Normal Tissue Complication Probability Models

UC San Diego
RETHINKING MEDICAL PHYSICS

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Outline

- Dose-response and dose-volume response
- Accounting for volume effects, LKB
- Regional effects
- Selective sparing

NORMAL TISSUE RESPONSE

- Acute (early): inflammation, edema, denudation of mucosal surfaces
- Late: fibrosis, atrophy, ulceration, stricture, stenosis, obstruction

COMPLICATION SCORING

- Several systems
- Usually graded from 0 – none to 5 – death, although grade 5 complications are often omitted
- Grade 1 complications are mild and often do not require treatment
- Grade 2 or higher complications are clinically important

RTOG/EORTC TOXICITY CRITERIA: HEART

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Acute	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities, no evidence of other heart disease	Symptomatic with EKG changes and radiological findings of congestive heart failure or pericardial disease/no specific treatment required	Congestive heart failure, pericardial disease responding to therapy	Congestive heart failure, pericardial disease, arrhythmias not responsive to nonsurgical measures
Late	Asymptomatic or mild symptoms	Moderate angina on effort, mild pericarditis	Severe angina; pericardial effusion; constrictive pericarditis;	Tamponade/Severe heart failure/Severe constrictive pericarditis

CLINICALLY SIGNIFICANT TOXICITY

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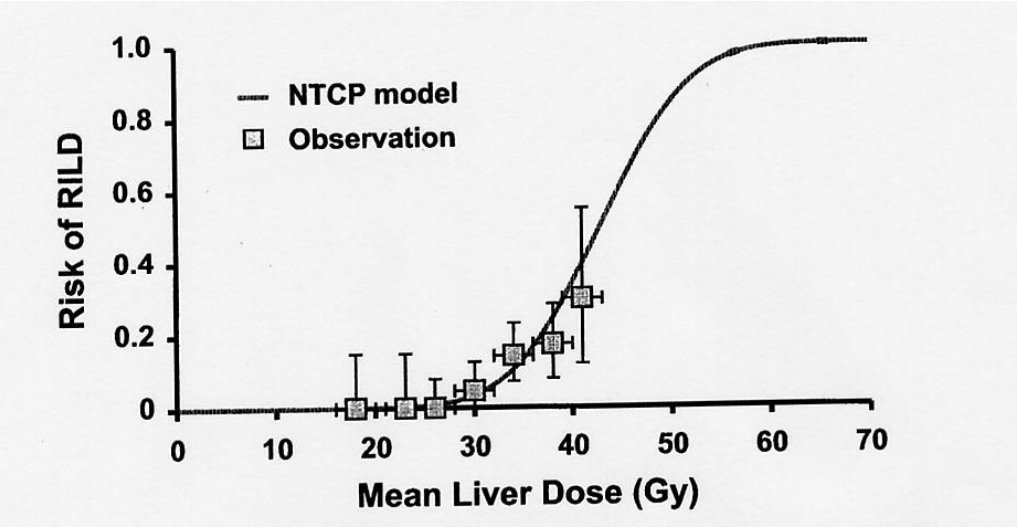
Late	Asymptomatic or mild symptoms	Moderate angina on effort, mild pericarditis	Severe angina; pericardial effusion; constrictive pericarditis;	Tamponade/Severe heart failure/Severe constrictive pericarditis

SIMPLE GOALS FOR NORMAL TISSUE SPARING



Mean liver dose associated with the predicted NTCP; no radiation-induced liver disease (RILD) for Mean Liver Dose ≤ 30 Gy. *Dawson et al, IJROBP 53,4:810, 2002*

Volume irradiated important for determining tissue tolerance

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	
Optic nerve / chiasm	Whole organ	3D-CRT	Optic neuropathy	Dmax <55	<3	Given the small size, 3D CRT is often whole organ‡‡
	Whole organ	3D-CRT	Optic neuropathy	Dmax 55–60	3–7	
	Whole organ	3D-CRT	Optic neuropathy	Dmax >60	>7-20	
	Whole organ	SRS (single fraction)	Optic neuropathy	Dmax <12	<10	
Spinal cord	Partial organ	3D-CRT	Myelopathy	Dmax = 50	0.2	Including full cord cross-section
	Partial organ	3D-CRT	Myelopathy	Dmax = 60	6	
	Partial organ	3D-CRT	Myelopathy	Dmax = 69	50	

Fig. A17. Complication probability vs. dose for the lung.

Fig. A26. Complication probability vs. dose for the spinal cord.

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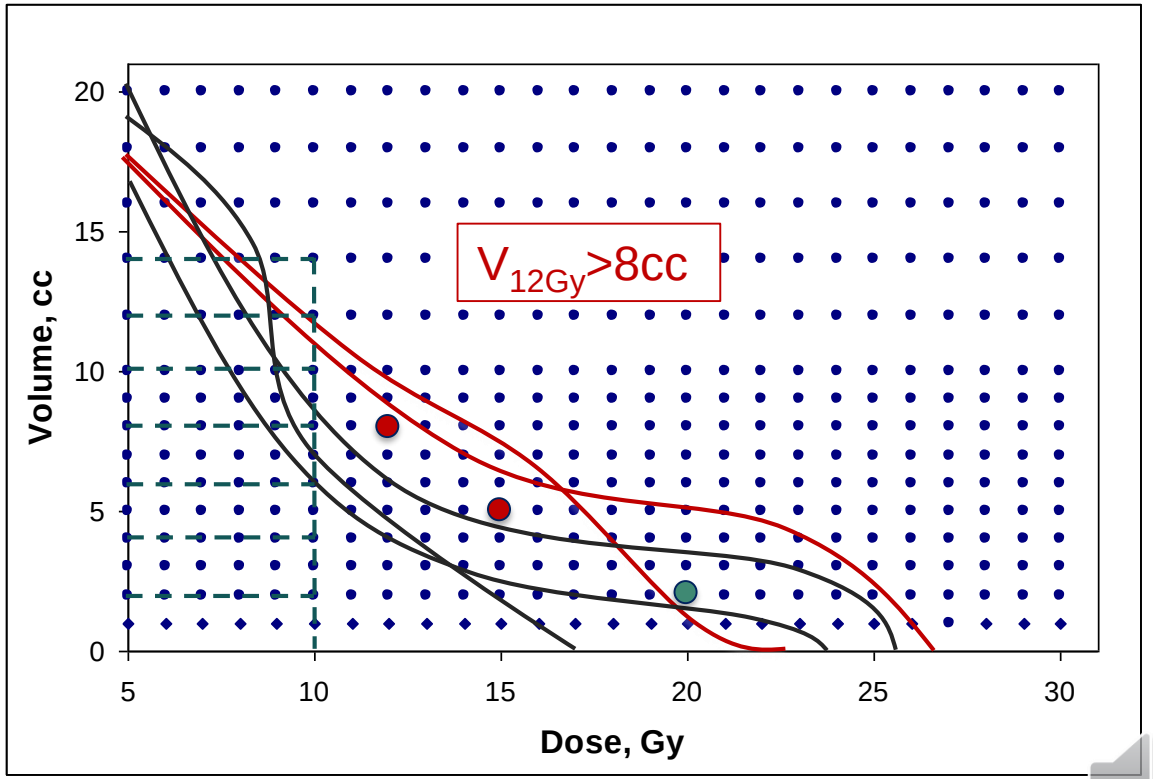
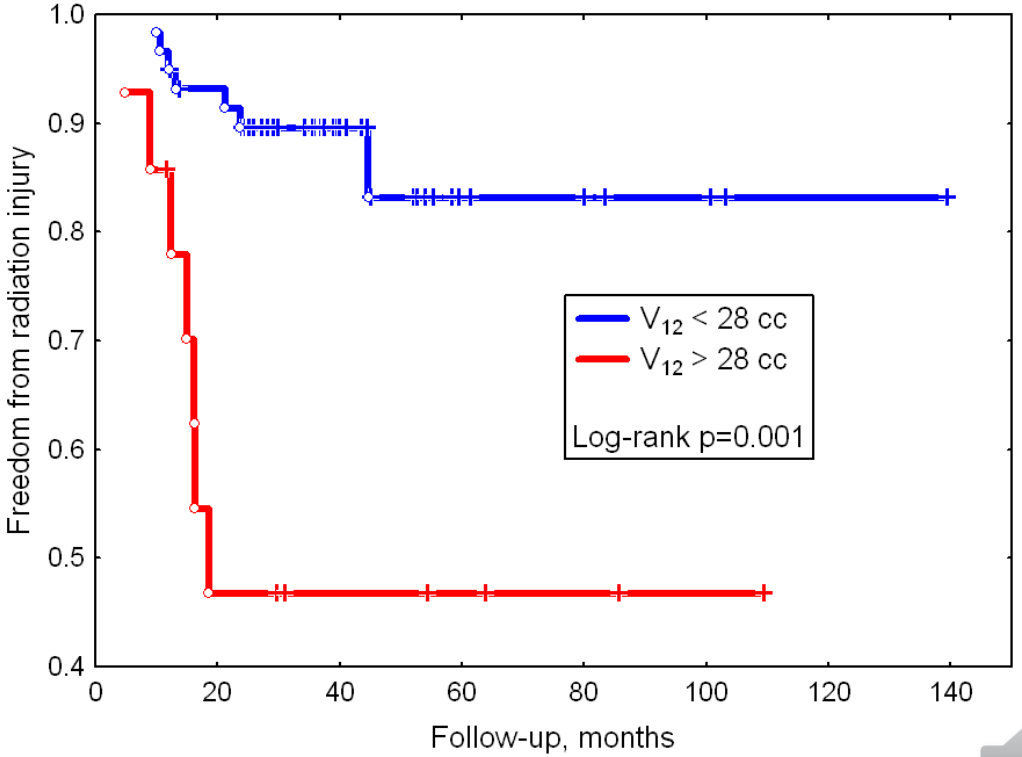
V_x (or D_x) cut-off approach

- Does median V_x separate patients into groups different in incidence?
- Can we find a V_x which separates patients into likely and unlikely to develop complications with the most predictive power?
- This separates patients into groups, does not always tell us if risk is acceptable
- Need incidence-V_x data



V_x – which cut-off is the chosen one?

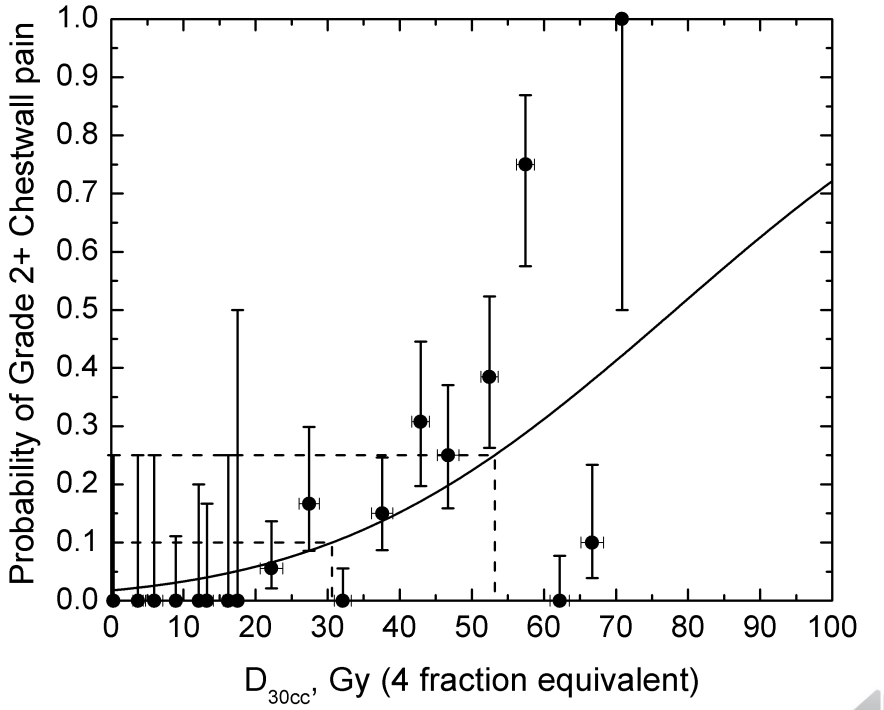
- Multiple tests
- Balance of evidence
- Maximum predictive power
- Can be transferred to other data sets, e.g., training vs test?



V_x – incidence approach

- Logistic or probit
  - Level of acceptable risk can be set
  - Recommendations for dose-volume constraints can be made

Kimsey et al 2016



Volume effects

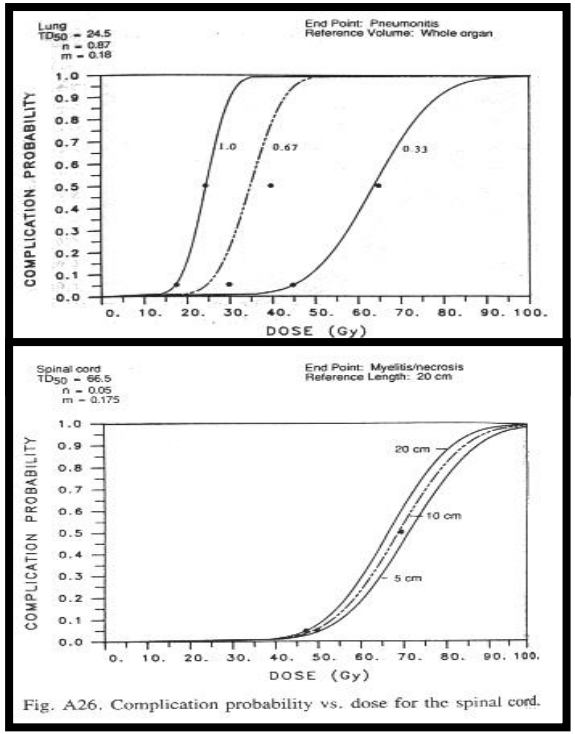
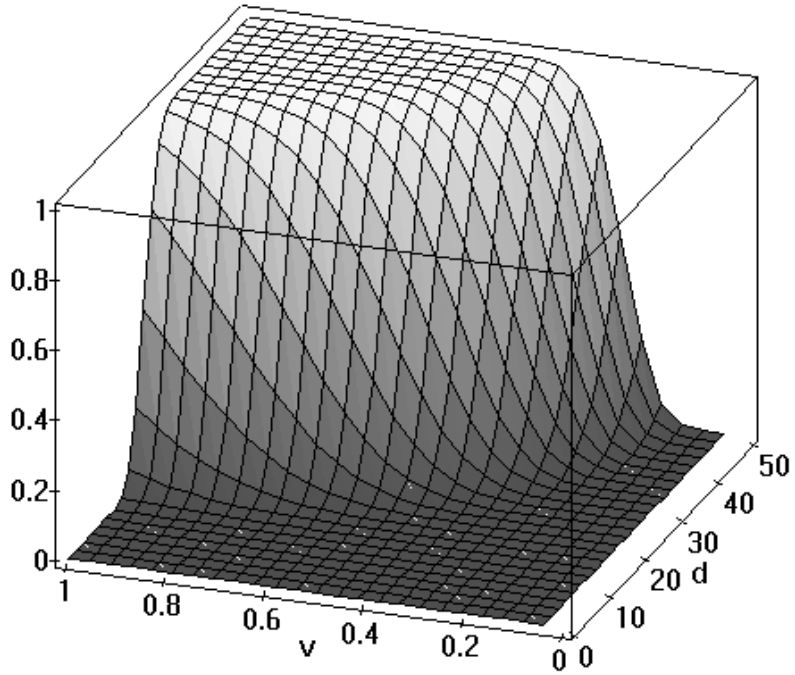
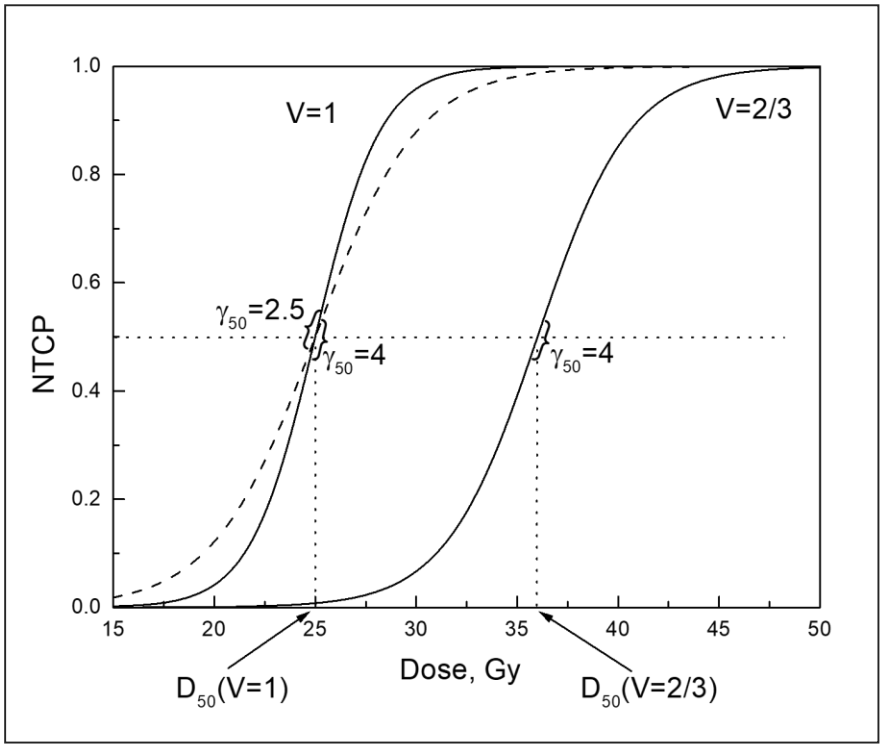


Fig. A26. Complication probability vs. dose for the spinal cord.



Emami et al 1991 & Burman et al 1991

GENERIC NTCP DOSE DEPENDENCE



- Characterized by D_{50} and γ_{50}
- $\gamma 50 = D50 \partial P(D)/\partial D$ – normalized slope
- γ_{50} for normal tissue response in humans is 2-4

POWER LAW FOR TOLERANCE DOSES

$$D_V = \frac{D_1}{V^n}$$

- D_V is the tolerance dose (TD) for the volume (or area, or length) of interest; D_1=TD for whole (reference) volume
- *n* is the exponent which is determined specifically for the tissue of interest
- *n* describes the strength of volume dependence
- *n*≈1 iso-effective tolerance dose depends on irradiated volume substantially, parallel organ or very little (*n* approaches zero), serial organ

POWER LAW FOR TOLERANCE DOSES

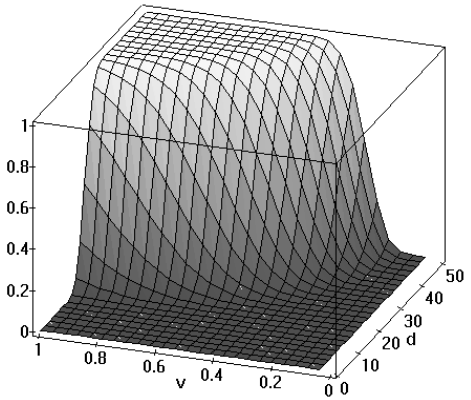
OAR	D_{50}, Gy		$D_V = D_1 / V^n$
	V=1	V=1/3	
Esophagus	68	72	Serial, weak volume dependence, n→0
Lung	24.5	65	Parallel, strong volume dependence, n→1

POWER-LAW BASED DVH REDUCTION

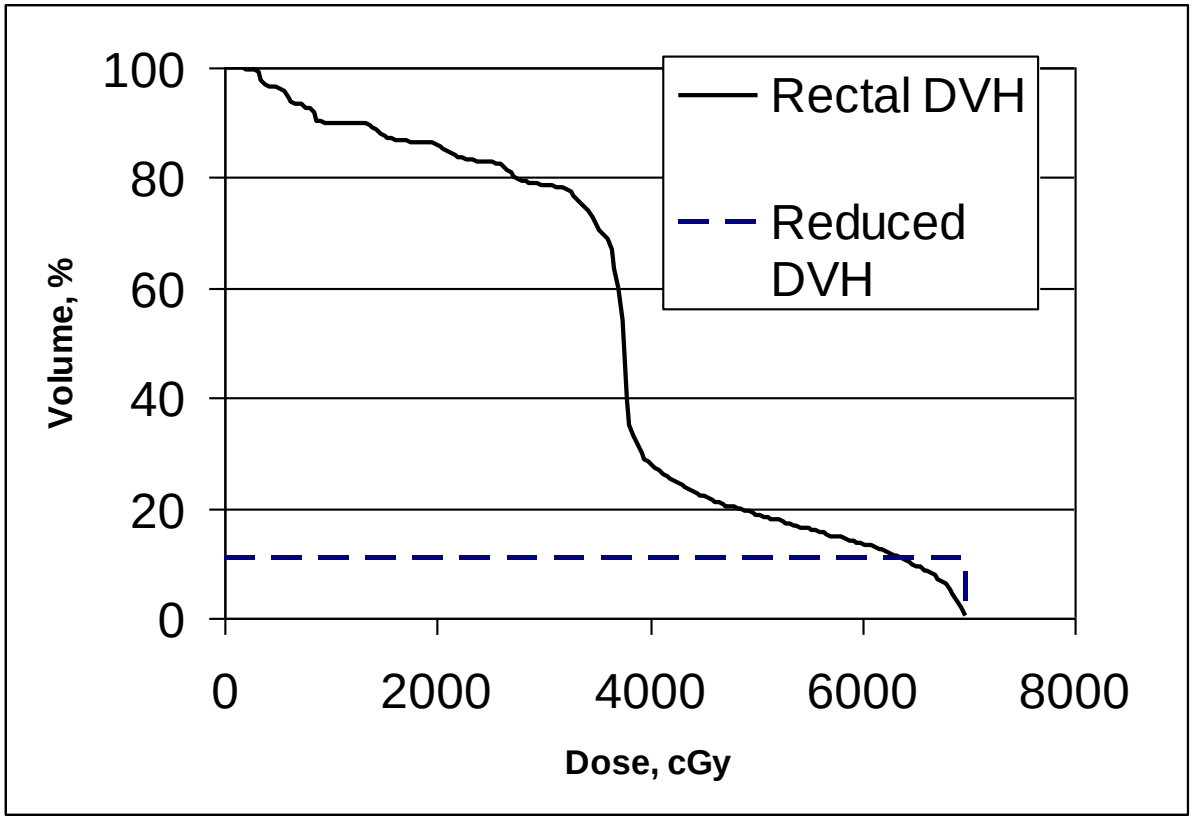
- Based on isoeffect formalism
- Effective volume - reference dose (e.g., prescribed dose or max dose) in DVH uniformly delivered to effective volume
- Effective dose – isoeffective dose uniformly delivered to whole volume

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

$$\sum v_i = 1$$



POWER-LAW BASED DVH REDUCTION

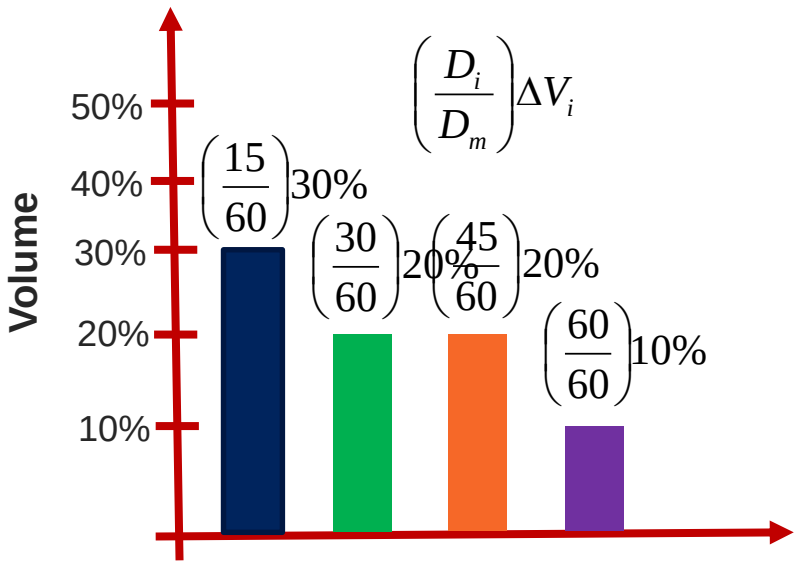


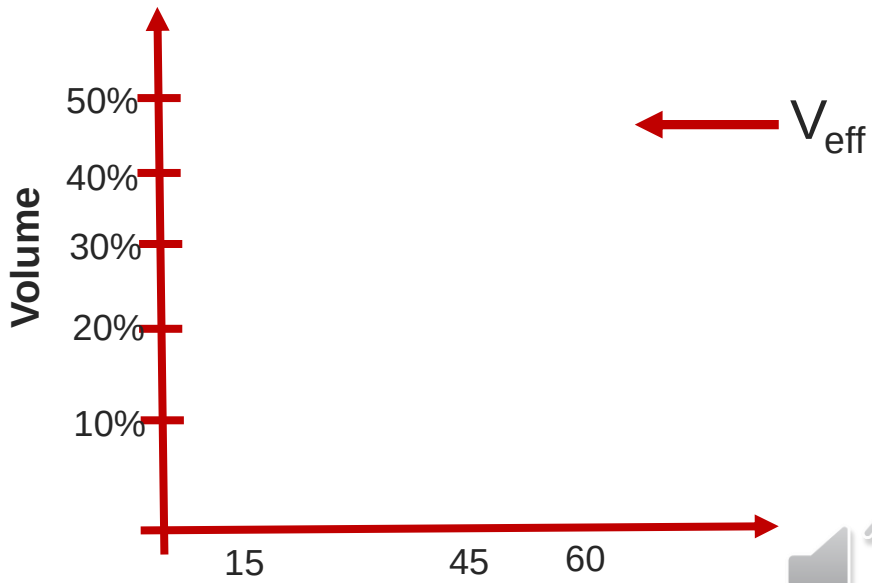
Calculation of V_{eff}

$$V_{eff} = \sum \left(\frac{D_i}{D_m} \right)^{1/n} \Delta V_i$$

n=1, for simplicity
D_m= Rx

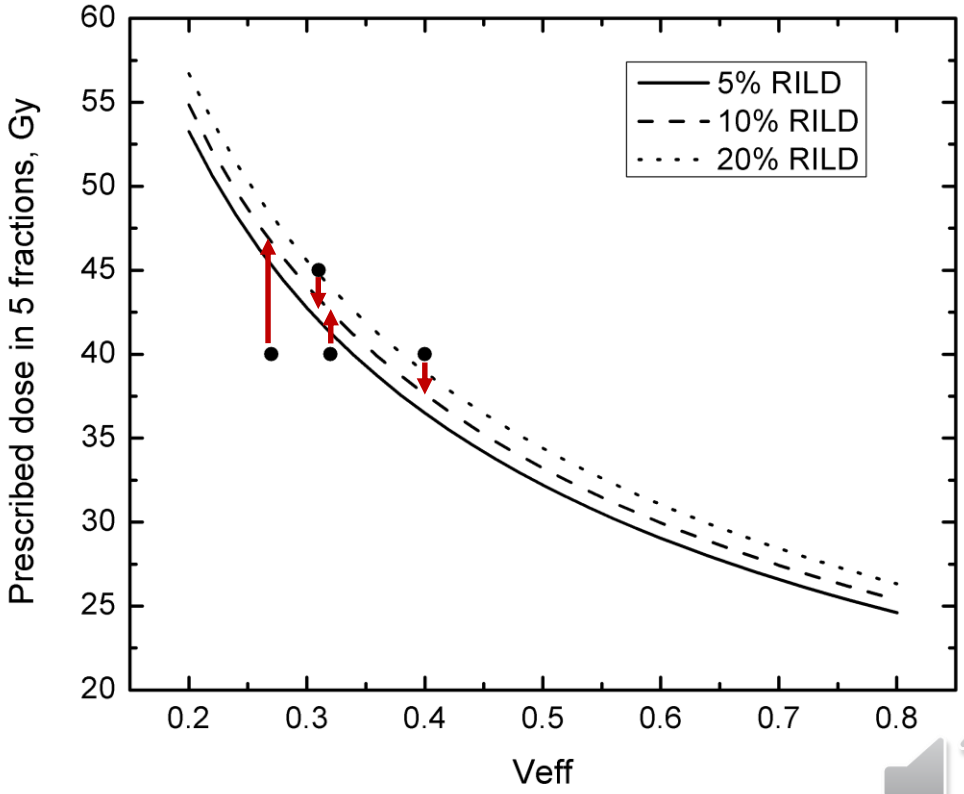
DVH:
20%=0 Gy
30%=15 Gy
20%=30 Gy
20%=45 Gy
10%=60 Gy





Choice of prescribed dose, V_{eff} approach

Primary Liver Cancer: Dose per fraction (Gy)					
Level	level 1	level 2	level 3	level 4	level 5
Max dose (Gy)	9.0	9.0	9.0	9.5	10
NTCP	0.05	0.10	0.20	*0.20**	*0.20**
Veff					
<0.16	9.0	9.0	9.0	*9.5*	*10.0*
0.18	9.0	9.0	9.0	*9.5*	*10.0*
0.20	8.8	9.0	9.0	*9.5*	*9.5*
0.22	8.4	8.7	9.0	*9.0*	*9.0*
0.24	8.0	8.2	8.5	*8.5*	*8.5*
0.26	7.6	7.9	8.1	*8.1*	*8.1*
0.28	7.3	7.5	7.8	*7.8*	*7.8*
0.30	7.0	7.3	7.4	*7.4*	*7.4*
0.32	6.7	7.0	7.3	*7.3*	*7.3*
0.34	6.6	6.7	7.0	*7.0*	*7.0*
0.36	6.4	6.6	6.7	*6.7*	*6.7*
0.38	6.2	6.4	6.6	*6.6*	*6.6*
0.40	6.0	6.2	6.4	*6.4*	*6.4*



Lyman-Kutcher-Burman (LKB) MODEL

Three parameters:

$D_{50}(1)$ – whole organ dose to cause 50% of patients having complications

n – volume effect

m - slope

$$NTCP(V,D) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(-u^2/2) \cdot du$$

$$t = [D - D_{50}(V)] / \sigma(V)$$

$$D_{50}(V) = D_{50}(1)/(V)^{n}$$

$$\sigma(V) = mD_{50}(V)$$

LKB MODEL

In actual calculations take advantage of error function available in most applications (MS Excel)

$$NTCP(V,D) = 0.5 + 0.5erf\,(r)$$

$$erf\,(r) = \frac{2}{\sqrt{\pi}} \int_0^r e^{-x^2} dx \qquad r = t/\sqrt{2}$$

$$\gamma_{50} = \frac{1}{m\sqrt{2\pi}}$$

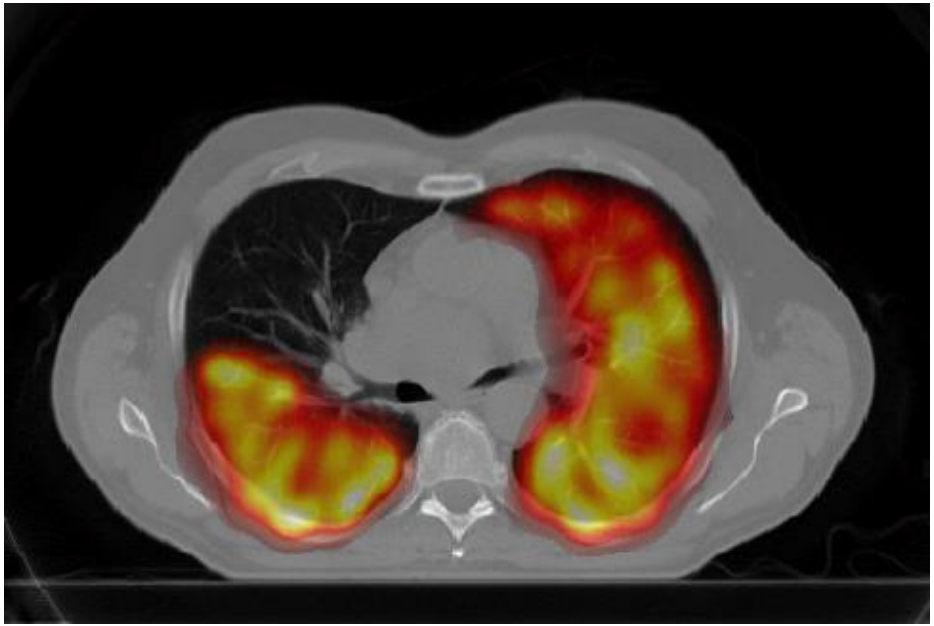
Other models

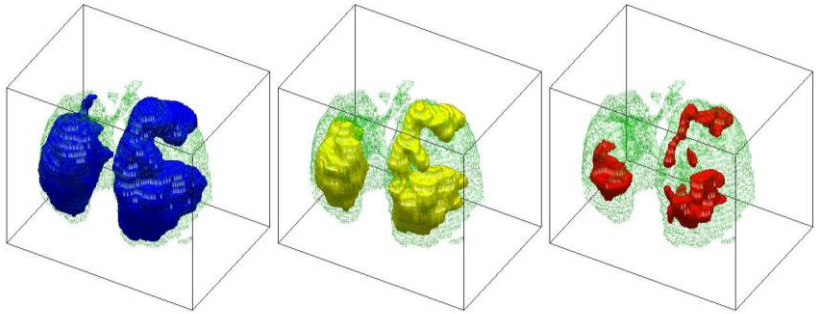
- Critical elements, primarily for serial organs
- Poisson model (k-model and s-model), s-model explicitly accounts for organ seriality
- Parallel model, converts “local damage” into a metric to estimate overall probability of complications

Does geometry matter?

- Function not uniformly distributed
- Rescue units (stem cells) not uniformly distributed
- Radiosensitivity not uniform

Lung perfusion - SPECT

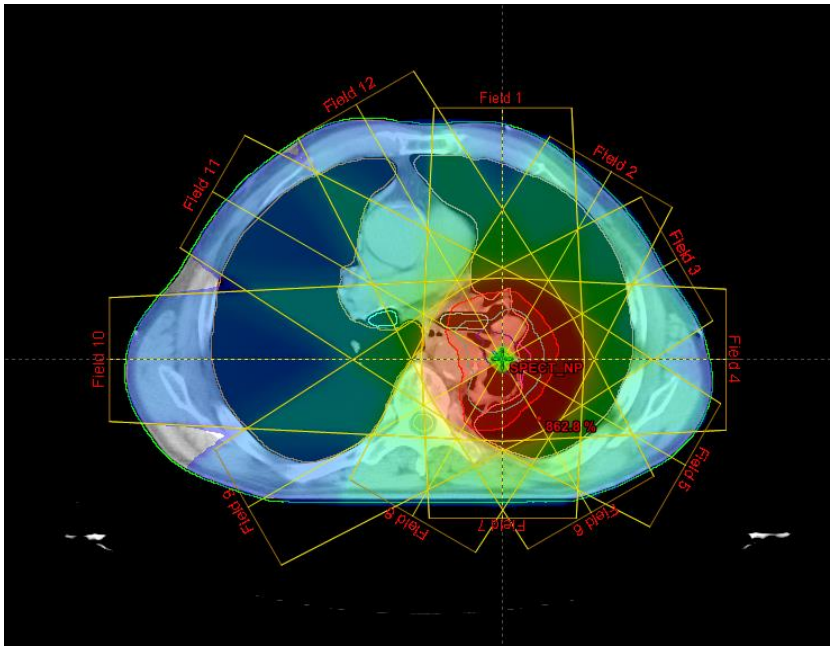




Approach 1 – define a new structure, “functional lung”, develop constraints for this structure

Slide: L.Yin

Lung perfusion - SPECT



Approach 2 – SPECT-weighted mean dose for normal lung

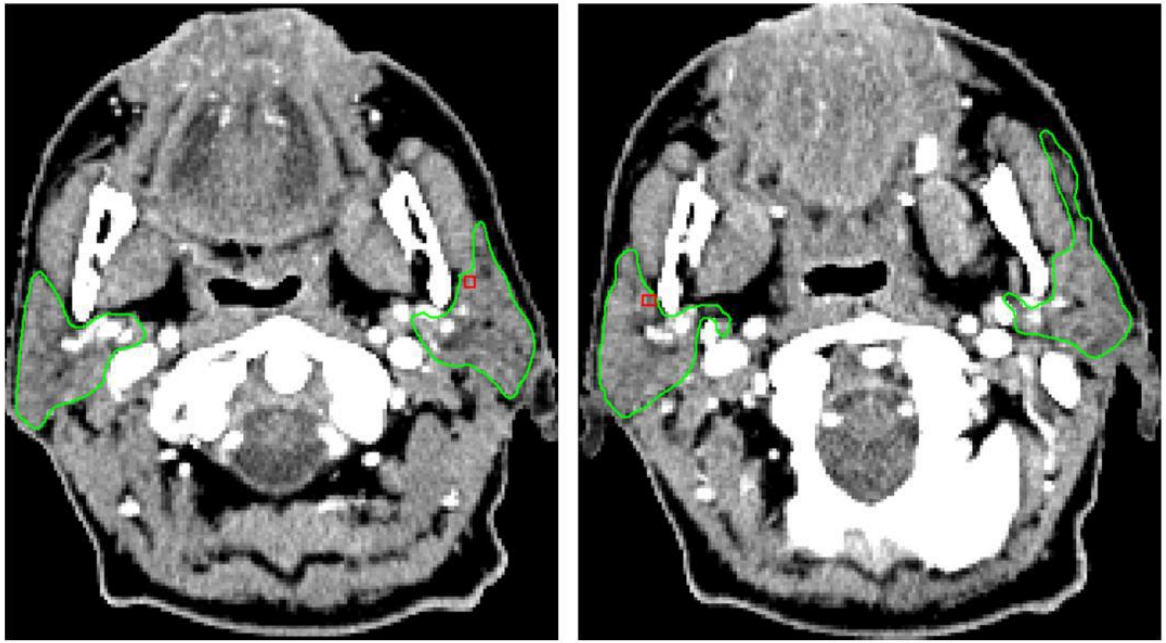
Dose to each voxel, v_i, is assigned "weight" according to how much function it carries, f_i

Function-weighted mean dose, FWMD:

$$FWMD = \frac{\sum v_i D_i f_i}{\sum f_i}$$

$$\sum v_i = 1$$

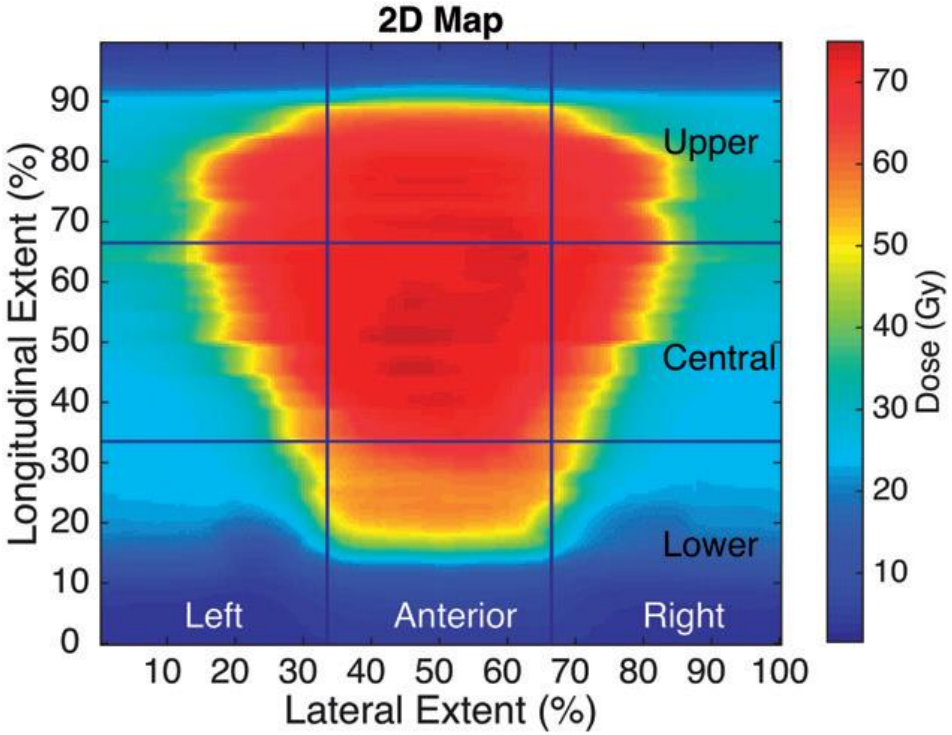
Can simple geometry help?



Critical regions identified and shown to contain stem cells

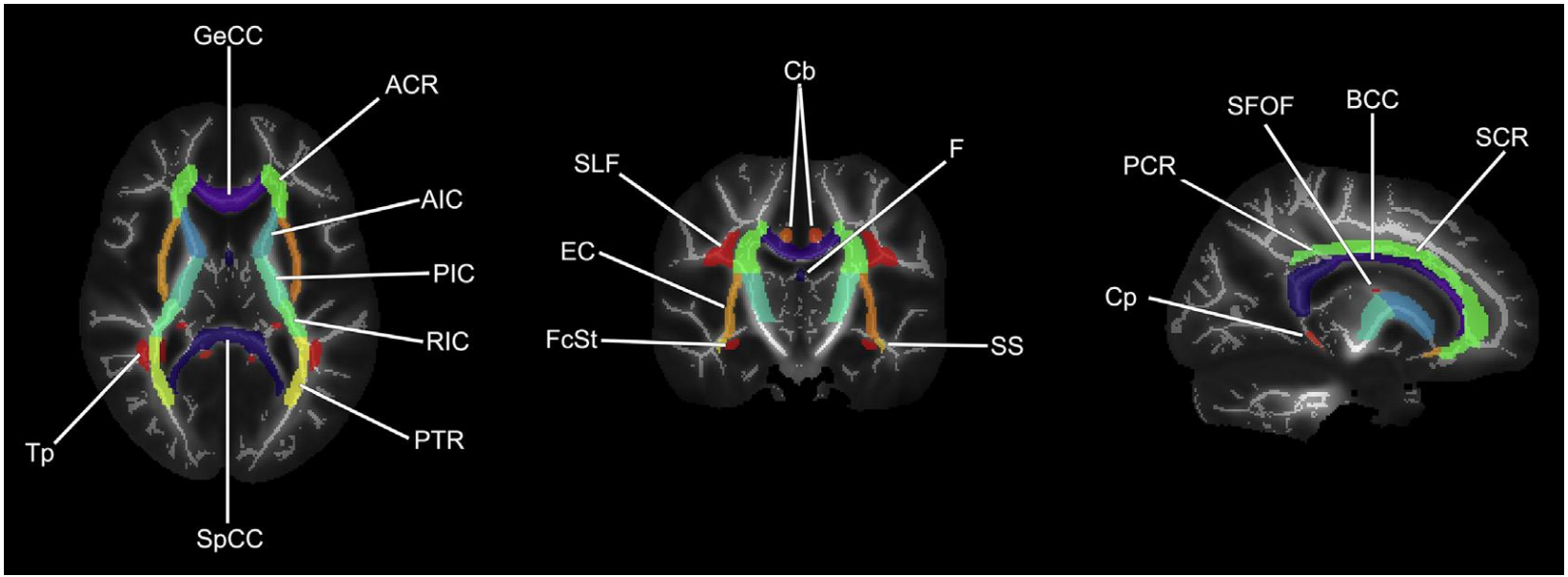
Van Luijk et al. 2015

Rectal toxicity: can we identify regions that matter?



- Subsegment
- Test for correlation with toxicity
- Search for mechanistic explanation

Brain: white matter tracts



Optimization on brain as whole may not reduce risk of particular complication

Connor et al. 2017

Brain: white matter tracts

- Follow-up for toxicity (cognitive function)
- Connect to dose-volume in specific tracts
- Develop planning goals to specifically spare bran regions

- Can DTI help? DO changes in MD and FA correlate with changes in cognitive function?

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