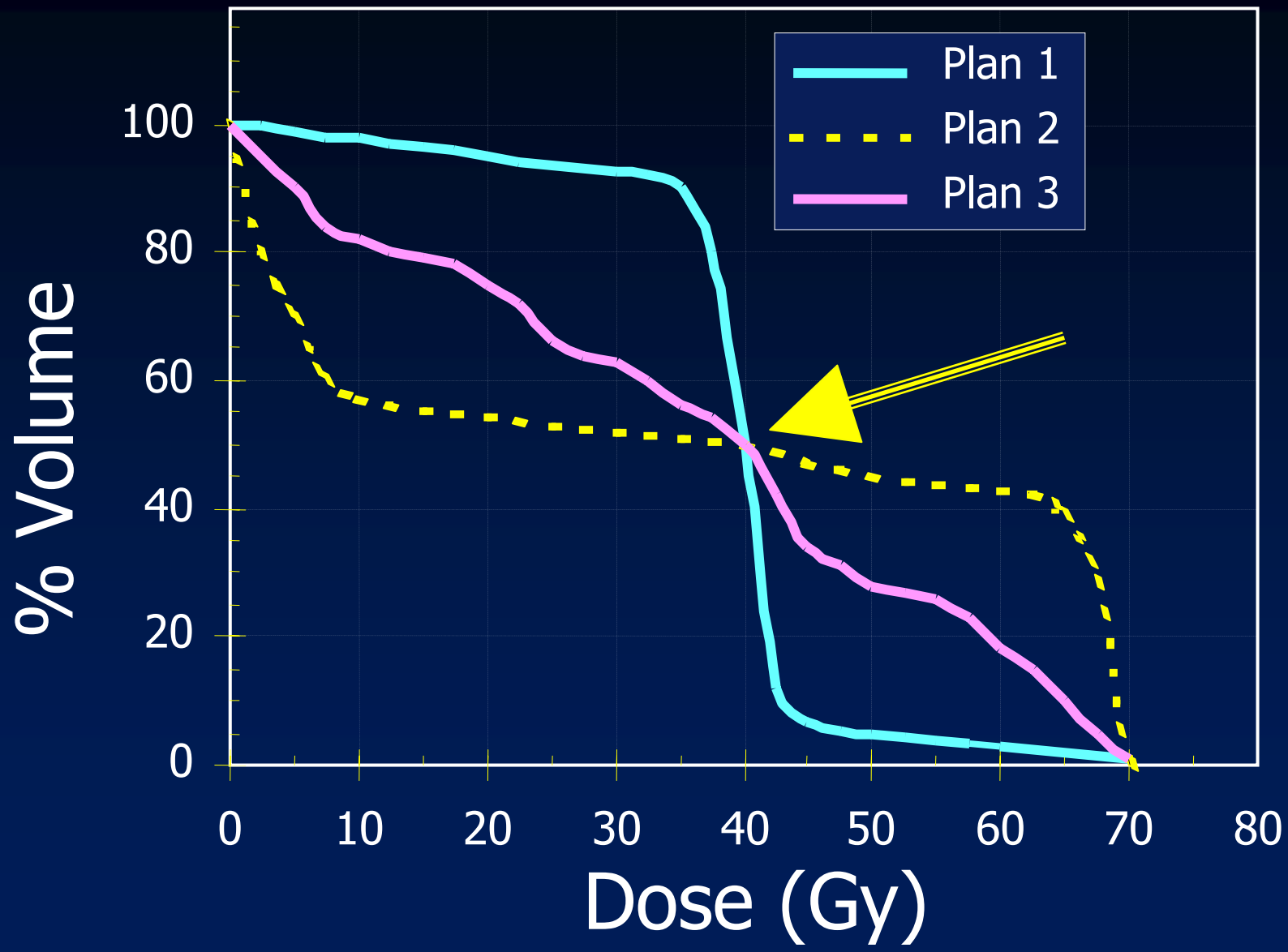
Normal Tissue (Max Dose Constraint)



Normal Tissue (Single Point Constraint)



Normal Tissue (Single Point Constraint)



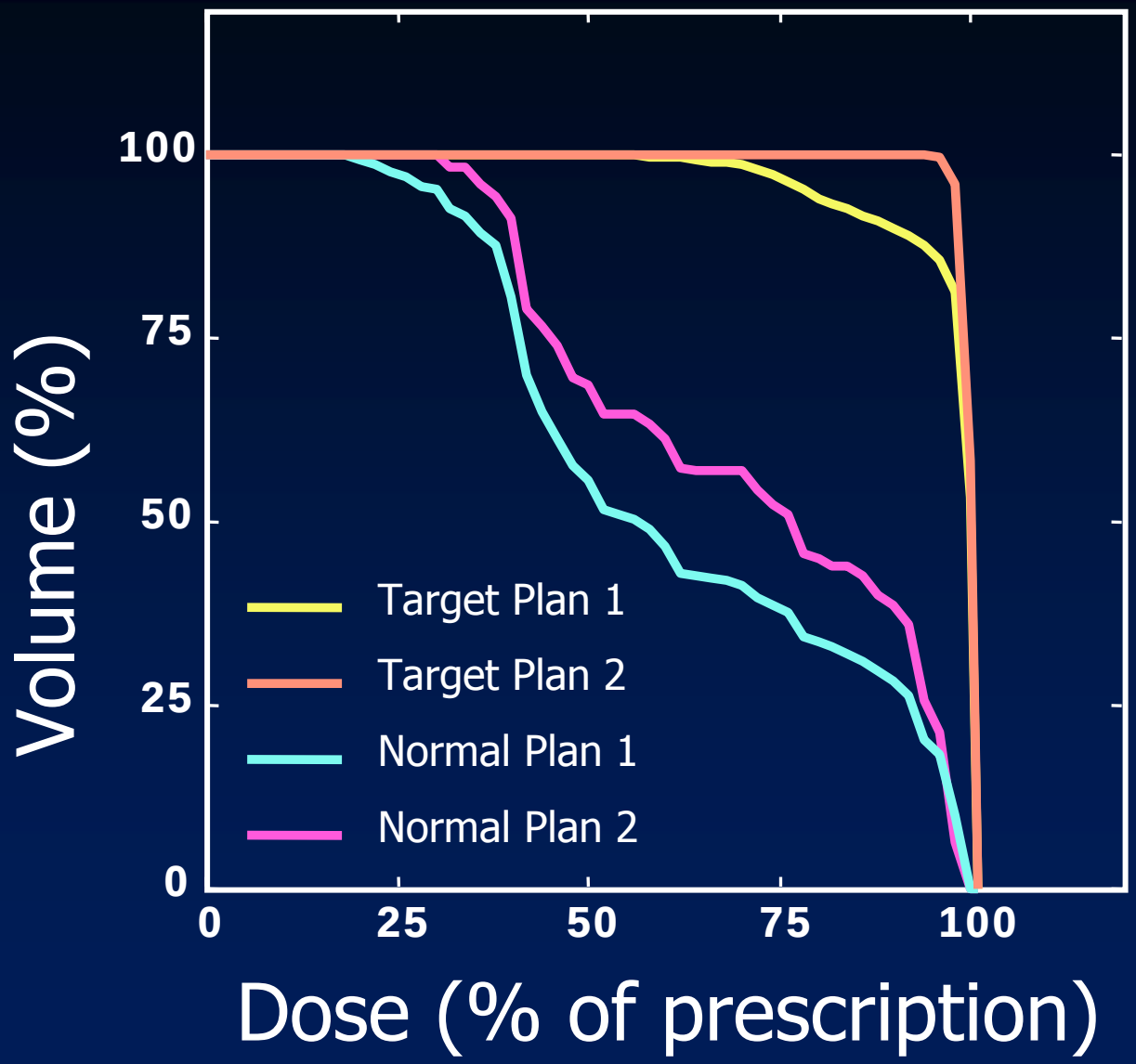
Normal tissue issues

- The applicability of dose/volume criteria alone is dependent on:
  - Tissue type
  - Standardization of technique
- Use of models could assimilate effects of irregular dose distribution across the entire normal tissue/organ under consideration.

Overall Plan Evaluation

- Optimization of IMRT is an inherently multicriteria problem as it involves multiple planning goals for target volumes and their neighboring critical tissue structures.
- **Successful achievement of one planning goal often competes with those of other planning goals.**

Overall plan evaluation?



Models could make things easier

- Thanks to the prevalence of 3D CRT, considerable data exist relating tumor and normal tissue outcomes with planned dose distributions.
- From the purely technical perspective, such information could supplement or replace simple dose-volume criteria for inverse planning and/or treatment plan evaluation.

Outline

- Normal Tissue Complication Probability (NTCP) models
- Tumor Control Probability (TCP) models
- Equivalent Uniform Dose (EUD) for tumors and normal tissues
- Clinical Response Modeling
  - Maximum likelihood analysis
  - Confounding variables and problems

Why use an NTCP model?

- We would like to be able to fully describe complications as a function of any dose to any volume.
- Most clinical trials will only sample the low portion of any normal tissue complication probability (NTCP) frequency distribution.
- Start with a model based on normal statistical distributions
  - Try to parameterize the model for future use using a limited amount of information

The Lyman NTCP Model

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

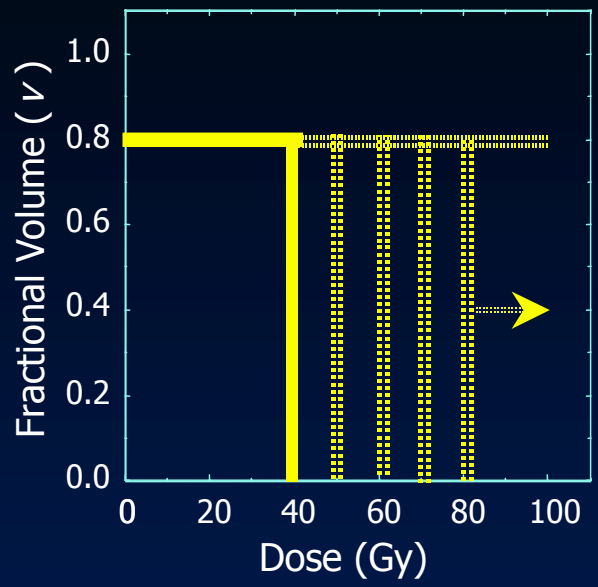
The Lyman NTCP Model

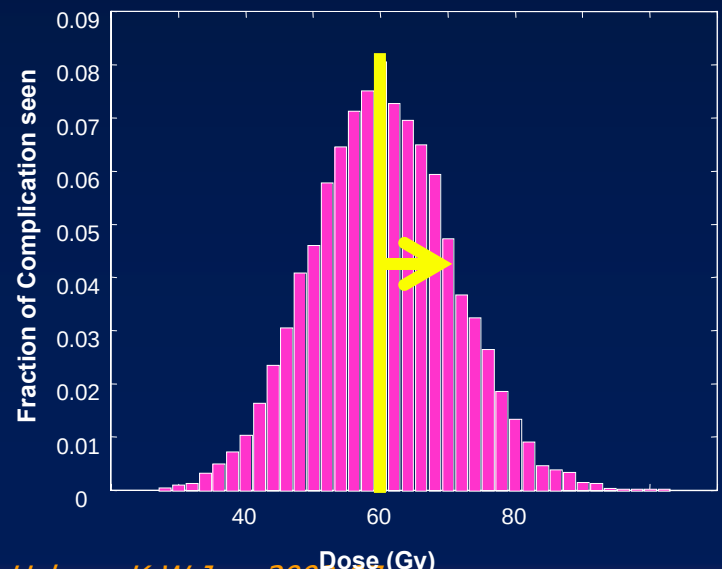
- The Lyman NTCP model attempts to mathematically describe complications associated with uniform partial organ irradiation.
- This implies:
  - A fractional volume, V, of the organ receives a single uniform dose, D.
  - The rest of the organ, (1 – V), receives zero dose.
  - i.e., a single step DVH,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

NTCP *vs* Dose for a fixed volume

For each uniformly irradiated fractional volume (v_i), the Lyman model assumes that the distribution of complications as a function of Dose (D) can be described by a normal distribution

- with mean $TD_{50}(v_i)$
- standard deviation $m \cdot TD_{50}(v_i)$





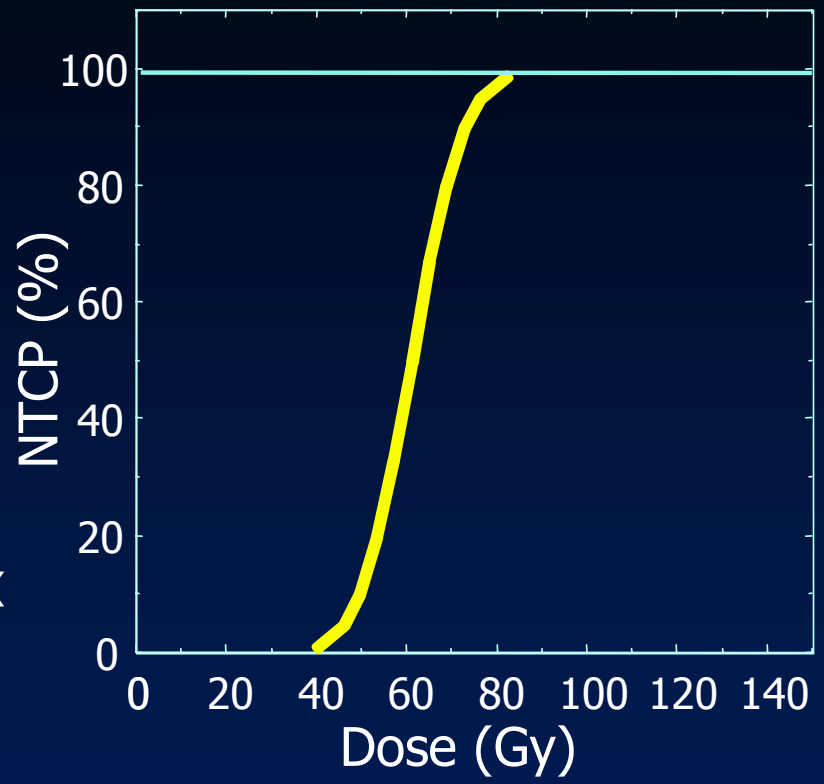
NTCP vs Dose for a fixed volume

The NTCP as a function of dose, D , to that uniformly irradiated volume, v_i , can then be described by the integral probability:

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

where;

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



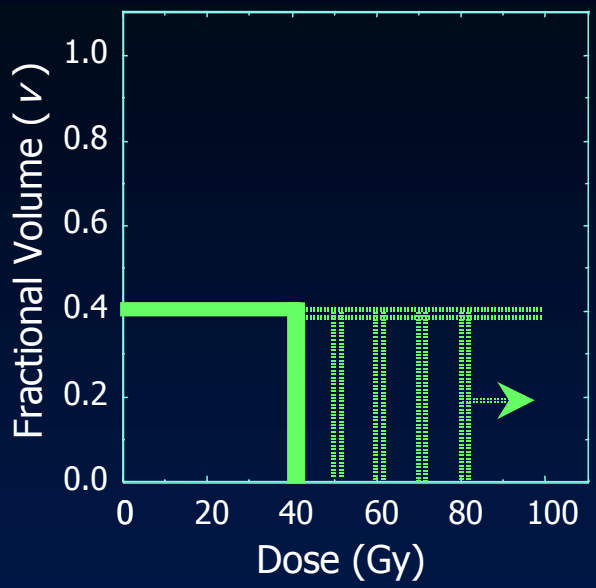
NTCP vs Dose for a different volume

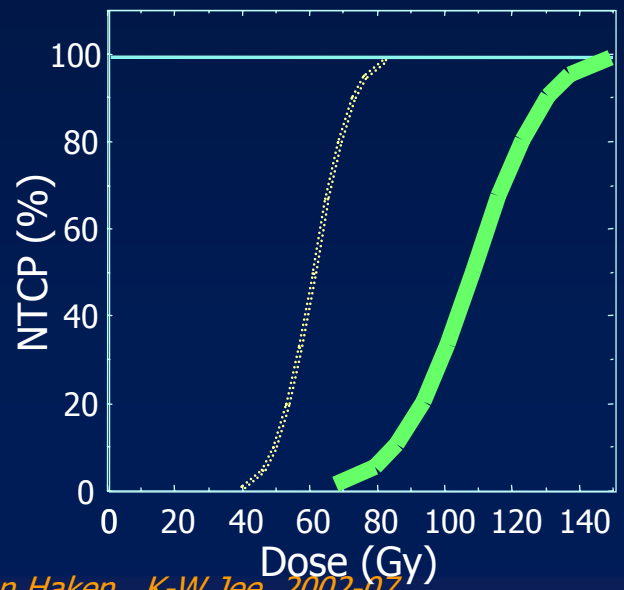
Similarly for a different uniformly irradiated fractional volume (v_j):

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

where;

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





Lyman NTCP description

The final step:

- assume that the mean dose, $TD_{50}(v)$, for the distribution of complications for each uniformly irradiated fractional volume v,
- is related to the mean dose for the distribution of complications for uniform irradiation of the whole organ volume, $TD_{50}(1)$,
- through a power law "volume effect" relationship:

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

The Lyman NTCP Description

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

where;

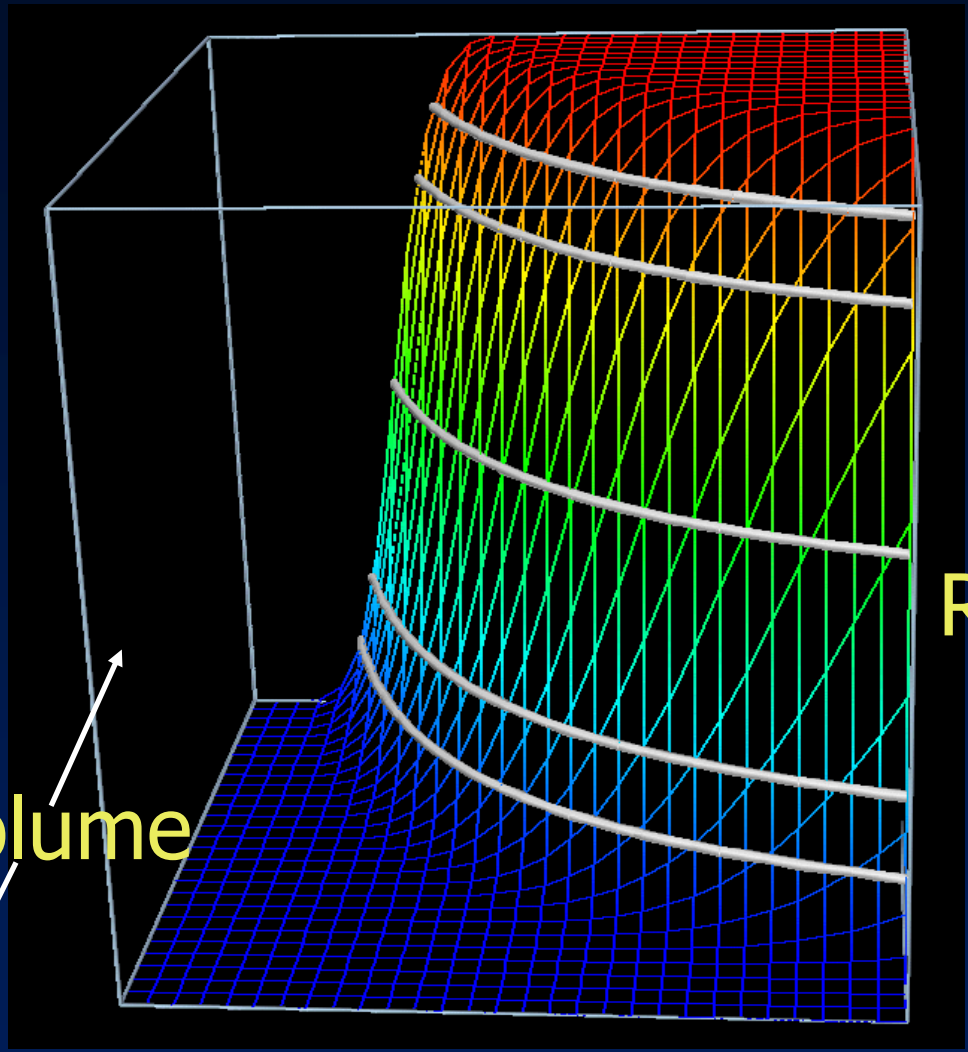
$$t = (D - TD_{50}(v)) / (m \bullet TD_{50}(v)),$$

and;

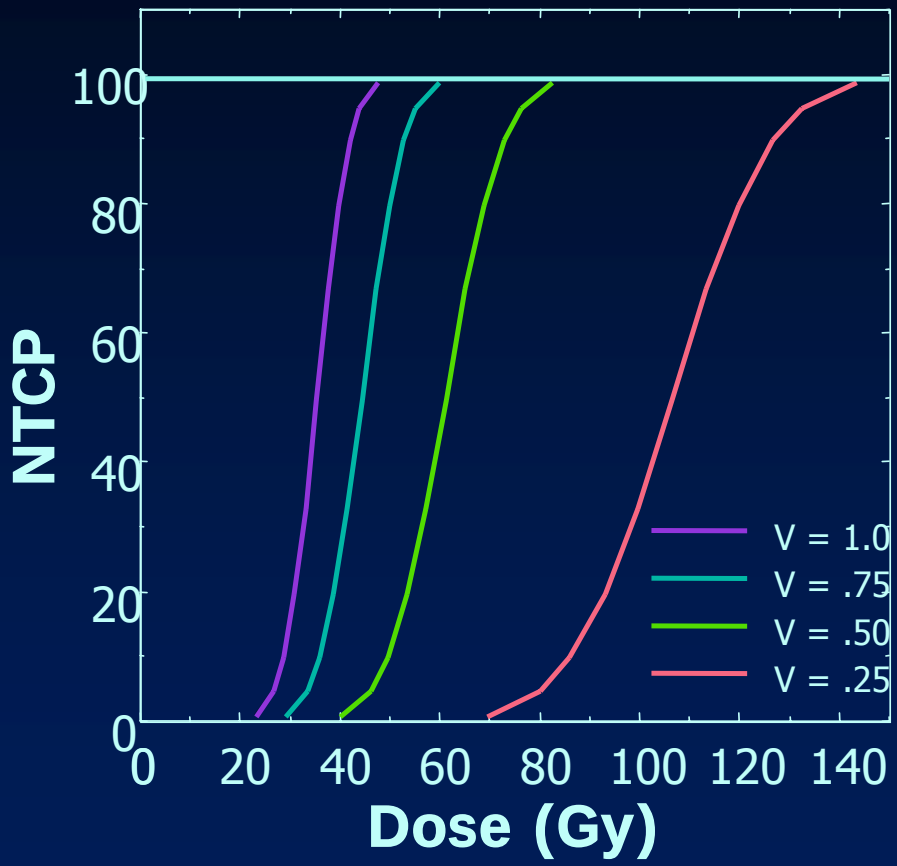
$$TD_{50}(v) = TD_{50}(1) \bullet v^{-n}$$

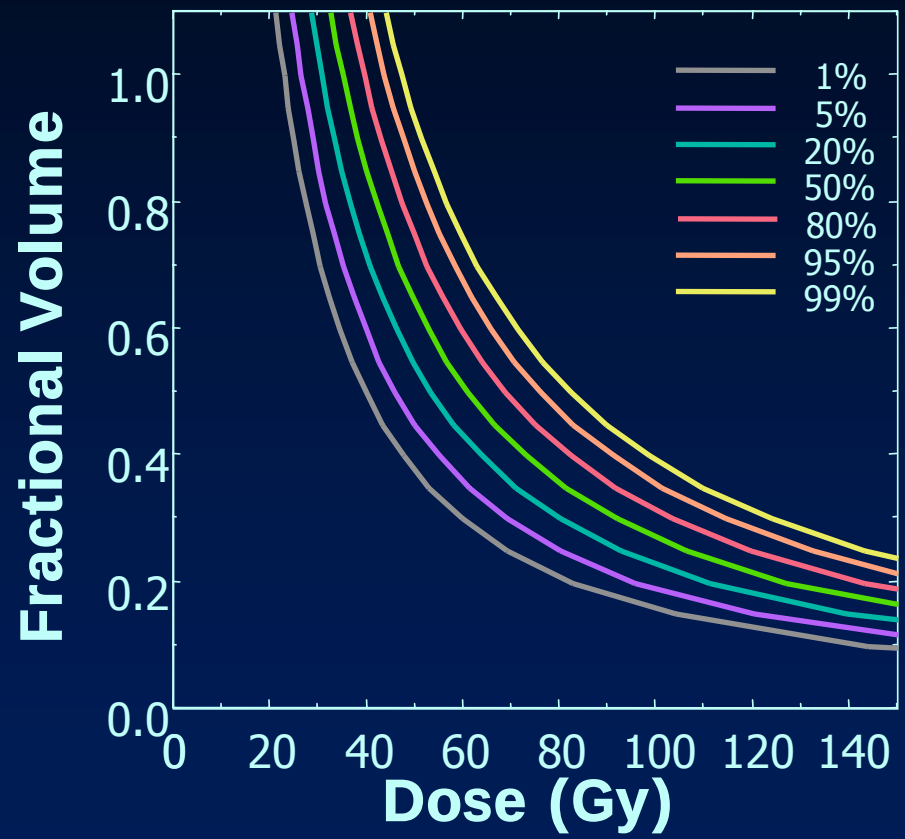
Lyman JT: Complication probability – as assessed from dose-volume histograms. Radiat Res 104:S13-S19, 1985.

Lyman Model dose-volume-response surface

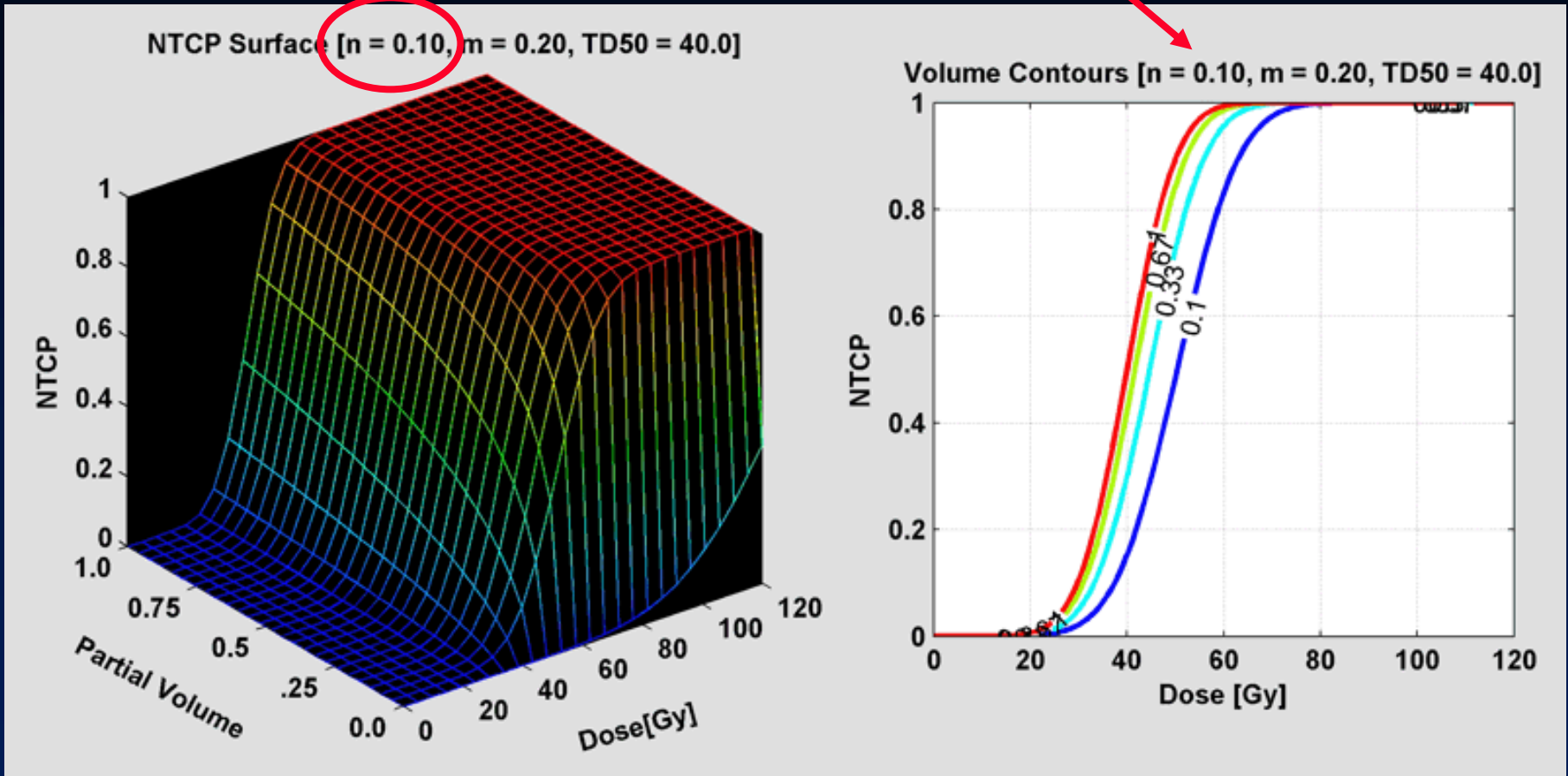


Dose-volume-response contours for a tissue with a large volume effect *(n = 0.80, m = 0.15, TD_{50} = 35 Gy)*

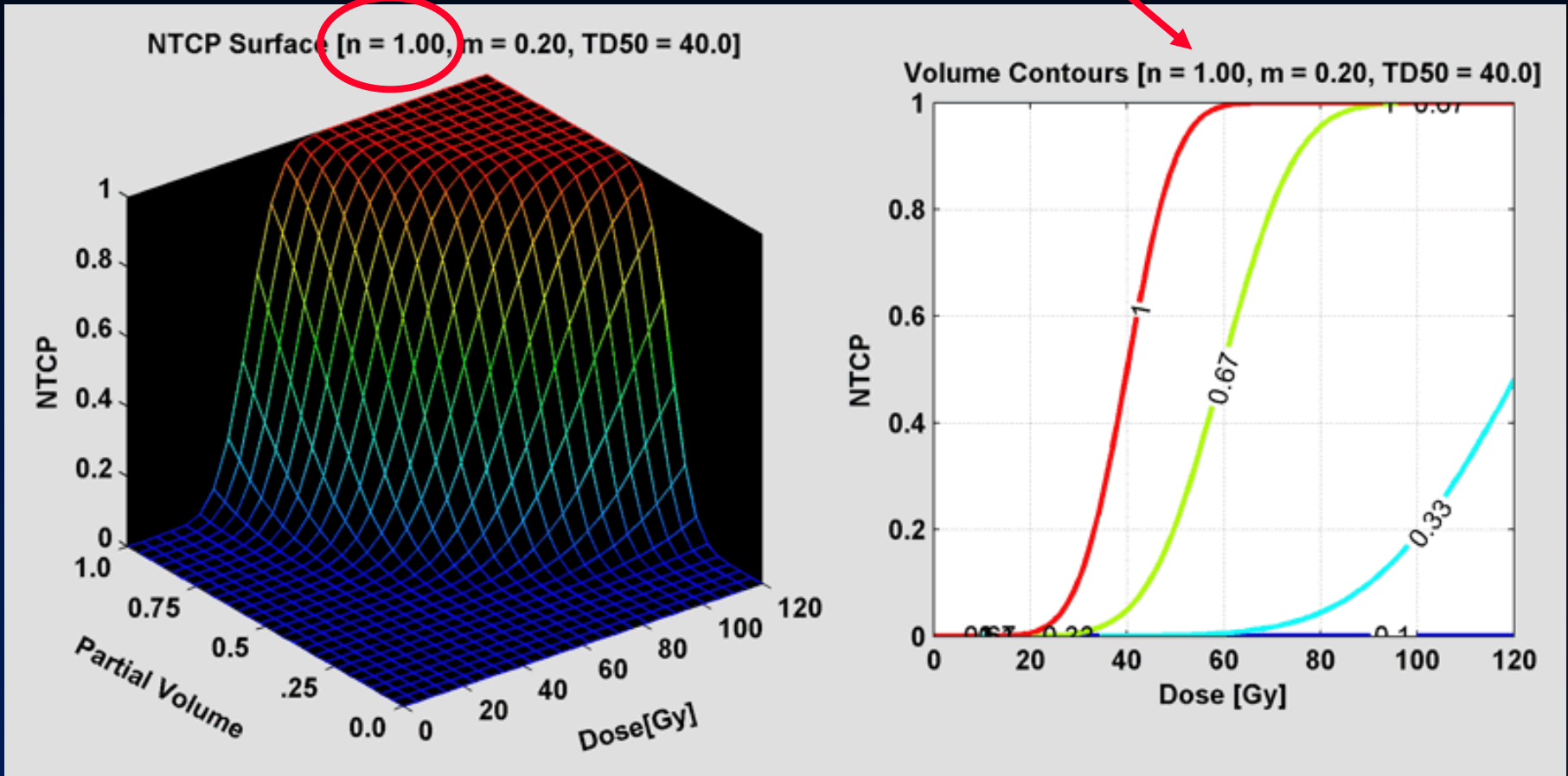




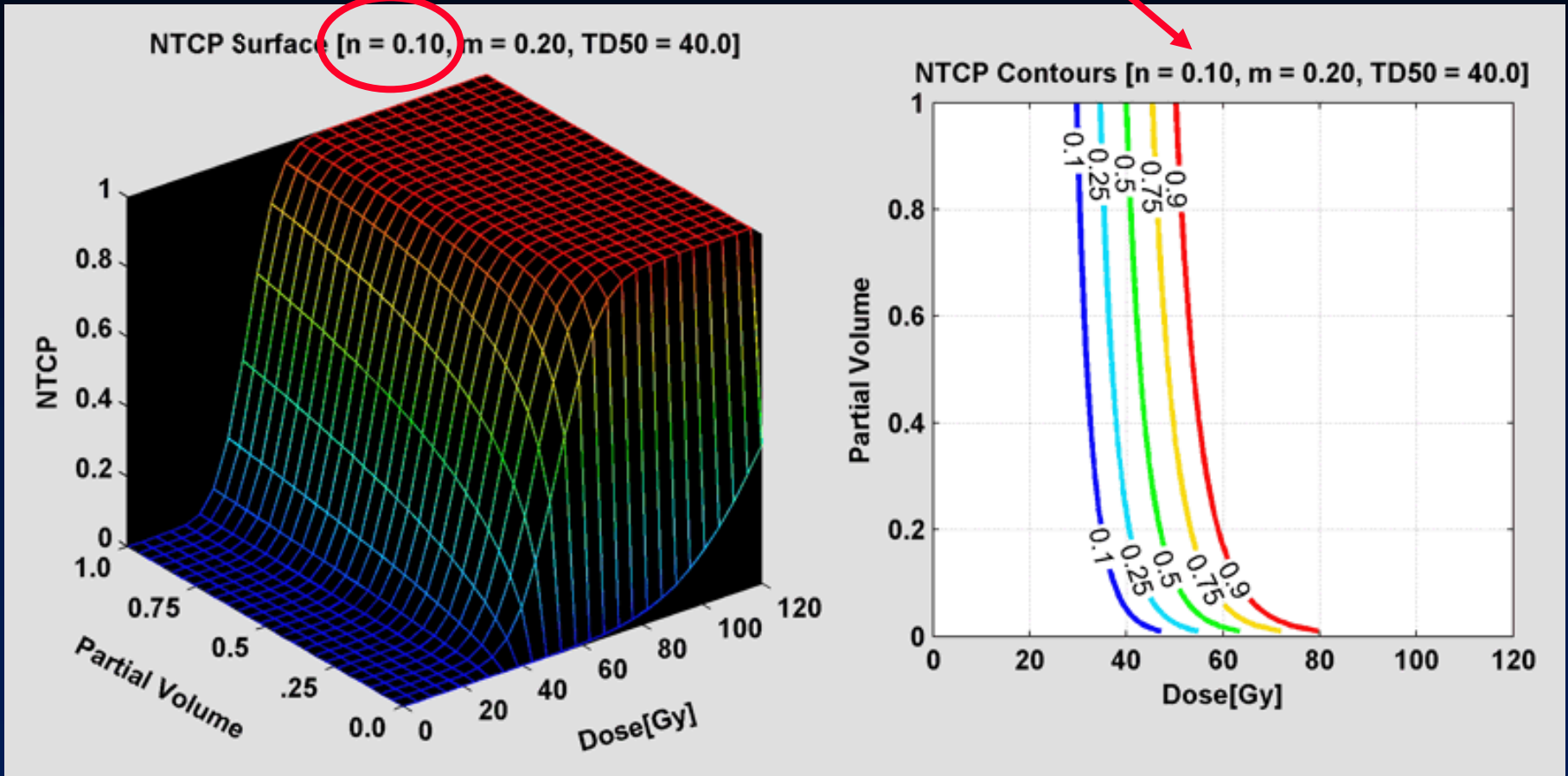
Volume Effect (partial volume contours)



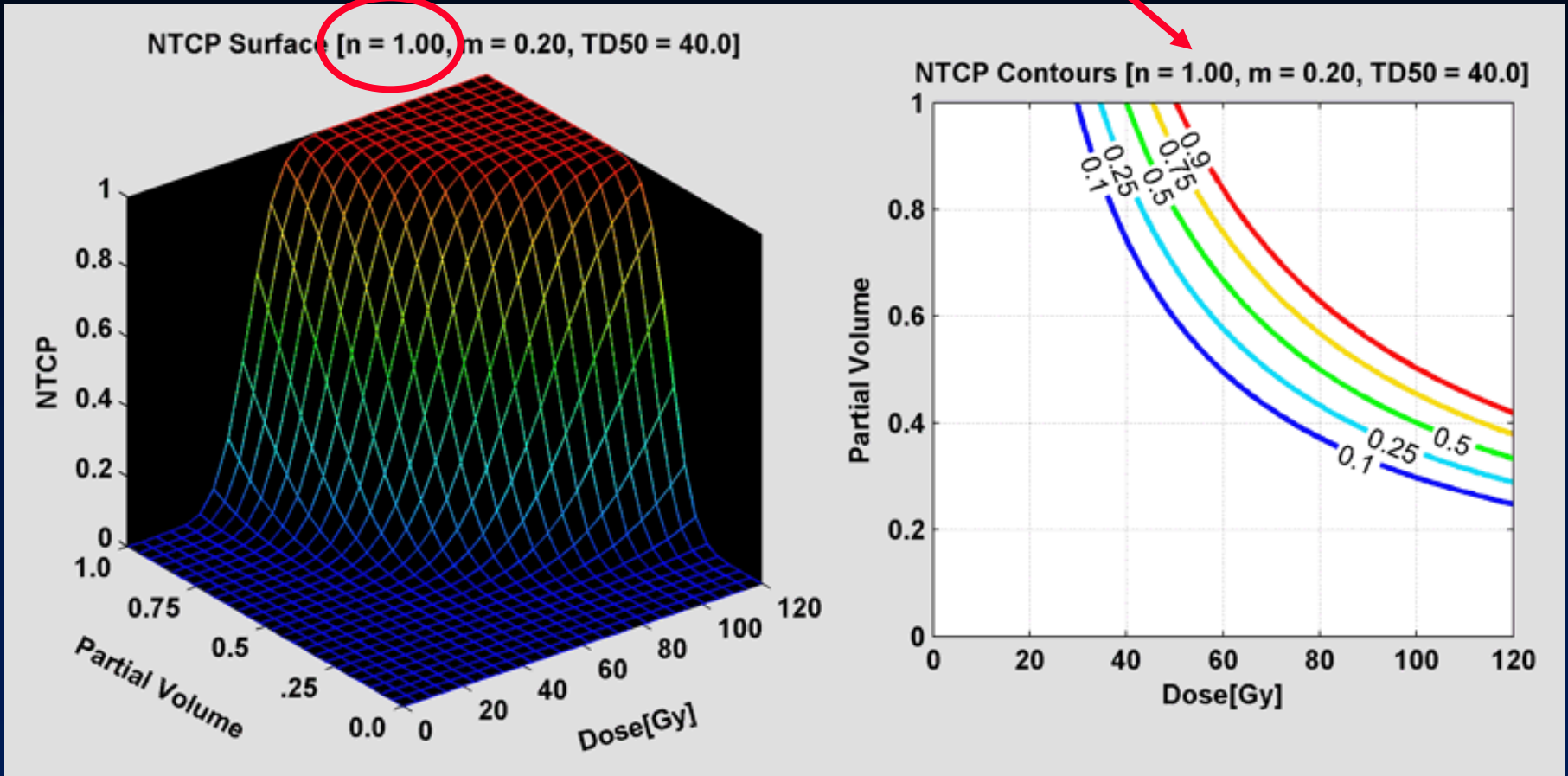
Volume Effect (partial volume contours)



Volume Effect (Iso-NTCP contours)



Volume Effect (Iso-NTCP contours)



Using the Lyman NTCP description

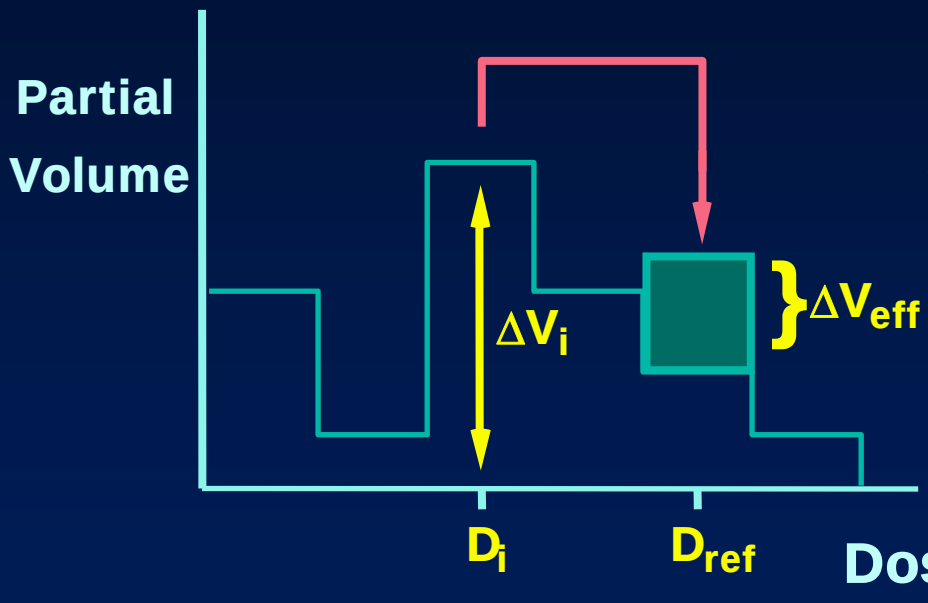
- The Lyman NTCP description attempts to describe uniform partial organ irradiation.
- This implies:
  - A fractional volume, V, of the organ receives a single uniform dose, D.
  - The rest of the organ, (1 - V), receives zero dose.
  - *i.e.*, a single step DVH, {D , V}

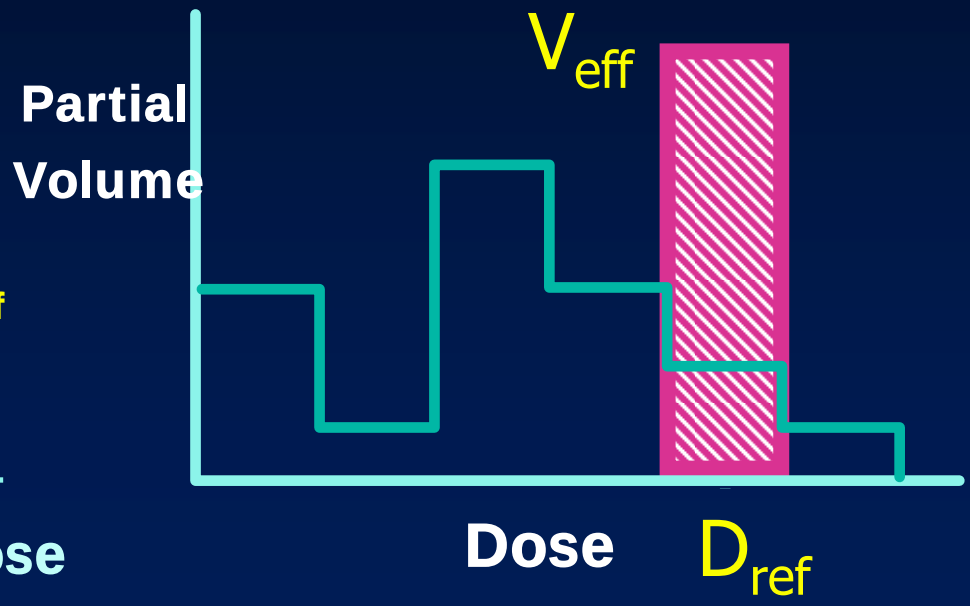
DVH reduction schemes

- 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.
  - Wolbarst & Lyman schemes reduce DVHs to uniform irradiation of entire organ (V=1) to some reduced effective dose, D_{eff} .
  - Kutcher & Burman scheme reduces a DVH to uniform irradiation of an effective fraction of the organ, V_{eff} , to some reference dose, D_{ref}.

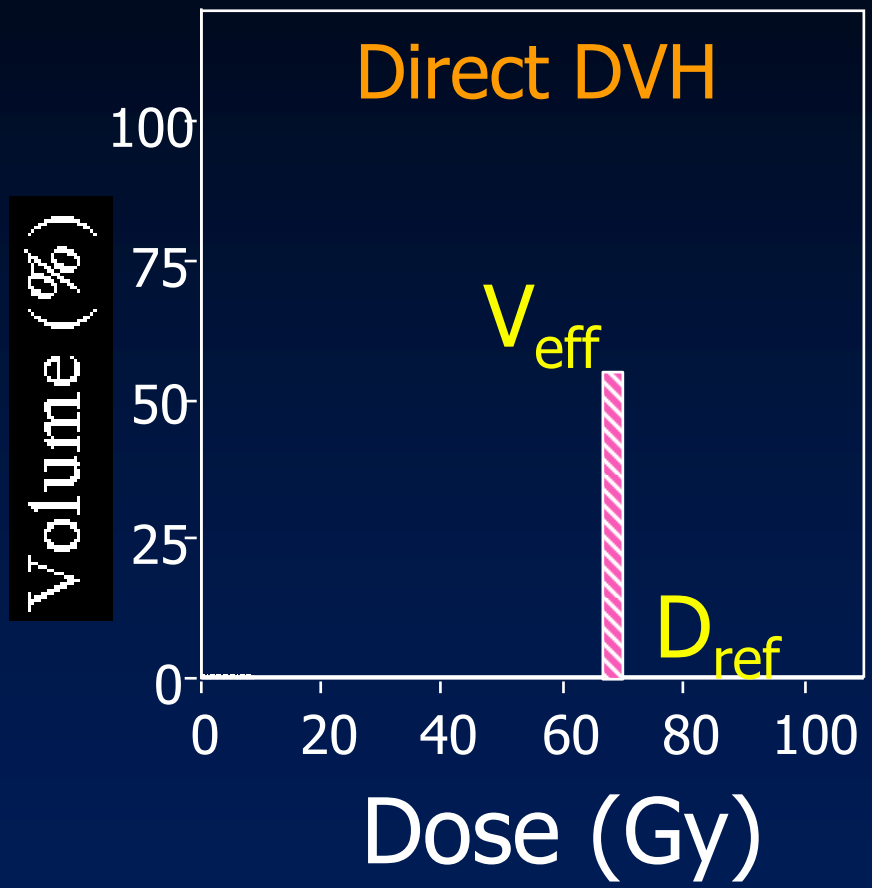
Effective Volume DVH reduction scheme

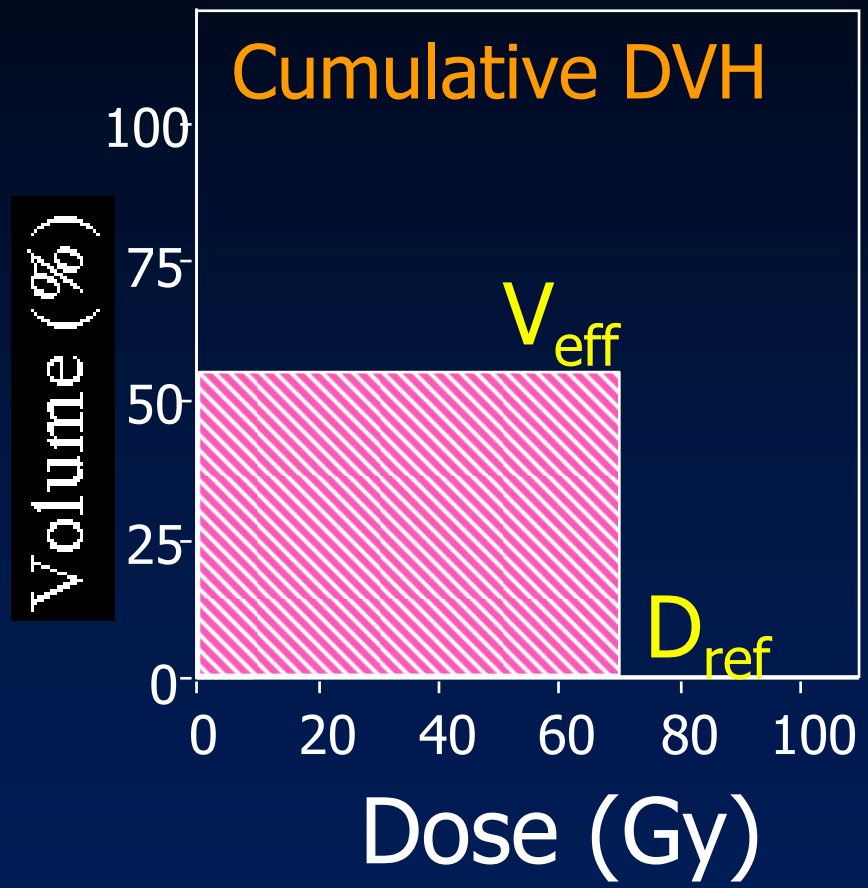
$$V_{eff} = \sum \{ v_i \bullet (D_i / D_{ref})^{1/n} \}$$



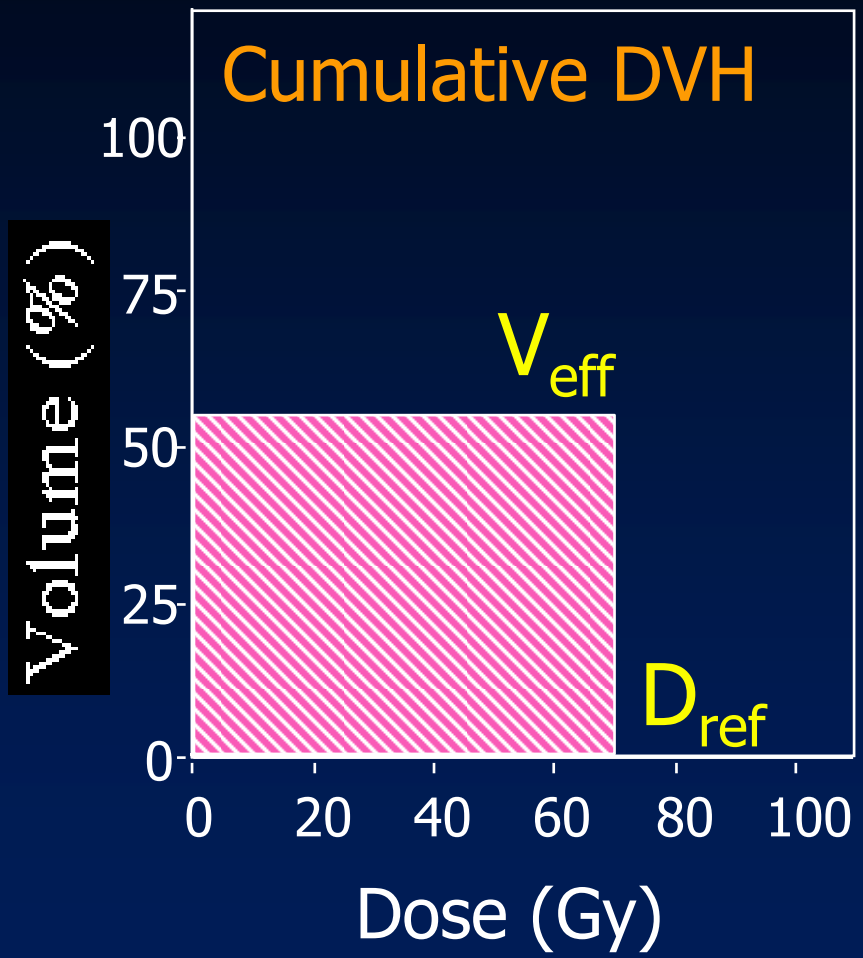


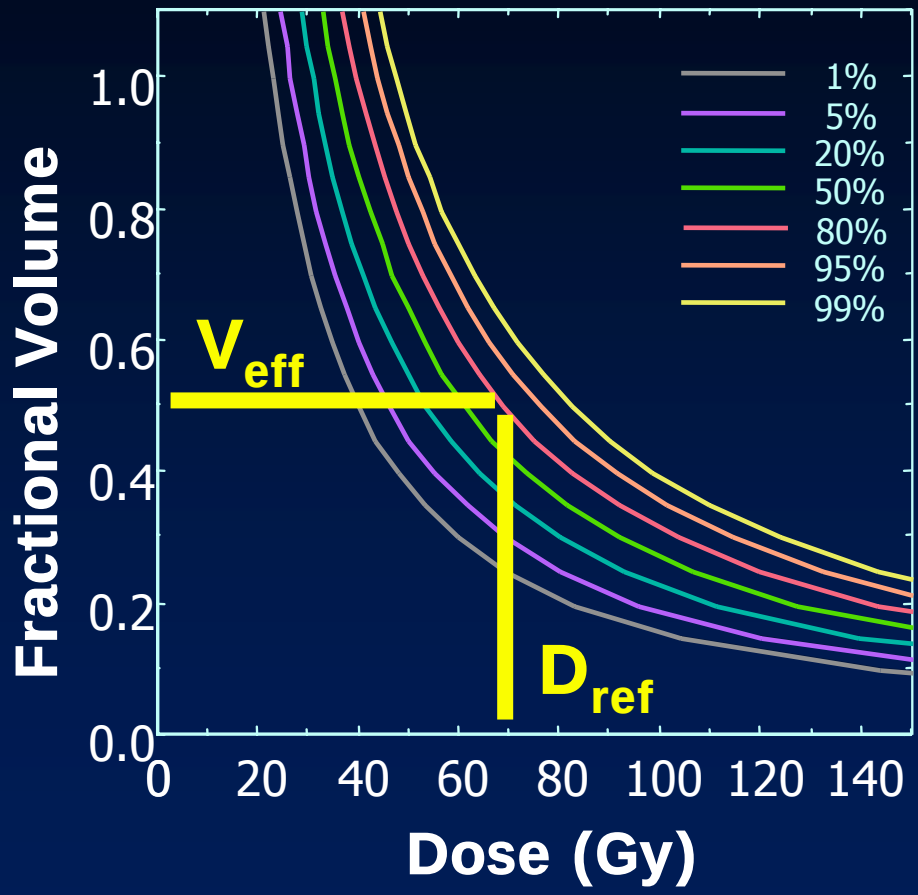
Single step $\{D_{ref}, V_{eff}\}$ DVHs





V_{eff} DVH reduction → *NTCP evaluation*





Local Radiation Response - Organ Functional Reserve Models

- Offer the potential for a more direct visualization of the relationship between the DVH and radiation damage
- May (ultimately) offer the possibility of linking cellular and organ subunit radiobiology to the prediction of radiation complications.

Local Radiation Response - Organ Functional Reserve Models

- Jackson A, Kutcher GJ, Yorke E. Med Phys 20:613-525, 1993.
- Niemierko A, Goitein M. Int J Radiat Oncol Biol Phys 25:135-145, 1993.

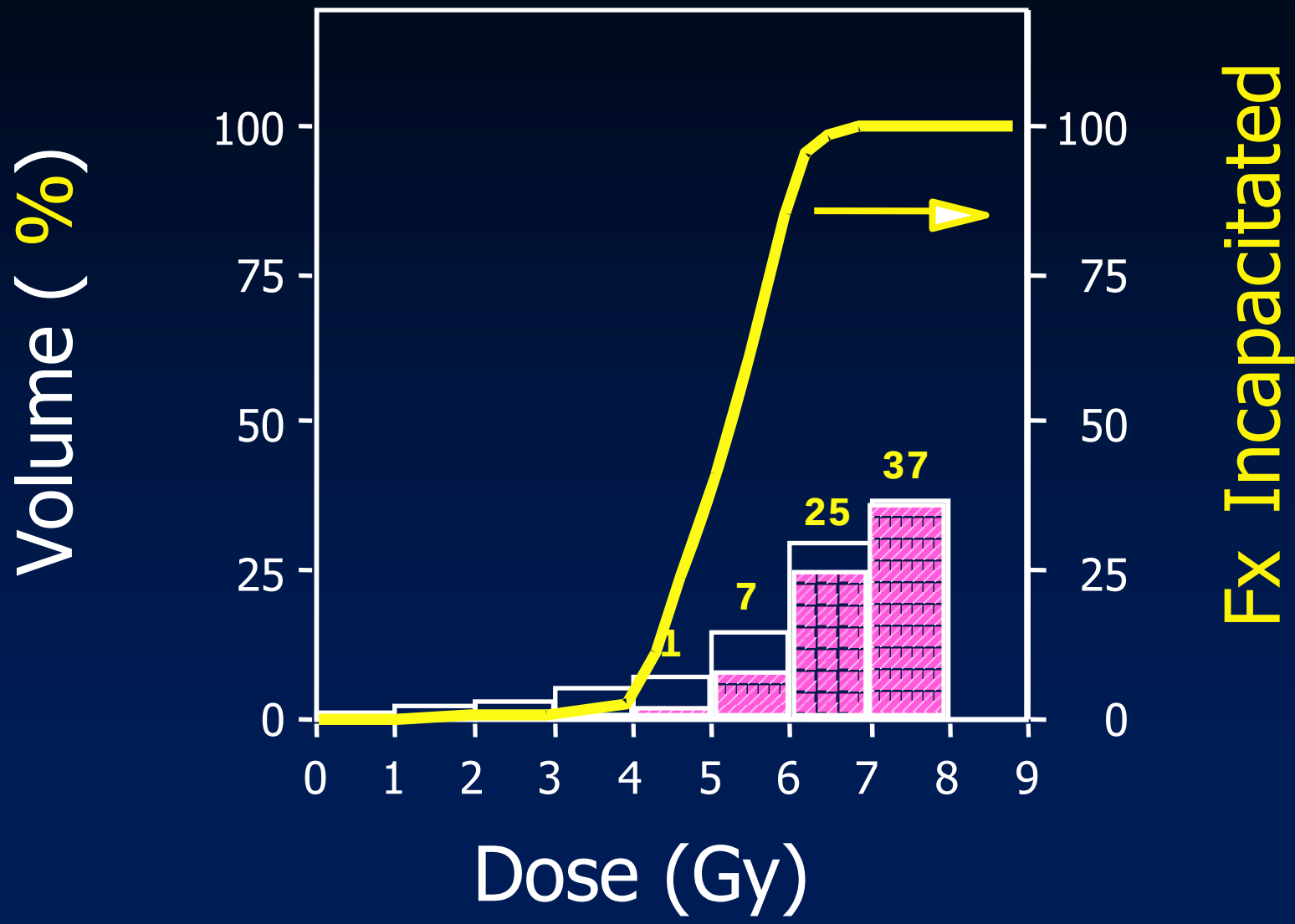
Local Damage Function

Fraction (f) of a macroscopic volume element incapacitated by a dose D can be described by a simple response function:

$$f = \frac{1}{\left(1 + \left(D_{50} / D\right)^{k}\right)}$$

where D_{50} is the dose which incapacitates half the volume and "**k**" describes the steepness of the "local damage" function.

Local Damage Function



Total Estimated Damage

Total fraction (***F***) of the organ that is incapacitated is equal to the sum of the fractions of the individual macroscopic volume elements destroyed.

$$F = \Sigma f_i$$

Organ Injury Function

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

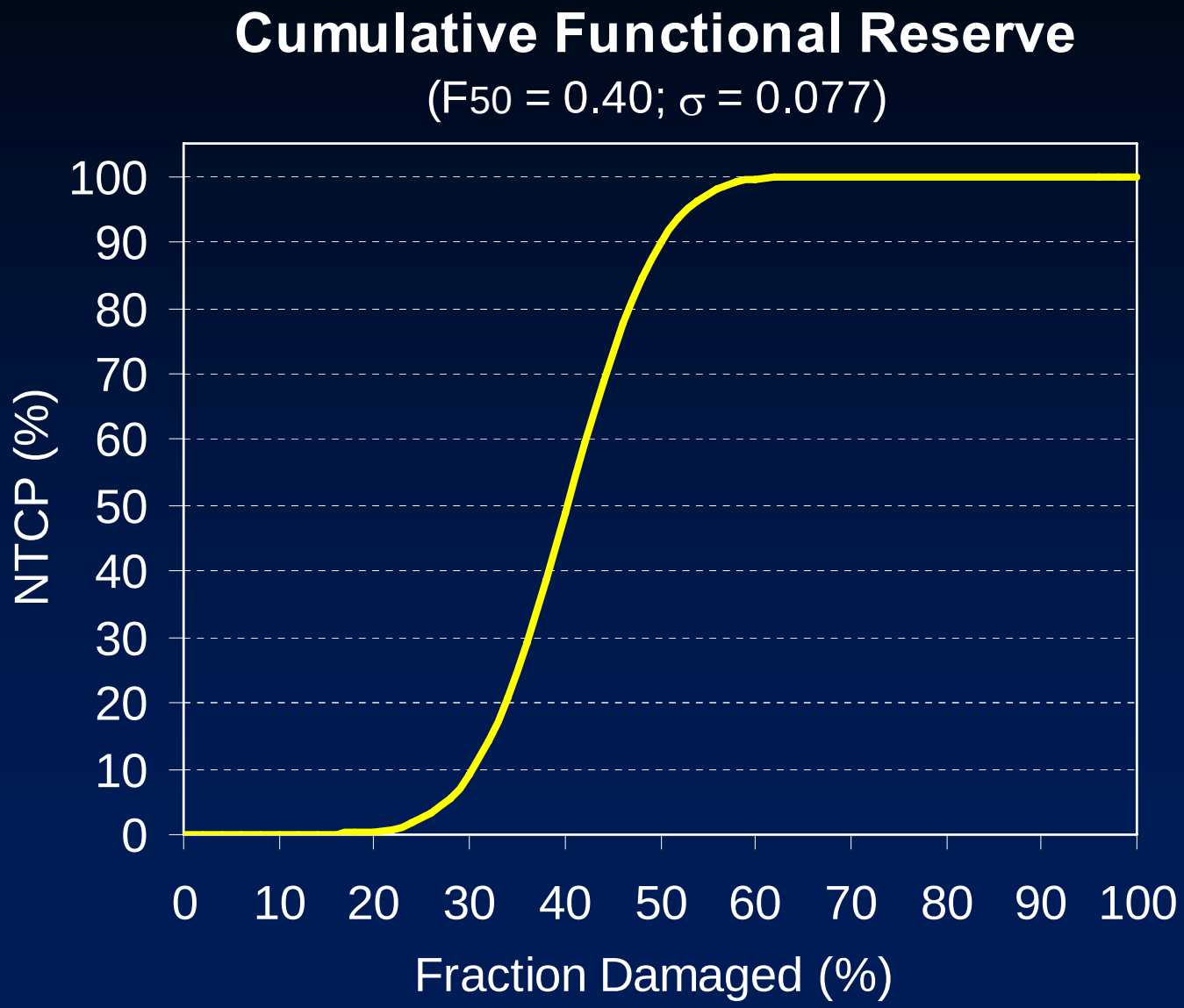
where

$$t = (F - F_{50}) / \sigma_\nu$$

F_{50} is the fraction of the total organ damaged which would produce a 50% complication rate,

σ_ν describes the steepness of the "organ" response function

Organ Injury Function



Tumor Control Probability (TCP) Calculations

TCP Calculation Assumptions

- An inhomogeneously irradiated tumor volume is composed of smaller volume elements,
  - each with uniform dose,
  - each responding independently to radiation.

Basic TCP Models

- "Tumorlet" model (Goitein, Brahme...
- Survival of clonogenic cells (Webb, Nahum, ...

“Tumorlet” TCP Model

- Tumorlet radiosensitivity estimated from the dose-response assumed for the entire tumor.
- Overall TCP predicted by product of the TCPs for each tumorlet.

"Tumorlet" TCP Assumptions

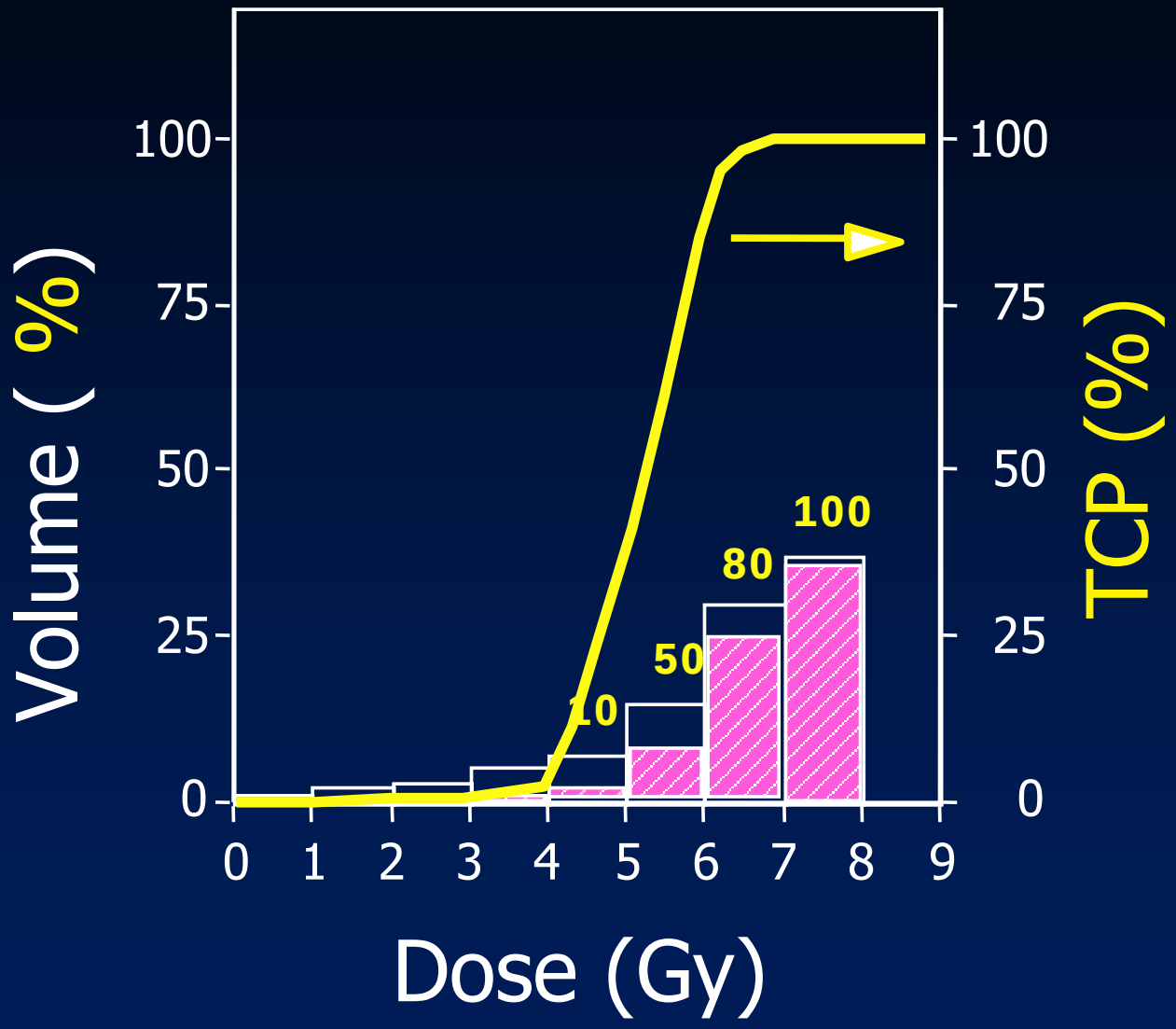
TCP of uniformly irradiated "tumorlet" with partial fractional volume V_i is estimated from the dose response assumed for uniform irradiation of the entire tumor to the same dose D_i :

$$TCP(D_i, 1) = 1 \;/\; \{1 + (D_{50} / D_i)^k\}$$

using:

$$TCP(D_i, \mathbf{V_i}) = [TCP(D_i, 1)]^{\mathbf{Vi}}$$

Tumorlet TCPs



"Tumorlet" TCP Assumptions

Overall TCP predicted by product of the TCPs for each tumorlet.

$$TCP_{total} = \prod_i TCP(D_i, V_i)$$

Clonogenic Cells TCP Model

- Number of surviving clonogenic cells estimated for each dose level and summed to obtain total number of surviving cells
- Overall TCP related to total number of surviving clonogenic cells

Surviving Clonogenic Cells TCP Calculation

For uniform initial clonogenic cell density ρ, and uniform radiosensitivity α, the number of surviving clonogenic cells for each bin of the DVH $\{V_j\ (cm^3), D_j\ (Gy)\}$ is estimated as:

$$N_{s,\,j} = \rho V_j \exp(-\alpha D_j)$$

Surviving Clonogenic Cells TCP Calculation

The total number of surviving clonogenic cells is then the sum over all bins of the DVH:

$$N_{s,\,tot} = \Sigma_j \, \rho \, V_j \exp(-\alpha \, D_j),$$

from which the TCP is estimated:

$$TCP = \exp(-N_{s,\,tot})$$

Equivalent Uniform Dose

- Uniform dose distribution that if delivered over the same number of fractions would yield the same radiobiological or clinical effect.
  - Niemierko 1996
  - Brahme 1991
  - Niemierko 1999 (abstract) gEUD

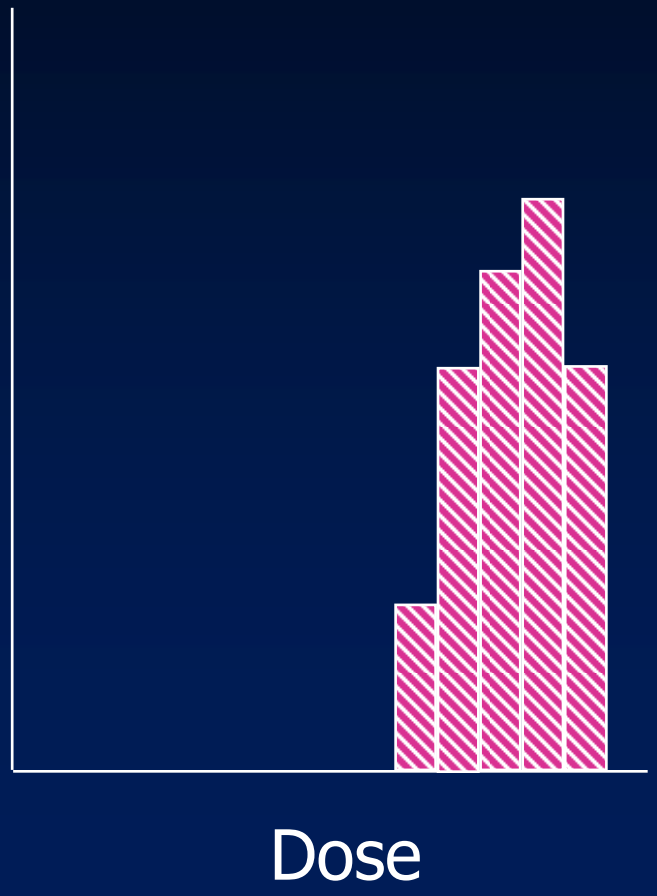
Equivalent Uniform Dose for Target Volume

$$EUD = 2 \bullet \ln \{ \Sigma v_i (SF_2)^{Di/2} \} / \ln (SF_2)$$

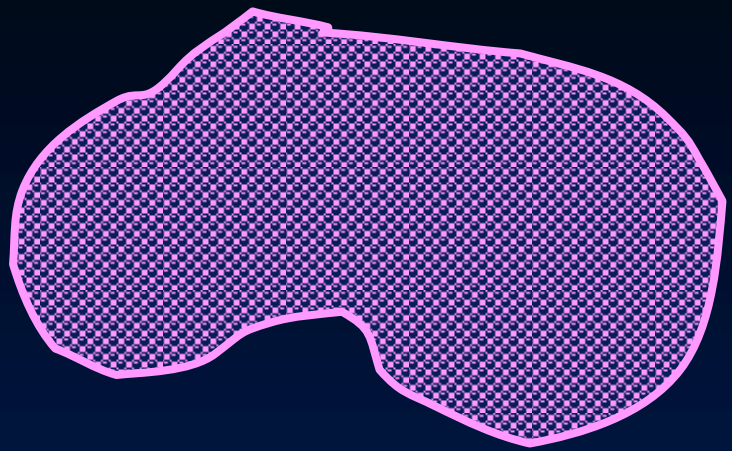
SF_2 = Fx of clonogens surviving single 2 Gy dose

v_i = fractional volume

D_i = uniform dose to v_i

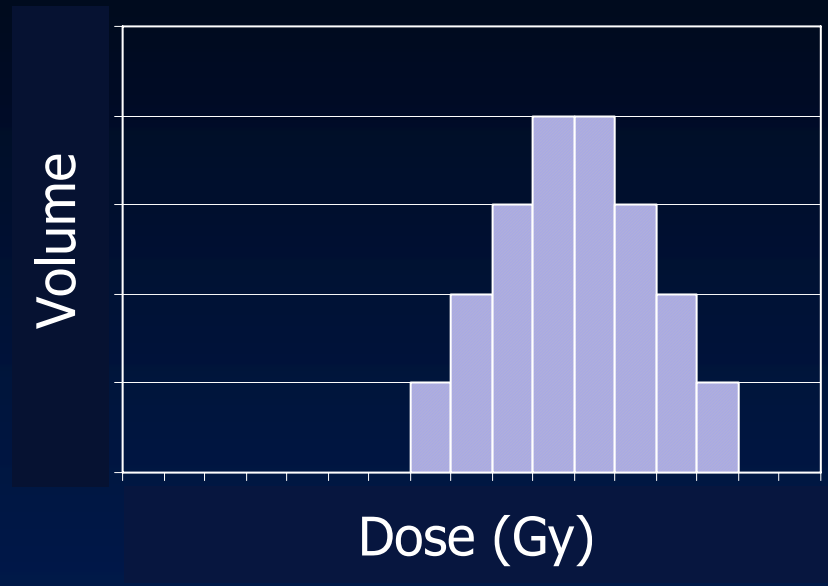


Generalized Equivalent Uniform Dose (gEUD)



ROI with N dose points d_i

DVH (fractional volume v_i receives dose d_i)



$$gEUD \equiv \left(\frac{\sum_{i=1}^{N} d_i^a}{N} \right)^{1/a} \equiv \left(\sum_i v_i \, d_i^a \right)^{1/a}$$

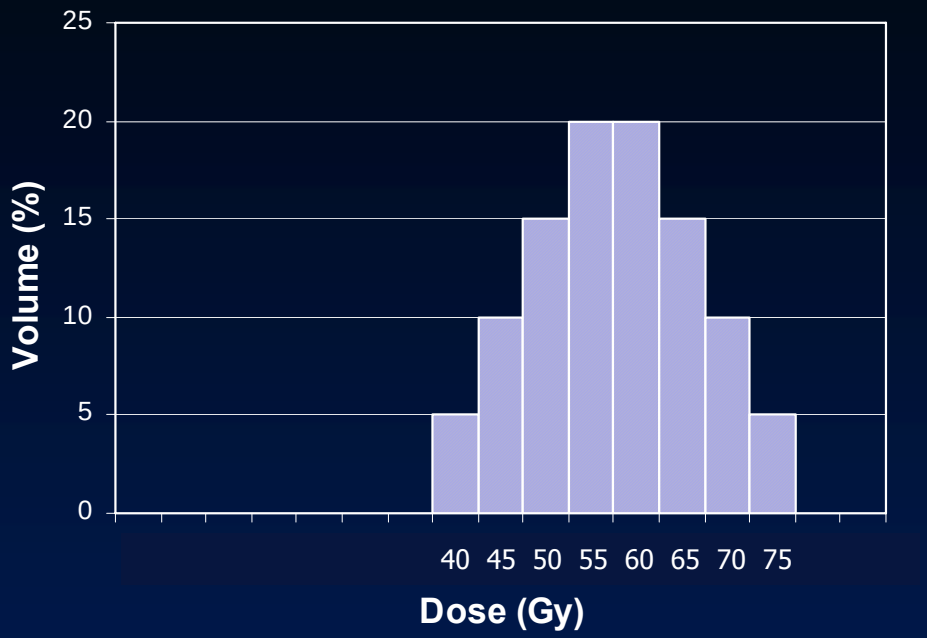
gEUD

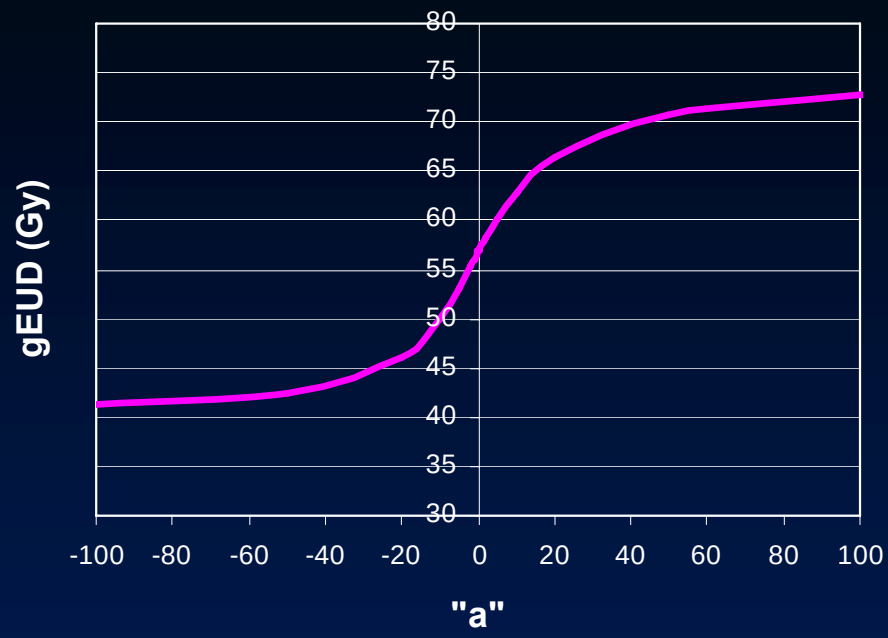
$$gEUD \equiv \left(\frac{\sum_{i=1}^{N} d_i^a}{N} \right)^{1/a} \equiv \left(\sum_i v_i \, d_i^a \right)^{1/a}$$

Tumors: ***a*** is a negative number
Normal Tissues: ***a*** is a positive number

For $a = 1$, $gEUD$ = mean dose
For $a = 2$, $gEUD$ = rms dose
For $a = -\infty$, $gEUD$ = minimum dose
For $a = +\infty$, $gEUD$ = maximum dose
(discontinuous at $a = 0$)

$$gEUD \equiv \left(\sum_i v_i d_i^a \right)^{1/a}$$





Tumors: ***a*** is negative
- aggressive a = -20
- non a = -5

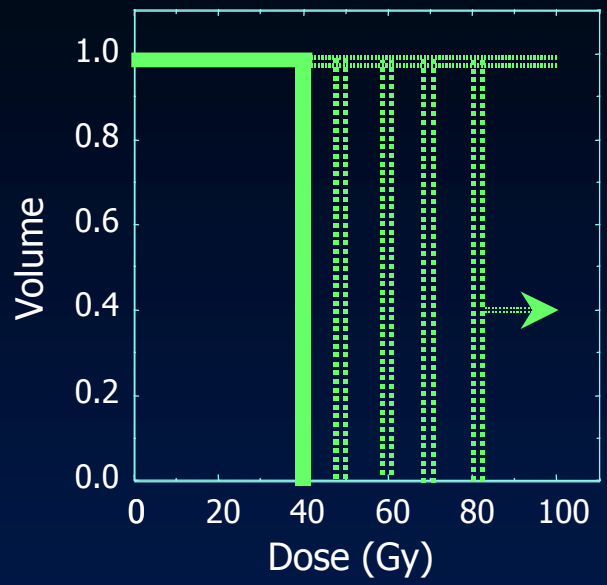
Normal Tissues: ***a*** is positive
- LKB Model $a = 1/n$

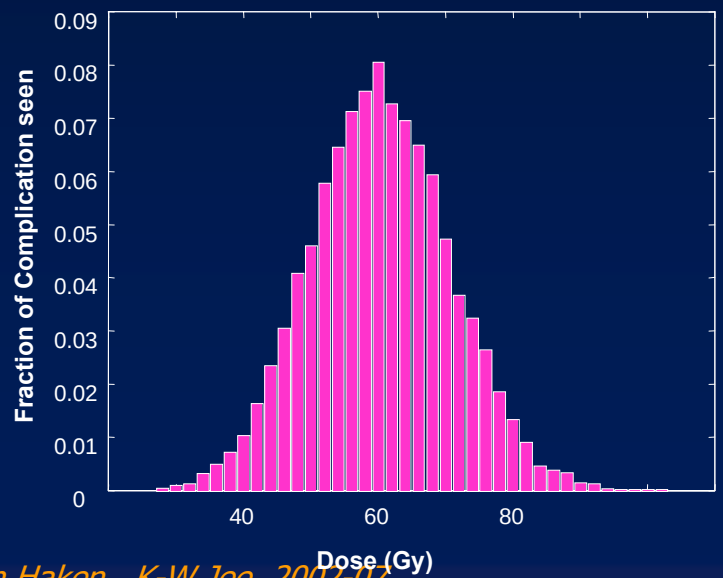
For a = 1, $gEUD$ = mean dose
For a = 2, $gEUD$ = rms dose
For $a = -\infty$, $gEUD$ = minimum dose
For $a = +\infty$, $gEUD$ = maximum dose
(discontinuous at a = 0)

EUD NTCP description

For uniform irradiation of the whole organ, assumes that the distribution of complications as a function of dose can be described by a normal distribution

- with mean TD_{50}
- standard deviation $m \bullet TD_{50}$





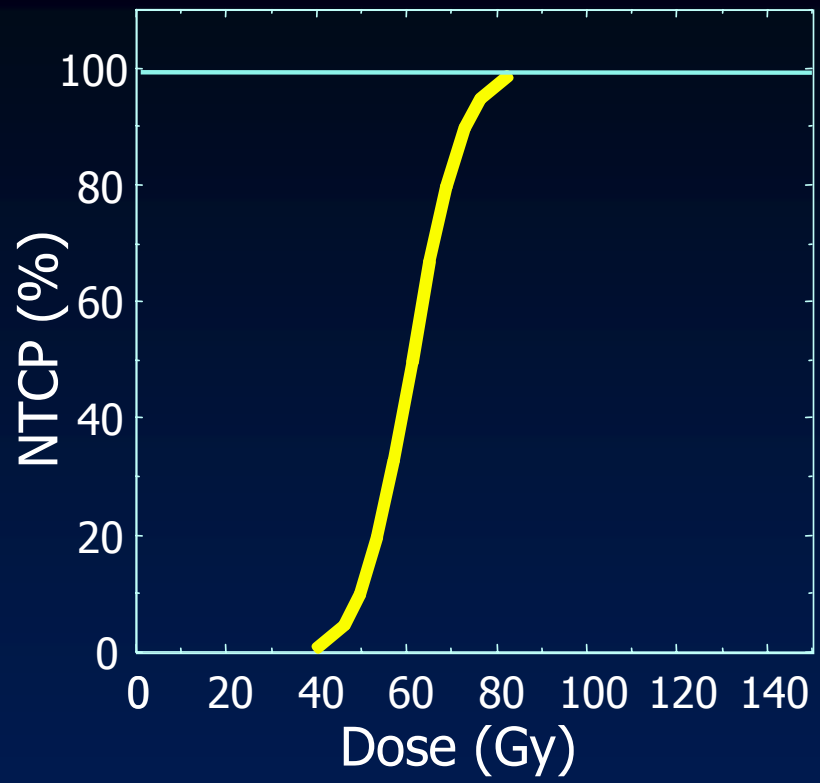
The EUD NTCP description

The NTCP as a function of uniform dose, *EUD* , to the whole volume can then be described by the integral probability:

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

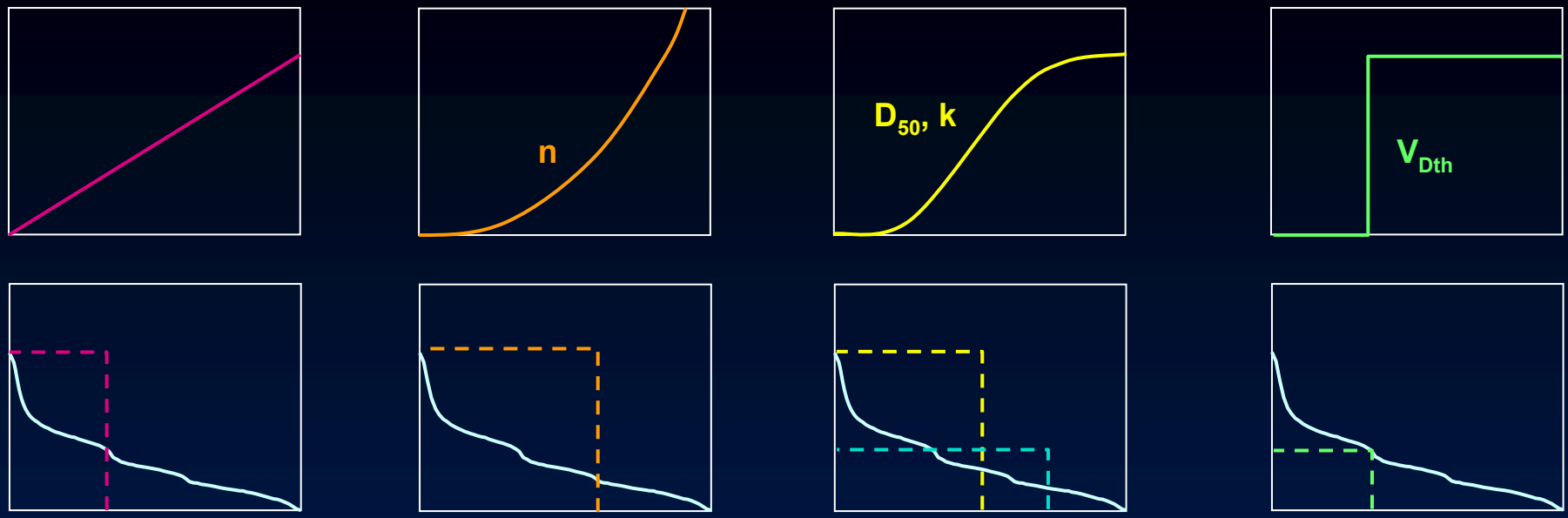
where;

$$t = (\boldsymbol{EUD} - EUD_{50}) / (m \bullet EUD_{50})$$



Local response function

- Required to change non-uniformly irradiated volume to equivalent uniform dose EUD
- gEUD is one very general form of this function (their can be many others):
  - **Seppenwoolde Y**, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, Henning GT, Hayman JA, Martel MK, Ten Haken RK: *Comparing different NTCP models that predict the incidence of radiation pneumonitis.* Int J Radiat Oncol Biol Phys 55:724-735, 2003.


2 parameters
3 parameters
4 parameters
3 parameters
n
D50, k
VDth
EUD=MLD
n = 1
EUDLKB
D50 = ∞
EUDLogistic
rdV= FD
k = ∞
VDth
NTCP = 1/√2π ∫ from −∞ to t of e^(−x²/2) dx
EUD50, m
NTCP
EUDmodel
t = (EUD − EUD50) / (m · EUD50)
NTCP = 1/√2π ∫ from −∞ to t of e^(−x²/2) dx
VDth50, m
NTCP
VDth
t = (rdV − rdV50) / (m · rdV50)

cast of thousands here...
would you believe 100's??
...maybe tens?

NTCP/TCP modeling

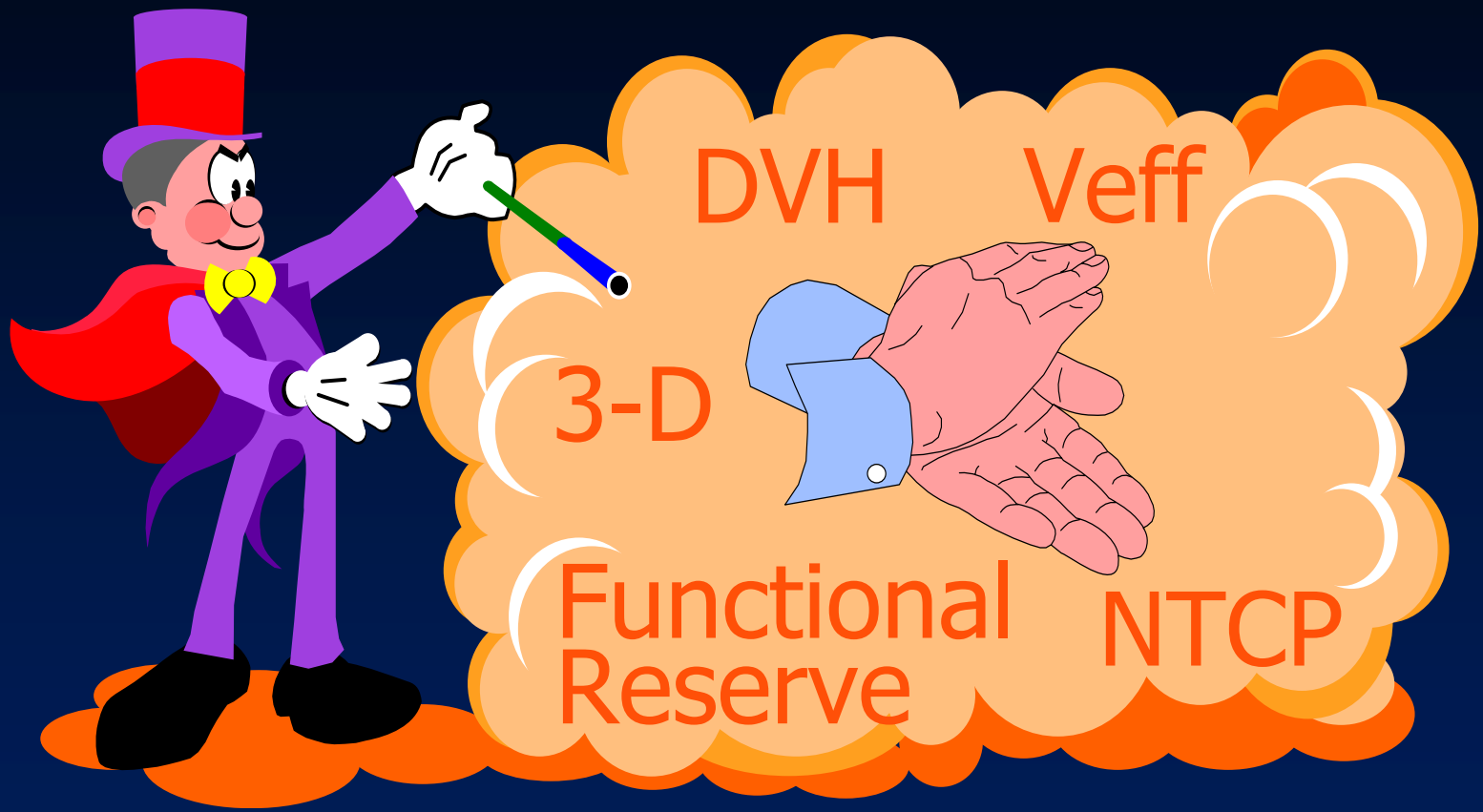
We've come a long way.....
But.....

OK, beware! mostly personal opinion may follow

Conceptually Simple

- Pick a Model
- Look at some Patients
  - Have 3-D Dose Distributions
  - Have 3-D Volumes
  - Have Outcomes
- Use patient data to parameterize and/or test model

¿No Problemo?



Well.....

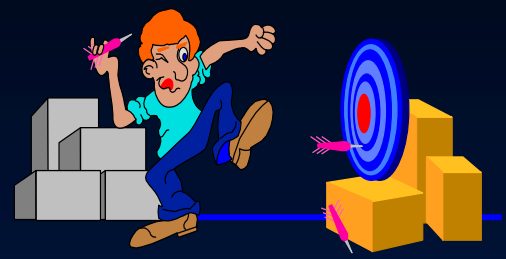
The Models

Biologists and Physicists and Physicians Agree the Models are:

- **Too simple or naive (*papa bear*)**
  - Biology is more complex than this
  - Not enough parameters
- **Too complex (*mama bear*)**
  - Too many parameters
  - Is this still biology?
- Still looking for *baby bear's* model

Modeling

- Model vs. Theory
  - + Models interpolate
  - + Theories extrapolate



- Mathematics vs. Biology
  - + K.I.S.S.

Models?

- Probably best to say that at this point much of this is still phenomenological and "descriptive" rather than predictive.

Model Fitting

- Generally not enough solid data points (complications) to yield quantitative results
- Large confidence limits on model parameters
- No effective means of determining "goodness of fit"

Model Fitting (the good news!)

- We now have collaborations with genuine bio-statisticians who are applying valid statistical methods to the data analyses and the new protocol designs.

Input Data: Dose

- Calculational algorithms are better
- Can compute 3-D distributions
- Dose distributions are complex
  - Non-uniform
  - Daily variations not easily included

Input Data: Volume

- 3-D yields Volumes
  - Physical Volume (size and shape)
  - Position
- How accurate are the input data?
  - For first treatment?
  - As a basis for the whole treatment?

Input Data: Dose-Volume

- Difficult to track which volume receives what dose
  - Time factors often ignored
- Changes not easily accommodated
  - Tumor shrinkage
  - Inter and Intra treatment changes and processes

Modeling Summary

- Careful studies of the partial organ tolerance of normal tissues to therapeutic ionizing radiation are emerging, as are attempts to model these data.
- We should be encouraged by the progress in this area.

Modeling Summary

- However, the ability to use the NTCP models themselves reliably, and in a predictive way is still an area of active research and should be approached with great caution in a clinical setting.

“All models are wrong, but some are useful.”

G.E.P. Box, 1979*

*”Robustness in the Strategy of Scientific Model Building." IN: Robustness in Statistics. 201-236. R. L. Launer and G. N. Wilkinson, eds. Academic Press, NY. 1979

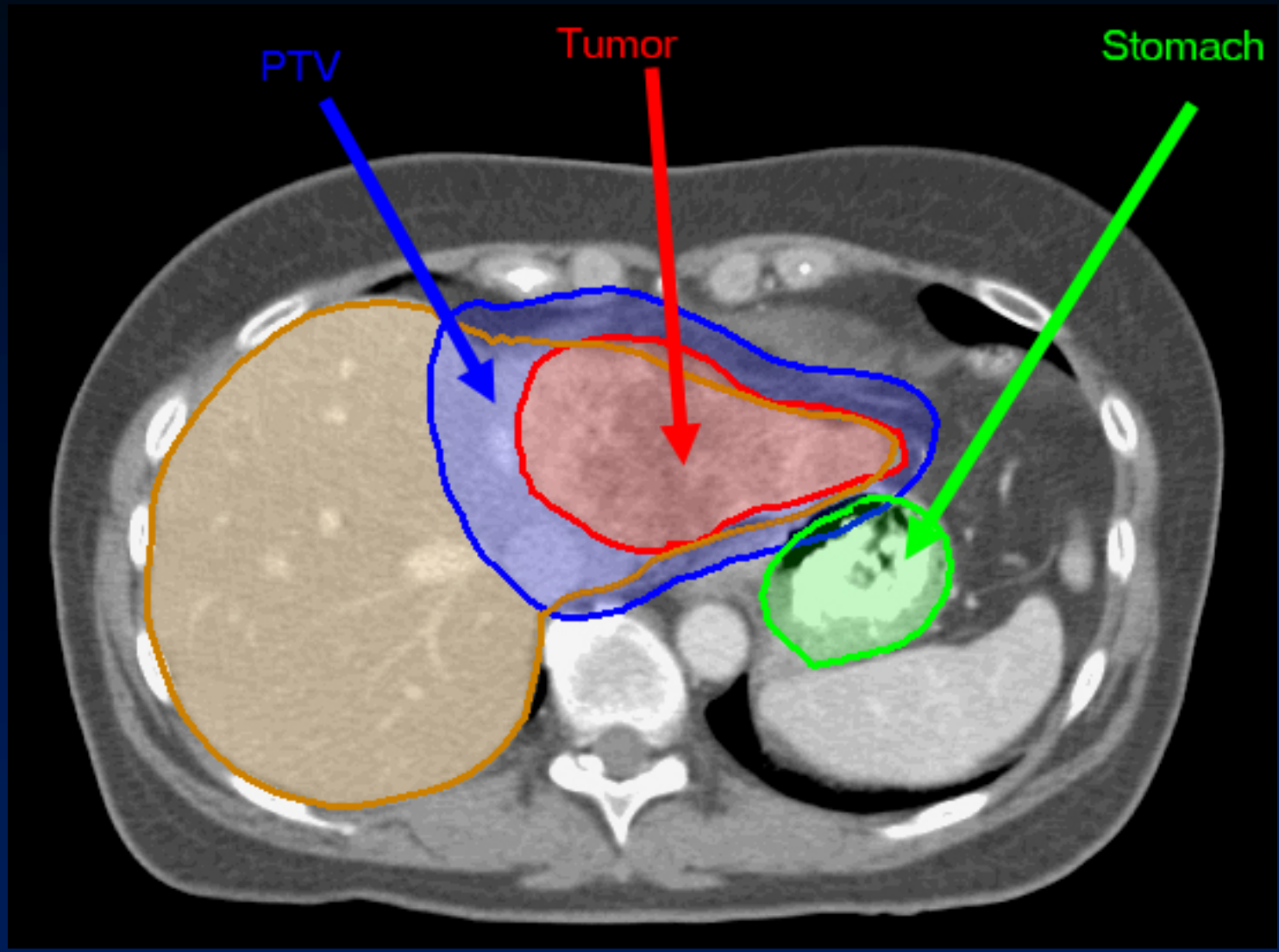
A clinical example

- Patients at our institution with tumors in the liver or lung 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.

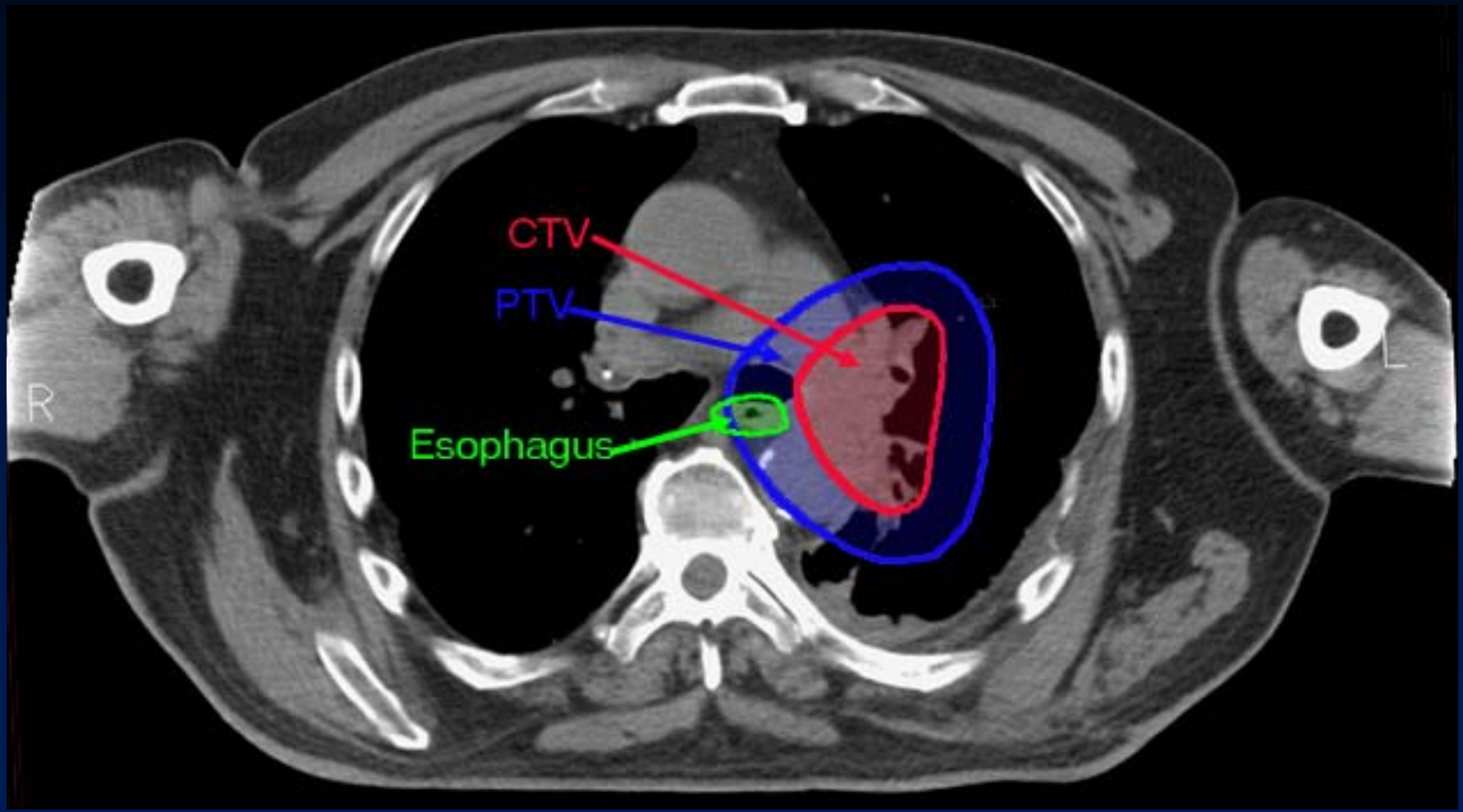
Difficulties in implementation

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

Liver tumor PTV-OAR overlap



Lung 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.

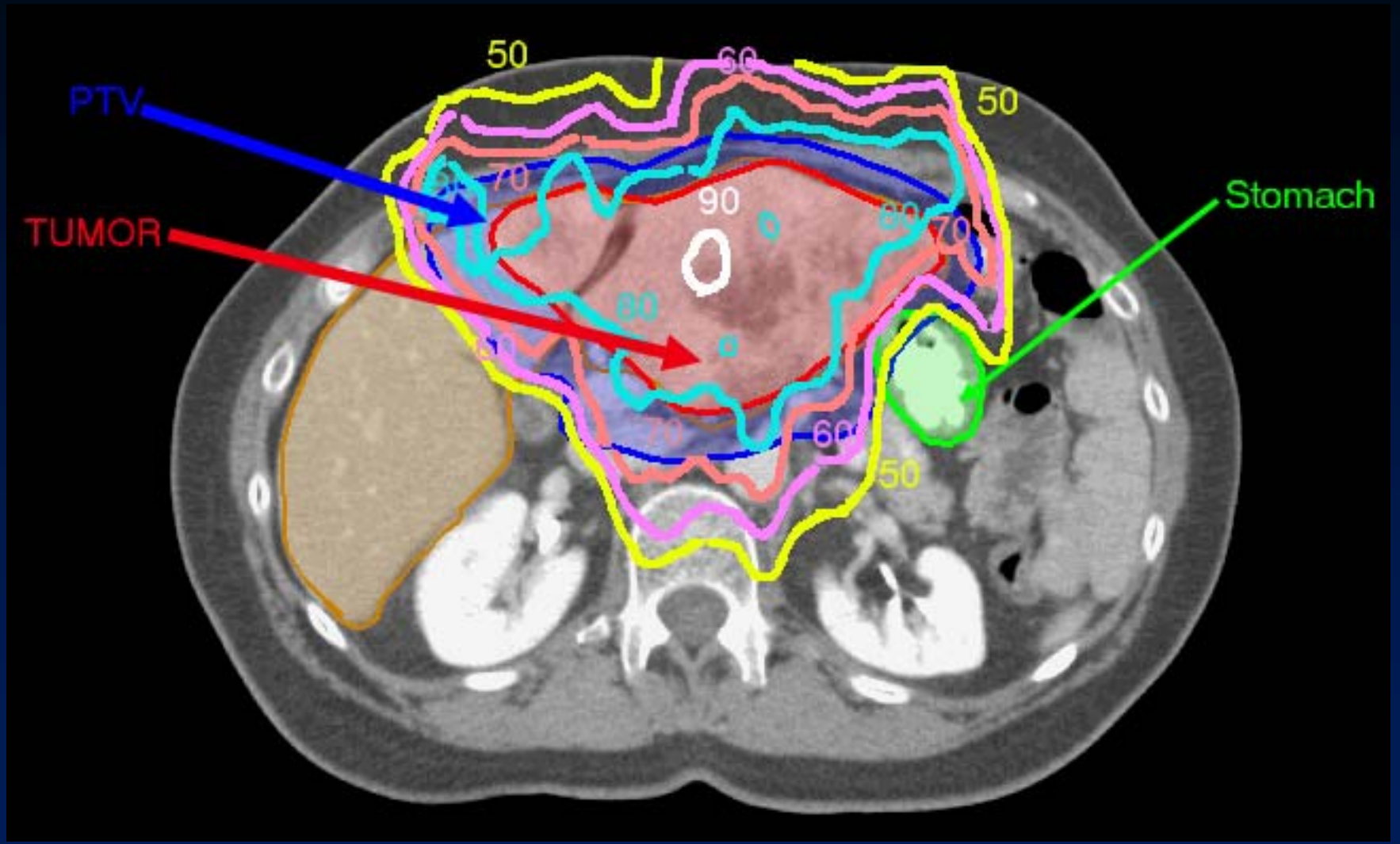
Use of models in optimization

- We explored IMRT optimization utilizing:
  - gEUD costlets for the PTVs to maximize anti-tumor effects,
  - NTCP costlets to maintain OAR doses within protocol limits.

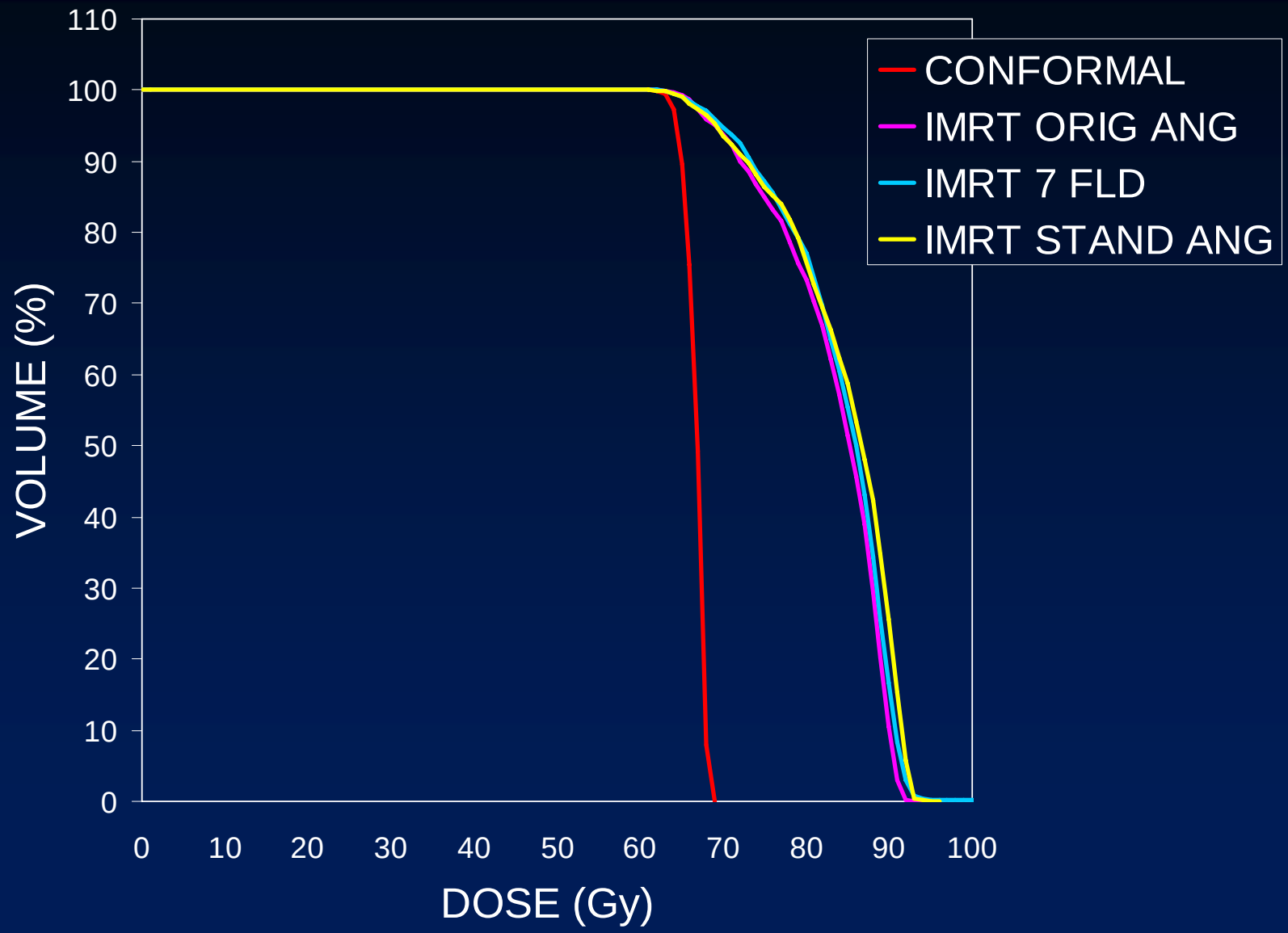
Thomas E, Chapet O, Kessler ML, Lawrence TS, Ten Haken RK: The benefit of using biological parameters (EUD and NTCP) in IMRT optimization for the treatment of intrahepatic tumors. Int J Radiat Oncol Biol Phys 62:571-578, 2005.

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.

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.

Implementation

- Issues related to implementing and using the biological models within optimization systems
- Short survey of existing software tools that utilize the biological models

General optimization problem

Objective Function

$$\min_{x \in \mathrm{R}^n} f(x)$$

Opt. Variables

$$\text{subject to} \begin{cases} c_i(x) = 0, & i \in \varepsilon, \\ c_i(x) \geq 0, & i \in I. \end{cases}$$

Constraints

IMRT Optimization problem

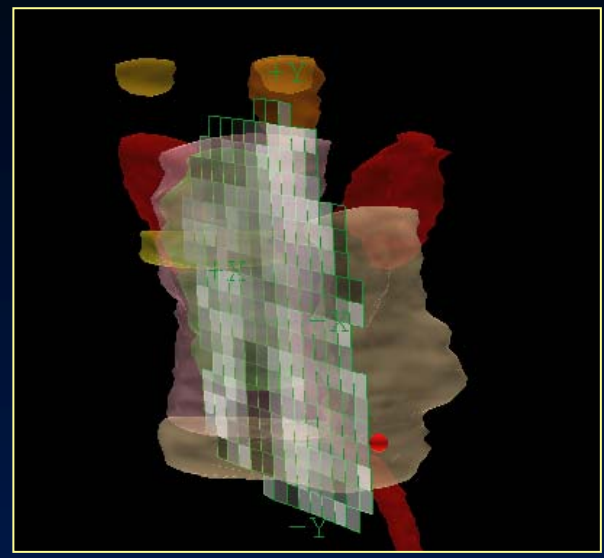
1. Beamlet intensities, x
   Opt. variables (100s ~ 1000s)

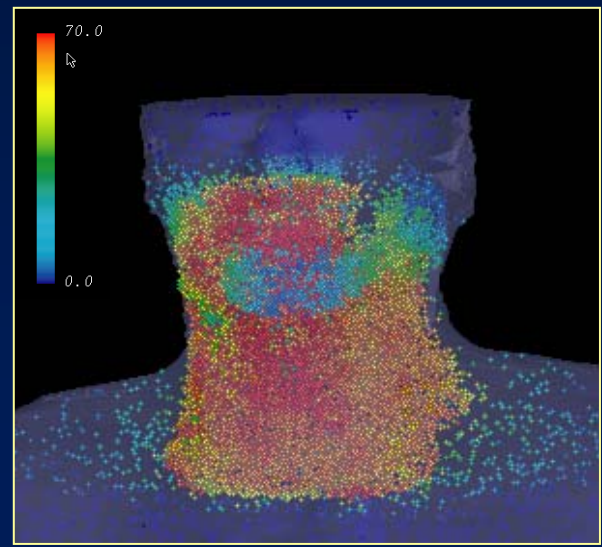
   ↓ Dose-to-Point calculations (Linear)

2. Dose distributions, $d_i(x)$

   ↓ Biological Models (Nonlinear)

3. Obj. & Constraint functions ,
   $f(d_i)$, $c(d_i)$





Example functions to minimize

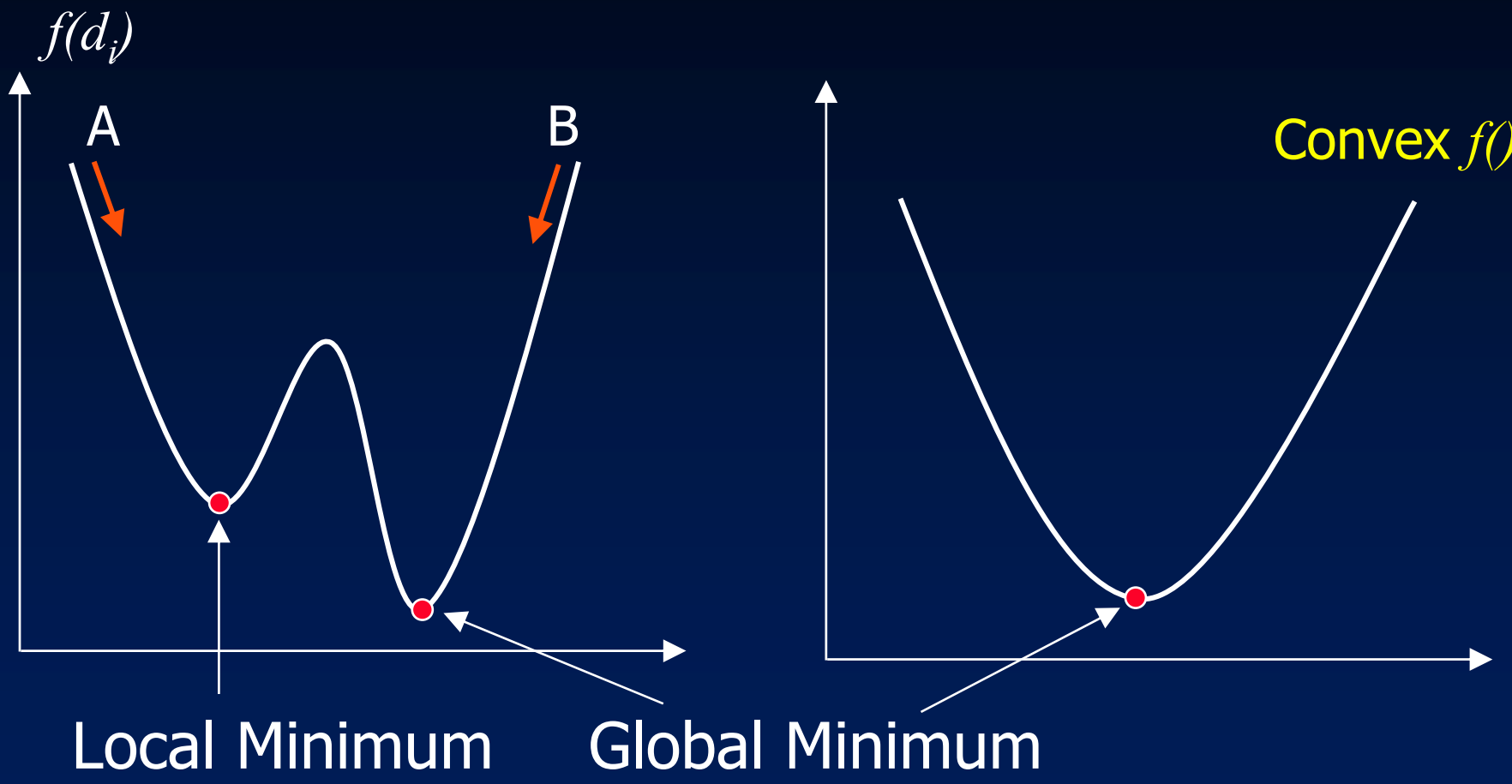
- Physical Dose

$$\sum_{i \in PTV} w_{PTV} (d_i - d_{PTV})^2 + \sum_{i \in \mathrm{OAR}} w_{PTV} (d_i - d_{OAR})^2 + \ldots$$

- Biological Models

$$\prod_{OAR} NTCP_{OAR} - TCP_{PTV}$$

Minima are not necessary
Global minimum.



Are biological models convex?

gEUD(d;a) concave $-\infty \le a \le 0$

convex $0 \le a \le \infty$

Choi B. and Deasy J. 2002 Phys. Med. Biol. ***47*** *3579-89*

EUD(d;α) concave $0 \le \alpha$

Romeijn H. 2004 Phys. Med. Biol. ***49*** *1991-2013*

NTCP-Lyman quasi-convex

Börgers C 1997 Proceedings of IMA Workshop

TCP-Possion locally concave at high dose regions

ln(TCP-Possion) strictly concave

Choi B. and Deasy J. 2002 Phys. Med. Biol. ***47*** *3579-89*

But a little can be said about the obj. function itself...

$$P_+ = TCP - \prod_i NTCP_i + \delta(1 - TCP)\prod_i NTCP_i$$

Brahme A. 1993 Med. Phys. ***20*** *1201-10*

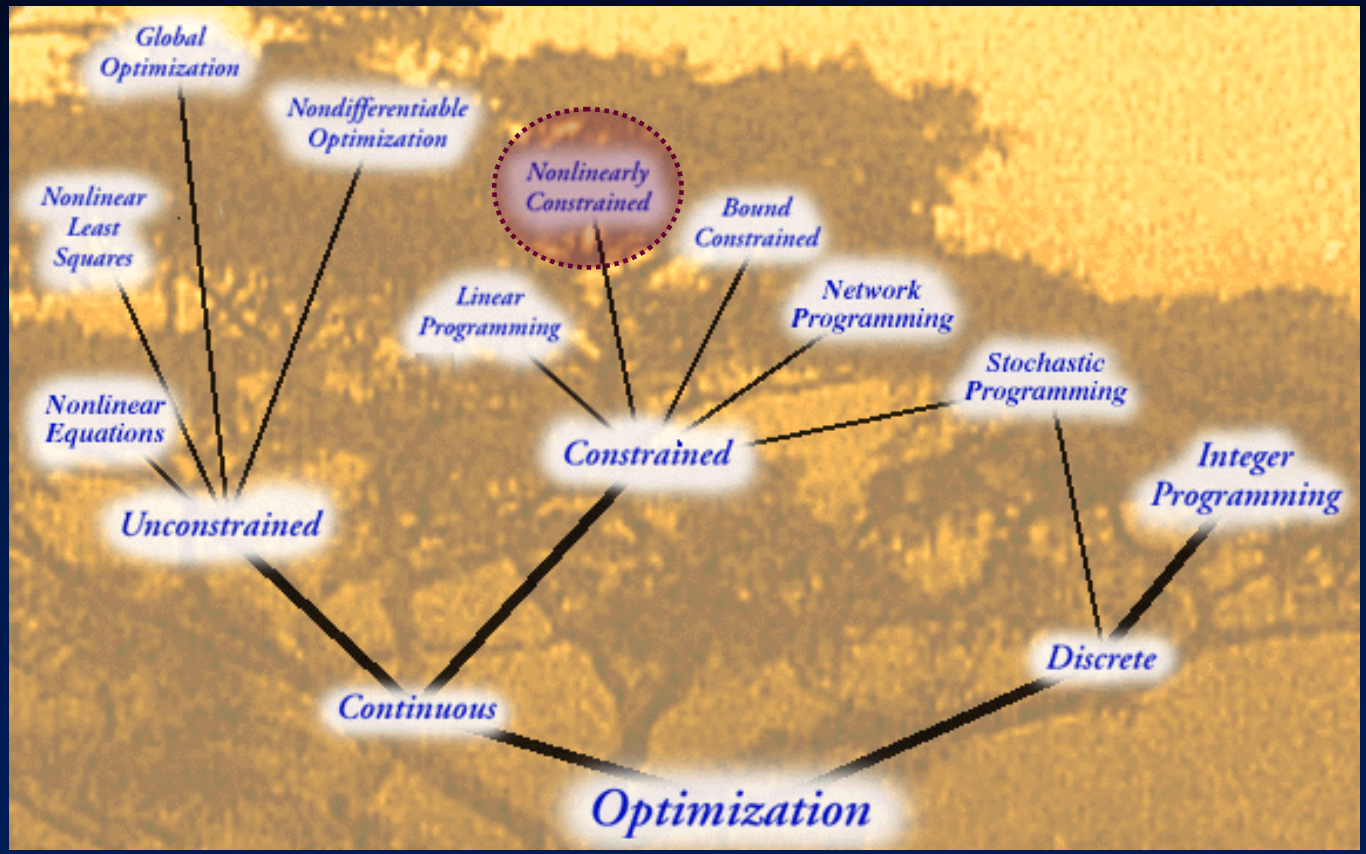
non-convex

$$f = \left[1 + \left(EUD_{t,0} \Big/ EUD_t\right)^n\right]^{-1} \prod_i \left[1 + \left(EUD_{OAR,i} \Big/ EUD_{OAR,0,i}\right)^n\right]^{-1}$$

Wu Q. 2002 Int. J. Rad. Onc. Biol. Phys. ***52*** *224-235*

non-convex

Most TPS solves nonlinearly constrained optimization problem



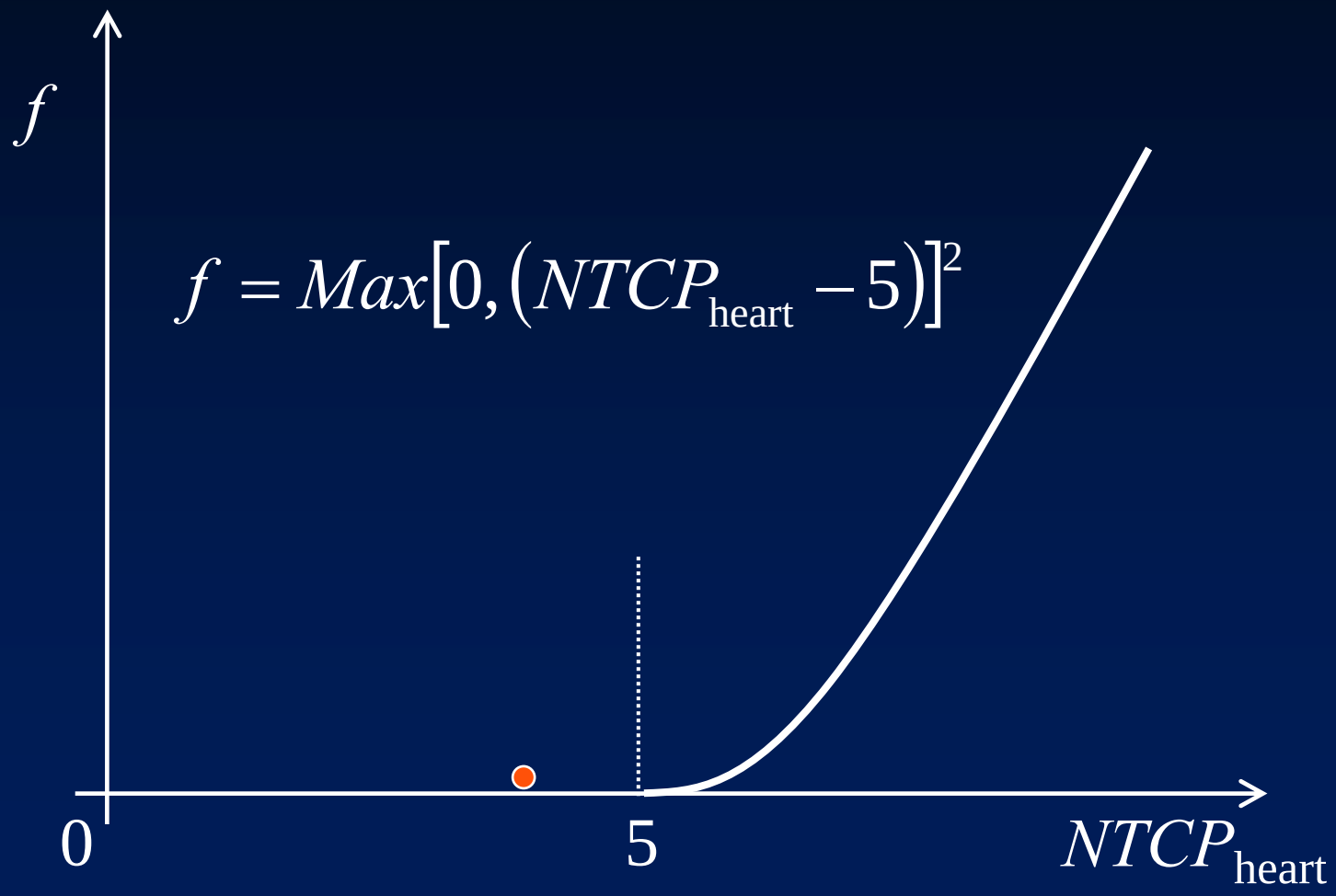
http://www-fp.mcs.anl.gov/otc/GUIDE/OptWeb/

What we do..
Preemptive NL-Goal programming

- Multicriteria optimization strategies based on soft-constraints with priority
- Solves a sequence of nonlinearly constrained optimization sub-problems (SQP)
- Maintains convexity at least locally...

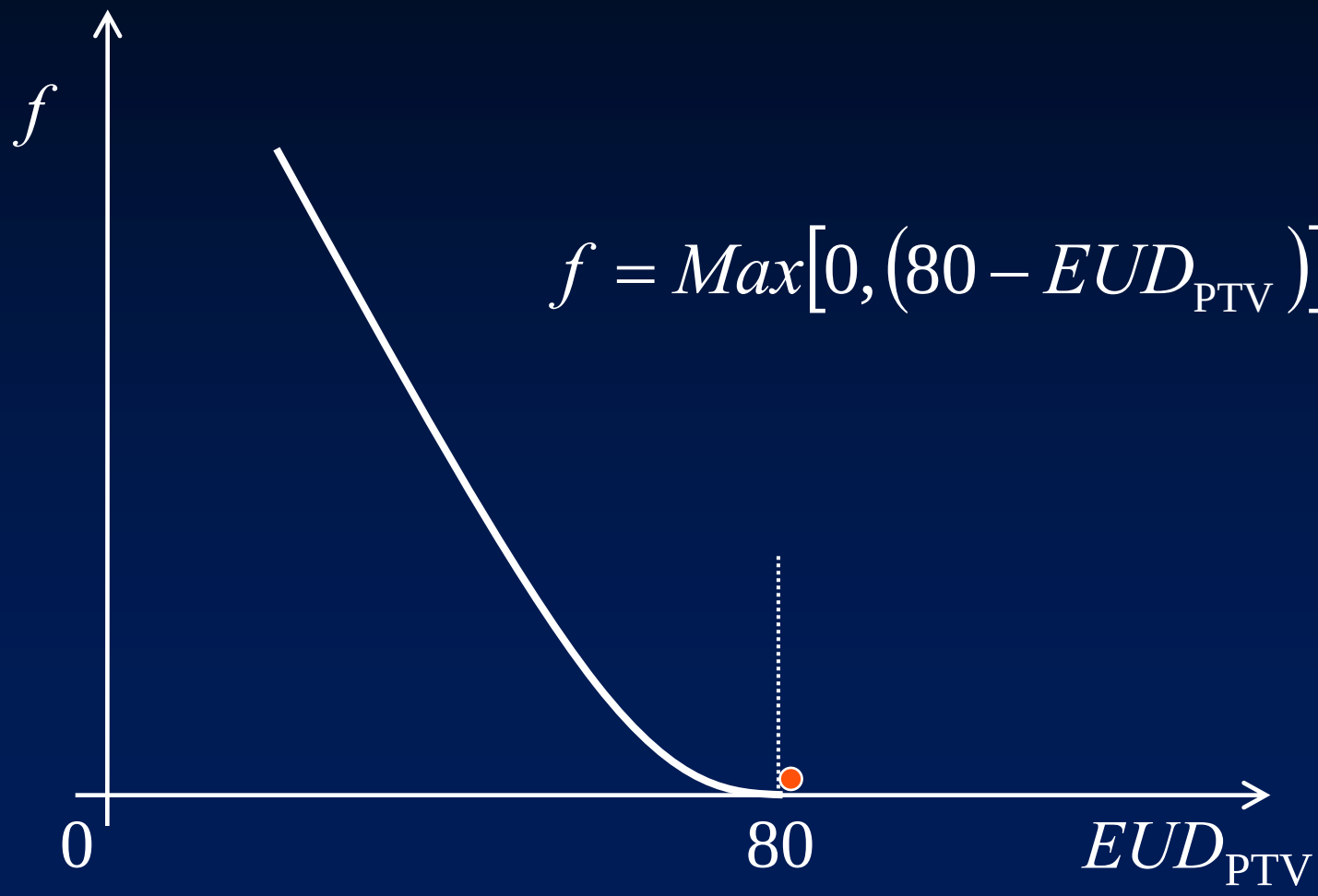
Soft-constraint example

Make the heart NTCP less than 5 %



Soft-constraint example

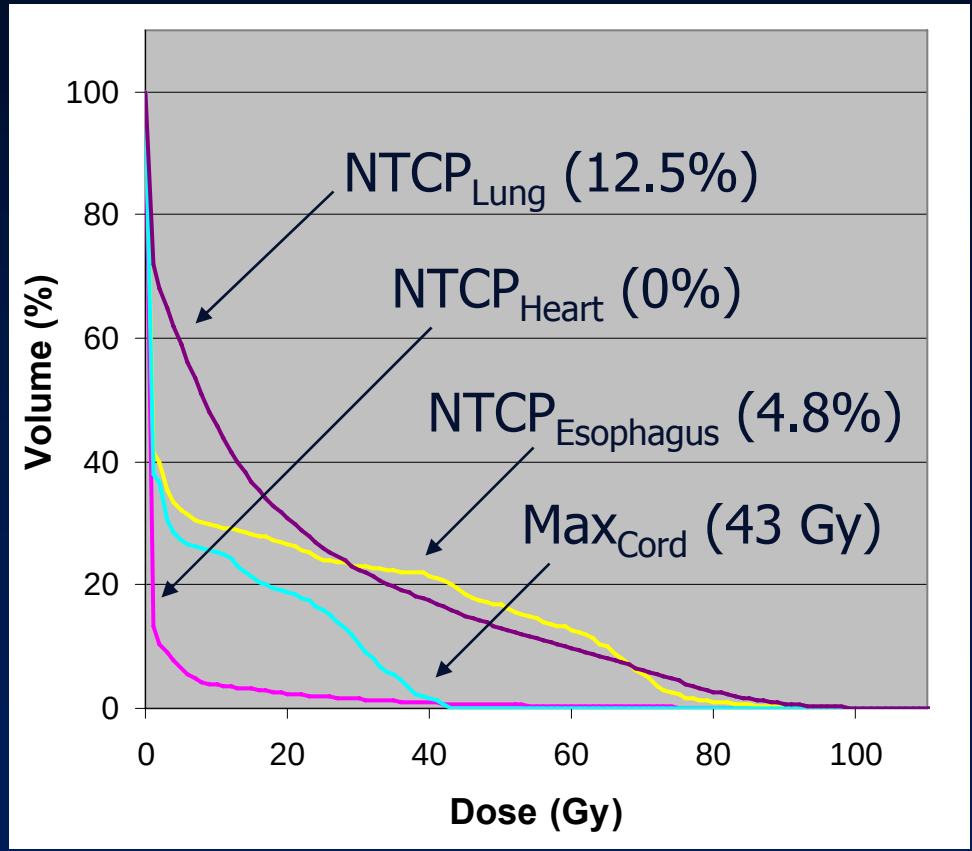
Make the PTV EUD greater than 80 Gy



$$f = Max\left[0, \left(80 - EUD_{\text{PTV}}\right)\right]^2$$

NSCLC Example
Priority 1: Protect Critical Tissues

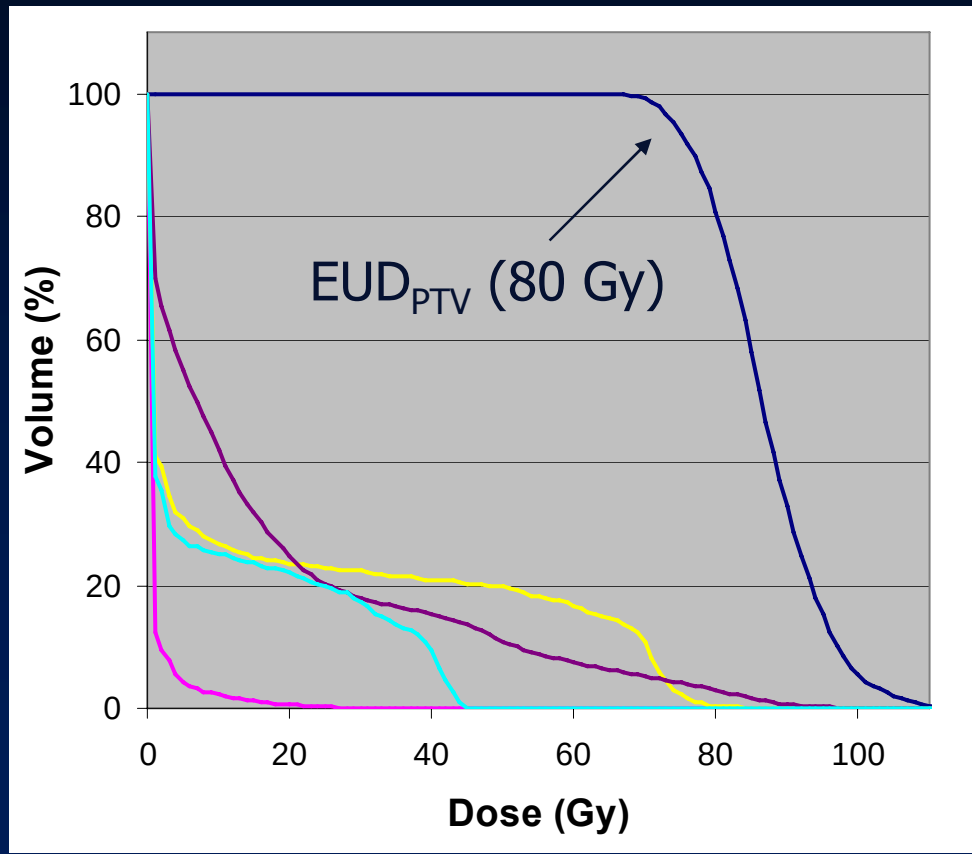
$NTCP_{Lung}$ < 15%
$NTCP_{Heart}$ < 5%
$NTCP_{Esophagus}$ < 5%
Max_{Cord} < 45 Gy



NSCLC Example
Priority 2: Achieve Target Dose

EUD_{PTV} > 80 Gy

$NTCP_{Lung}$ = 8.3%
$NTCP_{Heart}$ = 0%
$NTCP_{Esophagus}$ = 3.2%
Max_{Cord} = 44.3 Gy



Plan Evaluation Software

- Adelaide Bioeffect Planning System (Wigg D)
- Bioplan
  (Sanchez-Nieto B, Nahum A at Royal Marsden)
- TCP_NTCP_CALC module
  (Warkentin B, Fallone B at U of Alberta)
- Albireo
  (Wals A at Regional U. Carlos Haya Hospital)
- DREES (Naqa I, Deasy J at Washington U.)
- EUCLID (Gayou O, Mifften M at Drexel U.)

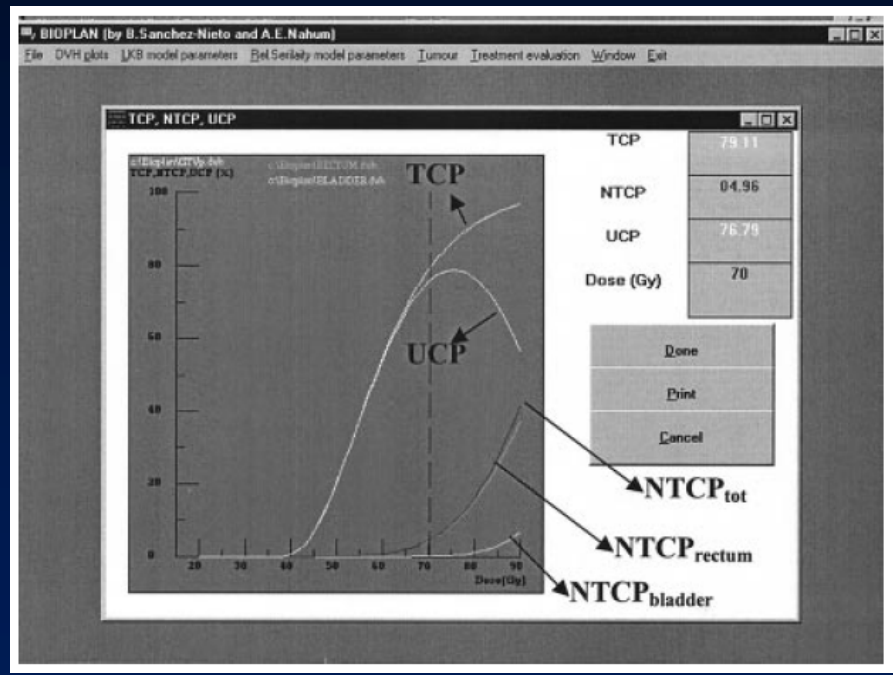
and probably more..

Bioplan
TCP_NTCP_CALC module
Albireo

Inputs:
formatted text or
TPS exported plans

Outputs:
fx size normalized dose,
Seriality, Critical Volume,
Poisson NTCP & TCP

Model parameter database

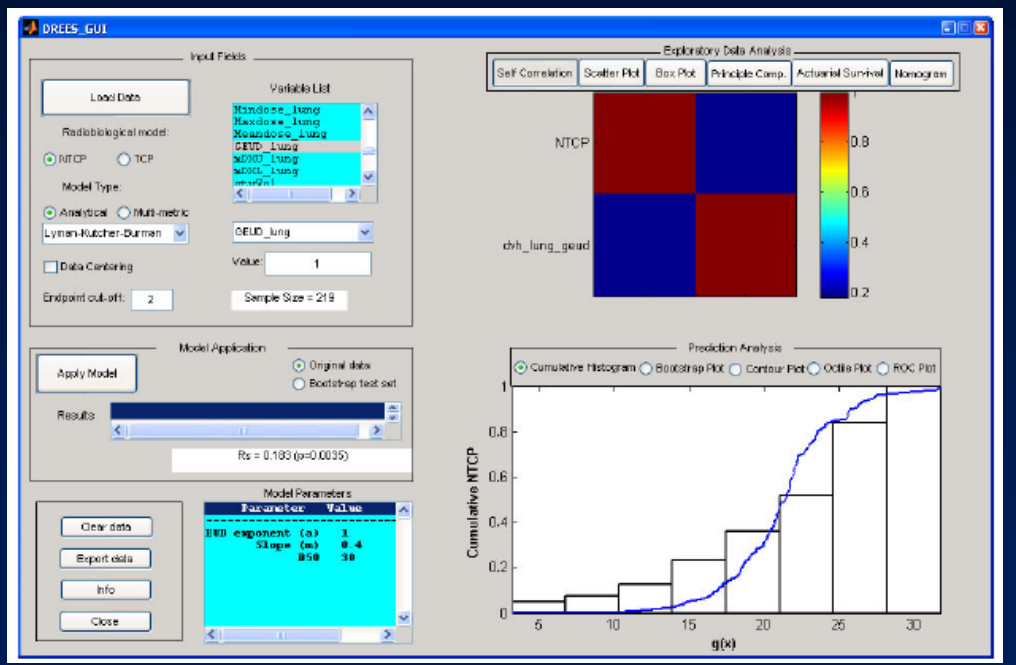


Sanchez-Nieto B. Medical Dosimetry, Vol. 25, No. 2, pp. 71–76, 2000

DREES, radium.wustl.edu/drees
EUCLID

Outcome Model Building Tools

- Multivariate regression
- Fitting to NTCP/TCP
- Uncertainty Estimation



Naqa I. Phys. Med. Biol. 51 (2006) 5719–5735

IMRT optimization conclusions

- It appears that the direct use of "outcome" cost functions for both target and normal tissues should allow:
  - significant *(i.e., multi-fraction)* increases in the calculated gEUD for the PTV,
  - in a much more intuitive (and efficient) manner than might be realized using multiple dose/volume based optimization sessions.