Predicting Normal Tissue Injury in the Modern era: A Review of QUANTEC

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Disclosures

- Grants: NIH, Lance Armstrong
- Advisor: Impac (Mosaiq)
- UNC: Research grant-Siemens
- Recent:
  - Varian: grant, speaker
  - Dept of Defense: grant

TABLE 5.4
CLASS I ORGANS: FATAL/SEVERE MORBIDITY

Organ	Injury	$TD_{5/5}$*	$TD_{50/5}$**	Whole or Partial Organ (Field Size or Length)
Bone marrow	Aplasia, pancytopenia	250 3,000	450 4,000	Whole Segmental
Liver	Acute and chronic hepatitis	2,500 1,500	4,000 2,000	Whole Whole (strip)
Stomach	Perforation, ulcer, hemorrhage	4,500	5,500	100 cm
Intestine	Ulcer, perforation, hemorrhage	4,500 5,000	5,500 6,500	400 cm 100 cm
Brain	Infarction, necrosis	5,000	6,000	Whole
Spinal cord	Infarction, necrosis	4,500	5,500	10 cm
Heart	Pericarditis, pancarditis	4,500 7,000	5,500 8,000	60% 25%
Lung	Acute and chronic pneumonitis	3,000 1,500	3,500 2,500	100 cm Whole
Kidney	Acute and chronic nephrosclerosis	1,500 2,000	2,000 2,500	Whole (strip) Whole
Fetus	Death	200	400	Whole

Early summary table (Rubin, Cooper, Phillips)

TD 5/5 = Max Tolerated Dose 5% rate at within 5 years.

TD 50/5 = Max Tolerated Dose 50% rate within in 5 years.

● *Original Contribution*

Int J Radiat Oncol Biophys 1991:21;109-122.

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

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The importance of knowledge on tolerance of normal tissue organs to irradiation by radiation oncologists cannot be overemphasized. Unfortunately, current knowledge is less than adequate. With the increasing use of 3-D treatment planning and dose delivery, this issue, particularly volumetric information, will become even more critical. As a part of the NCI contract N01 CM-47316, a task force, chaired by the primary author, was formed and an extensive literature search was carried out to address this issue. In this manuscript we present the updated information on tolerance of normal tissues of concern in the protocols of this contract, based on

Task force estimated normal tissue tolerance

TD 5/5, TD 50/5 (5% or 50% risk at 5 years)

for 1/3, 2/3 and whole organ, using

- **Literature review**
- **Task force members' "own experience"**

. . . for 26 organs

Organ	TD 5/5 Volume 1/3	TD 5/5 Volume 2/3	TD 5/5 Volume 3/3	TD 50/5 Volume 1/3	TD 50/5 Volume 2/3	TD 50/5 Volume 3/3	Selected endpoint
Kidney I	5000	3000*	2300		4000*	2800	Clinical nephritis
Kidney II							
Bladder	N/A	8000	6500	N/A	8500	8000	Symptomatic bladder contracture and volume loss
Bone:							
Femoral Head I and II	—	—	5200	—	—	6500	Necrosis
T-M joint mandible	6500	6000	6000	7700	7200	7200	Marked limitation of joint function
Rib cage	5000	—	—	6500	—	—	Pathologic fracture
Skin	10 cm^2 / —	30 cm^2 / —	100 cm^2 / 5000	10 cm^2 / —	30 cm^2 / —	100 cm^2 / 6500	Telangiectasia
	7000	6000	5500	—	—	7000	Necrosis Ulceration
Brain	6000	5000	4500	7500	6500	6000	Necrosis Infarction
Brain stem	6000	5300	5000	—	—	6500	Necrosis Infarction
Optic nerve I & II	No partial volume		5000	—	—	6500	Blindness
Chiasma	No partial volume		5000	No partial volume		6500	Blindness
Spinal cord	5 cm / 5000	10 cm / 5000	20 cm / 4700	5 cm / 7000	10 cm / 7000	20 cm / —	Myelitis necrosis
Cauda equina	No volume effect		6000	No volume effect		7500	Clinically apparent nerve damage
Brachial plexus	6200	6100	6000	7700	7600	7500	Clinically apparent nerve damage
Eye lens I and II	No partial volume		1000	—	—	1800	Cataract requiring intervention
Eye retina I and II	No partial volume		4500	—	—	6500	Blindness
Ear mid/external	3000	3000	3000*	4000	4000	4000*	Acute serous otitis
Ear mid/external	5500	5500	5500*	6500	6500	6500*	Chronic serous otitis
Parotid* I and II	—	3200*	3200*	—	4600*	4600*	Xerostomia
				(TD 100/5 is 5000)			
Larynx	7900*	7000*	7000*	9000*	8000*	8000*	Cartilage necrosis
Larynx	—	4500	4500*	—	—	8000*	Laryngeal edema
Lung I	4500	3000	1750	6500	4000	2450	Pneumonitis
Lung II							
Heart	6000	4500	4000	7000	5500	5000	Pericarditis

"3D Hope"

Dose/volume

☺

↓

Normal tissue outcome

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"3D Hope"

Dose/volume

Normal tissue outcome

"Reality"

Information overload.
Which parameters?
DVH limitations

Patient/tumor factors

Which endpoints?

Applicability? Evolving therapies, SRS, IMRT, Hypo fxn

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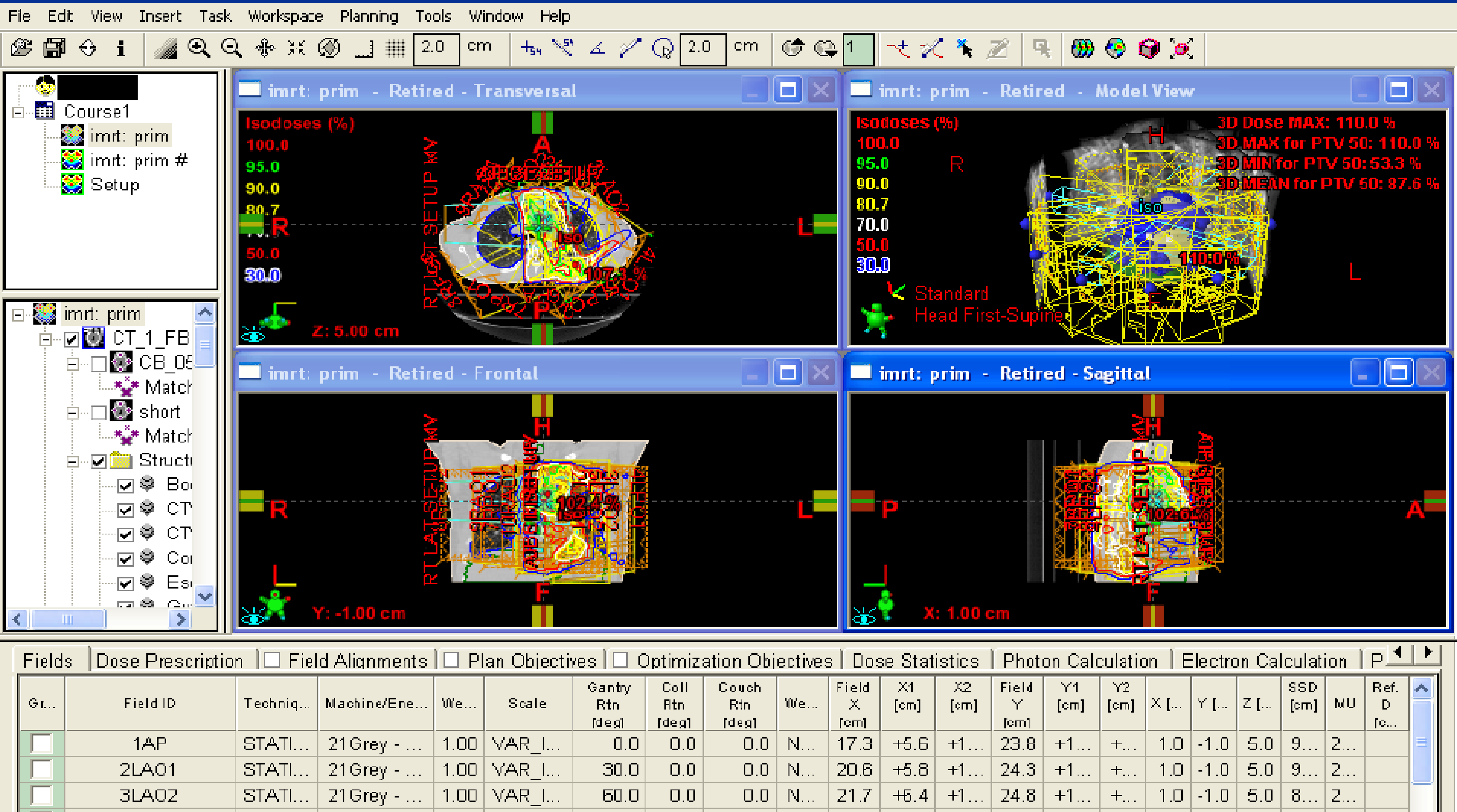
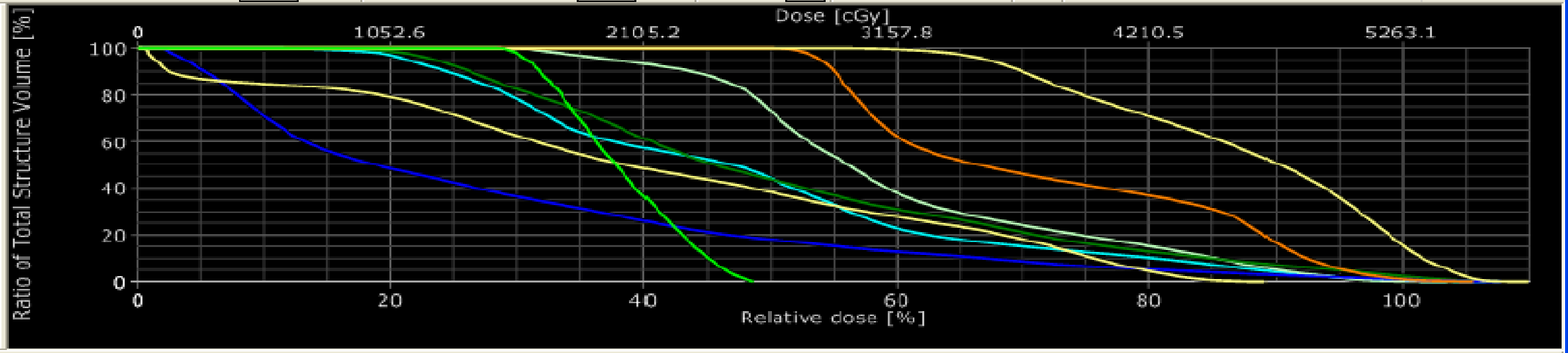
Information overload. Revenge!



No wonder we crave models, figures of merit



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

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

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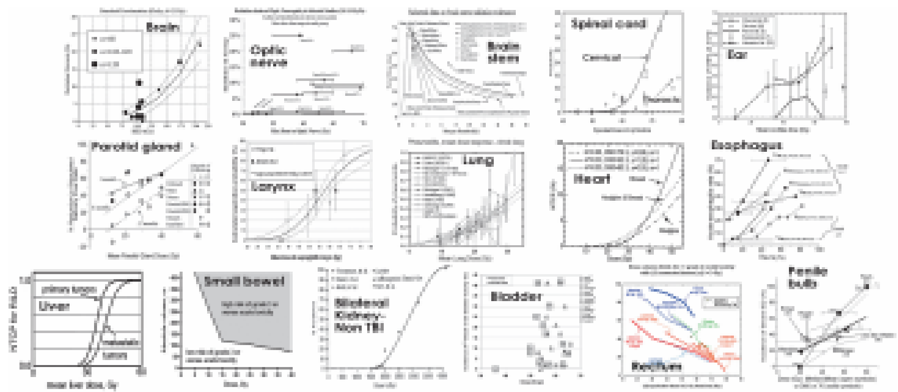
Supplement to
INTERNATIONAL JOURNAL OF

Radiation Oncology

BIOLOGY • PHYSICS

VOLUME 76, NUMBER 3, SUPPLEMENT 2010

QUANTITATIVE ANALYSES OF NORMAL TISSUE EFFECTS IN THE CLINIC



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Official Journal of
ASTRO AMERICAN SOCIETY FOR RADIATION ONCOLOGY
PAEDIATRIC RADIATION ONCOLOGY SOCIETY

Affiliated with
LATIN AMERICAN ASSOCIATION OF THERAPEUTIC RADIATION AND ONCOLOGY

ELSEVIER
ISSN 0360-3016

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY • BIOLOGY • PHYSICS
Vol. 76, No. 3, Supplement, 2010

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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

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

Objective: MDs, physicists, statistician
Clinically relevant: pneumonitis vs CT or PFT

Comparison of Emami vs QUANTEC

	Emami et al	QUANTEC
Number of organs	26	16
3D data available	Minimal	More/Moderate (18 year interval)
Format dose/volume limits	Uniform TD 5/5, 50/5 for 1/3, 2/3, 3/3	Non-uniform
Endpoints	Specific	Specific
Expert Opinion	Moderate	Less

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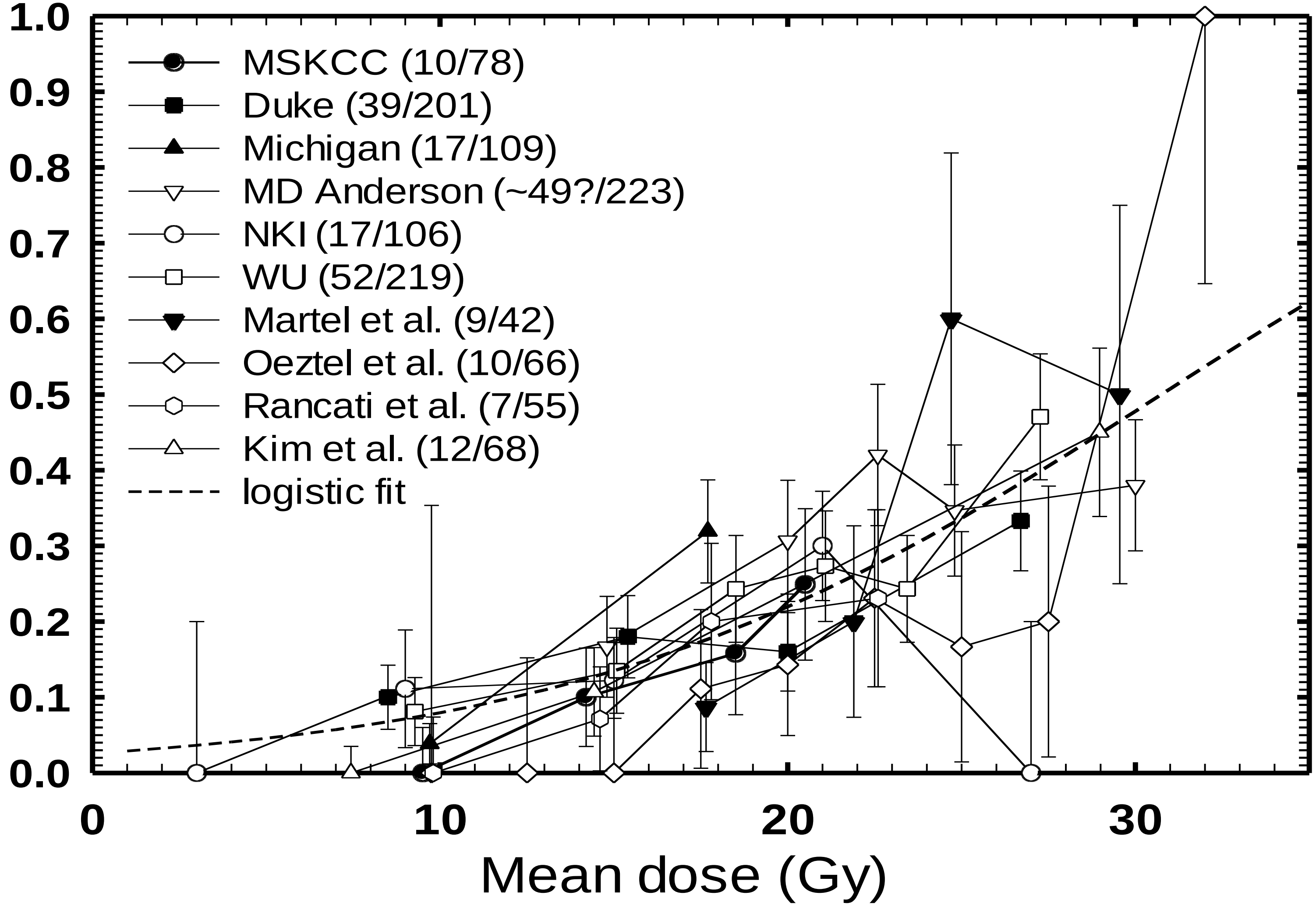
Examples from Quantec

Mean dose response of pneumonitis

(Andy Jackson and others)

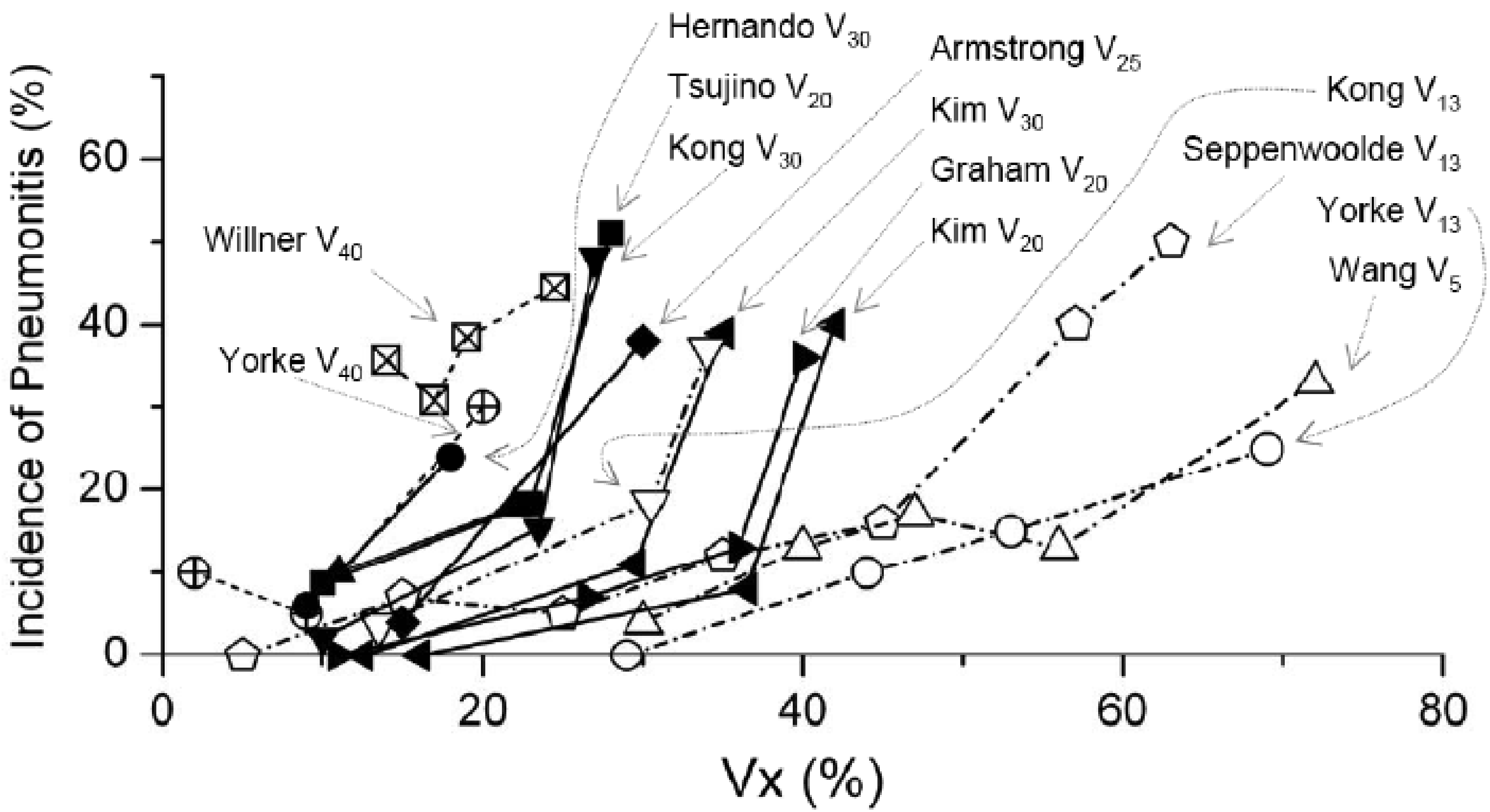
- Patients treated for NSCLC
  - Data from 9 institutions, 10 separate studies
- 1,167 patients with 222 cases of pneumonitis
- ≥ Grade 3 RTOG ~ ≥ Grade 2 SWOG
  - (requiring steroids)
  - accepted ≥ grade 1 definition if few grade 1 cases

Pneumonitis, mean dose response - whole lung

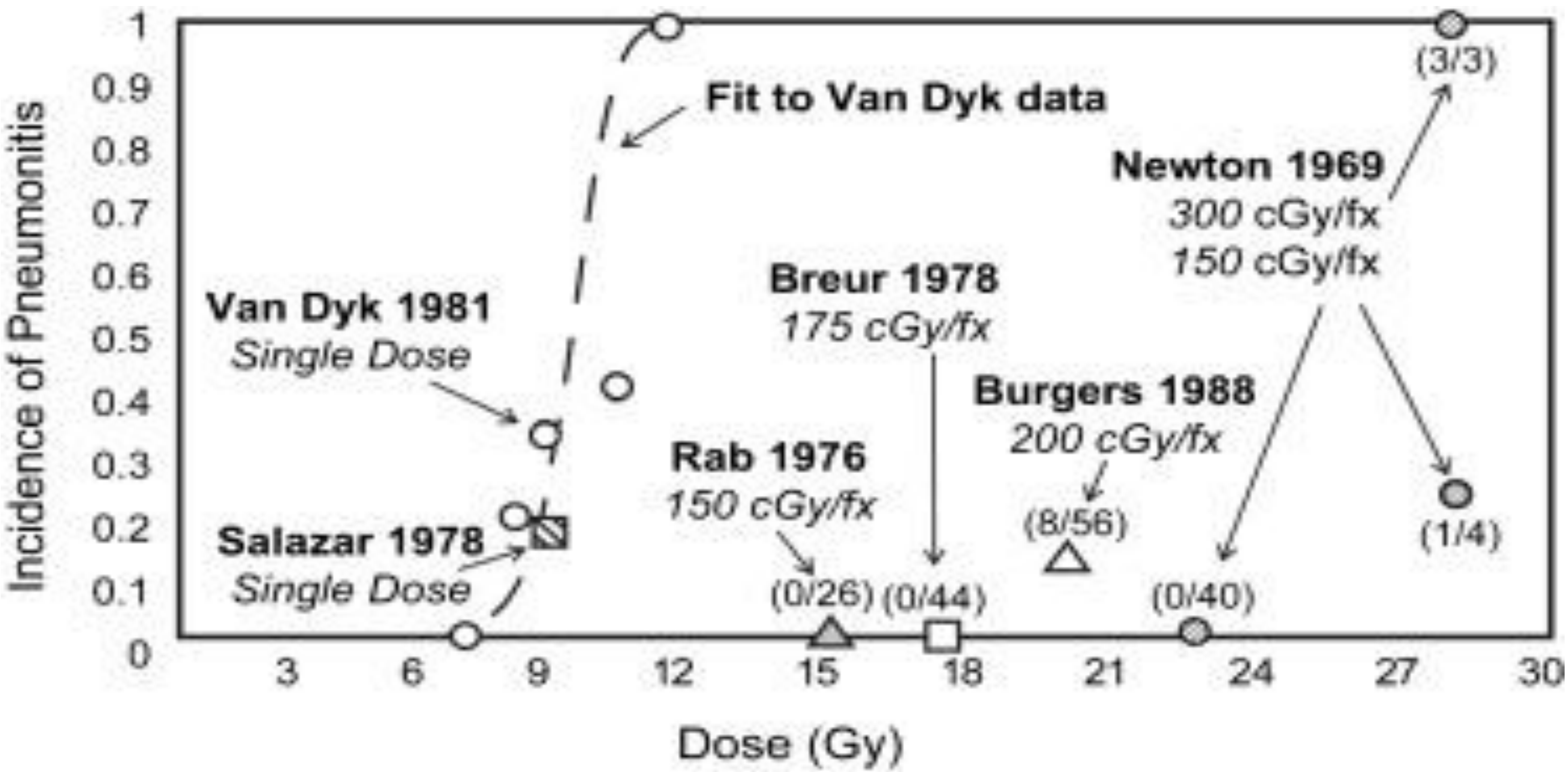


Objective data review: Jackson, Deasy, Martel, Bentzen

1,167 pts NSCLCa, 9 centers



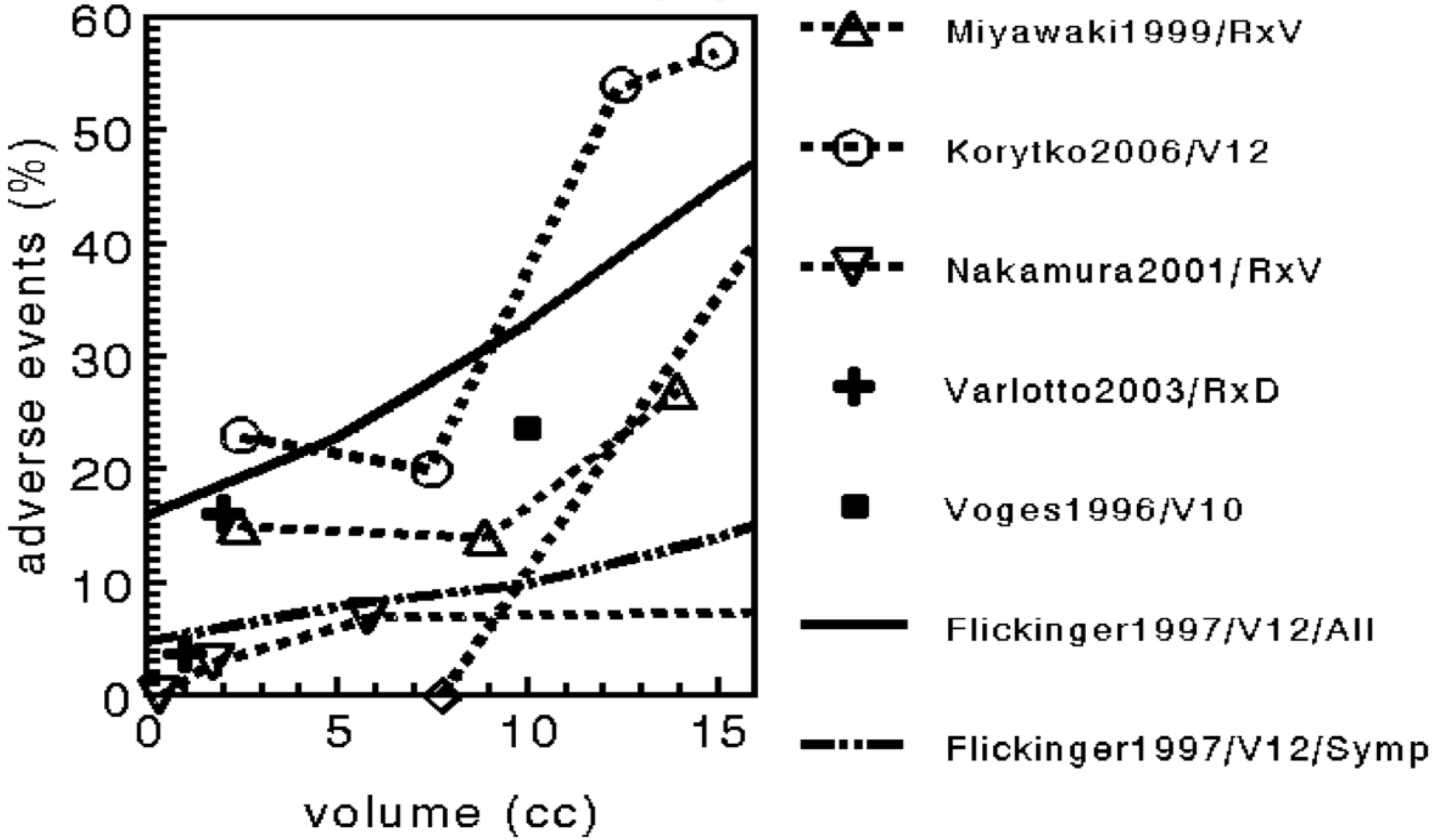
Quantec Lung: Figure by Jessica Hubbs



Fit to Van Dyk data
Newton 1969
300 cGy/fx
150 cGy/fx
(3/3)
Van Dyk 1981
Single Dose
Breur 1978
175 cGy/fx
Burgers 1988
200 cGy/fx
Rab 1976
150 cGy/fx
Salazar 1978
Single Dose
(8/56)
(1/4)
(0/26)
(0/44)
(0/40)
Incidence of Pneumonitis
Dose (Gy)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
3
6
9
12
15
18
21
24
27
30

Single Fraction Radiosurgery

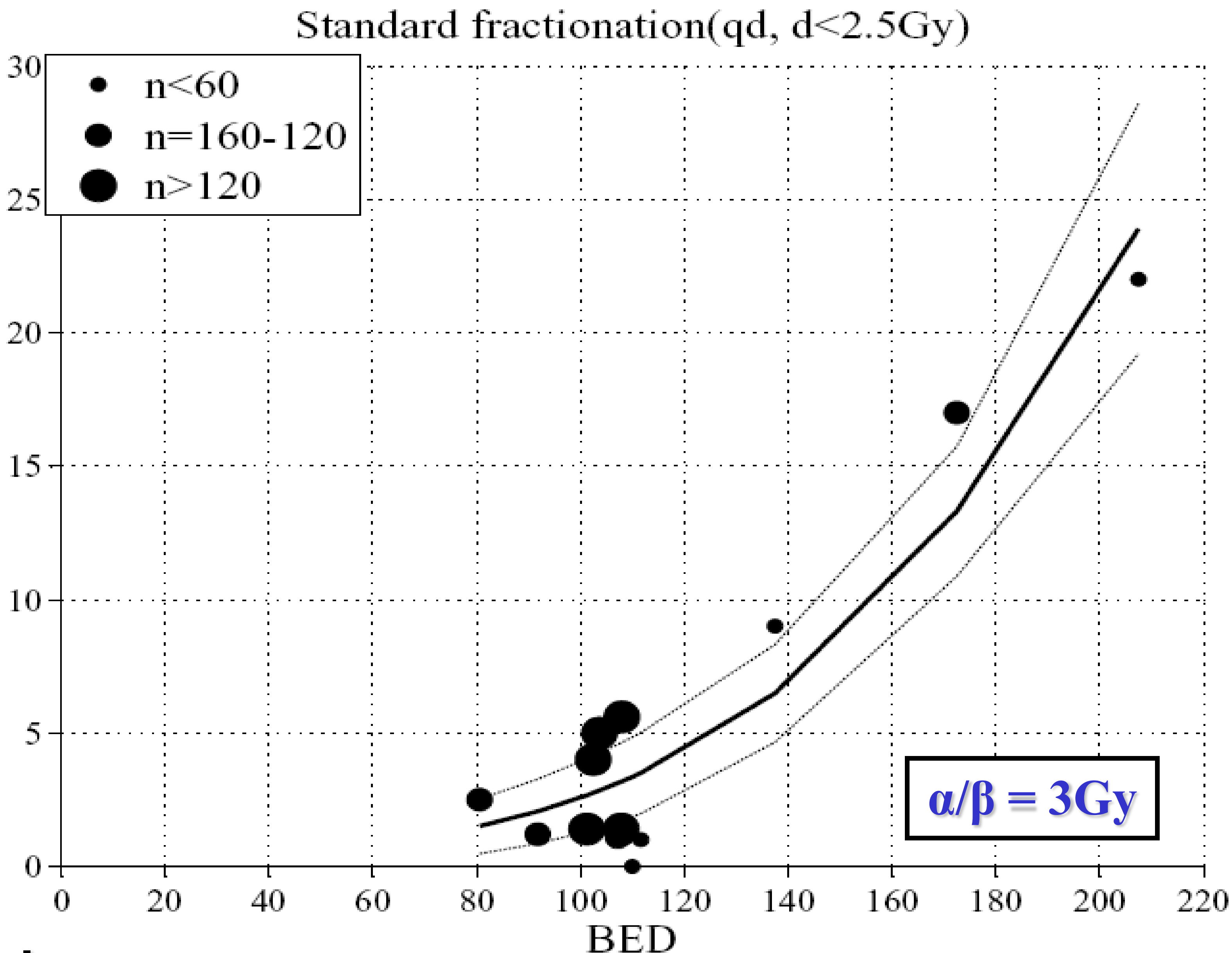
Brain (1)



Yaakov Lawrence

Brain (2)

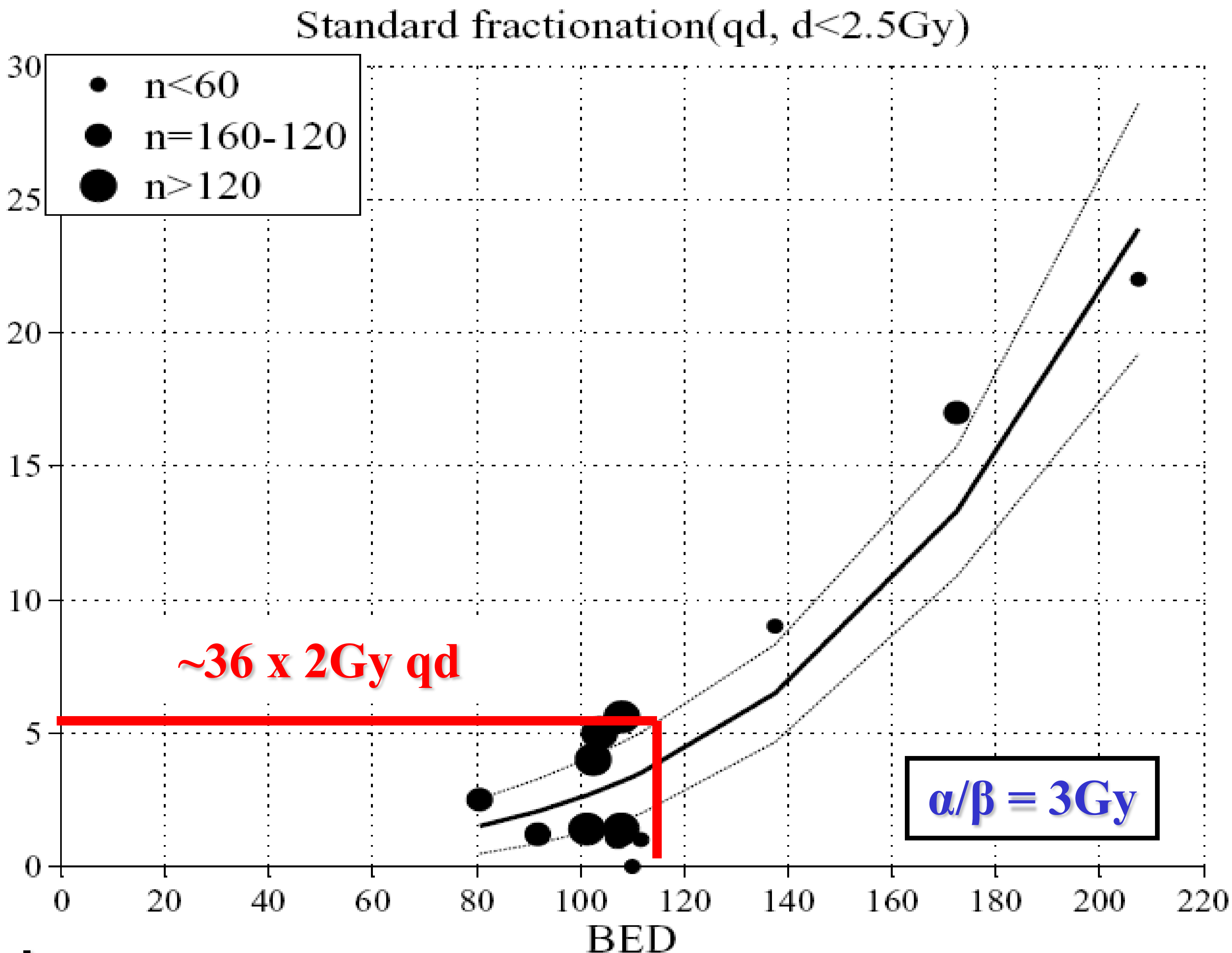
Long Term Side Effects



Yaakov Lawrence

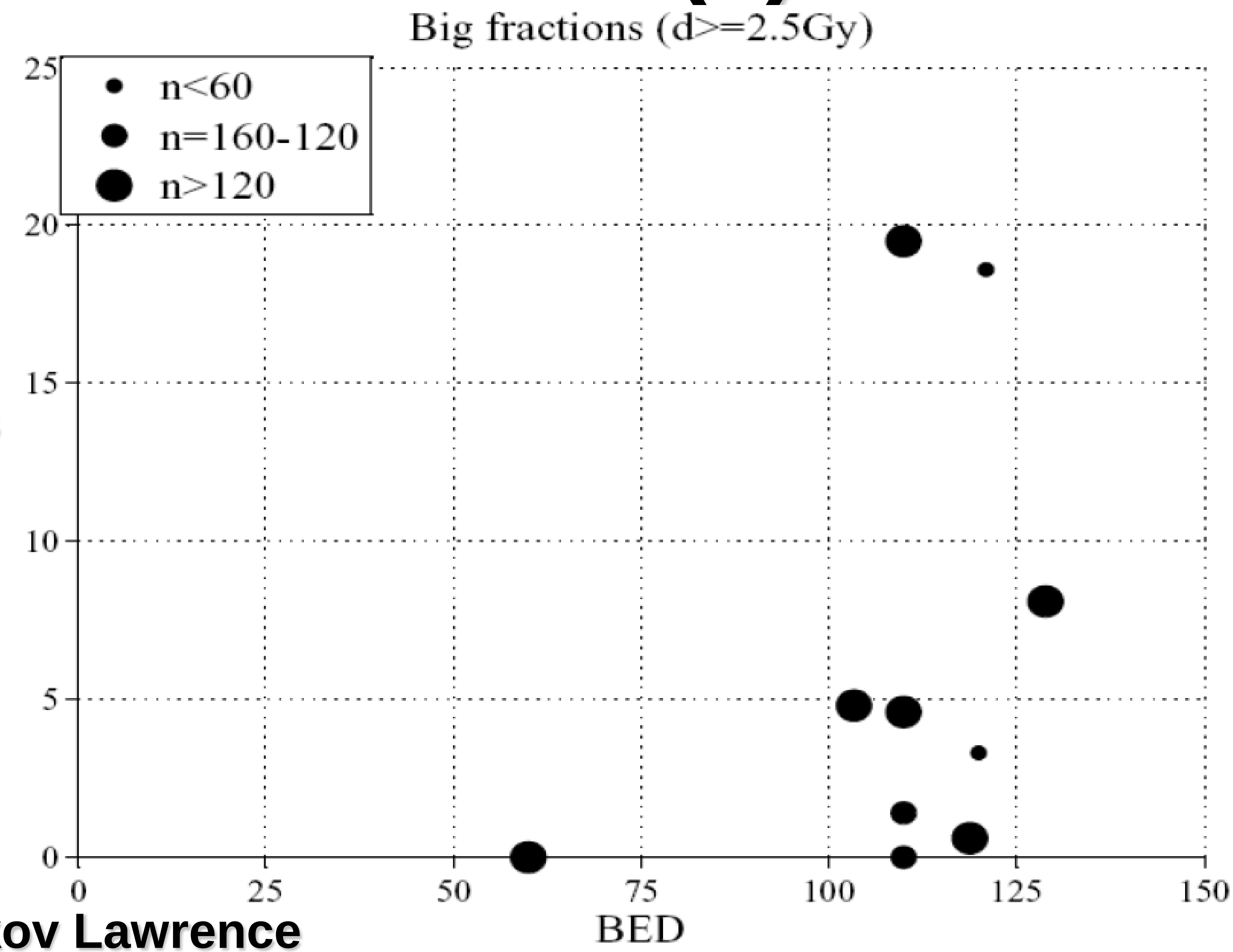
Brain (2)

Long Term Side Effects



Yaakov Lawrence

Brain (3)

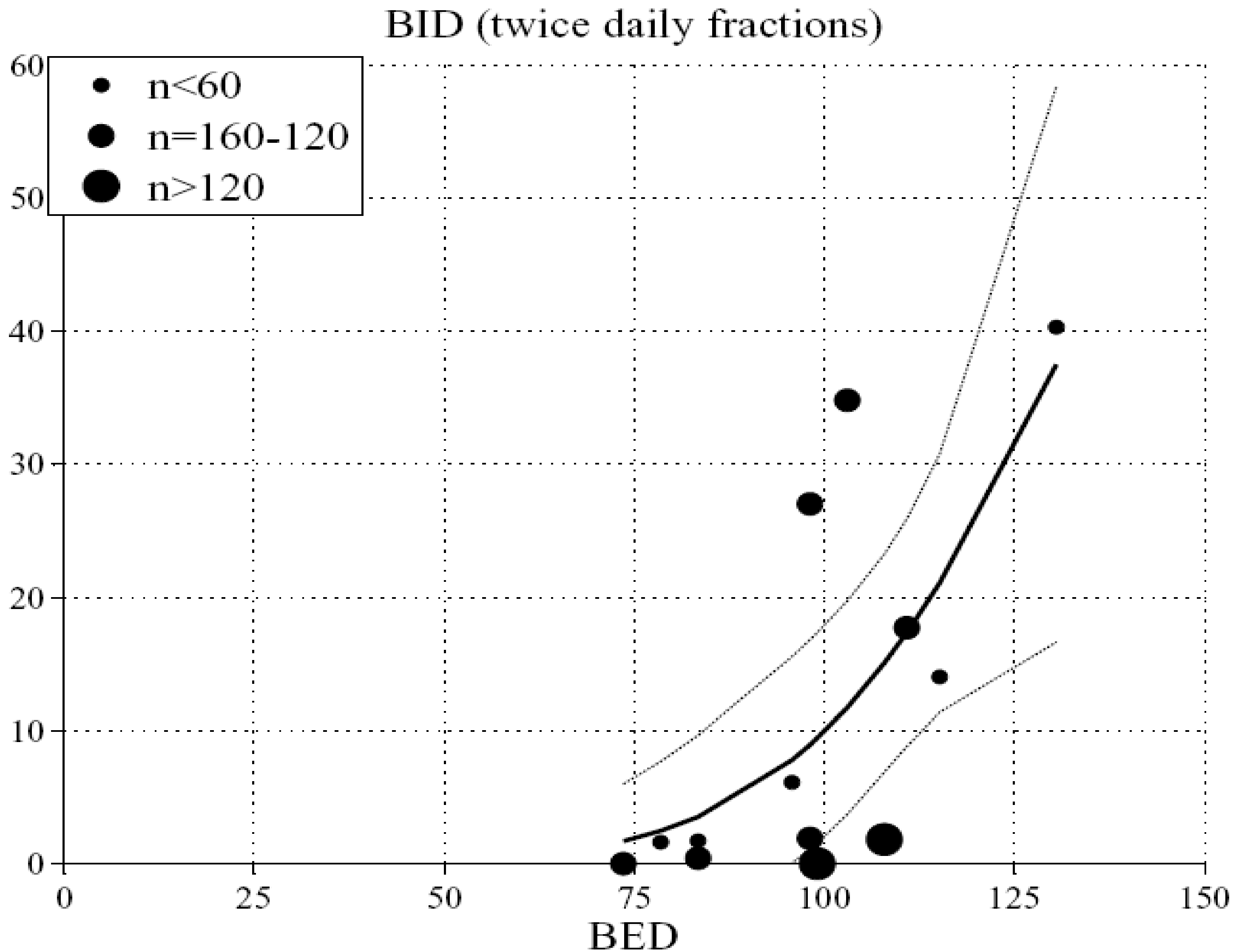


Long Term Side Effects

Yaakov Lawrence

Brain (4)

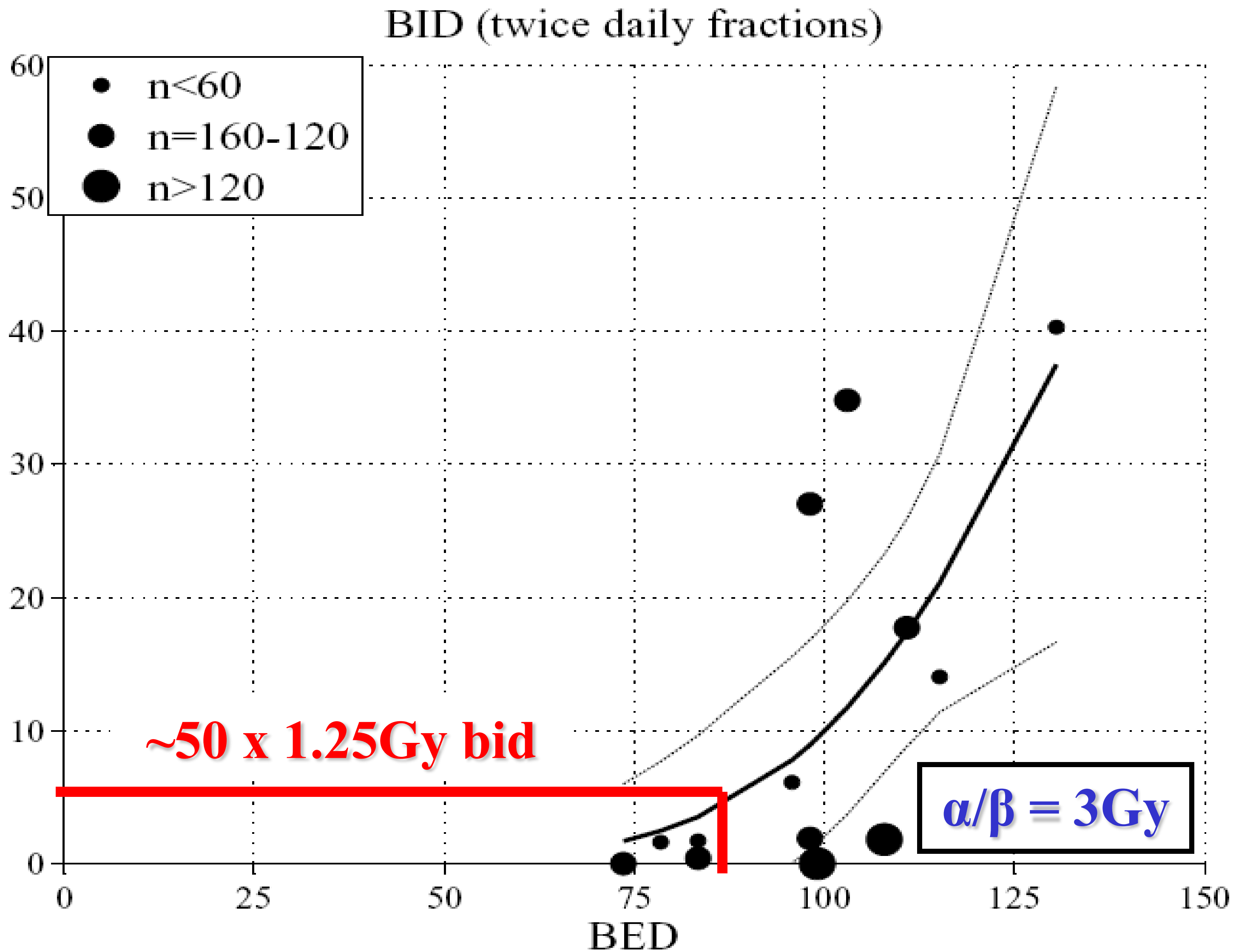
Long Term Side Effects



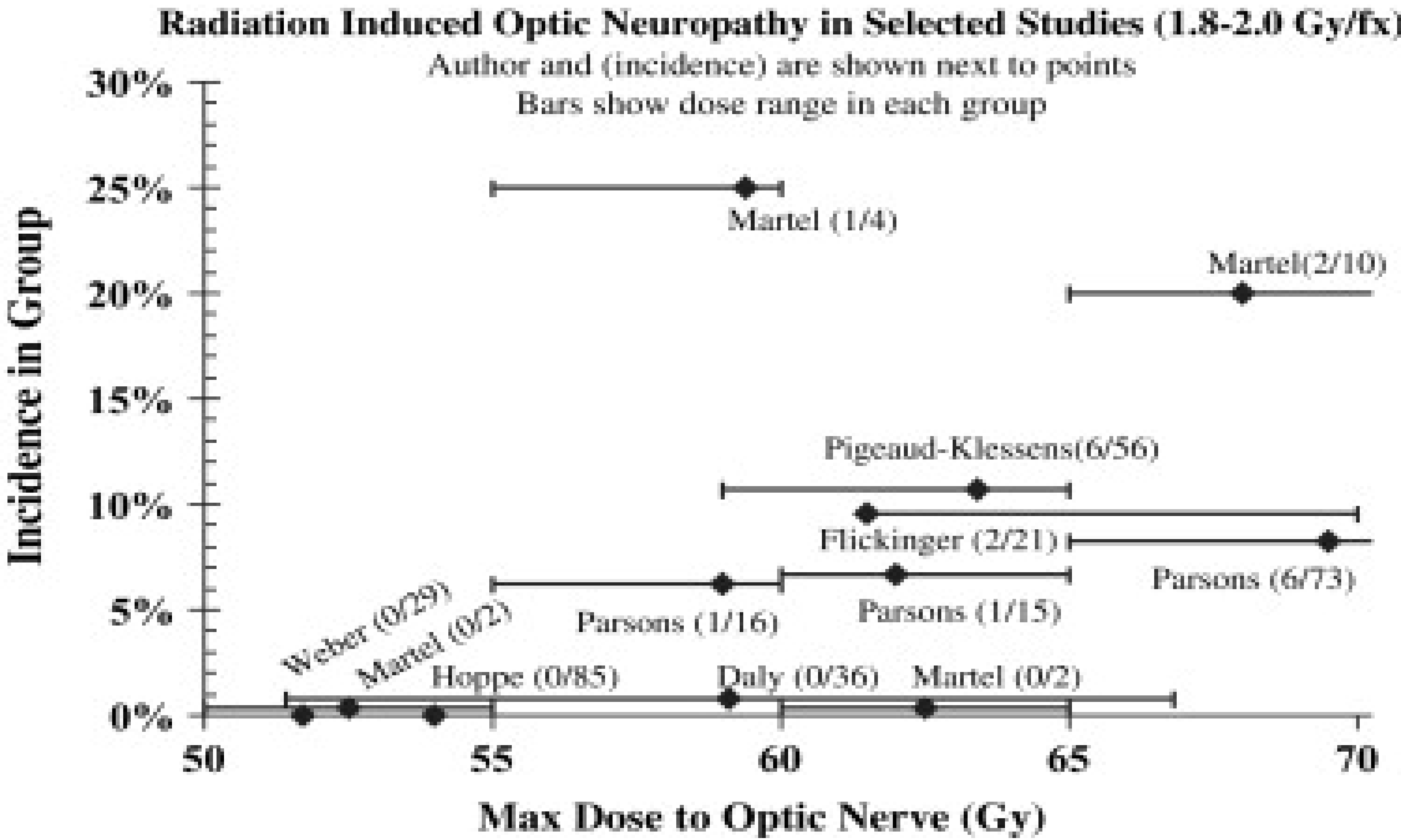
Yaakov Lawrence

Brain (4)

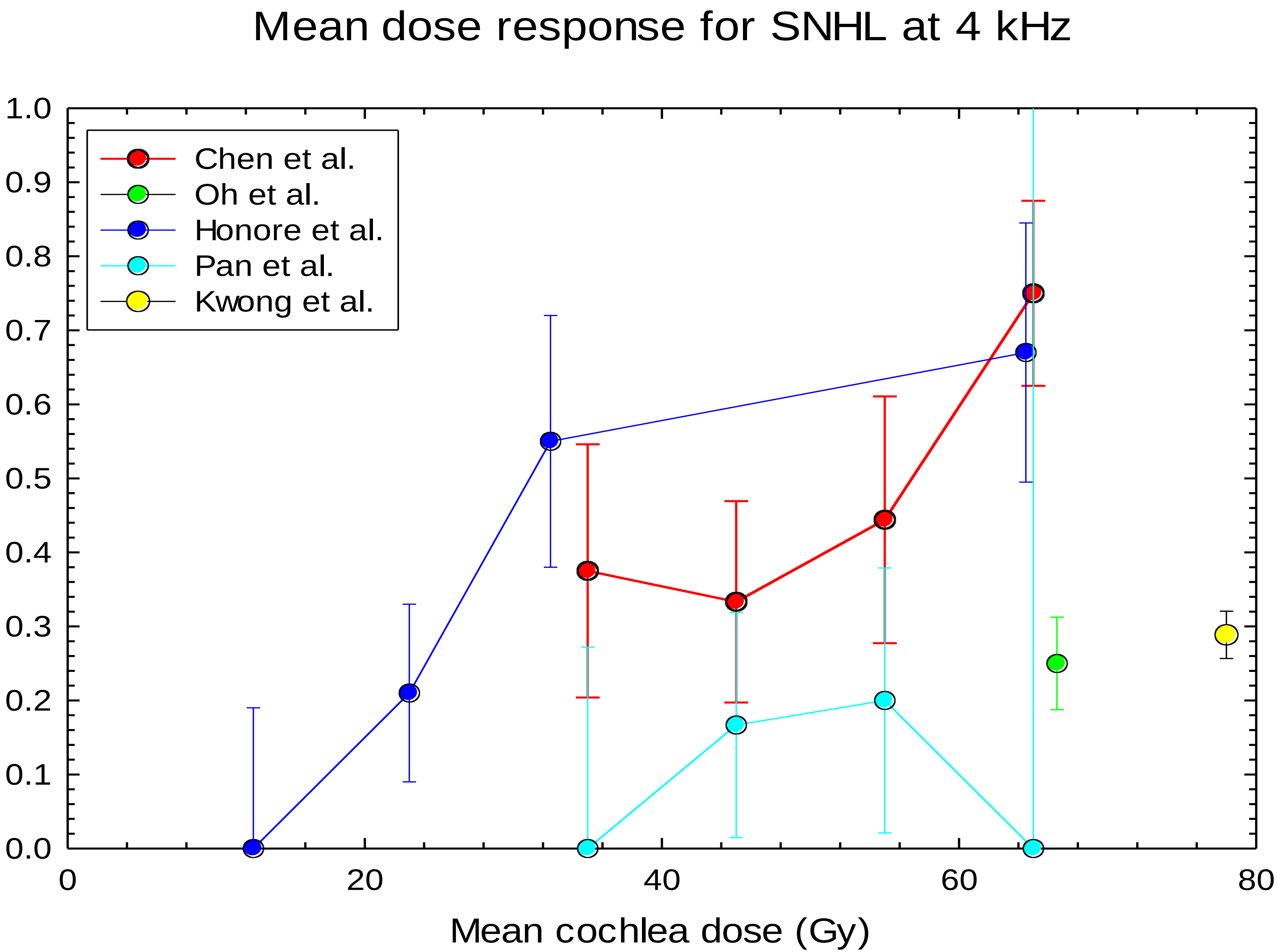
Long Term Side Effects



Yaakov Lawrence

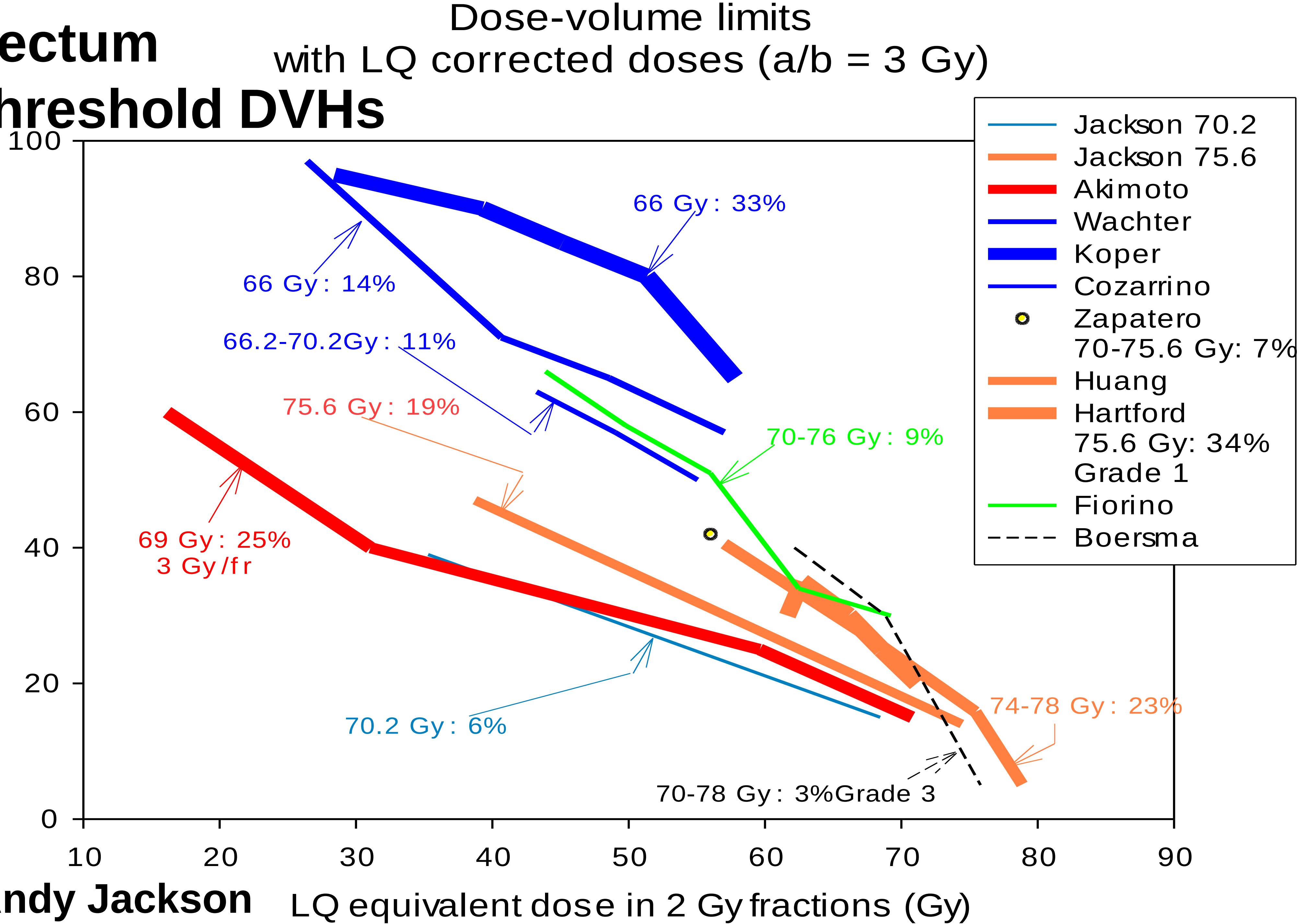


Mayo et al, Optic Nerve

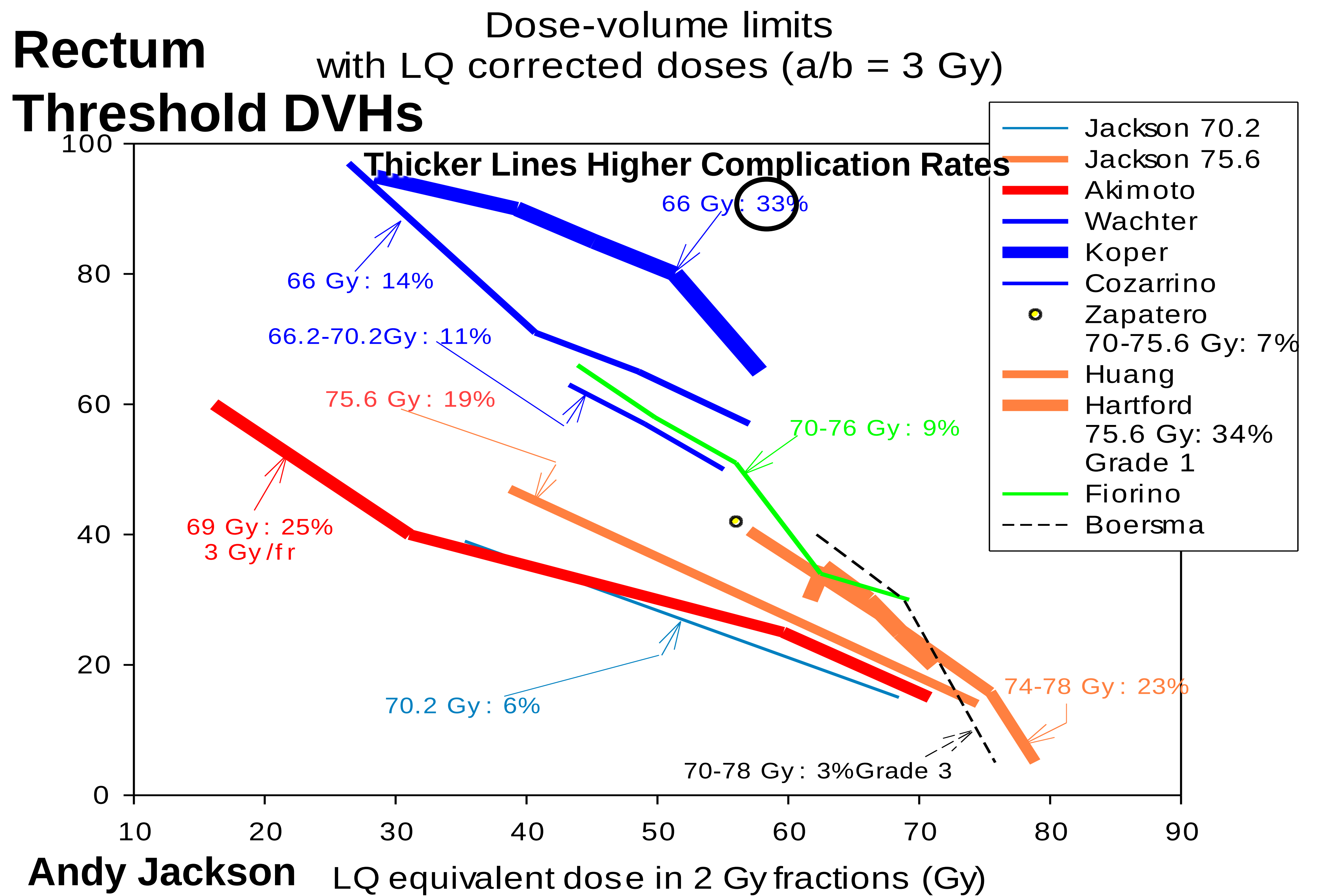


Niranjan Bhandare et al, Ear

Rectum Threshold DVHs



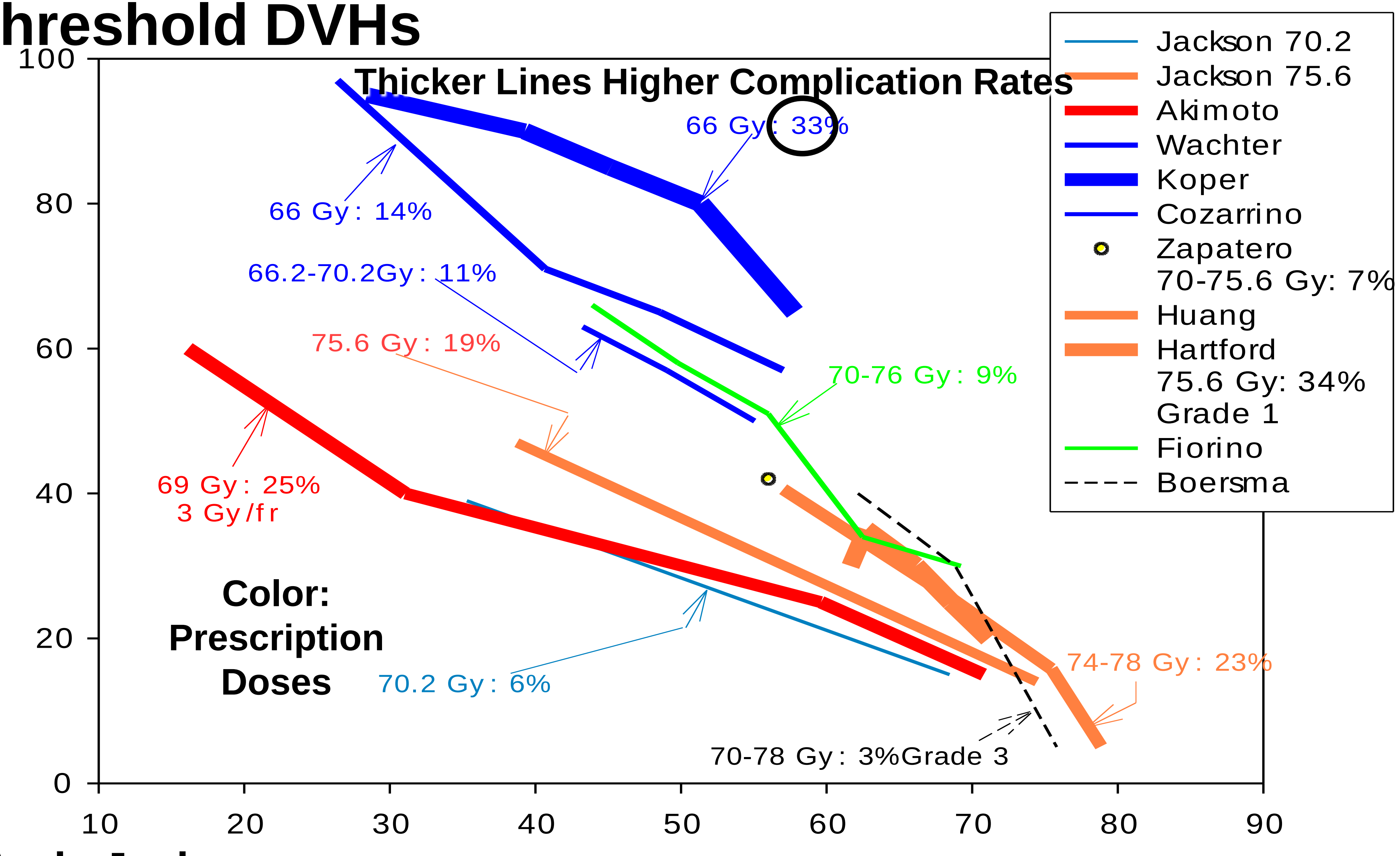
Andy Jackson



Rectum
Threshold DVHs
Dose-volume limits
with LQ corrected doses (a/b = 3 Gy)
Thicker Lines Higher Complication Rates
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
0
20
40
60
80
100
10
20
30
40
50
60
70
80
90
Andy Jackson
LQ equivalent dose in 2 Gy fractions (Gy)

Rectum Threshold DVHs

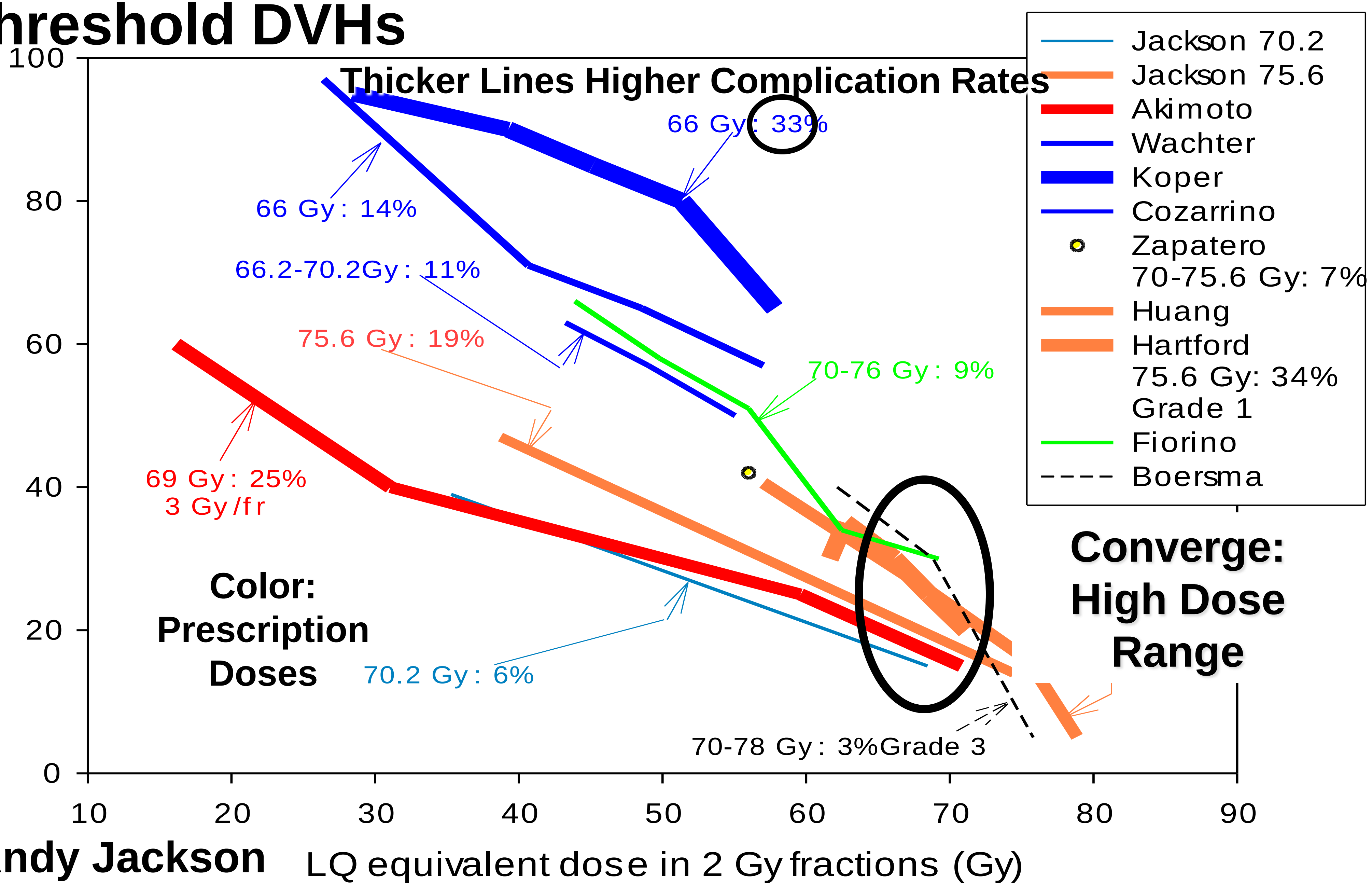
Dose-volume limits
with LQ corrected doses (a/b = 3 Gy)



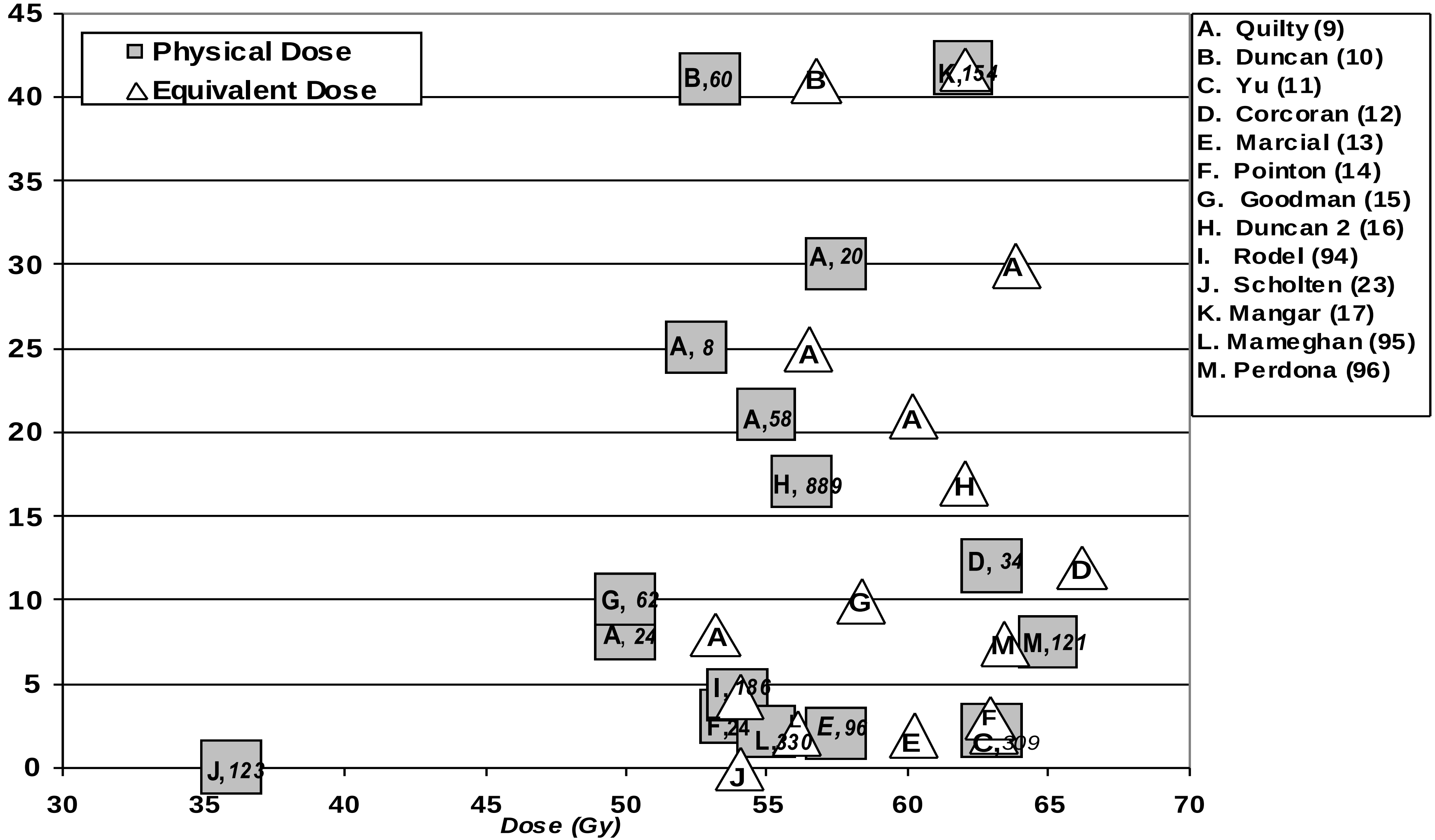
Andy Jackson LQ equivalent dose in 2 Gy fractions (Gy)

Rectum Threshold DVHs

Dose-volume limits
with LQ corrected doses (a/b = 3 Gy)

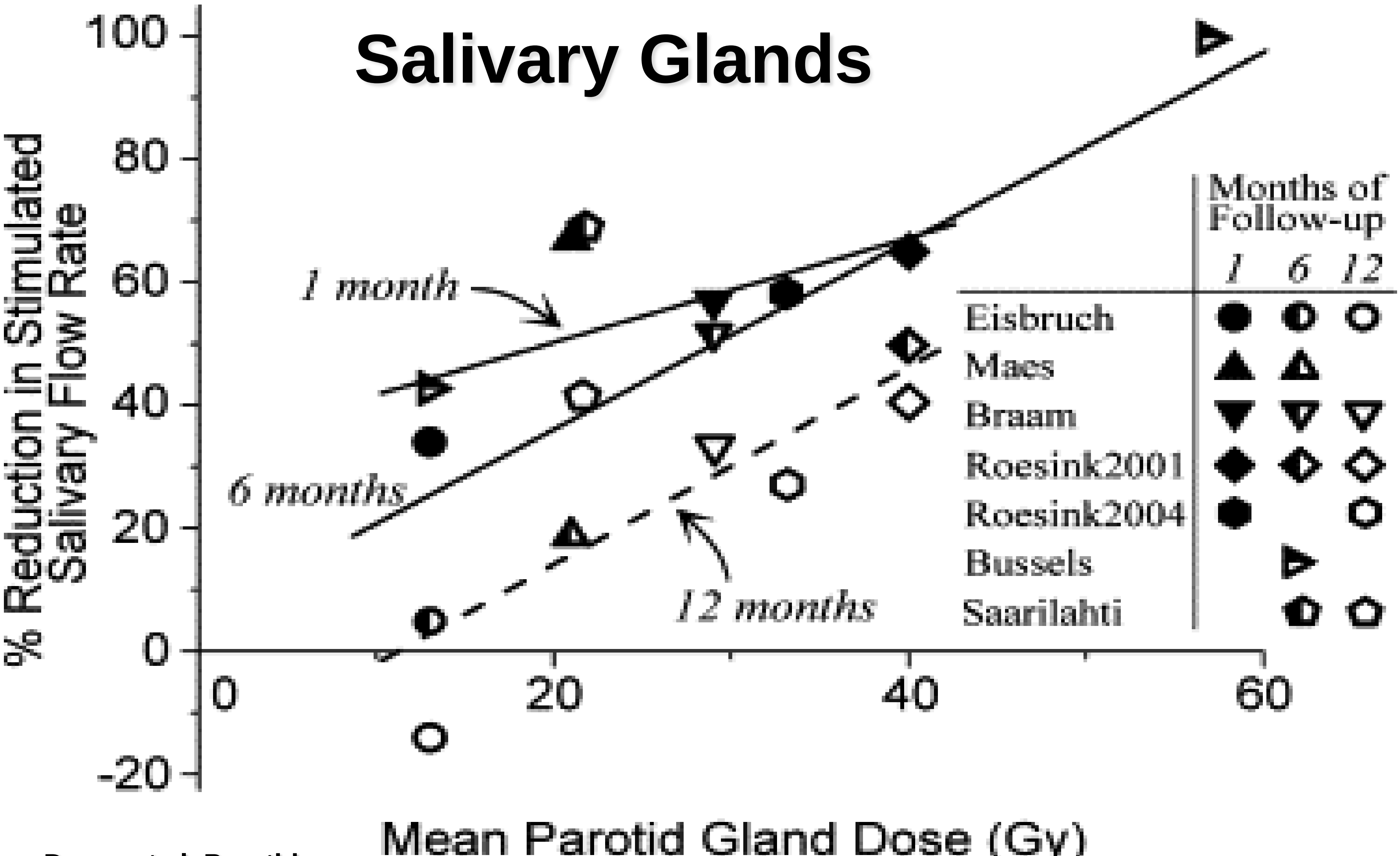


Andy Jackson

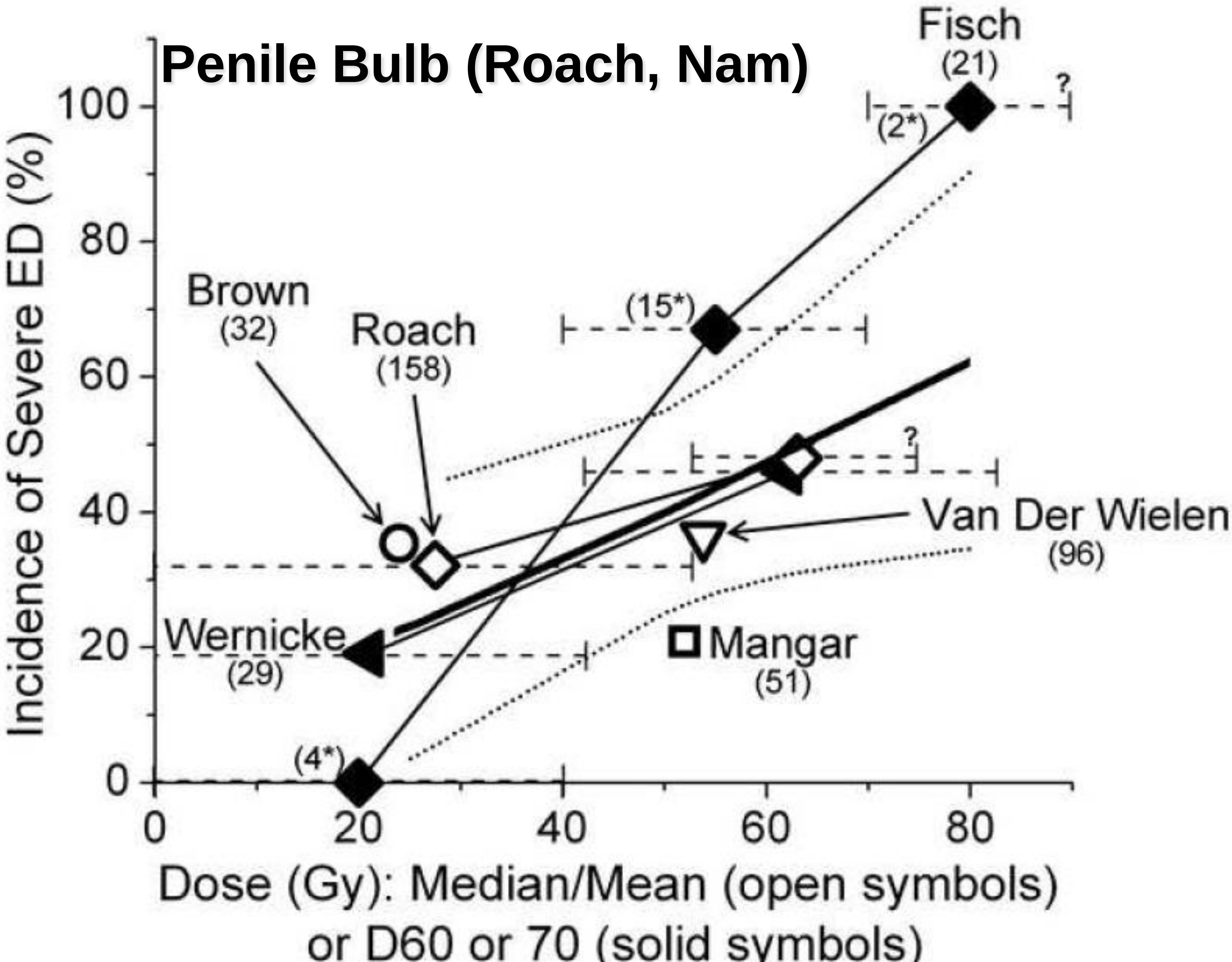


Bladder: Yorkee and Viswanathan

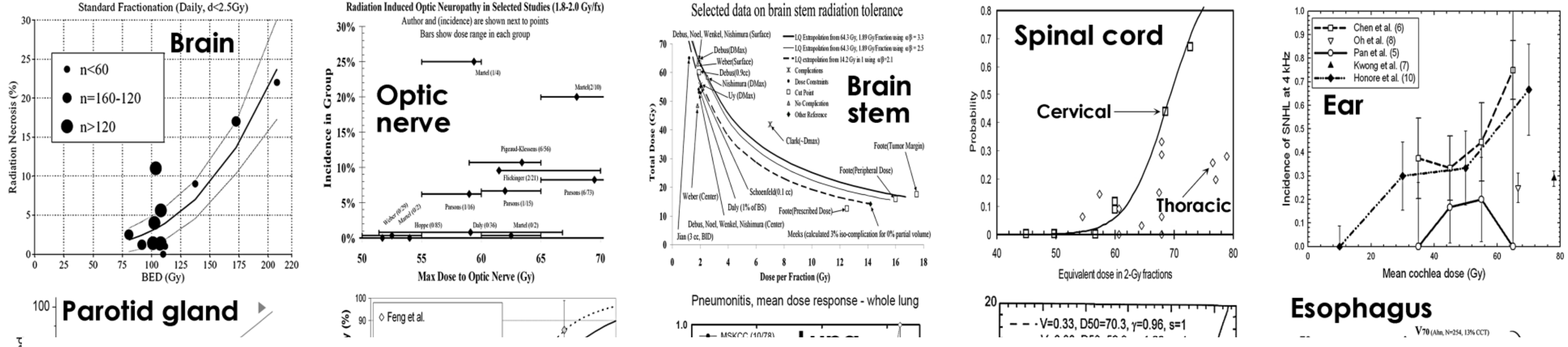
Salivary Glands

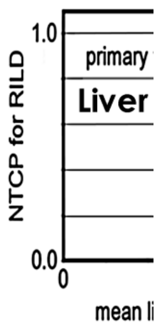


Deasy et al, Parotid



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 (%)
100
80
60
40
20
0
0
20
40
60
80
Dose (Gy): Median/Mean (open symbols)
or D60 or 70 (solid symbols)





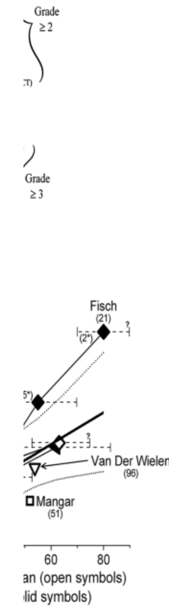


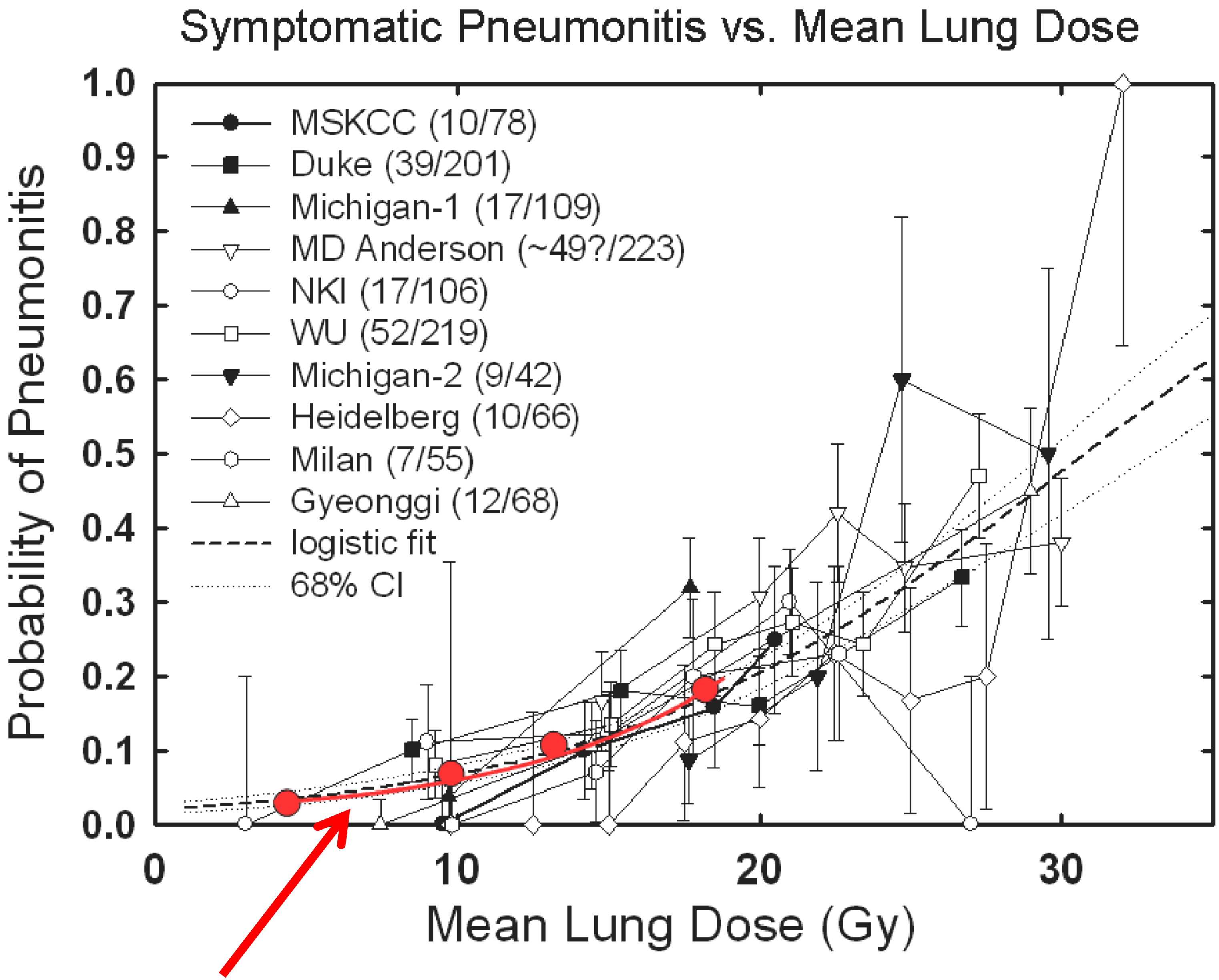
Table 1. Normal tissue tolerance to therapeutic irradiation

Organ	TD 5/5 Volume 1/3	2/3	3/3	TD 50/5 Volume 1/3	2/3	3/3	Selected endpoint
Kidney I	5000	3000*	2300	—	4000*	2800	Clinical nephritis
Kidney II							
Bladder	N/A	8000	6500	N/A	8500	8000	Symptomatic bladder contracture and volume loss
Bone:							
Femoral Head I and II	—	—	5200	—	—	6500	Necrosis
T-M joint mandible	6500	6000	6000	7700	7200	7200	Marked limitation of joint function
Rib cage	5000	—	—	6500	—	—	Pathologic fracture
Skin	10 cm² —	30 cm² —	100 cm² 5000	10 cm² —	30 cm² —	100 cm² 6500	Telangiectasia
	7000	6000	5500	—	—	7000	Necrosis Ulceration
Brain	6000	5000	4500	7500	6500	6000	Necrosis Infarction
Brain stem	6000	5300	5000	—	—	6500	Necrosis Infarction
Optic nerve I & II	No partial volume		5000	—	—	6500	Blindness
Chiasma	No partial volume		5000	No partial volume		6500	Blindness
Spinal cord	5 cm 5000	10 cm 5000	20 cm 4700	5 cm 7000	10 cm 7000	20 cm —	Myelitis necrosis
Cauda equina	No volume effect		6000	No volume effect		7500	Clinical

QUANTEC: Adult Focused

- Guidelines may apply
  - lung
  - heart
  - bowel
  - kidney
  - liver

Missing
  - growth
  - neurocognitive
  - endocrine
  - cancer induction



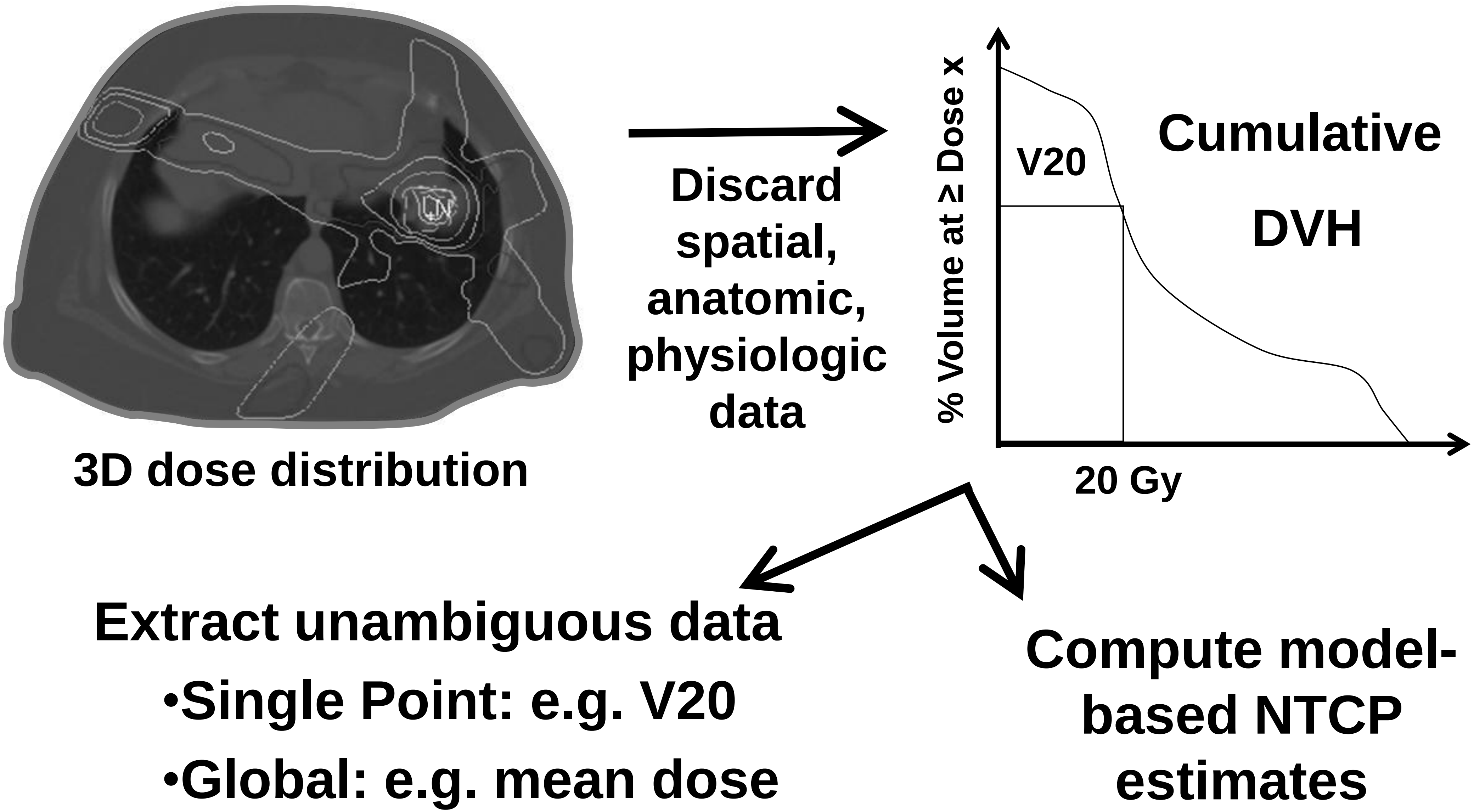
Data in children from Matthew Krasin, St Jude

Quantec: Mostly conventional fractionation

Some hypo-fractionation
brain
lung
liver

Context/Limitations

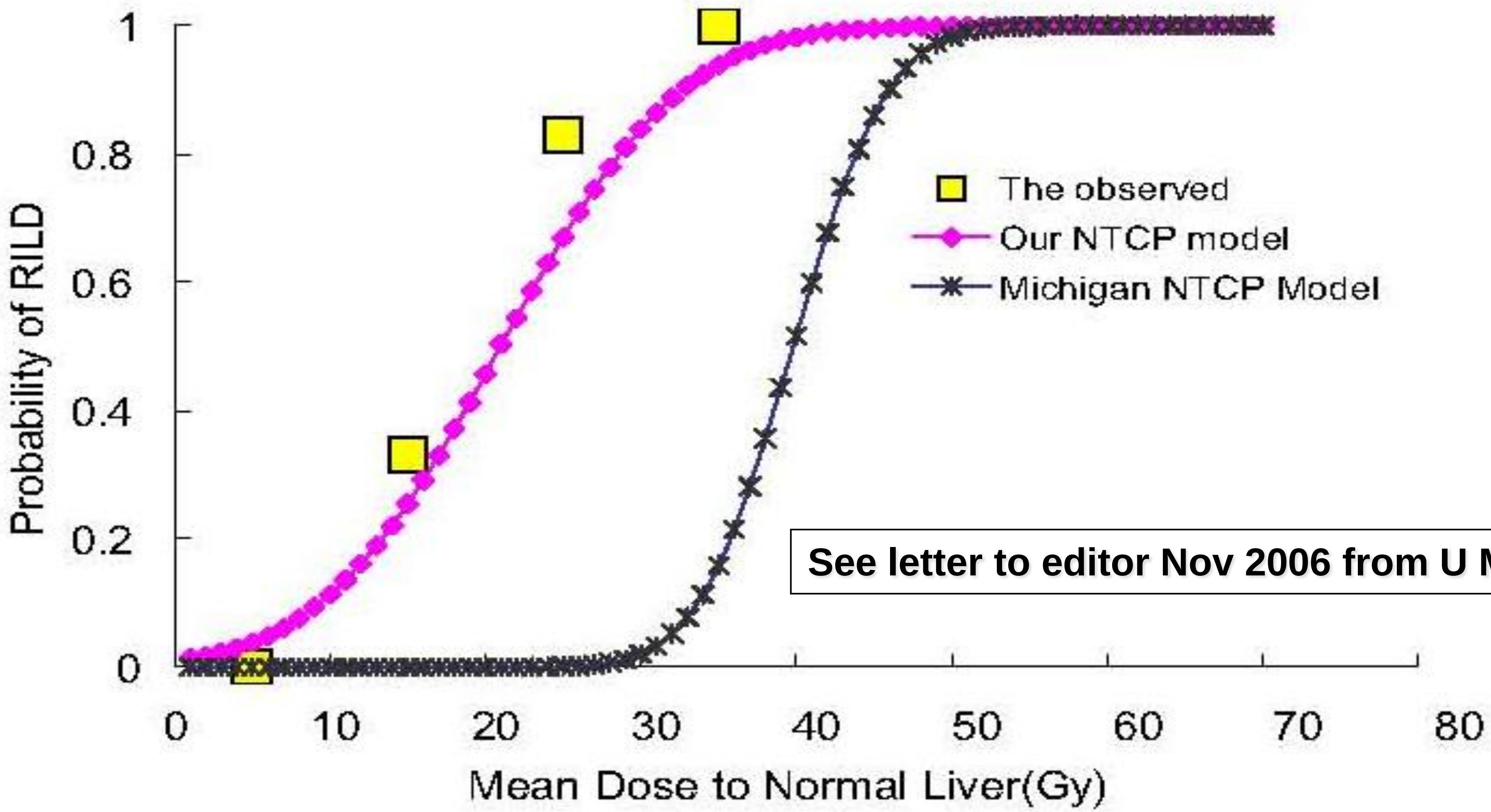
- Data is NOT great!!!
- Incomplete (16 vs 26 organs); e.g. small bowel
- Clinically useful, MD's
- MD's want it made simple
- Be careful, recognize uncertainties


3D dose distribution
Discard spatial, anatomic, physiologic data
% Volume at ≥ Dose x
V20
Cumulative DVH
20 Gy
Extract unambiguous data
•Single Point: e.g. V20
•Global: e.g. mean dose
Compute model-based NTCP estimates

DVH-Based Models

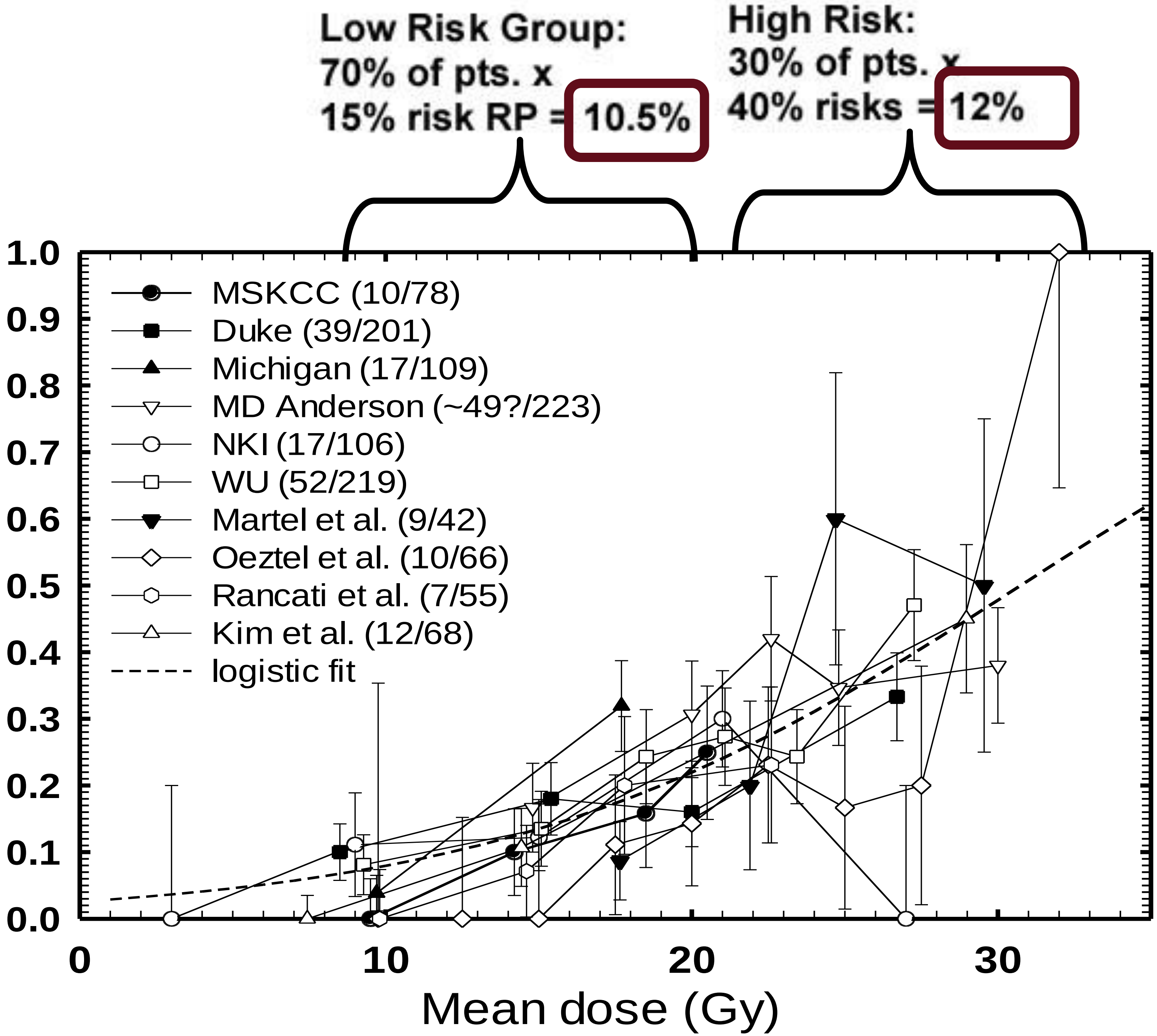
- Exportability
- Applicability
  - IMRT vs. 3D
  - SRS
- Model limitations
  - Fractionation
  - Anatomy

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



See letter to editor Nov 2006 from U Mich

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



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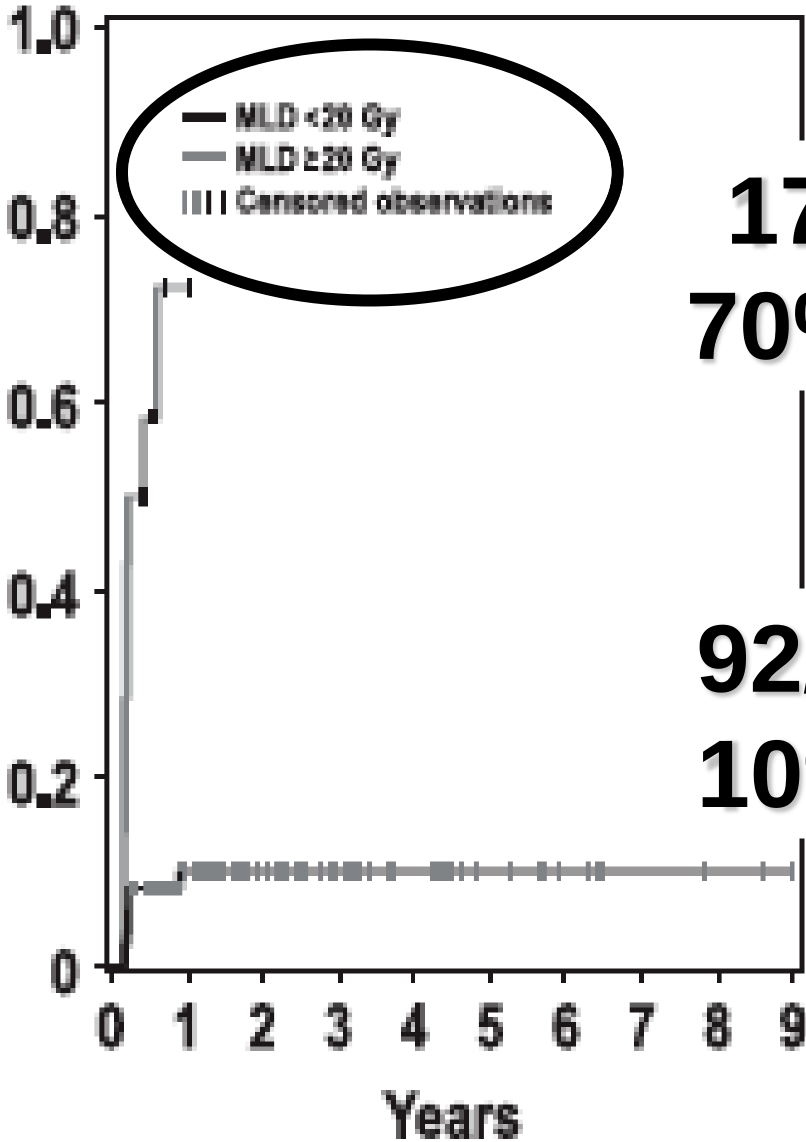


17/109 with MLD >20
70% x 17 = <u>12 patients</u>

92/109 with MLD < 20
10% x 92 = <u>9 patients</u>

Kong, U Mich, IJROBP 2006

Ignores Anatomy/Physiology

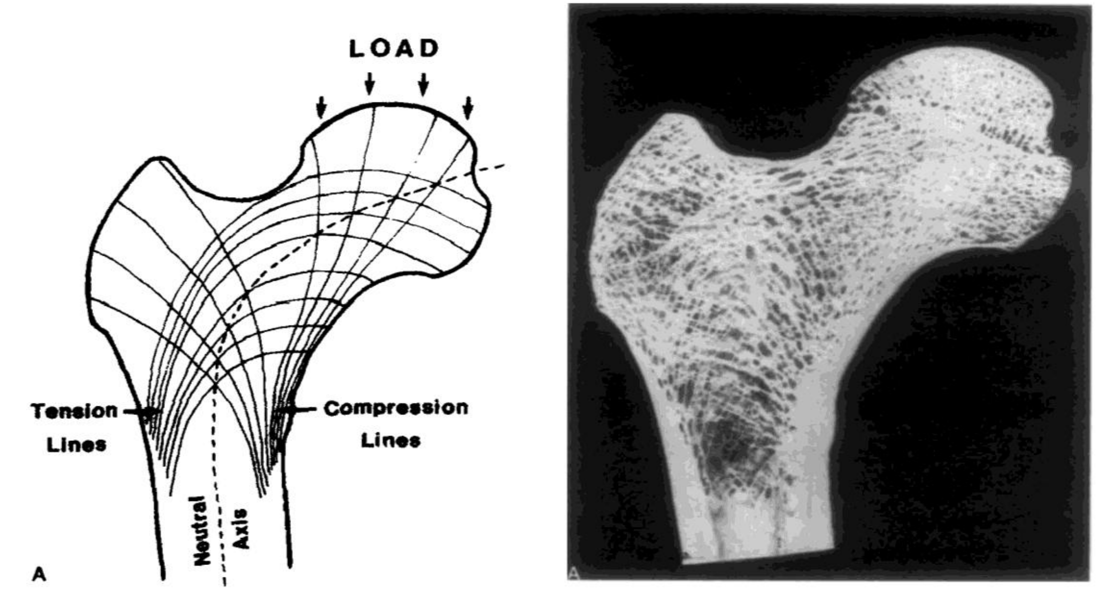


Fig. 3. Schematic diagram illustrating the compression and tension stresses that exist in the normal femur (a). ... in the anatomic gross section of the bone

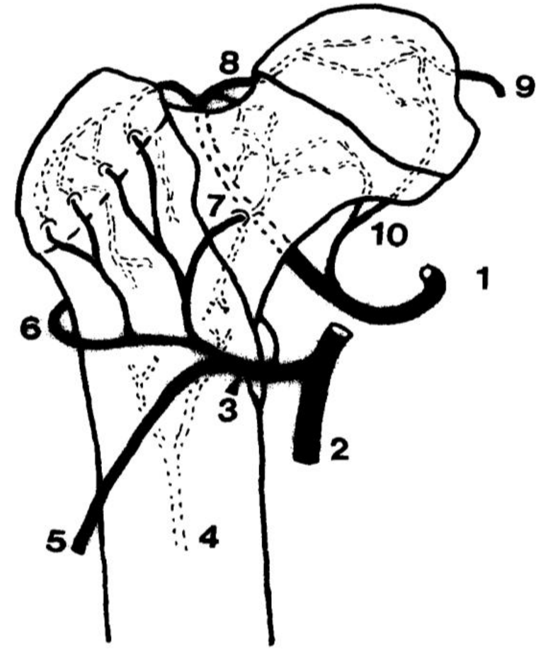
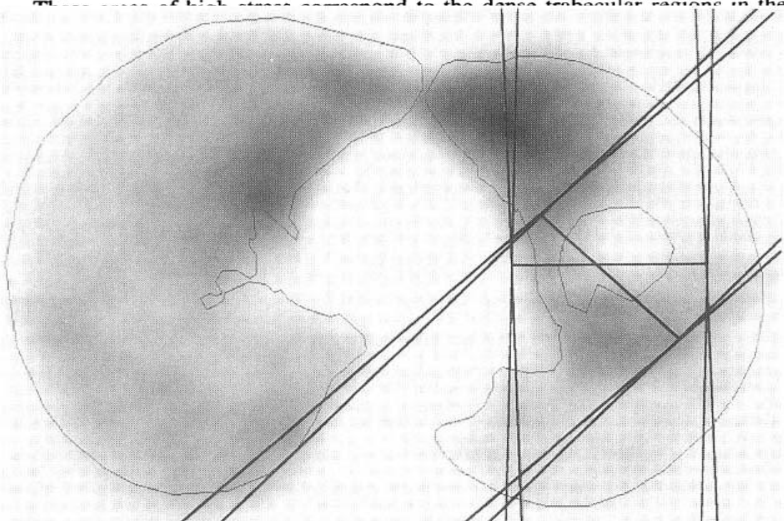
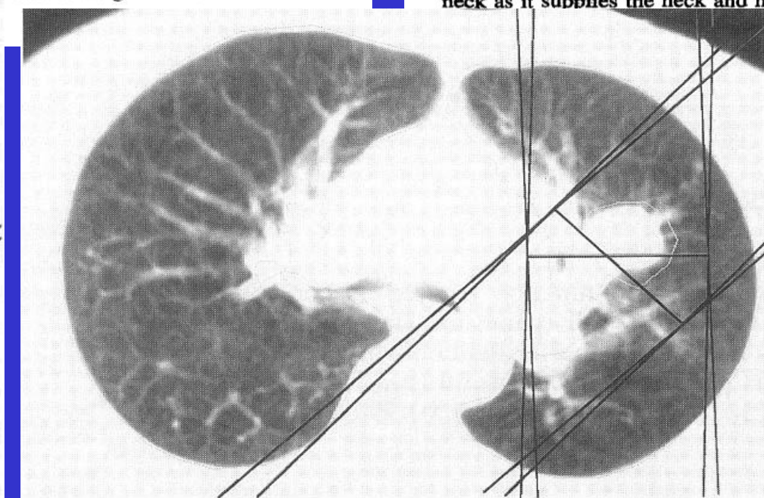
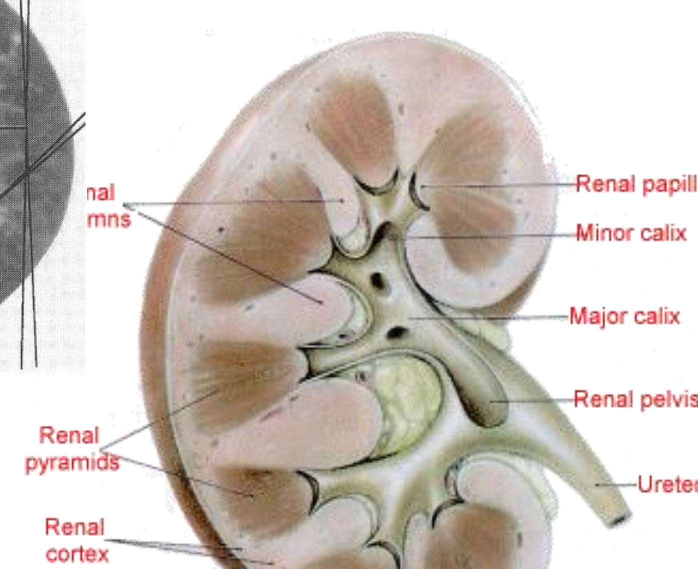


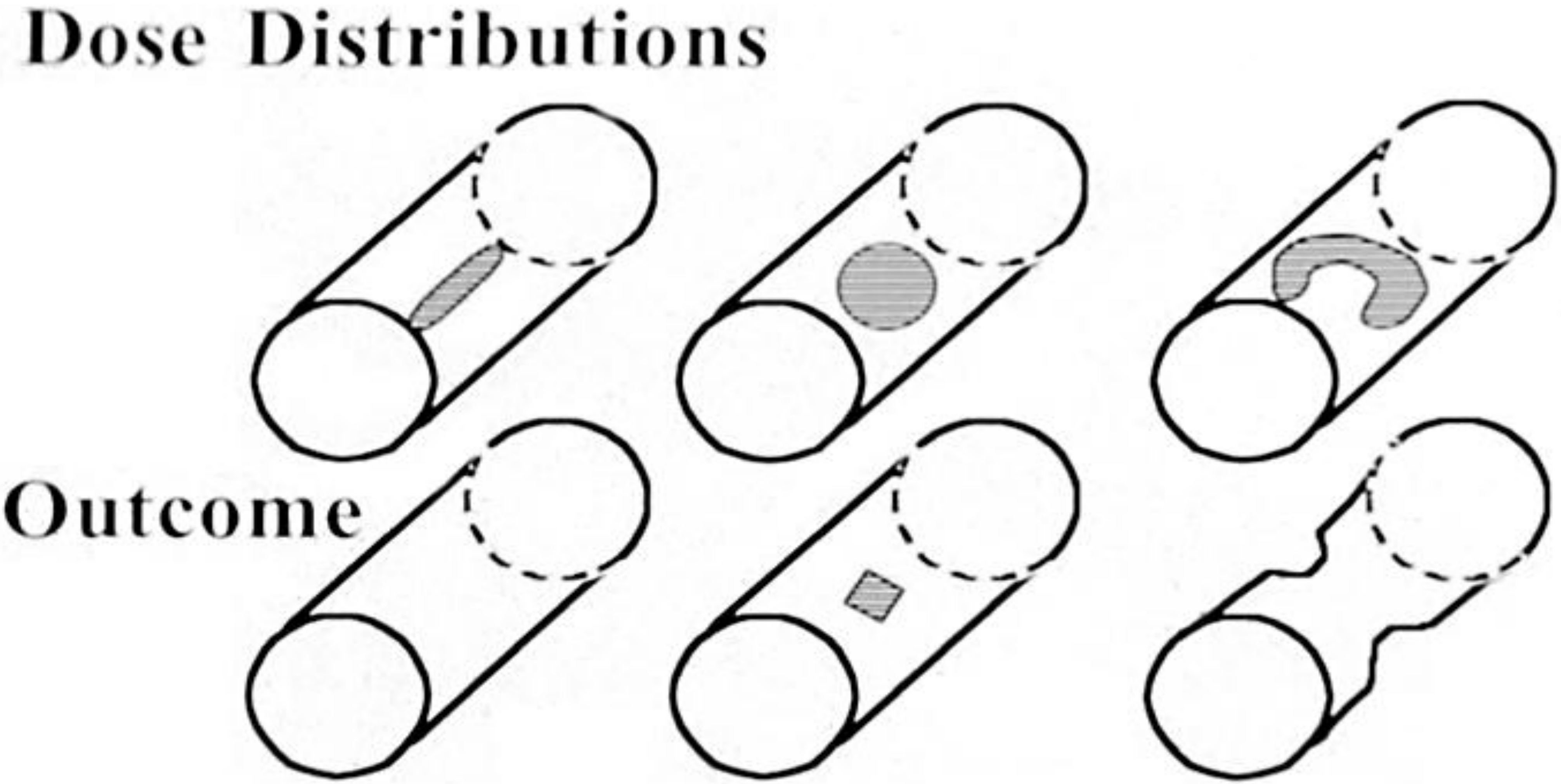
Fig. 4. Diagram illustrating the vascular supply of the proximal femur. The majority of blood t
femur is delivered via the medial circumflex artery [1]. This artery passes medially and posterior
neck as it supplies the neck and head. The secondary vessel is the lateral femoral circumflex arter
oral artery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

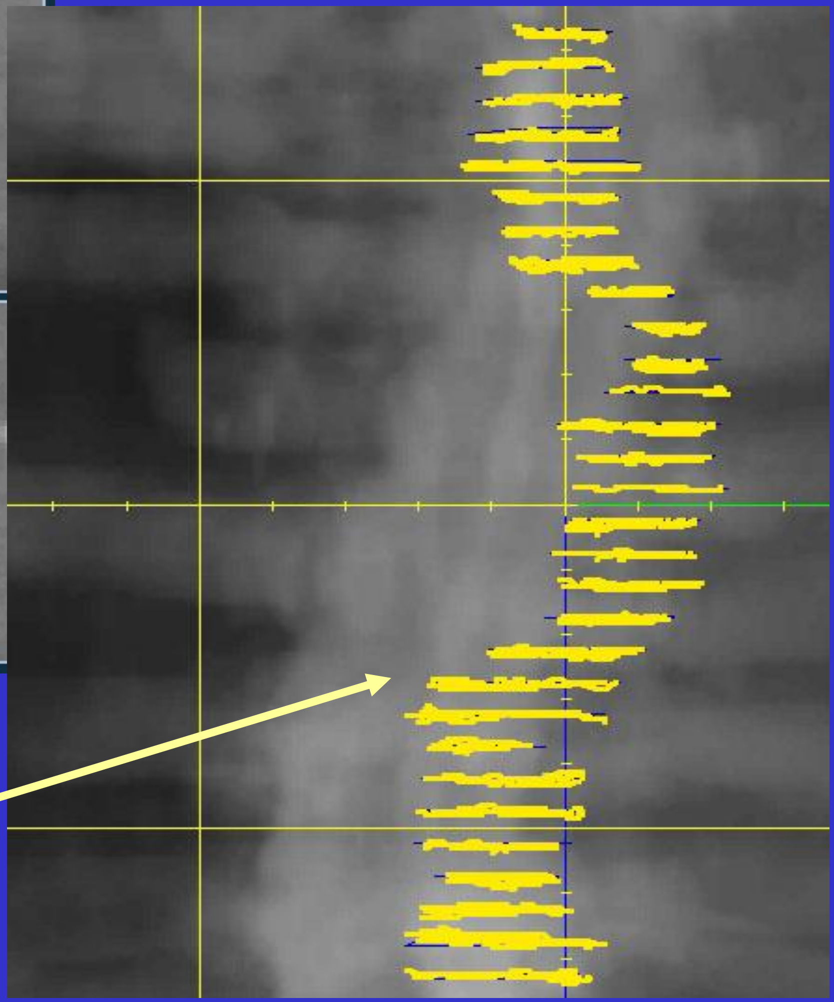






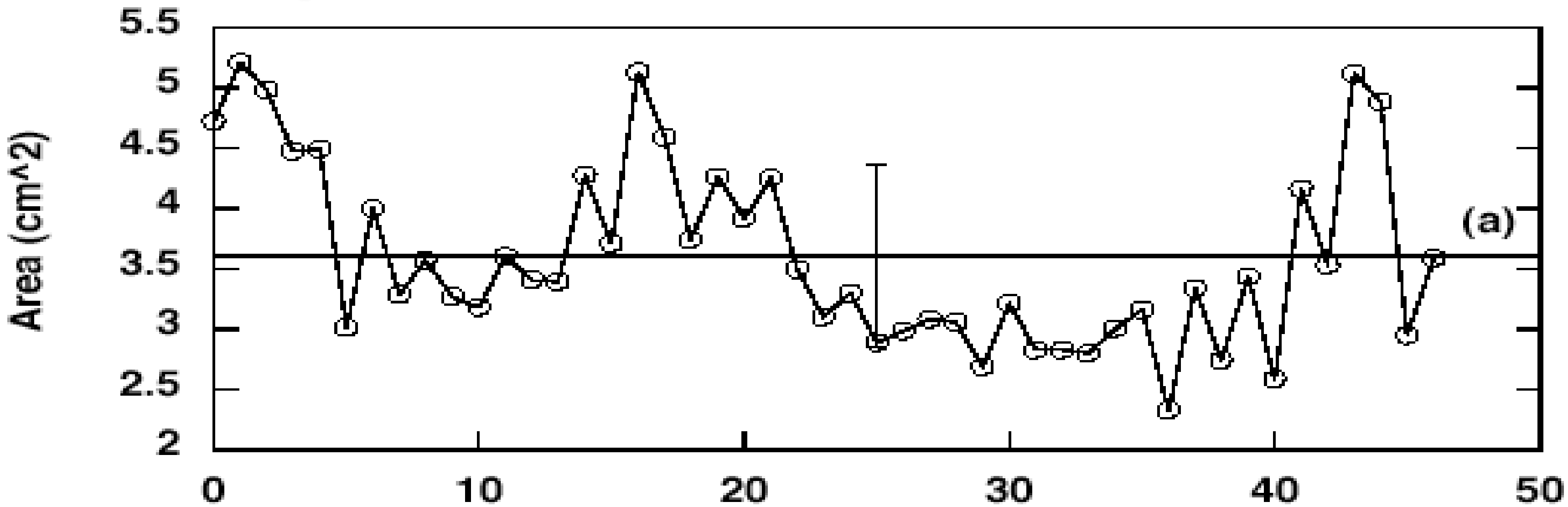
Marks *IJROBP* 34:1168, 1996


Dose Distributions
Outcome



Esophagus contours: variable area (volume)

Superior **Inferior**



Univariate and Multivariate Analyses

CT → esophageal contours → 3D metrics

esophageal contours ↓ **Anatomic** correction ↓ "corrected" 3D metrics

3D metrics ↓ Outcome

"corrected" 3D metrics → Outcome

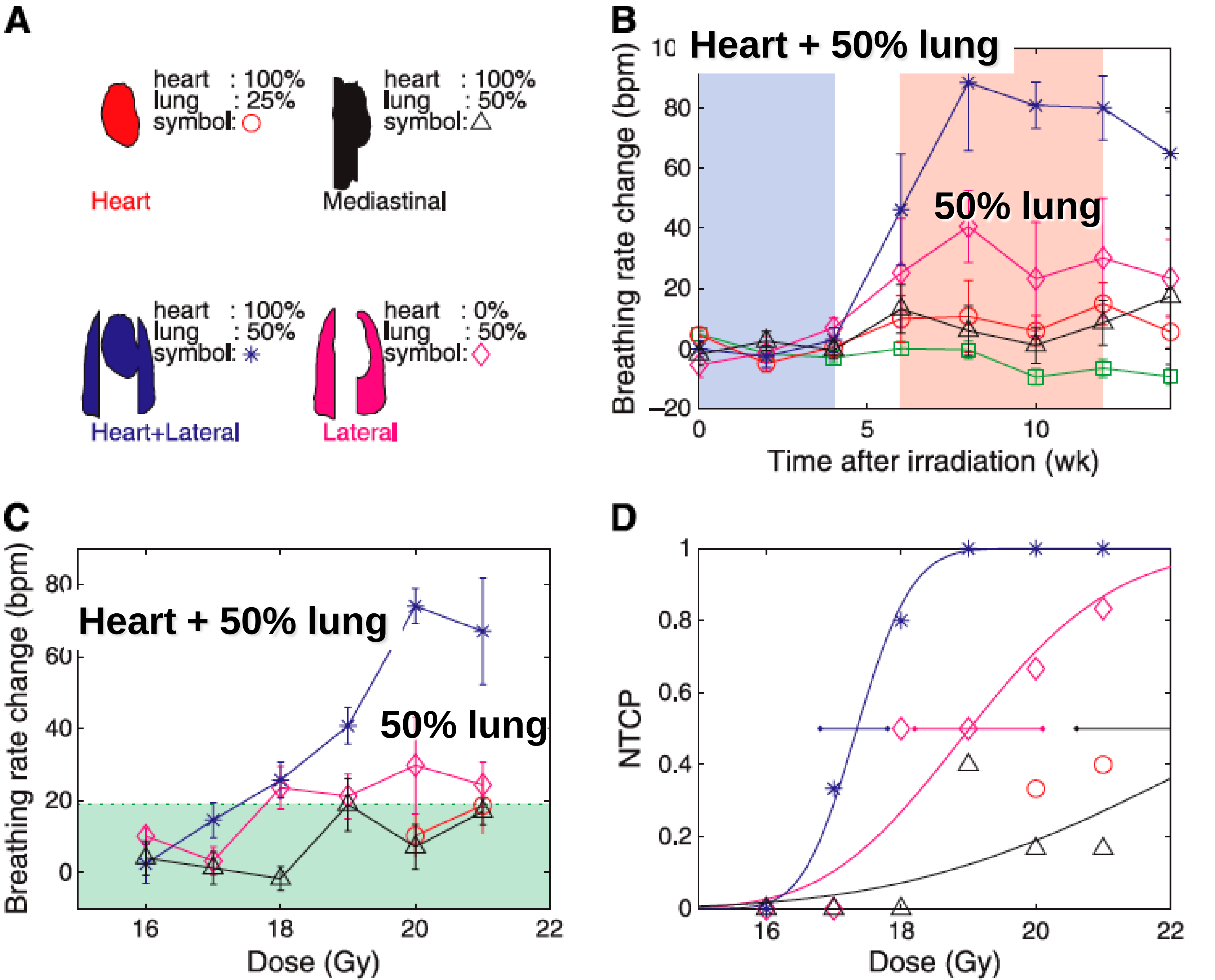
Outcome
RTOG acute
& late toxicity

Toxicity = f (Dosimetric Parameters)

	p-values	
	V 50 Uncorrected	V 50 Corrected
Acute ≥ grade 2	0.008	0.005
Acute ≥ grade 3	0.05	0.003
Late ≥ grade 1	0.14	0.08

Adapted from Kahn *et al.* 2004 (Duke)

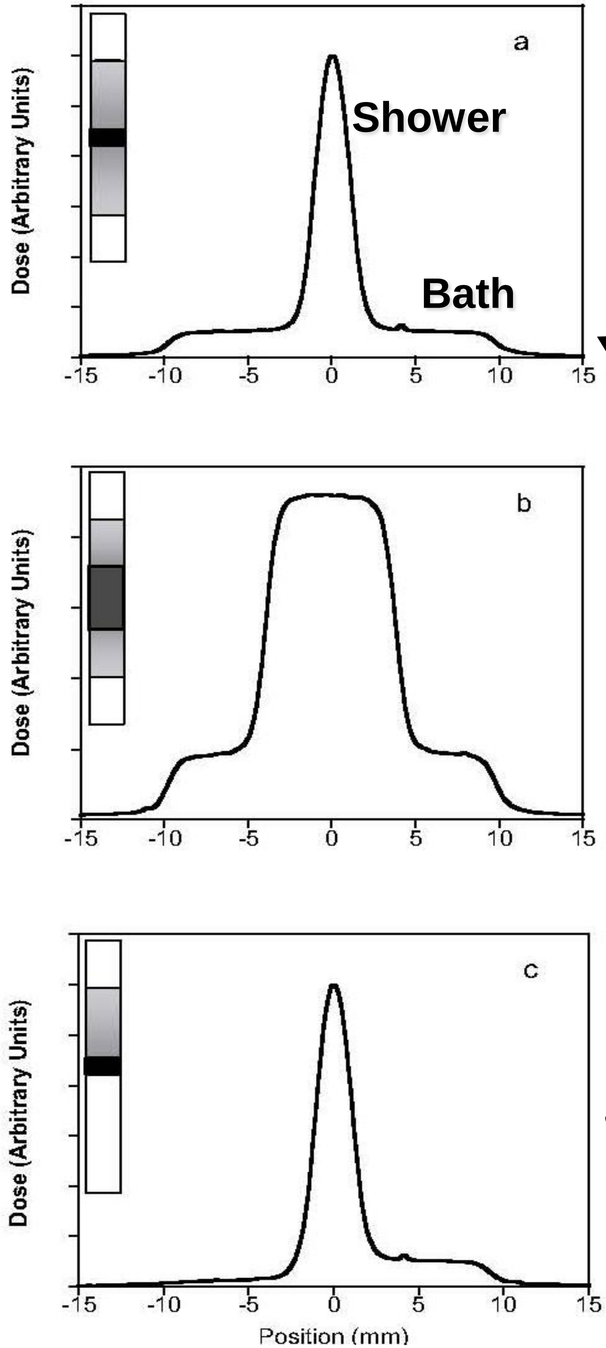
Organ interactions



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

Luijk Ca Res 65:6509, 2005

Neighborhood Effects



Rat Proton Cord RT

	ED 50 (Gy) to “shower”
No bath (control):	88 (dose in peak)
4 Gy bath, both sides	61
4 Gy bath, one side	69
18 Gy bath, both sides	31
Wide shower, 8 mm	No bath effect

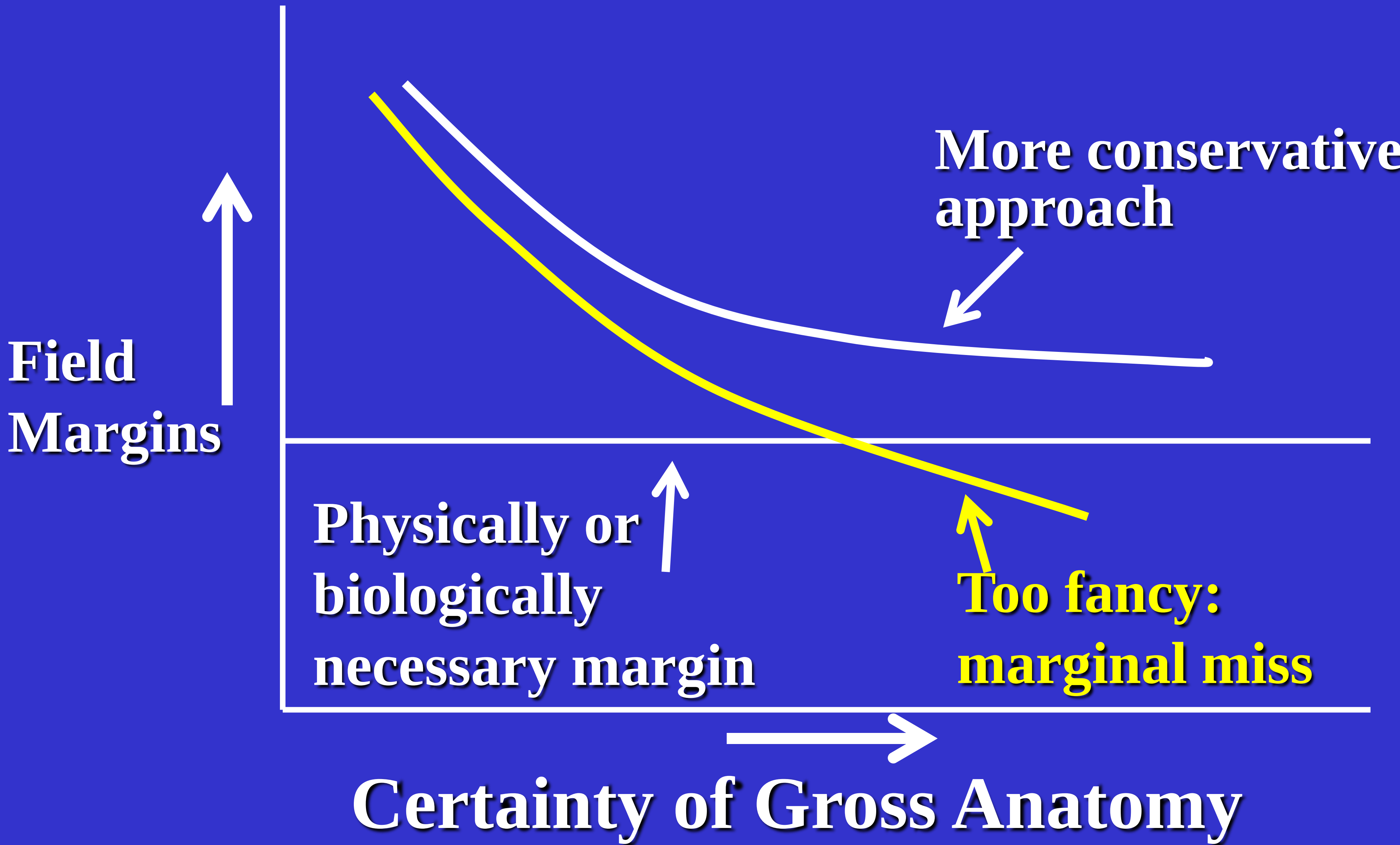
Serial vs. parallel

Less well defined
Migration of stem cells
Cytokine/neighborhood effects
Vascular

Bisl *et al. IJROBP* 64:1204-1210, 2006

What I really worry about

- Missing the tumor; Unrealistic fears
  - Blocking chiasm for GBM
- Large palliative fields work!! (fast, cheep)
  - Generation of fear, slaves to DVH’s
  - There was RT pre DVH’s
- Complication = death? Usually not
  - Grade 1 pneumonitis, rectal bleeding
- Don’t take data too seriously (models)
- Chemo, fraction size


More conservative approach
Field Margins
Physically or biologically necessary margin
Too fancy: marginal miss
Certainty of Gross Anatomy

Prostate: Too Fancy?

Method	Margins (mm)	Biochemical Disease Free Survival (5yrs)	P- Value
Implanted Seeds for Localization (N = 25)	3-5	58%	0.02
No Implanted Seeds (N =213)	6-10	91%	

Engels, IJROBP 74:388, 2009

UNC

Too Fancy? Orbital Lymphoma

Method	Local Control	Grade ≥2 Toxicity
GTV + Margin (12)	67%	25%
Whole Orbit (12)	100%	33%

From Pfeffer et al., IJROBP 2004

UNC

Used to lump them together: 1.5-2.0 cm margins routinely

Gross Tumor Volume (GTV) + Microscopic Spread + Internal Motion + Set-up Errors

Clinical Target Volume (CTV)

Internal Target Volume (ITV)

Planning Target Volume (PTV)- treated volume

Addressing physical uncertainties unmasked biological ignorance

Imaging-
CT, PET

biologic uncertainties

Respiratory gating

Gross Tumor Volume (GTV) + Microscopic Spread + Internal Motion + Set-up Errors

Clinical Target Volume (CTV)

On board imaging

Internal Target Volume (ITV)

Planning Target Volume (PTV)- treated volume

Old fashioned ways to reduce toxicity

- Positioning
  - Neck
  - Decubital
- Reducing skin folds
- Barium in bowel
- Careful team work
- Keep it simple!!, use time wisely

Applicable in Modern Era!

QUANTEC

- Each Organ-Specific Paper:
  - Needed research, challenges
- End of the issue: “Vision Papers”
  - True dose
  - Imaging
  - Biomarkers
  - Data Sharing
  - Lessons of Quantec

Research ideas

Summary

- Since Emami
  - More 3D dosimetry--> toxicity data
  - DVH-based predictions sub-optimal (physiology)
  - Quantec incomplete; Emami still relevant
- Is the prior data still applicable?
  - 3D beams --> IMRT
  - Chemo- moving target
  - BID RT
- Challenges for normal tissue injury studies
- Over-Reliance on technology to reduce morbidity (e.g. IMRT, OBI, CBCT)

Acknowledgments

- David Fried, Liyi Xie, Janet Bailey, Micheal Lawrence, Jessica Hubbs, Jiho Nam, Mert Saynack, John Kirkpatrick
- Quantec Steering Committee: Joe Deasy, Soren Bentzen, Randy Ten Haken, Ellen Yorke, Andy Jackson, Sandy Constine, Avi Eisbruch, David Morris
- Emami et al, Rubin, Cooper, Phillips, et al
- ASTRO, AAPM; Authors, Reviewers

Our quest for better dose distributions

- Complex solutions; e.g. IMRT
- Workload increased
- Safety concerns