ICRO Teaching course: 1st August 2020

Proton therapy for Prostate cancer: Past and Future

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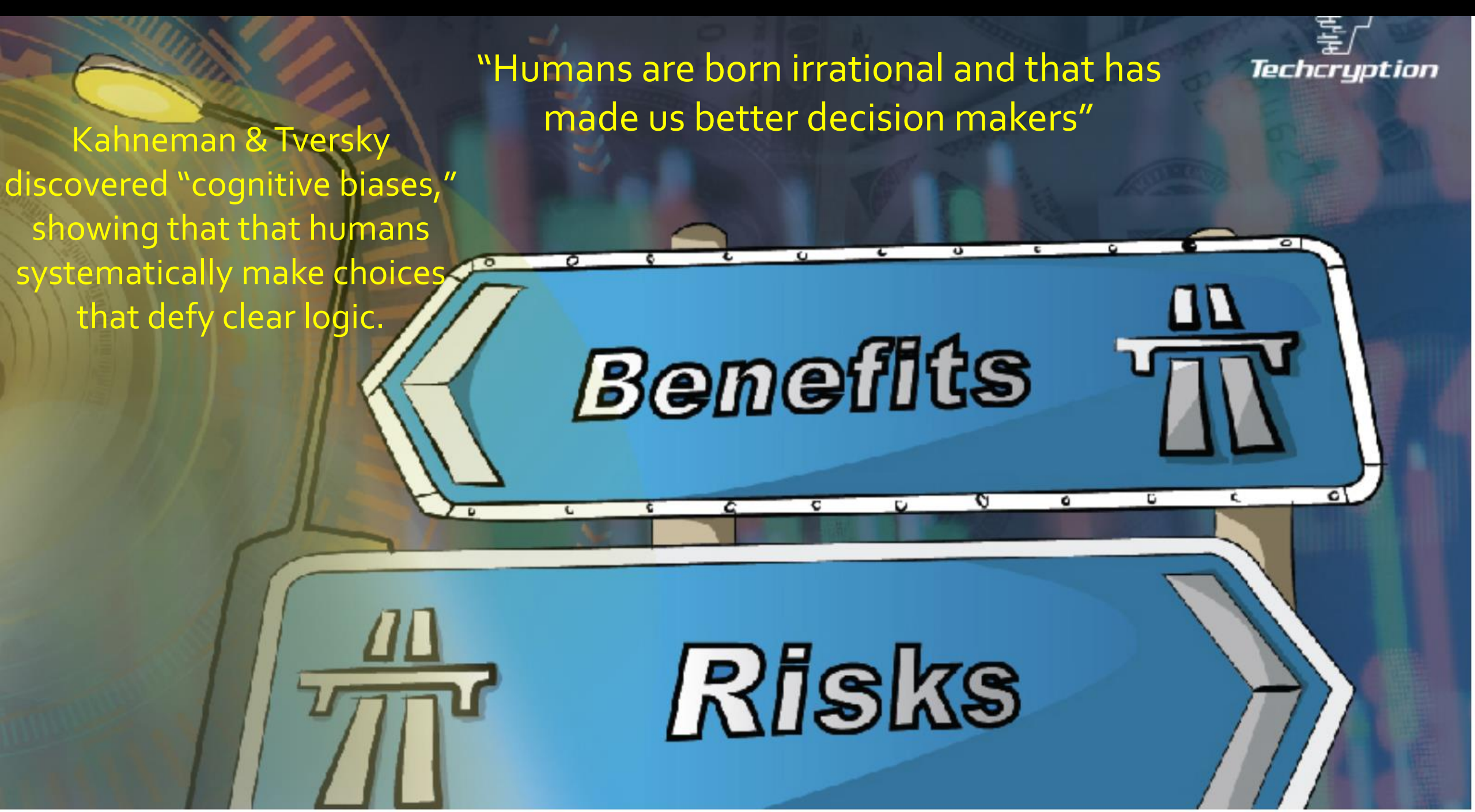
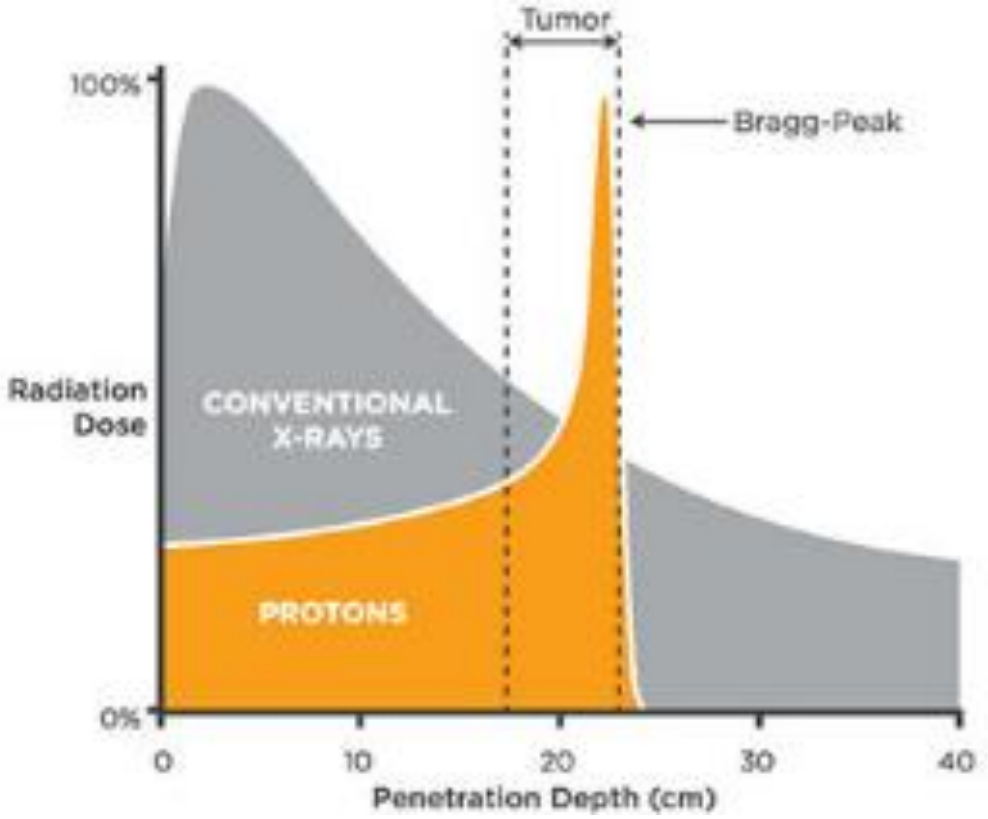
"Humans are born irrational and that has made us better decision makers"

Techcryption

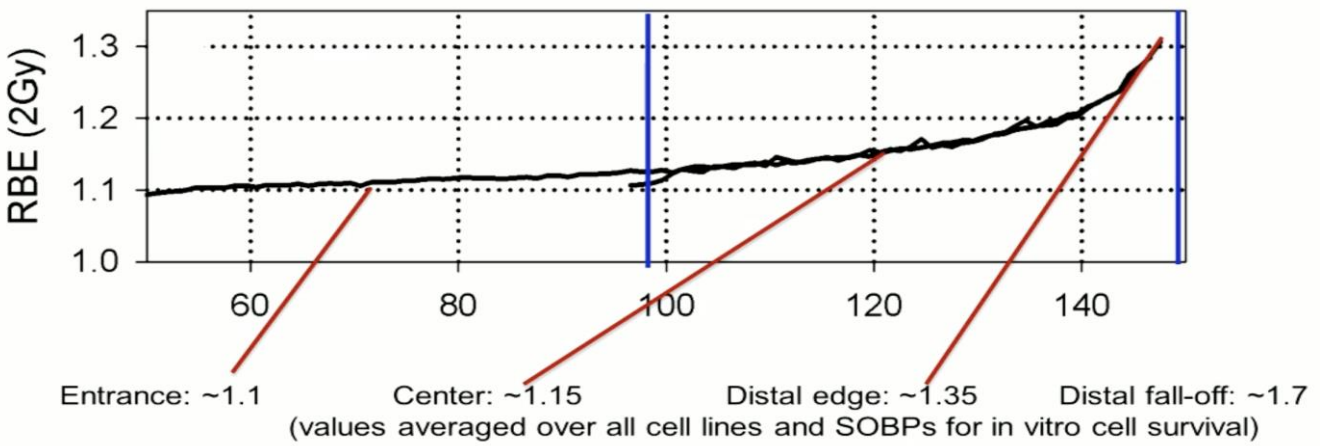
Kahneman & Tversky discovered "cognitive biases," showing that that humans systematically make choices that defy clear logic.



Proton Therapy



Protons Stop
RBE is Variable



Radiation for Prostate Cancer

Image guided IMRT

Crisp margins

Modern algorithms

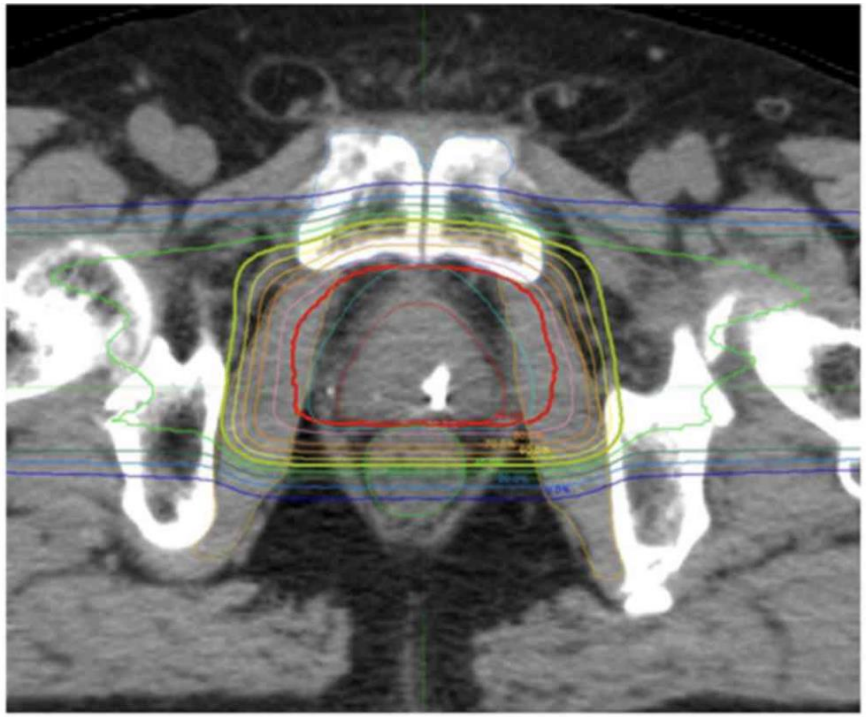
2004/2005

Low risk of SV involvement[1]		Moderate risk of SV involvement[1]		Dose				Minimum iso-dose coverage
				74Gy Group	60Gy Group	57Gy Group	2Gy equivalent^{+++}	
GTV1 CTV1 PTV1	P P+base of SV+5mm CTV1 +5mm	GTV1 CTV1 PTV1	P P+SV+5mm CTV1 +5mm	59.2	48.0	45.6	54Gy	76%
GTV2 CTV2 PTV2	P P+5mm CTV2 +5mm/0mm*	GTV2 CTV2 PTV2	P P± base of SV^{++} +5mm CTV2 + 5mm/0mm*	71.0	57.6	54.7	70Gy	91%
GTV3 CTV3 PTV3	P P+0mm CTV3 +5mm/0mm^{+}	GTV3 CTV3 PTV3	P P+0mm CTV3 + 5mm/0mm^{+}	74.0	60.0	57.0	74Gy	95%

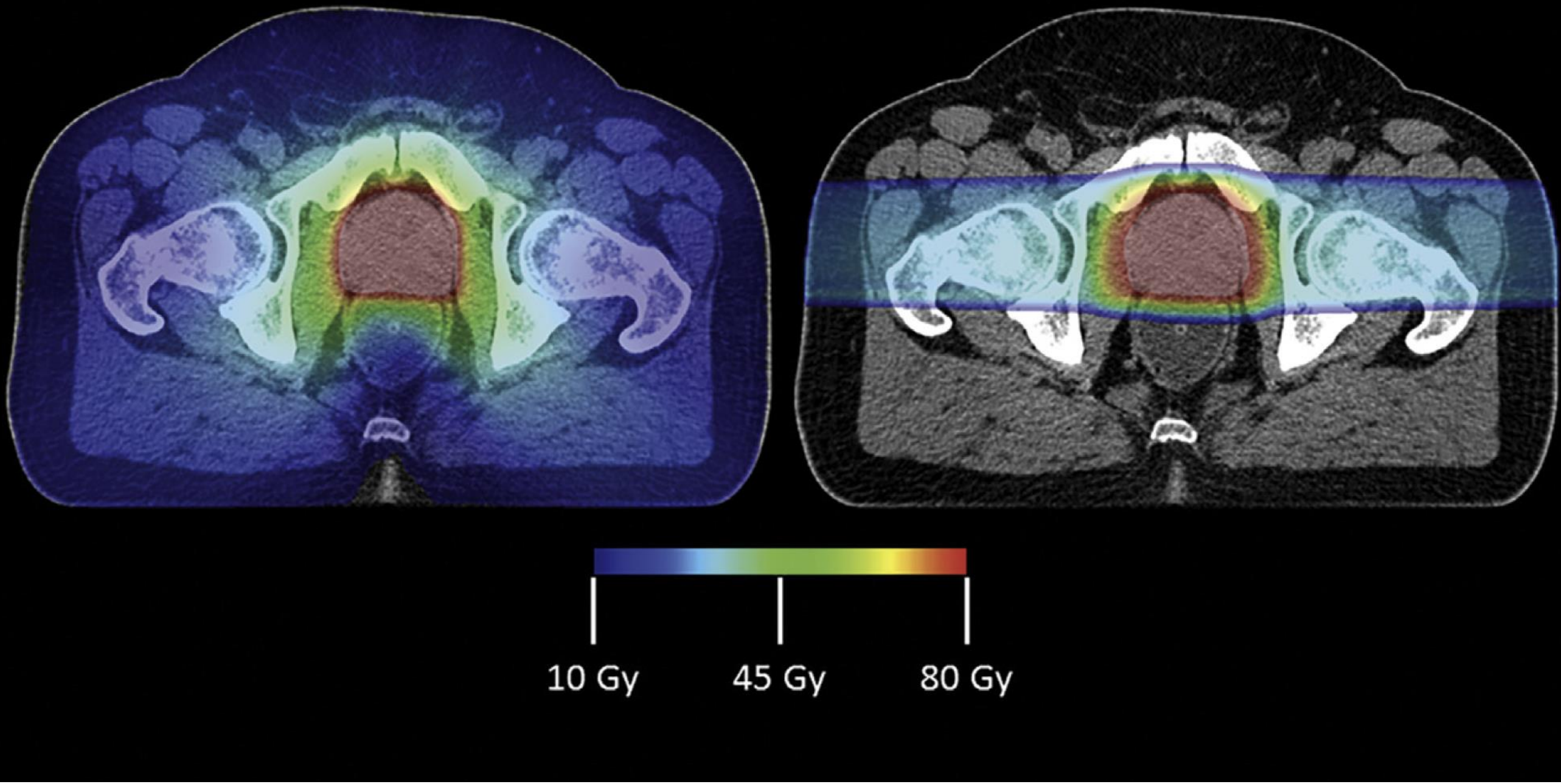
Proton therapy for Prostate cancer

Has been there since a long time

Passive scattering Proton therapy



- Relatively large margins
- No image guidance/Image guidance since 2010
- Primitive algorithms
- Prostate only

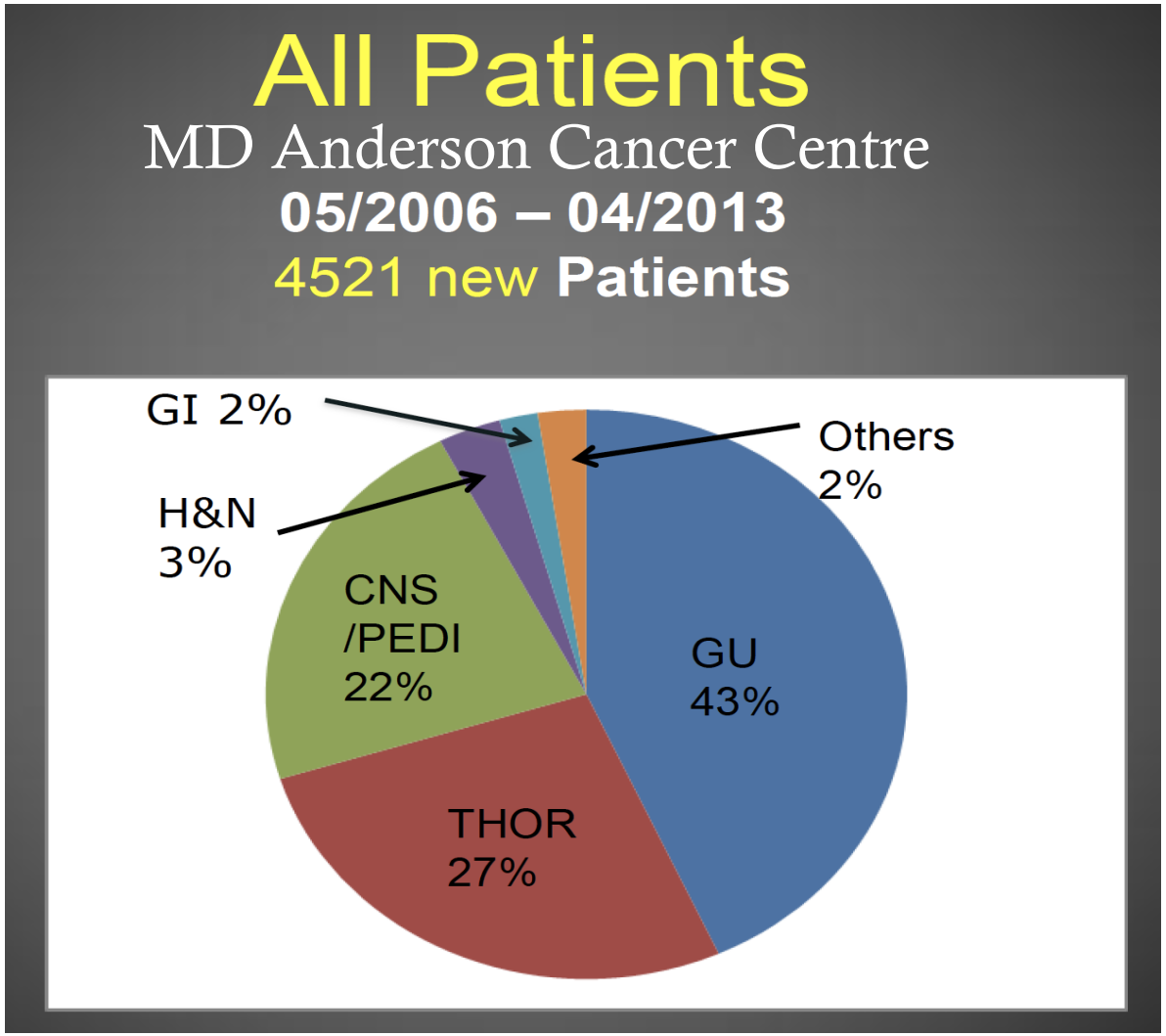

10 Gy
45 Gy
80 Gy

Review of evidence

Study	Data Source	*N*	Target/Dose/Image Guidance	Rectal Toxicity	Urinary Toxicity	Erectile Toxicity
Gray et al[67]	IMRT: PROSTQA* (2003-2006)	IMRT: 153	NR	↓ with PBT (2-3 mo)	↓ with PBT (2-3 mo)	NR
	PBT: MGH (2004-2008)	PBT: 95	76.6-79.2 Gy (IMRT), 74-82 Gy (PBT) NR	≈ (12 mo)	↑ with PBT (12 mo) ≈ (24 mo)	
Hoppe et al[68]	IMRT: PROSTQA* (2003-2006)	IMRT: 204	Prostate ± SV	↓ with PBT (6 mo)	≈ (6, 12, 24 mo)	≈ (6, 12, 24 mo)
	PBT: Univ. of FL (2006-2010)	PBT: 1243	75.6-79.2 Gy (IMRT), 78-82 Gy (PBT) Daily	≈ (12, 24 mo)		
Fang et al[69]	Univ. of PA (2010-2012)	IMRT: 94† PBT: 94	Prostate + SV 79.2 Gy Daily	≈ (≤3 or >3 mo)	≈ (≤3 or >3 mo)	≈ (≤3 or >3 mo)

Eric Ojerholm, et al. Seminars in Radiat Oncol 2017

Protons for Prostate Cancer



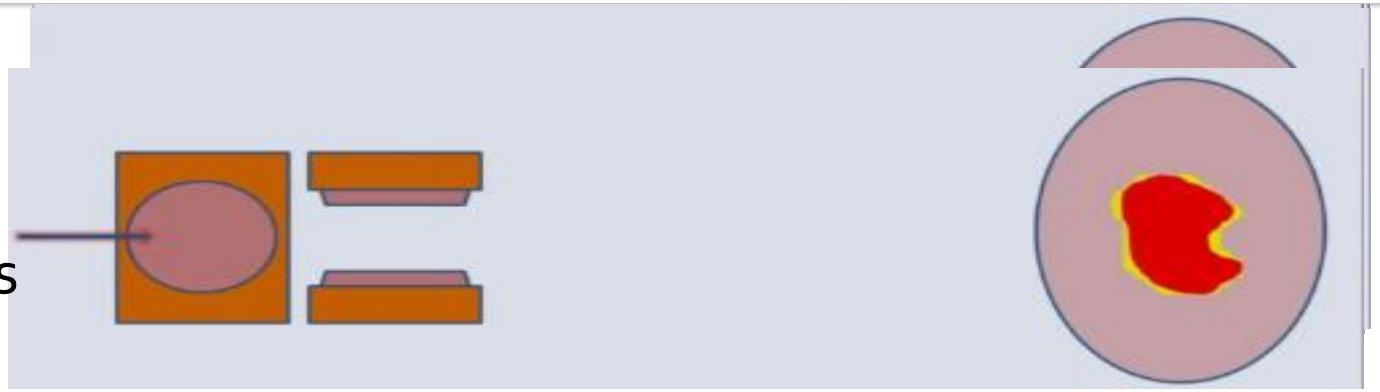
Use or abuse?

What is missing?

1. Data for comparison of modern IMRT with modern Proton therapy
2. Data for pelvic nodal irradiation

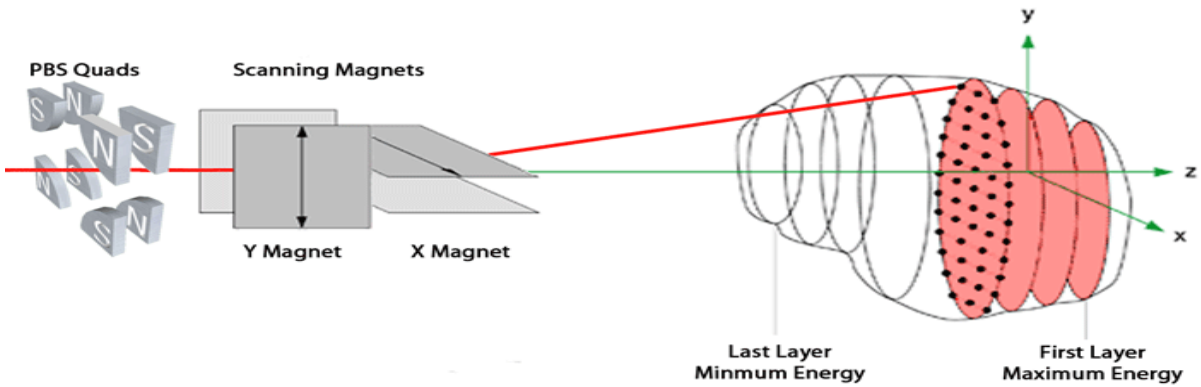
Contemporary Proton Therapy

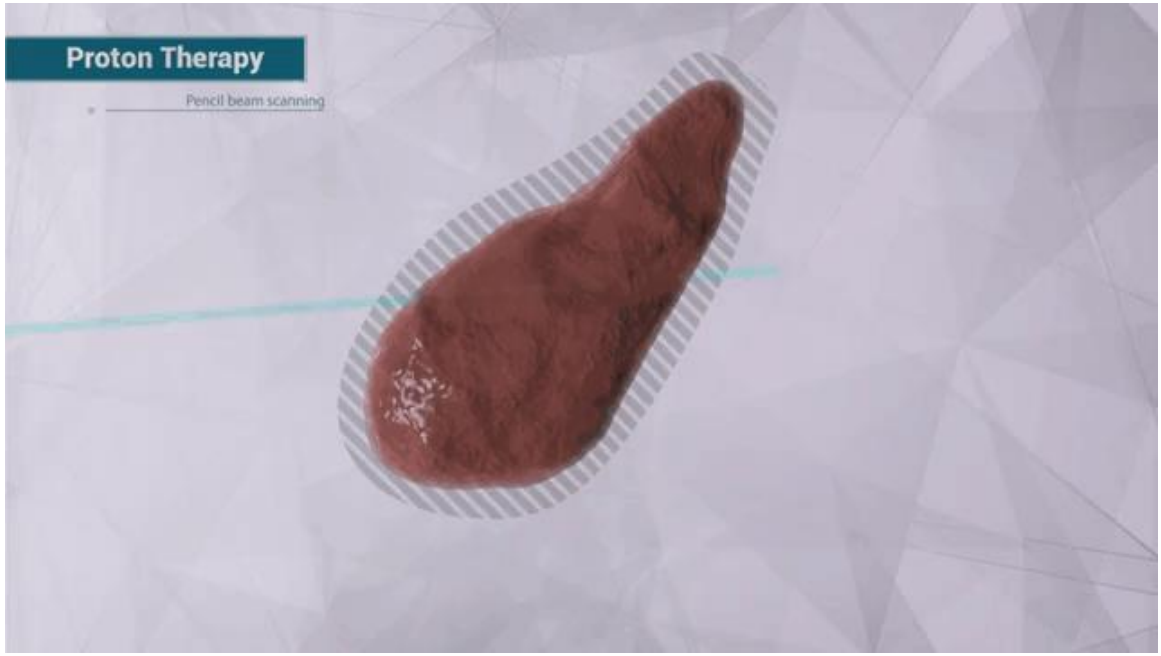
- Rectal ballons
- PBS systems- smaller spot sizes



Cone beam CT
IGRT

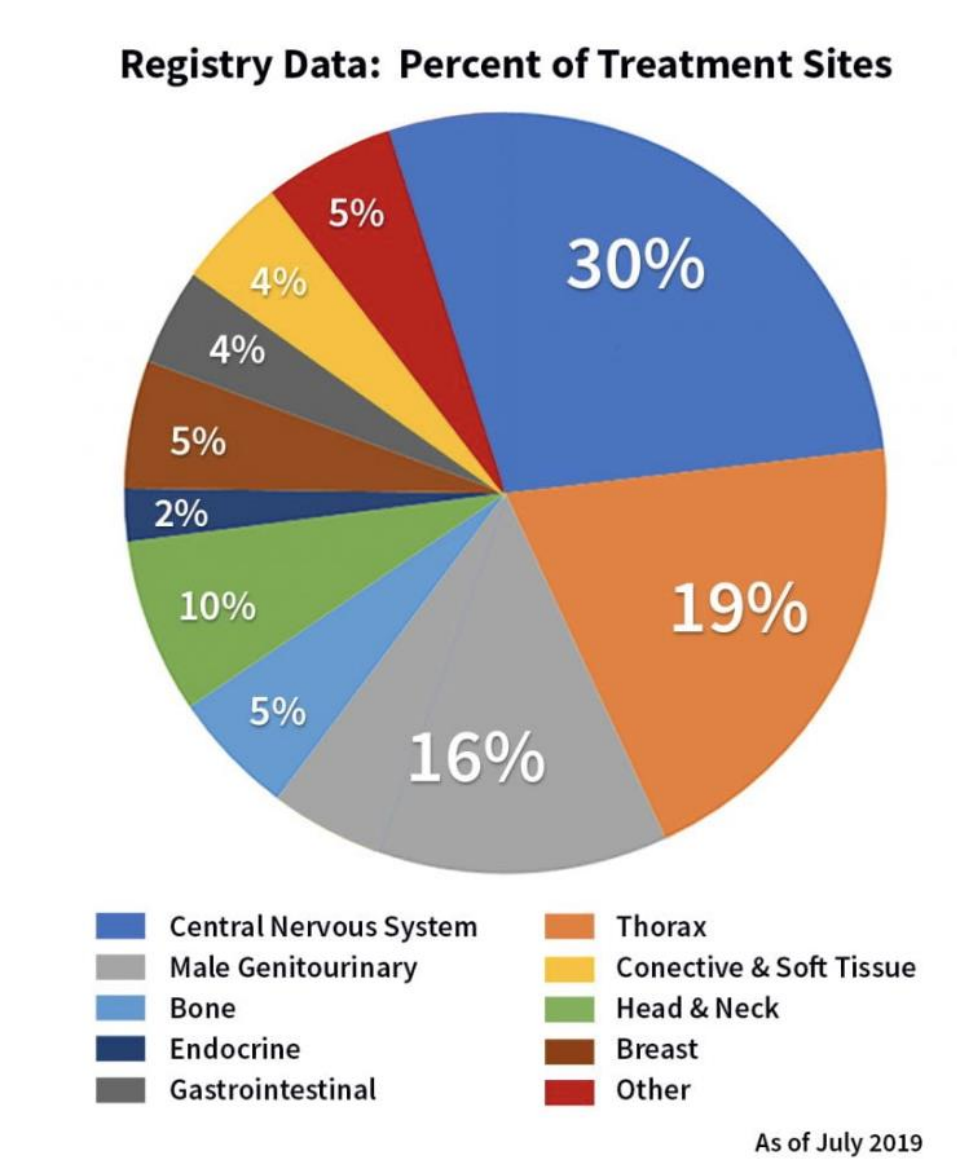
Monte Carlo algorithms





Spot by spot, line by line, layer by layer

Prostate Cancer-Contemporary



Univ of Washington: 16%

ORIGINAL ARTICLE

OPEN ACCESS

Five-year outcomes from a prospective trial of image-guided accelerated hypofractionated proton therapy for prostate cancer

Randal H. Henderson, Curtis Bryant, Bradford S. Hoppe, R. Charles Nichols, William M. Mendenhall, Stella Flampouri, Zhong Su, Zuofeng Li, Christopher G. Morris and Nancy P. Mendenhall

University of Florida Health Proton Therapy Institute, Jacksonville, FL, USA

Genitourinary Cancers

Five-Year Biochemical Results, Toxicity, and Patient-Reported Quality of Life After Delivery of Dose-Escalated Image Guided Proton Therapy for Prostate Cancer

Curtis Bryant, MD, MPH,* Tamara L. Smith, MD,*

MULTI-INSTITUTIONAL PHASE II STUDY OF PROTON BEAM THERAPY FOR ORGAN-CONFINED PROSTATE CANCER FOCUSING ON THE INCIDENCE OF LATE RECTAL TOXICITIES

Keiji Nihei, M.D., Ph.D.,* Takashi Ogino, M.D., Ph.D.,* Masakatsu Onozawa, M.D.,*

Potential Benefits

High Risk Prostate Cancer

Pelvic nodes and prostate Radiation

Oligometastatic Prostate Cancer

Prostate and metastatic/nodal sites

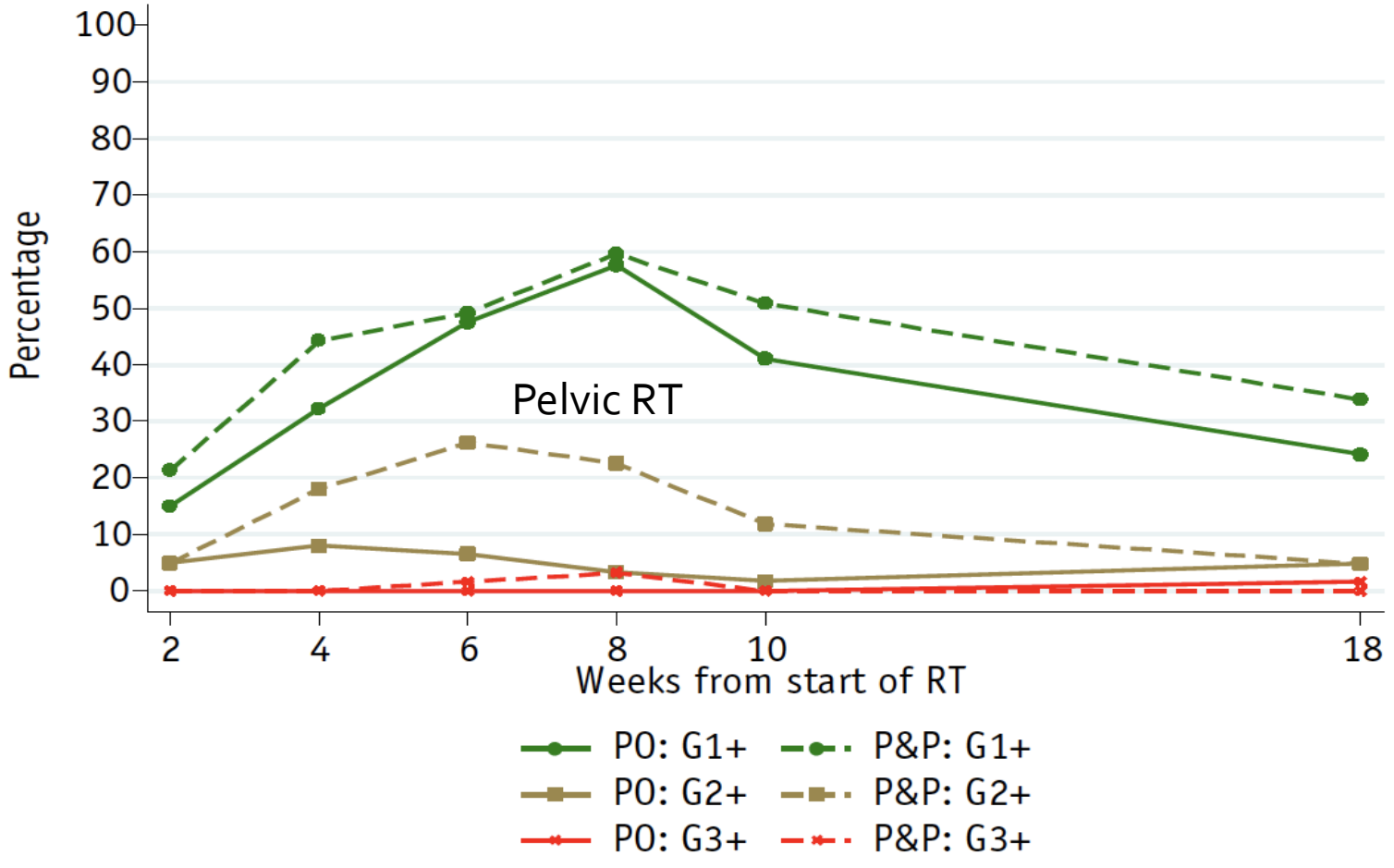
Low and Intermediate Risk prostate cancer

Reduction in late GU toxicity
Reduction in late GI toxicity
Reduction in acute small bowel toxicity

Younger patients
Pts with poor baseline IPSS scores
Reduction in sexual dysfunction
Reduction in second cancer risk

High Risk Prostate Cancer

Acute GI toxicity when treating pelvic nodes



Pivotal Study

RCT between Prostate only vs. WPRT

Dearnaley, et al. IJROBP Oct 2019

High Risk Prostate Cancer

GI toxicity when treating pelvic nodes

Median follow-up: 37 months (35-38 mo)

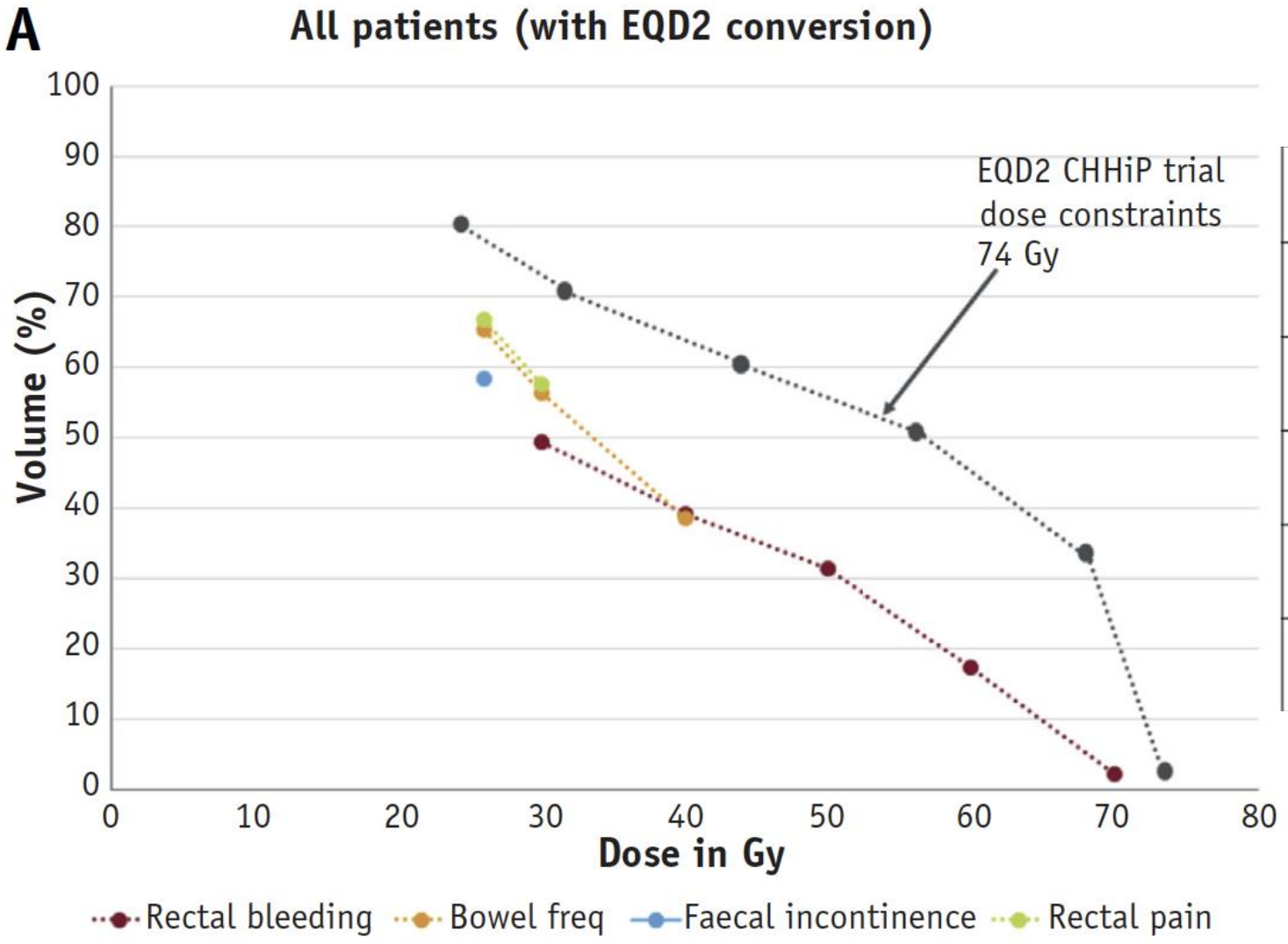
	Prostate Only	Prostate + Pelvis
Week 6 grade 2+ Lower GI toxicity	7%	26%
Week 18 grade 2+ Lower GI toxicity	3.3%	4.6%
2 years grade 2+ GI toxicity	17%	24%

RTOG Physician reported toxicity

SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula

Tenesmus- Ineffectual or painful straining ?

Impact of DVH parameters: GI



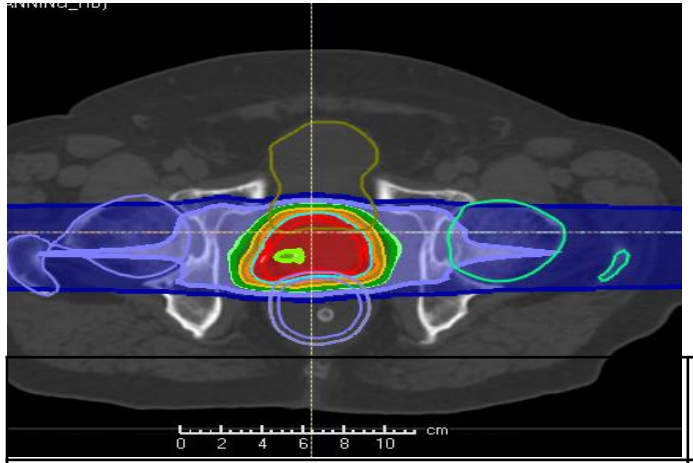
Recommended anorectal dose constraints for hypofractionated radiotherapy to 60 Gy or 57 Gy	
$V20_{Gy}$	85%
$V30_{Gy}$	57%
$V40_{Gy}$	38%
$V50_{Gy}$	22%
$V60_{Gy}$	<0.01%

Anna Wilkins, et al. IJROBP 2020

Possible Impact on GI toxicity

Dosimetric Impact	Likely Clinical Impact
reduction **in high doses**	Less or similar probability of rectal bleeding
reduction in **intermediate doses**	Reduction in tenesmus and rectal urgency

Rectal Dosimetry
Penumbra Differences



Dose fall off is 2 times more rapid in high dose region

Dose fall off is 4 times more rapid in the intermediate to low dose region.

	Dose fall off per mm			
	95%-80% IDL		80%-20% IDL	
	Protons	**IMRT**	**Protons**	**IMRT**
Posterior direction	4.1%	2.0%	6.2%	1.5%
Superior direction	4.1%	7.5%	6.2%	5.8%

High dose region

	IMRT plans
	Rectum V70
MSKCC	14%
MGH	14.5%
MADCC	15.5%
UF	14%
Protons UF	**8%**
Protons APCC	8%

V70 accepted surrogate for toxicity

Zelefsky et al Radiotherapy and oncology 2000; 55:241-249

Trofimov et al IJROBP 2007; 69:pp. 444–453,

Zhang et al IJROBP 2007; 67: 620–629

Vargas et al IJROBP 2008; 70: pp. 744–751

Low to Intermediate Doses

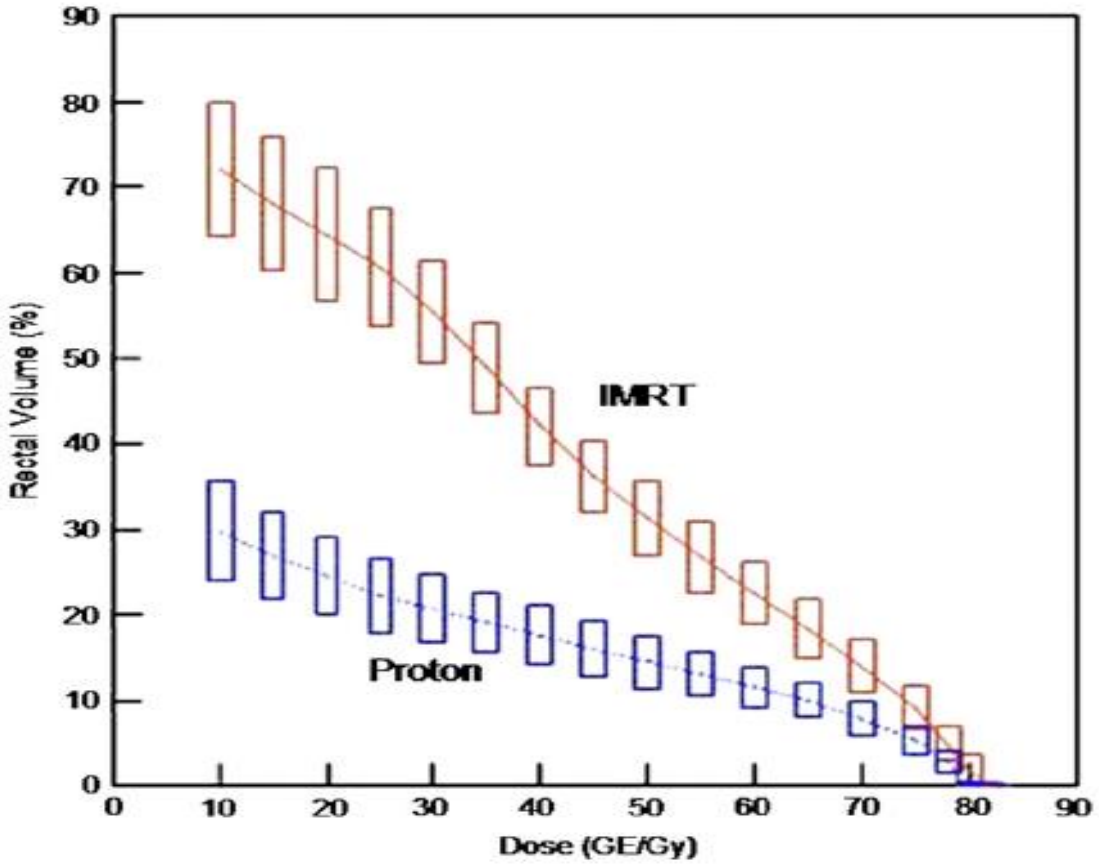


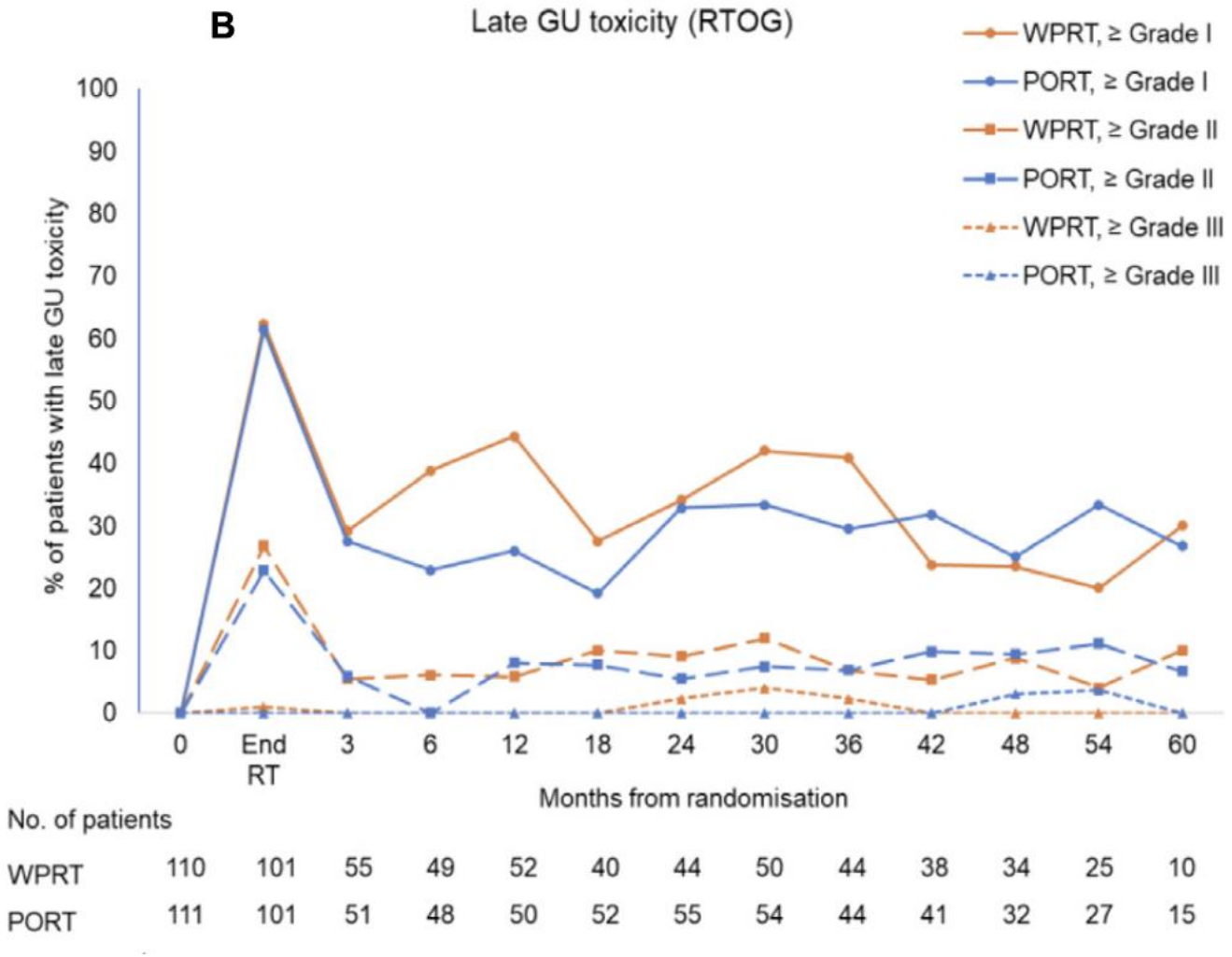
Fig. 3. Combined rectal dose–volume curves for proton therapy and intensity-modulated radiotherapy (IMRT) (n = 20 plans); error box shows 95% standard error.

V30-V60Gy

Tenesmus
Rectal urgency

Vargas et al IJROBP 2008; 70: pp. 744–751

Bladder toxicity when treating Pelvic nodes



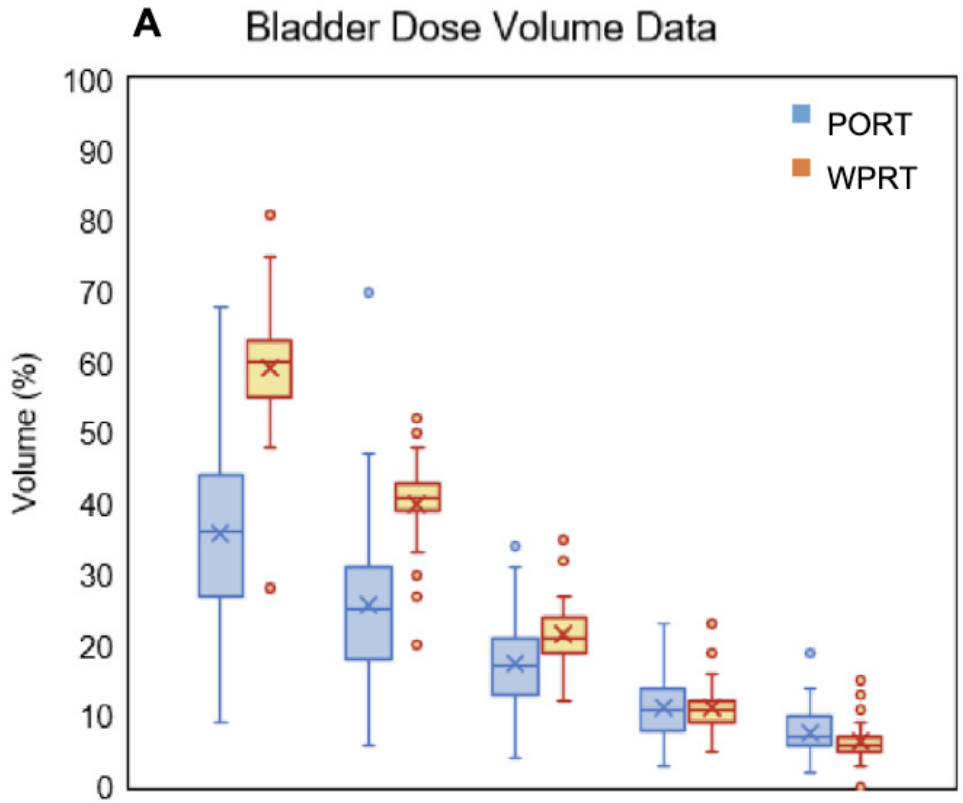
POP-RT Trial

V Murthy, et al, Green Journal 2020

15% grade 2+ toxicity in patients who received Pelvic RT

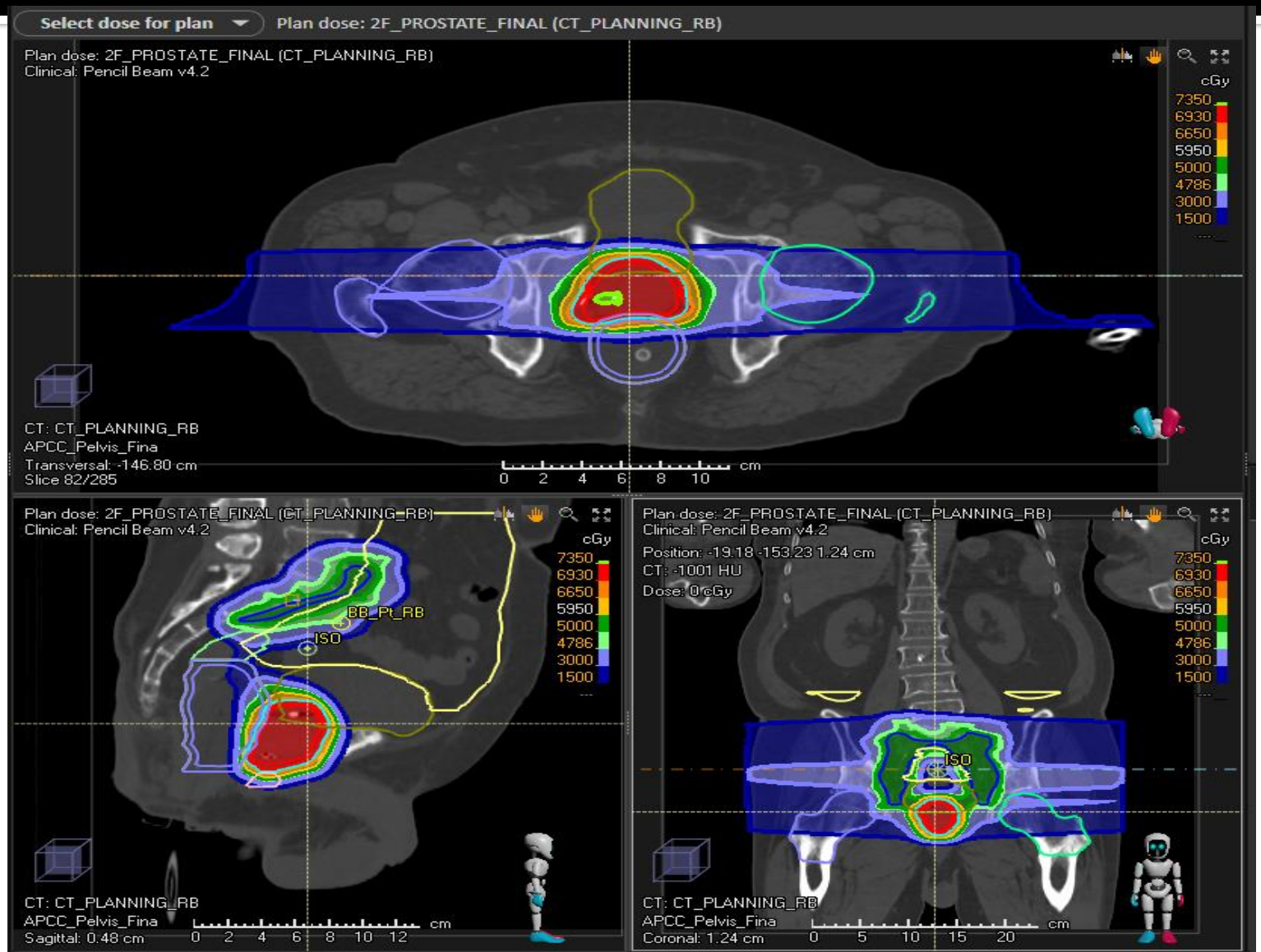
Impact of intermediate doses

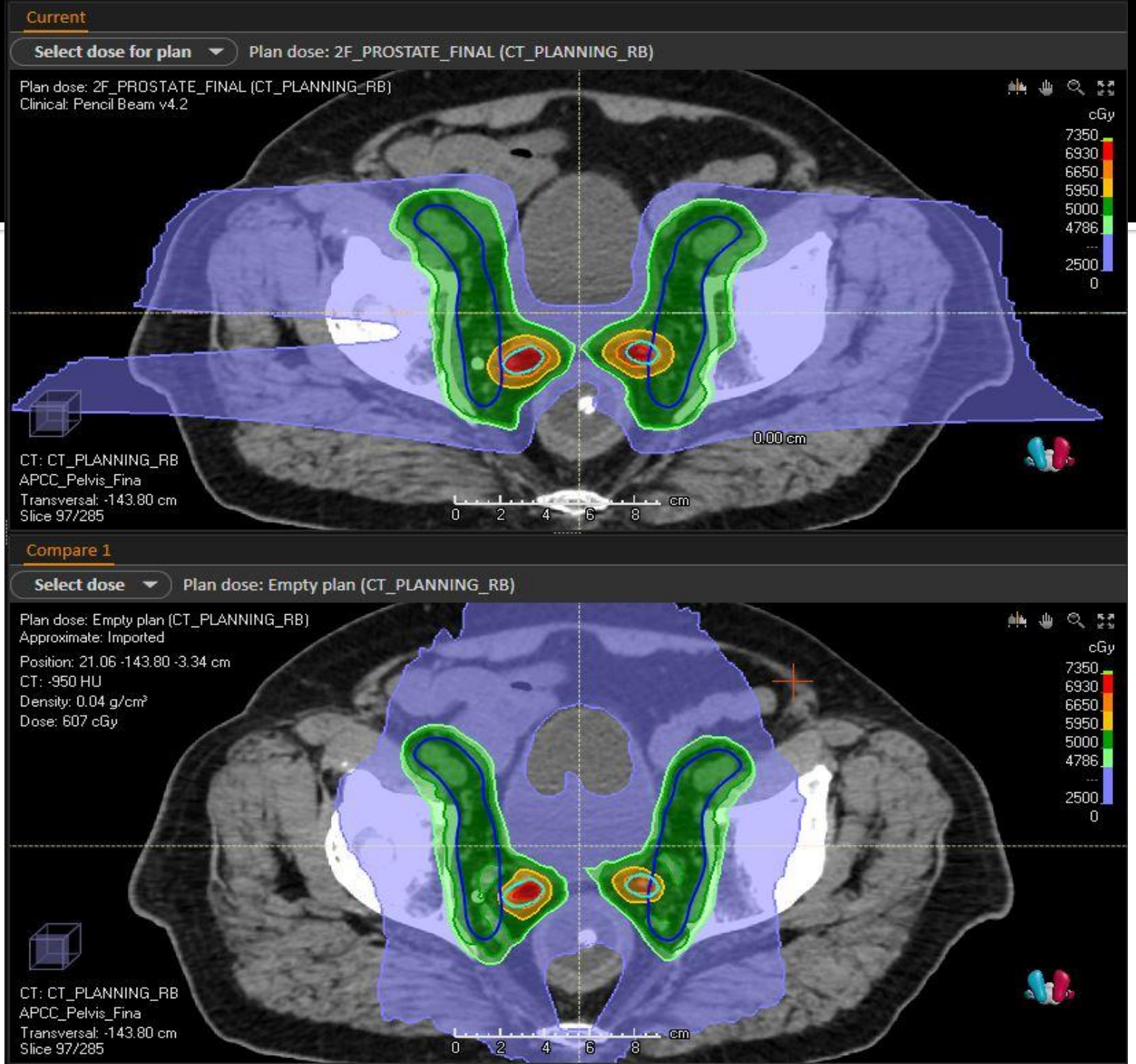
V30-V50 contributing to toxicity as >V50 there was very little difference



Median volume (%)	V30	V40	V50	V60	V65
PORT	36	25	17	11	7
WPRT	60	41	21	11	6
p	<0.001	<0.001	0.01	0.53	0.05

Impact of Proton therapy on Bladder dosimetry

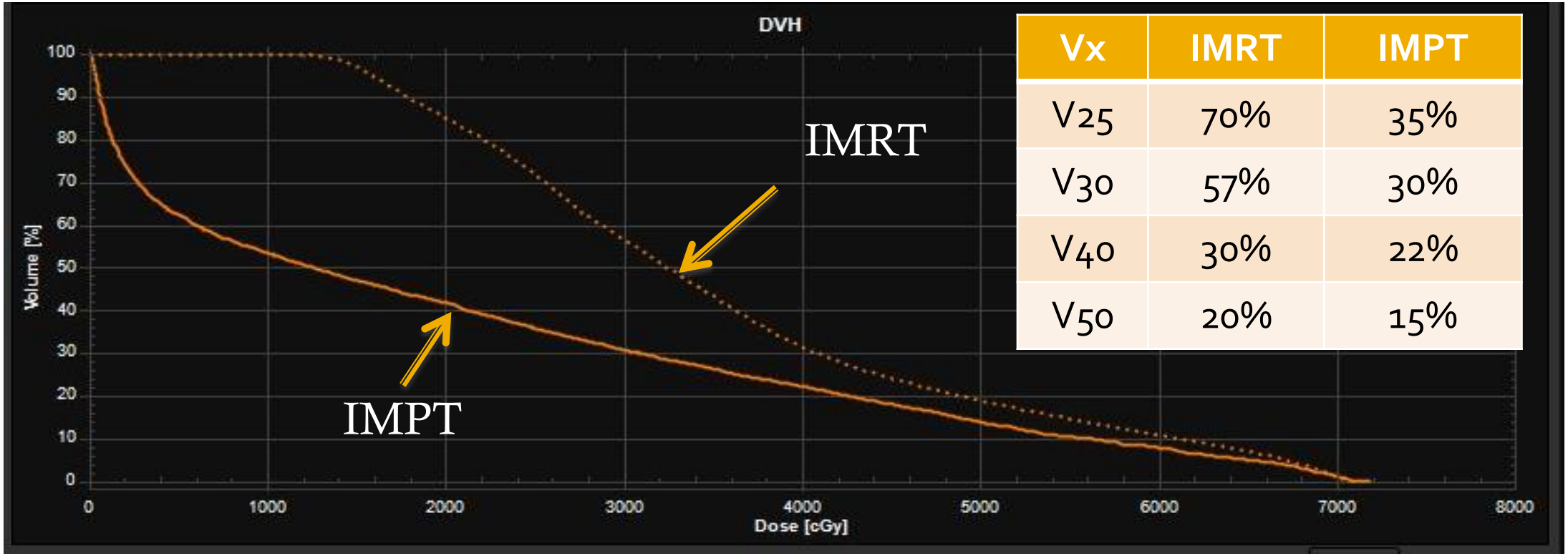




Proton Therapy

Tomotherapy

Bladder Dosimetry



Vx	IMRT	IMPT
V25	70%	35%
V30	57%	30%
V40	30%	22%
V50	20%	15%

Proton therapy-GU toxicity outcomes

Table 5 Factors associated with late grade 3+ genitourinary toxicity on multivariate analyses

Factors	No	Yes	*P*-value
Prostate volume $\geq$60 cm^3	38/1097 (3.5%)	23/188 (12.2%)	<.0001
α-blockers	37/1044 (3.5%)	24/245 (9.8%)	.0002
Pretreatment TURP*	44/1193 (3.7%)	17/96 (17.7%)	<.0001
Absolute bladder V30 $\geq$ 19.2 cm^3	34/989 (3.4%)	27/298 (9.1%)	.0002

Grade3+ GU-2.9%

Table 4 Factors associated with late grade 3+ genitourinary toxicity on multivariate analyses

No. of risk factors	Total with grade 3+ toxicity/no. of patients	5-year estimates of freedom from grade 3+ toxicity
0	14/720 (1.9%)	1.9%
1	13/355 (3.7%)	3.6%
2	26/174 (14.9%)	11.3%
3 or 4	8/40 (20.0%)	17.8%

Factors tested in this multivariate analysis included prostate volume, anticoagulation, pretreatment cytoreductive prostate procedures, pre-treatment treatment with α-blockers, International Prostate Symptom Score, and 8 dose-volume histogram (DVH) parameters.

1257 pts

1. Prostate volume> 40cc
2. Alfa blockers
3. Pre-treatment TURP
4. V30 Bladder >19.2cc
5. Anti-coagulation
6. Poor IPSS score
7. Diabetes

Bryant C, et al, IJROBP 2015

Urinary functional outcomes and toxicity five years after proton therapy for low- and intermediate-risk prostate cancer: Results of two prospective trials

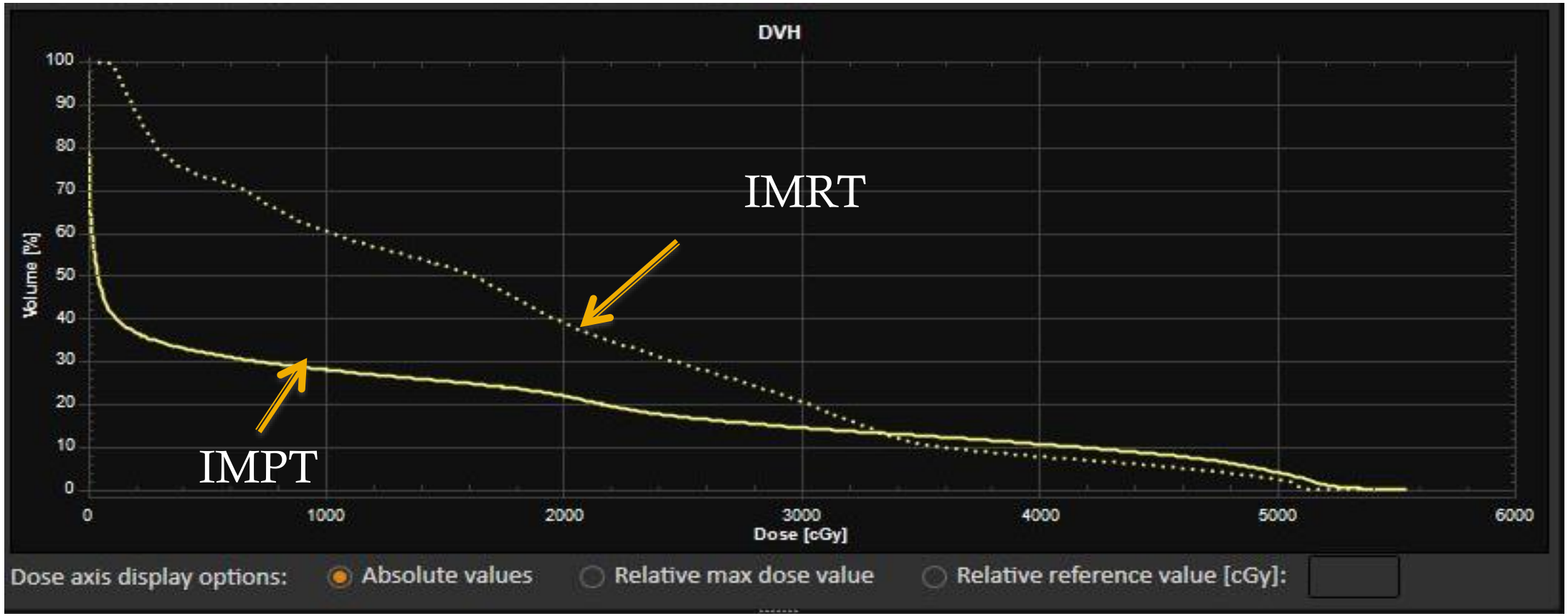
Decrease in post-treatment IPSS

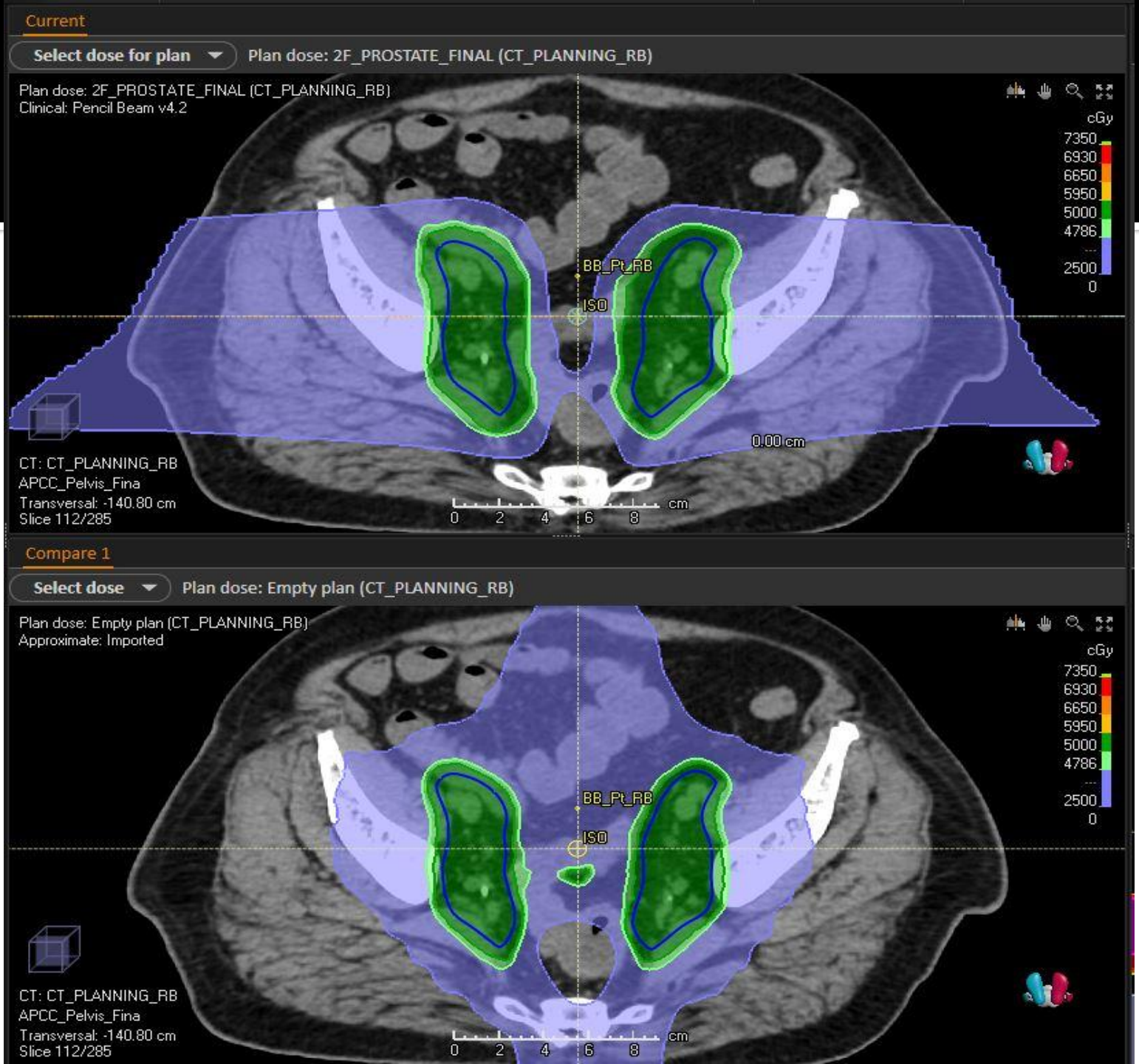
Baseline IPSS	N	No. of patients with ≥5-point decrease at any point after treatment (%)	No. of patients with ≥5-point decrease at last follow-up (%)	No. of patients with ≥5-point decrease in IPSS no longer present at last follow-up (%)
<15	89**	35 (39.3%)	20 (22.5%)	15 (16.9%)
15–25	33	29 (87.9%)	18 (54.5%)	11 (33.3%)
Total	122	64 (52.5%)	38 (31.1%)	26 (21.3%)

- Pts with pretreat IPSS of <15 had stable urinary function five years after PT,
- Pts with 15 – 25 showed substantial improvement (decline) in median IPSS.

PT leads to a minimal toxicity in low/intermediate risk, including those with significant pretreatment GU dysfunction (IPSS 15 – 25).

Small Bowel


DVH
100
90
80
70
60
50
40
30
20
10
0
Volume [%]
0
1000
2000
3000
4000
5000
6000
Dose [cGy]
IMRT
IMPT
Dose axis display options:
Absolute values
Relative max dose value
Relative reference value [cGy]:



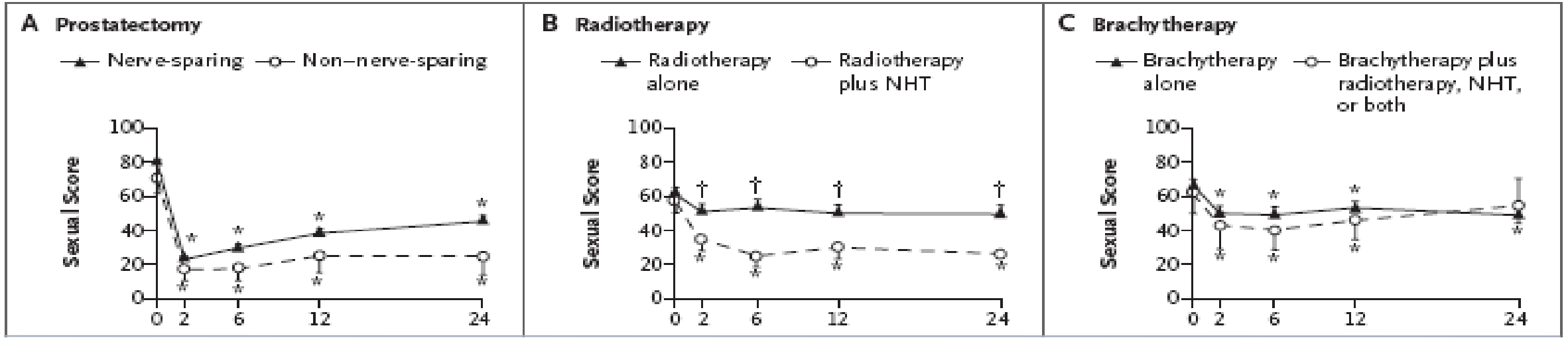
Proton Therapy

Tomotherapy

Sexual Dysfunction: Patient Reported QOL

Sanda et al, N Engl J Med. 2008 Mar 20;358(12):1250-61.

Sexual Scores



Long-term outcomes following proton therapy for prostate cancer in young men with a focus on sexual health

Clement K. Ho[a], Curtis M. Bryant[a], Nancy P. Mendenhall[a], Randal H. Henderson[a], William M. Mendenhall[a],

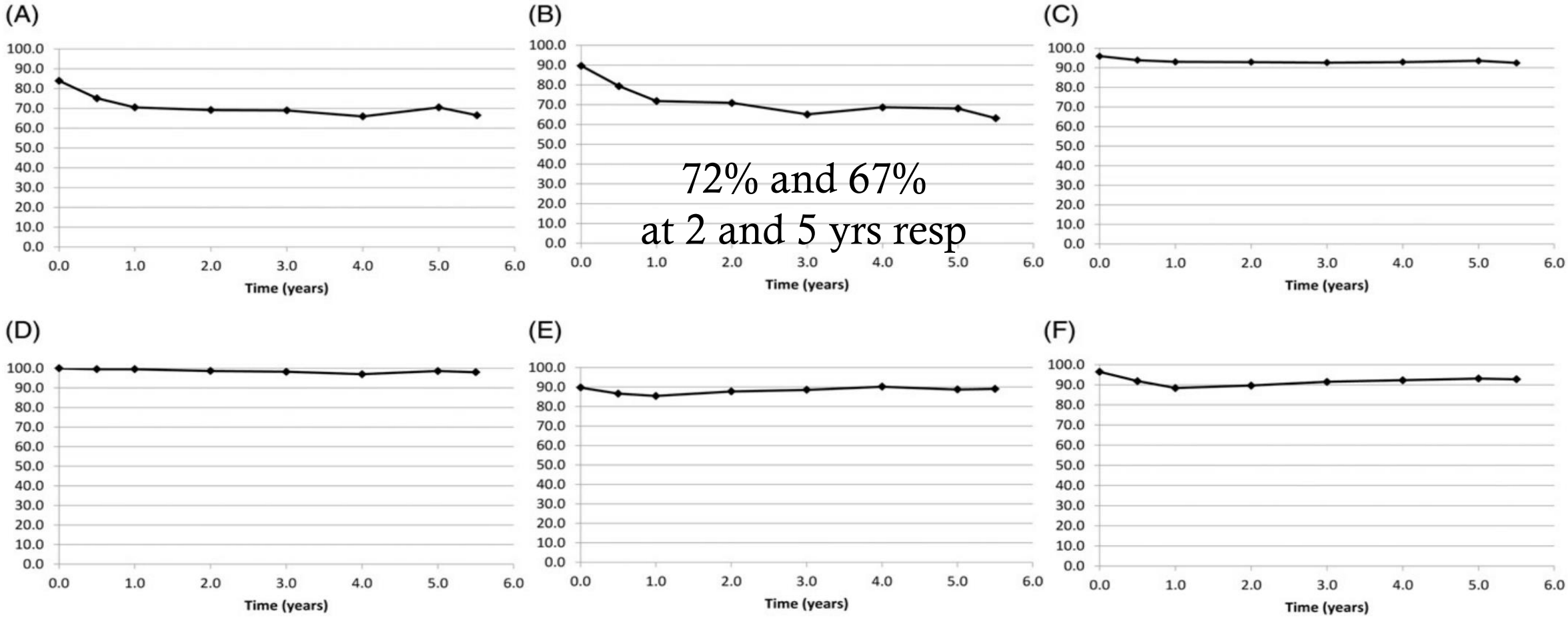
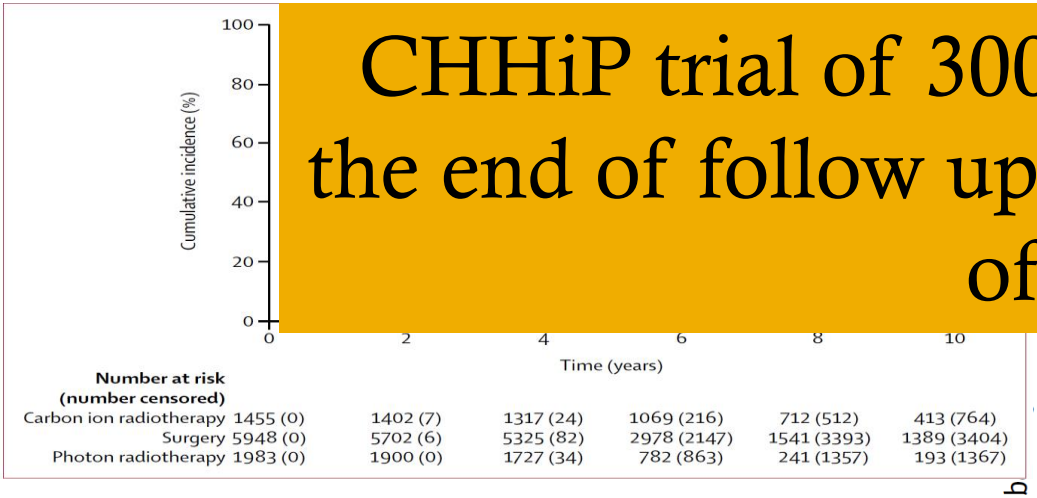
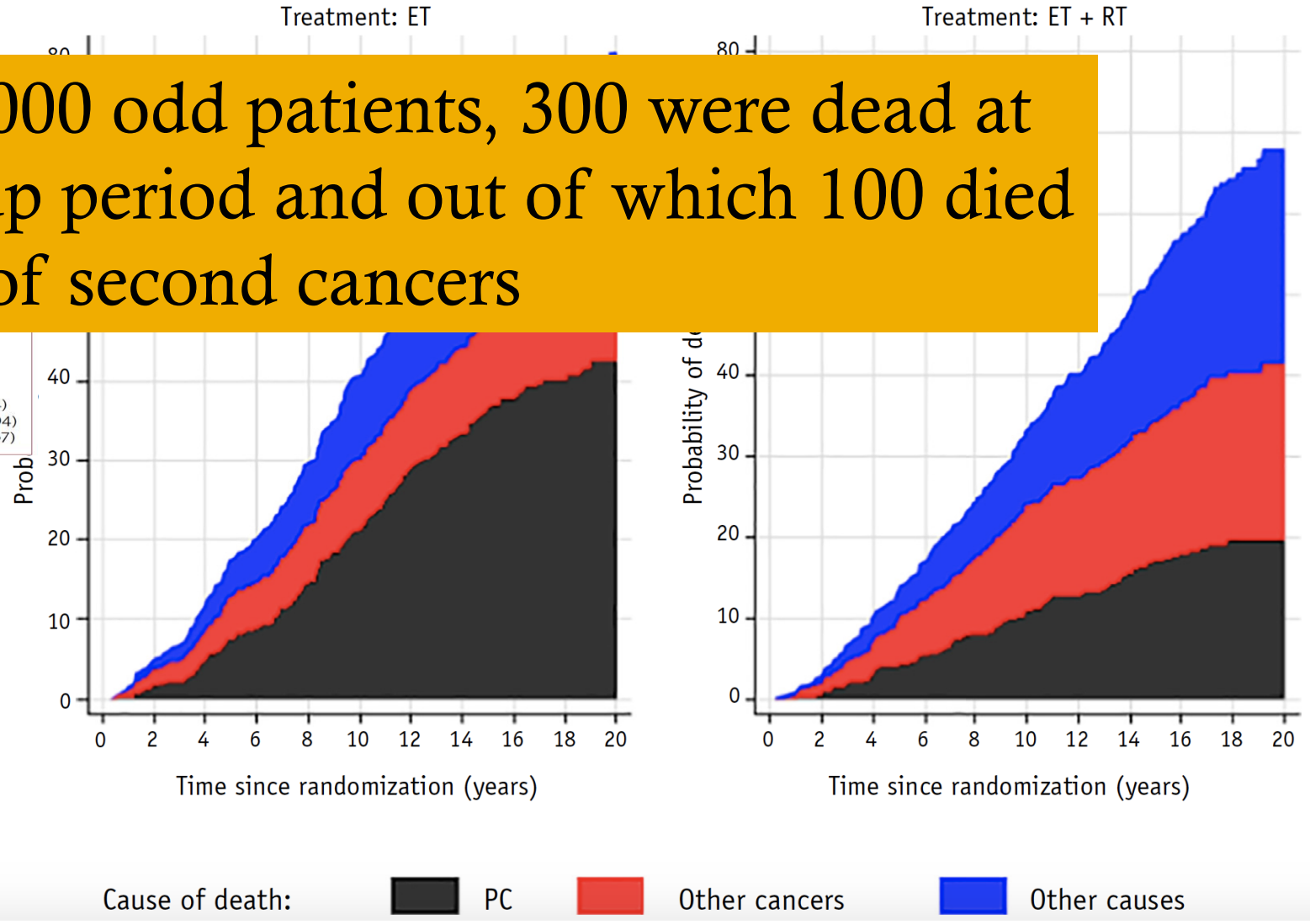


Figure 1. Results of the patient-reported expanded prostate cancer index composite (EPIC) questionnaire in men 60 years old and younger over time. This data shows the baseline 0-, 0.5-, 1-, 2-, 3-, 4-, 5- and ≥5-year data (A) sexual summary score, (B) incidence of potency, (C) urinary incontinence score, (D) percentage of men pad-free on a daily basis, (E) urinary irritative score and (F) bowel summary score.

Second cancer risk



CHHiP trial of 3000 odd patients, 300 were dead at the end of follow up period and out of which 100 died of second cancers

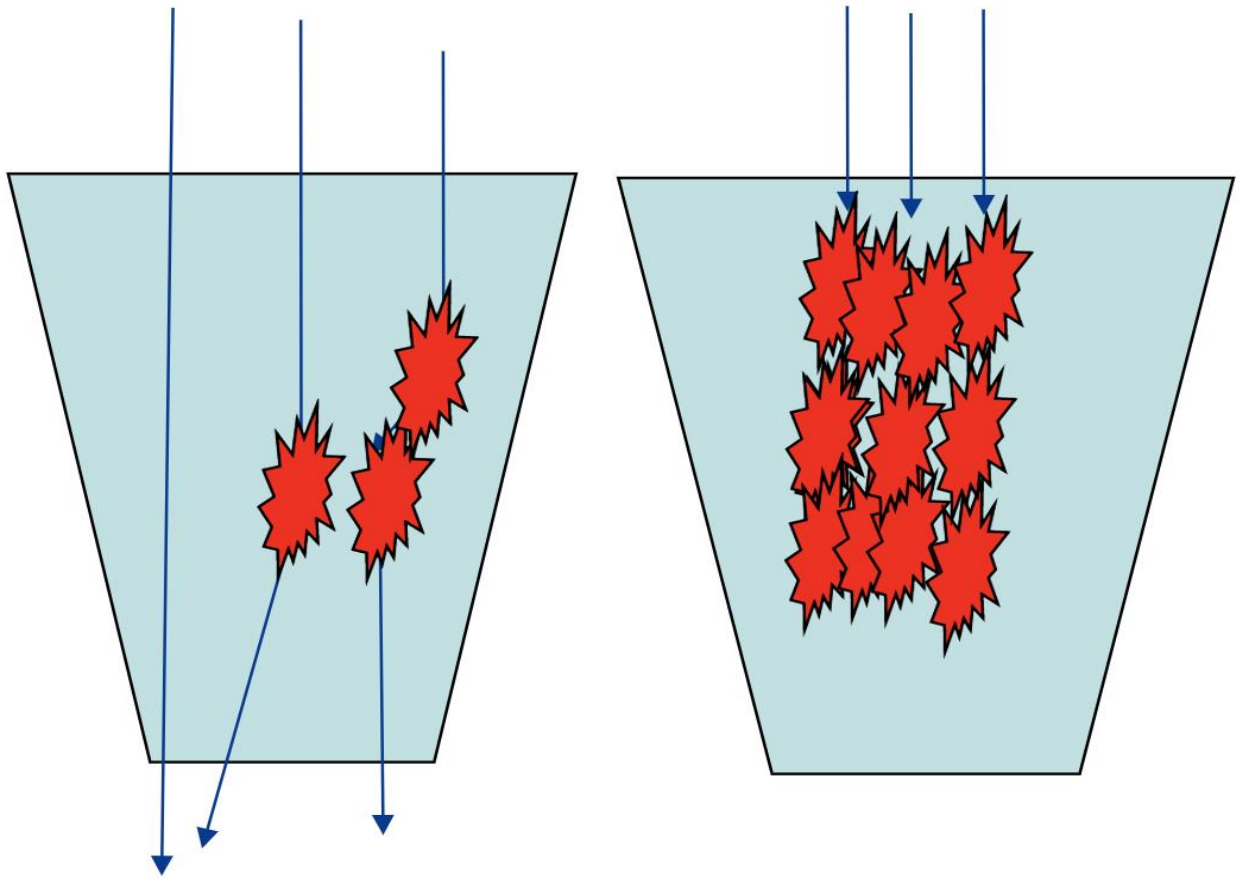


Real Clinical Data

Modality	SCR at 9.9 yrs
Particle	16.1%
Photons	24%
Surgery	18.7%

IJROBP 2020, Lancet Oncol 2019, Lancet 2016

Biology of proton therapy



Dense concentration of DNA damage vs. Sparsely distributed DNA damage

Greater complexity of damage - requires different mechanisms for DNA repair

Protons may result in greater down regulation of certain genes that could impact metastases

Girdhani, et al. Radiation Research 2013, Amundsen et al IJPT 2018

Indirect Comparison

Modern Approaches/optimal dose	5 yr FFBP Low Risk	5yr FFBP Intermediate risk
Conventional # Photon series	92-98% (MSKCC)	85-86%
Conventional # Proton series	99% (UFPTI)	95%
Hypo Photon	96% (Chhip)	84%
Hypo Proton	98% (UFPTI)	93%

Is extreme hypofractionation an option?

Acute GU Toxicities

Acute GI Toxicities

TABLE 3. Urinary and Gastrointestinal Tract Grade 2 Adverse Events

Time of Grade 2 Adverse Events	38 Gy RBE in 5 Fractions (Arm I)	79.2 Gy RBE in 44 Fractions (Arm II)	*P*
Urinary tract			
Before radiotherapy (n/N [%])	7/46 (15.2)	5/27 (18.5)	0.76
During treatment (n/N [%])	9/46 (19.6)	7/27 (25.9)	0.77
After treatment (n/N [%])			
3 mo	4/40 (10.0)	0 (0)	0.29
6 mo	7/40 (17.5)	0 (0)	0.04
1 y	7/31 (22.6)	2/17 (11.8)	0.46
2 y	2/16 (12.5)	5/16 (31.3)	0.39
Overall (n/N [%])	17/46 (37.0)	11/27 (40.7)	0.48
Gastrointestinal tract			
Before radiotherapy (n/N [%])	0 (0)	0 (0)	>0.99
During treatment (n/N [%])	2/49 (4.1)	0 (0)	0.53
After treatment (n/N [%])			
3 mo	1/40 (2.5)	0 (0)	0.99
6 mo	3/40 (7.5)	1/26 (3.8)	0.99
1 y	1/31 (3.2)	3/17 (17.6)	0.12
2 y	1/16 (6.3)	1/17 (5.9)	0.77
Overall (n/N [%])	6/46 (13.0)	3/27 (11.1)	0.99

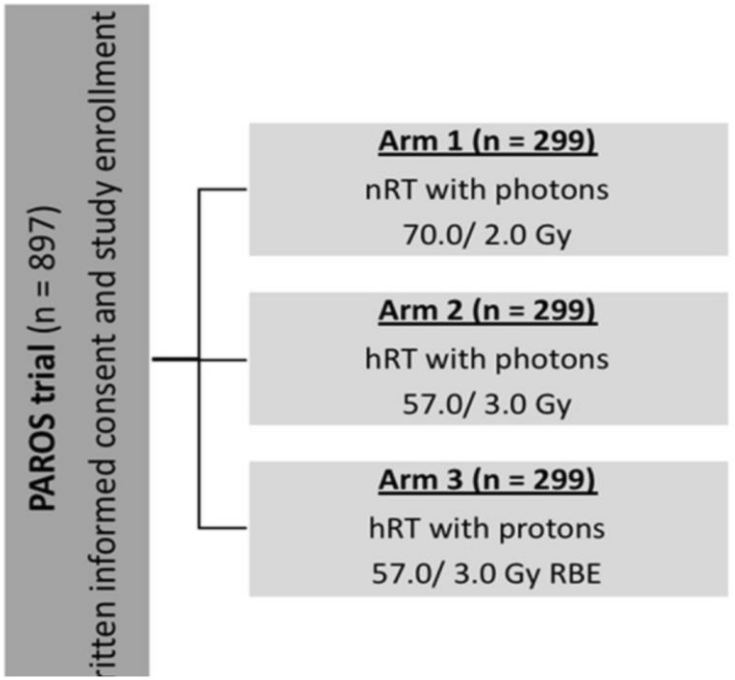
Postop setting for salvage

Table 2. Acute and late maximum GU and GI CTCAE v 4.0 toxicities for post-prostatectomy PT.

Toxicity Grade	GU		GI	
	Acute[a]	Late[b]	Acute[a]	Late[b]
0	14 (14.0)	14 (17.7)	66 (66.0)	58 (73.4)
1	71 (71.0)	49 (62.0)	34 (34.0)	21 (26.6)
2	15 (15.0)	16 (20.3)	–	–

[a] $N = 100$ during PT and up 3 months after completion.

[b] $N = 79$ patients with minimum 3 months follow up. There were no grade ≥ 3 toxicities.



Deville Jr et al, Acta Oncology 2018

APCC Experience

1. Standardized Protocol- Hypofractionated Treatment

Low Risk/Low Intermediate Risk

High Risk/Very high risk

Oligometastatic

Rectal Balloon ± fiducials
Margin recipe
Surface guidance
Target Delineation
Image guidance and verification
Treatment duration and intensity

Prospectively collecting- IPSS scores, QOL-PR25, EPIC bowel, bladder and sexual scores

Road Ahead

2. Extremely hypofractionated IMPT- 5#, 40Gy in 5#

- Thinnest possible fiducials/no fiducials
- low risk prostate cancer

- Single arm prospective study
- With non inferiority endpoint of bPFS with non-inferiority threshold of +/-5% and +/-9% at 2yrs and 5 yrs.
- Sample size: 65 pts, 20/year

Reality vs. Assumption

COMPPARE Study: RCT of 3000 pts,
Protons vs. photons,
EPIC scores as primary endpoint

PARTIQOL study: RCT of 400 pts of low and intermediate risk prostate cancer, EPIC bowel scores as primary end point