



Ente Ospedaliero Cantonale

THE PROSTATE CANCER JOURNEY: WHAT HAVE WE NOT TO FORGET?

*SESSION 7: BACK TO THE FUTURE:
PELVIS (PROSTATE, RECTUM, CERVIX)*

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Roma, October 10th 2023

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IN ONCOLOGIA

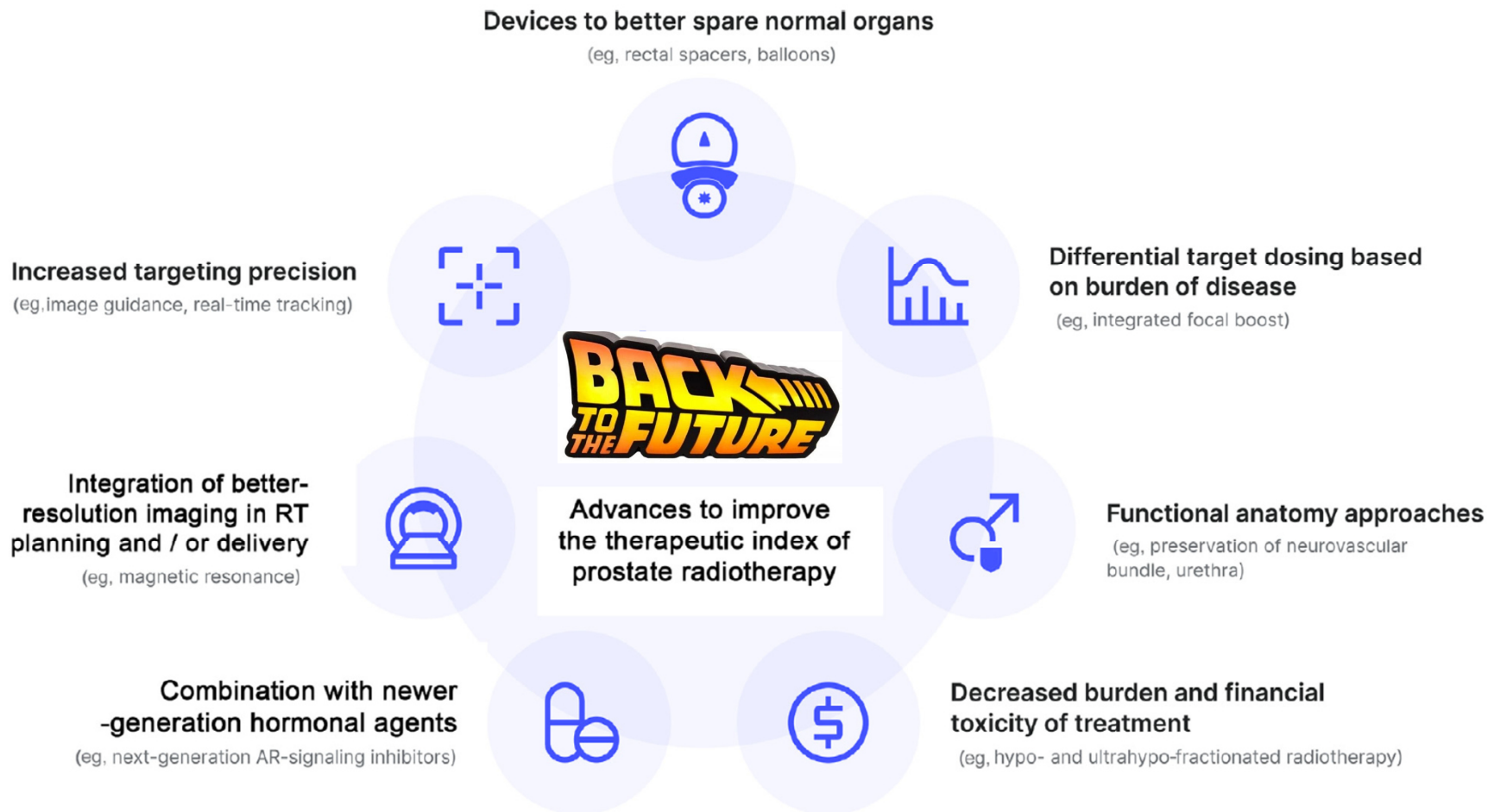
Istituto Oncologico della Svizzera Italiana
Oncology Institute of Southern Switzerland



Disclosures

- Honoraria - Travel costs: Janssen, Amgen, Ferring, Debiopharm, Bayer, Astellas, Telix, MVsion
- Research Grants: Varian Medical Systems, Debiopharm
- Advisory Boards: Janssen, Accord

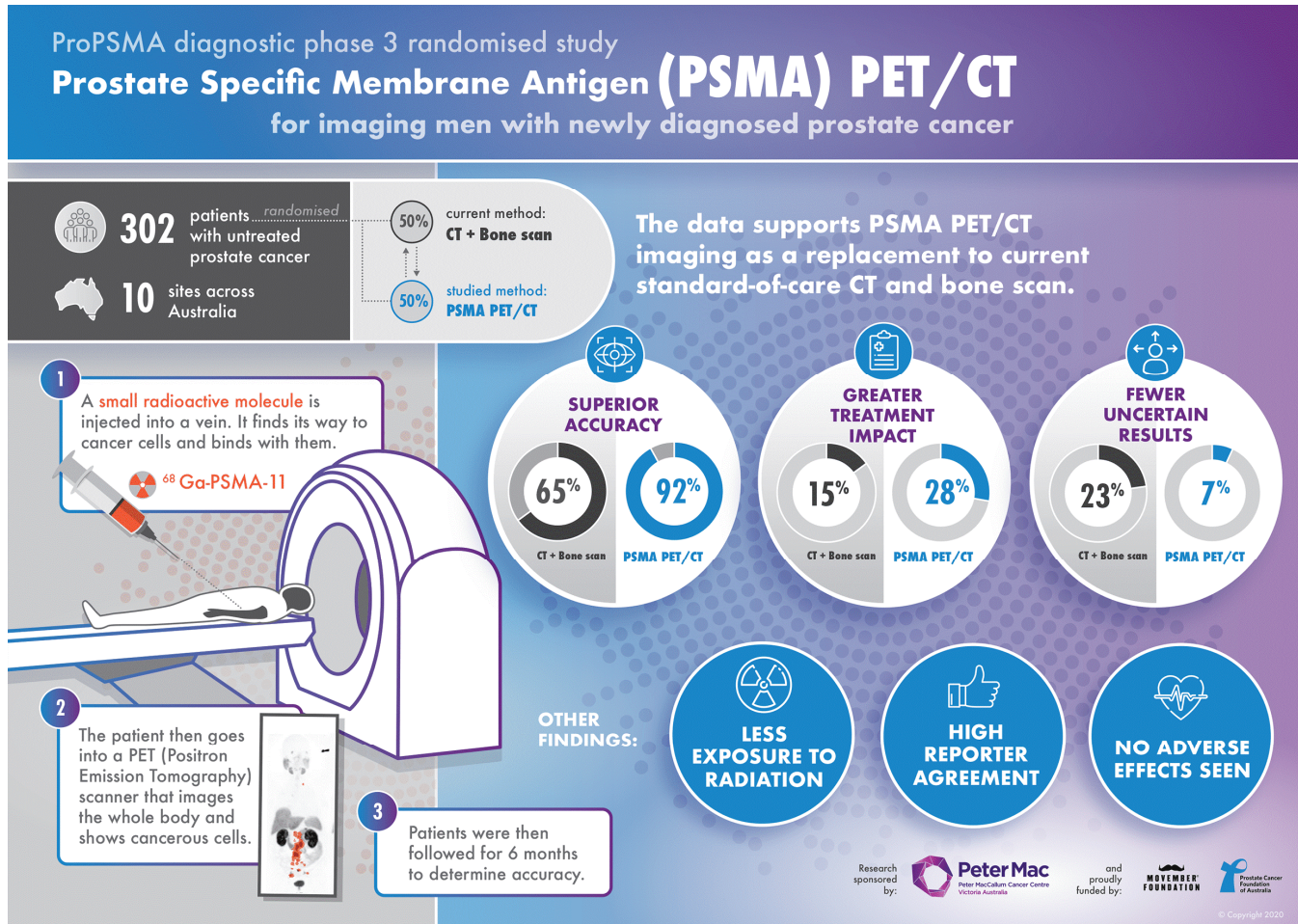
Therapeutic index: ways for improvement



Better-resolution imaging (staging and planning)



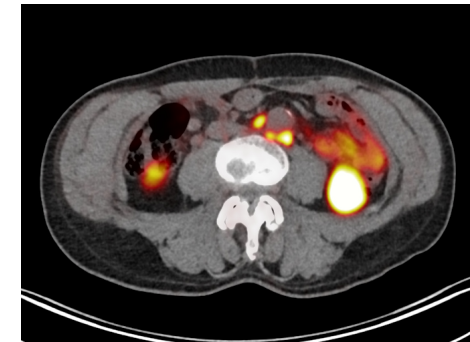
The molecular imaging



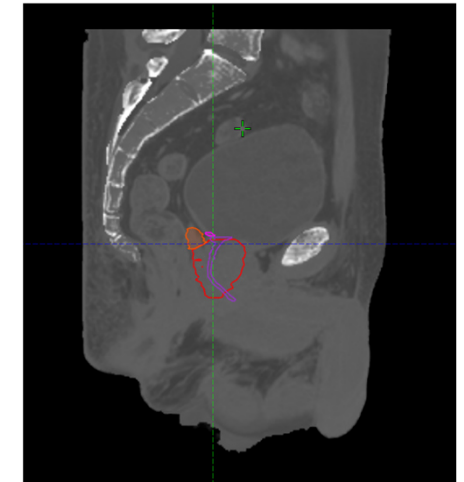
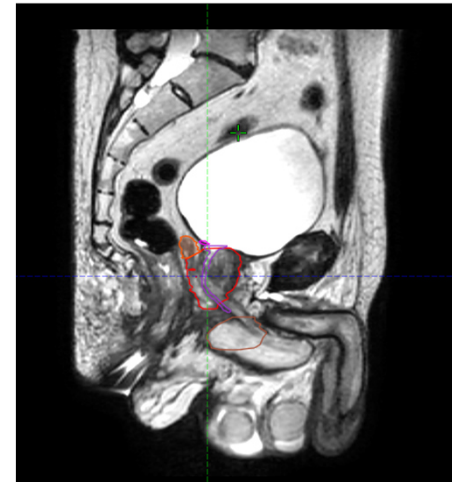
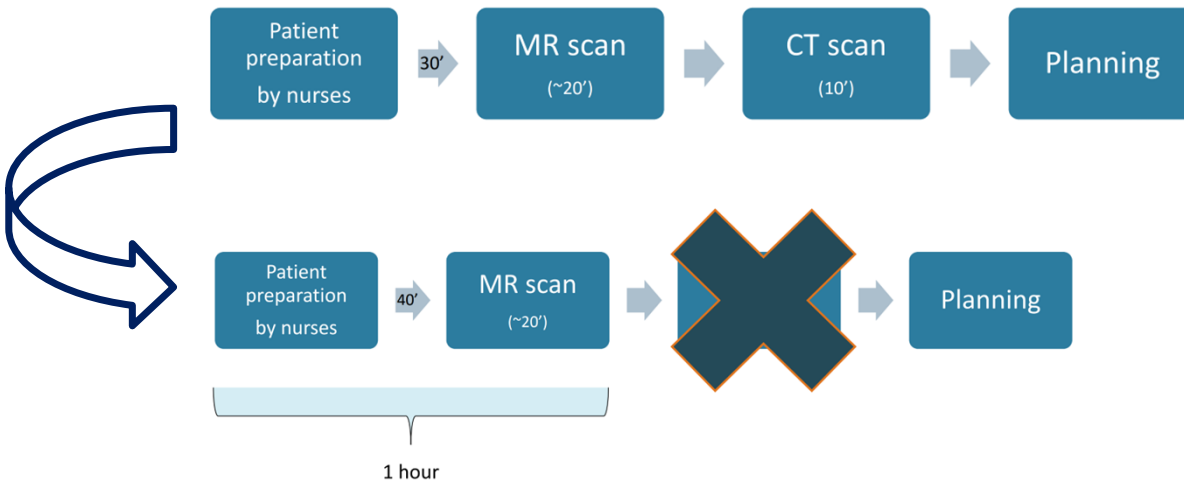
CT scan
Node negative



↓ PSMA PET/CT
Node positive



The planning MRI and synthetic CT



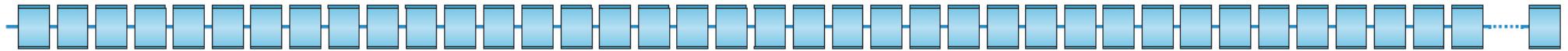
MRI-based planning contouring and synthetic CT (MRCAT, Magnetic Resonance for Calculating Attenuation)

More dose in less fractions

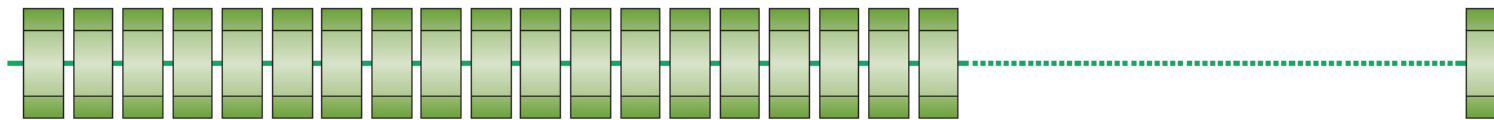


Hypofractionation

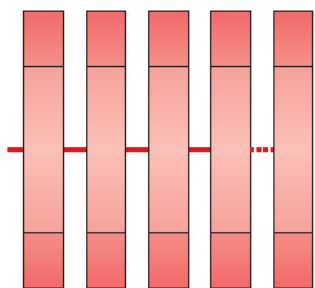
Conventional radiotherapy



Moderate hypofractionation



Extreme hypofractionation



	Fractionation schedule		
	Conventional	Moderate	Extreme
Total dose (Gy)	76–80	57–70.2	38–50
Total treatment duration (weeks)	8–9	4–6	1–2
Number of fractions (n)	38–40	19–30	4–5
Dose per fraction (Gy)	1.8–2	2.4–4	6–10
Interval between fractions (days)	1	1	1–2

5-fraction SBRT as a new standard

M Lifestyle Health Prostate cancer

Prostate cancer could be cured in one week thanks to incredible new treatment

It comes after Sir Rod Stewart revealed he has beaten the disease after a two-year battle

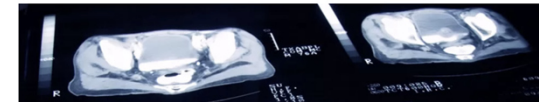


Prostate cancer trial: Radiotherapy doses can be cut safely

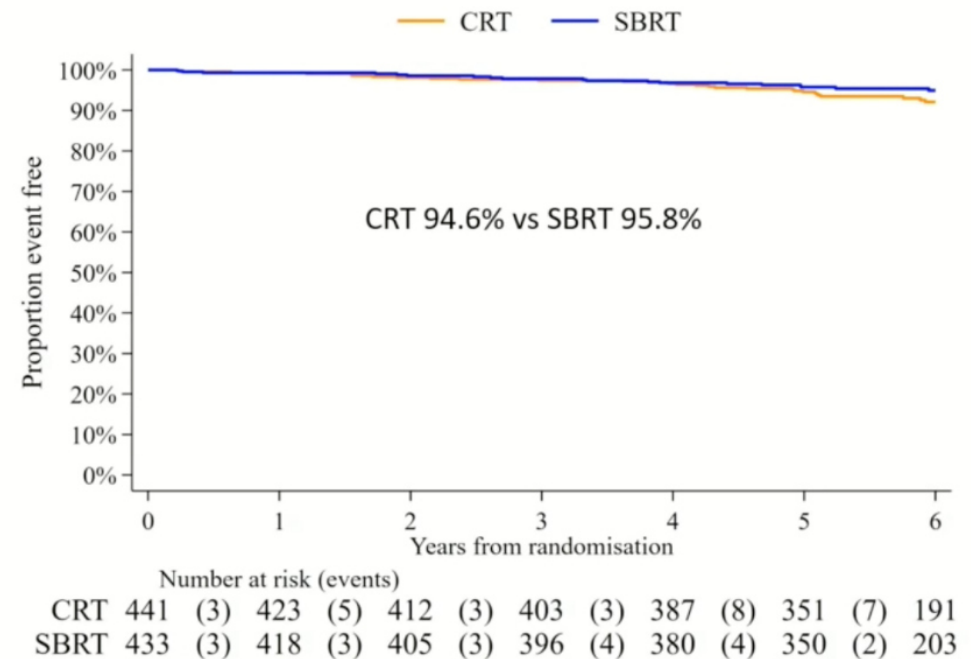
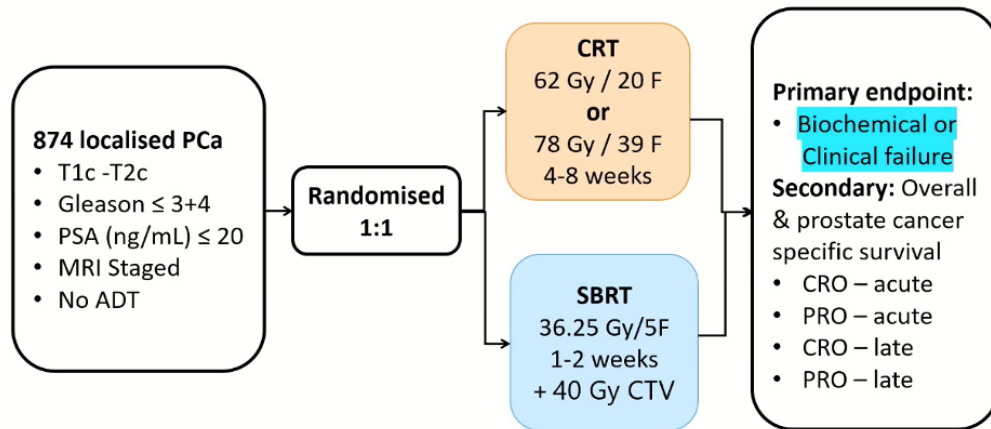
© 4 days ago

BBC

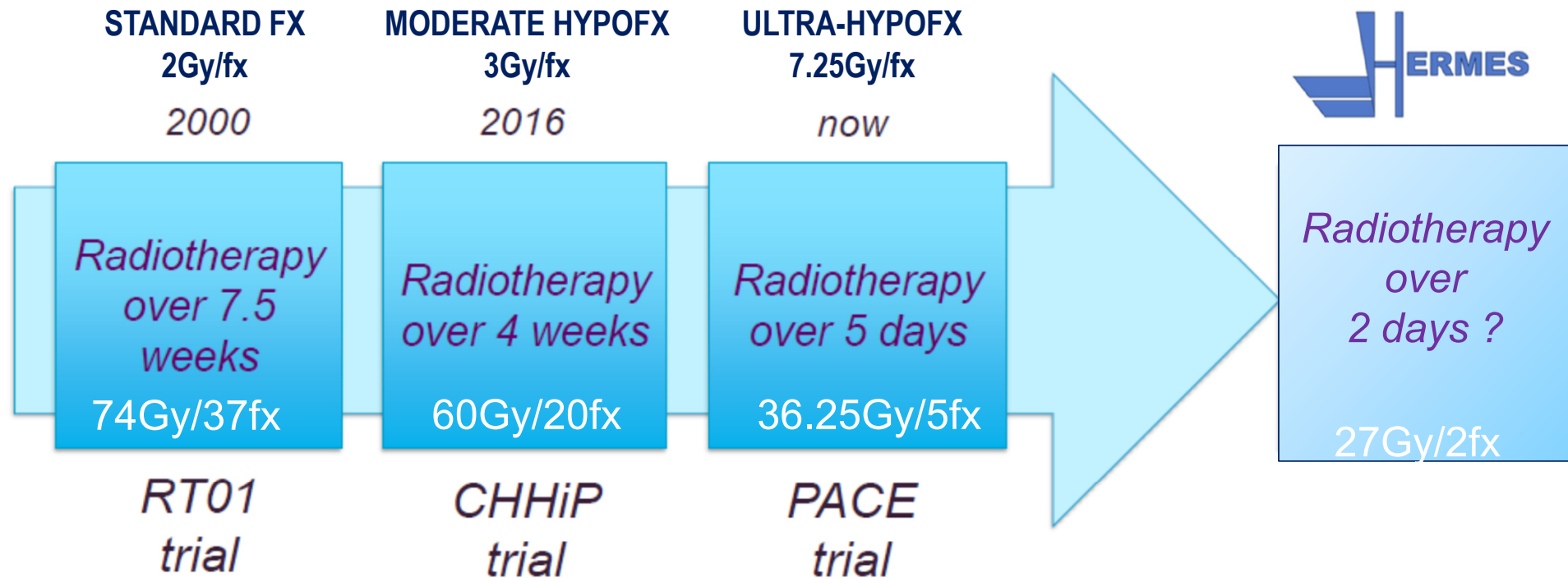
NEWS



PACE B trial schema & endpoints



The UK experience



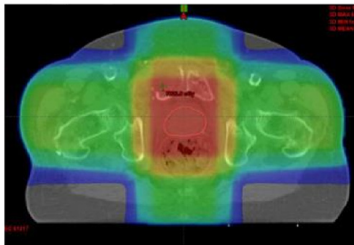
Increased targeting precision



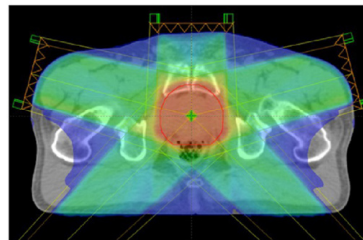
Better targeting and organ sparing

Adaptive RT (ART)

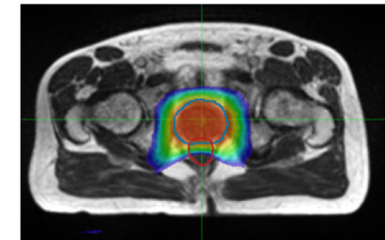
2D-RT



IMRT



MRI-based IMRT



1980

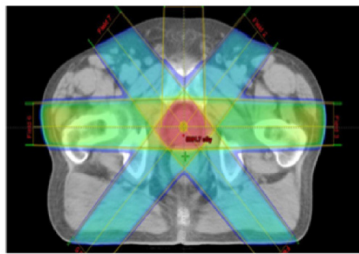
1990

2000

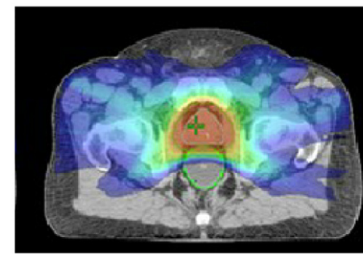
2010

2020

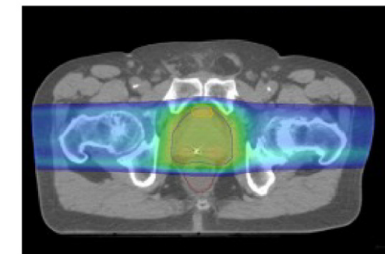
Years



3D-CRT

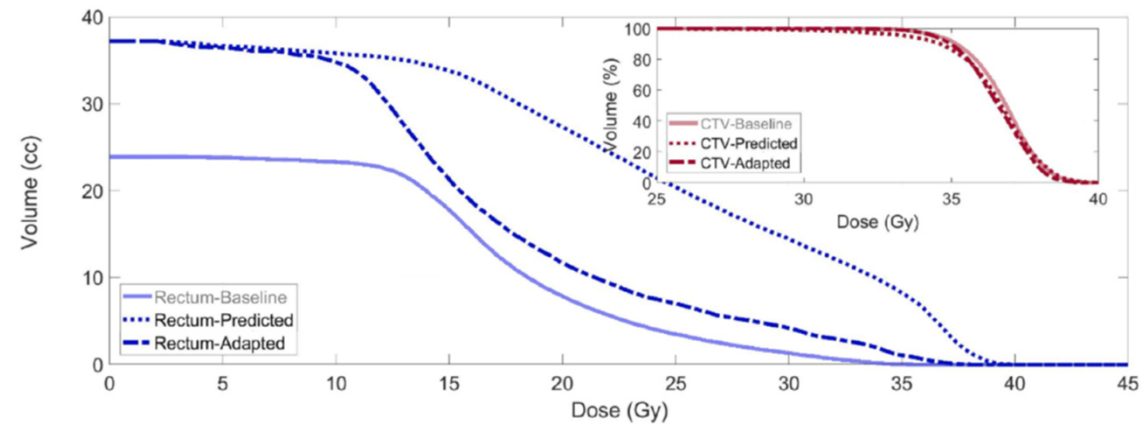
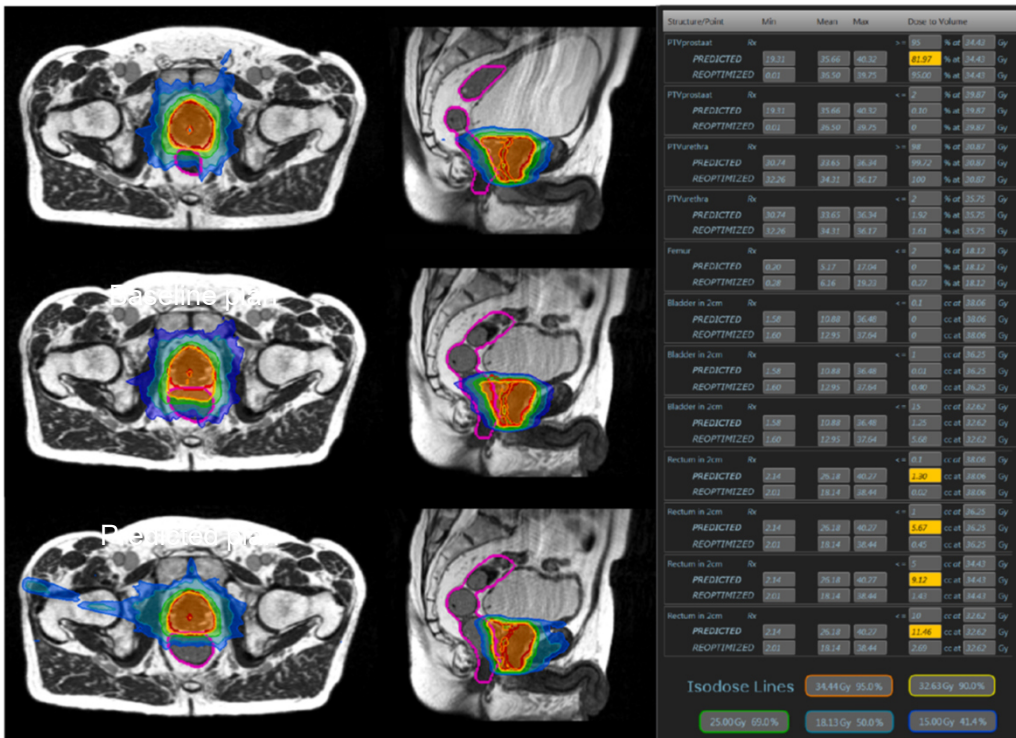


VMAT



IMPT-protons

Why adaptive radiotherapy (ART)?



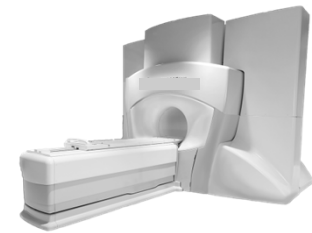
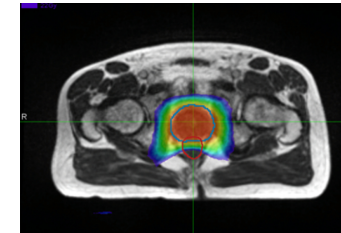
Daily online adaptive MRgRT can spare OARs from unplanned RT dose

MR-based adaptive radiotherapy

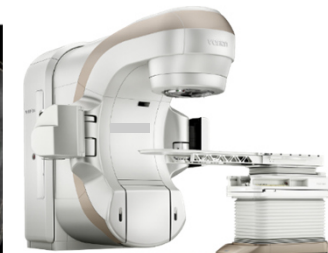
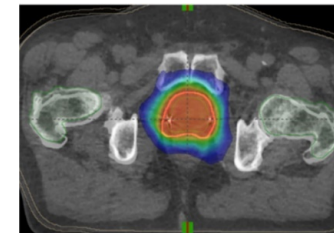
JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer The MIRAGE Randomized Clinical Trial

Amar U. Kishan, MD; Ting Martin Ma, MD, PhD; James M. Lamb, PhD; Maria Casado, BS; Holly Wilhalme, MSc; Daniel A. Low, PhD; Ke Sheng, PhD; Sahil Sharma, BS; Nicholas G. Nickols, MD, PhD; Jonathan Pham, PhD; Yingli Yang, PhD; Yu Gao, PhD; John Neylon, PhD; Vincent Basehart, BS; Minsong Cao, PhD; Michael L. Steinberg, MD



VS



POPULATION

156 Men



Men with clinically localized prostate adenocarcinoma receiving stereotactic body radiotherapy (SBRT)

Median age, 71 y

LOCATION



One large US medical center

INTERVENTION

154 Participants randomized and analyzed



76 CT-guided SBRT

SBRT to the prostate using computed tomography (CT) guidance and a standard 4-mm planning margin

78 MRI-guided SBRT

SBRT to the prostate using magnetic resonance imaging (MRI) guidance with a 2-mm planning margin

No ATS (adapt-to-shape)

PRIMARY OUTCOME

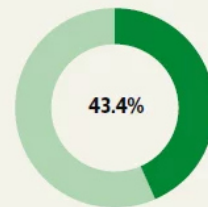
Incidence of acute grade ≥ 2 genitourinary (GU) toxic effects from the start of SBRT to ≤ 90 d post-SBRT, as measured by the Common Terminology Criteria for Adverse Events, version 4.03 scale

FINDINGS

Incidence of acute grade ≥ 2 GU toxic effects was significantly lower with MRI-guided SBRT compared with CT-guided SBRT

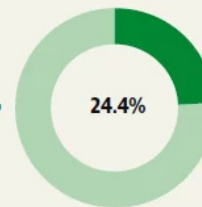
Proportion with acute grade ≥ 2 GU toxic effects

CT-guided SBRT



95% CI, 32.1%-55.3%

MRI-guided SBRT



95% CI, 15.4%-35.4%

P value for comparison = .01

Compared with CT-guidance, MRI-guided SBRT significantly reduce both moderate acute physician-scored toxicities and decrements in patient-reported QoL

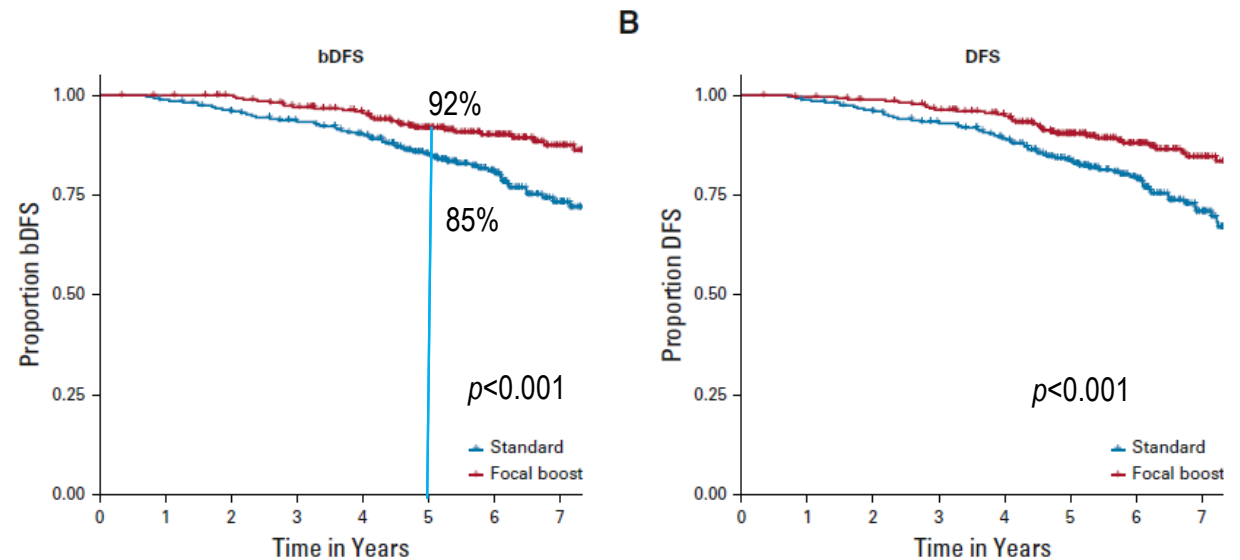
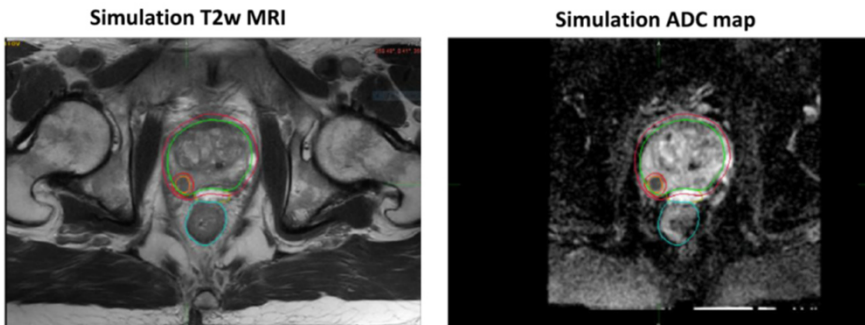
Differential target dosing



Dose escalation: focal boosting

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

- Phase III, RCT, multicenter Dutch
- 571 high-risk pts
- PORT (77Gy/35#) +/- focal boost (95Gy/35#)
- Median FU: 72 mo



*Similar late toxicity and impact on health-related QoL
No differences in OS and CSS*

	GU Toxicity				GI Toxicity			
	77 Gy	95 Gy	Difference in % (95% CI)	P	77 Gy	95 Gy	Difference in % (95% CI)	P
Grade ≥ 2	23.0	27.8	4.8 (-2.3 to 12.0)	.19	12.2	12.7	0.5 (-5.0 to 5.9)	.86
Grade ≥ 3	3.5	5.6	2.1 (-1.3 to 5.6)	.22	1.4	1.4	0 (-1.9 to 2.0)	.99

Better organs at risk sparing and functional anatomy approaches



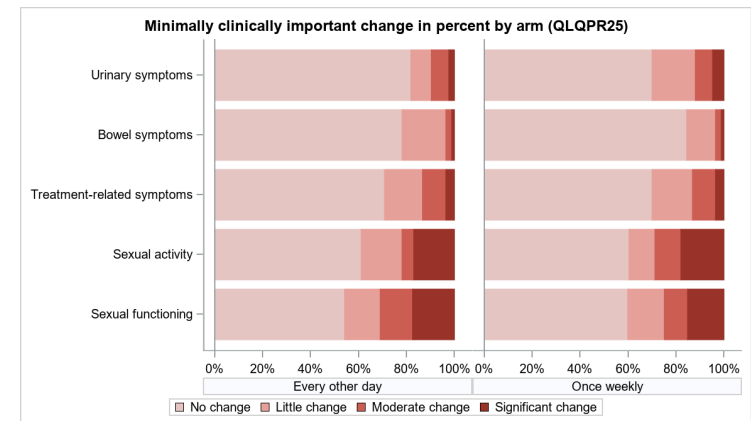
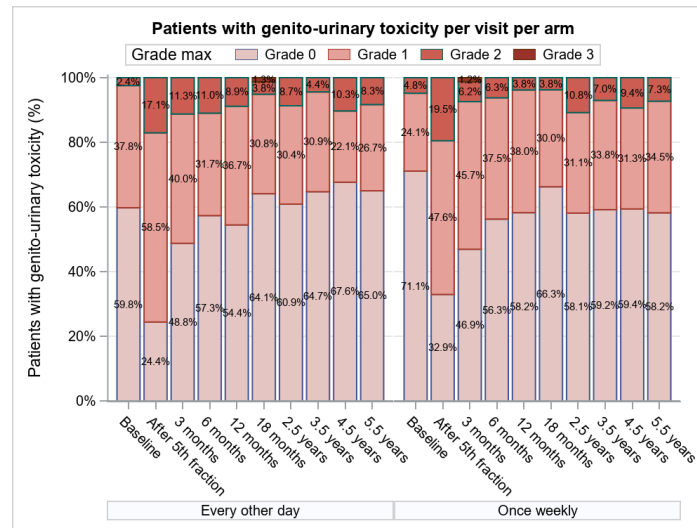
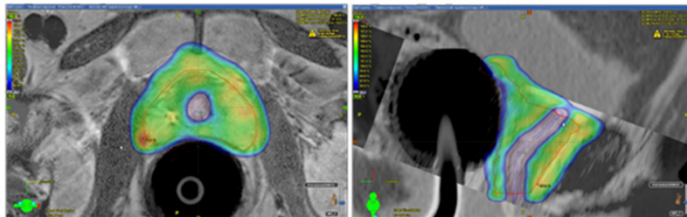
Urethra-sparing

NOVALIS CIRCLE trial (NCT01764646)

Eligibility
cT1c-T3a; GS ≤ 7;
Roach index for N+ ≤ 20%
IPSS < 19
WHO 0-1

Arm A
7.25 Gy x 5 fx
9 days,
every other day

Arm B
7.25 Gy x 5 fx
28 days,
once a week



**SBRT: 7.25 Gy in 5 fx with dose reduction to urethra PRV (6.5 Gy in 5 fx)
Less than 10% of long-term G2+ GU toxicity and minimal impact on QoL**

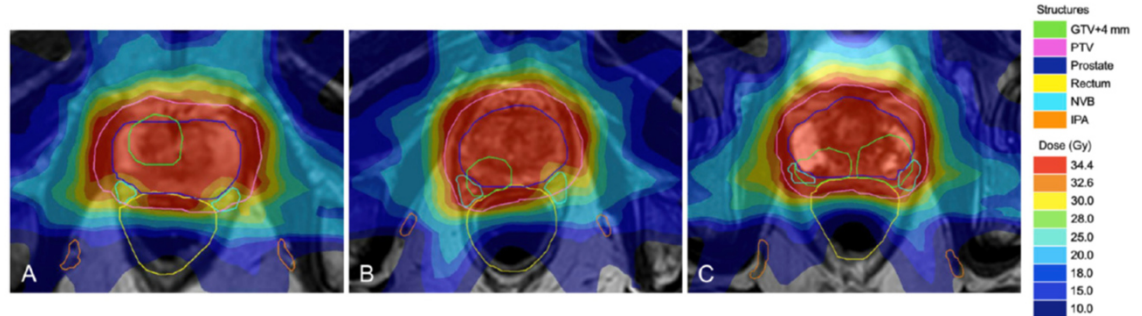
Erectile function preservation

Original Research Article

Adaptive magnetic resonance-guided neurovascular-sparing radiotherapy for preservation of erectile function in prostate cancer patients

Frederik R. Teunissen^{a,*}, Ruud C. Wortel^b, Jochem Hes^a, Thomas Willigenburg^a, Eline N. de Groot-van Breugel^a, Johannes C.J. de Boer^a, Harm H.E. van Melick^c, Helena M. Verkooijen^{d,e}, Jochem R.N. van der Voort van Zyp^a

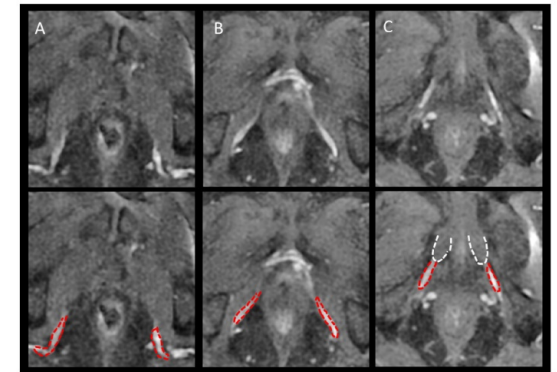
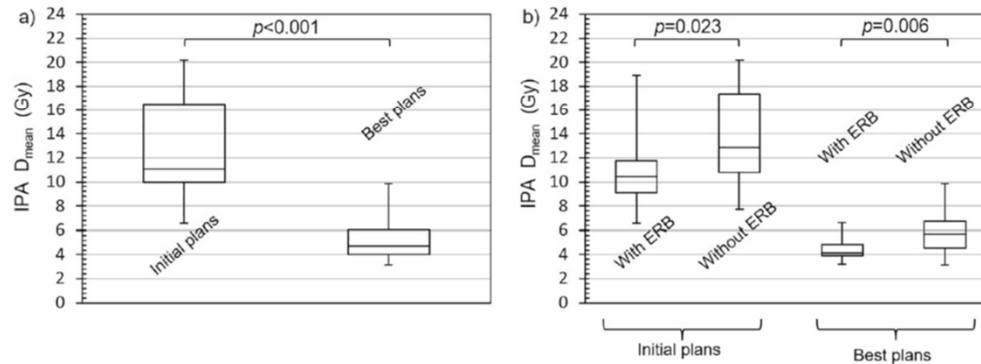
^a Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, The Netherlands
^b Department of Urology, University Medical Center Utrecht, Utrecht, The Netherlands
^c Department of Urology, St. Antonius Hospital, Nieuwegein, Utrecht, The Netherlands
^d Imaging and Oncology Division, University Medical Center Utrecht, Utrecht, The Netherlands
^e Utrecht University, Utrecht, The Netherlands



Dose optimization and endorectal balloon for internal pudendal arteries sparing in prostate SBRT

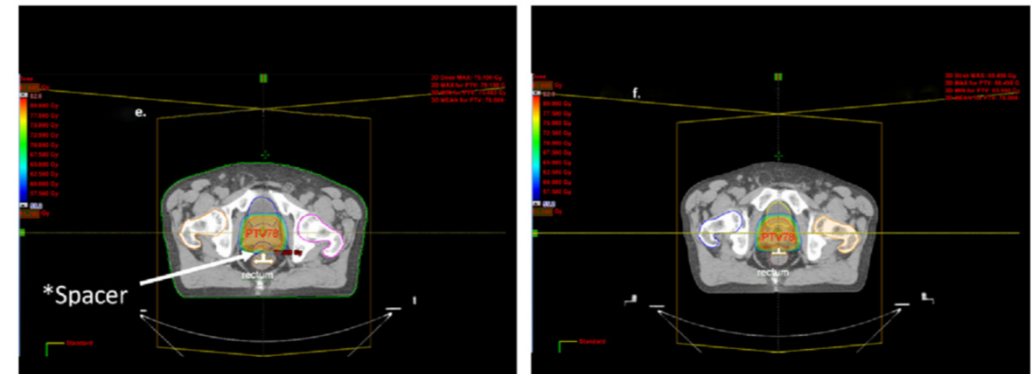
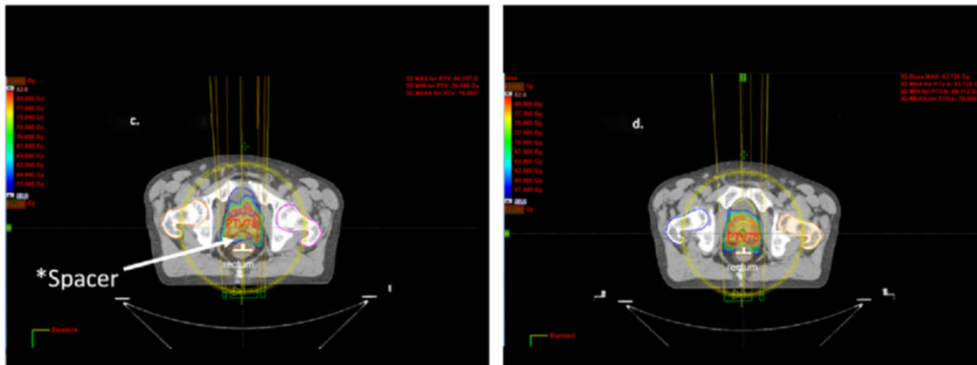
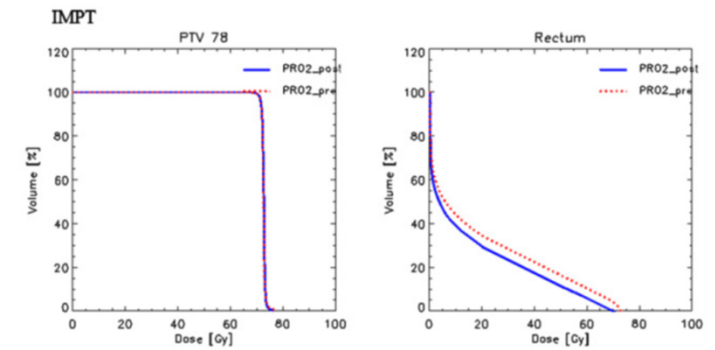
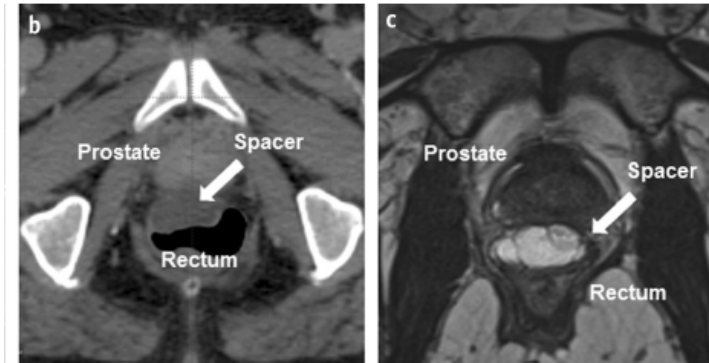
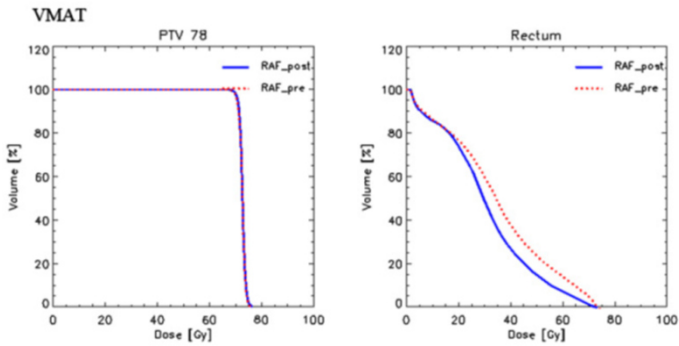
Maud Jaccard^{a,*}, Giorgio Lamanna^a, Angèle Dubouloz^a, Michel Rouzaud^a, Raymond Miralbell^{a,b,c}, Thomas Zilli^{a,b}

^a Radiation Oncology, University Hospital of Geneva, Geneva, Switzerland
^b Faculty of Medicine, Geneva University, Geneva, Switzerland
^c Radiation Oncology, Teknon Oncologic Institute, Barcelona, Spain



Optimization on penile base structures is feasible and may improve sexual function

Rectal preservation



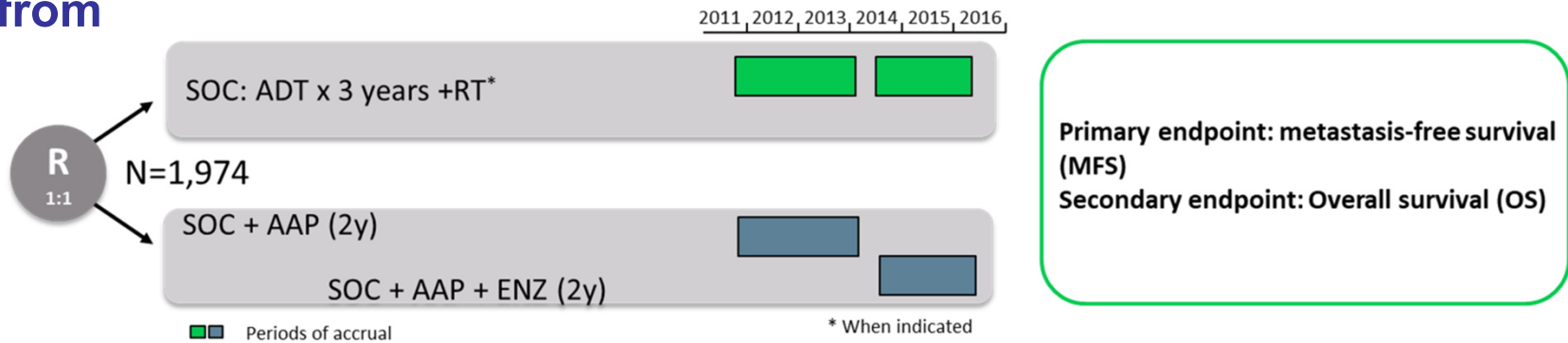
Rectal sparing with recto-prostatic spacers improves dosimetry and may mitigate rectal toxicity

Intensified systemic treatments



Systemic treatment intensification

Meta-analysis from 2 STAMPEDE phase III RCT



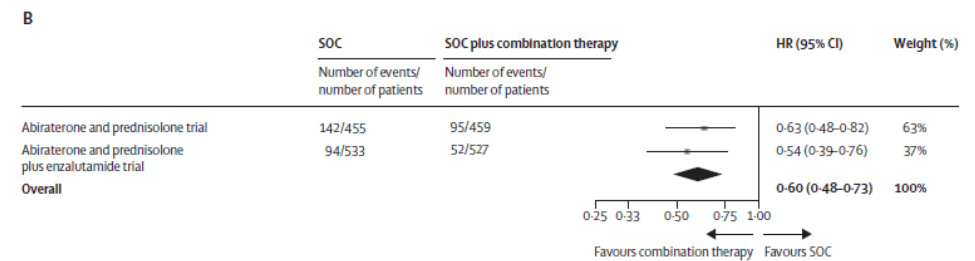
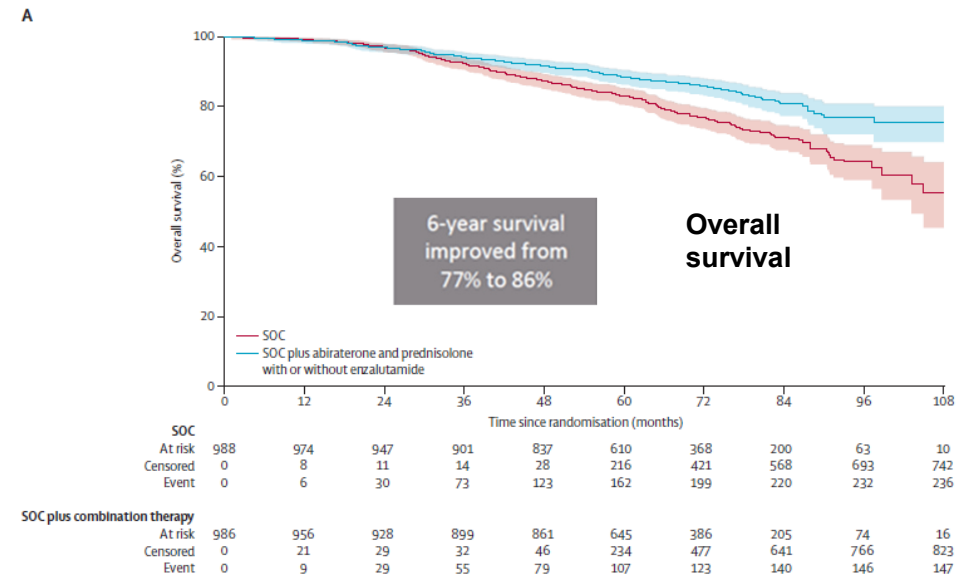
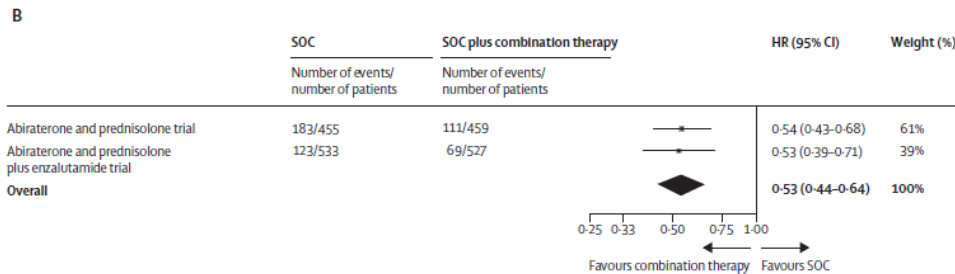
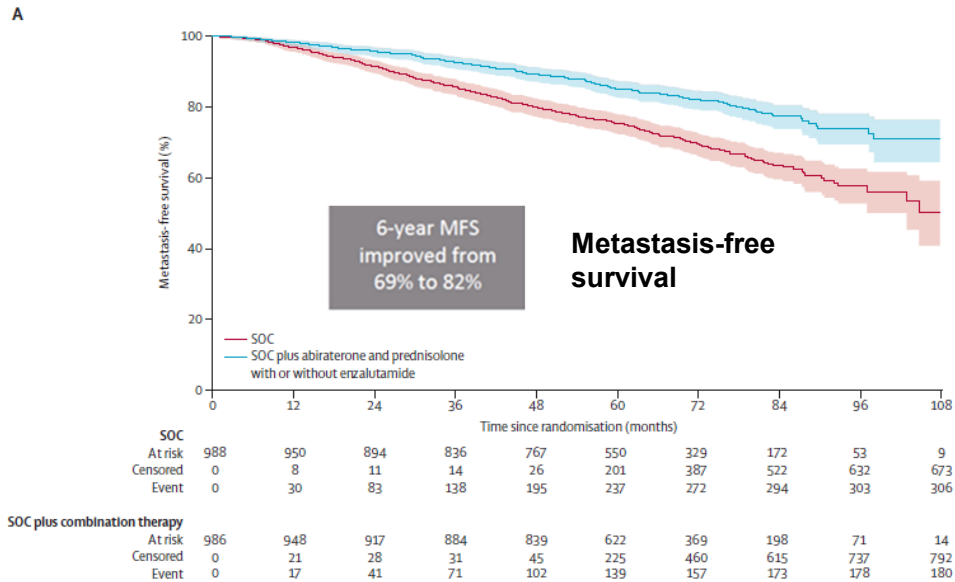
AAP, abiraterone and prednisone; ADT, androgen deprivation therapy; APA, apalutamide; ENZ, enzalutamide; M0, non-metastatic; M1, metastatic; MFS, metastasis-free survival; OS, overall survival; PCa, prostate cancer; RT, radiotherapy; SOC, standard of care
 Attard G, et al. Abstract #LBA4_PR. ESMO 2021. Oral presentation

RT : btw 81% and 89% of the pts (74 Gy +/- WPRT)
RT : 99% cN0 ; 71% cN1

Patient population

M0 No evidence of metastases on bone and CT scan of pelvis, abdo, chest (pre-defined stratification criterion)	Newly-diagnosed Any of: <ul style="list-style-type: none"> • Node-Positive • ≥2 of: Stage T3 or T4 PSA ≥40ng/ml Gleason 8, 9 or 10 	Relapsing after previous RP or RT Any of: <ul style="list-style-type: none"> • Node-positive • PSA ≥4ng/ml, rising & doubling time <6m • PSA ≥20ng/ml 	All patients Written informed consent Fit for all protocol treatment Fit for follow-up Full criteria: www.stampetrials.org
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Systemic treatment intensification



Improved patient selection



Genomic classifier-based risk profile

Analysis of a Biopsy-Based Genomic Classifier in High-Risk Prostate Cancer: Meta-Analysis of the NRG Oncology/Radiation Therapy Oncology Group 9202, 9413, and 9902 Phase 3 Randomized Trials

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**RTOG 94-13:
RT + 4 months ADT**

**RTOG 92-02:
RT + 4 months ADT
vs
RT + 28 months ADT**

**RTOG 99-02:
RT + 24 months ADT**

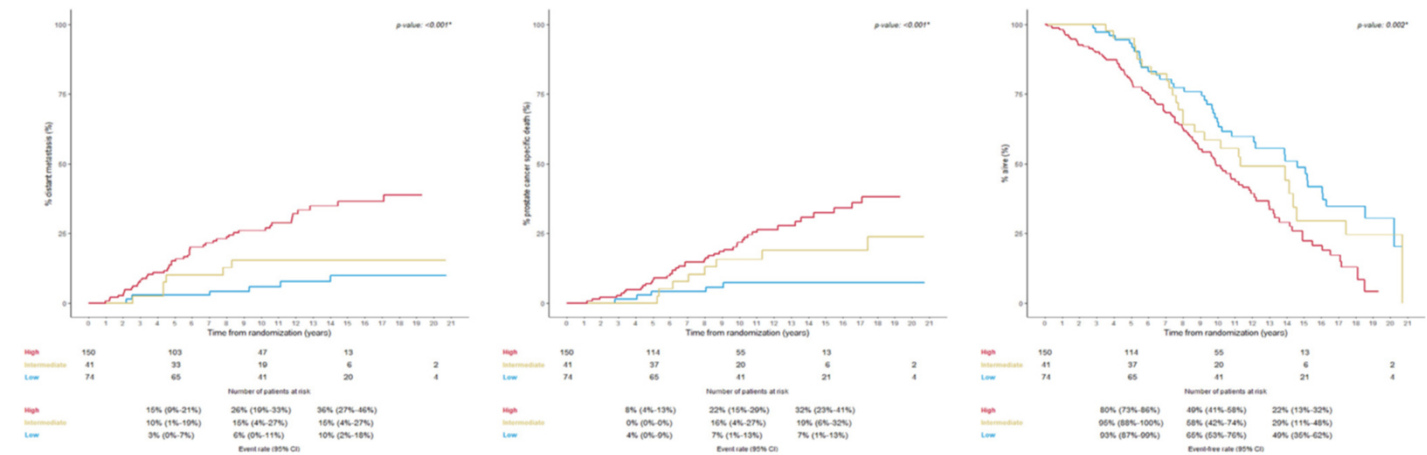


Table 2 Multivariable models

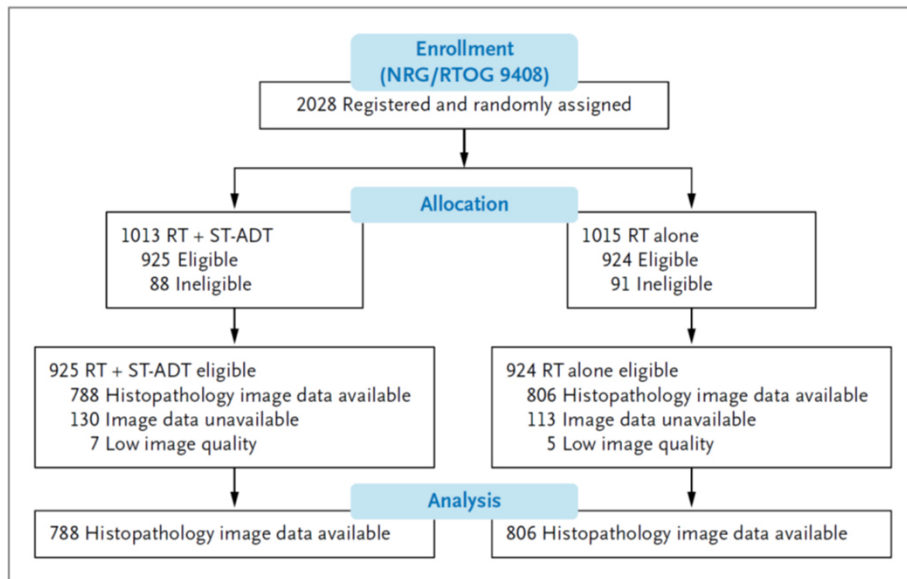
Variable	Hazard ratio (95% CI), P value		
	DM	PCSM	OS
GC score	1.22 (1.09-1.36), <.001*	1.23 (1.09-1.39), <.001*	1.12 (1.05-1.20), <.001*
Age	1.00 (0.96-1.04), .98	1.00 (0.96-1.04), .97	1.07 (1.04-1.10), <.001*
Log ¹⁰ pretreatment PSA	0.99 (0.80-1.22), .91	0.96 (0.78-1.18), .68	1.01 (0.88-1.15), .90
T3-T4 vs T1-T2	1.52 (0.89-2.62), .13	1.40 (0.80-2.43), .24	1.19 (0.85-1.67), .30
Gleason 8-10 vs <8	2.46 (1.41-4.31), .002*	1.31 (0.73-2.36), .36	1.40 (0.99-1.99), .06

Hazard ratios of genomic classifiers were per 0.1-unit increased. Strata = original arm. Death was considered a competing risk for DM and PCSM.
Abbreviations: CI = confidence interval; DM = distant metastases; GC = genomic classifier;
OS = overall survival; PCSM = prostate cancer-specific mortality; PSA = prostate specific antigen.

Genomic classifier on pre-treatment biopsies of high-risk prostate cancer is independently associated with distant metastasis, prostate cancer-specific mortality and overall survival

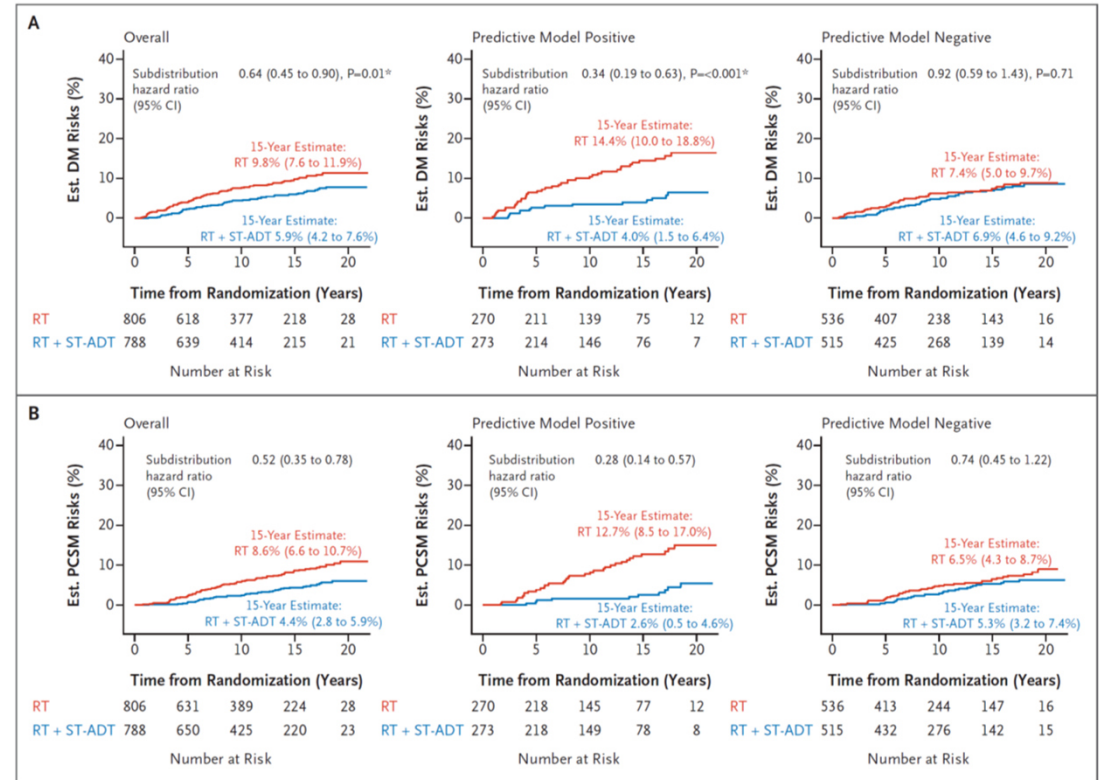
Artificial intelligence digital pathology predictive model

Artificial Intelligence Predictive Model for Hormone Therapy Use in Prostate Cancer



14.9 years of median follow-up

Only 34% of the patients (model positive) benefit from short-term androgen deprivation to reduce the risk of distant metastases



Back to the future: a future of more and less!



- **More dose per fraction in less fractions** (hypofractionation & SBRT)
- **More precision** (IGRT, adaptive & molecular imaging)
- **More disease control** (optimized RT & systemic treatments)
- **Less side effects** (IGRT & treatment optimization)
- **Less overtreatments** (GC and AI models)

THANK YOU FOR YOUR ATTENTION



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DE GENÈVE**



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