Predicting Normal Tissue Injury in the Modern era: An Update on QUANTEC

Lawrence B. Marks, M.D.

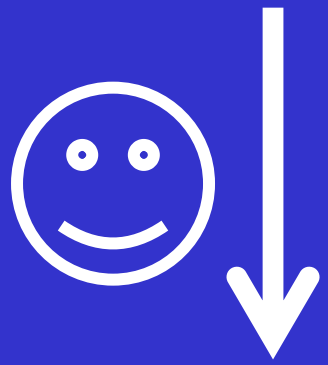
Professor and Chair

University of North Carolina at Chapel Hill, NC



“3D Hope”

Dose/volume



Normal tissue outcome

"3D Hope"

Dose/volume →



Normal tissue outcome →

"Reality"

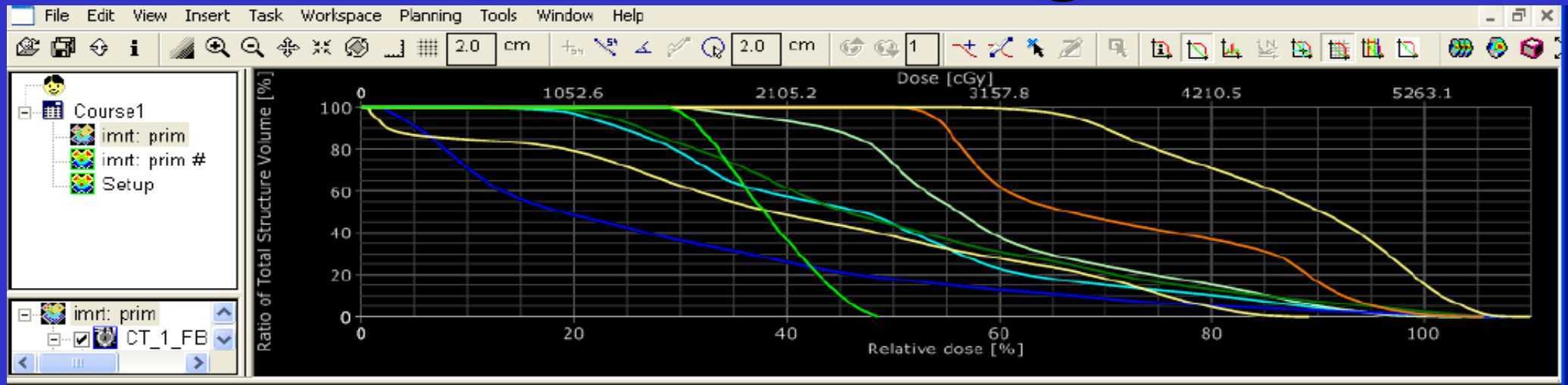
Information Overload.
Which parameters?
DVH limitations

Patient/tumor factors

Which endpoints?

Applicability? Evolving therapies, BID, SRS, IMRT, Fx size

No wonder we crave models, figures of metric



Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Photon Calculation | Electron Calculation | P

View	DVH Line	Structure	Plan	Course	Volume [cm³]	Dose Cover....	Sampling C...	Min Dose [%]	Max Dose [%]	Mean Dose [...
☐		CTV 50	imrt: prim	Course1						
☐		CTV Low Risk	imrt: prim	Course1						
☐		Cord	imrt: prim	Course1						
☐		Esophagus	imrt: prim	Course1						
☐		Gut	imrt: prim	Course1						
☑		Heart	imrt: prim	Course1	882.7	100.0	100.0	9.9	106.7	47.9
☑		LV	imrt: prim	Course1	299.1	100.0	100.0	27.1	103.5	59.9
☐		Liver	imrt: prim	Course1						
☐		Lt Kidney	imrt: prim	Course1						
☑		Lt Lung	imrt: prim	Course1	1284.6	100.0	100.0	7.7	107.8	51.1
☑		Lungs	imrt: prim	Course1	3337.1	100.0	100.0	0.6	107.8	28.1
☑		PTV 42	imrt: prim	Course1	237.4	100.0	100.1	48.4	105.6	71.6
☑		PTV 50	imrt: prim	Course1	1328.7	100.0	100.0	51.9	110.0	87.7
☐		Thyroid	imrt: prim	Course1						
☑		cord+10mm	imrt: prim	Course1	263.4	100.0	99.9	0.4	89.3	41.0
☐		ctv42	imrt: prim	Course1						
☑		seg1	imrt: prim	Course1	0.3	100.0	99.8	28.6	48.7	38.2

Ready | jlh57 | Physicist | NUM

- **Help is on the way: QUANTEC**

QUANTEC: QUAntitative Normal Tissue Effects in the Clinic

Summarize Dose/Volume/Outcome data

Both AAPM and ASTRO recognized ($$)

Clinical need for updated data: 3D, and IMRT treatment planning and optimization (update Emami)

History of QUANTEC

2006 AAPM Science Council: Ellen Yorke, Rock Mackie
Steering Committee: Deasy, Bentzen, Yorke, Ten-Haken, Jackson, Marks, Eisbruch, Constine, Morris

2007 1st QUANTEC meeting: Madison Wisconsin
Initial review of tolerances: physicists, statisticians and physicians.

2008-9 Special Issue of Red Journal: in preparation

Organ specific QUANTEC articles

- Significance
- Clinically relevant endpoints
- Anatomic definitions
  - Segmentation challenges
- **Systematic review of literature dose/volume/outcome**
- Patient-related risk factors
- Data modeling
- Model caveats
- **Recommended Dose-volume constraints and models**
- Future studies
- Recommended toxicity scoring system

Organs Included

- Brain, Brainstem, Optic Structures, Ear, Cord (Merchant)
- Salivary Glands, Larynx & Pharynx (Eisbruch)
- Lung , Heart, Esophagus (Marks)
- Liver, Kidney, Bowel (Kavanagh)
- Rectum, Bladder, Penile Bulb (Michalski)
- Data available variable, systematic

Organs Included

- Brain: Yaakov Lawrence
- Brainstem: Charles Mayo
- Optic Nerve: Charles Mayo
- Ear: Niranjan Bhandare
- Cord: John Kirkpatrick
- Salivary Glands: Joe Deasy
- Larynx/Pharynx: Avi Eisbruch
- Lung: Larry Marks
- Heart: Giovanna Gagliardi
- Esophagus: Maria Werner-Wasik
- Liver: Charlie Pan
- Kidney: Laura Dawson
- Bowel: Charlie Pan
- Rectum: Jeff Michalski
- Bladder: Akila Viswanathan
- Penile Bulb: Mack Roach

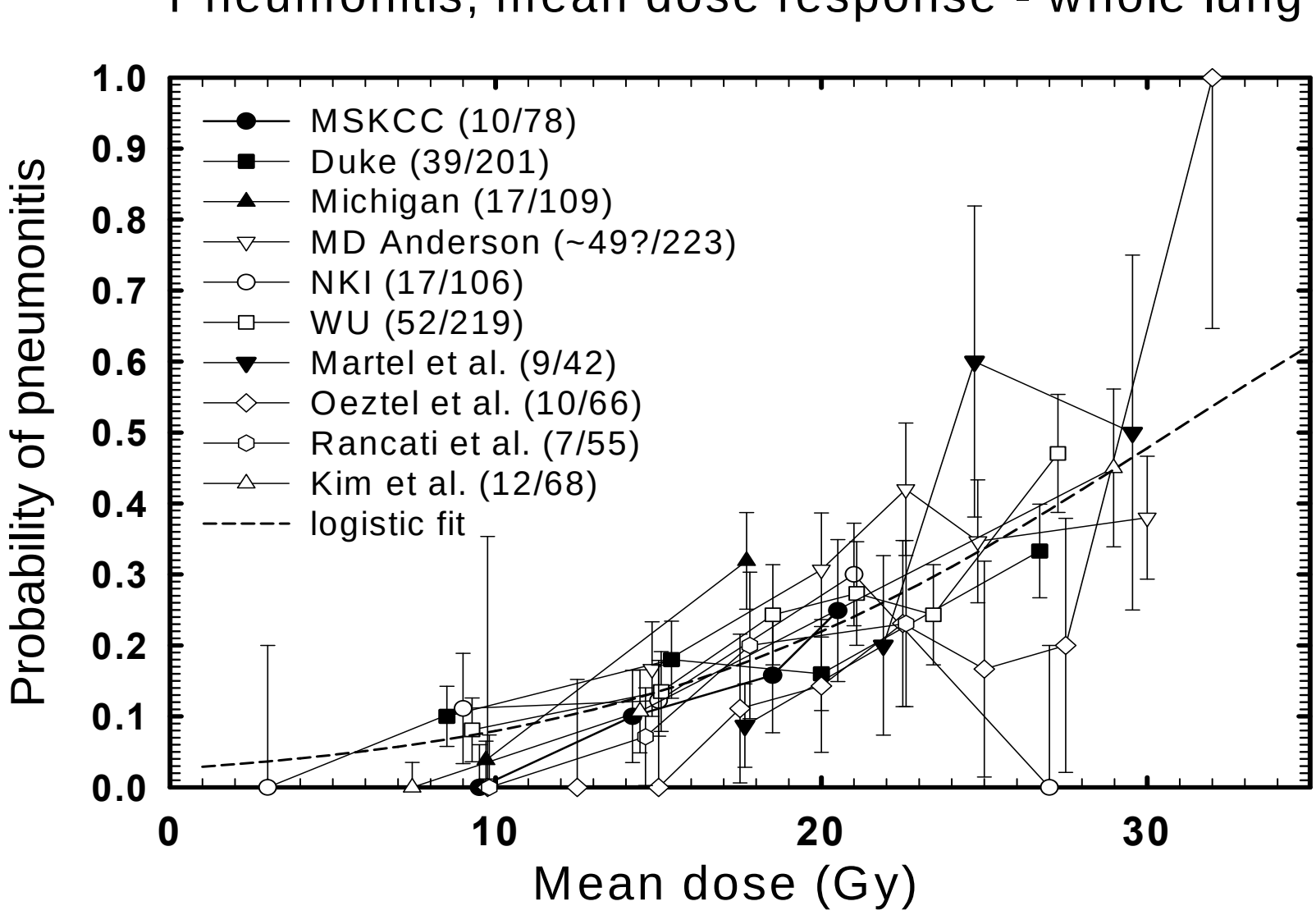
Systematic Review

- Physics
- Statistics
- MD
- Objective data review
- Variable endpoints
  - Clinically-relevant
  - Pneumonitis vs radiographic effects or PFTs

Mean dose response of pneumonitis

(A. Jackson with L. Marks/S. Kong/J.Deasy/J.Bradley/M. Martel/S. Bentzen)

- Patients treated for NSCLC
  - Data from 9 institutions, 10 separate studies
- 1,167 patients with 222 cases of pneumonitis
- ≥ Grade 3 RTOG ~ ≥ Grade 2 SWOG
  - (requiring steroids)
  - accepted ≥ grade 1 definition if few grade 1 cases

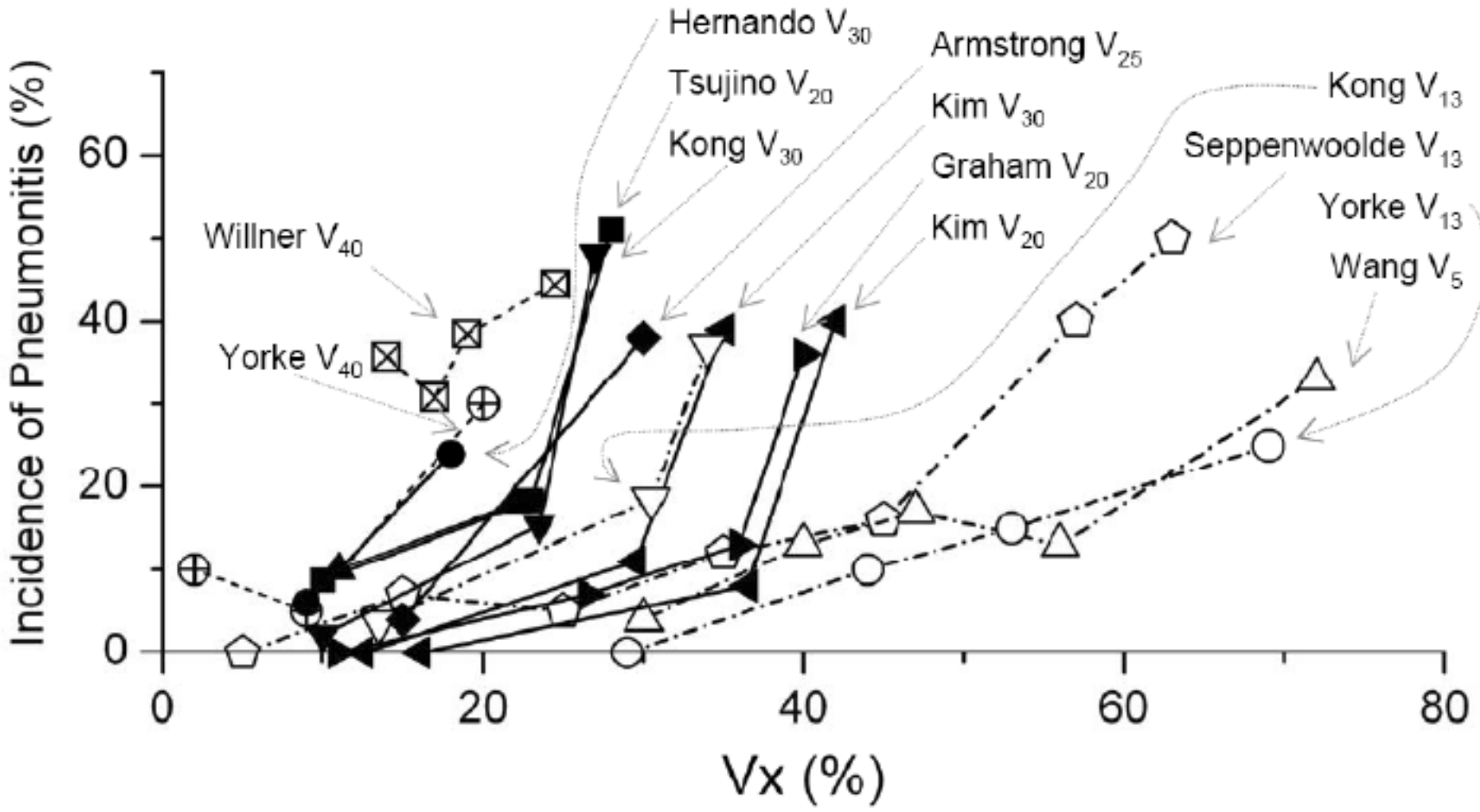


Objective data review: Jackson, Deasy, Martel, Bentzen

1,167 pts NSCLCa, 9 centers

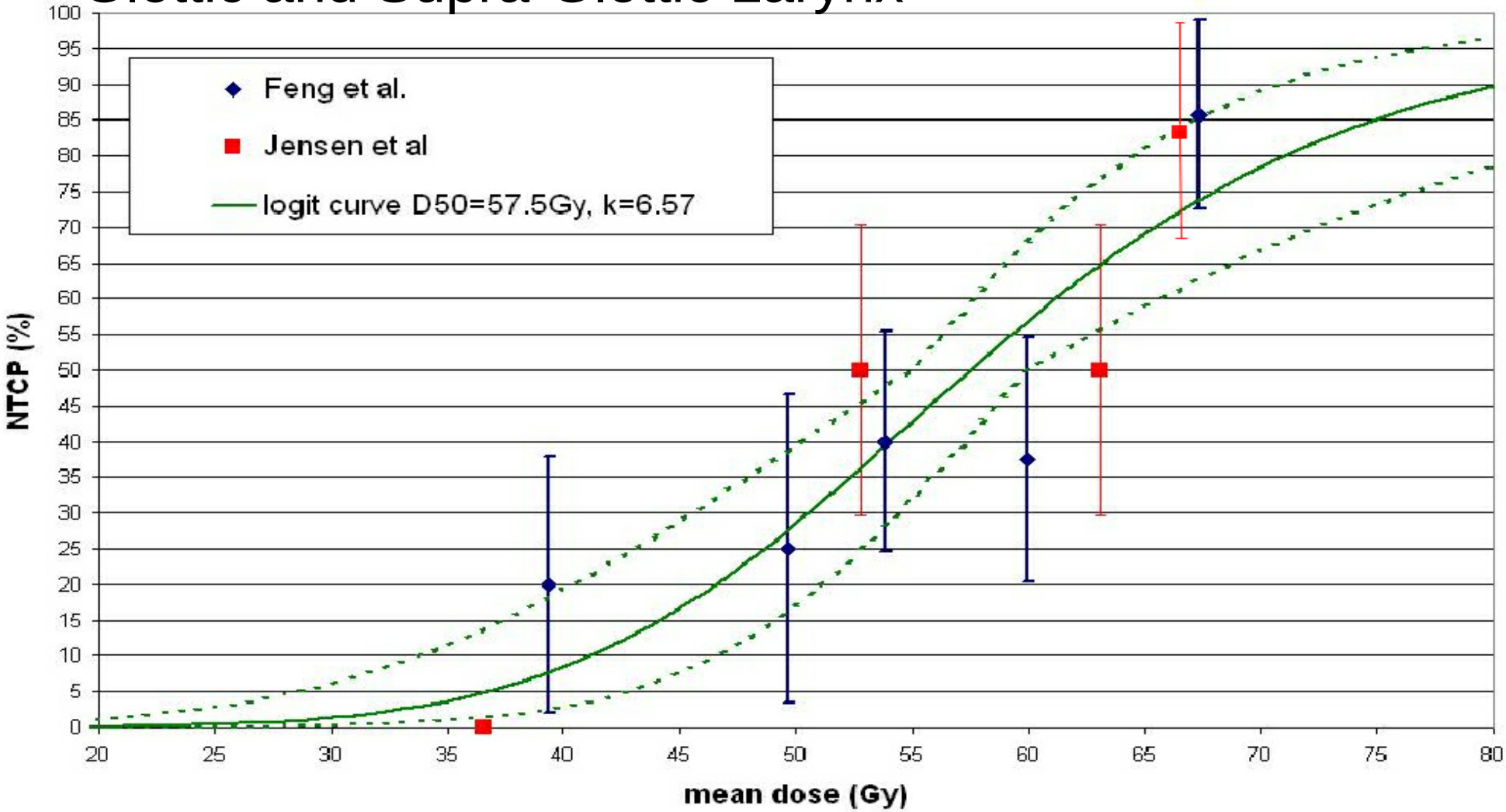
Model Fit (LKB usually) Lung (LKB and Logistic)

- n = 1
- TD 50 = 31.4 Gy
- m = 0.45



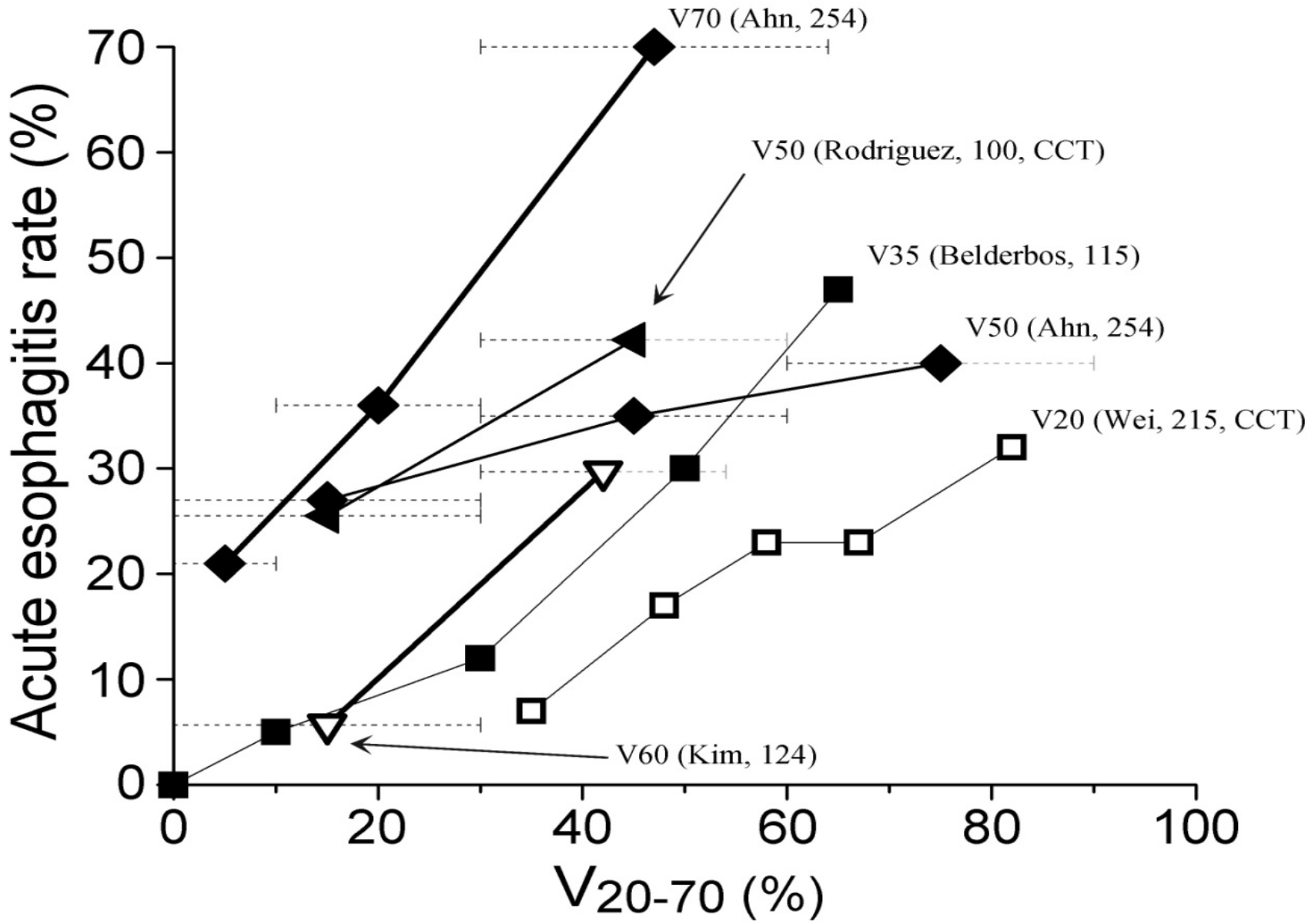
Jessica Hubbs

Probability of aspiration as function of mean dose to Glottic and Supra-Glottic Larynx

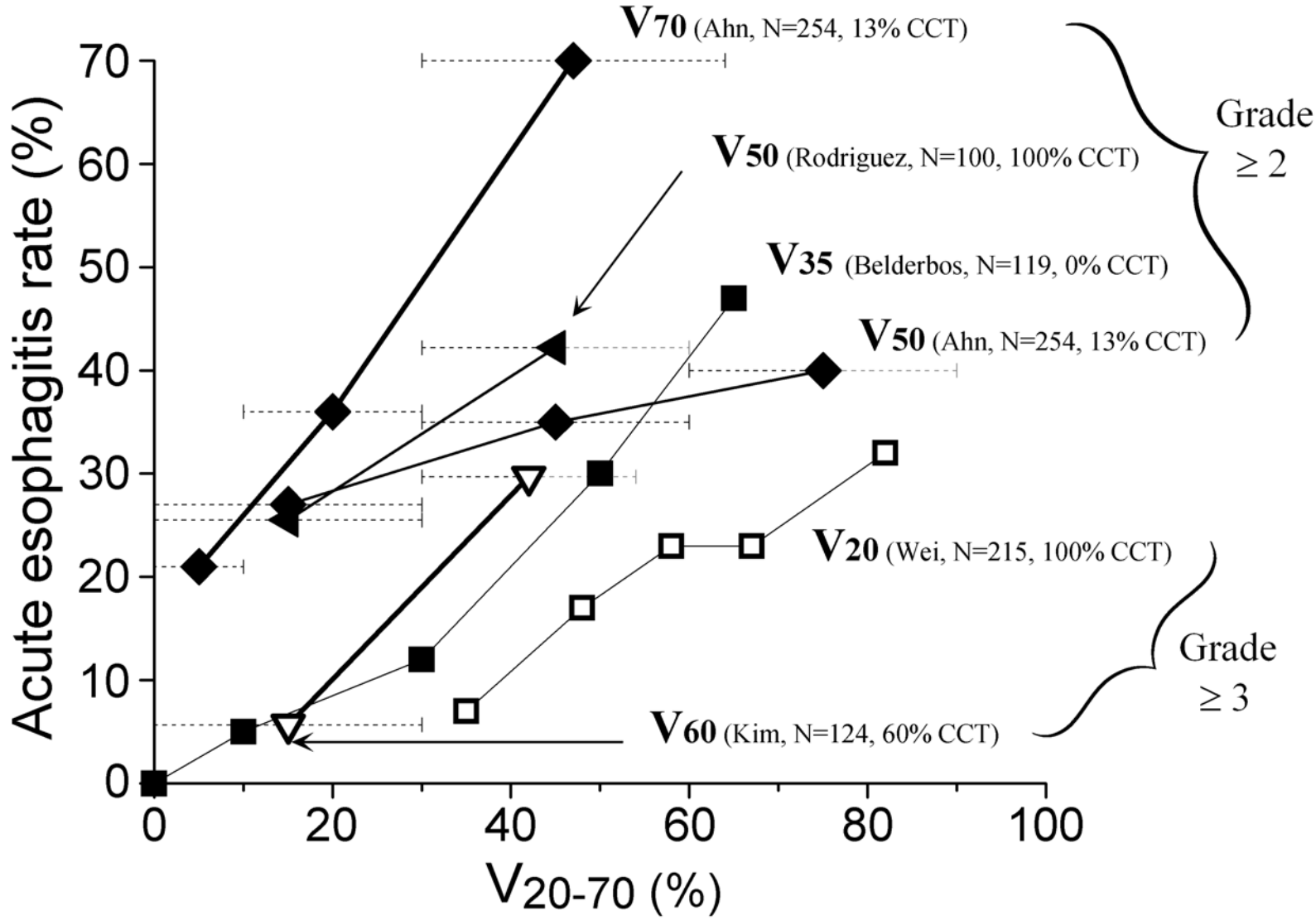


(T. Rancati, M. Schwartz, A. Allen, F. Feng, A. Popovtzer, B. Mittal, and A. Eisbruch)

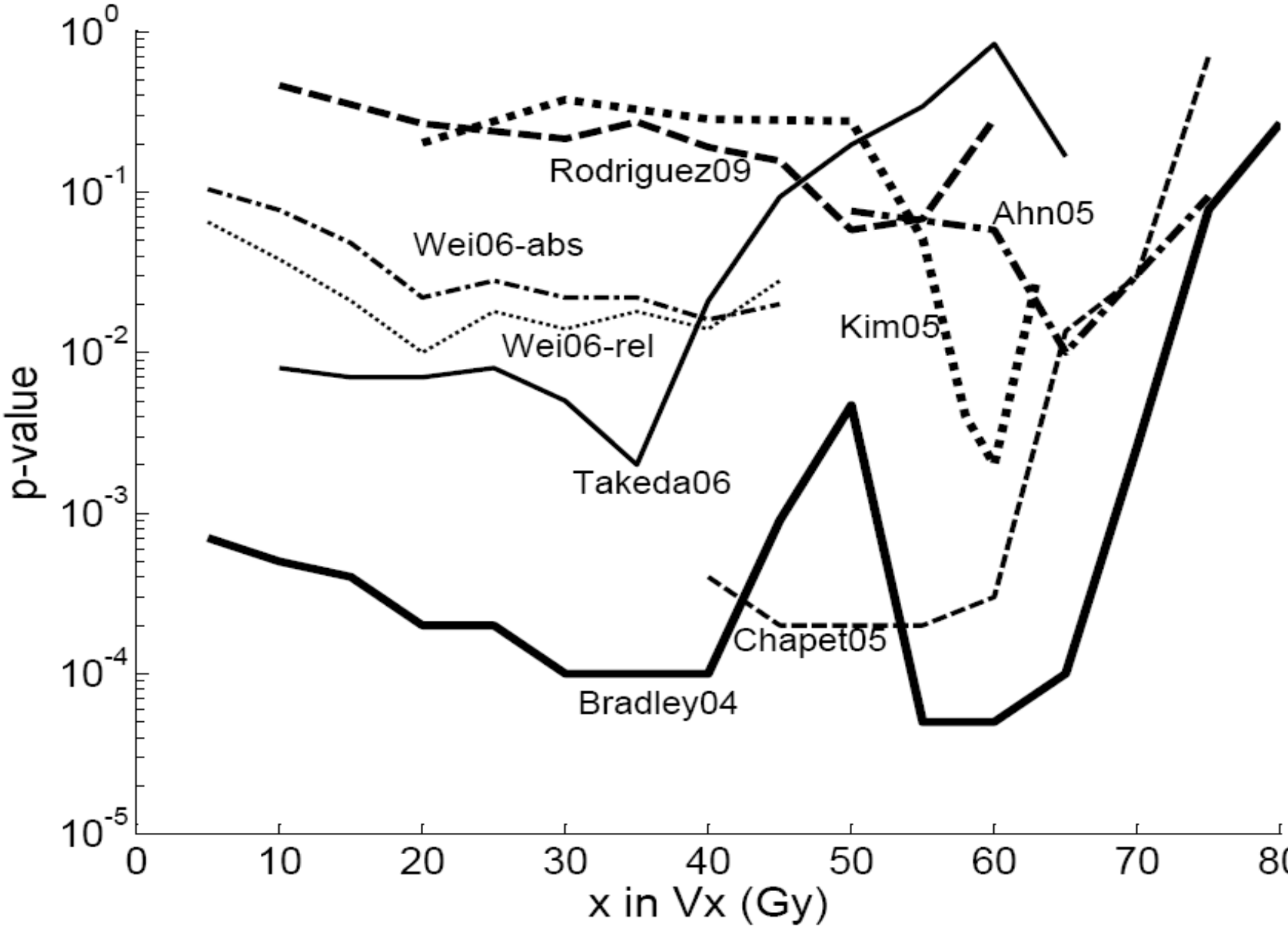
Esophagus: Werner-Wasik, Jiho Nam, Yorke, Deasy, Marks



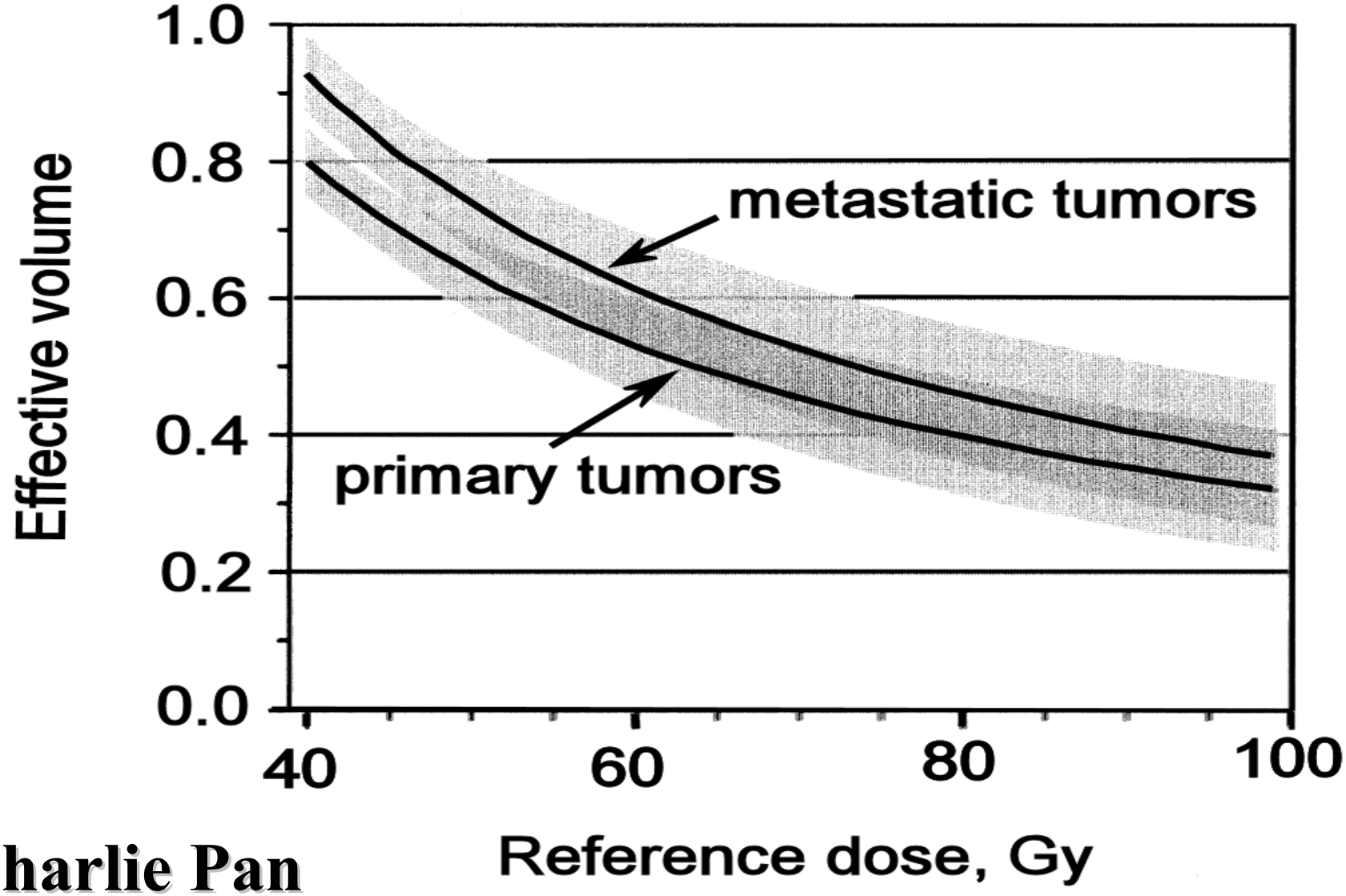
Esophagus Nam, Yorke, Deasy, Werner-Wasik



Esophagus QUANTEC, Yorke, Deasy, Werner-Wasik



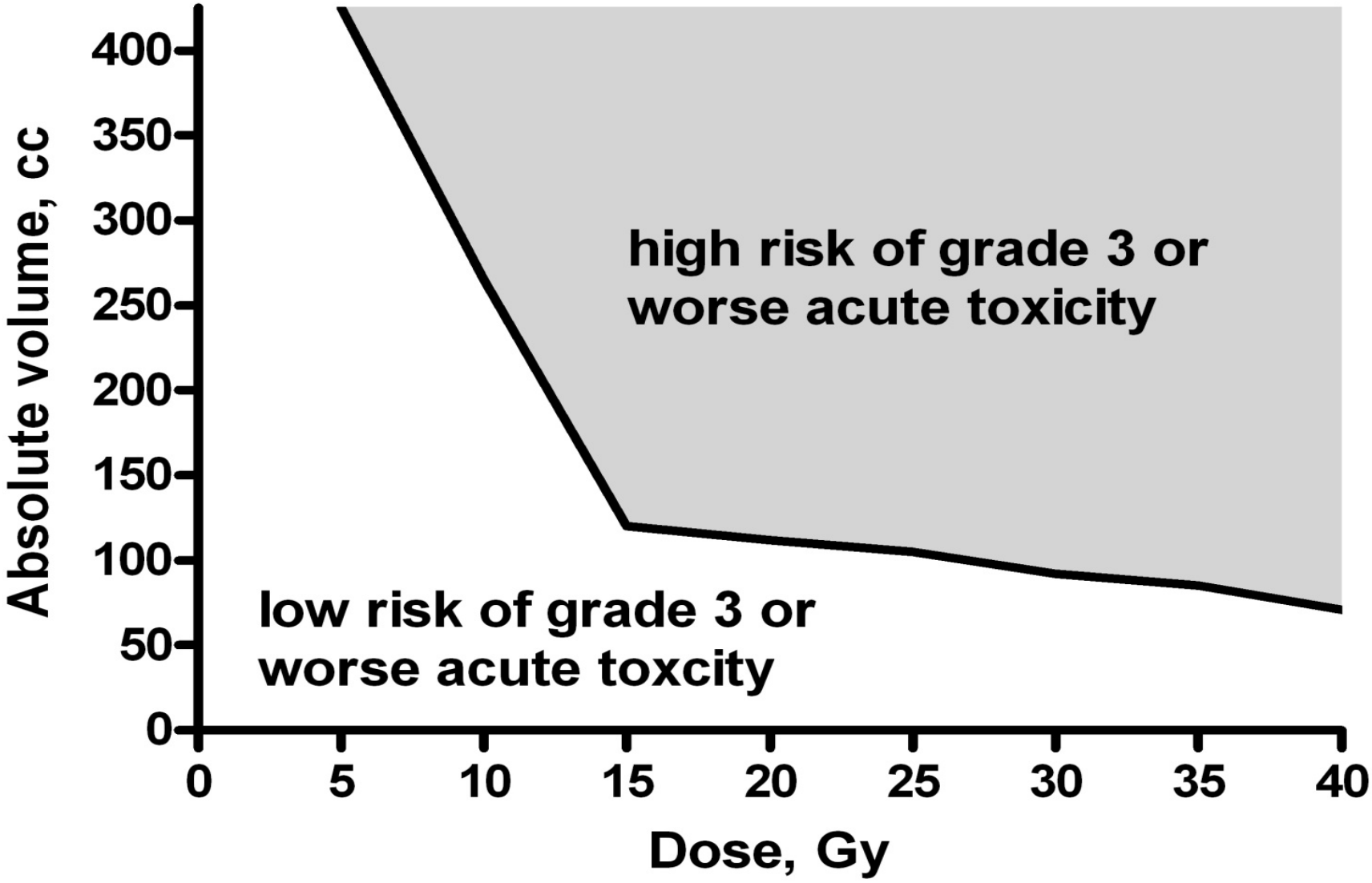
Liver (1)

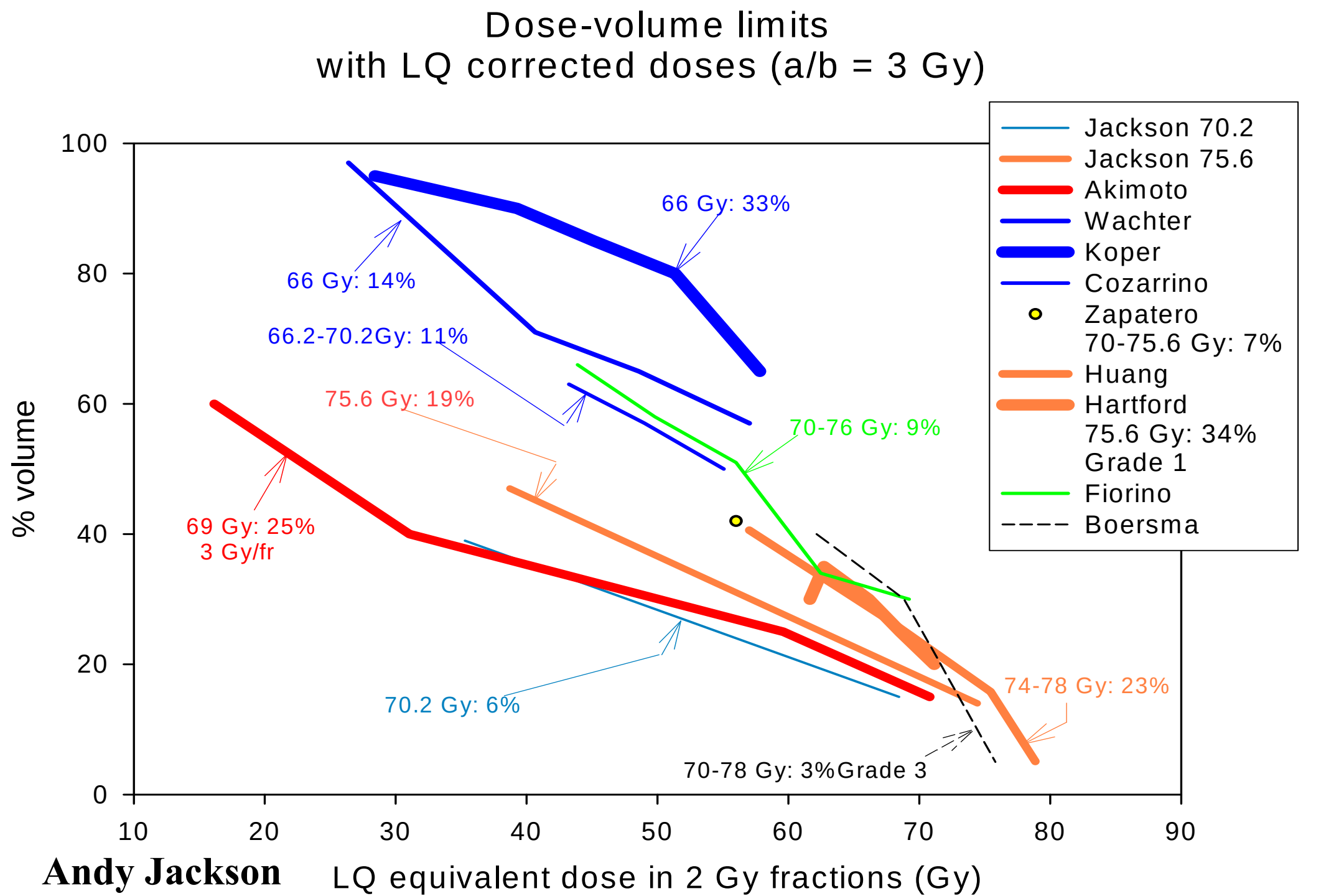


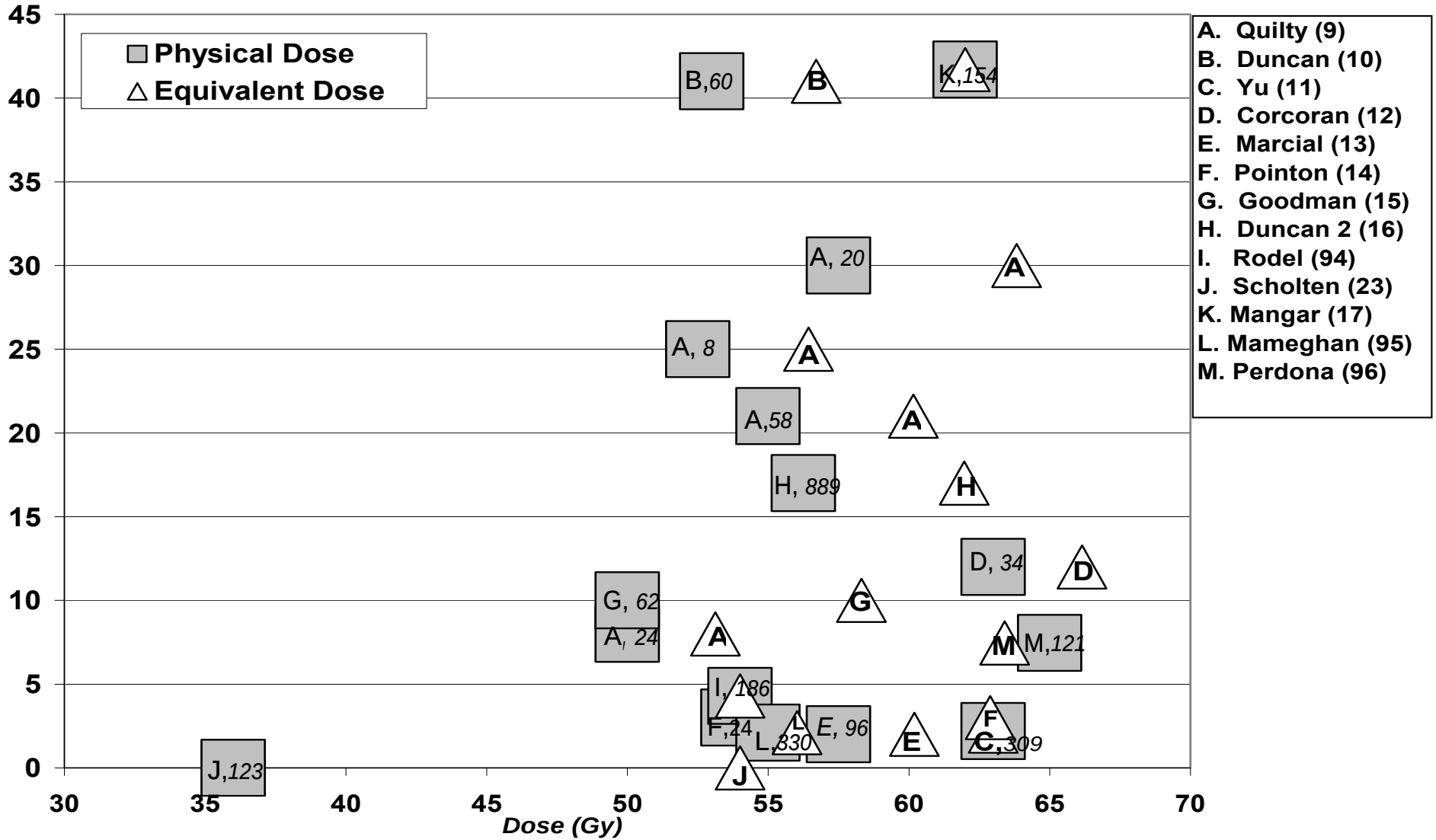
Charlie Pan

Small bowel

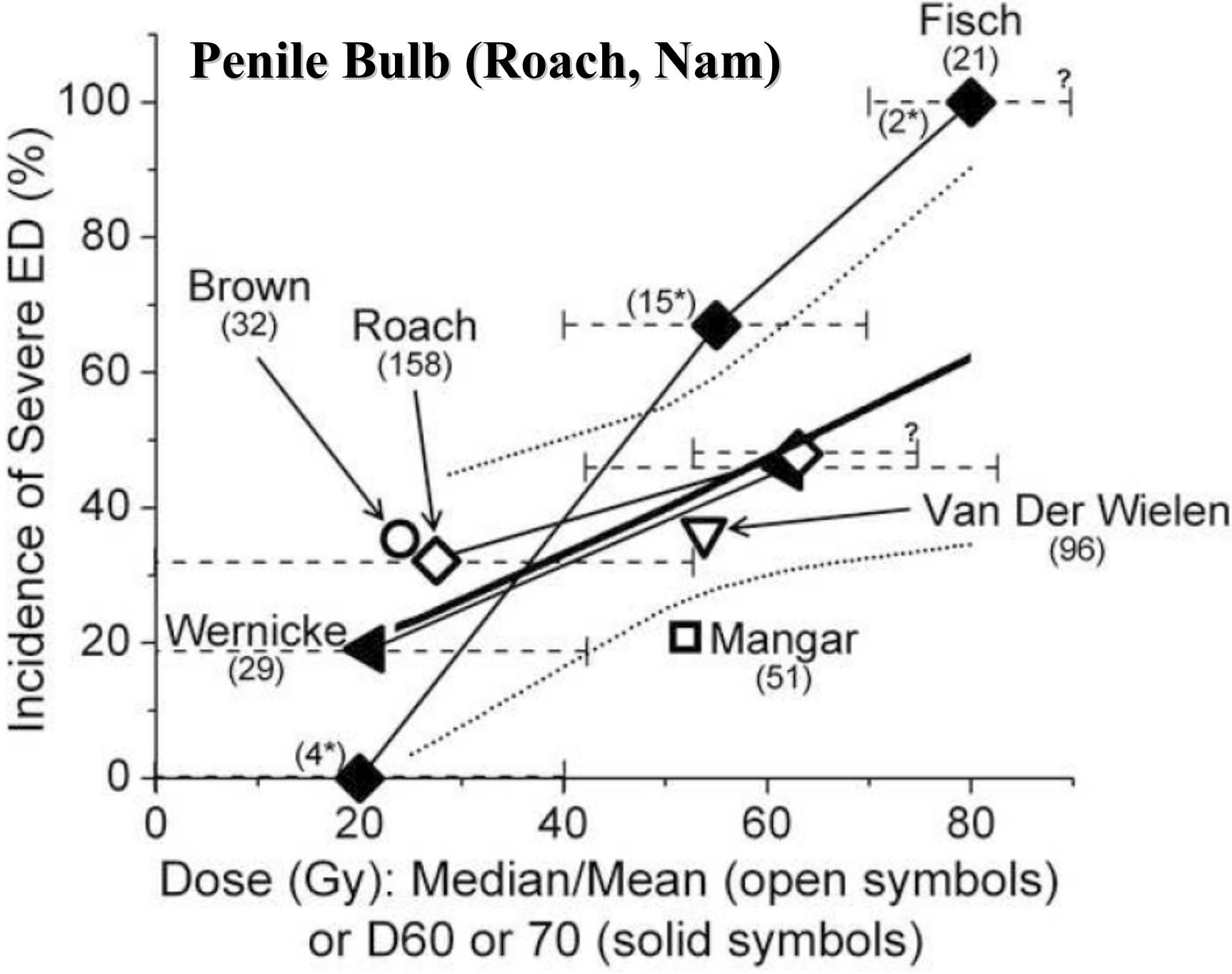
Charlie Pan

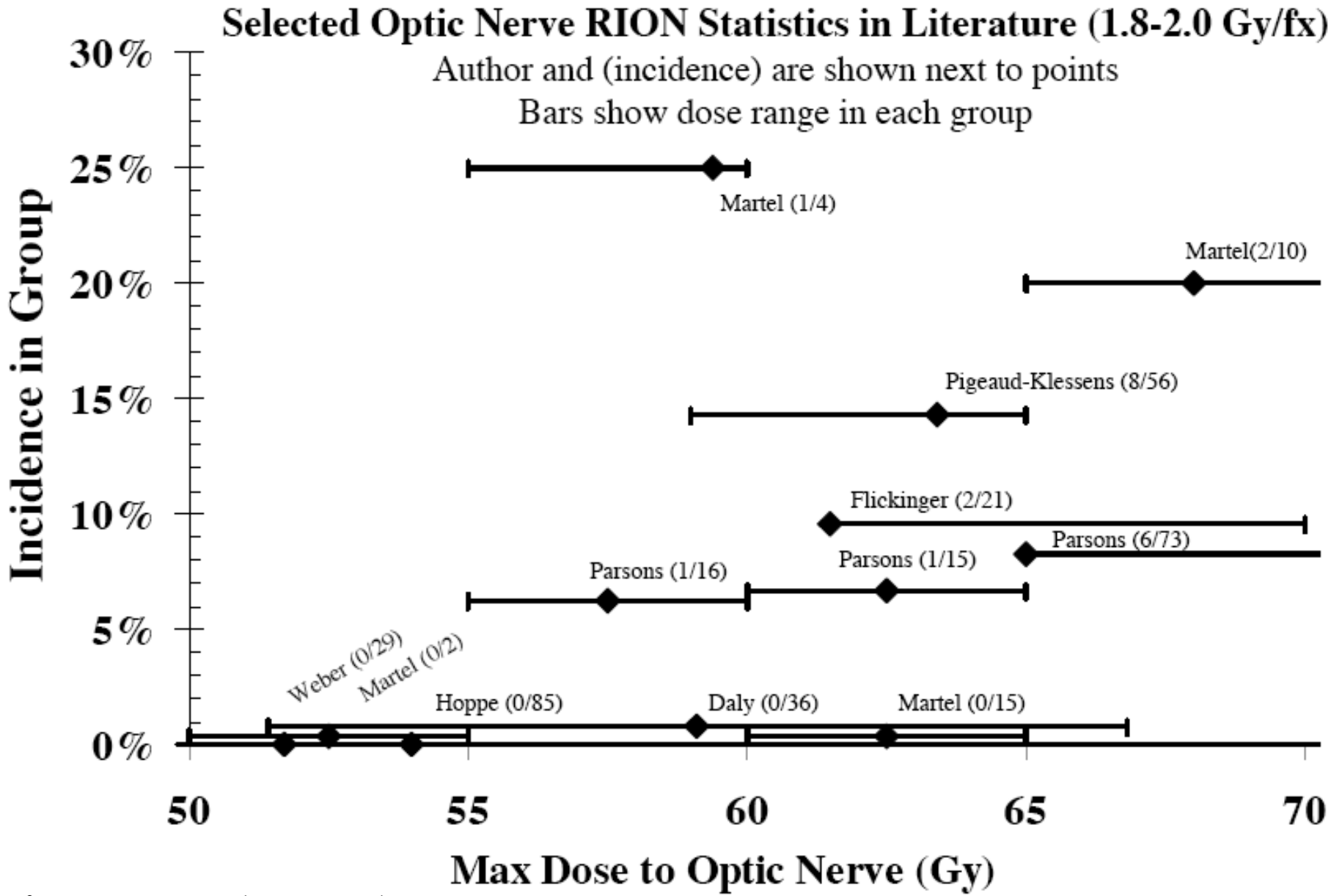



Dose-volume limits
with LQ corrected doses (a/b = 3 Gy)
Jackson 70.2
Jackson 75.6
Akimoto
Wachter
Koper
Cozarrino
Zapatero
70-75.6 Gy: 7%
Huang
Hartford
75.6 Gy: 34%
Grade 1
Fiorino
Boersma
66 Gy: 33%
66 Gy: 14%
66.2-70.2Gy: 11%
75.6 Gy: 19%
70-76 Gy: 9%
69 Gy: 25%
3 Gy/fr
70.2 Gy: 6%
74-78 Gy: 23%
70-78 Gy: 3%Grade 3
% volume
LQ equivalent dose in 2 Gy fractions (Gy)
100
80
60
40
20
0
10
20
30
40
50
60
70
80
90
Andy Jackson

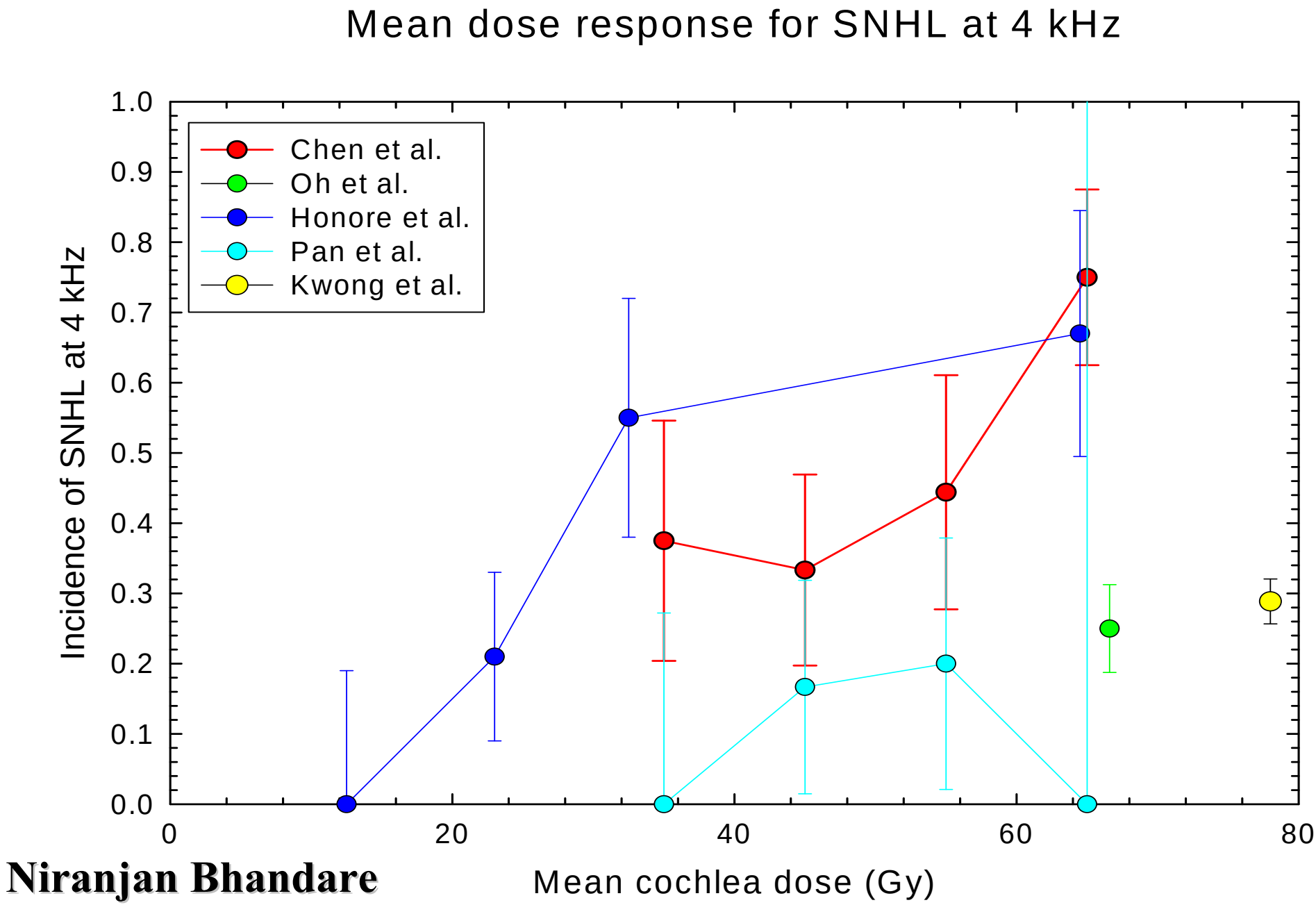


Bladder: Yorkee and Viswanathan


Penile Bulb (Roach, Nam)
Fisch
(21)
?
(2*)
Brown
(32)
Roach
(158)
(15*)
?
Van Der Wielen
(96)
Wernicke
(29)
Mangar
(51)
(4*)
Incidence of Severe ED (%)
0
20
40
60
80
100
0
20
40
60
80
Dose (Gy): Median/Mean (open symbols)
or D60 or 70 (solid symbols)

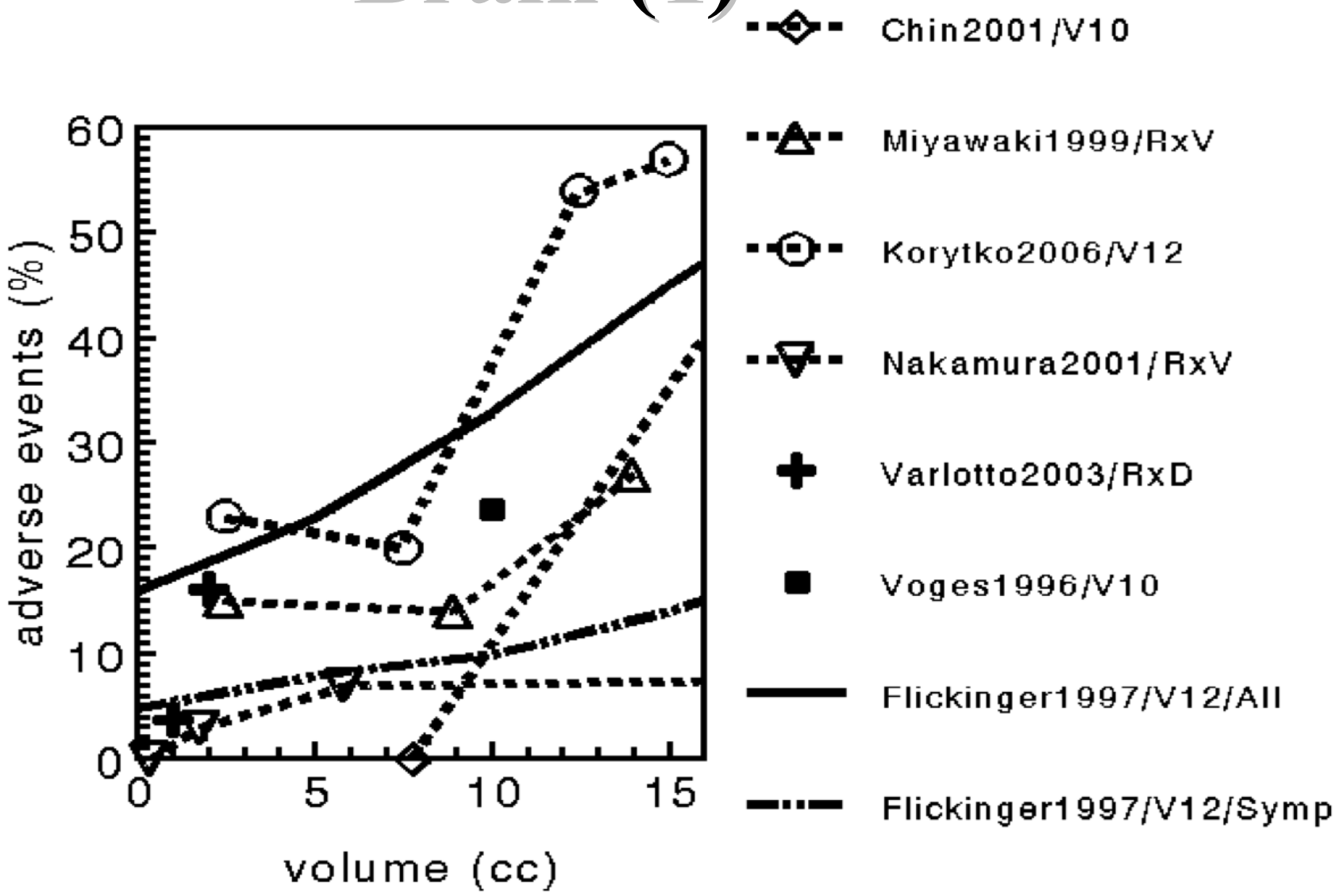


Optic Nerve (Mayo)



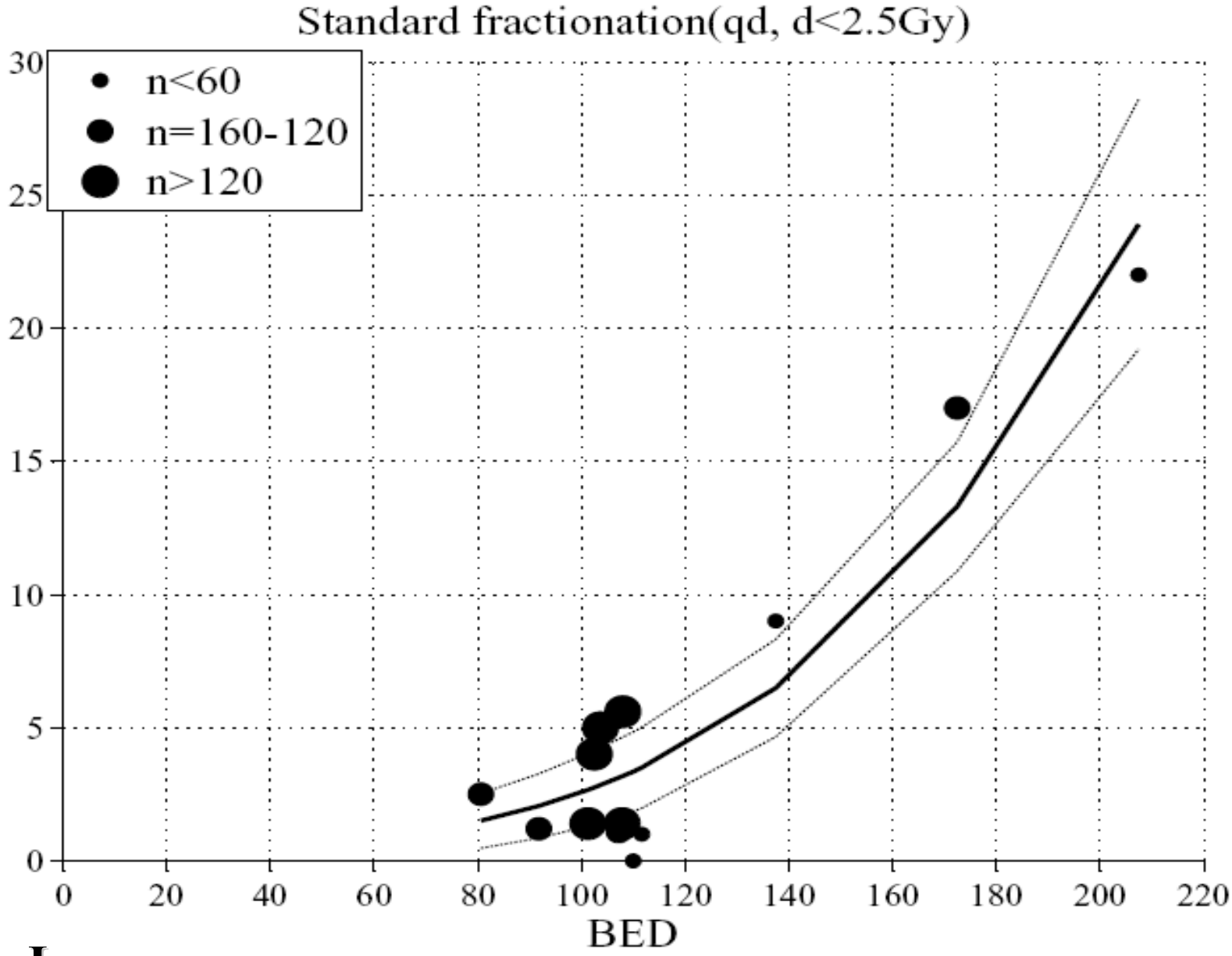
Niranjan Bhandare

Brain (1)



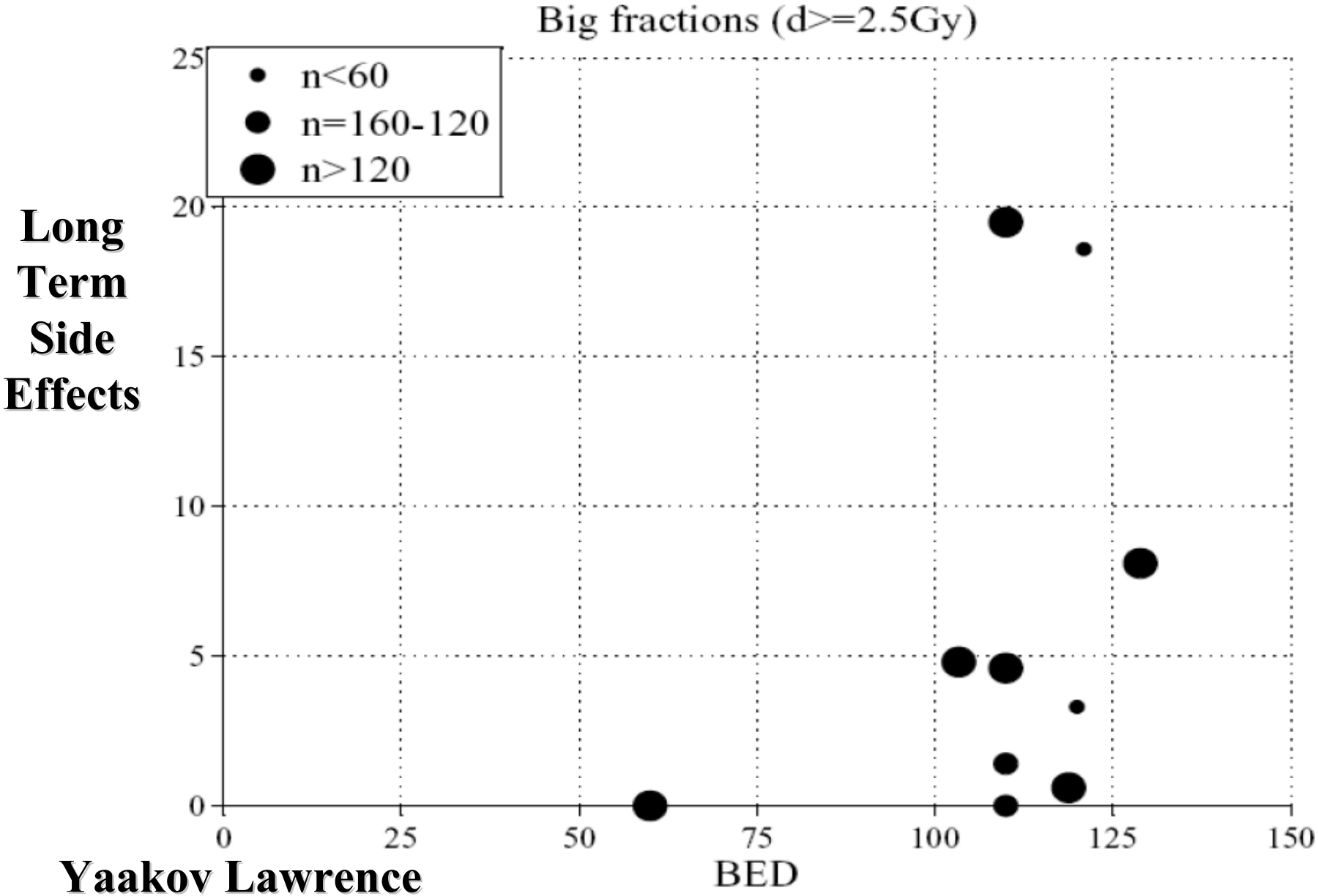
Yaakov Lawrence

Brain (2)



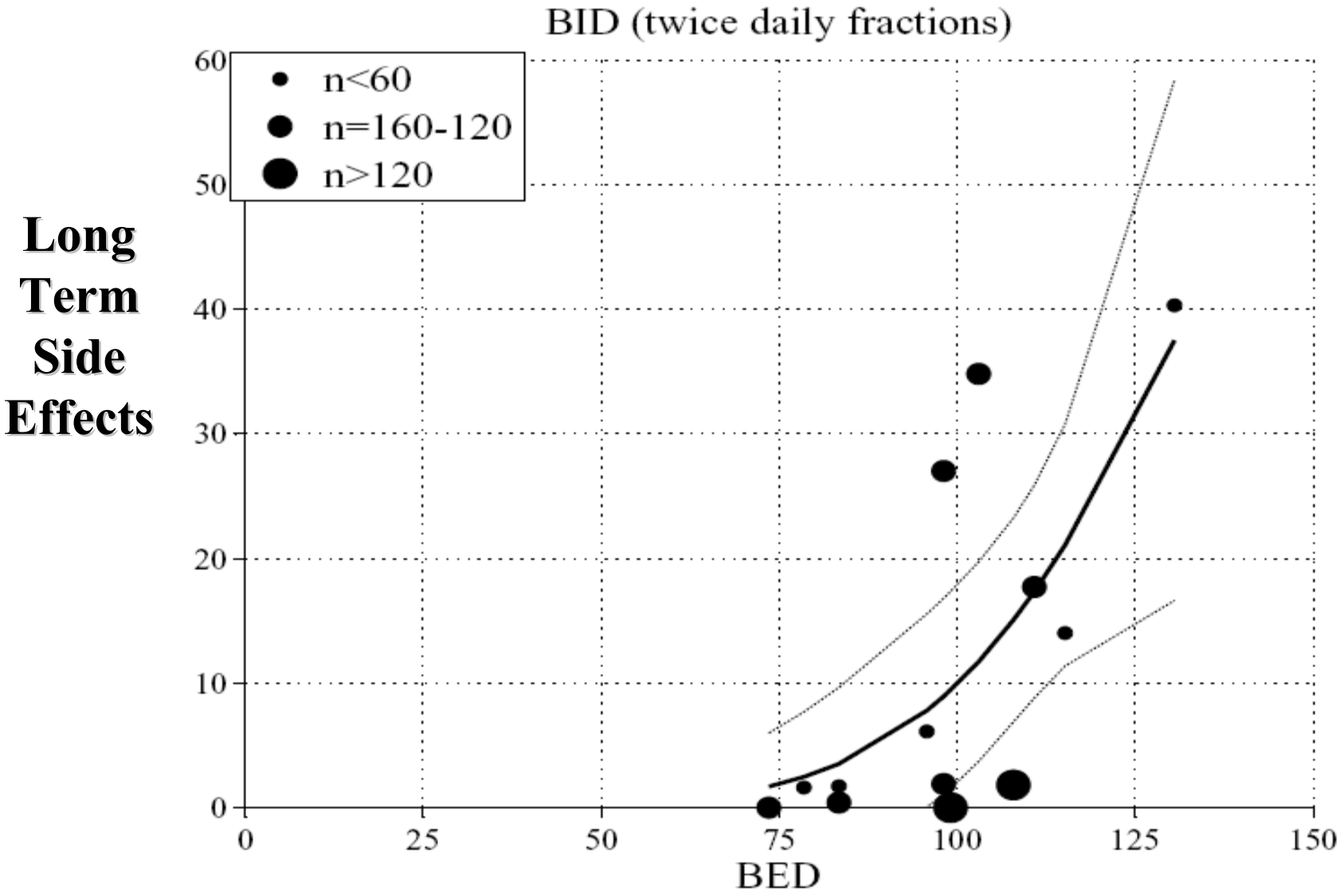
Yaakov Lawrence

Brain (3)



Yaakov Lawrence

Brain (4)



Yaakov Lawrence

QUANTEC Summary Table: Approximate Dose/Volume/Outcome Data for Several Organs^

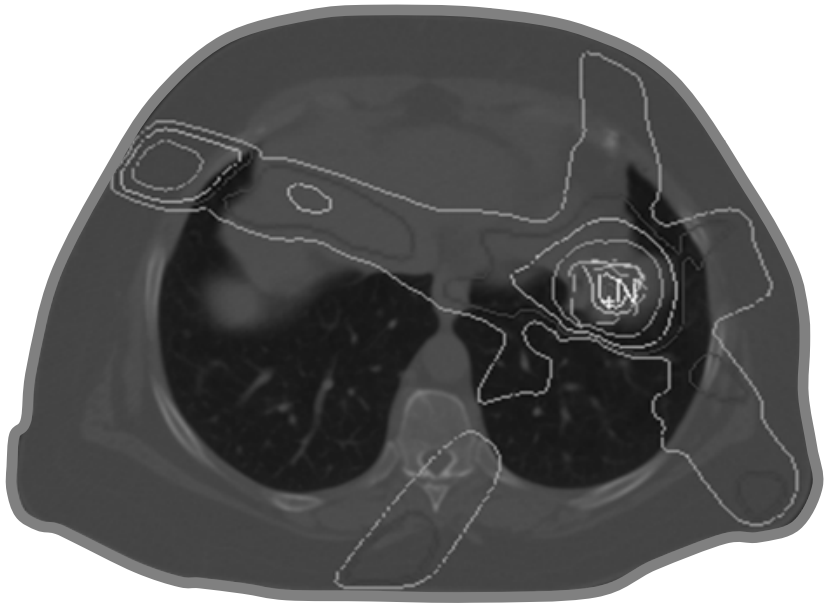
blessed by author	Organ	Volume being considered	Dose (in Gy), or dose/volume parameter*	endpoint	rate (%)	Often-used / suggested model	Model parameters
Akila N. Viswanathan	**Bladder**	whole organ	< 65	grade ≥3 RTOG	< 6%	No model	
Yaakov R. Lawre	**Brain**	partial organ	78	symptomatic necrosis	5%	No model	
		(fractionated)	93	symptomatic necrosis	10%		
		partial organ (single fraction)	V12 < 5-10 cc	symptomatic necrosis	< 20% ???		
Charles S. Mayo	**Brain stem**	whole organ	< 54	neurological toxicity	< 5%	LKB	TD50- 72, m- 0.1, n- 0.25
		partial organ	D5cc Š 59	neurological toxicity	< 5%	Lyman plus LQ model	TD50=15.3, m=0.15, n=0.04
		partial organ (single fraction)	Dmax < 12	neurological toxicity	< 5%		
Charles S. Mayo	**Optic nerve / Chiasm**	whole organ	D max < 55	optic neuropathy	< 3%	Neuret	30% risk if NTD > 60 Gy at 1.8 Gy/fx
			D max = 55-59	optic neuropathy	3-10%	Optic RET	Total dose/Number of fractions^0.53 = 8.9 Gy
			D max > 60	optic neuropathy	> 20%	LKB	TD50 = 70 ~ 72 Gy
		partial organ (single fraction)	Dmax < 12	optic neuropathy	< 5%		
	Penile bulb	95% of the organ	mean dose < 50	severe erectile dysfunction	< 35%	No model	
			D90** < 50	severe erectile dysfunction	< 35%		
			D60-70 = 20	severe erectile dysfunction	10%		
			D60-70 = 40	severe erectile dysfunction	35%		
			D60-70 = 60	severe erectile dysfunction	55%		
Giovanna Gagliardi	**Heart**	pericardium	mean dose < 26	pericarditis	< 15%	LKB	TD50=50.6 Gy, m=0.13, n=0.64
		pericardium	V30 < 46%	pericarditis	< 15%		
		whole organ	mean dose < 25	long-term cardiac mortality	< 1%		
		partial organ	V25 < 5%	long-term cardiac mortality	< 1%		
		partial organ	V40 < 5%	long-term cardiac mortality	< 5%		
Laura Dawson	**Kidney**	bilateral whole kidneys***	mean dose < 15	symptomatic renal dysfunction	< 1%	LKB	TD50=28 Gy, n=0.70, m=0.10
		bilateral whole kidneys***	mean dose < 20	symptomatic renal dysfunction	< 10%	LKB	m=0.26
		bilateral whole kidneys***	mean dose < 27	symptomatic renal dysfunction	< 50%		
		partial organ	mean dose < 18	symptomatic renal dysfunction	< 5%		
		partial organ	D50 < 18	symptomatic renal dysfunction	< 1%		
Laura Dawson	**Liver**	whole organ	< 30	symptomatic liver dysfunction	< 5%	LKB	TD50=39.8-46.1 Gy, n=0.86-1.1, m=0.12-0.31
		whole organ	33	symptomatic liver dysfunction	10%	LKB	TD50=23-50 Gy, n=0.26-0.7, m=0.4-0.43
		whole organ	36	symptomatic liver dysfunction	40%		
		partial organ	mean dose < 28	symptomatic liver dysfunction	< 1%		
		partial organ	mean dose = 34	symptomatic liver dysfunction	5%		
		partial organ	mean dose = 44	symptomatic liver dysfunction	50%		
		partial organ	mean dose = 30	symptomatic liver dysfunction	5%		
		partial organ	mean dose = 37	symptomatic liver dysfunction	50%		
Marks	**Lung**	partial organ	V20 Š 30%	symptomatic pneumonitis	<20%	MLD model (logistic)	D50=30.8, _50=0.97
		partial organ	mean dose = 10	symptomatic pneumonitis	5%		
			mean dose = 15	symptomatic pneumonitis	10%		
			mean dose = 20	symptomatic pneumonitis	20%		

Kidney	bilateral whole kidneys***	mean dose < 15	symptomatic renal dysfunction	< 1%
	bilateral whole kidneys***	mean dose < 20	symptomatic renal dysfunction	< 10%
	bilateral whole kidneys***	mean dose < 27	symptomatic renal dysfunction	< 50%
	partial organ	mean dose < 18	symptomatic renal dysfunction	< 5%
	partial organ	D50 < 18	symptomatic renal dysfunction	< 1%

Laura Dawson	**Liver**	whole organ	< 30	symptomatic liver dysfunction	< 5%	patients with preexisting liver disease or hepatocellular carcinoma, as tolerance doses are lower in these patients
		whole organ	33	symptomatic liver dysfunction	10%	
		whole organ	36	symptomatic liver dysfunction	40%	
		partial organ	mean dose < 28	symptomatic liver dysfunction	< 1%	Excluding patients with preexisting liver disease or hepatocellular carcinoma
		partial organ	mean dose = 34	symptomatic liver dysfunction	5%	
		partial organ	mean dose = 44	symptomatic liver dysfunction	50%	
		partial organ	mean dose = 30	symptomatic liver dysfunction	5%	In patients with Child-Pugh A preexisting liver disease or hepatocellular carcinoma, excluding Hepatitis B reactivation as an endpoint
		partial organ	mean dose = 37	symptomatic liver dysfunction	50%	

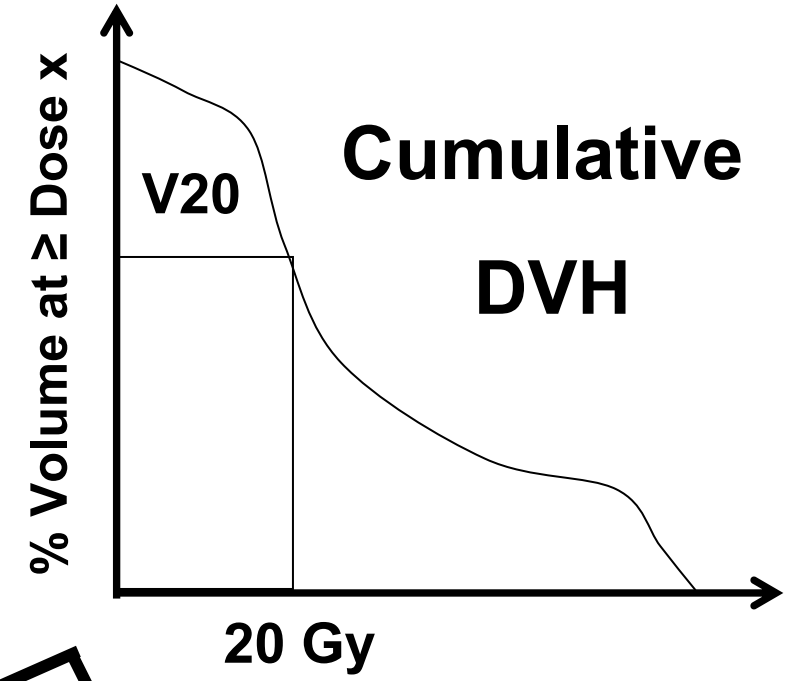
Context/Limitations

- Data is NOT great!!!
- Clinically useful, MD's
- MD's want it made simple
- Be careful, recognize uncertainties



3D dose distribution

Discard spatial, anatomic, physiologic data



Cumulative DVH

Extract unambiguous data

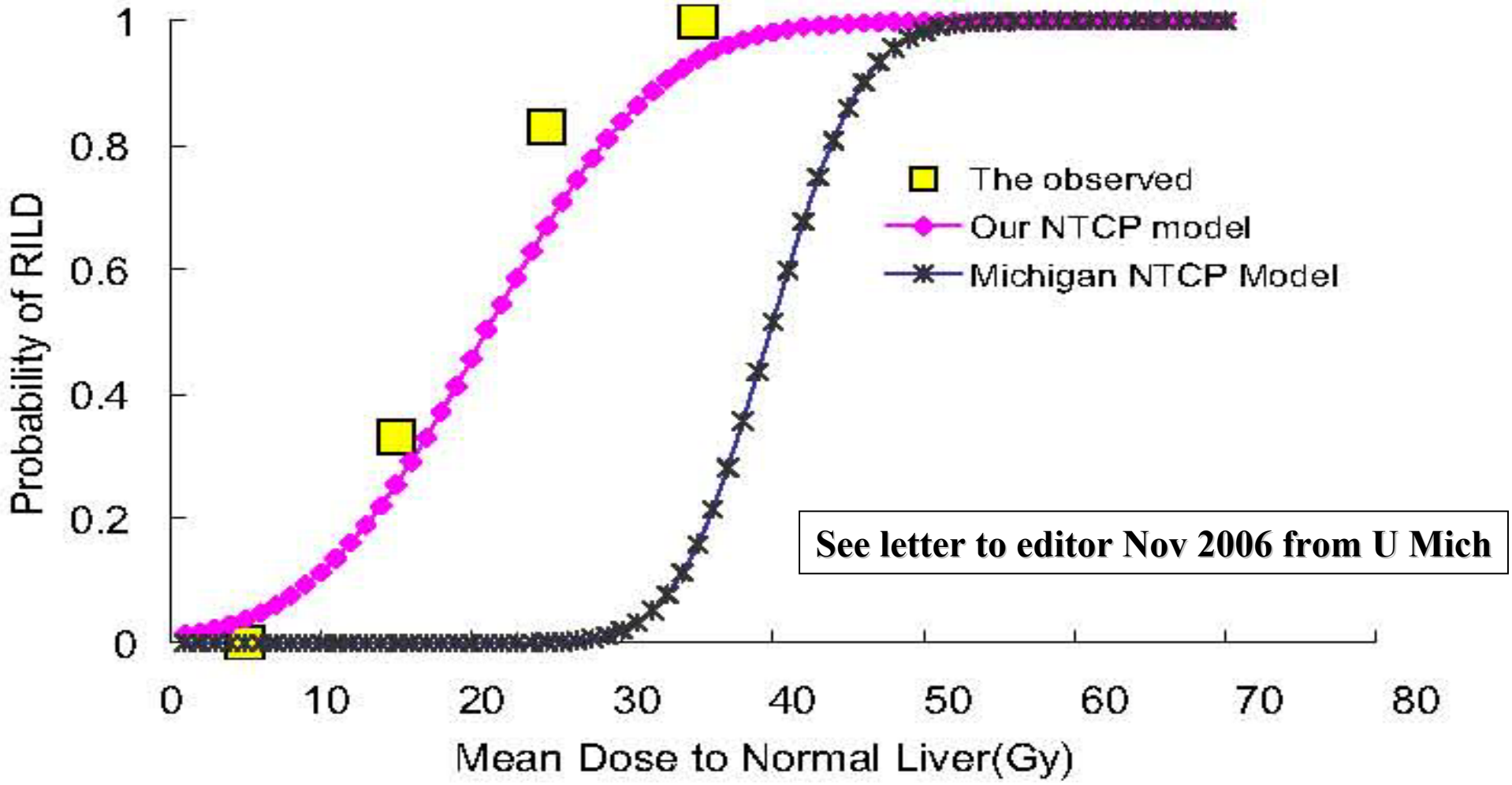
- Single Point: e.g. V20
- Global: e.g. mean dose

Compute model-based NTCP estimates

DVH-Based Models

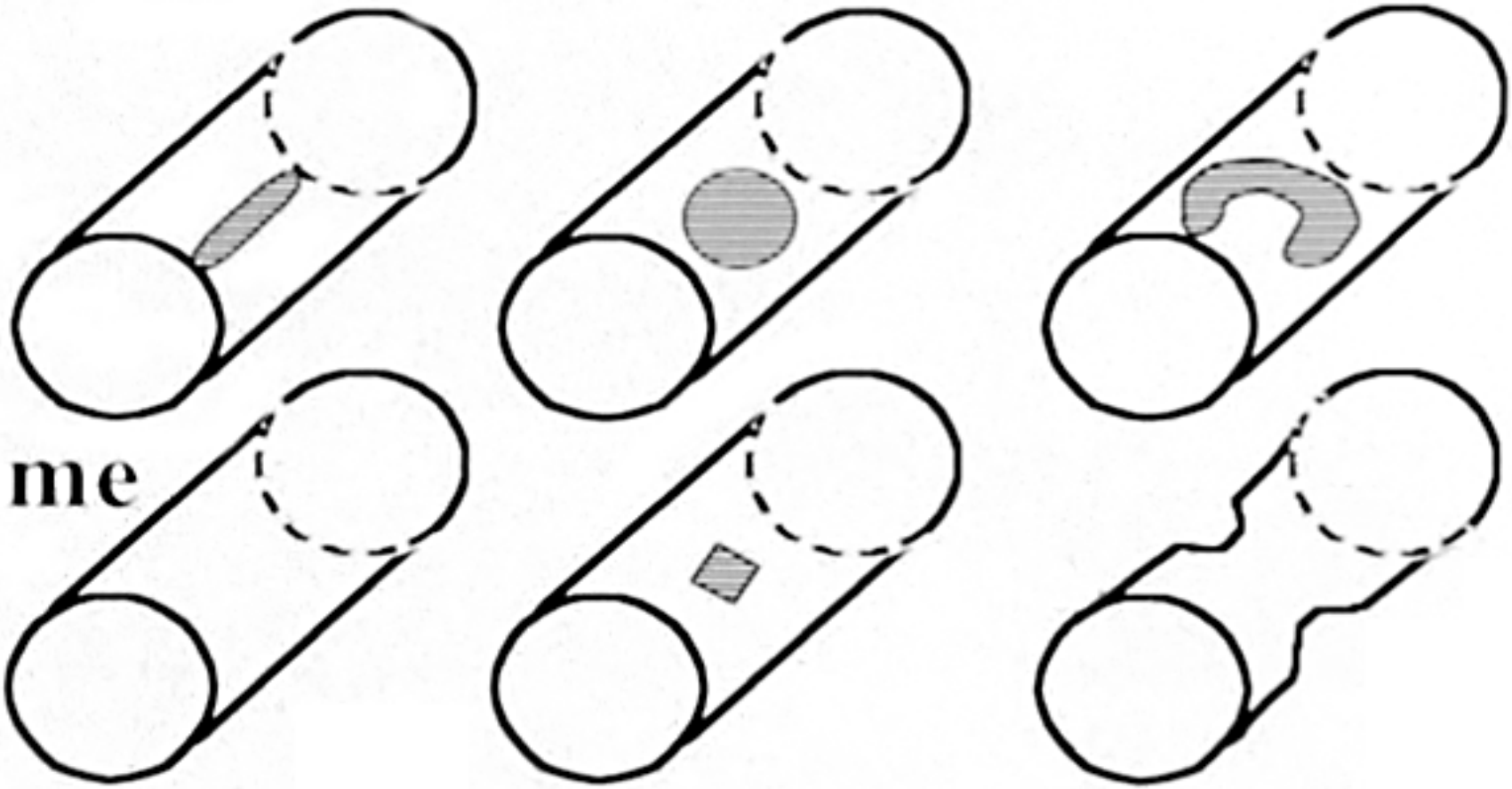
- Exportability
- Applicability
  - IMRT vs. 3D
  - SRS
- Model limitations
  - Fractionation
  - Anatomy

Exportability?
Michigan (mets) vs. Fudan/Guangxi (primary liver tumors)

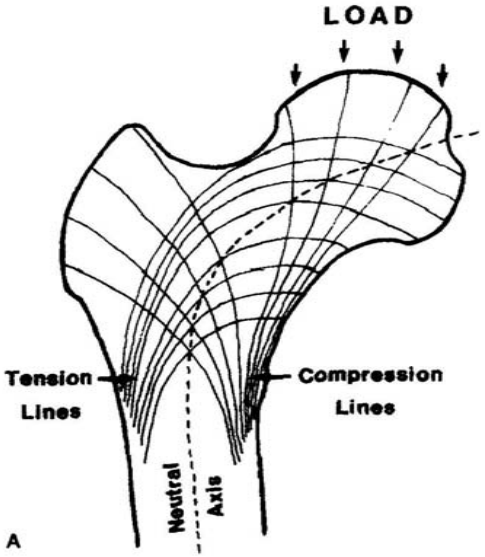


Xu *et al. IJROBP* 65:193, 2006; Fudan University, Shanghai, Cancer Hospital, Guangxi Medical University, Nanning, China

Dose Distributions



Outcome



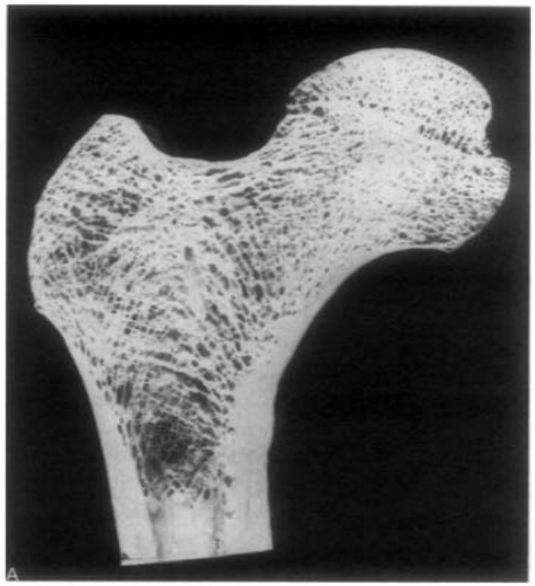
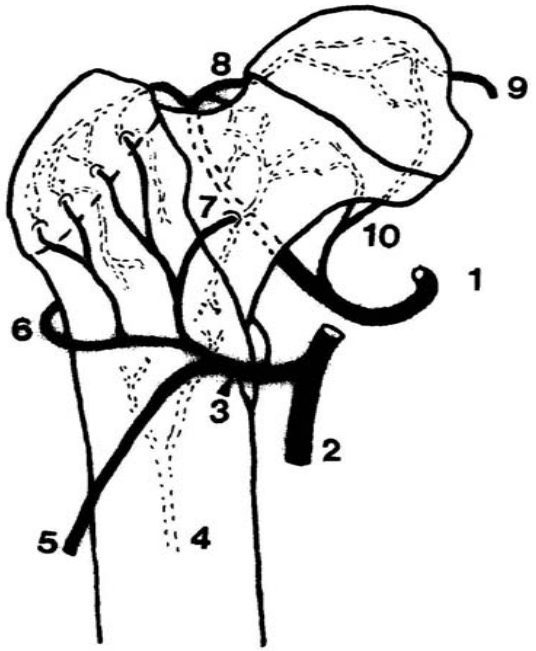
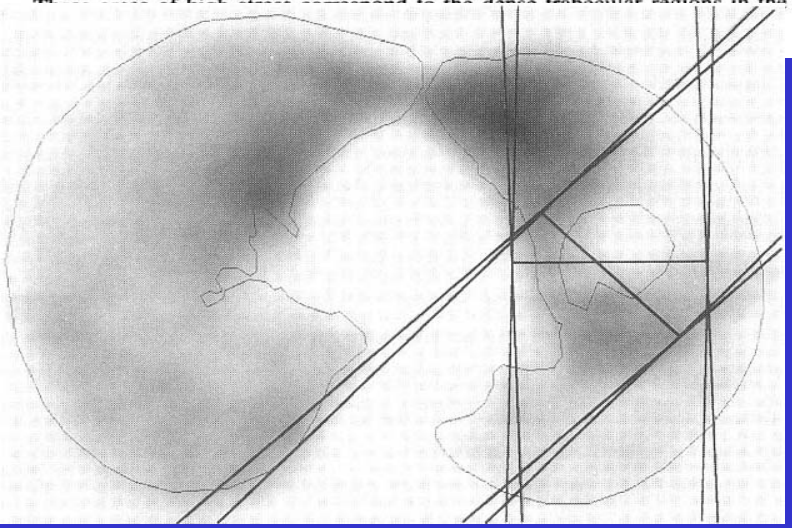


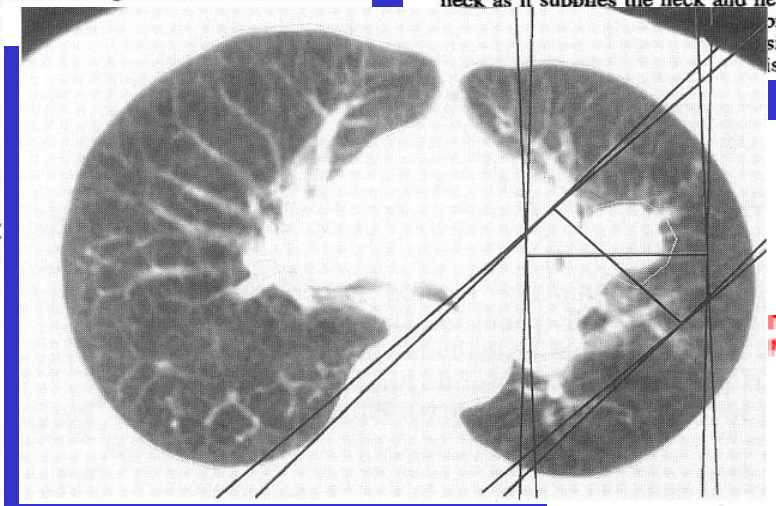
Fig. 3. Schematic diagram illustrating the compression and tension stresses that exist in the normal femur (a). anatomic gross section of the bone

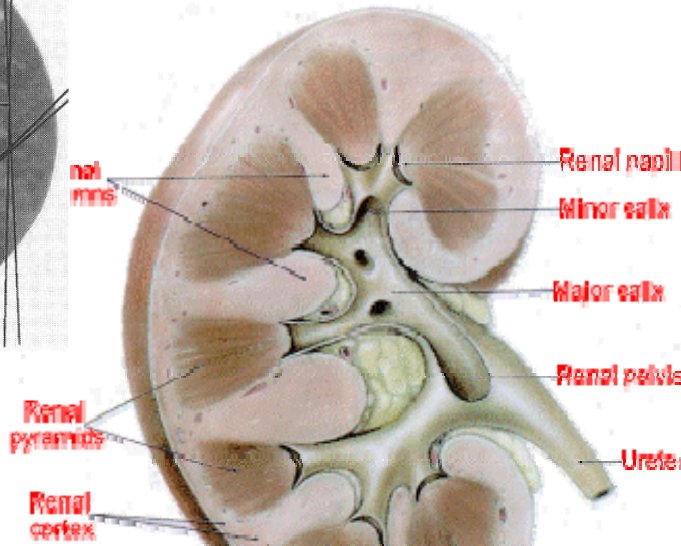


1. Medial femoral circumfl
2. Deep femoral a.
3. Lateral femoral circumfl
4. Ascending branch of inte nutrient a.
5. Muscular branch to qu ceps
6. Circumflex femoral bran
7. Anterior cervical branch
8. Superior branches of me femoral circumflex a.
9. Artery of ligamentum te
10. Inferior branches of me femoral circumflex a.

Fig. 4. Diagram illustrating the vascular supply of the proximal femur. The majority of blood t femur is delivered via the medial circumflex artery [1]. This artery passes medially and posterior neck as it supplies the neck and head. The secondary vessel is the lateral femoral circumflex arter ral artery [2]. If radiation-induced damage to the femur occur sition of these vessels and their branches relative to the XRT b ission from (20).

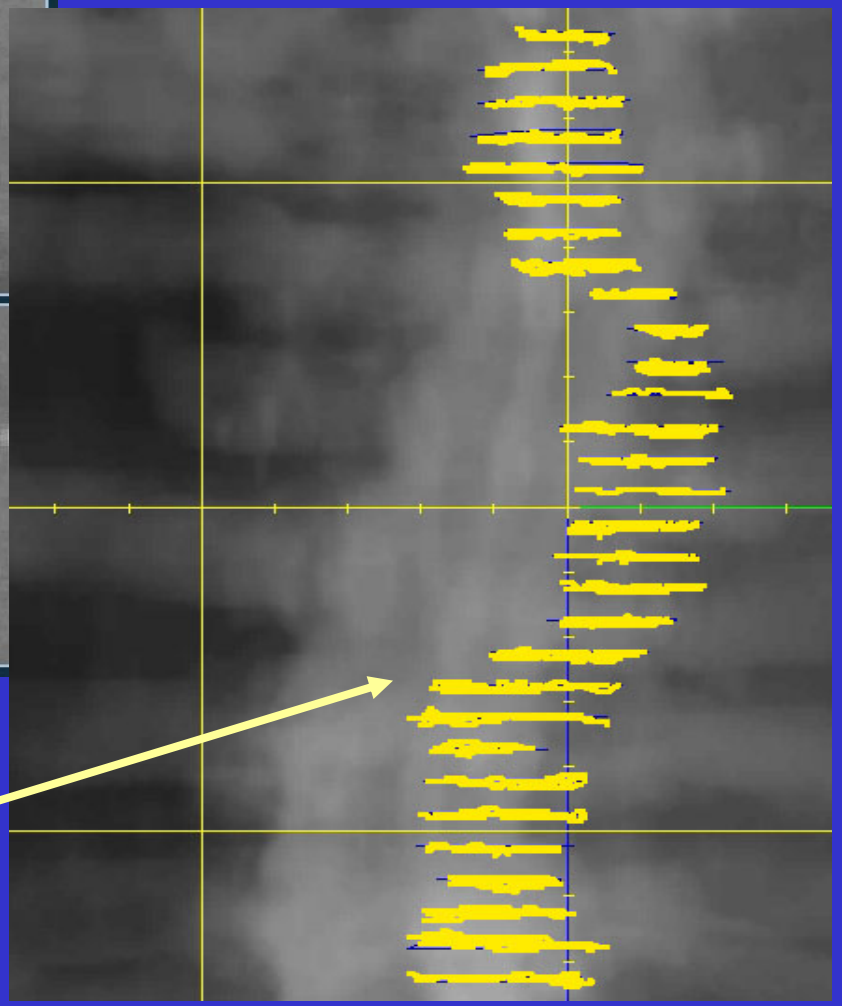




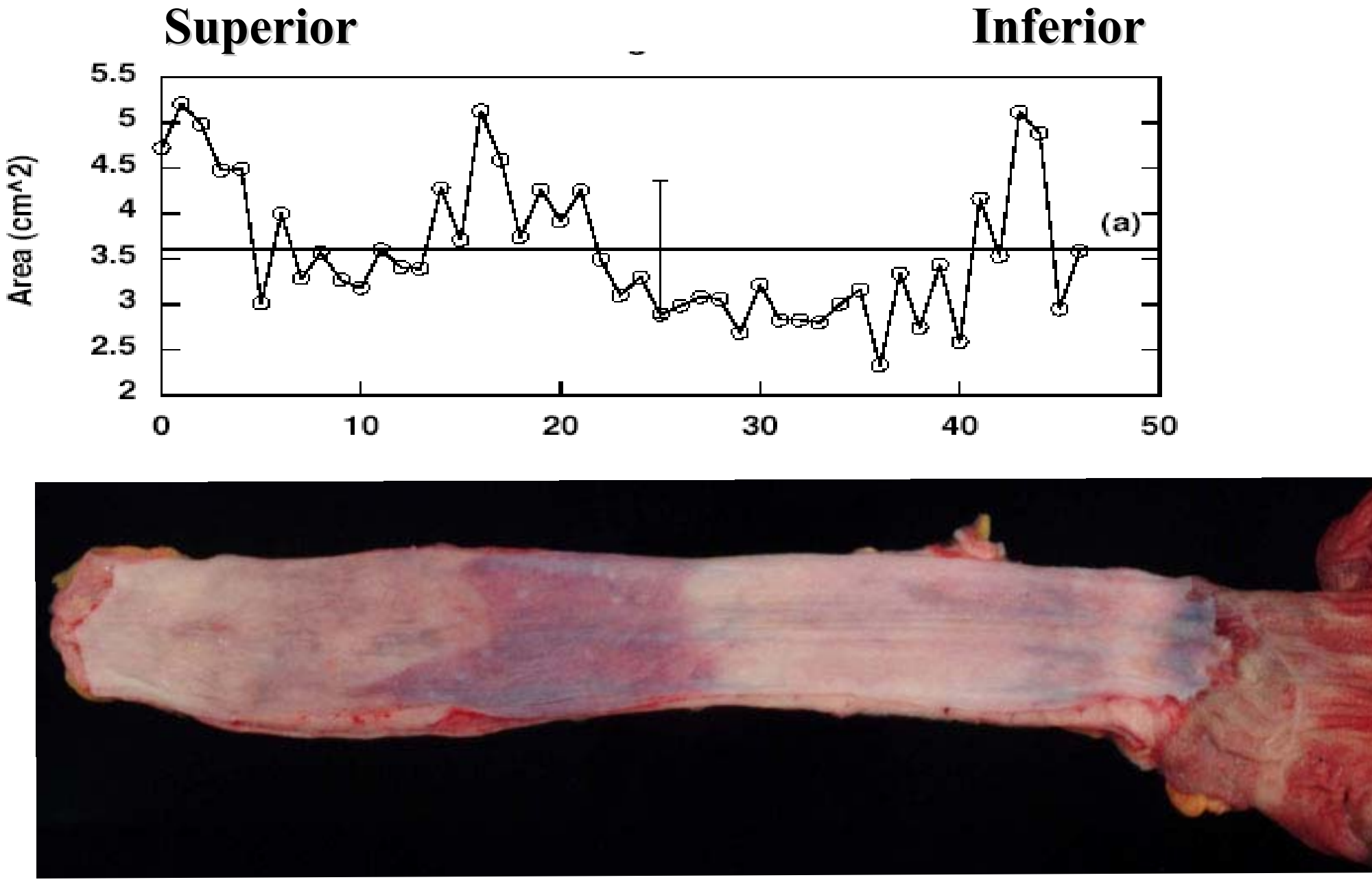


Marks *IJROBP* 34:1168, 1996

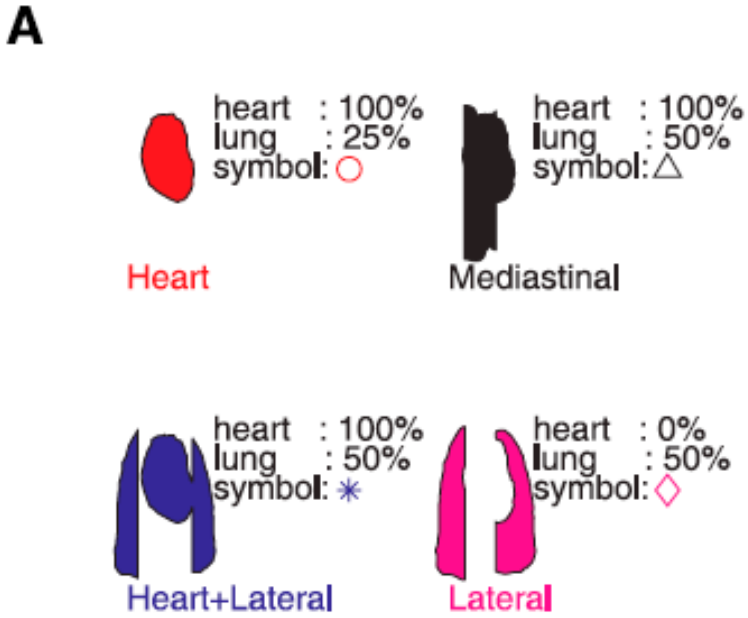


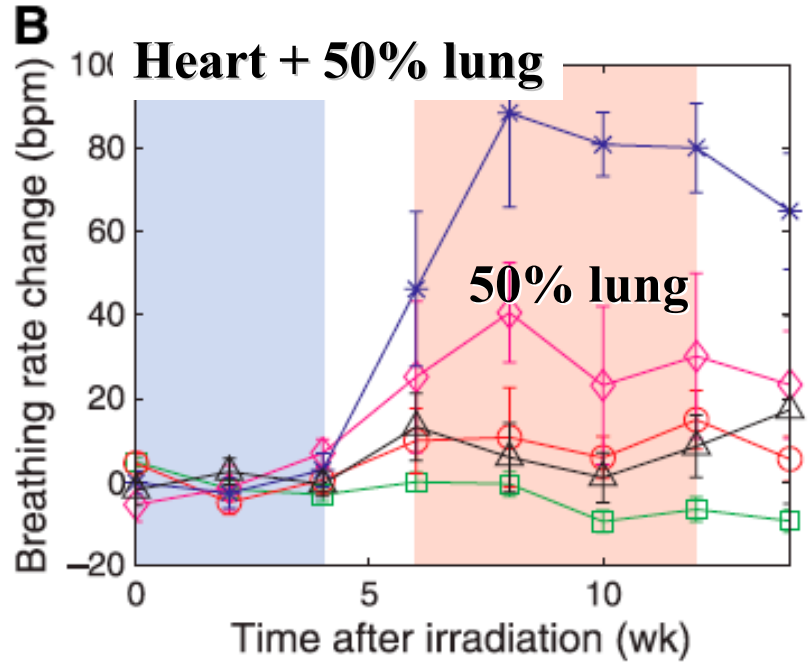


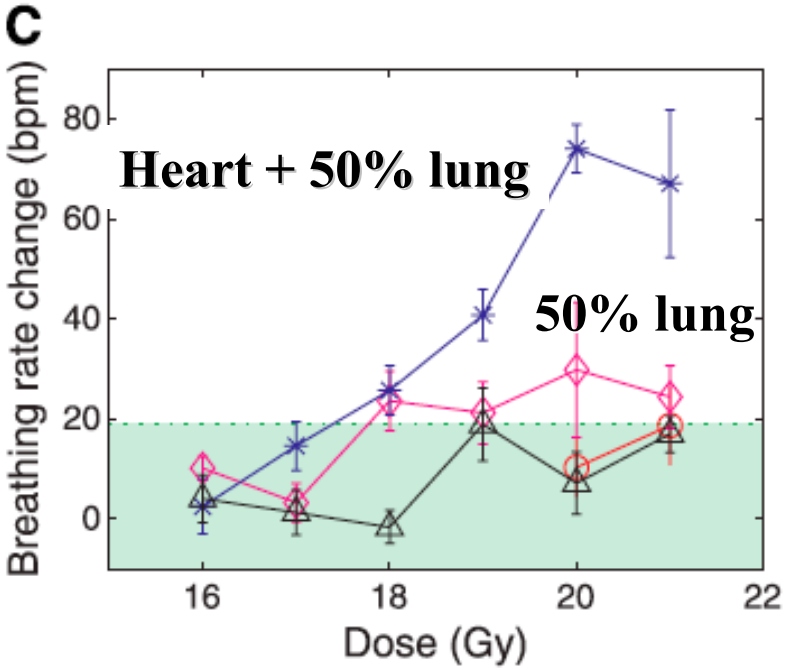
Esophagus contours:
variable area (volume)

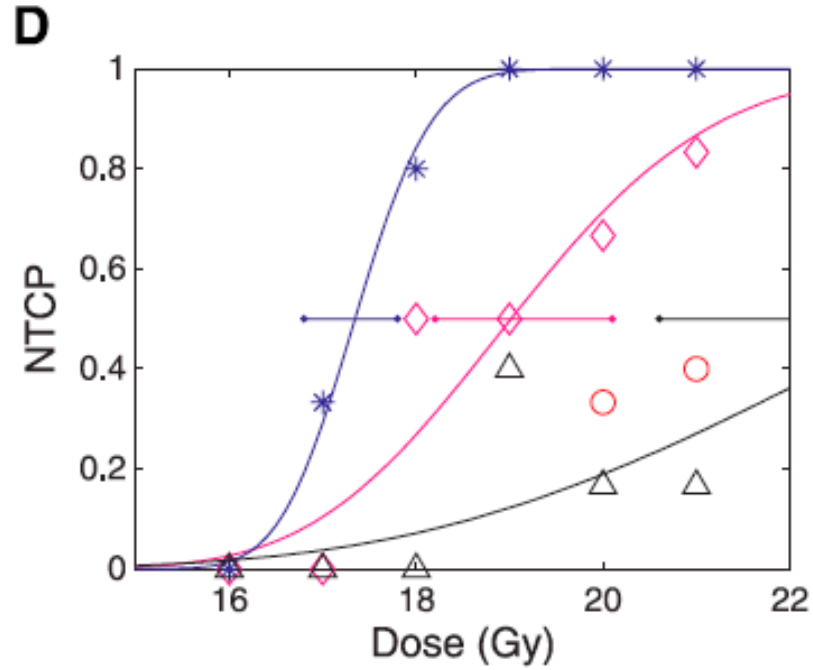

Superior
Inferior
Area (cm^2)
5.5
5
4.5
4
3.5
3
2.5
2
0
10
20
30
40
50
(a)

Organ interactions









Proton RT in Rats: Resp Rate = f (lung and heart RT)

Luijk Ca Res 65:6509, 2005

QUANTEC

- IJROBP Special Issue
- Recommendations (caveats)
  - Dose/Volume/Outcomes
  - Segmentation, imaging
  - Endpoints, reporting standards, scoring toxicities
  - Research: data sharing
- Web site: Blog, updates

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