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Radiotherapy for prostate cancer: an historical narrative review

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Radiotherapy for prostate cancer: an historical narrative review

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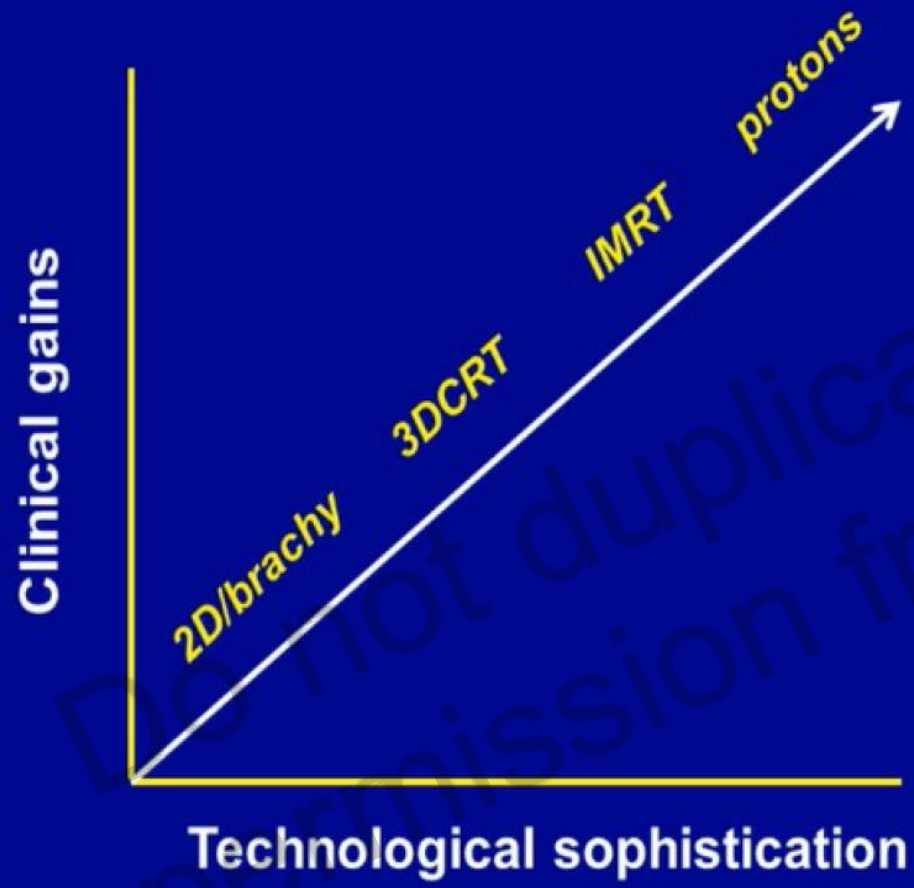
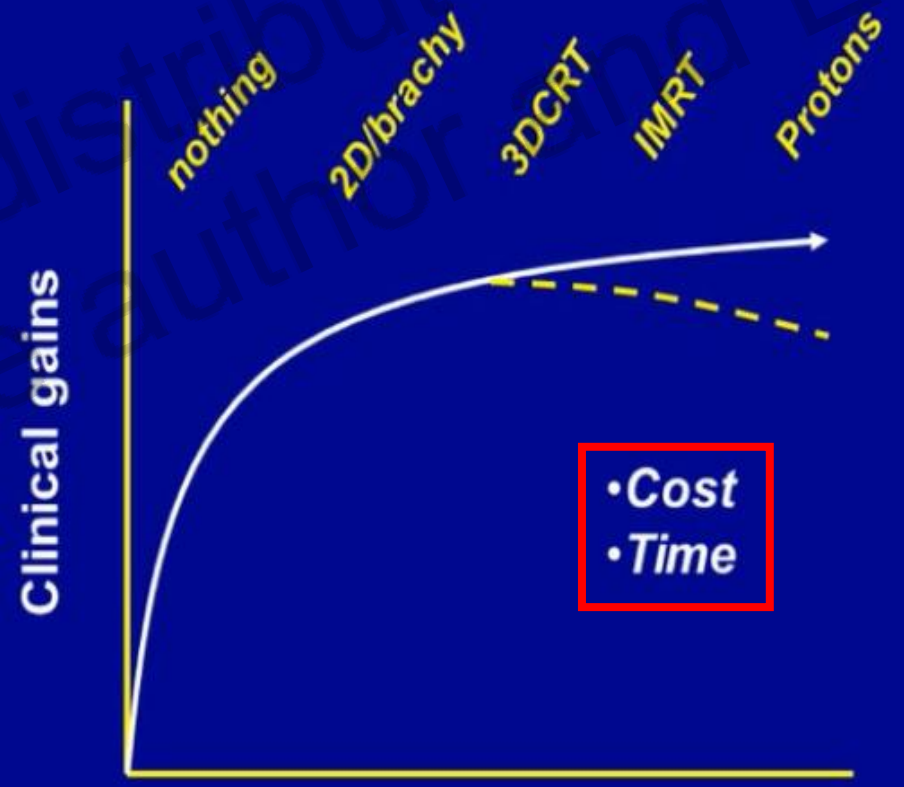
The "arrow of progress"



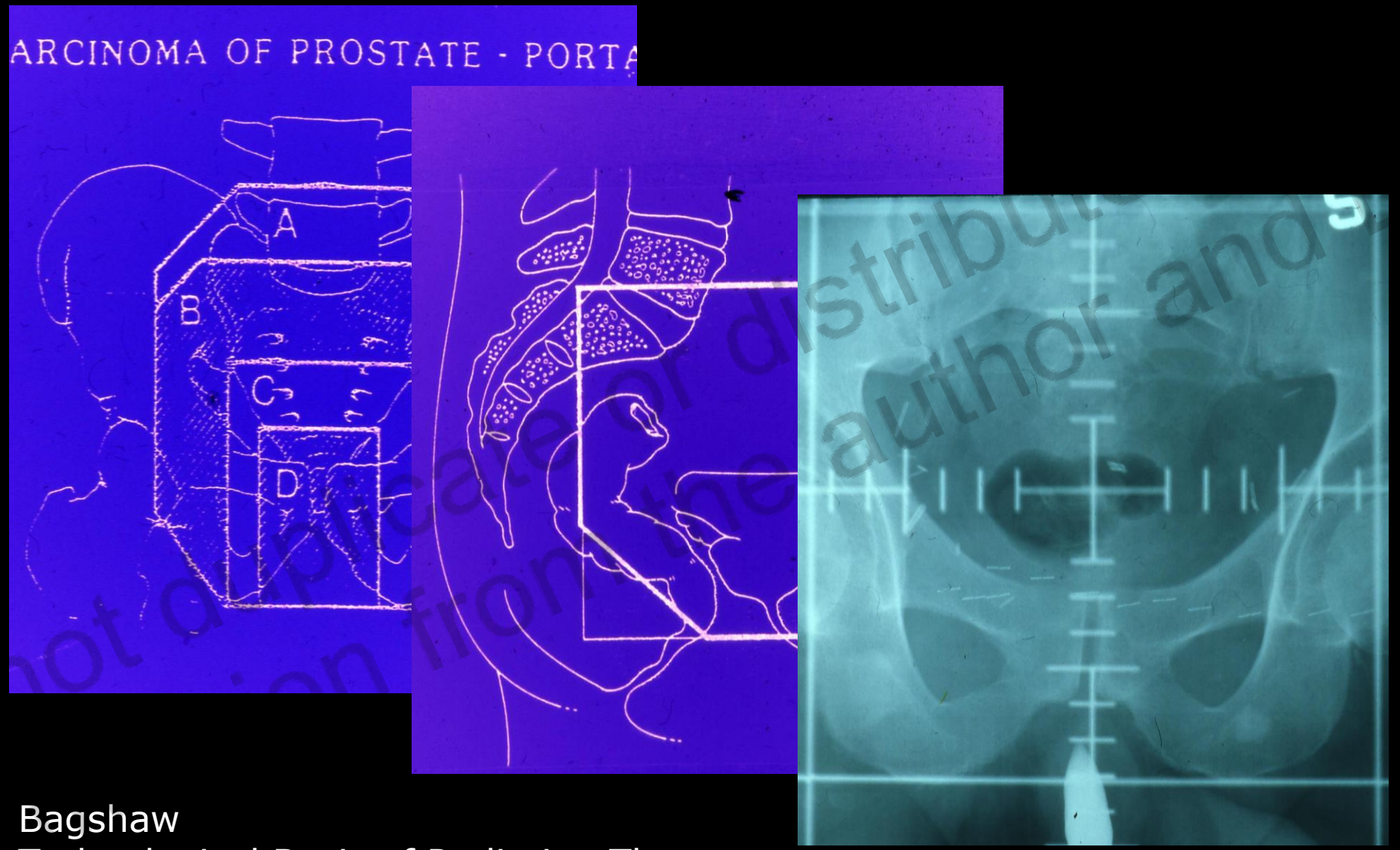
Is the "arrow of progress" model flawed?

In prostate cancer it may be

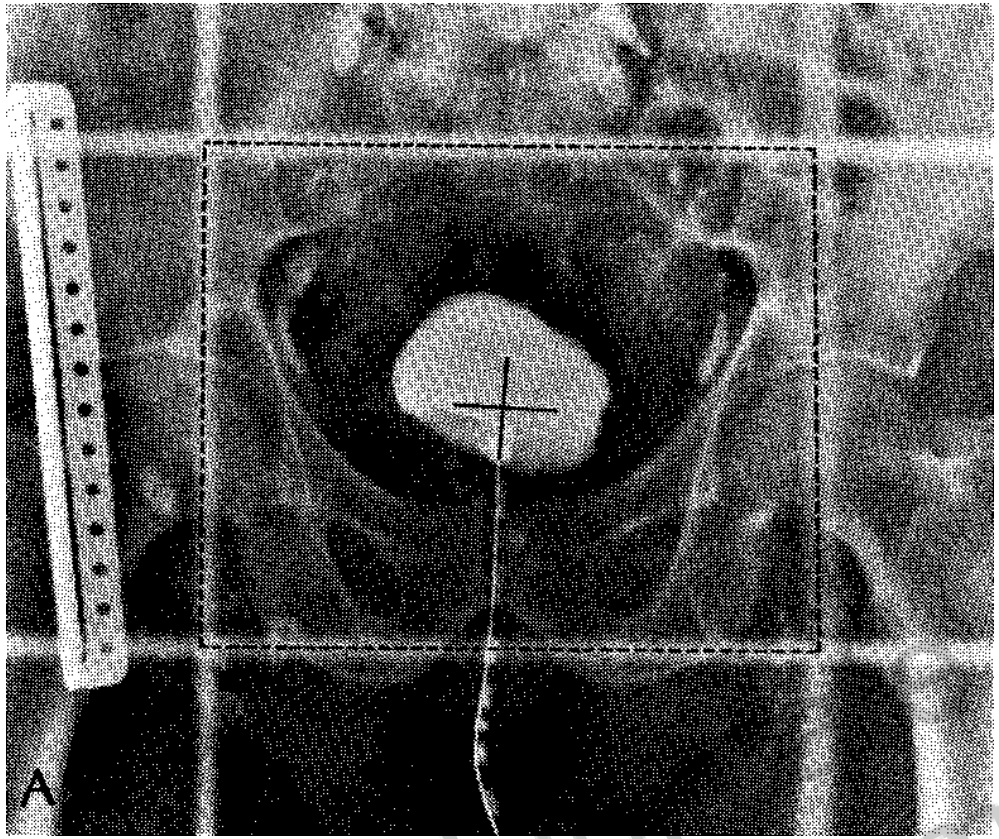


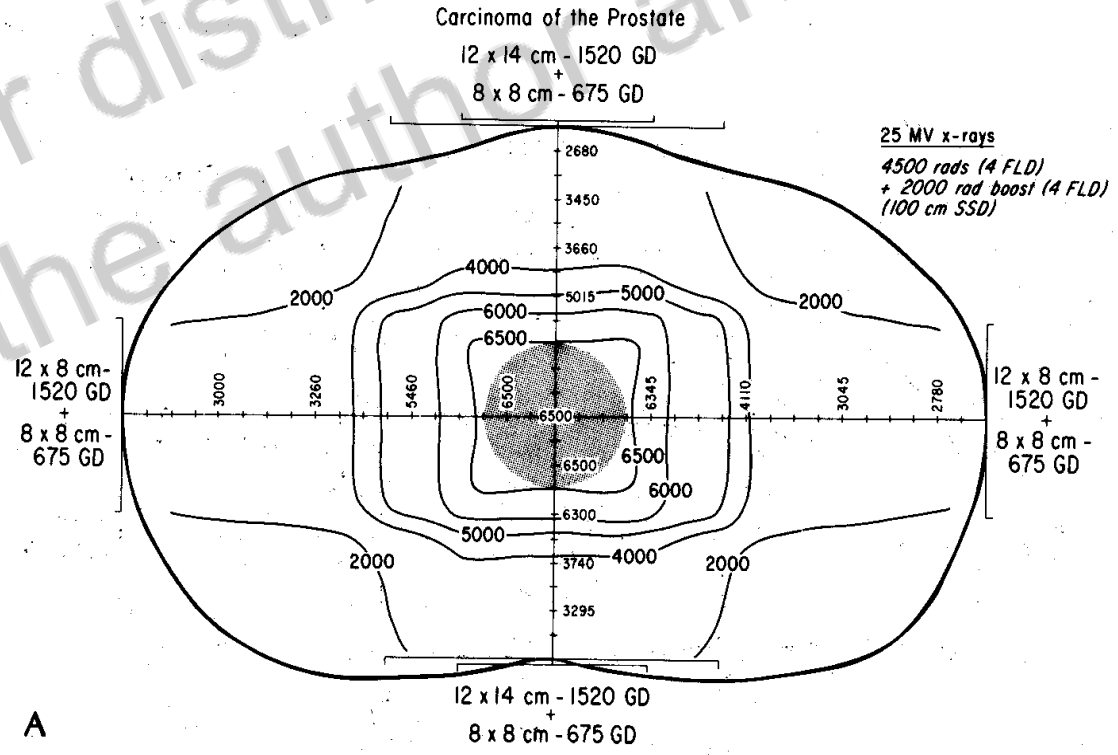
An improved means to an unimproved end?

courtesy of A Zietman

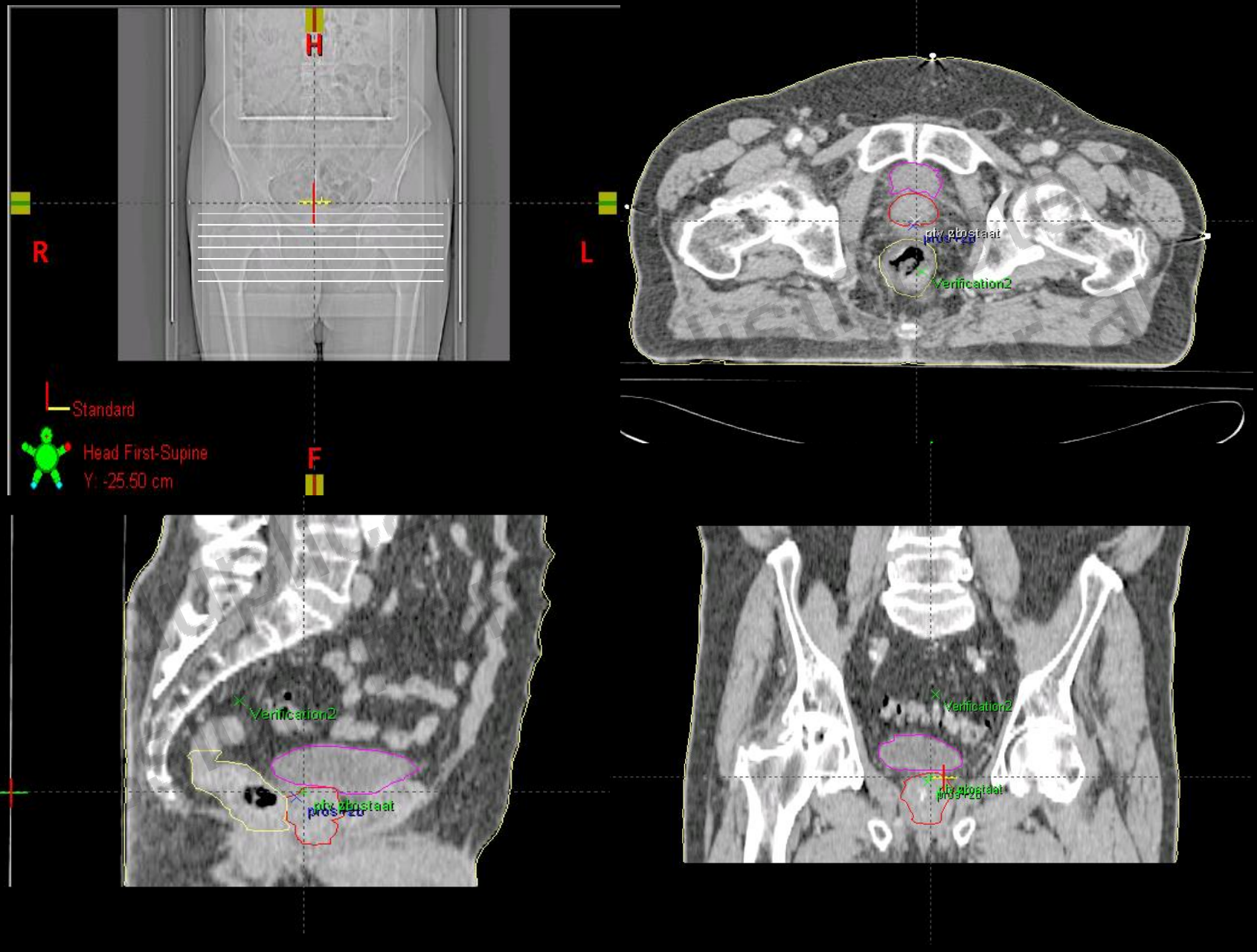


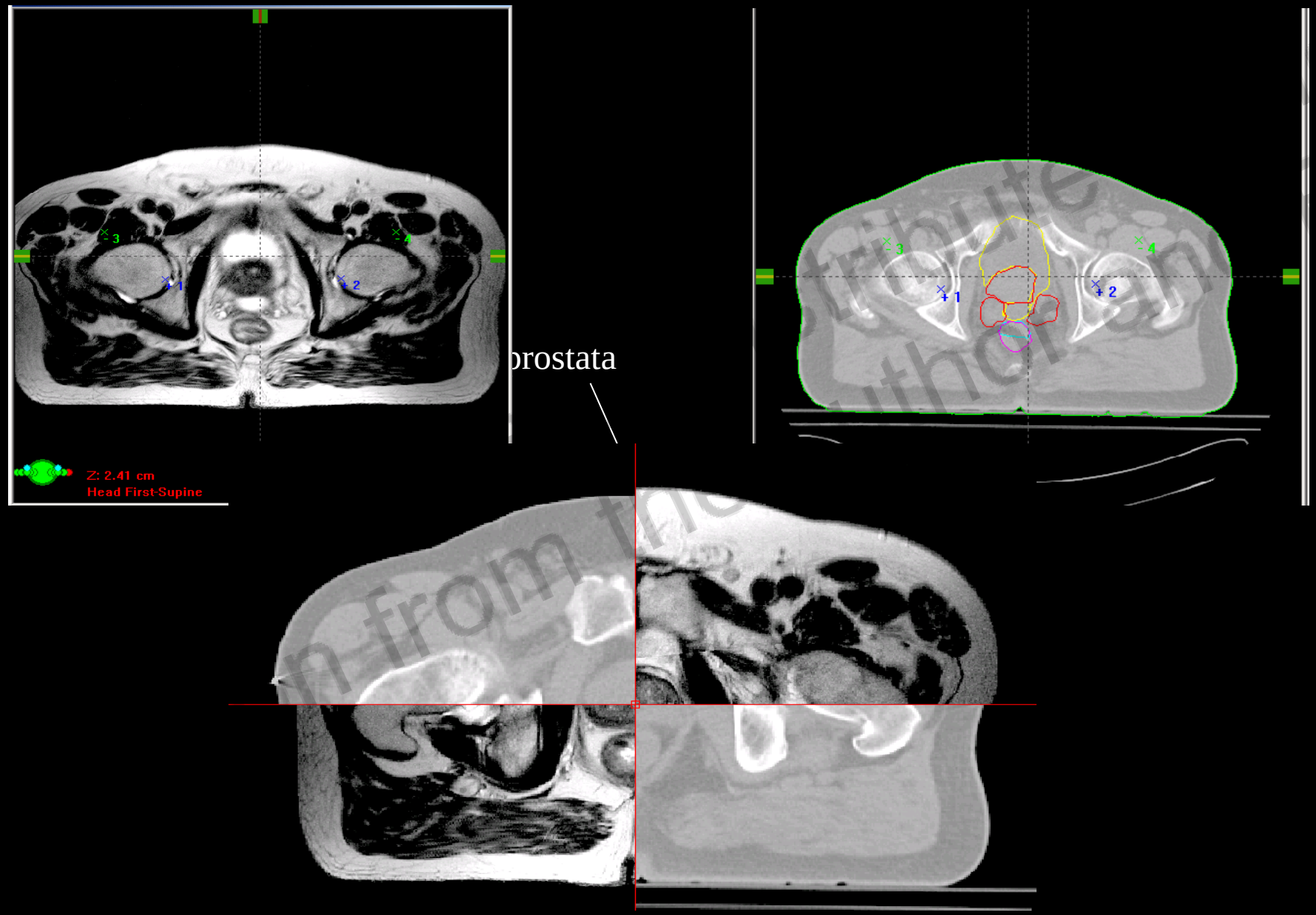
Bagshaw
Technological Basis of Radiation Therapy
Lea & Febiger Ed., 1984



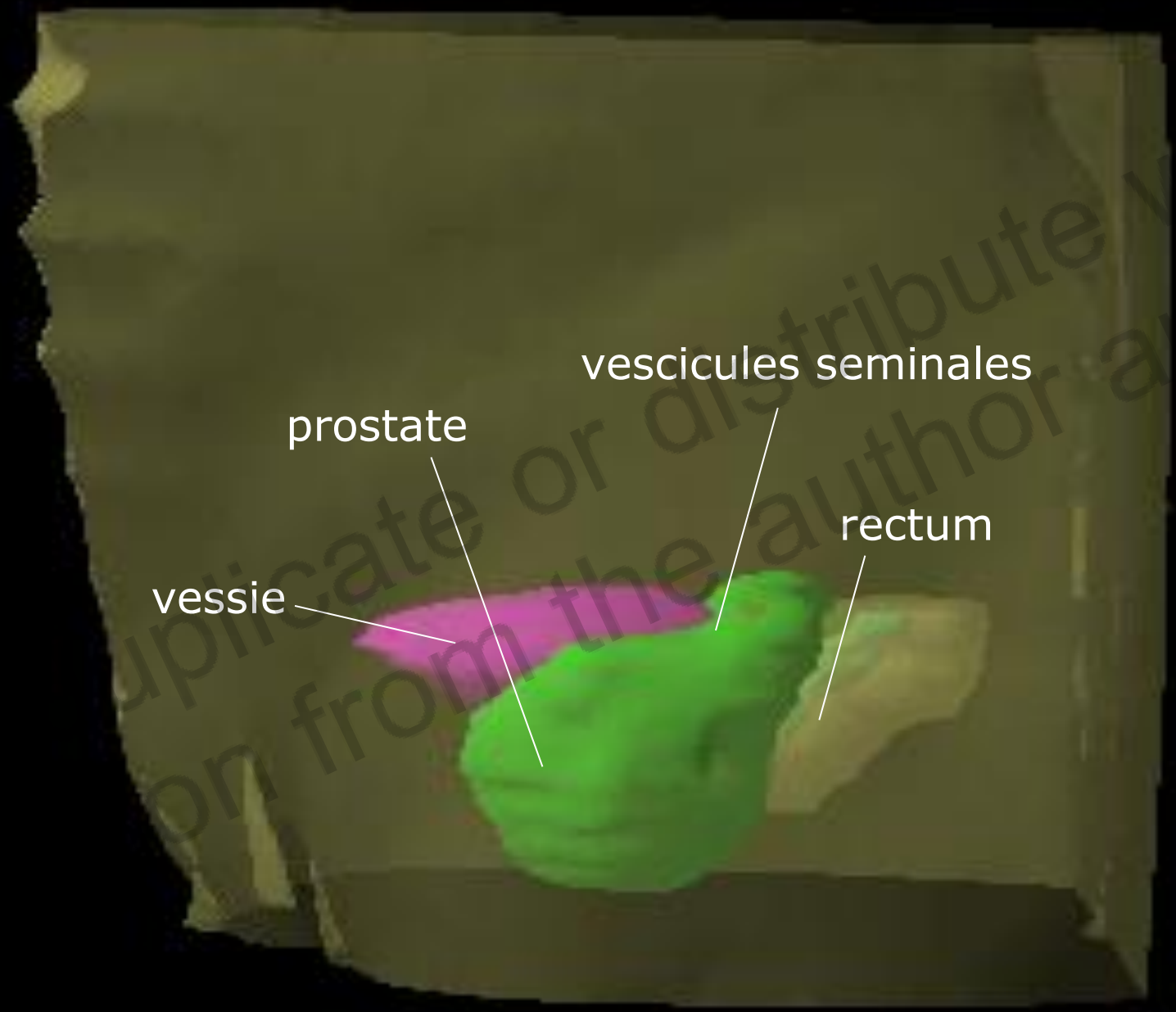


Hanks, 1989
Radiation Oncology
C.V. Mosby Company, Ed.


H
R
L
F
Standard
Head First-Supine
Y: -25.50 cm
ptv prostaat
Verification2
ptv prostaat
Verification2
ptv prostaat
Verification2

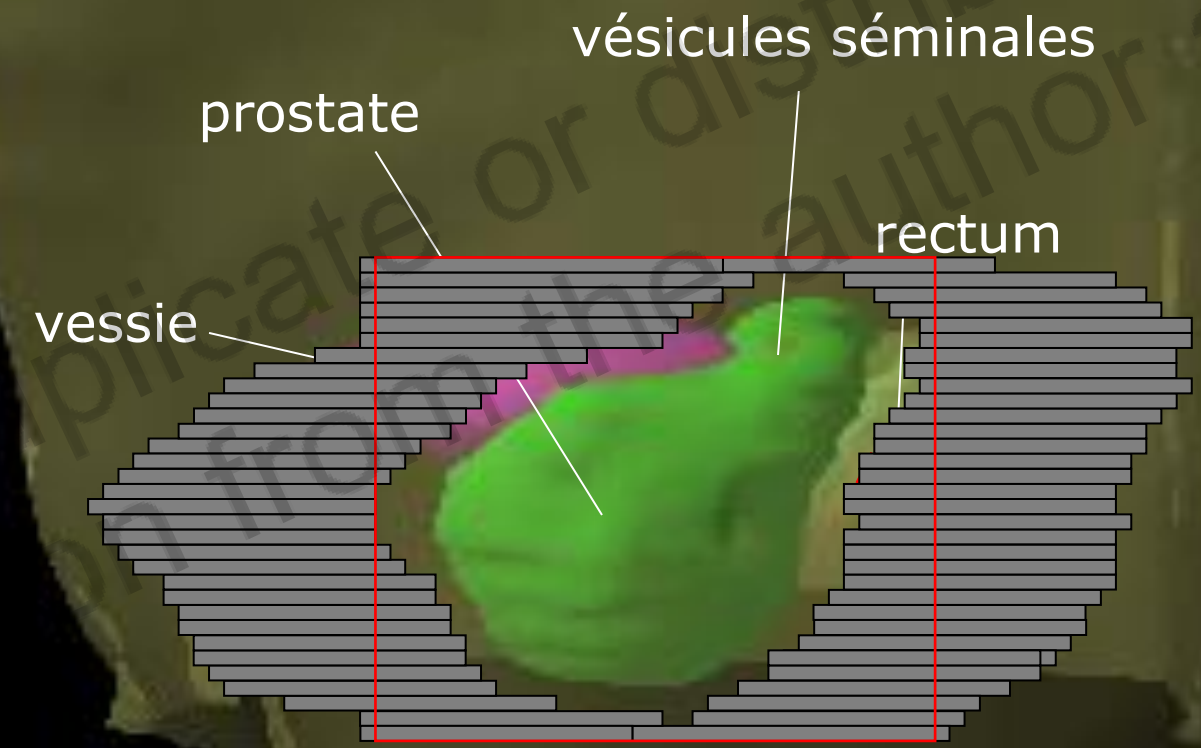


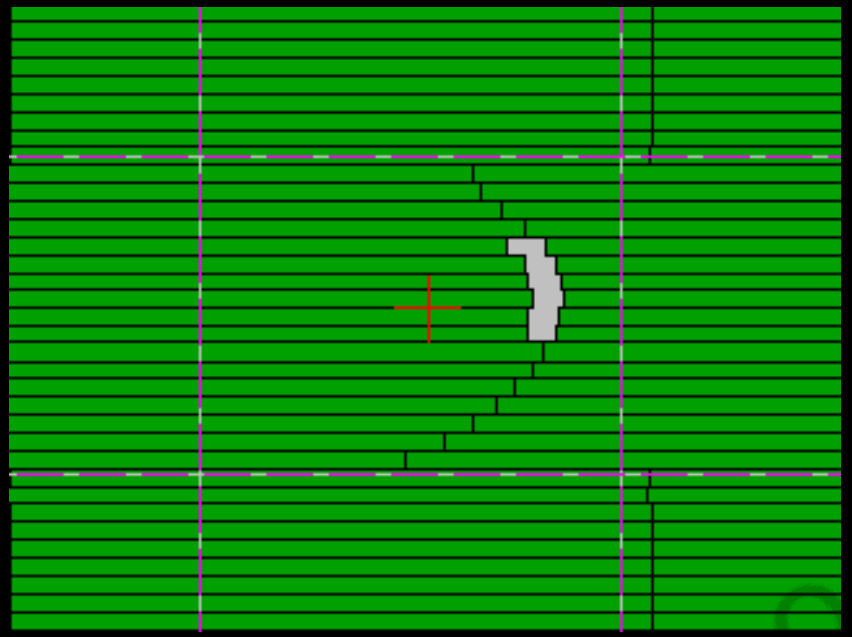
Debois M. et al. IJROBP 1999;45:857-65

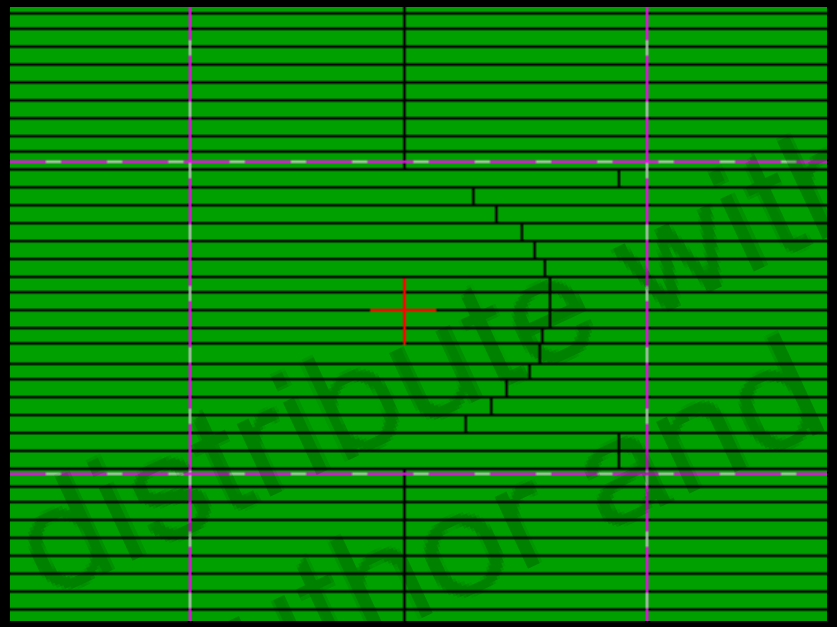


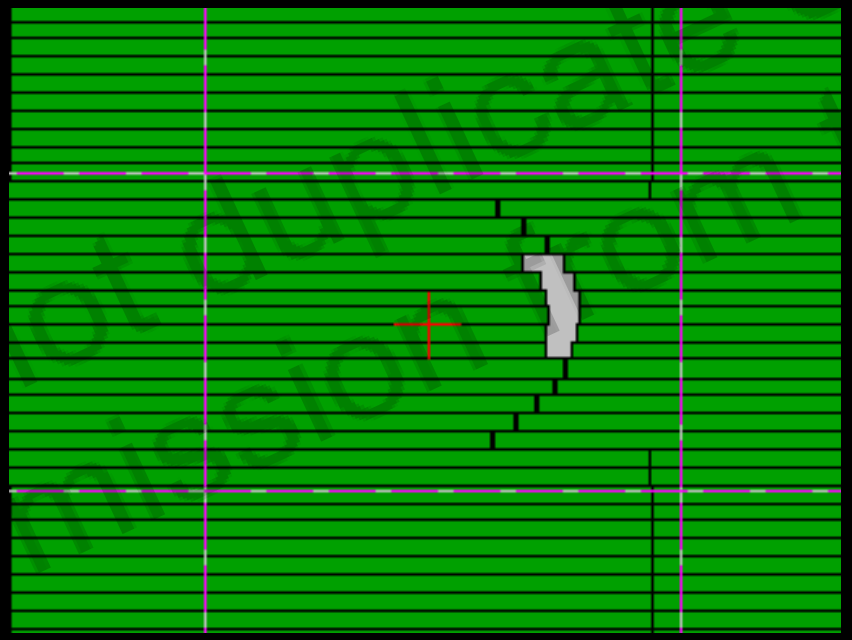
Collimateur multilames

Radiothérapie conformationelle: collimateur mutilâmes



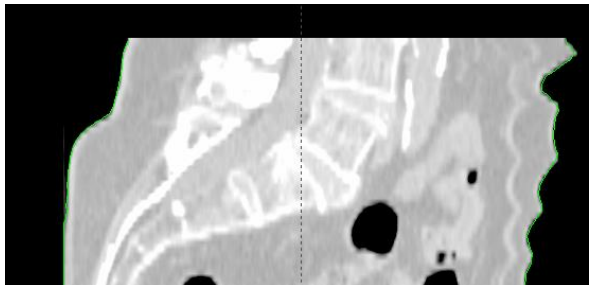


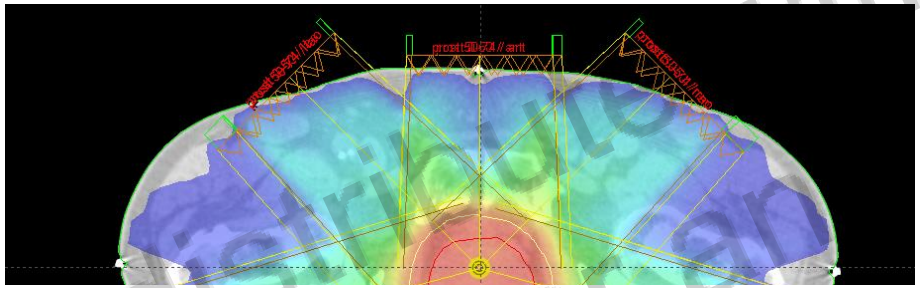




UZ Leuven, 2004

IMRT planning

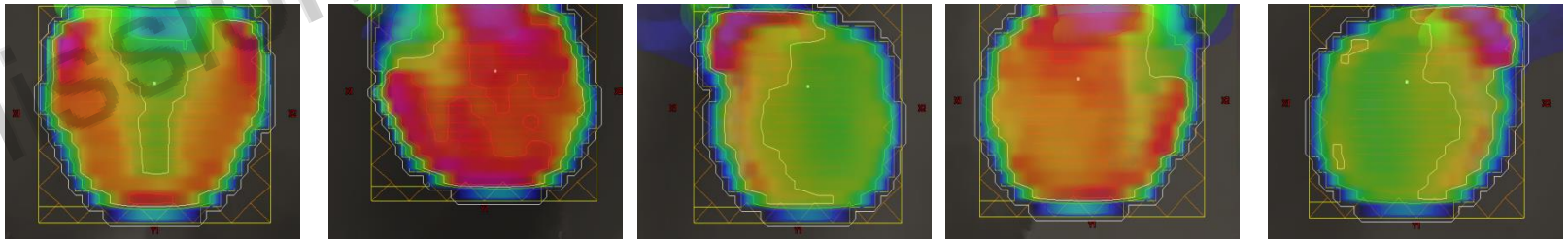




IMRT..... = Intensity

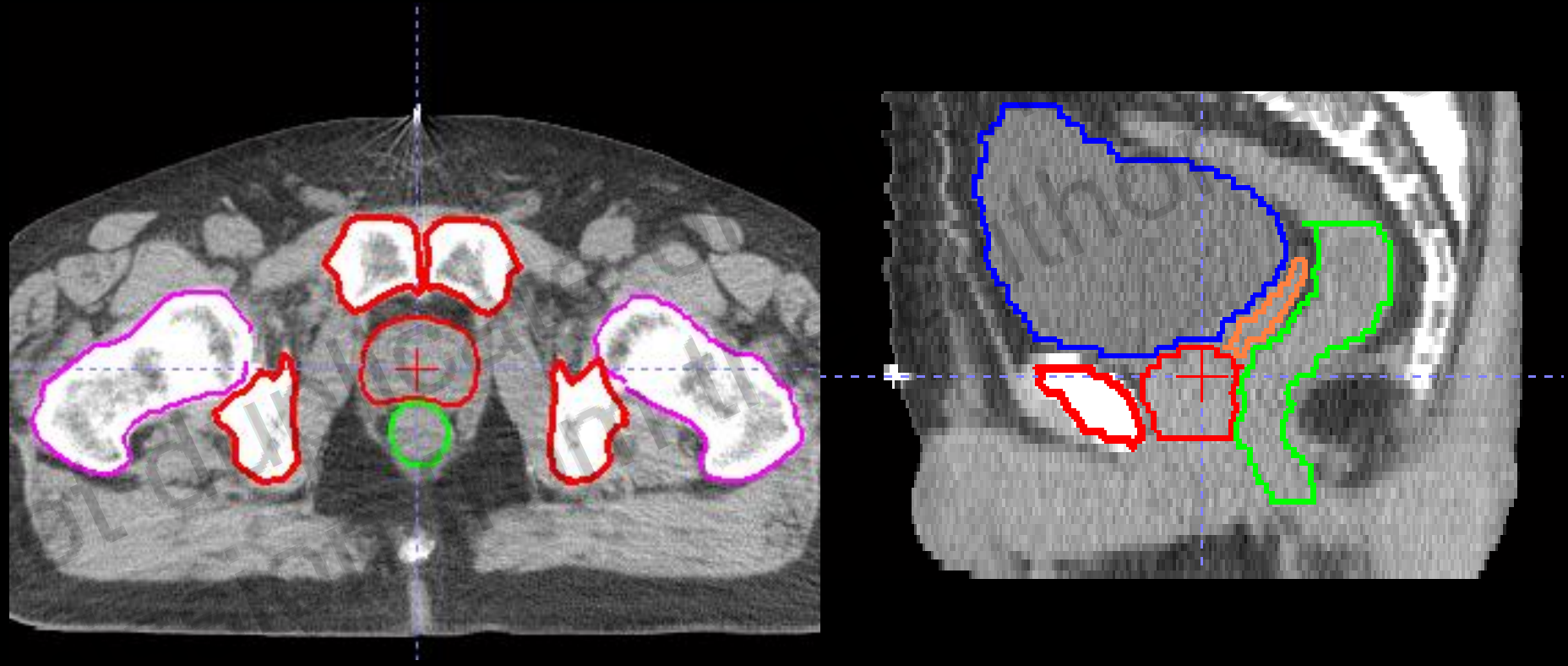
Modulated

Radio Therapy



Setup Error and Organ Motion

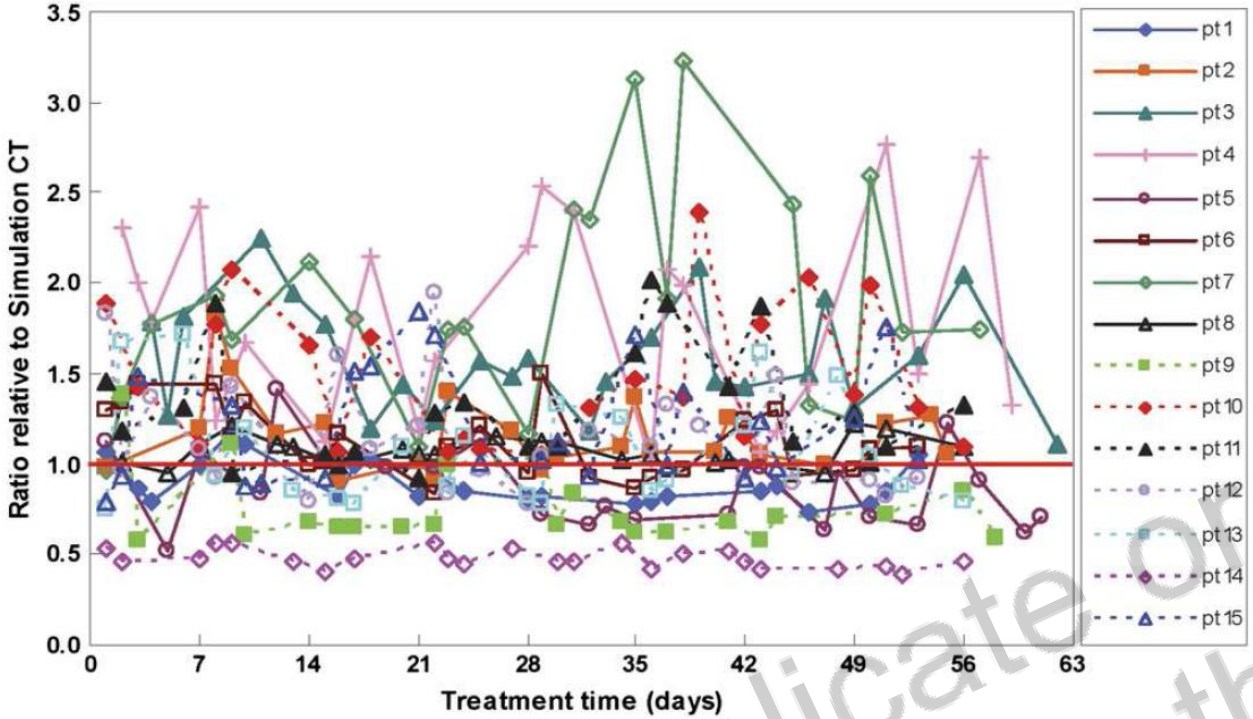
22 Treatment CT scans Aligned to Skin Marks



In-room CT-linear accelerator combination

courtesy of R. de Crevoisier, L. Dong, MDACC

VARIATIONS in **RECTAL** VOLUME DURING IMRT



Franck, IJROBP, 2008

…and in **BLADDER** VOLUME

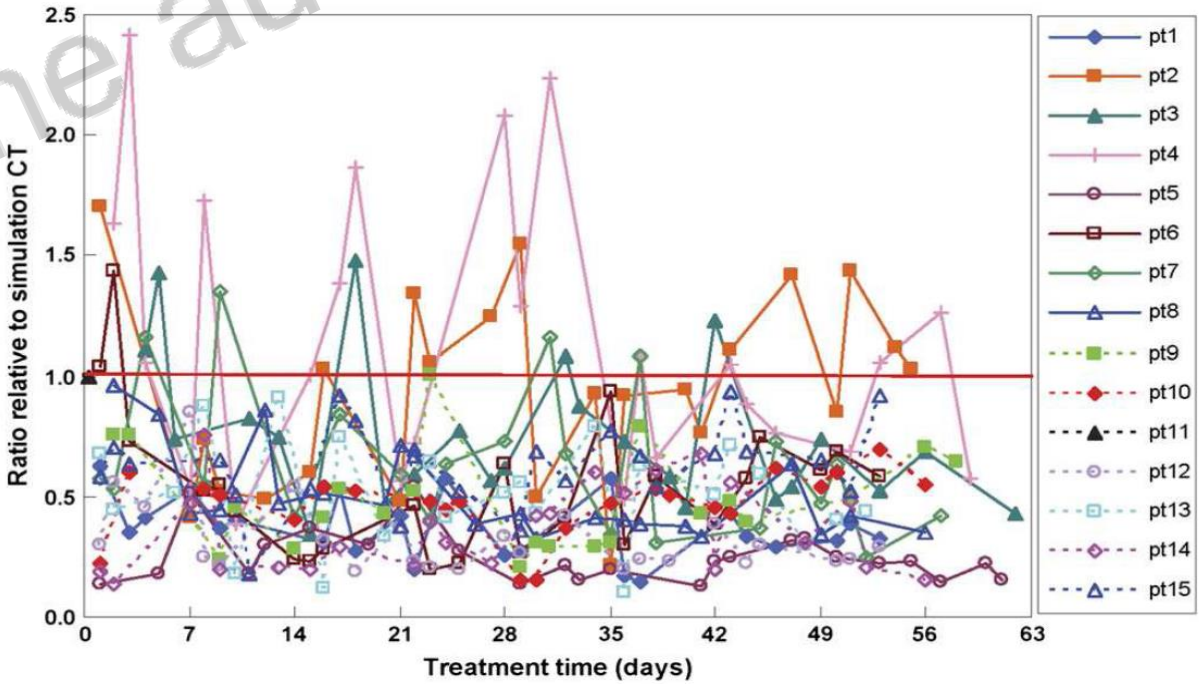


Image Guidance Technologies for Prostate Radiotherapy (1)

Technology	Quality of Alignement	Intrafraction Correction	Comments
Skin marks with weekly portals	Low	No	Baseline
Projected MV/kV x-rays	Medium	Possible	Bone is not a good surrogate
CT on rails for bone alignement	Medium	No	Time consuming
Ultrasound for prostate alignement	Medium / Good	Possible	Interobserver variation
Cone Beam CT	Medium / Good	Possible	Image quality challenging
Tomotherapy	Medium / High	Possible	Image resolution challenging

Image Guidance Technologies for Prostate Radiotherapy (2)

Technology	Quality of Alignement	Intrafraction Correction	Comments
Implanted Markers with AP-LL x-rays	High	Possible	No SV alignement Time consuming
CBCT+Implanted Markers	High	Possible	Image quality challenging
Ultrasound + Implanted Markers	High	Yes	Interobserver variation
Implanted Electromagnetic Transponder	High	Yes	No SV alignement
Real-Time in room MRI	High	Yes	Best solution ?

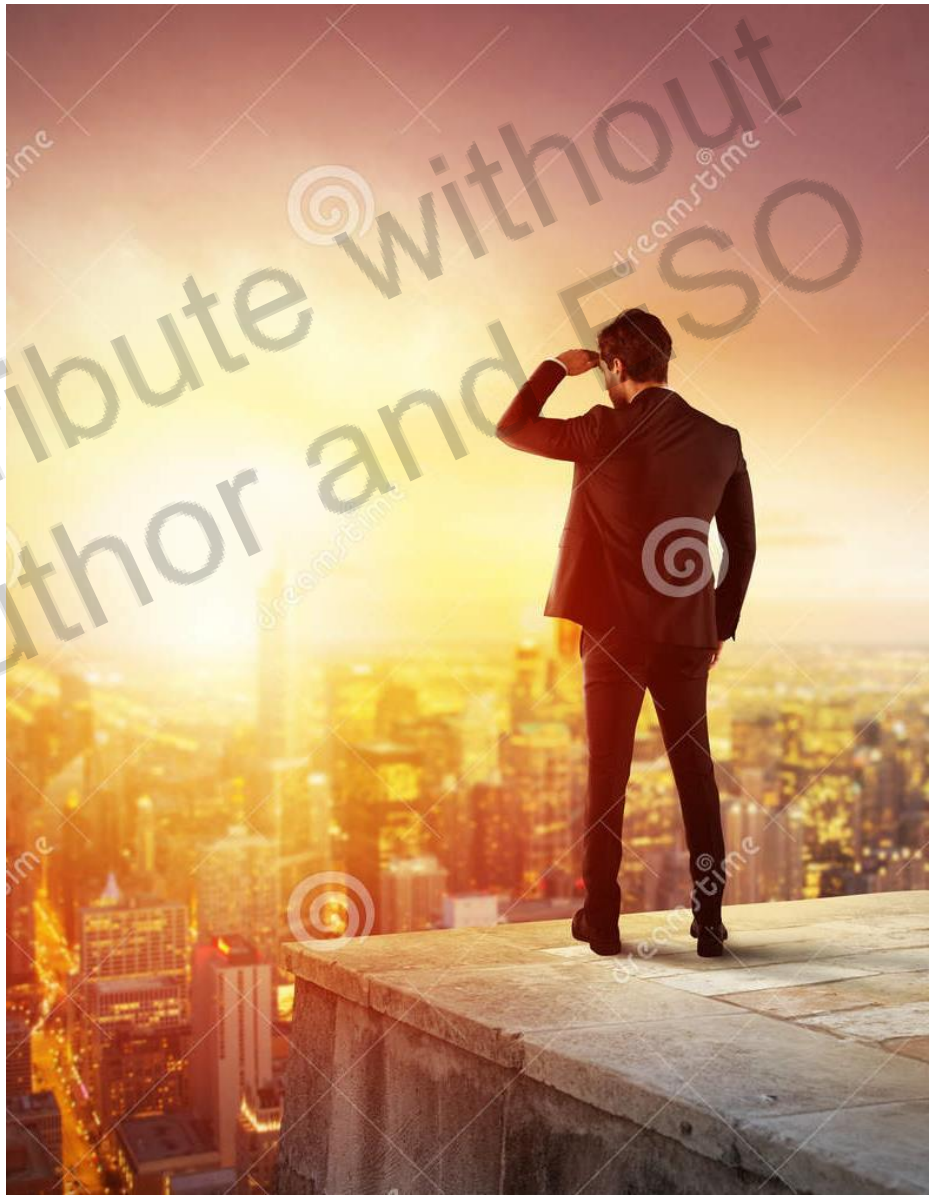
- A high-field, diagnostic-grade, 1,5 Tesla MR scanner.
- A treatment delivery solution, built specifically for this purpose.
- An integrated workflow to allow online treatment adaptation based on position and/or shape.

better use of (established) technologies

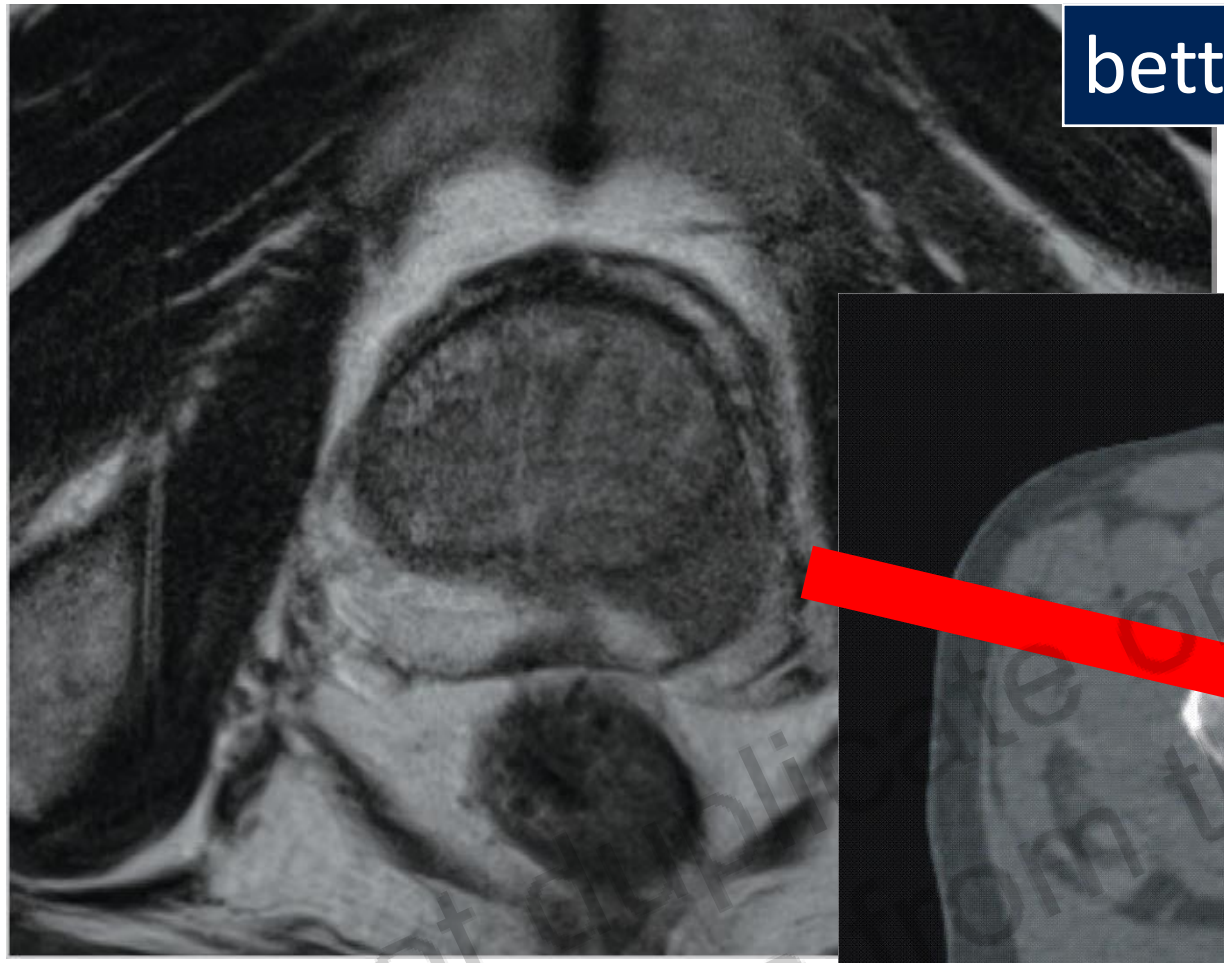
spread of (new) technologies

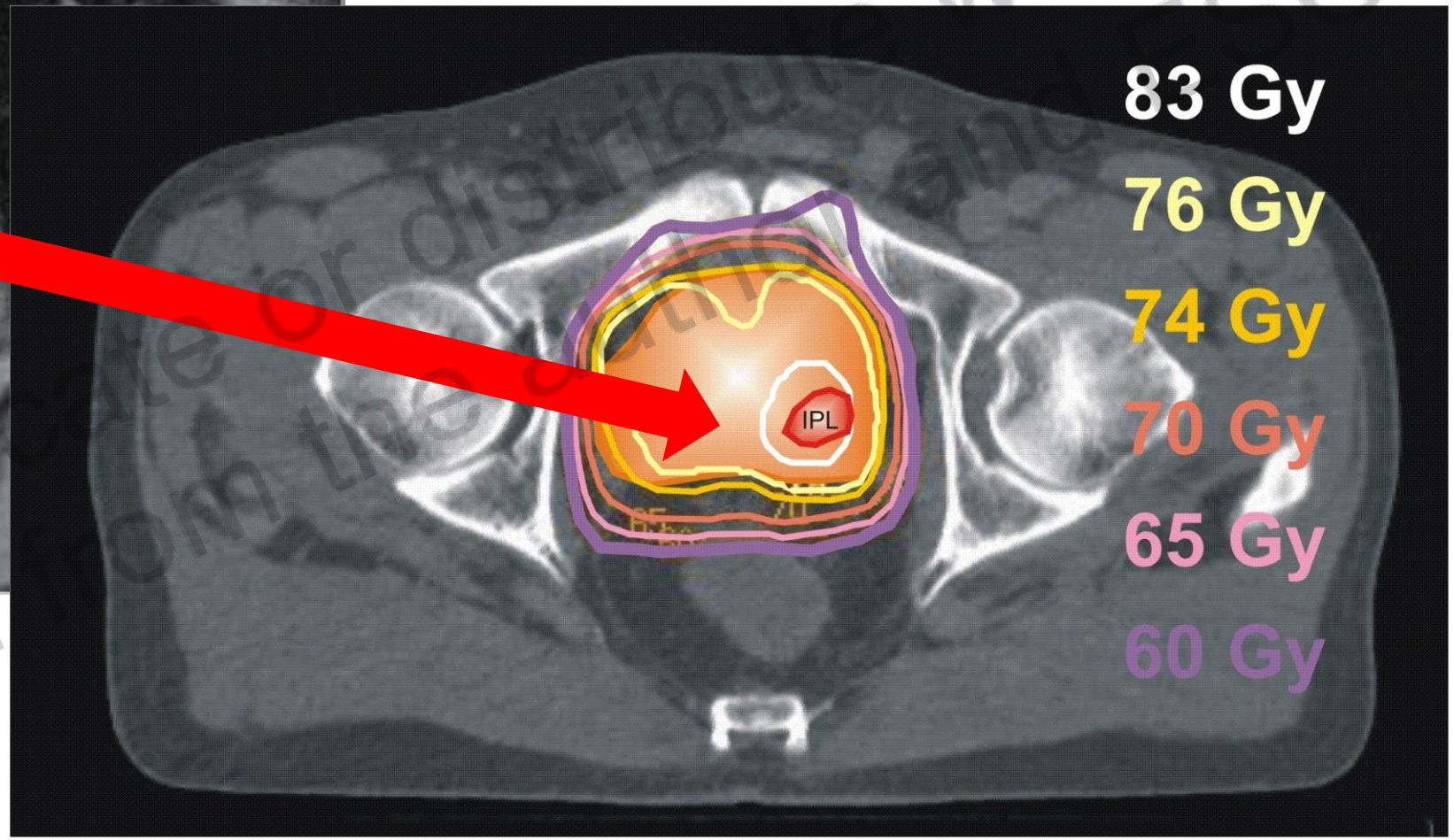
answers to (old) questions

patient- centred approach



better use of (established) technologies





original reports

Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial

Linda G. W. Kerkmeijer, MD, PhD[1,2]; Veerle H. Groen, MD[1]; Floris J. Pos, MD, PhD[3]; Karin Haustermans, MD, PhD[4]; Evelyn M. Monninkhof, PhD[5]; Robert Jan Smeenk, MD, PhD[2]; Martina Kunze-Busch, PhD[2]; Johannes C. J. de Boer, PhD[1]; Jochem van der Voort van Zijp, MD, PhD[1]; Marco van Vulpen, MD, PhD[6]; Cédric Draulans, MD, PhD[4]; Laura van den Bergh, MD, PhD[7]; Sofie Isebaert, PhD[4]; and Uulke A. van der Heide, PhD[3]

Focal Lesion Ablative Microboost in Prostate Cancer

Kerkmeijer et al, 2021

Journal of Clinical Oncology®

Baseline	Standard Treatment	Focal Boost Treatment
No. of subjects (n)	287	284
Mean age in years (SD)	70 (7)	70 (6)
Risk stratification (EAU criteria)	N (%)	N (%)
Low-risk	4 (1)	2 (1)
Intermediate-risk	43 (15)	43 (15)
High-risk	240 (84)	239 (84)

R

77 Gy, 35 fr (EQD2 81.8 Gy) +/- ADT

77 Gy, 35 fr (EQD2 81.8 Gy) +/- ADT
+ SIB on the mpMRI defined DIL of
95 Gy (EQD2 115.8 Gy) +/- ADT

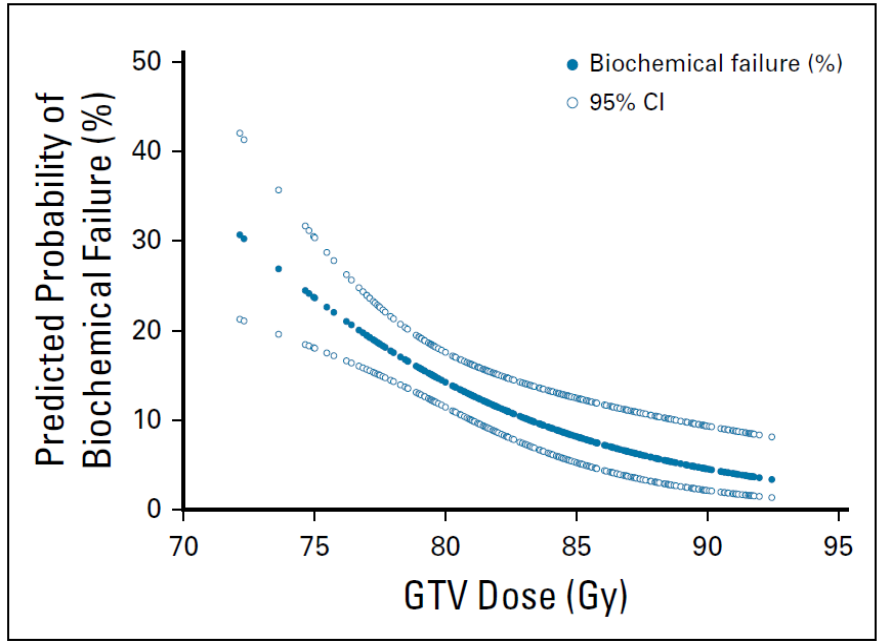


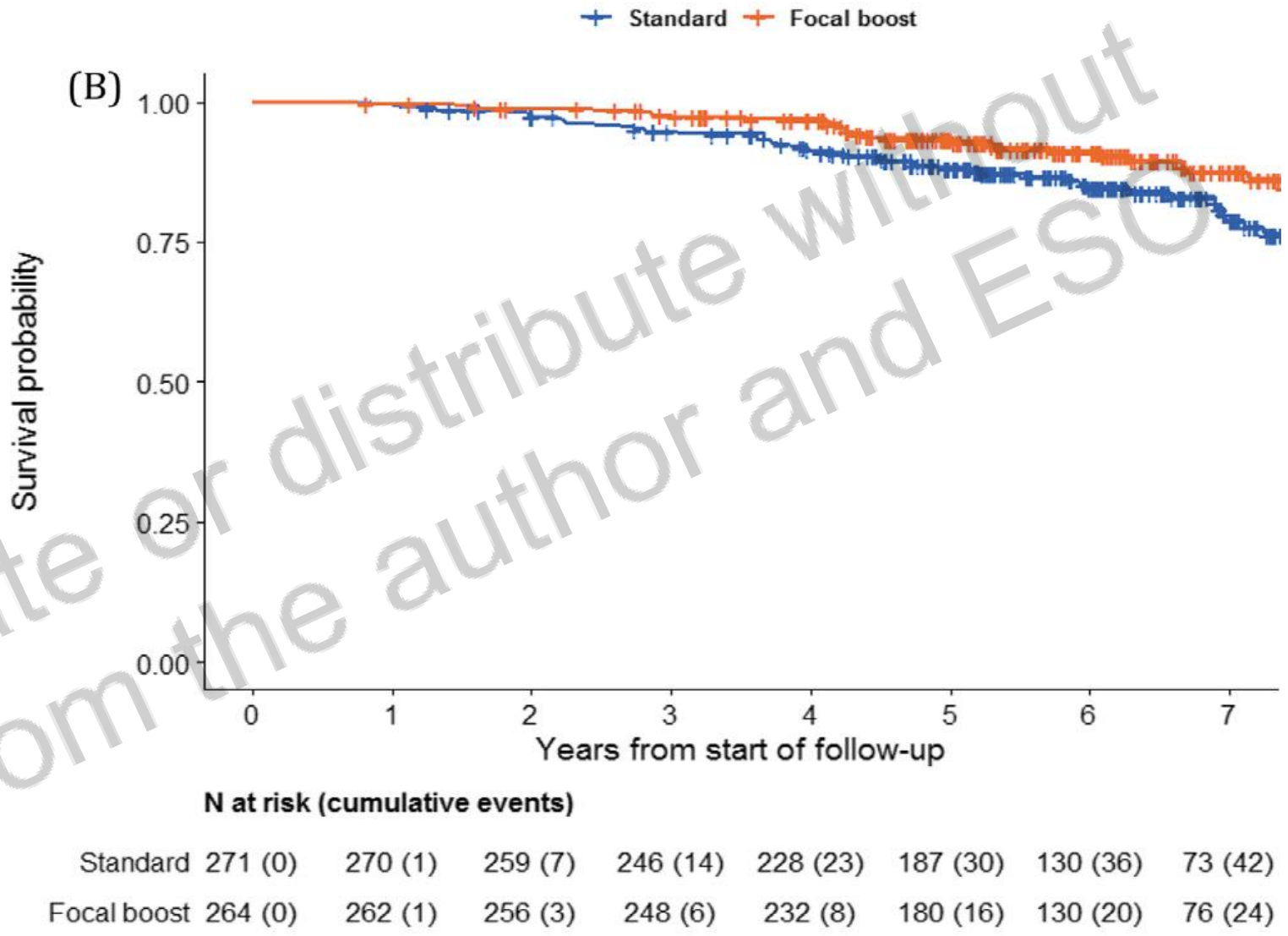
FIG 3. Predicted probability of biochemical failure up to 7 years as a function of achieved dose to the gross tumor volume (D98%; Gy).

FLAME

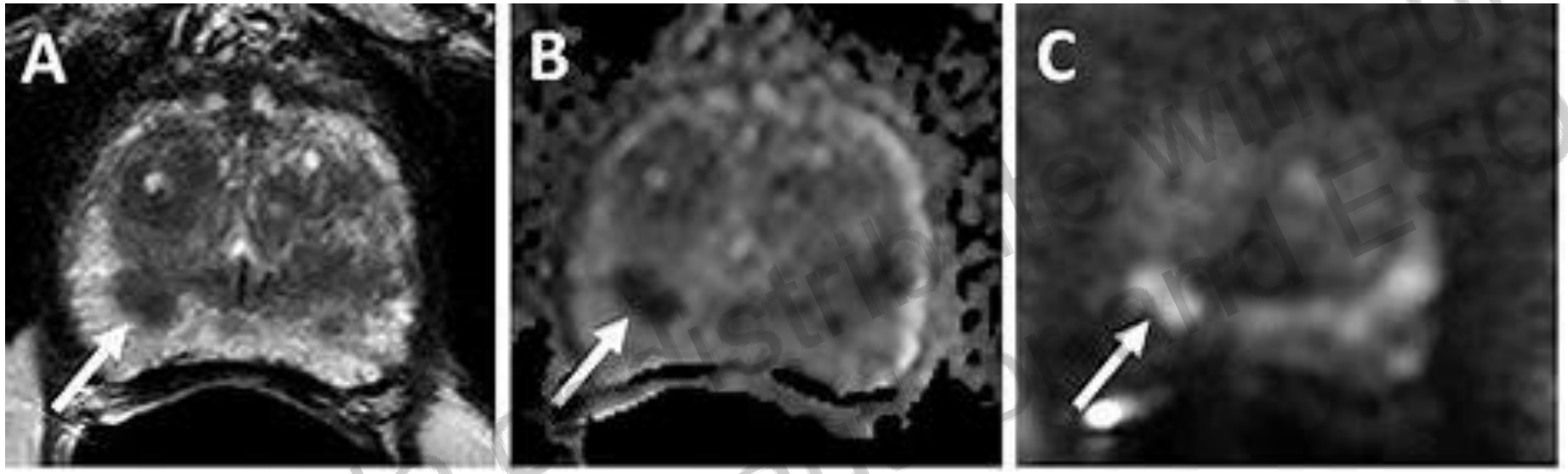
Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial

Kerkmeijer et al, JCO 2021

	HR	C.I.
Local Failure Free Survival	0.33	0.14 – 0.78
Regional + Distant Mets Free Survival	0.58	0.35 – 0.93



Groen et al, Eur Urol 2022

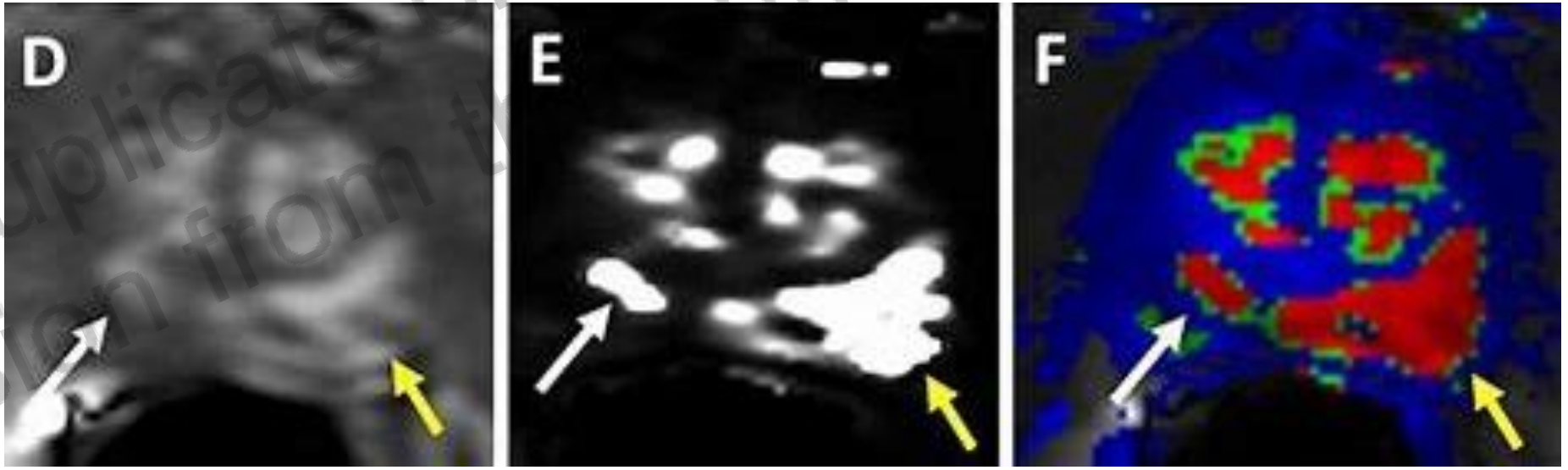


Biopsy Report:

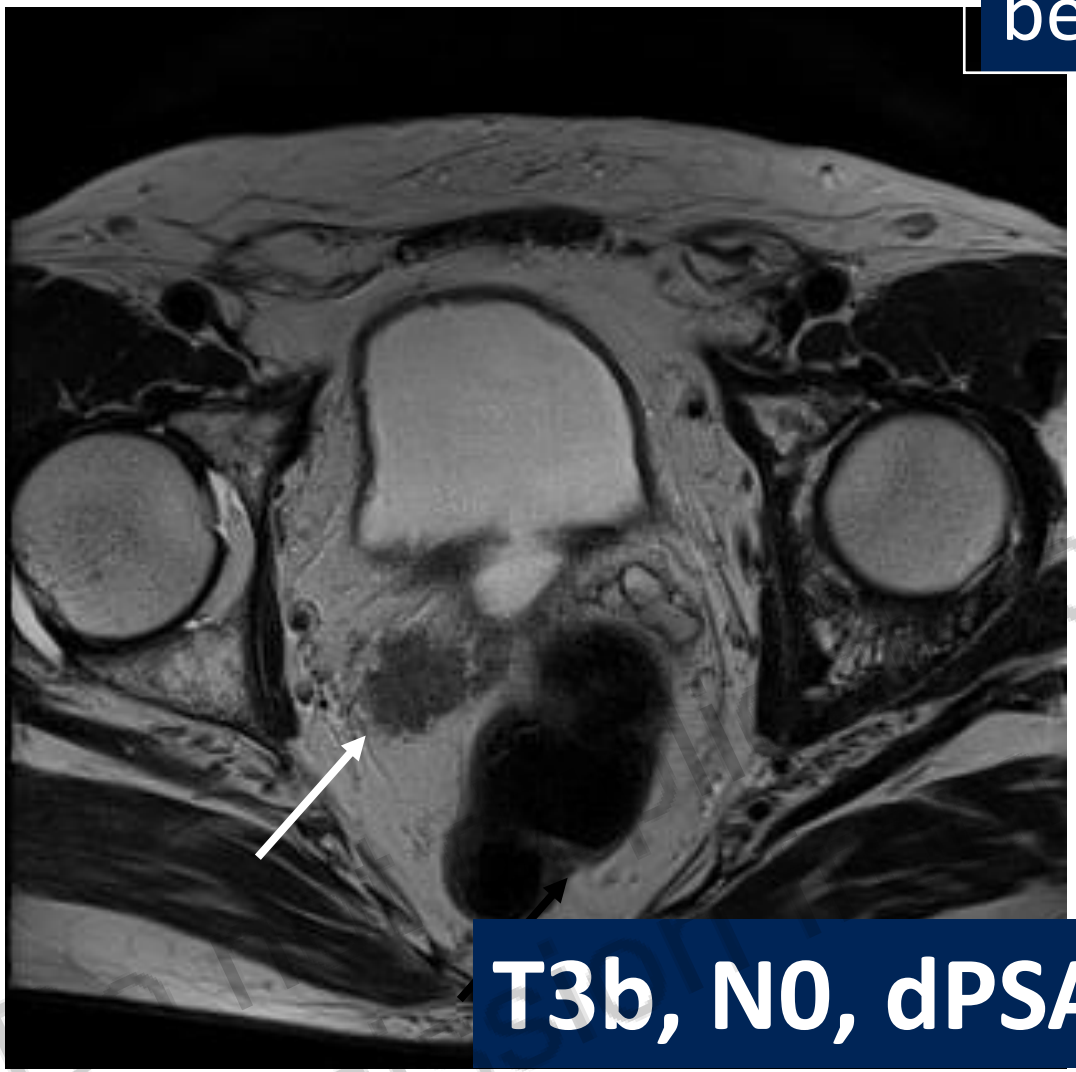
Left lobe : no cancer / 120 mm
Right lobe : 9 / 149 mm ISUP 3

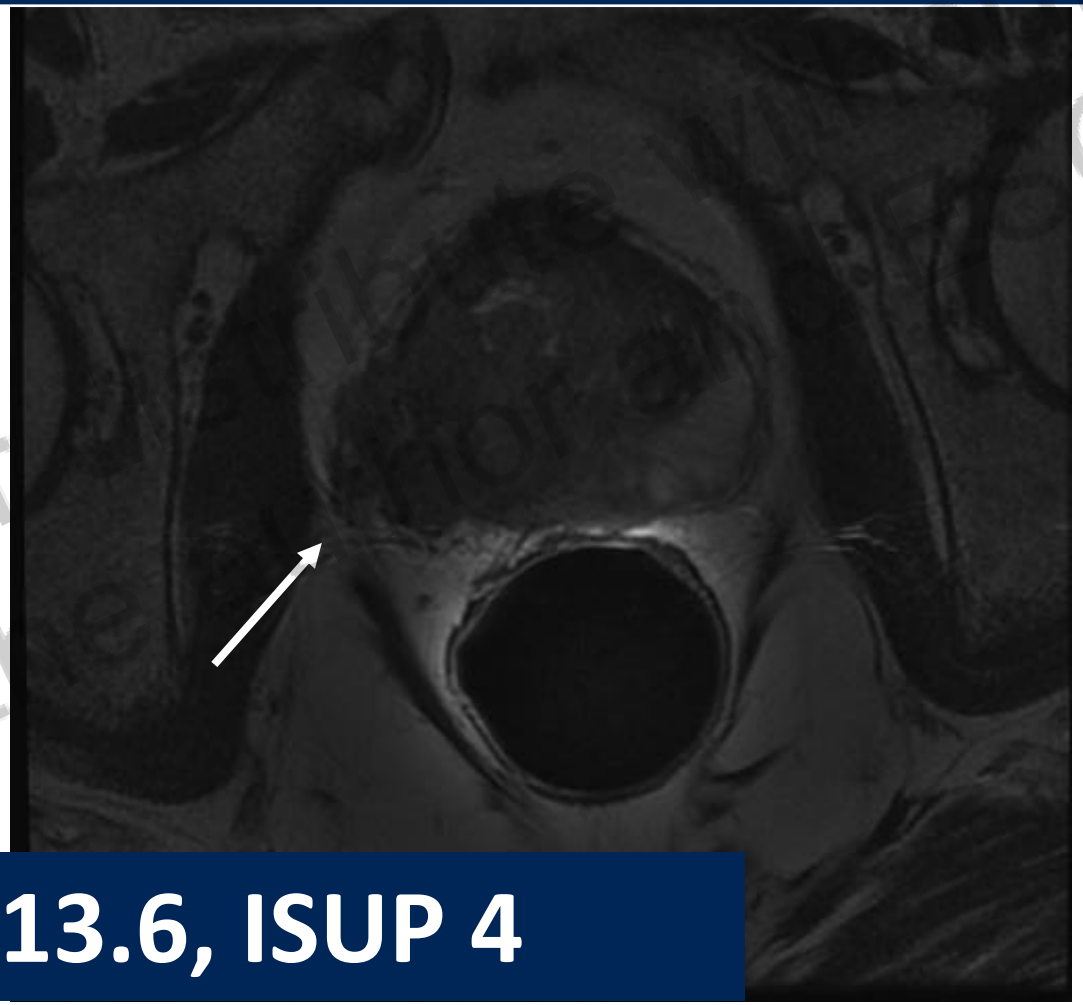
Biopsy Report:

Left lobe : 21 / 167 mm ISUP 3
Right lobe : 9 / 149 mm ISUP 3

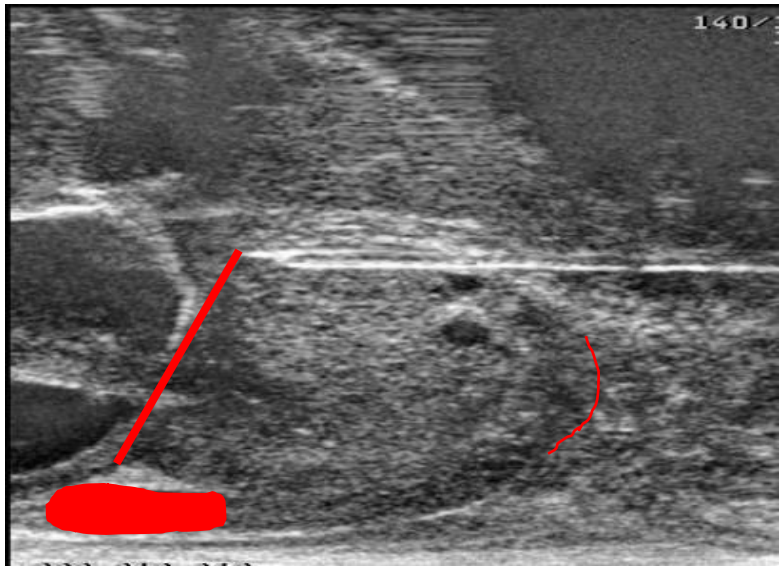


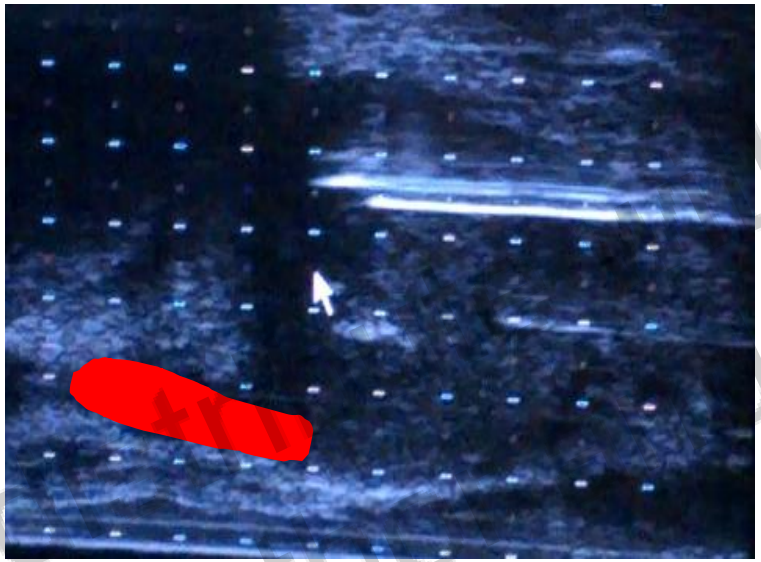
better use of (established) technologies

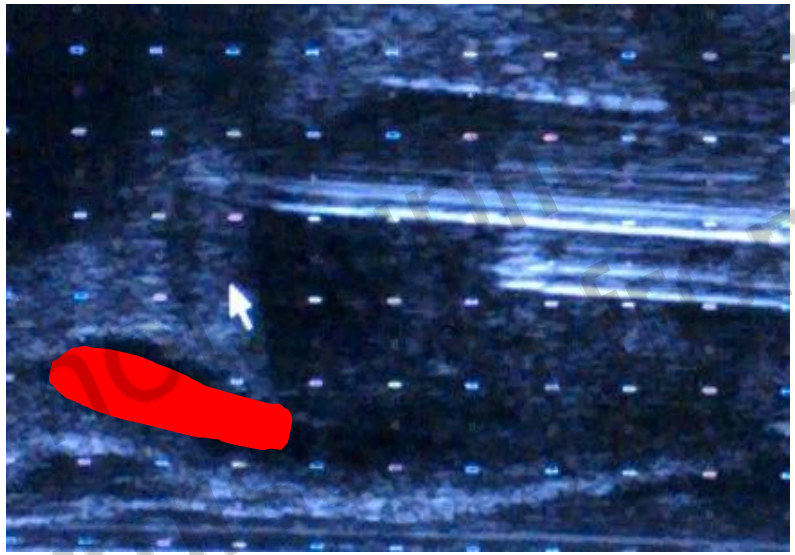


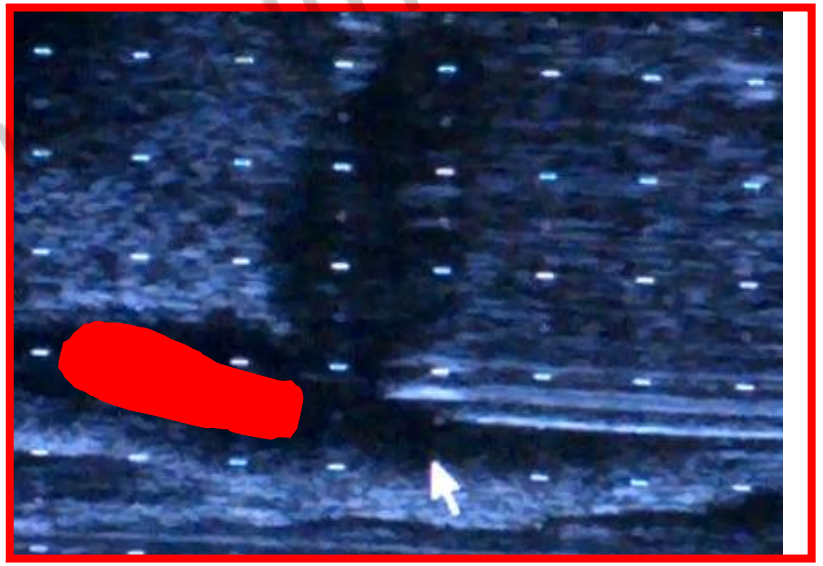


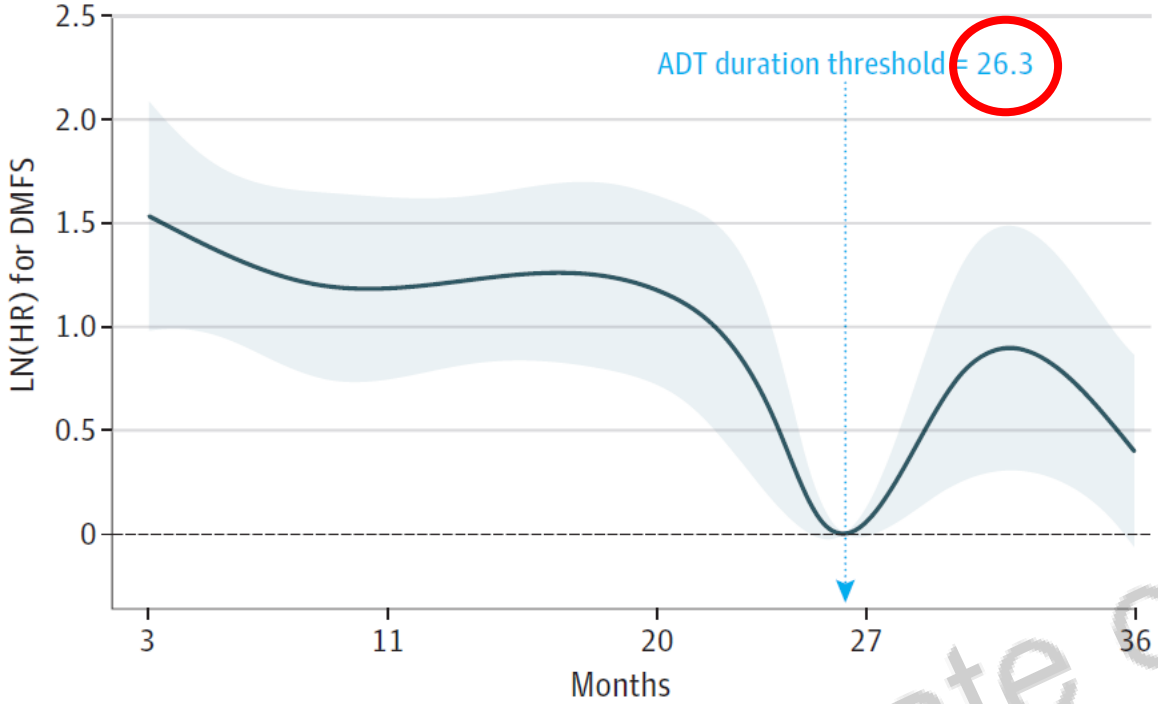
T3b, N0, dPSA 13.6, ISUP 4

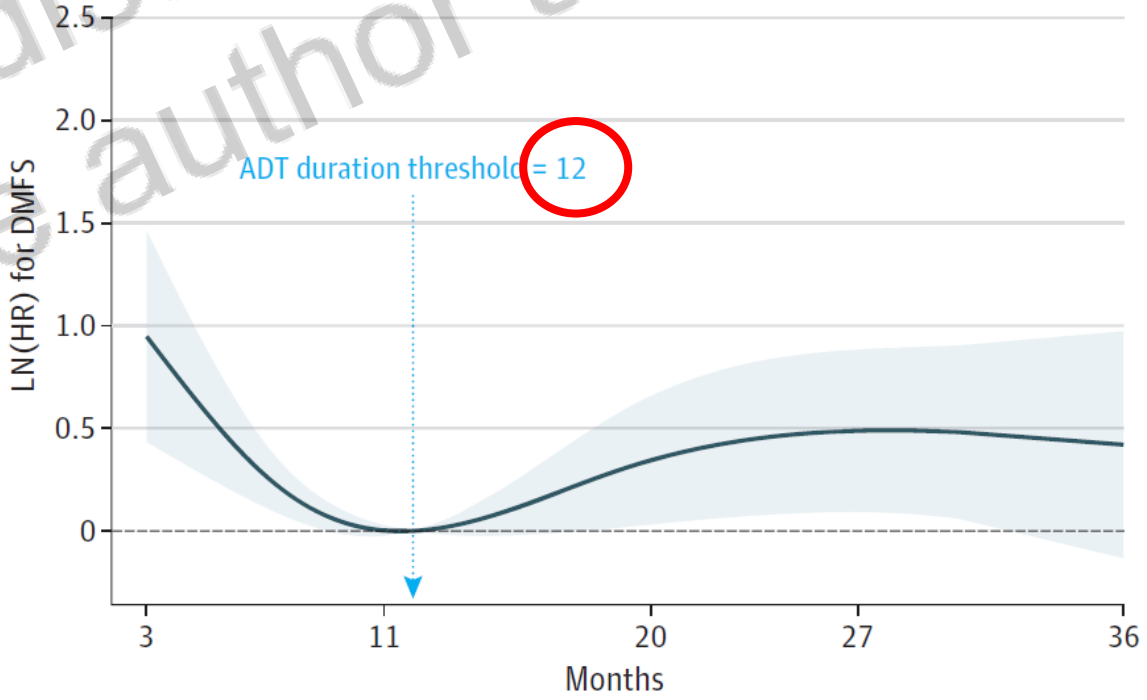






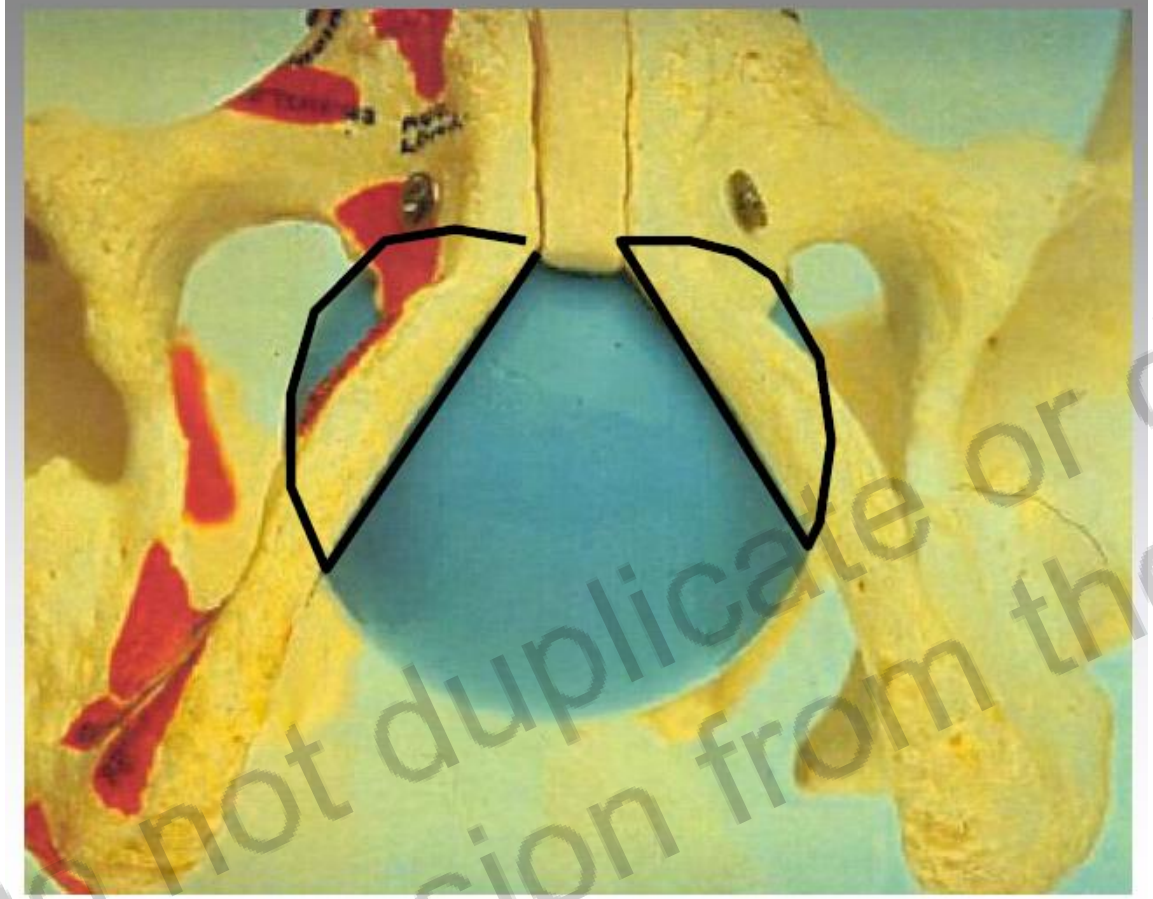






Kishan, Jama Oncol, 2022

Pubic arch interference



Ultrahypofractionation for prostate cancer: Outcome from the Scandinavian phase 3 HYPO-RT-PC trial

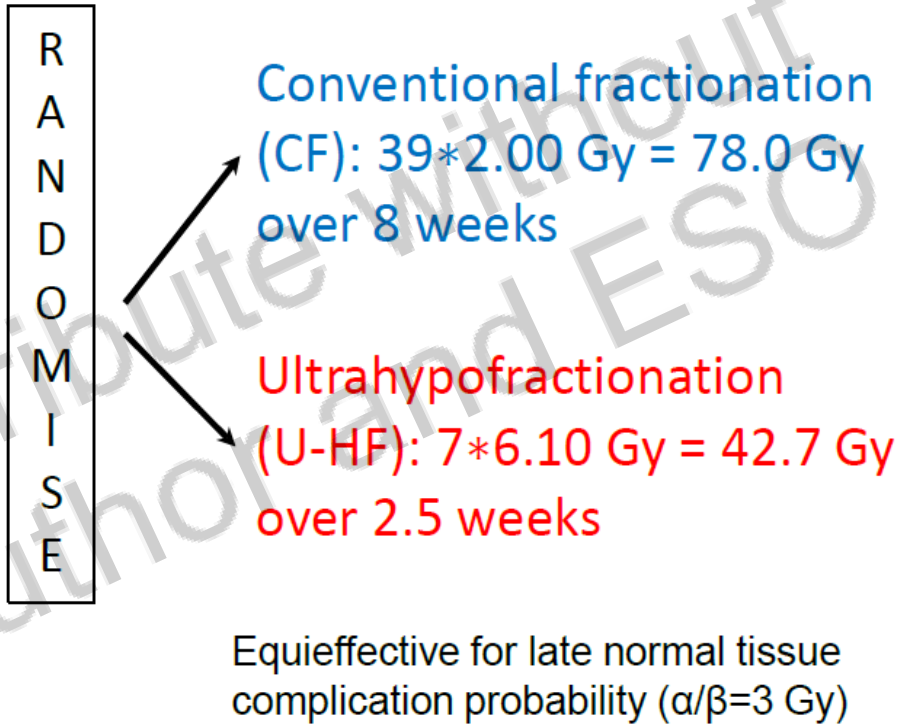
Anders Widmark[1], Adalsteinn Gunnlaugsson[2], Lars Beckman[3], Camilla Thellenberg-Karlsson[1], Morten Hoyer[11], Magnus Lagerlund[4], Per Fransson[1], Björn Tavelin[1], David Norman[1], Jon Kindblom[5], Claes Ginman[6], Bengt Johansson[7], Mihalj Seke[8], Kirsten Björnlinger[9], Måns Agrup[10], Elisabeth Kjellén[2], Lars Franzén[1] and Per Nilsson[2]

[1]*Umeå*, [2]*Lund*, [3]*Sundsvall*, [4]*Kalmar*, [5]*Göteborg*, [6]*Karlstad*, [7]*Örebro*, [8]*Växjö*, [9]*Jönköping*, [10]*Linköping, Sweden*

[11]*Århus, Denmark*

HYPO-RT-PC

- Open, randomised, phase III trial
  - Intermediate/high-risk prostate cancer*
  - 1200 patients accrued
    - July 2005-Nov 2015
  - No androgen deprivation therapy



courtesy of A Widmark

- Open, randomised, phase III trial
  - Intermediate/high-risk prostate cancer*
  - 1200 patients accrued
    - July 2005-Nov 2015
  - No androgen deprivation therapy

RANDOMISE

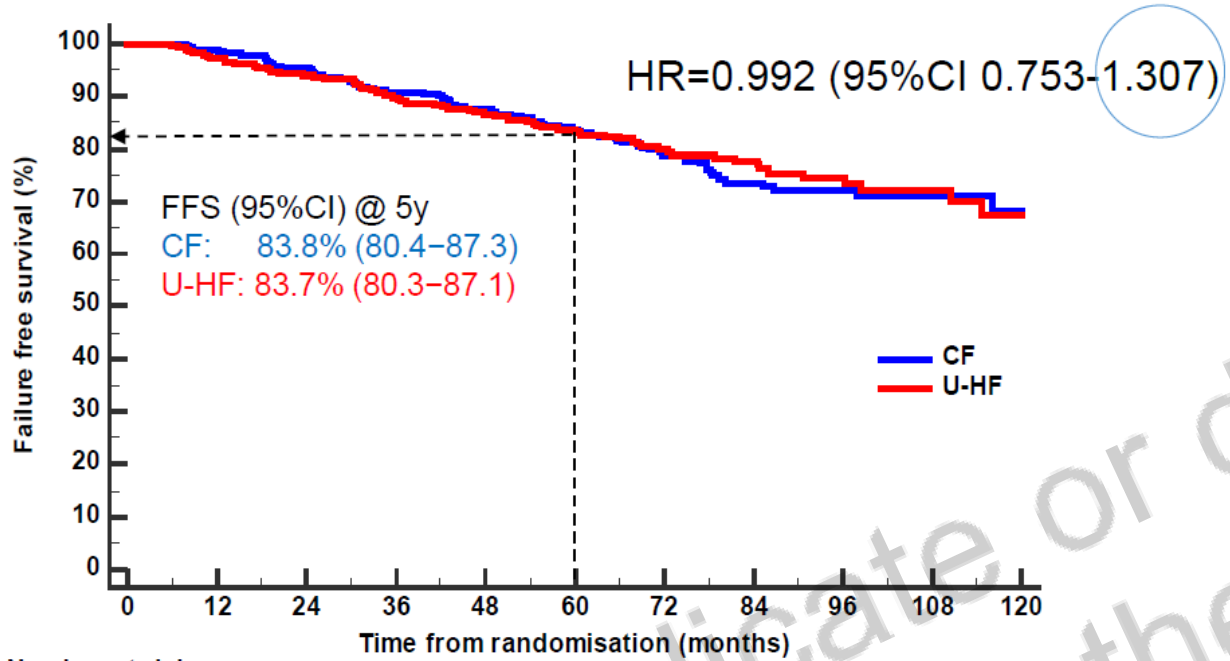
Conventional fractionation (CF): 39∗2.00 Gy = 78.0 Gy over 8 weeks

Ultrahypofractionation (U-HF): 7∗6.10 Gy = 42.7 Gy over 2.5 weeks

Equieffective for late normal tissue complication probability (α/β=3 Gy)

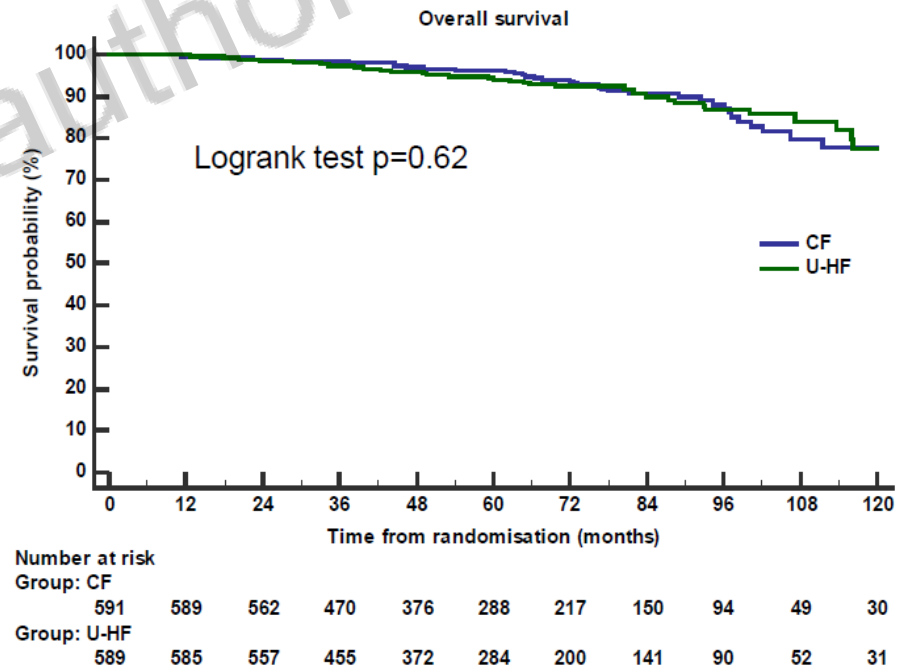
- Target volumes
  - CTV = prostate
    - SV not included
  - PTV=CTV + 7 mm isotropic margin
  - CTV delineated on CT
    - with MR guidance
- RT technique
  - 3D-CRT (80%)
  - IMRT/VMAT (20%)
- IGRT
  - implanted fiducial markers

Results – primary endpoint

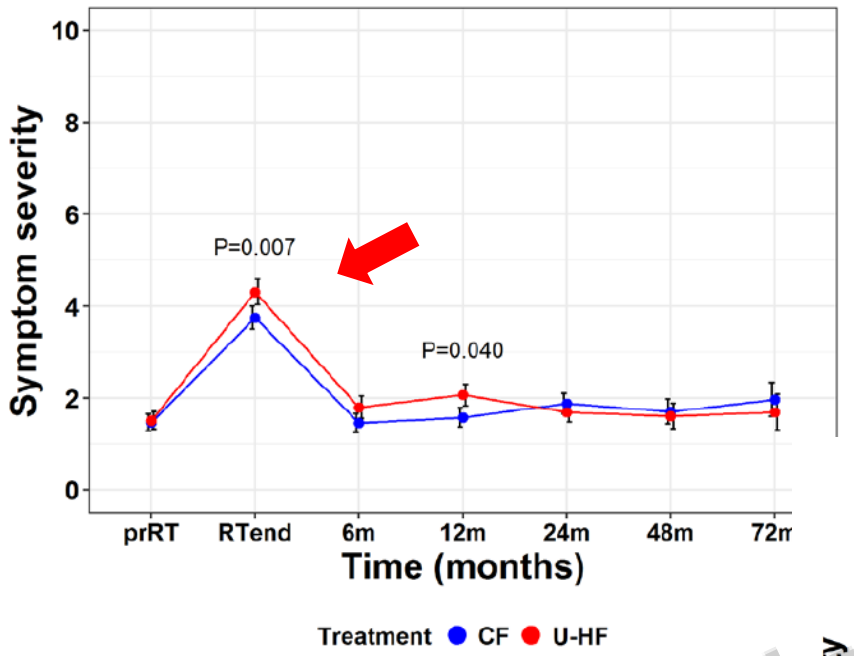


Results – secondary endpoints

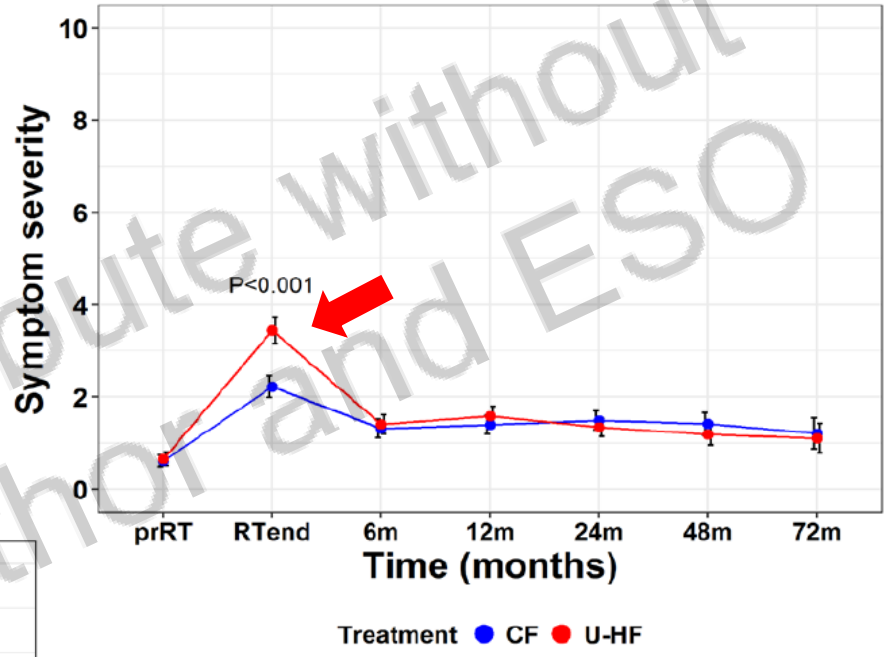
Deaths	CF (n=591)	U-HF (n=589)	Total (n=1180)
Overall	43 (7.3%)	46 (7.8%)	89 (7.5%)
Prostate cancer related	8 (1.4%)	11 (1.9%)	19 (1.6%)



Patient reported

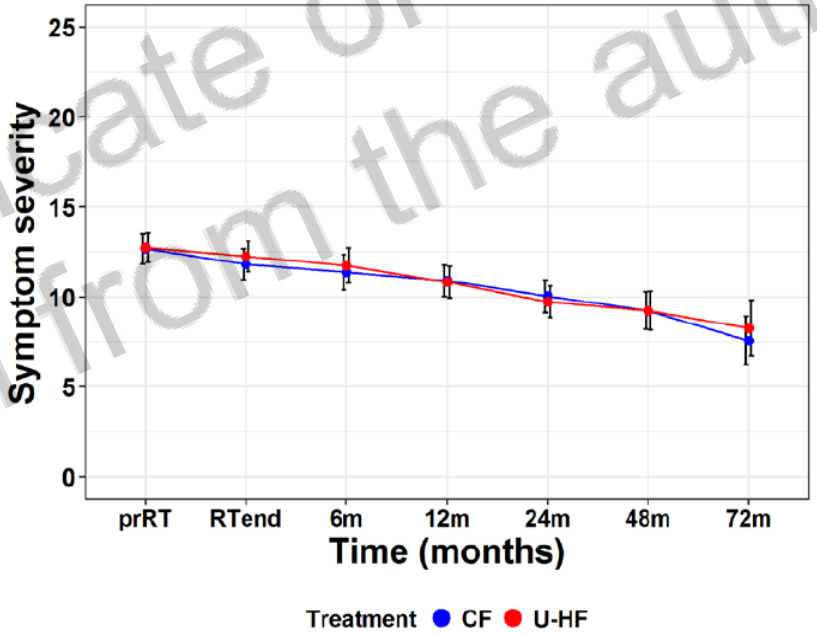


Patient reported



Patient reported

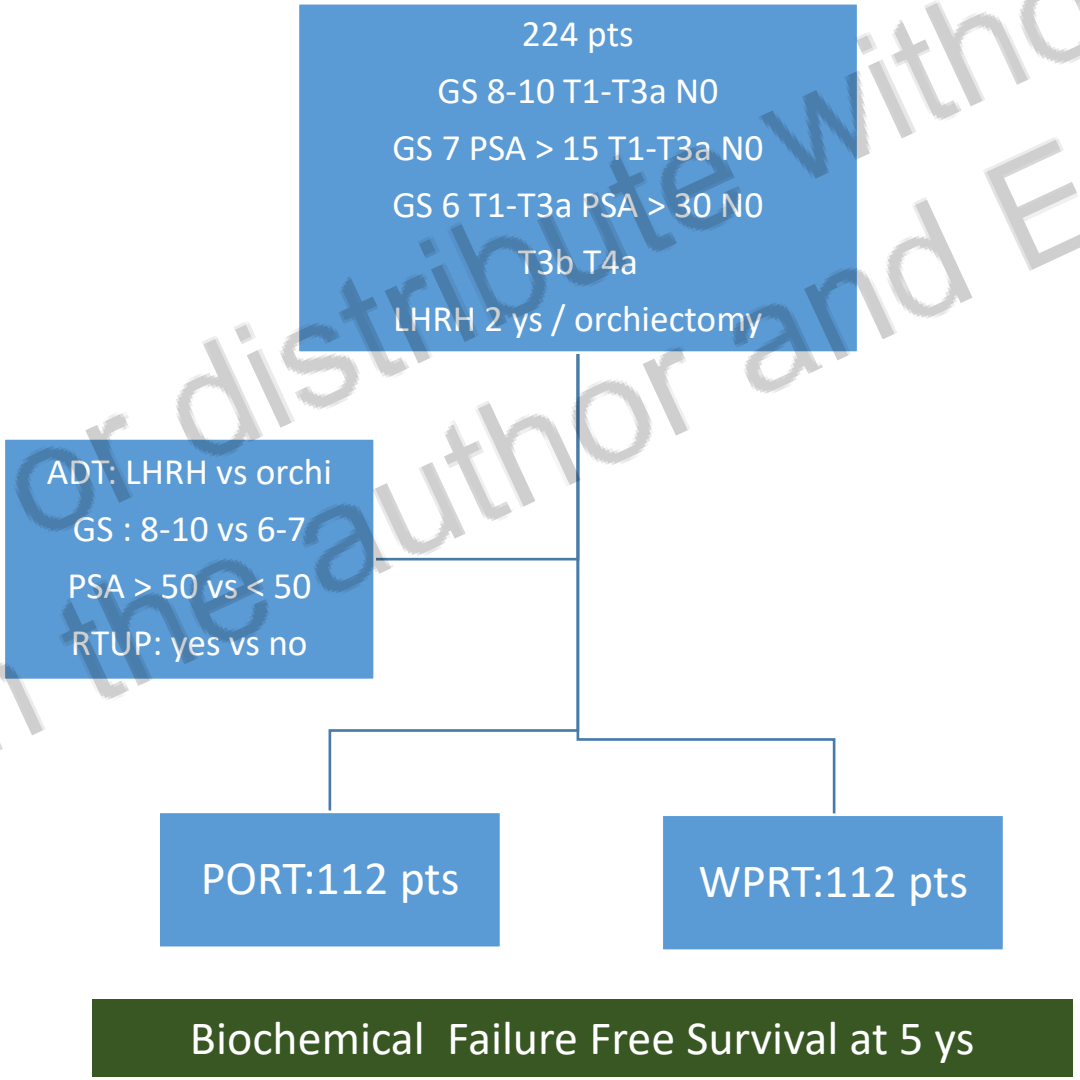
ED-Score



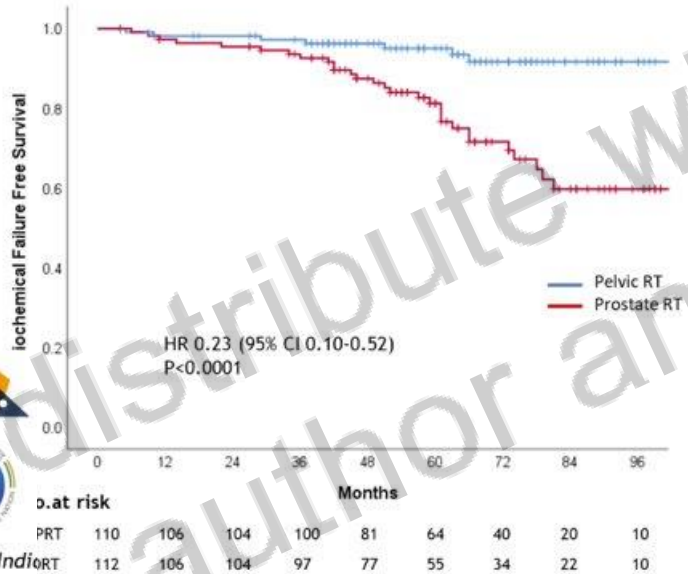
POP RT

Murthy et al, JCO, 2021

	POP RT
Roach > 20	Median: 38% > 35%: 55% > 50%: 29%
Gleason	8-10: 49.1%
Staging	MRI, PSMA PET (80 %)
Pelvis	50Gy /25 fr
Prostate	68Gy / 25 fr SIB
Technique	IG-IMRT



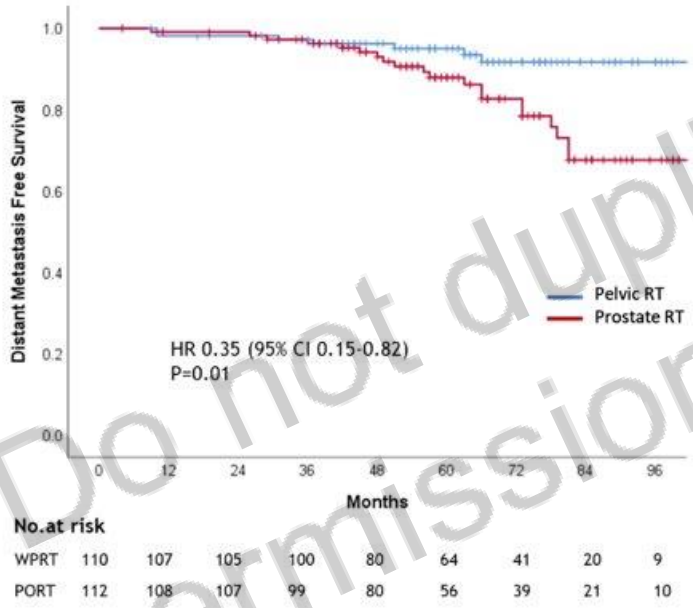
Biochemical Failure-Free Survival



Median Follow up: 68 Months

	WPRT	PORT
No. of events	7	29
5-yr BFFS	95.0%	81.2%

Distant Metastasis-Free Survival (Post Hoc)



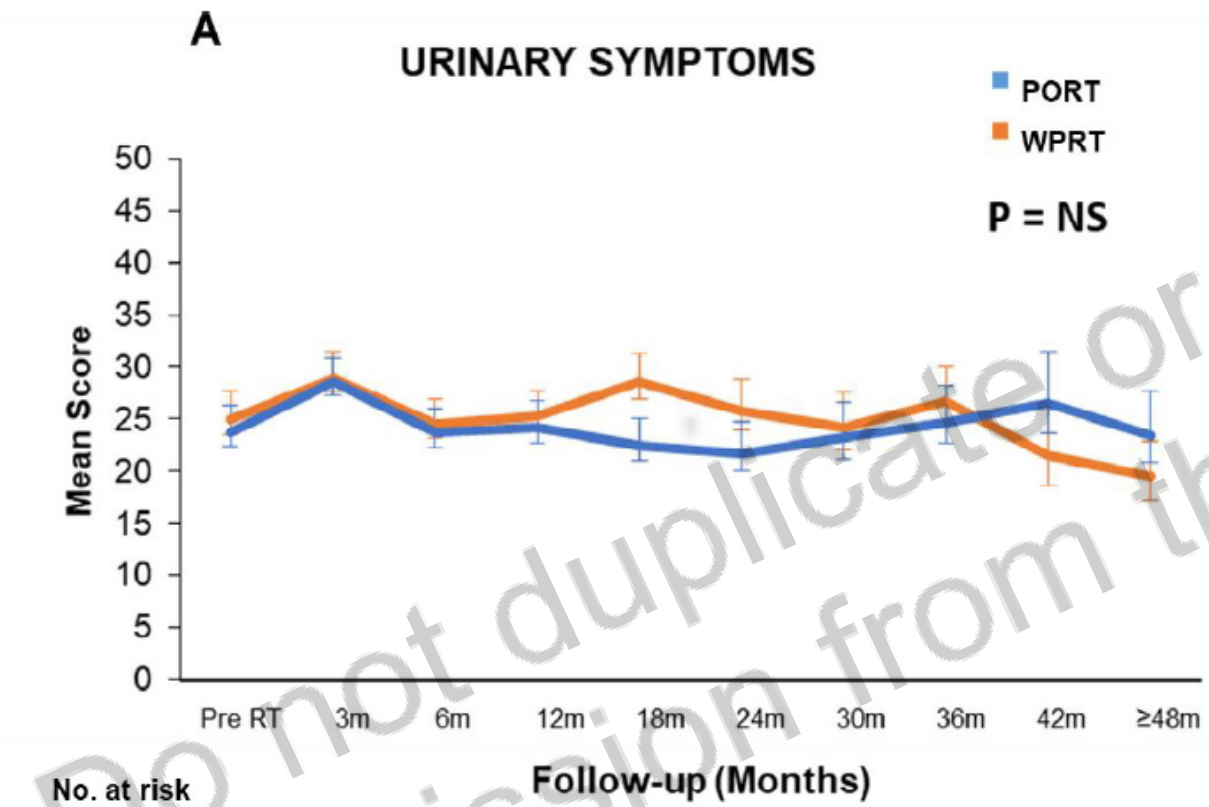
Median Follow up: 68 Months

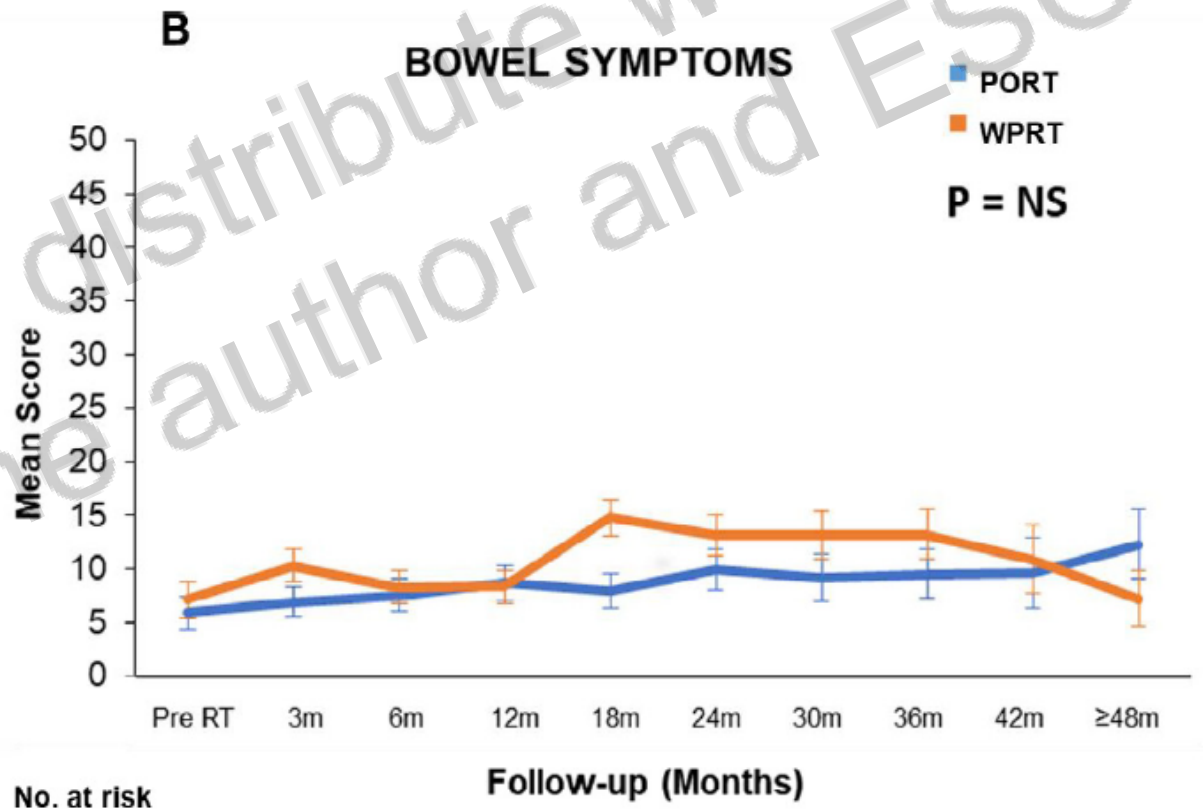
	WPRT	PORT
No. of events	7	20
5-yr DMFS	95.0%	87.9%

Patterns of disease recurrence at biochemical failure

Site of recurrence	WPRT	PORT
Regional pelvic nodes (With/without Distant Metastasis)	1	15
Distant metastases only	5	7
Local recurrence only	0	1
No radiological disease (only BCF)	0	2
Pattern unknown	2	4
Total	7	29

Patient-reported quality of life outcomes for EORTC PR-25 urinary and bowel symptom domains.

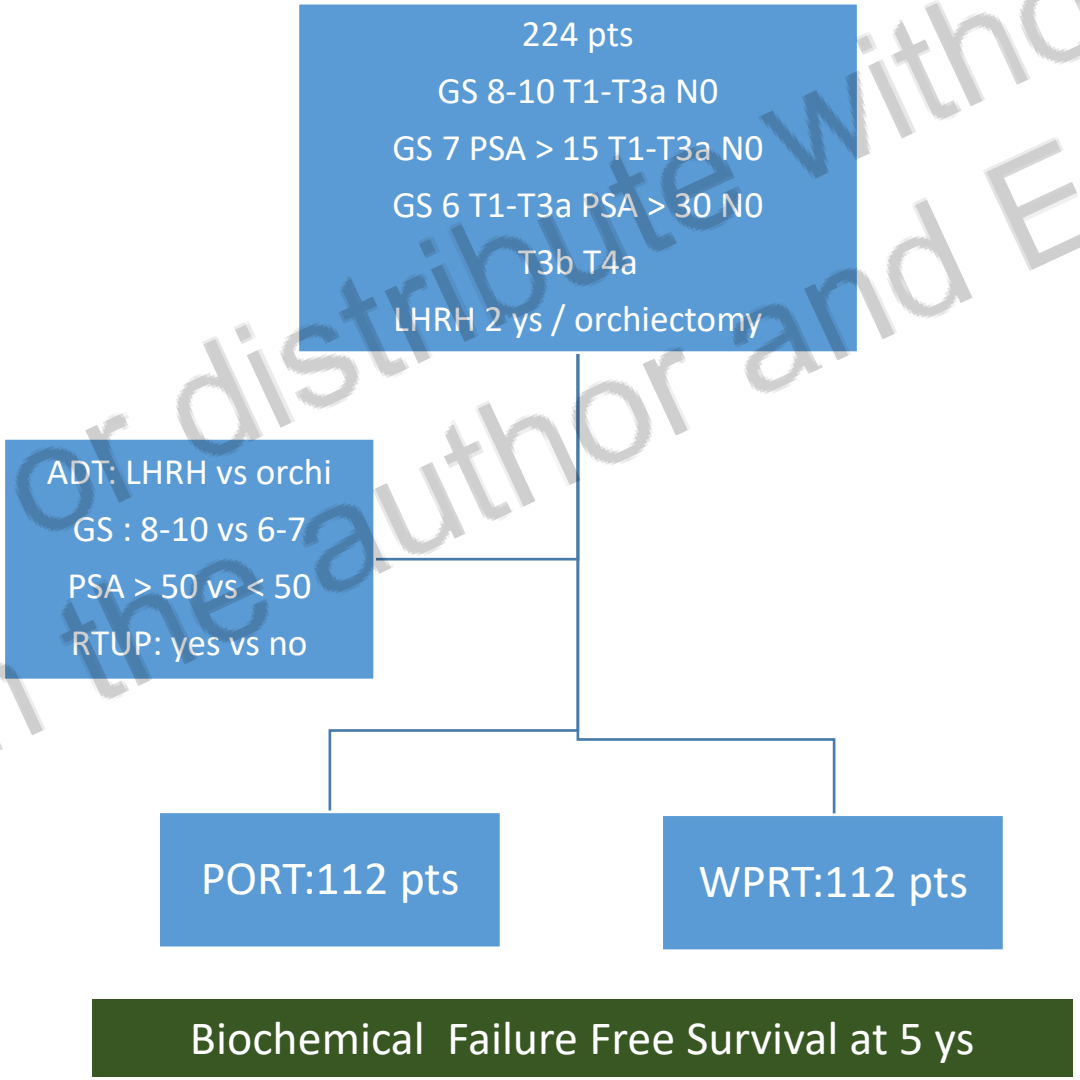




POP RT

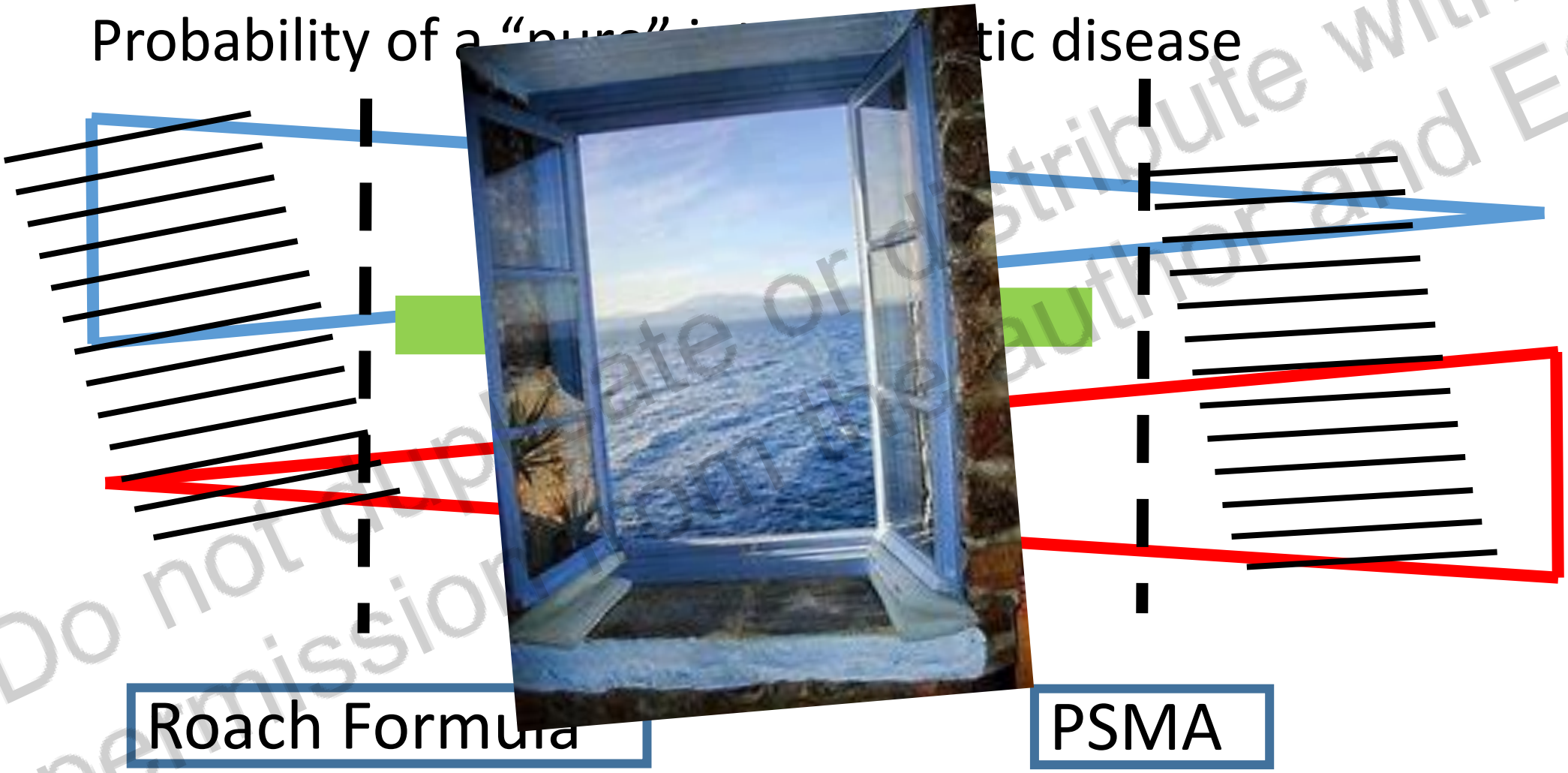
Murthy et al, JCO, 2021

	POP RT
Roach > 20	Median: 38% > 35%: 55% > 50%: 29%
Gleason	8-10: 49.1%
Staging	MRI, PSMA PET (80 %)
Pelvis	50Gy /25 fr
Prostate	68Gy / 25 fr SIB
Technique	IG-IMRT



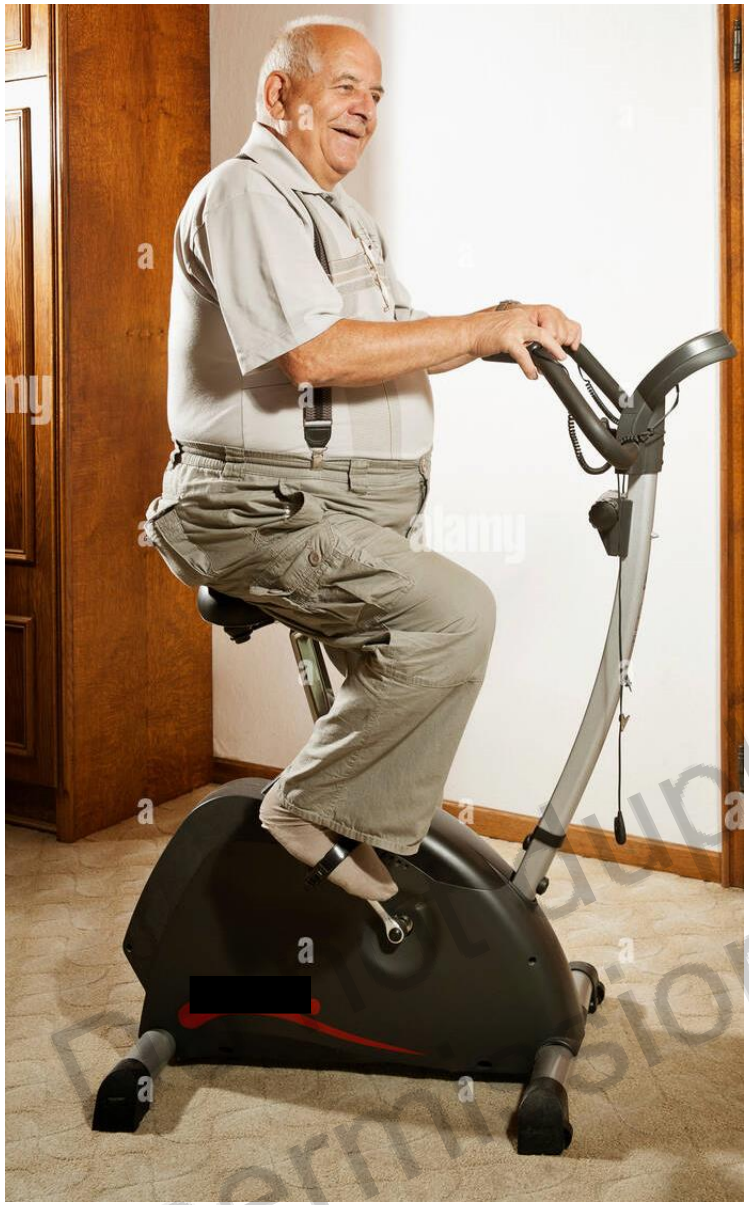
The “sliding window” of WPRT

Probability of a “pure” i tic disease



Roach Formula

PSMA



Clinical Investigations

Effects of Exercise During Radiation Therapy on Physical Function and Treatment-Related Side Effects in Men With Prostate Cancer: A Systematic Review and Meta-Analysis

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Colin Tang, MBBS, FRANZCR,*,‡ Raphael Chee, MBBS, FRANZCR,*,§
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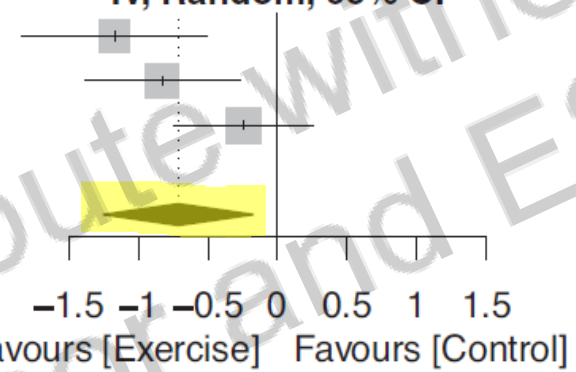
Schumacher, IJROBP, 2021

B. Urinary toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
McQuade et al. (2017)	1.51	7.63	19	10.33	7.17	22	29.3%	−1.17 [−1.84; −0.50]
Hojan et al. (2016)	1.90	18.50	27	16.40	16.00	27	34.1%	−0.83 [−1.38; −0.27]
Kapur et al. (2010)	0.68	0.64	29	0.86	0.81	33	36.7%	−0.24 [−0.74; 0.26]
Total (95% CI)			**75**			**82**	**100.0%**	**−0.71 [−1.25; −0.18]**

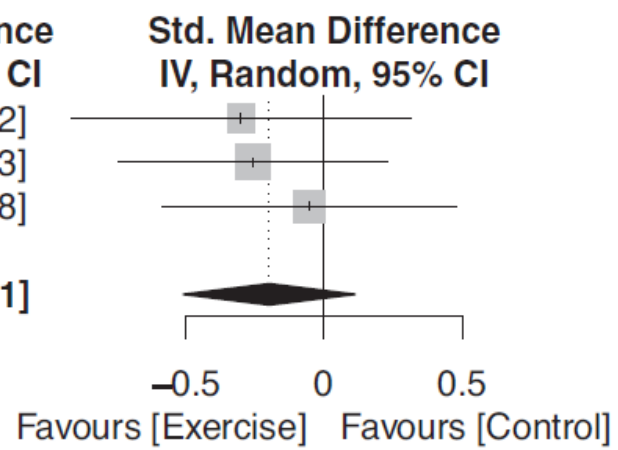
Heterogeneity: $Tau^2 = 0.1392$; $Chi^2 = 5.28$, df = 2 (P = 0.07); $I^2 = 62\%$
Test for overall effect: Z = −2.60 (P < 0.01)



C. Intestinal toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
McQuade et al. (2017)	4.16	11.06	19	7.44	10.34	22	25.4%	−0.30 [−0.92; 0.32]
Kapur et al. (2010)	1.48	0.83	32	1.66	0.52	33	40.6%	−0.26 [−0.75; 0.23]
Hojan et al. (2016)	8.83	13.67	27	9.67	17.23	27	34.0%	−0.05 [−0.59; 0.48]
Total (95% CI)			**78**			**82**	**100.0%**	**−0.20 [−0.51; 0.11]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = −1.25 (P = 0.21)



Schumacher, IJROBP, 2021

Conclusions/Take-Away

focal mpMRI guided boost

PRECISION / PERSONALIZED RT

extreme hypofractionation

pelvic lymph nodes irradiation