Massachusetts General Hospital

New Technologies in RT and Secondary Cancer

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New Technologies in RT

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New Technologies in RT

I. Basis for ↑ Concern
II. New Technologies
III. Experimental Model Systems
IV. Patient Data Analysis
V. Implications for New Technologies

Secondary Cancer Post RT

↑ in 20-30 year survivors

$\therefore$ ↑ Concern re Late Morbidity

Especially, Secondary Cancer

Radiation Treatment

Goal: Eradicate Tumor

No Complications

***ie* ↑ Complication Free Cures**

Medical Practice

There are no Risk Free Procedures

Aim: ↓ Frequency and Severity

of Complications

Radiation Complications

Late: Organ Dysfunction

Fibrosis   Necrosis

Cancer Induction

Fact of Radiation Oncology

Radiation Injury Never Develops

In Unirradiated Tissues

Radiation Treatment

Goal: Confine Dose to Target

Reduce or Eliminate Dose

to Normal Tissues

↑ Technology

Yield:

↑ TCP Tumor Control Probability

↓ NTCP Complication Probability

Accepted Advances

Portal Films

Simulation

2^o Collimination

^{60}Co, Lin Acc

Electrons

IORT

Accepted Advances

Computer Plans

US, CT BRT

Stereotactic RT

Accepted Advances

Aim of Each of These:

Reduce Irradiation of Normal Tissue

Accepted Advances

These have Increased Cost:

Time Staff Space

Yield has been Clinical Gains

Reduced Treatment Volume

That a ↓ Rx V is Superior is

not a Medical Research Question

Reduced Treatment Volume

The ↑ of the Gain *vs* Cost

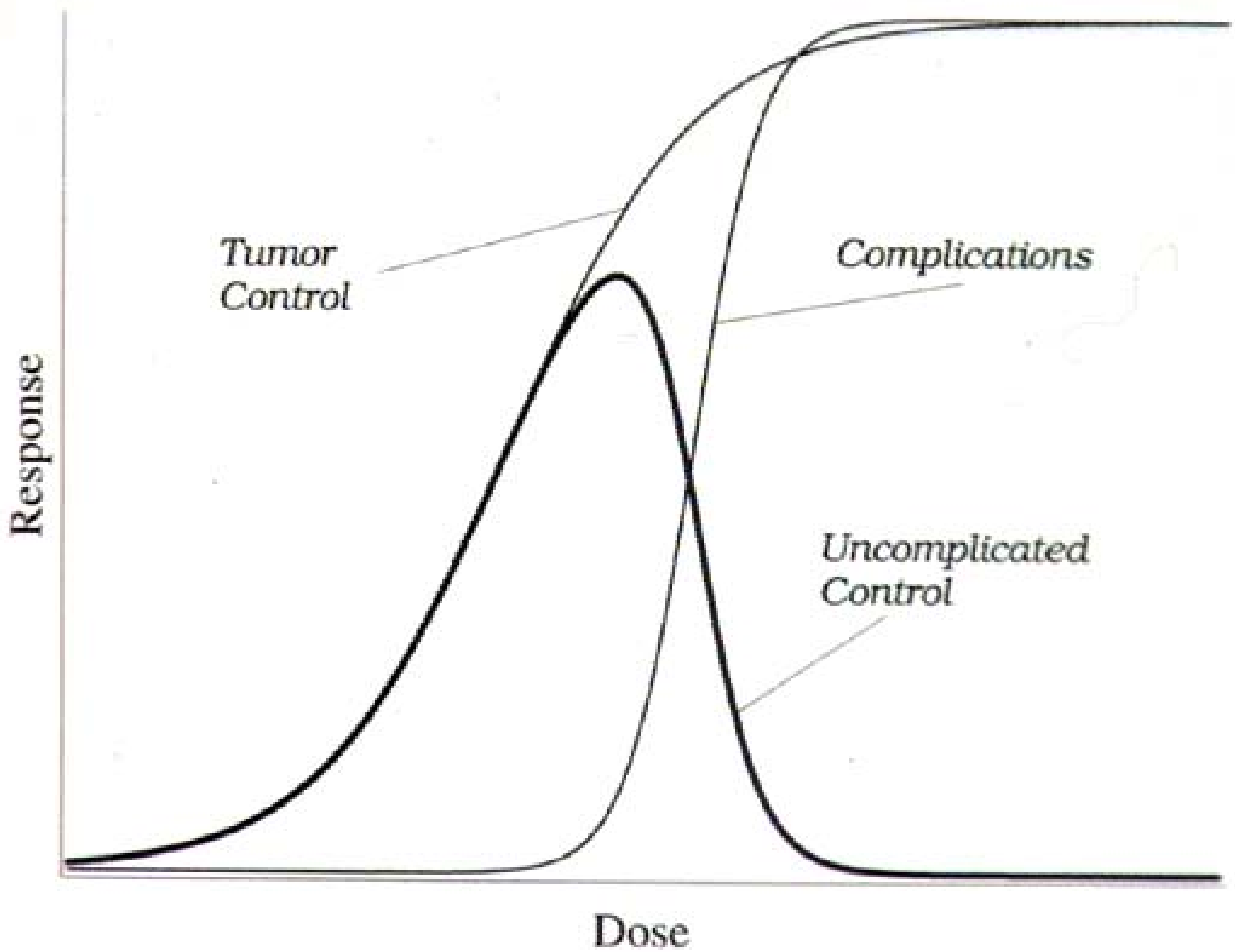
Constitutes a Research Question

<u>Accepted Advances</u>

Society Judges the Gain

***vs* the Cost**

Decides Yes/No for Small Gains


Tumor
Control
Complications
Response
Uncomplicated
Control
Dose

Risk Factors for 2^0 Rad Cancer

Dose Fractionation LET

Age Organ Irradiated Species

Observation Time Autopsy Data

Secondary Cancer Post RT

R T is Whole Body Irradiation

Heterogeneous Dose Distribution

Dose Gradient ≈ 10^3

New Technologies

IMXT	IMRT	^{12}C RT
IORT	4 D RT	Stereotactic

Image Guided Radiation Therapy

Intensity Modulated XRT

Vary Dose Across Each Beam

5-9 Beams

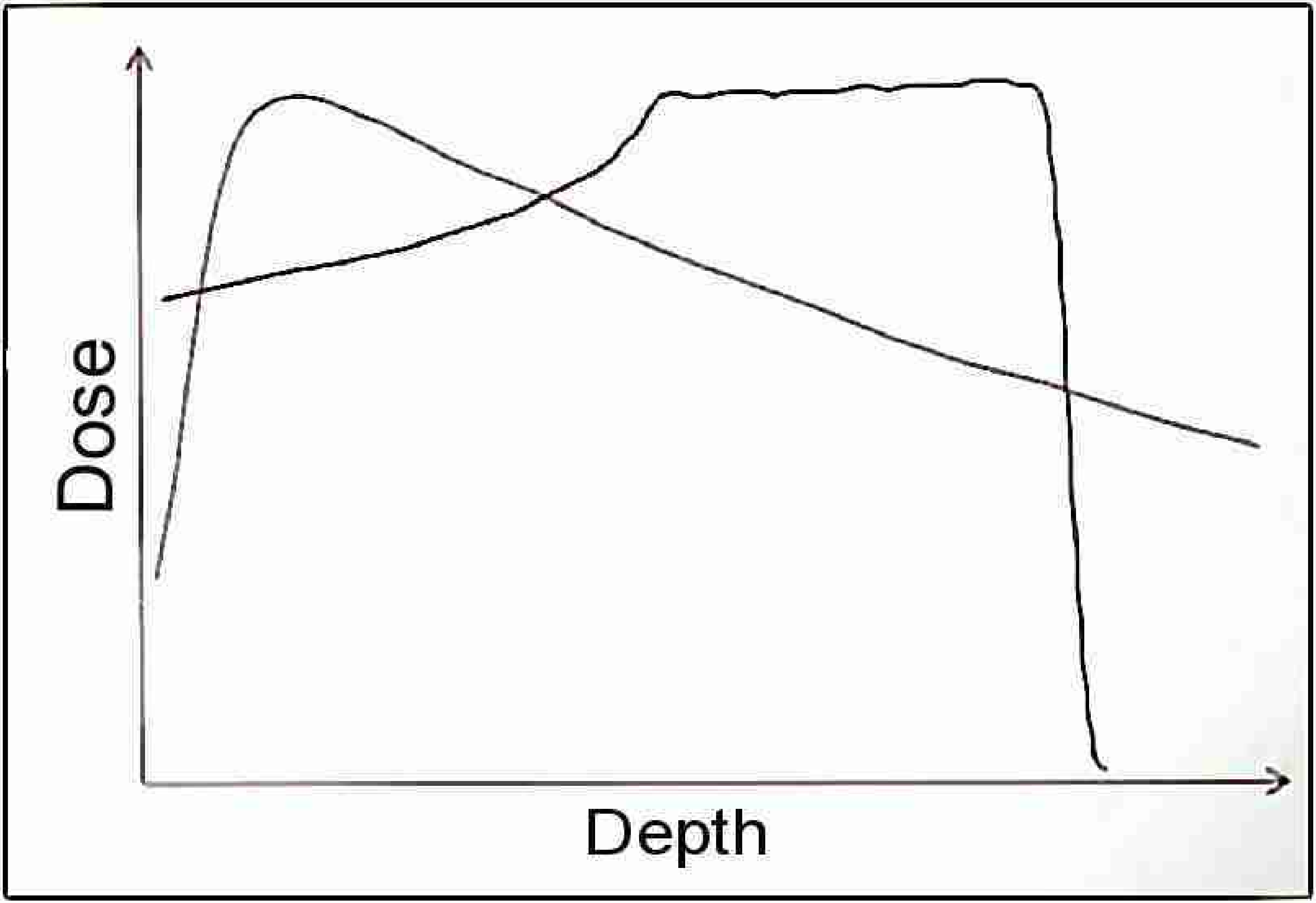
↑ Volume at Low Dose

Intensity Modulated PBRT

Proton Beam RT

No Dose Distal to Target for Each

Beam Path Less Dose Proximally


Dose
Depth

Intra-Operative β^- Therapy

Direct Electron Irradiation, *ie*

No Normal Tissues in Beam Path

Stereotactic Rad Therapy

Single Dose

Fractionated Dose

Cranial and Extra-Cranial Sites

Biomathematical Modeling

TCP	**Tumor Control Probability**
NTPC	**Complication Probability**

Biomathematical Modeling

Clinician Reviews Impact of

Changes in Value[s] of Radiation

Response Parameters, *eg* α, β

Biomathematical Modeling

Display Uncertain Bands on Each

Dose Display or Statement

4 D Radiation Treatment

Target and Normal Thoracic-Pelvic

Organs Move and Contour Distorted

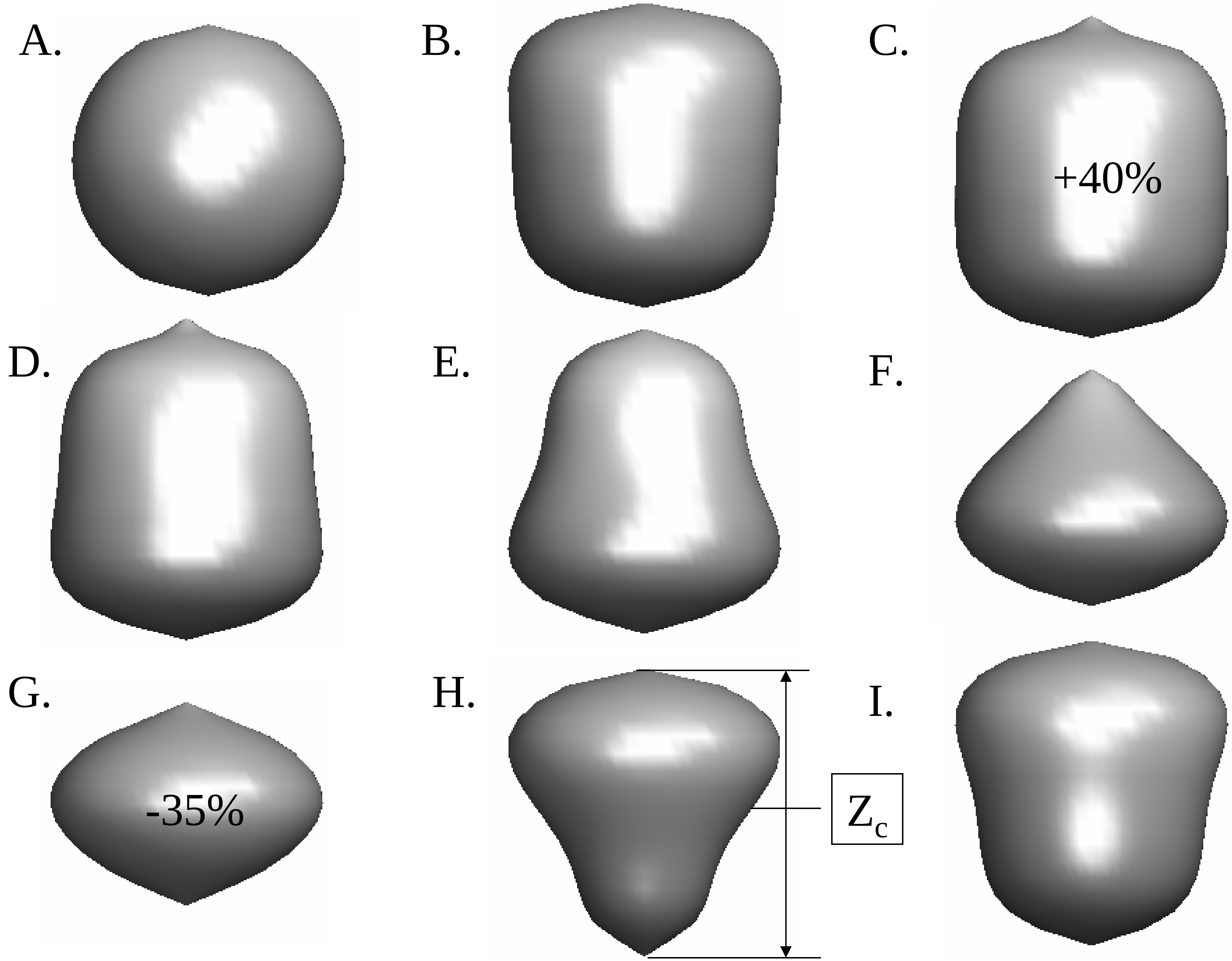
by Respiration, Heart Beat

4D CT of 6 cm Sphere

Respiration at 4 Sec 2 cm Motion

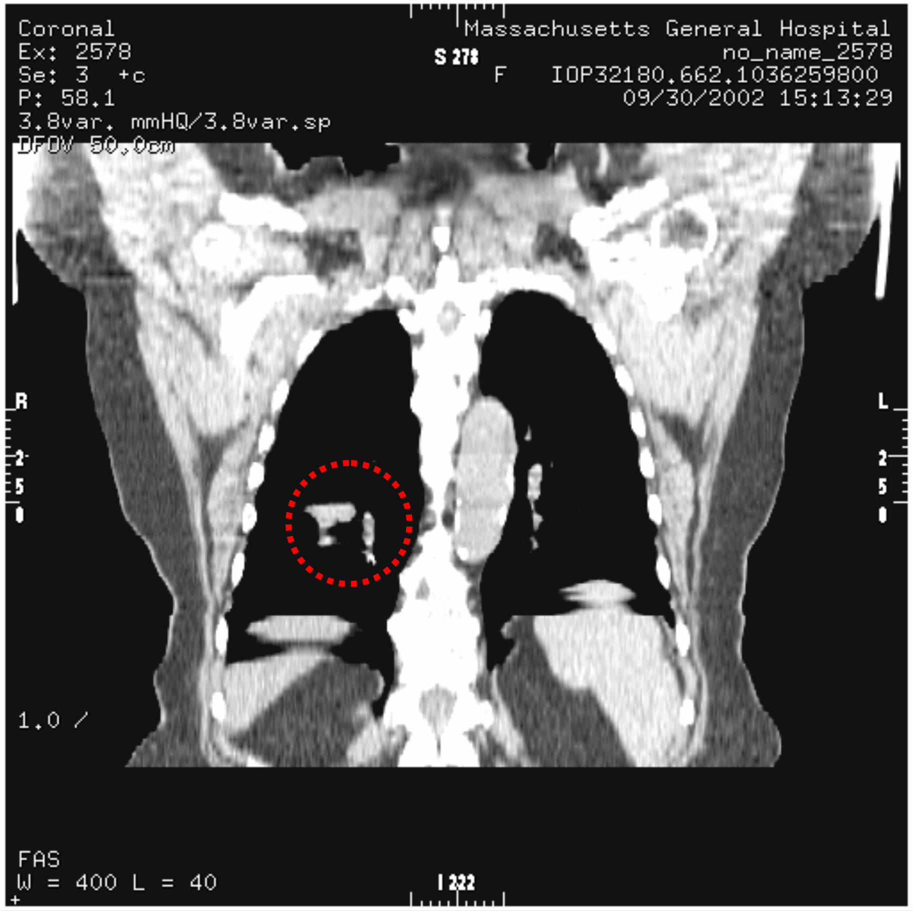
Image A 4 D CT

Images B-L Uncorrected for Motion



3 cm radius 1 cm amplitude HS mode Period 4 sec

Evidence:Reduced Artifacts / GTV



Std light breathing scan

0% Phase of 4D scan

New Technologies

Select Strategy with Best

Predicted

TCP: NTCP Relationship

Proton Beams

Heavy Charged Particles: H^+

Finite Range **Low LET**

Biological Effectiveness ≈ Photons

Proton Beams

RBE Values for *in vivo* Experimental

Systems: Mean Value is 1.1

This is Used as Generic RBE

Carbon Ion Beams

Heavy Charged Particles: ^{12}C

Finite Range High LET

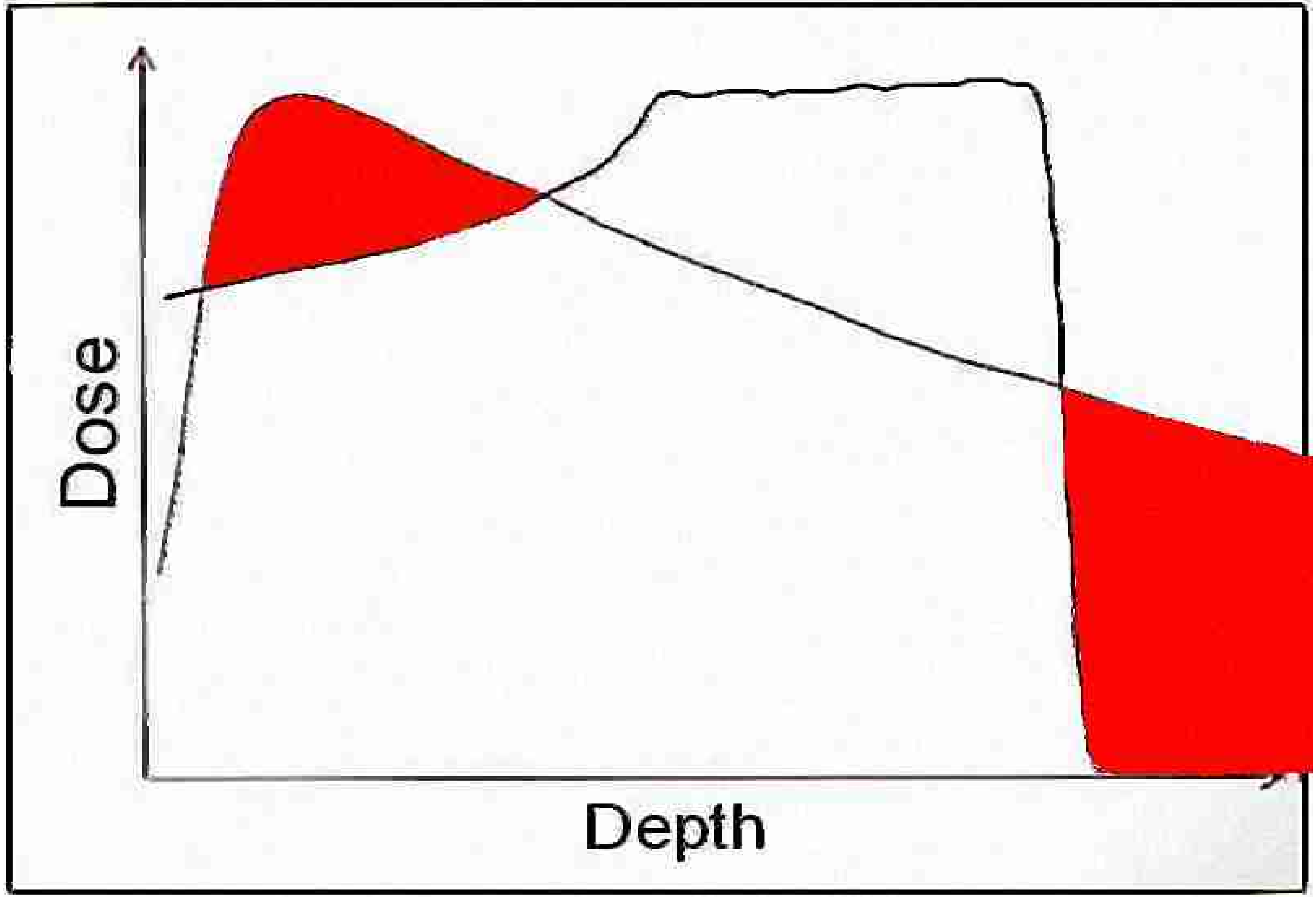
Biological Effectiveness ≈Neutrons

Proton Beam RT

Planning Options

Proton and Photon Beams

are Equivalent in Terms of:


Dose
Depth

Proton Beam RT

Beam Number Direction

Co-Planar/Non Co-Planar

Static/Dynamic

<u>Proton Beam RT</u>

Intensity Modulation

4 D Planning/ Delivery

Critical Historical Points

1919 E Rutherford

Manchester University

Demonstrated Protons

Ernest Rutherford

Ernest Rutherford

Natural Radioactivity

Age of Earth

Concept of Atom Structure

Discovered Proton

Postulated Neutron

Ernest Rutherford

Alpha Particles on Nitrogen

Products:

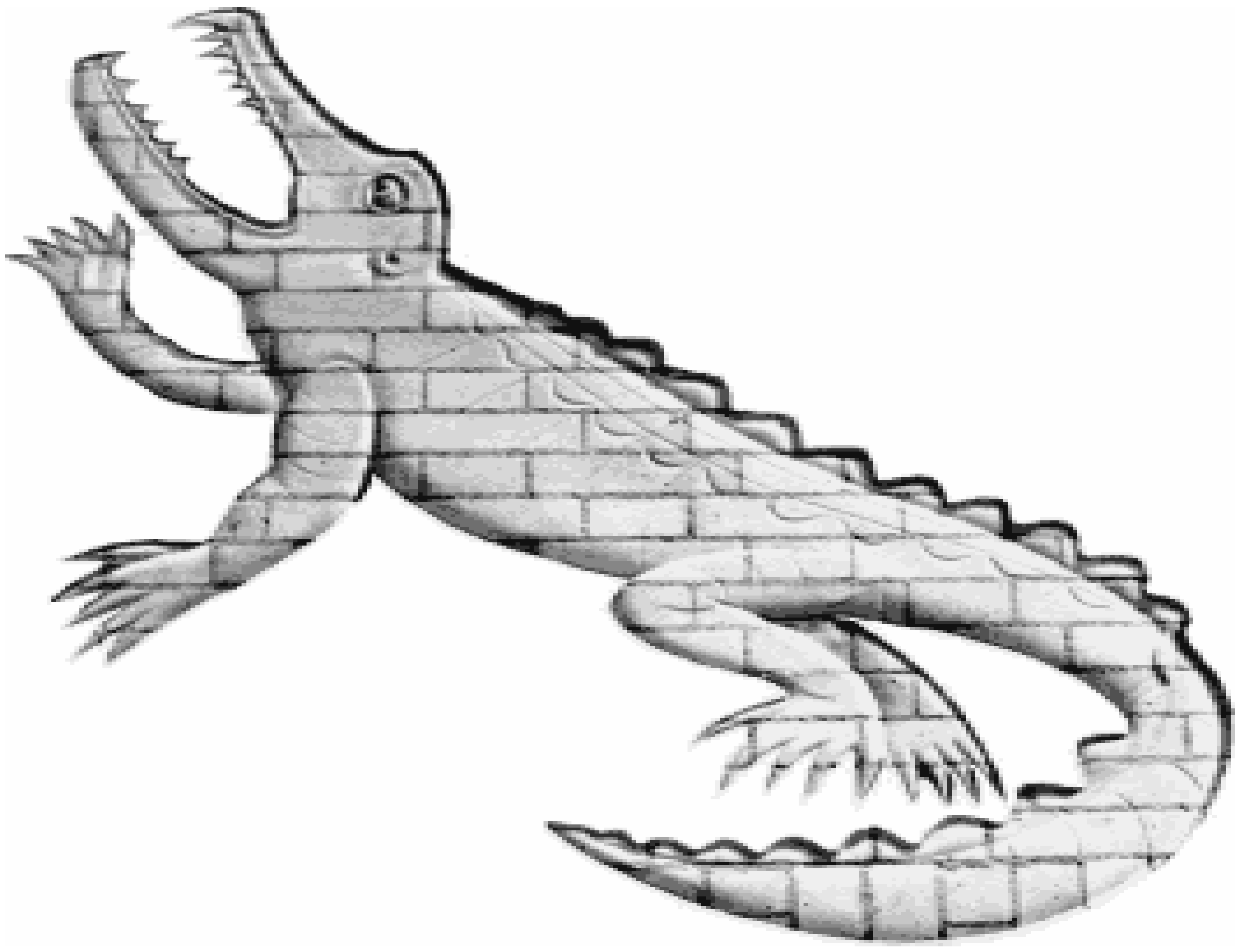
Oxygen and Protons

Ernest Rutherford

Proposed and Named Neutrons

His Student Chadwick Discovered

Neutron 1931



Robert Wilson

Robert Wilson

One of the Central Physicists

In Atom Bomb Project

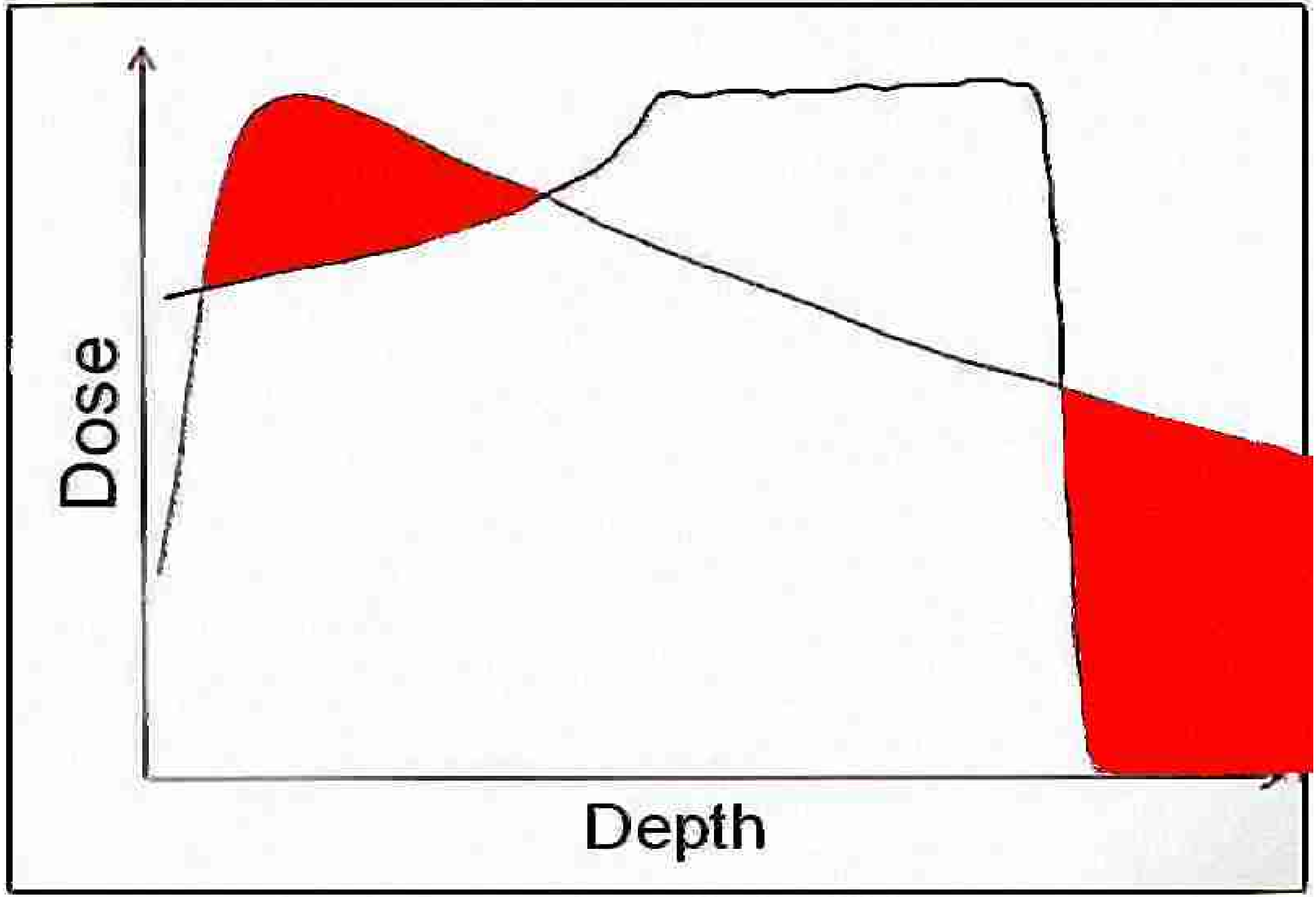
Wished to Benefit Mankind

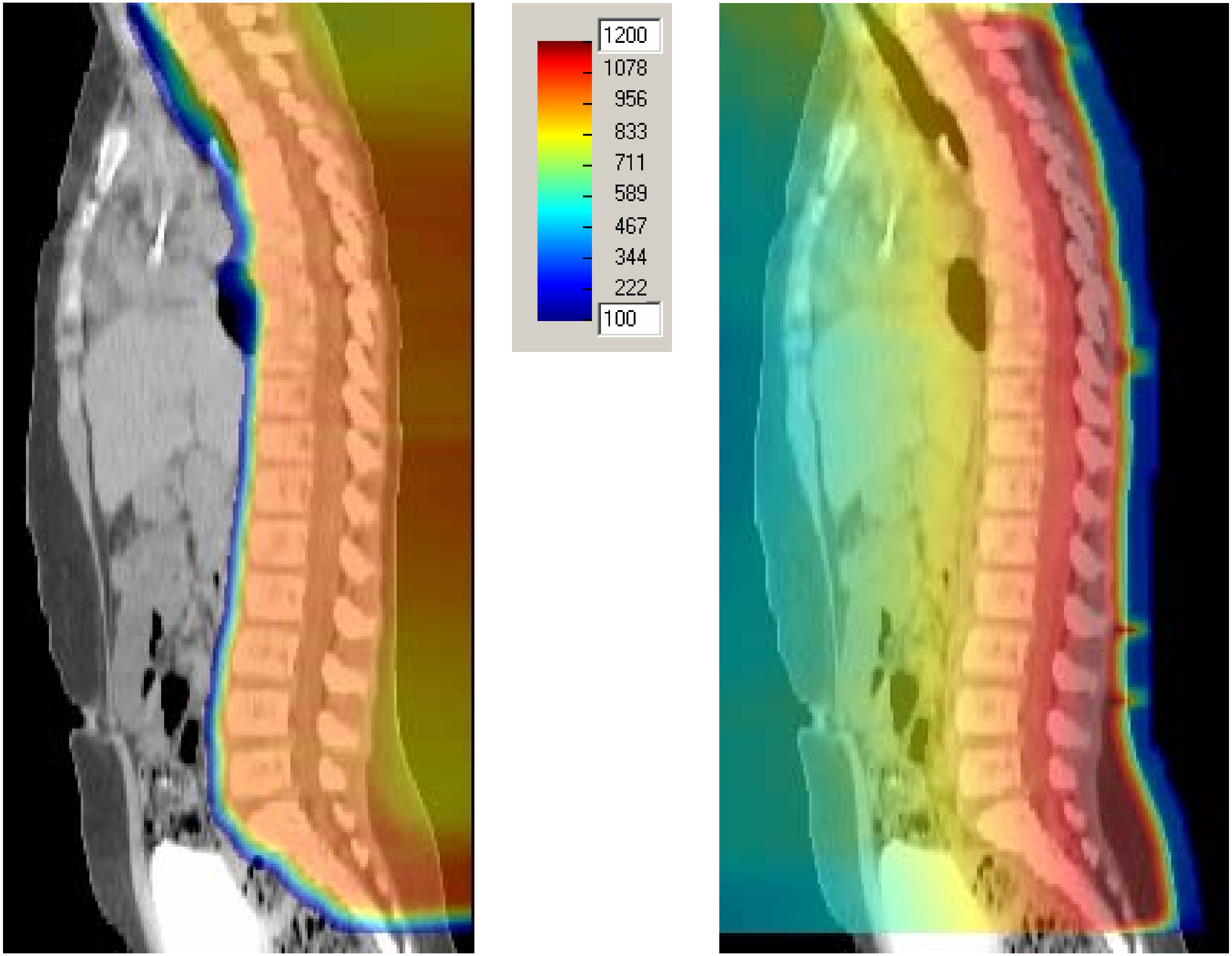
Historical Point

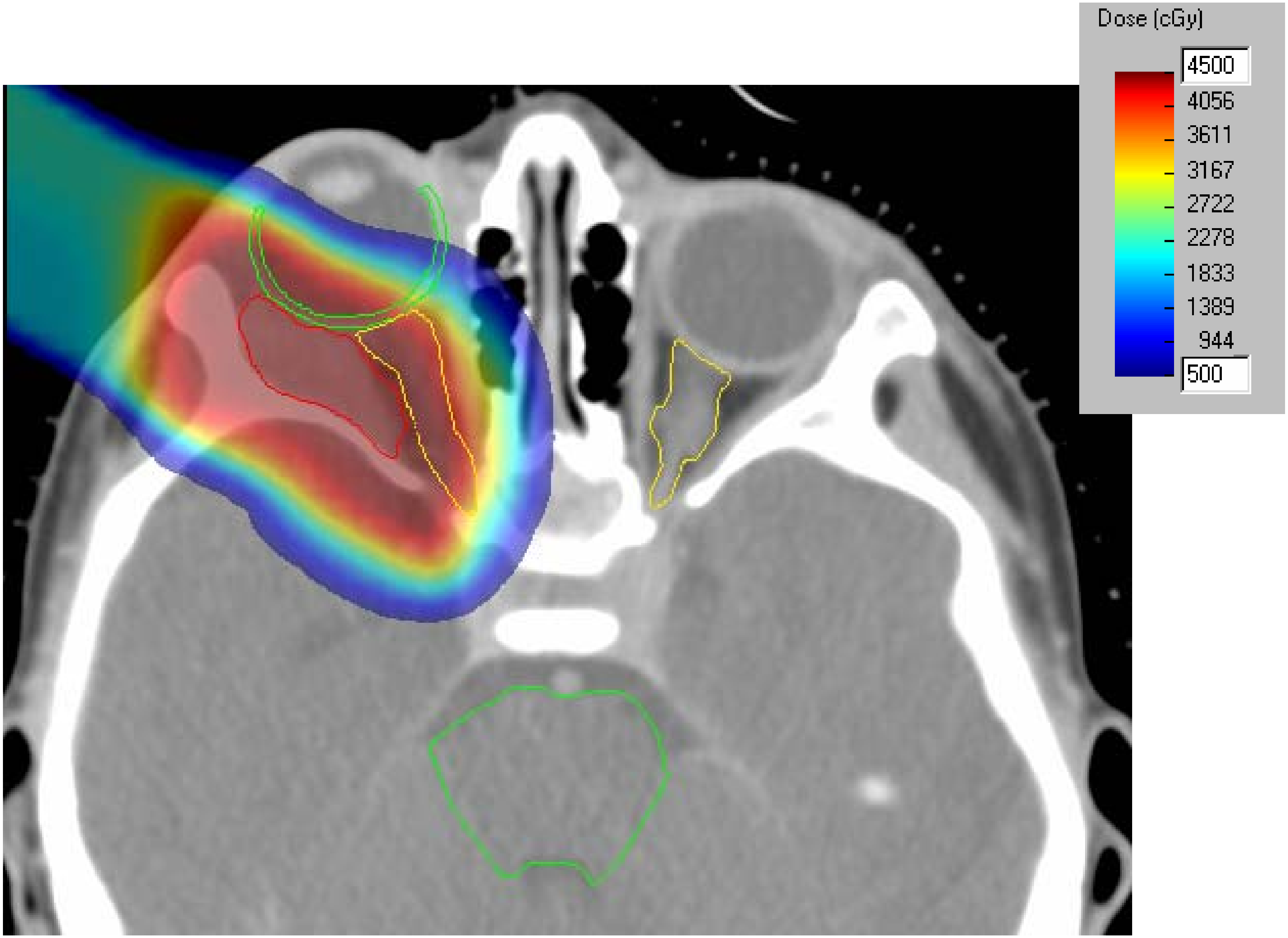
1946 R Wilson Harvard Univ

Proposed Proton Radiation Therapy

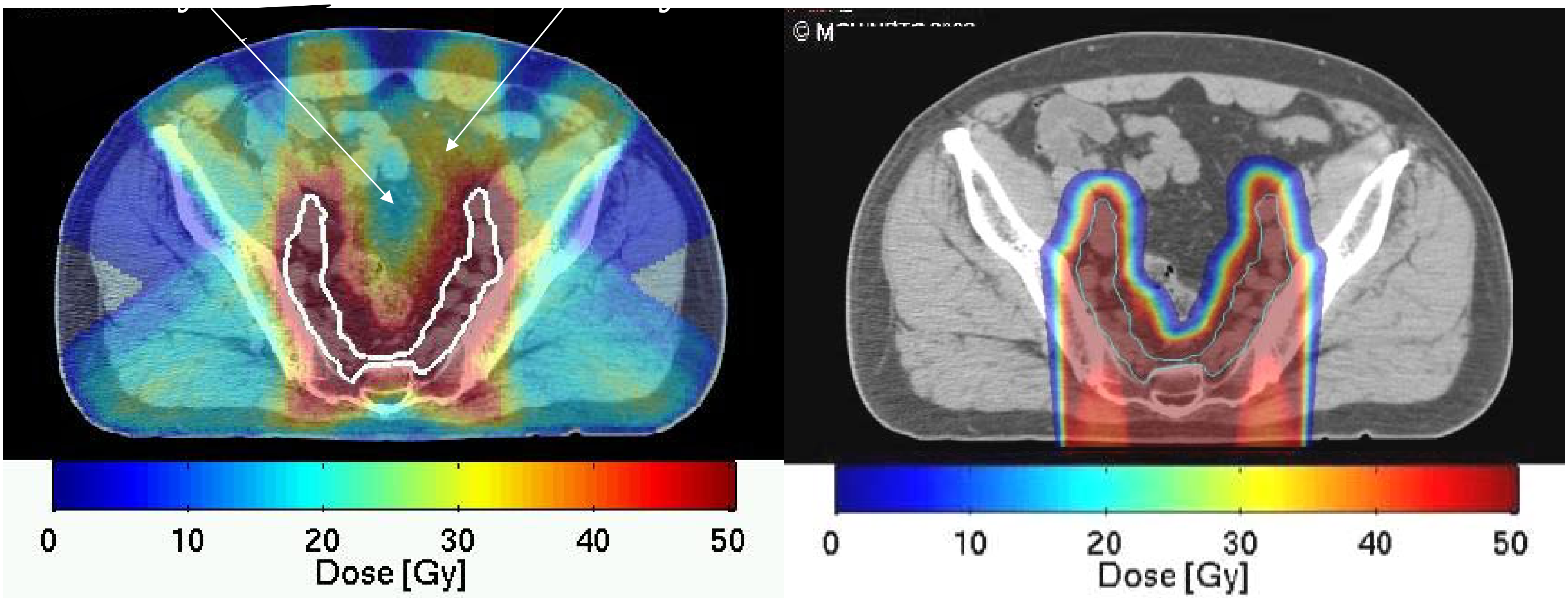
Article in Radiology


Dose
Depth

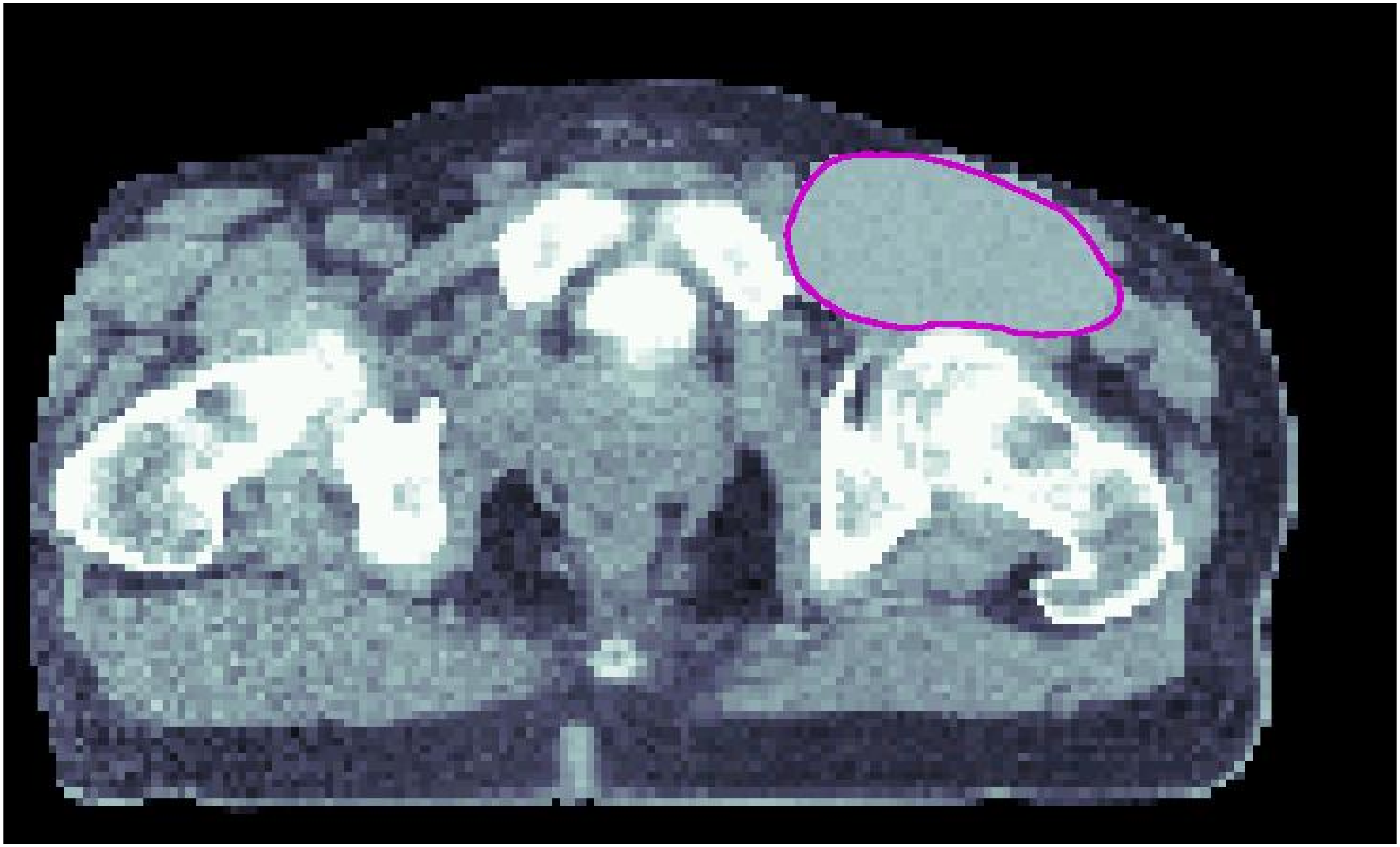

1200
1078
956
833
711
589
467
344
222
100



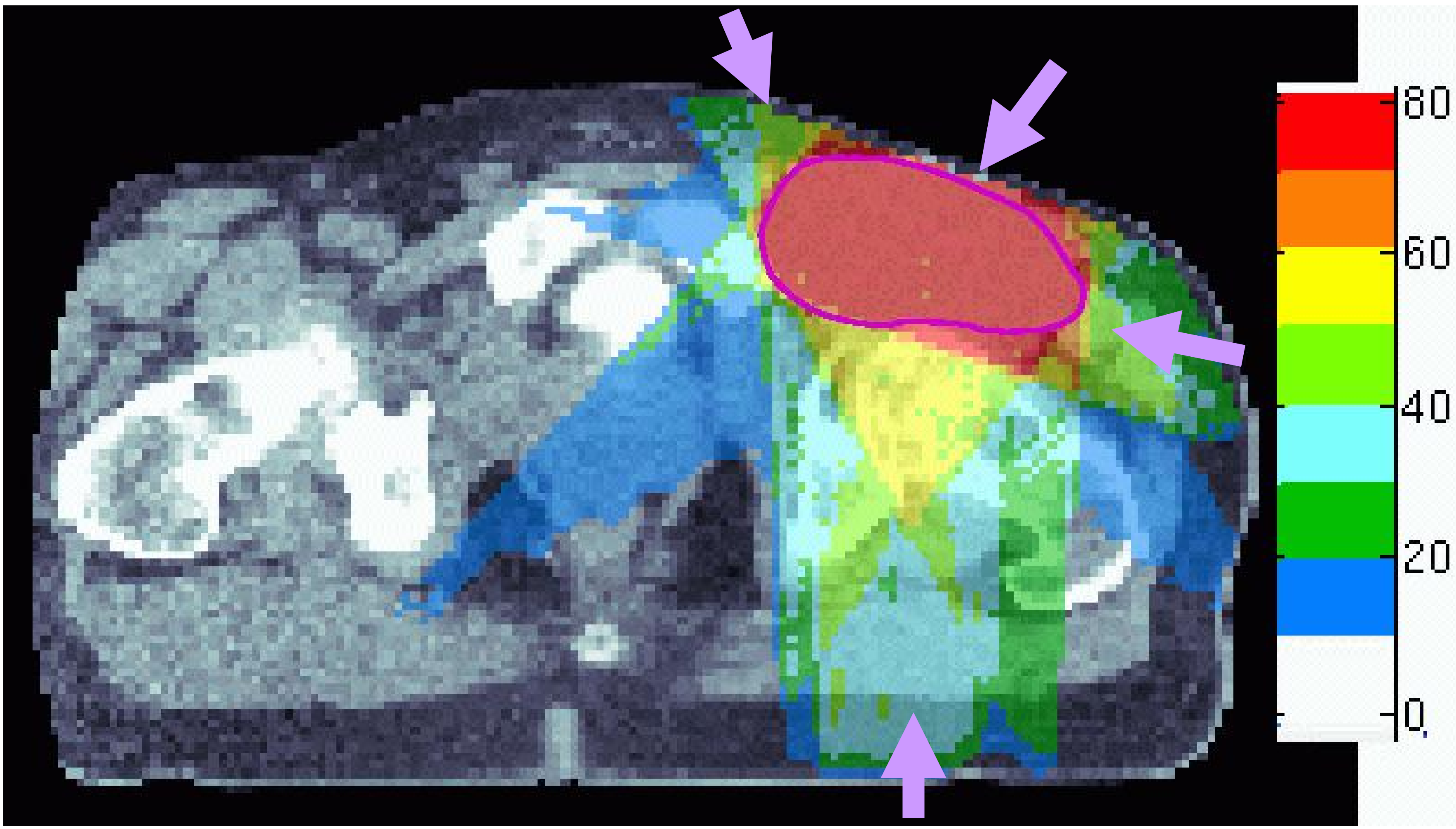
Dose (cGy)
4500
4056
3611
3167
2722
2278
1833
1389
944
500


0 10 20 30 40 50
Dose [Gy]
0 10 20 30 40 50
Dose [Gy]

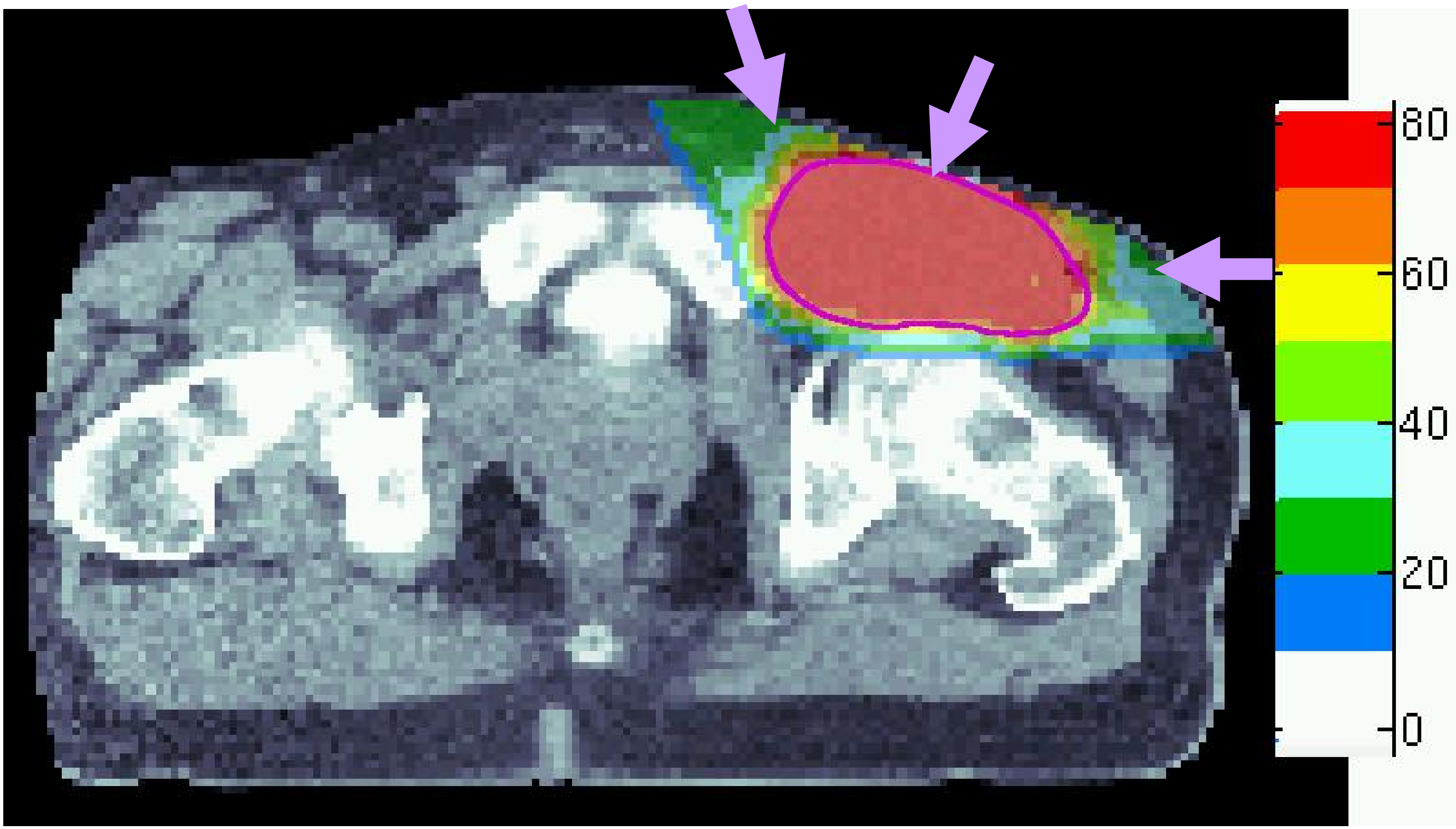
Patient B 4027418
CT scan



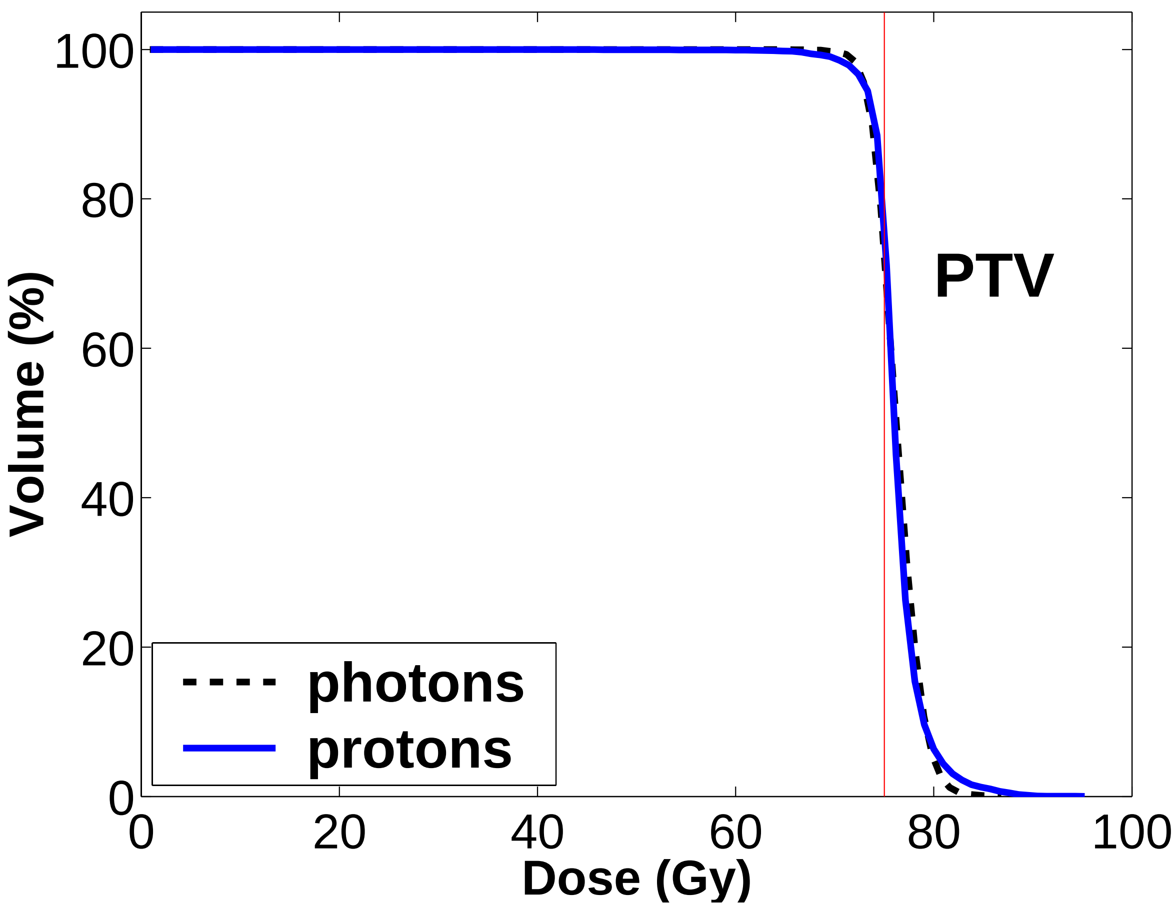
4027418
IMXT plan (dose in Gy)



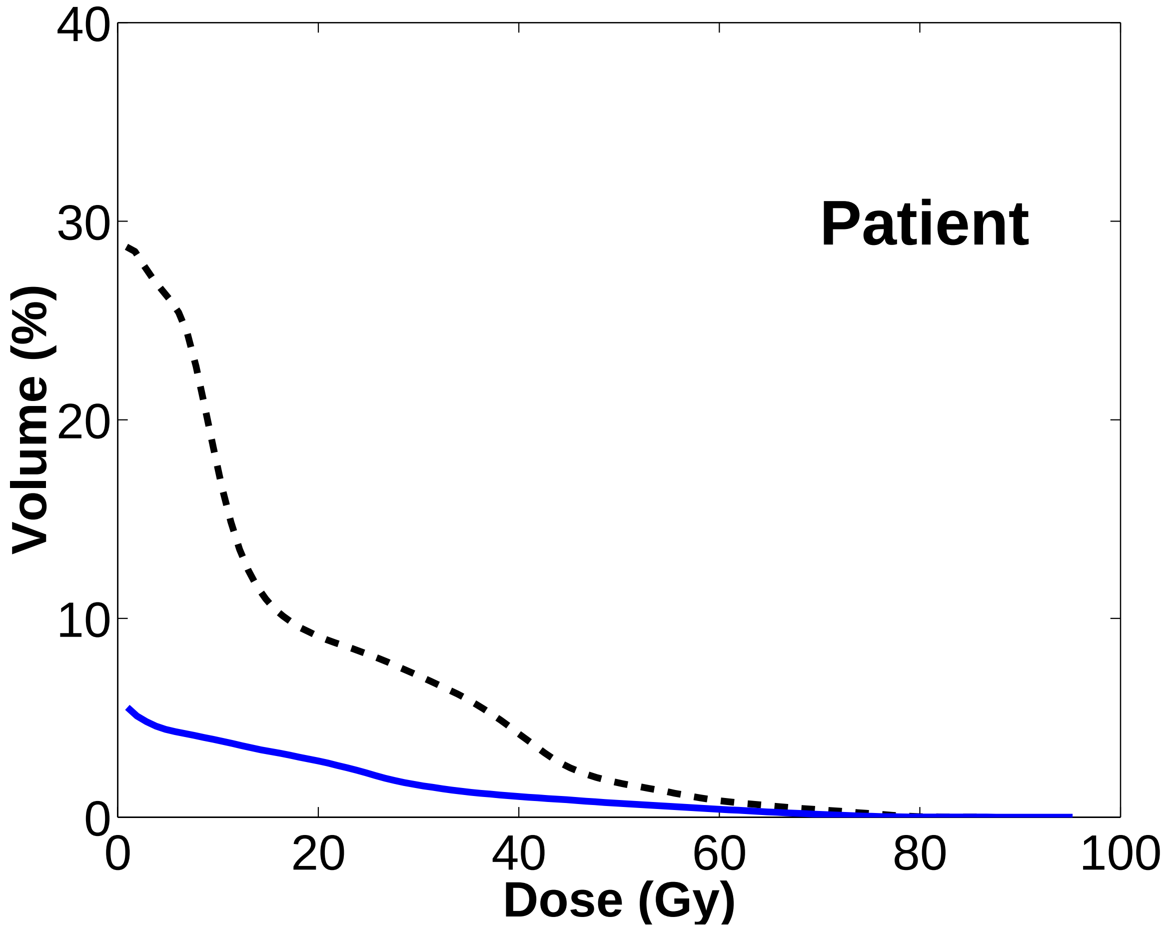
4027418
IMPT plan (dose in Gy)

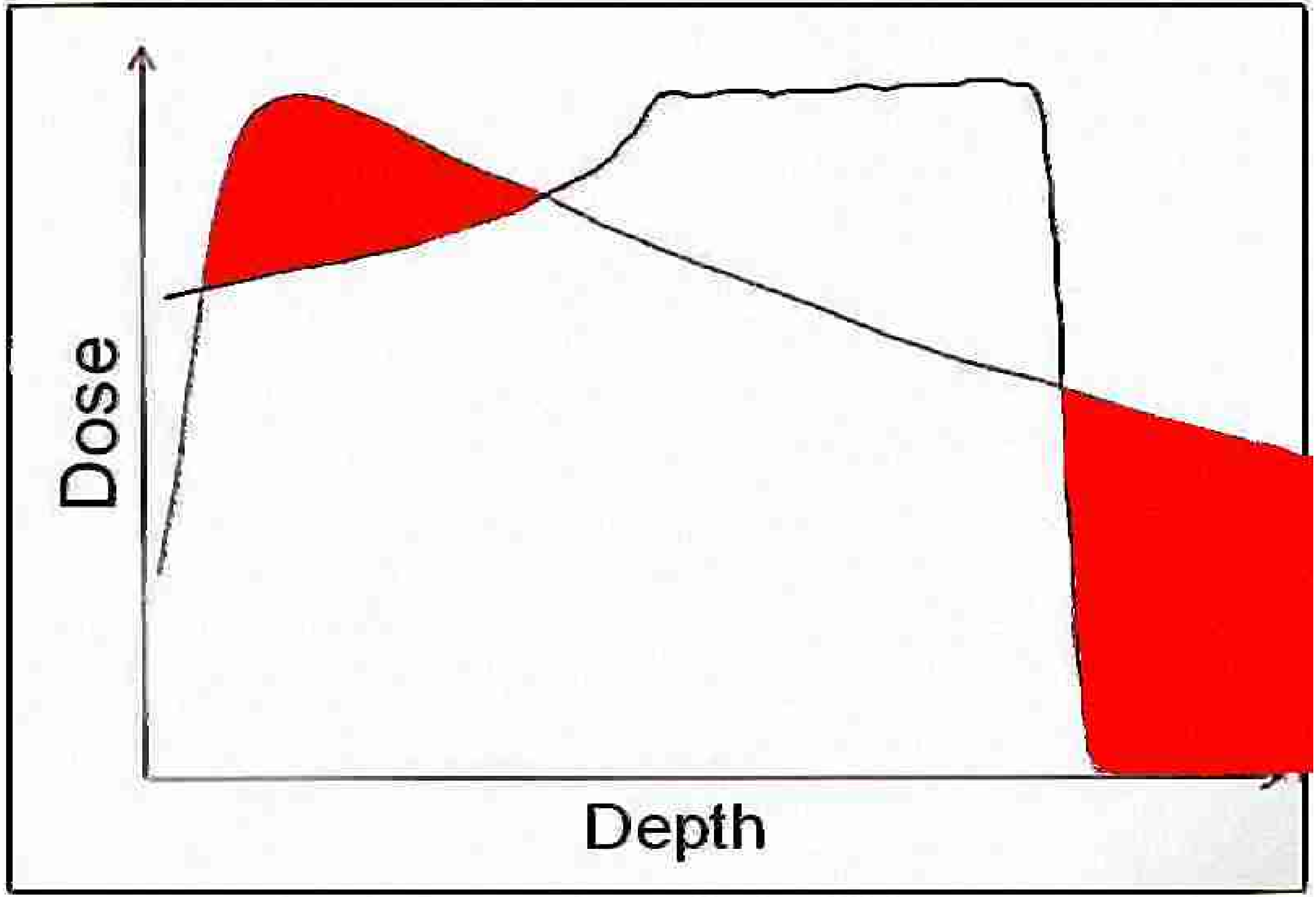


4027418
DVH comparison

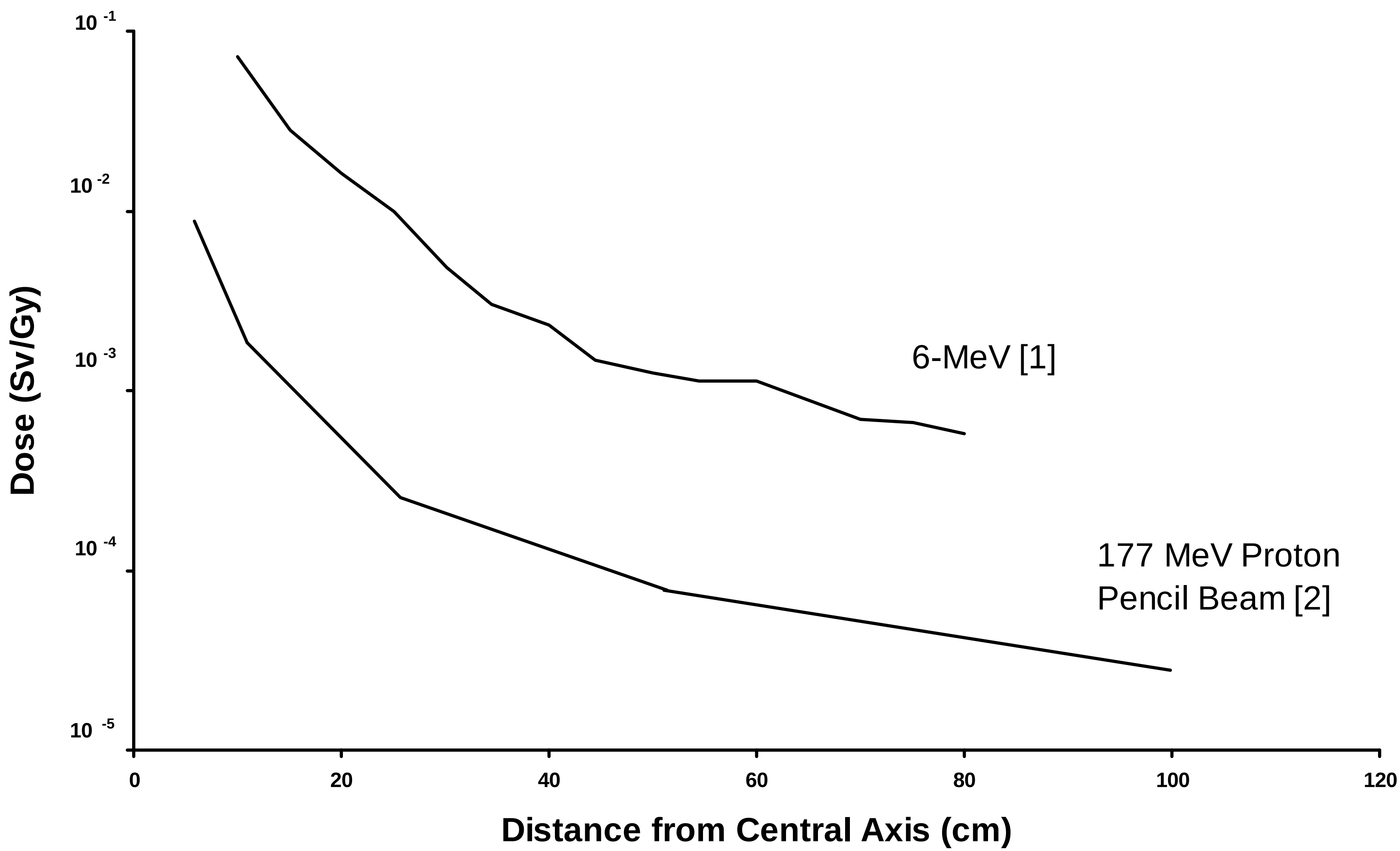


4027418
DVH comparison




Dose
Depth

Dose vs. Distance from Central Axis of 10x10 cm Field



Dose Lateral to Beam Paths

Target Dose is 70 Gy

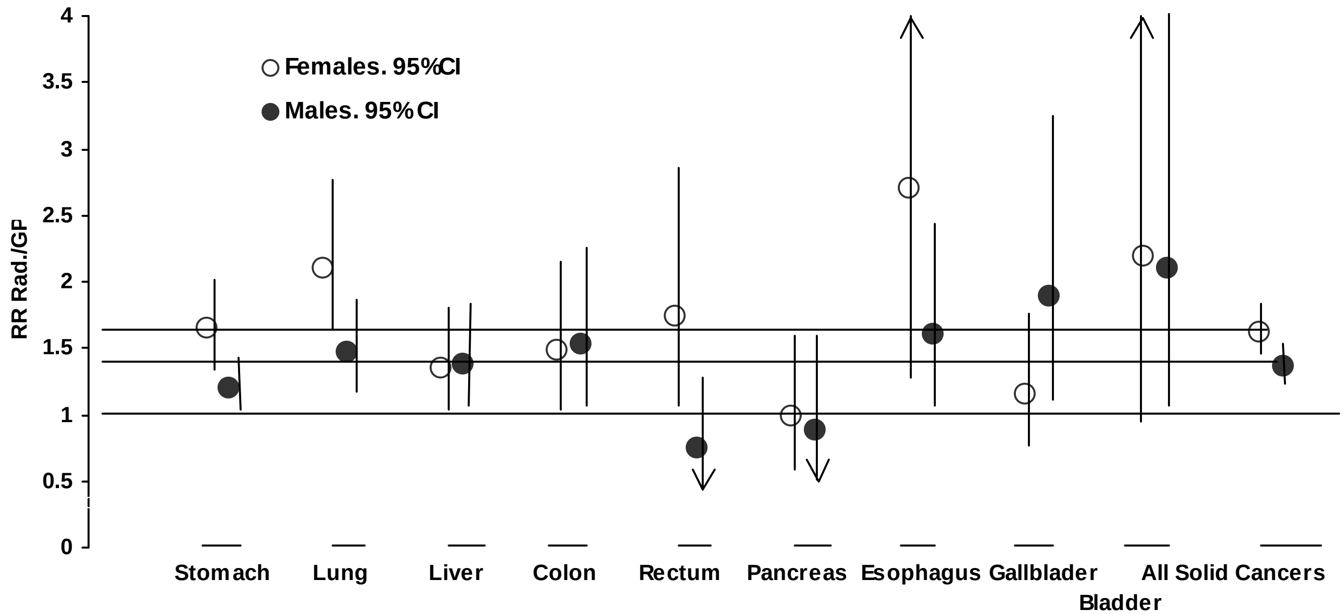
Dose at 70 cm is 0.07 Gy [0.001%]

Dose at 20 cm is 2 Gy [0.03%]

Radiation Carcinogenesis

86,572 Atom Bomb Survivors Very Intensively Studied for Cause of Mortality 1950-1997

Observed/Expected Cancer Mortality Atomic Bomb Survivors of 1 Sv from 1950 to 1997. [1]



Radiation Cancer in ABS

Risk $\rightarrow$ for $\geq$ 52 Yrs

Female > Males

$\downarrow$ with Age

Not Equal for All Organs

Radiation Cancer in ABS

114 of 440 [26%] of Cancer Deaths

Attributed to Radiation of ABS

Occurred at 45-52 Years

Human Rad Carcinogenesis

Uncommon

Late, viz > 5 - 10 - 50 years

FU Exams: $\downarrow$ Frequency
Thoroughness

Ca Cervix: O/E for Rad Ca

Yrs FU	O/E
1-9	1.1
10-19	1.4
20-29	1.6
30+ yrs	2.1

Klinnerman etal

Radiation Carcinogenesis

Life Time Risk to 30 y/o Person

of Fatal Cancer from 1 Sv Acute

Whole Body Dose is ≈ 10%

Radiation Carcinogenesis

Accepted: Risk ↑ Linearly with Dose

to 2 Gy for Worker Safety

Risk at Higher Dose Less Understood

Radiation Carcinogenesis

Some Data Are Not in Accord with

Linear Model For Dose <0.2-1 Gy

Consider Some Mice Experiments

In-Bred Mouse Studies

Minimal Heterogeneity in Subjects

Uniform: **Age**

Gender

In-Bred Mouse Studies

Minimal Heterogeneity in Subjects

Uniform: Uniform Treatment

Food, Bedding, Temp

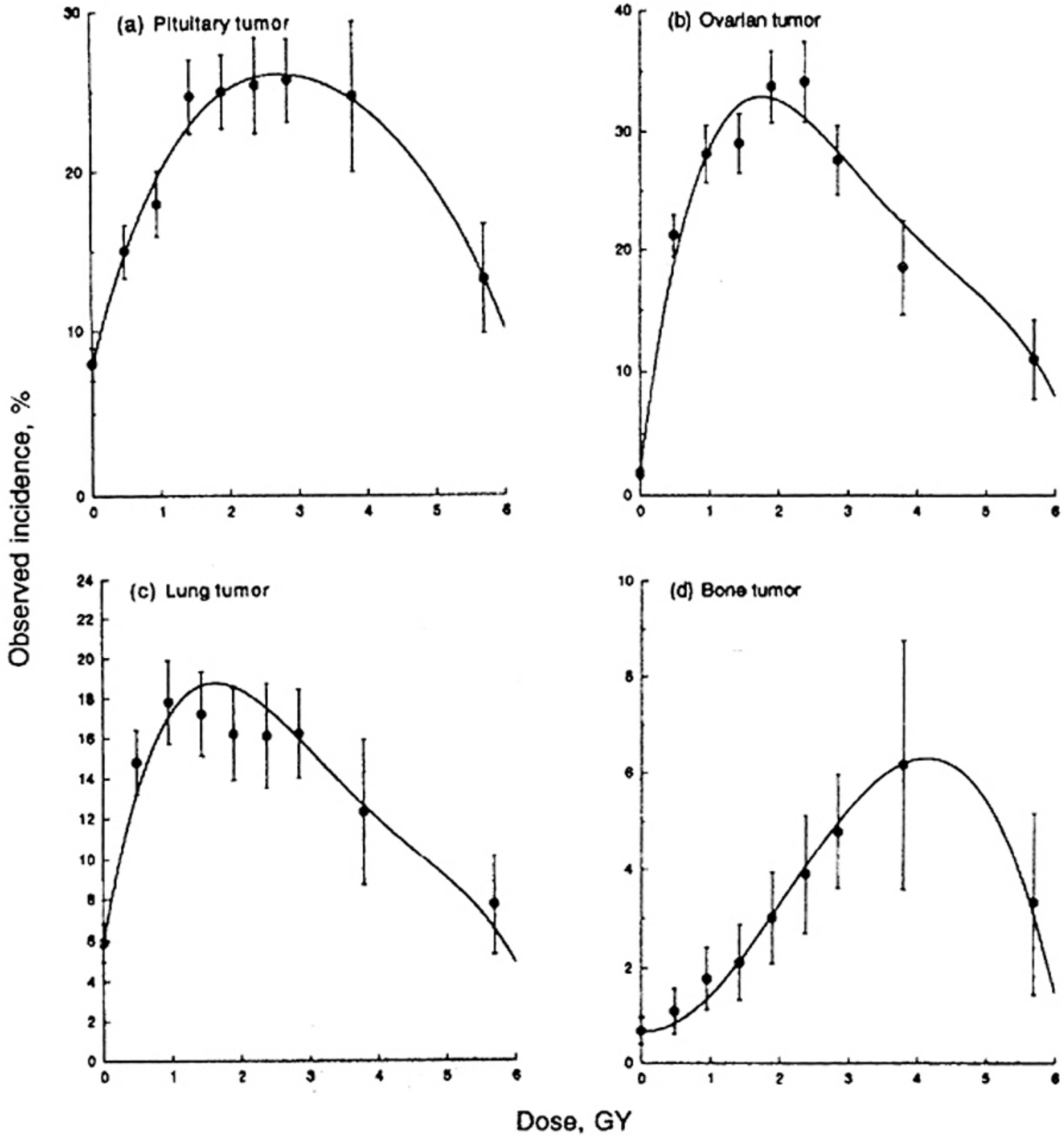
Autopsy Rate ≥ 95%

Mouse Model Studies

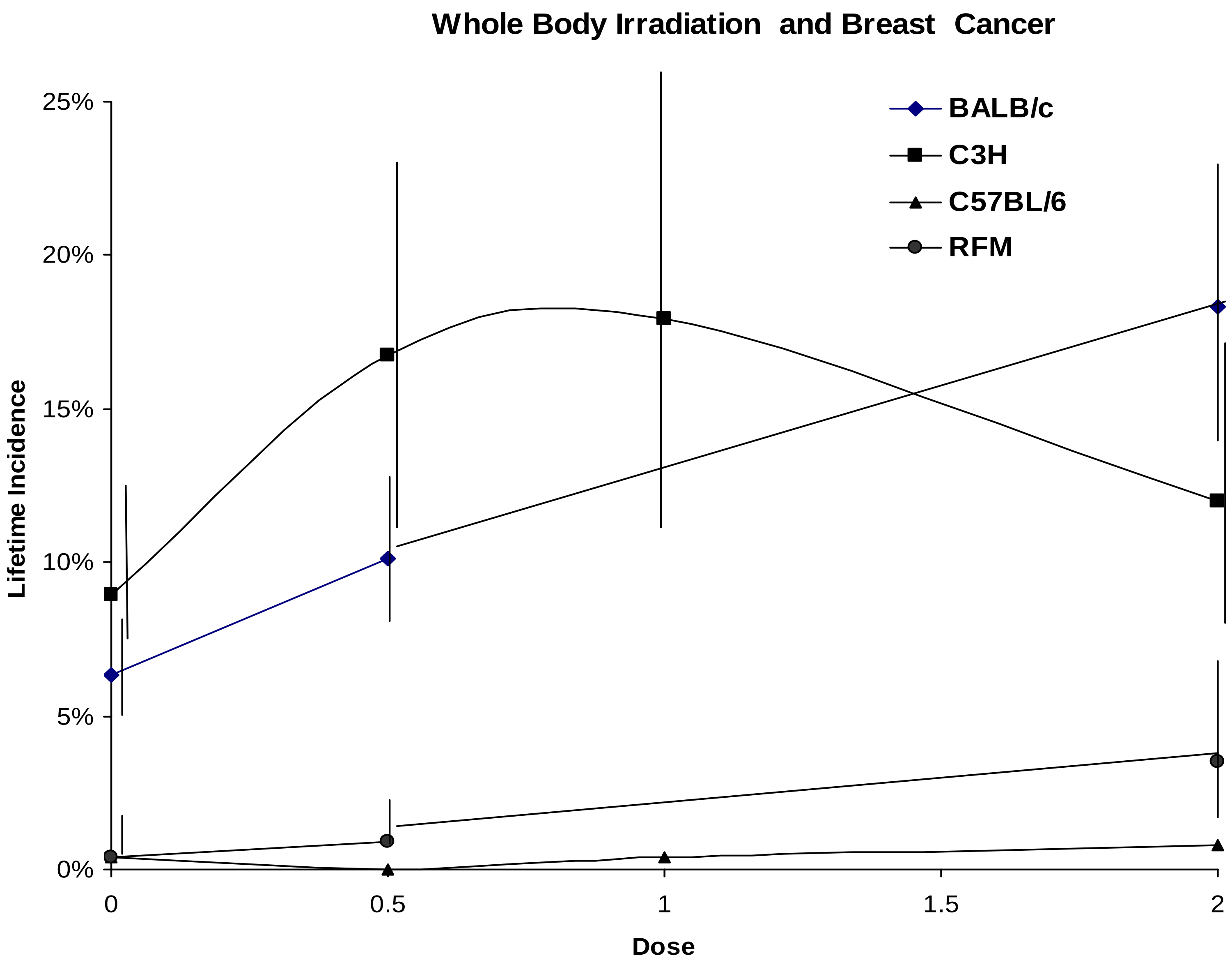
In-Bred Mice of One Strain are

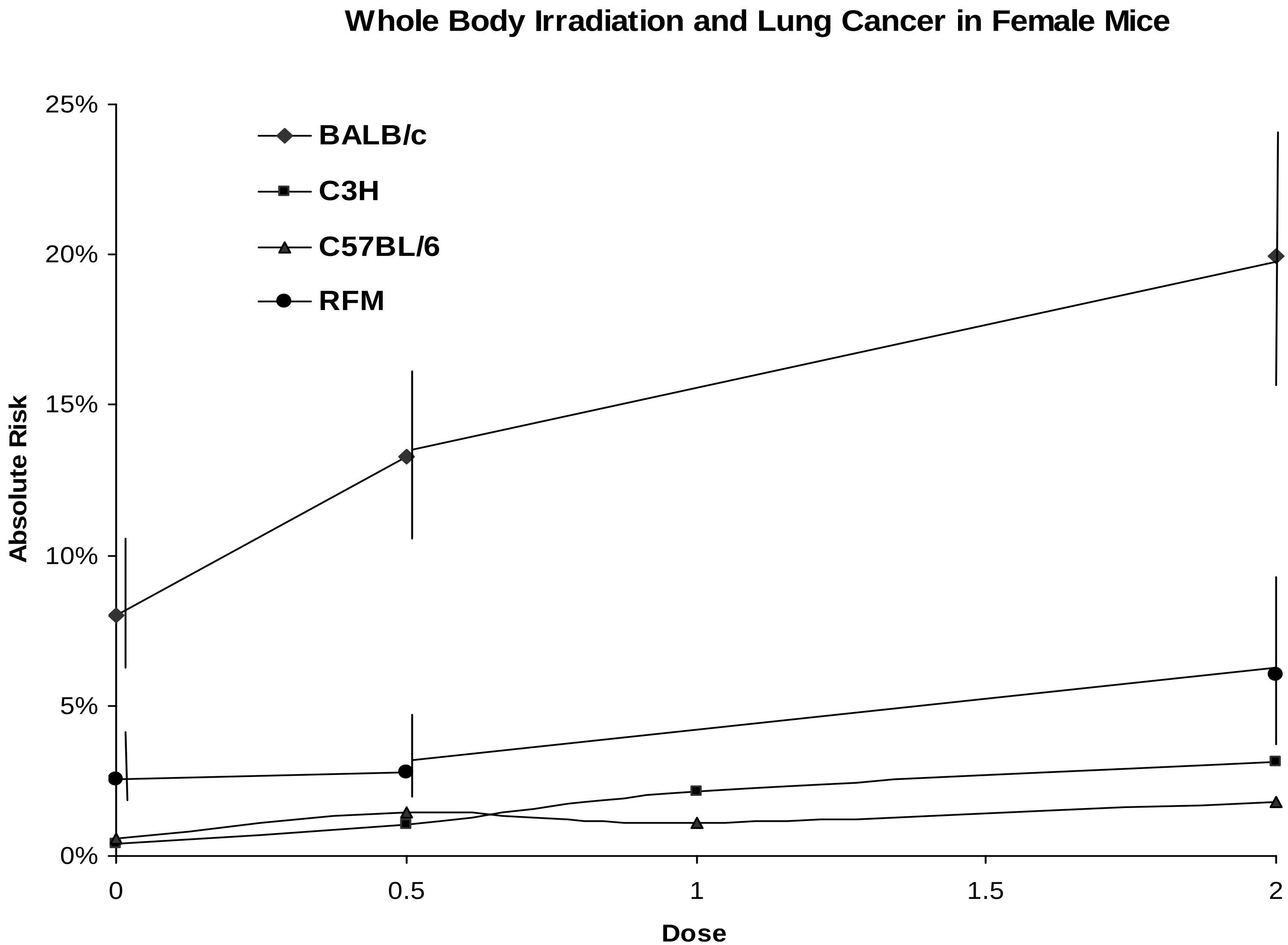
Extremely Close To Being Clones,

***viz* Nearly Identical Genetically**

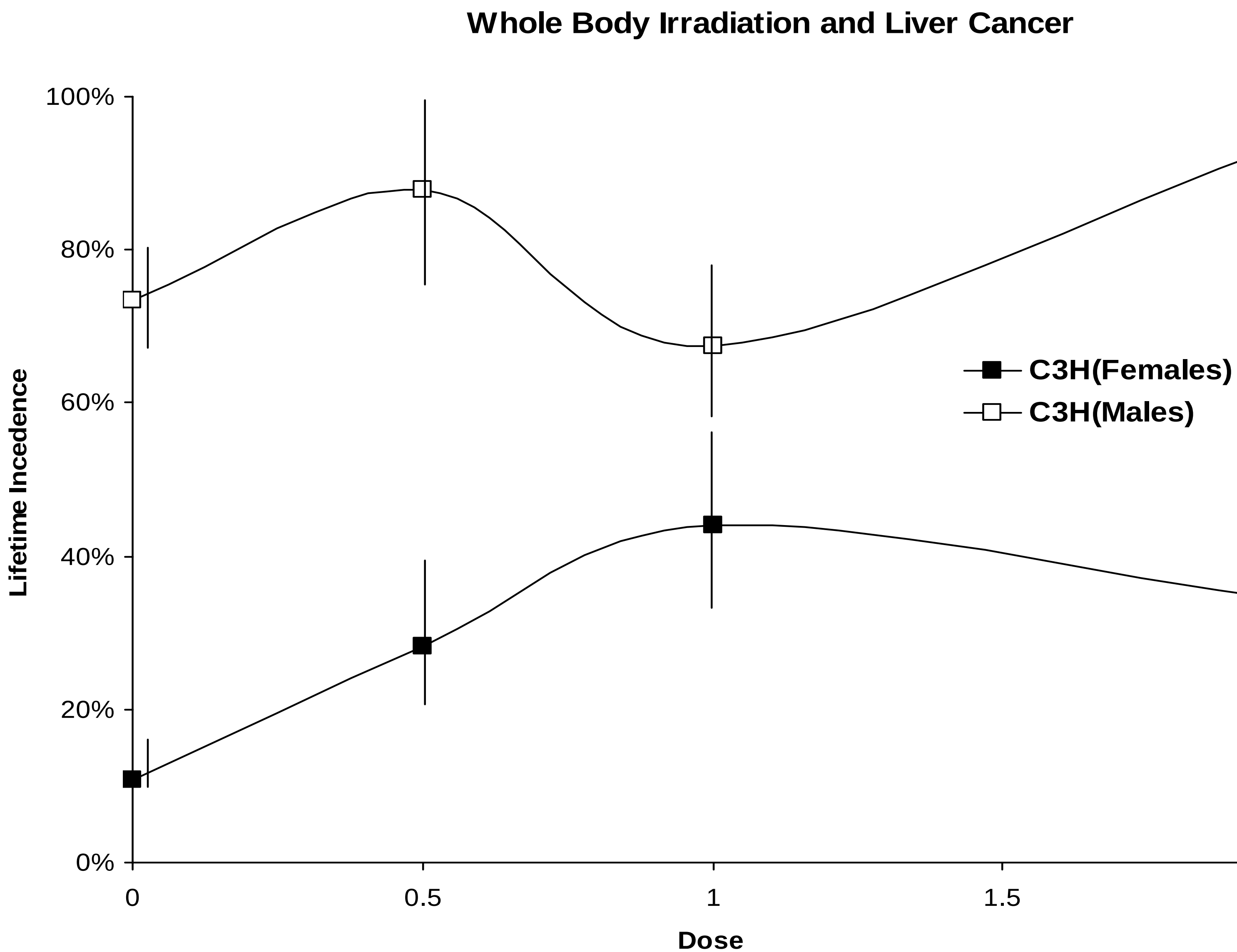


(a) Pituitary tumor
(b) Ovarian tumor
(c) Lung tumor
(d) Bone tumor
Observed incidence, %
Dose, GY


Whole Body Irradiation and Breast Cancer
BALB/c
C3H
C57BL/6
RFM
Lifetime Incidence
25%
20%
15%
10%
5%
0%
0
0.5
1
1.5
2
Dose



Whole Body Irradiation and Lung Cancer in Female Mice
BALB/c
C3H
C57BL/6
RFM
Absolute Risk
25%
20%
15%
10%
5%
0%
0
0.5
1
1.5
2
Dose


Whole Body Irradiation and Liver Cancer
100%
80%
60%
40%
20%
0%
Lifetime Incedence
0
0.5
1
1.5
2
Dose
C3H(Females)
C3H(Males)

Life Time Lung Cancer Incidence in I Mice

	#Mice	Control	2 Gy WBI
Balb/c	809	8%	20%
C_3H	258	0.4%	6%
C57BL	256	0.6%	2%
RFM	759	2%	6%

Storer *etal* 1988

Life Time Lung Cancer Rates

		Control	2 Gy
C_3H	é	0.4%	6%
	l	2%	11%
C57BL	é	0.6%	2%
	l	0.6%	8%

Storer *etal* 1988

2 Gy Life Shortening

F Mouse	Days Lost	%Life Short
Balb/c	110	14
C_3H	97	12
C57BL	25	3
RFM	162	25

Storer *etal* 1988

2 Gy Life Shortening

Mouse	Days Lost	%Life Short
C_3H F	97	12
M	54	7
C57 F	25	3
M	20	2

Storer *etal* 1988

Life Shortening in Mice by 2 Gy

Strain		Days	%
BALB/c	F	109	14
C3H	F	97	12
C3H	M	54	7
C57BL6	F	25	3
C57BL6	M	20	2
RFM	F	162	25

Rhesus Monkey 2^0 Cancer

WBI and Bone Marrow Salvage

Control 21 Monkeys

WBI	8 Gy	15	3.5 Gy	5 Monkeys
	4 Gy	Neutrons		9 Monkeys

Broerse etal; Hollander etal

WBI and Cancer in Monkeys

Gy	#	%
0.0	5/57	8.8
0.25-1.1	2/57	3.5
2-2.8	2/58	3.4
3.6-4	10/51	19.6
5-6.5	9/42	21.4
8	3/9	33.3

Rhesus Monkey 2^0 Cancer

WBI and Bone Marrow Salvage

	Control	WBI
Kidney	0/21	12/30
Osteo Sarc	0	4
Mal. Glomus	0	4
CNS	0	2
Soft Tiss	0	2

Broerse etal; Hollander etal

Rhesus Monkey 2^0 Cancer

WBI and B M Salvage

	Control	WBI
Intestine	3	3
Genital	2	0
Breast	1	0
Stomach	1	1

Broerse etal; Hollander etal

Radiation Brain Ca: Primates

Macaca mulatta Monkeys 3 y/o

3.5 Gy x 10 to Brain

GBM in 9 of 11 at 2.9 – 8.3 Yrs

Lonser et al 2002

Secondary Cancer Post RT

Analysis of 11 Series of Radiation

Treated Patients. Large Numbers

Observed > 10 Years

Patient Series Evaluated

Cervix	3	Prostate	3
Testis	2	Peptic Ulcer	1
Spine	1	Metropathia	1

Patient Series Evaluated

Cervix, Prostate and Peptic Series:

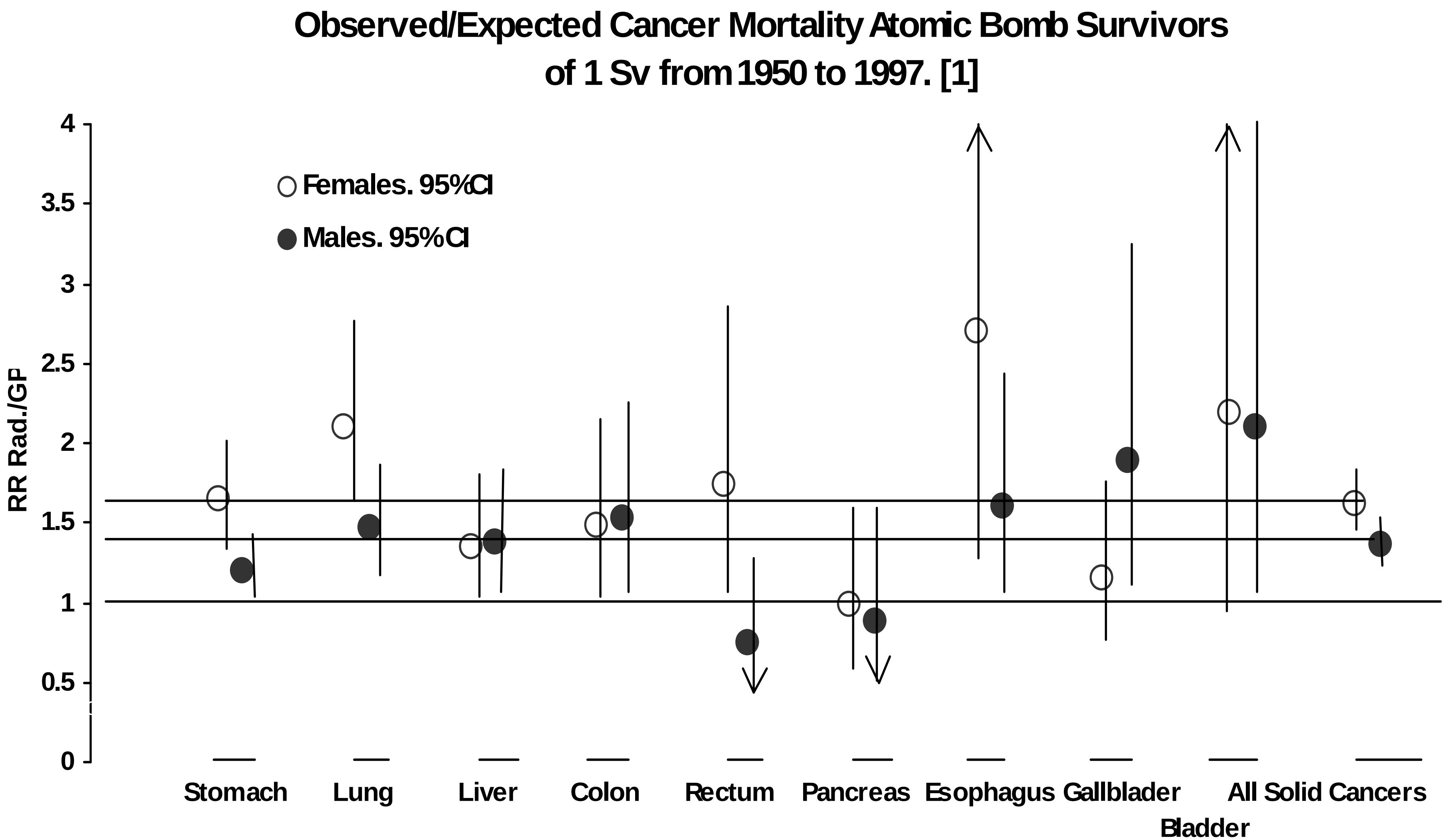
Also, NonRT Parallel Series

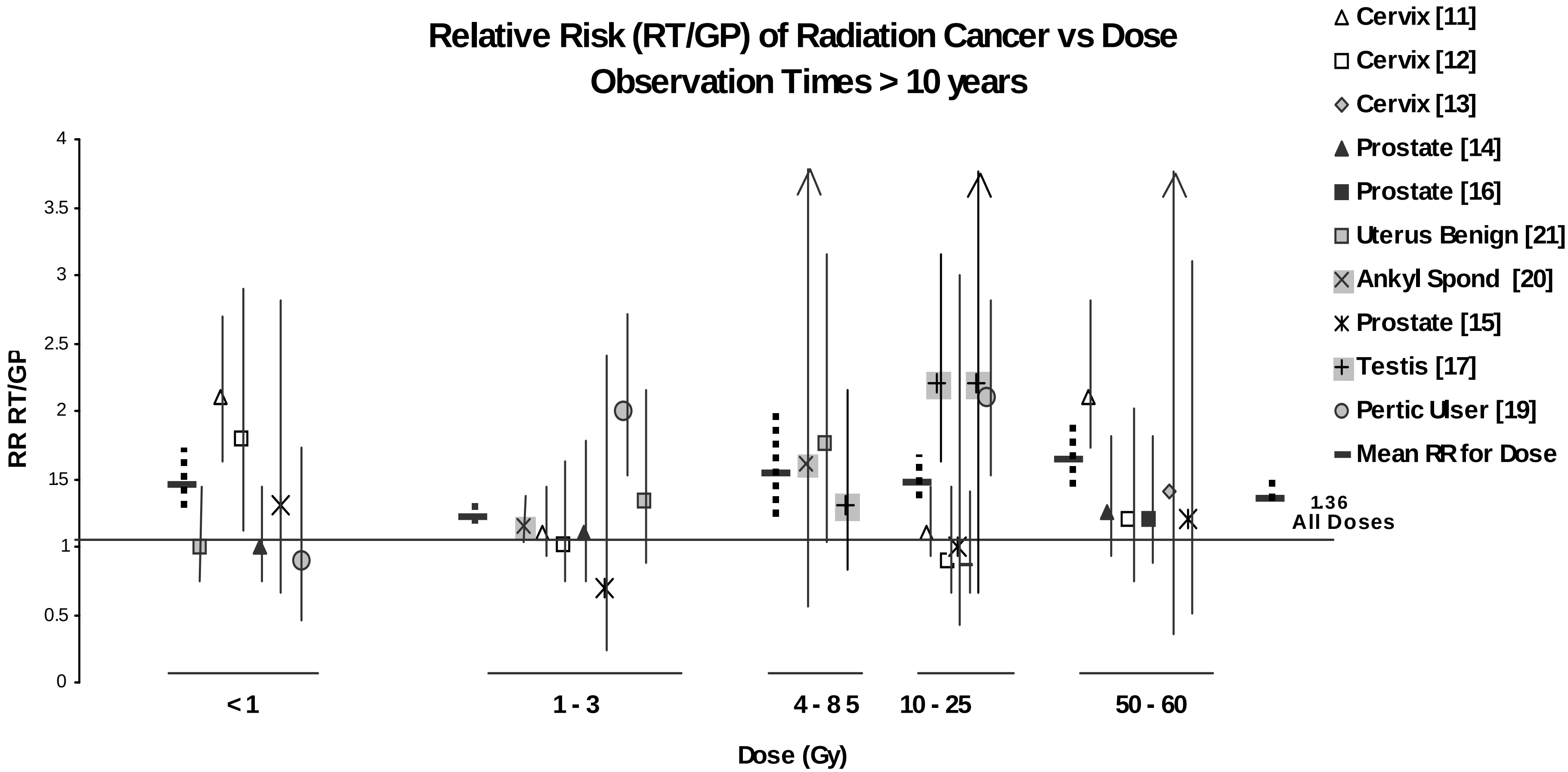
RR is Observed $\div$ Expected

Secondary Cancer In Radiation Treated Patients

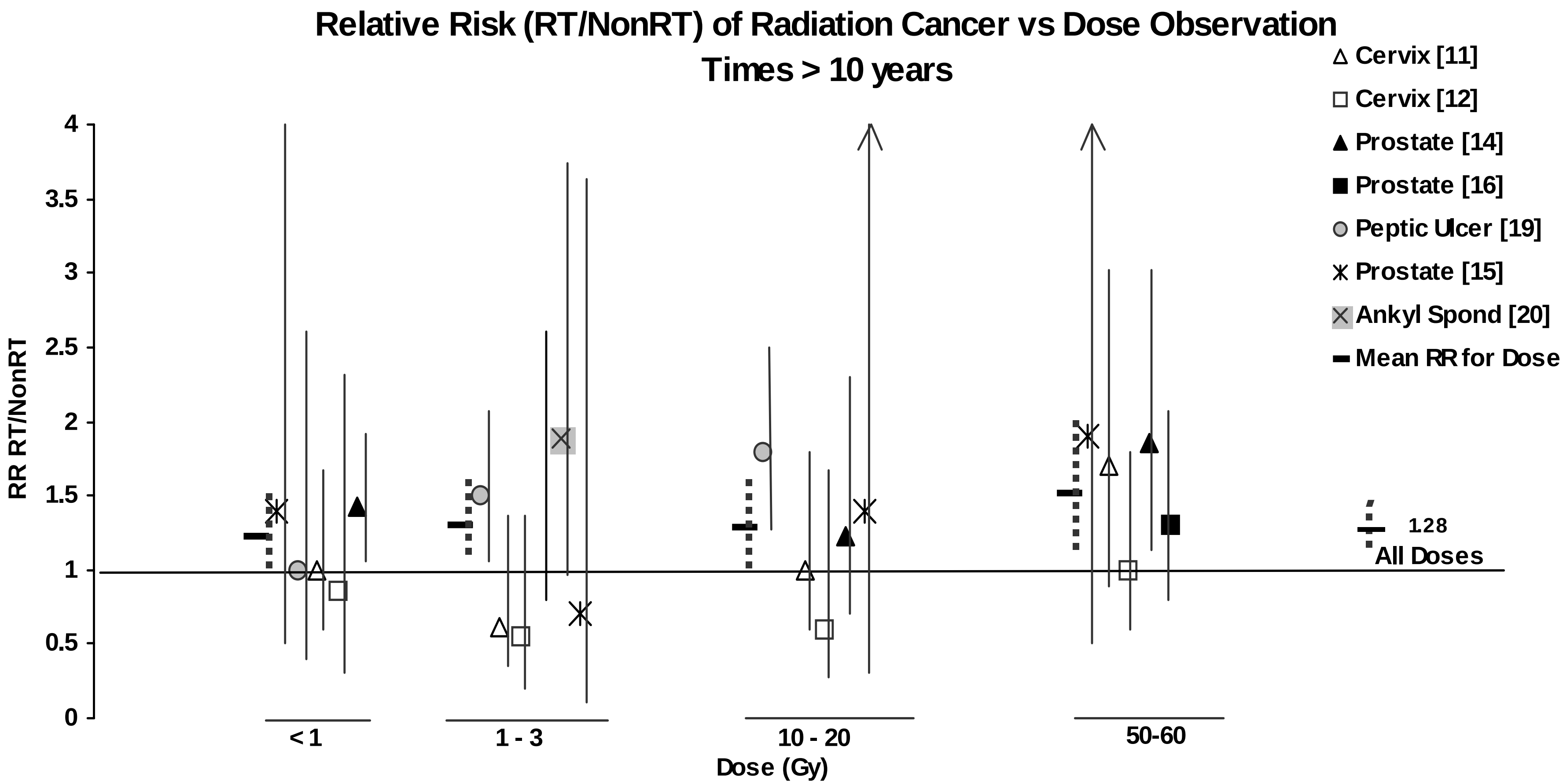
2^0 Cancer in Rad or Surgery Patients

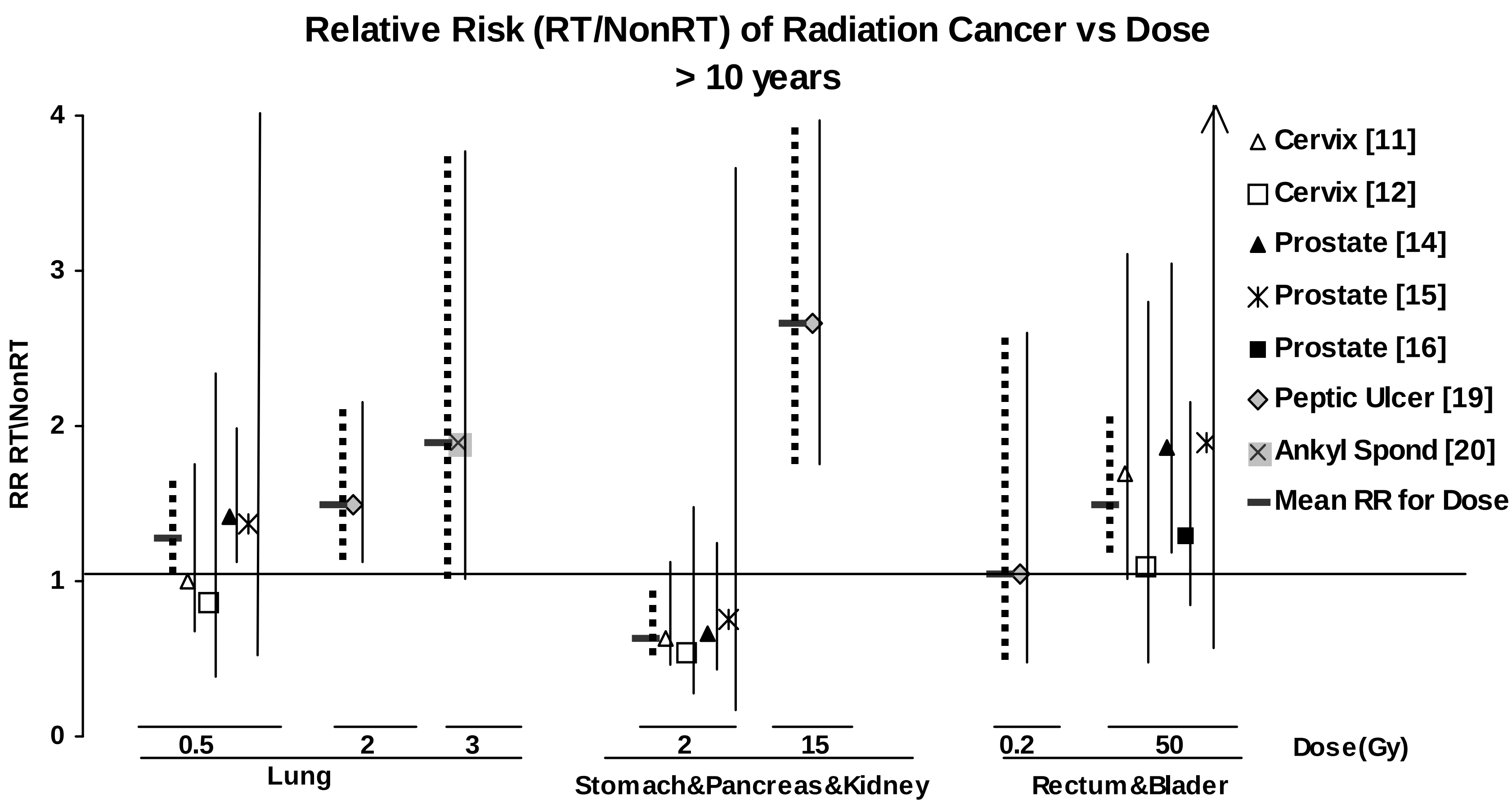
Uterine Cervix	86,000 Pts
Prostate	122,000 PTs


Observed/Expected Cancer Mortality Atomic Bomb Survivors
of 1 Sv from 1950 to 1997. [1]
Females. 95%CI
Males. 95%CI
RR Rad./GP
4
3.5
3
2.5
2
1.5
1
0.5
0
Stomach
Lung
Liver
Colon
Rectum
Pancreas
Esophagus
Gallblader
Bladder
All Solid Cancers



Relative Risk (RT/GP) of Radiation Cancer vs Dose
Observation Times > 10 years
RR RT/GP
4
3.5
3
2.5
2
15
1
0.5
0
< 1
1 - 3
4 - 8 5
10 - 25
50 - 60
Dose (Gy)
1.36
All Doses
Cervix [11]
Cervix [12]
Cervix [13]
Prostate [14]
Prostate [16]
Uterus Benign [21]
Ankyl Spond [20]
Prostate [15]
Testis [17]
Pertic Ulser [19]
Mean RR for Dose


Relative Risk (RT/NonRT) of Radiation Cancer vs Dose Observation
Times > 10 years
Cervix [11]
Cervix [12]
Prostate [14]
Prostate [16]
Peptic Ulcer [19]
Prostate [15]
Ankyl Spond [20]
Mean RR for Dose
RR RT/NonRT
4
3.5
3
2.5
2
1.5
1
0.5
0
1.28
All Doses
< 1
1 - 3
10 - 20
50-60
Dose (Gy)


Relative Risk (RT/NonRT) of Radiation Cancer vs Dose
> 10 years
RR RT\NonRT
4
3
2
1
0
Cervix [11]
Cervix [12]
Prostate [14]
Prostate [15]
Prostate [16]
Peptic Ulcer [19]
Ankyl Spond [20]
Mean RR for Dose
0.5
2
3
Lung
2
15
Stomach&Pancreas&Kidney
0.2
50
Rectum&Blader
Dose(Gy)

$RR_{RT/NonRT}$ [>10 yrs] *vs* Dose

Dose (Gy)	RR
50-70	1.52
10-25	1.28
4-8	0.84
1-3	1.30
<1	1.23
All Doses	1.28 (1.14-1.44)

Conclusions

New Technologies to Yield

Important Clinical Gains

Conclusions

↑ Dose to Target ↑ TCP

↓ Dose to NTs ↓ NTCP

Conclusions

New Techniques ↓ Lateral

Dose

Conclusions

Major ↓ Risk of Rad 2^0 Cancer

By ↓ Tissue Volume at <2 Gy

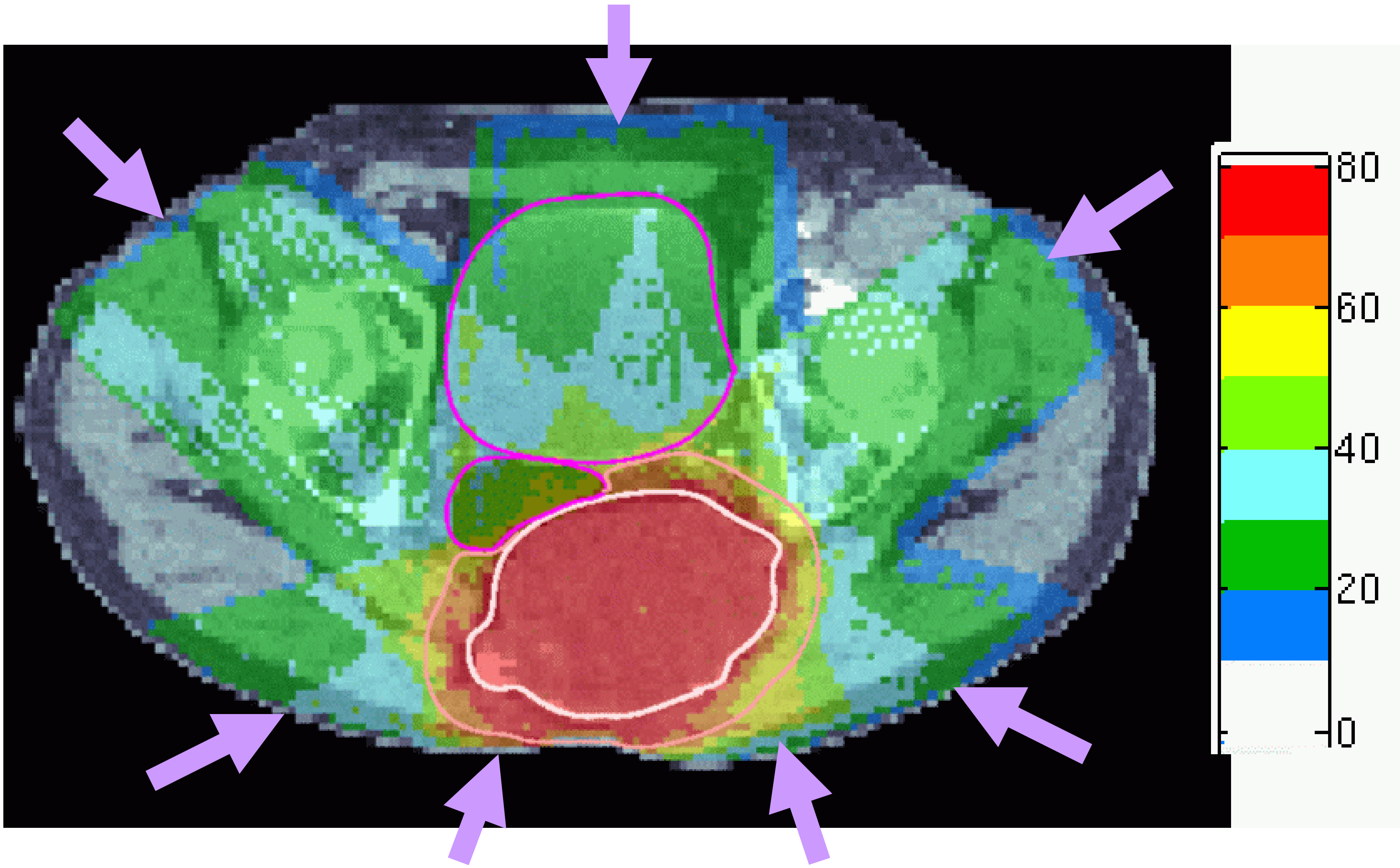
Conclusions

$\downarrow$ Risk of Rad 2^0 Cancer

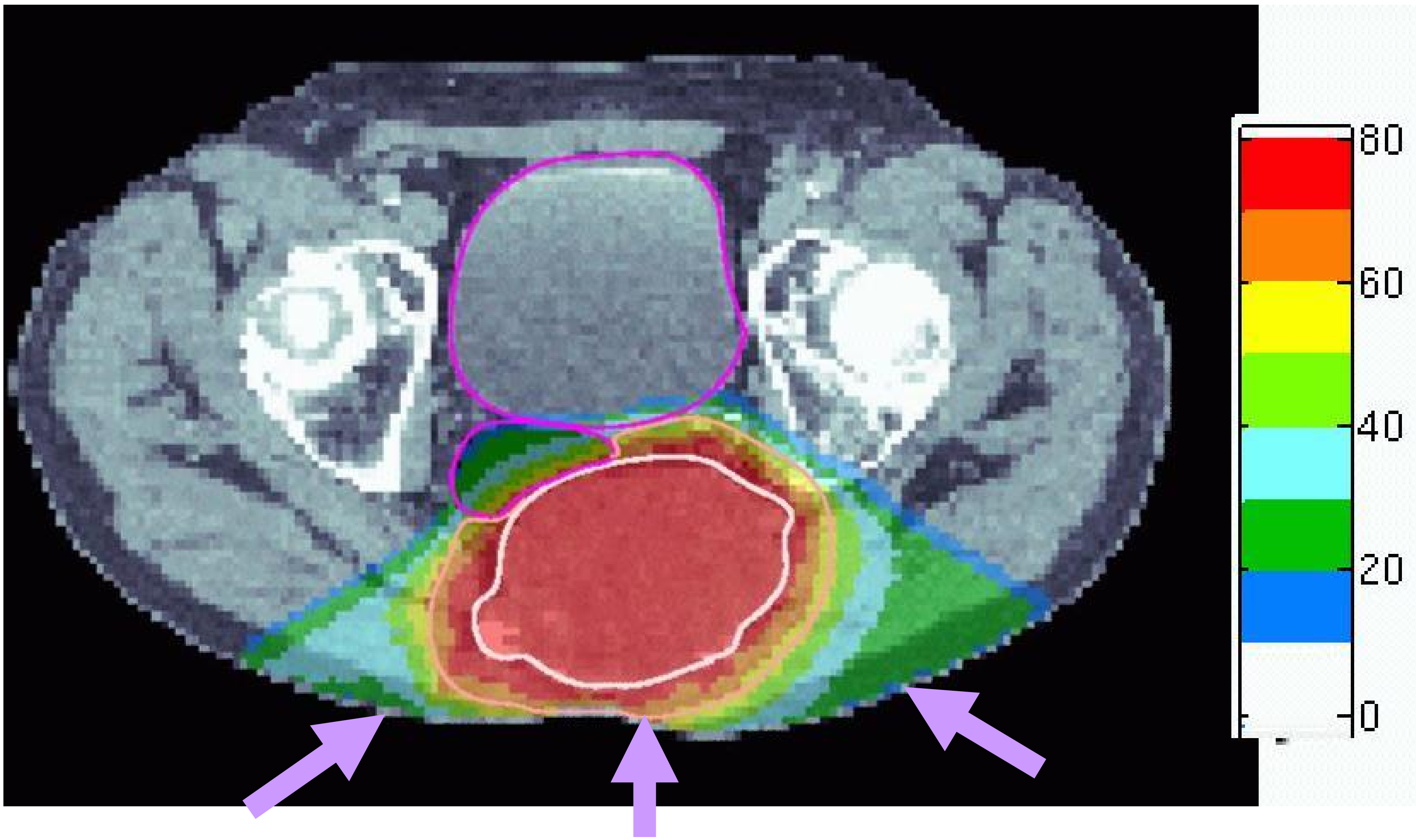
Independent of Dose Over

Range 2-50 Gy???

Sacral Chordoma
IMXT (Gy)



Sacral Chordoma
IMPT (Gy)



Conclusions

↓ Risk of Rad 2^0 Sarcoma

↑ With Dose > 50 Gy

Risk is Volume Dependent

Conclusions

Risk of Rad 2^0 Sarcoma >60 Gy

↓ Risk of Non Cancer Change

Fibrosis, Necrosis, Fistula

Conclusions

Risks are Small for 10 Yr FU

May ↑ Progressively with Time

***eg* to 50+ Yrs**