SISTEMA SANITARIO REGIONALE

AZIENDA OSPEDALIERO-UNIVERSITARIA SANT'ANDREA

REGIONE LAZIO

SAPIENZA UNIVERSITÀ DI ROMA

TUMORE DELLA PROSTATA: LO STATO DELL'ARTE

RADIOTERAPIA

Maurizio Valeriani

OSPEDALE SANDRO PERTINI

DIPARTIMENTO CHIRURGICO MISTO DI AREA CHIRURGICA

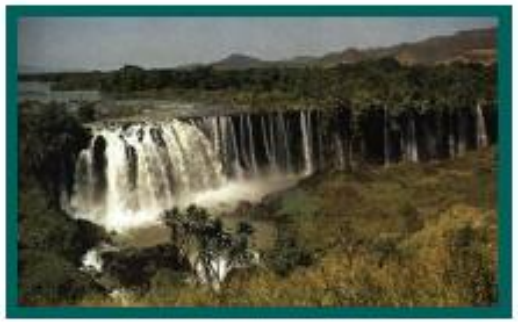
Coordinatore: Prof. Attilio Rota

UOC CHIRURGIA

Direttore Dott. Roberto Bruni

Chirurgia Urologica

Dirigente Responsabile: Prof. Massimo Schiavone



LA CHIRURGIA UROLOGICA ROMANA

2018

27 anni di chirurgia urologica all'Ospedale Sandro Pertini

XV Corso Teorico-Pratico per Medici e Infermieri

Presidenti

Dott. Roberto Bruni

Prof. G. Mazzocconi

Direttore

Prof. M. Schiavone

Roma, 26 – 27 Gennaio 2018

Epidemiologia

- 186.320 nuovi casi negli USA nel 2008
- Seconda causa di morte per cancro negli USA
- Età media >70 aa
- Razza nera/bianca = 1.5-2.0/1 (USA)
- Adenocarcinoma (≈95%)
- Spesso multifocale
- 42.804 nuovi casi in Italia (2005)
- 153/100000 abitanti (2005)
- 9925 nuovi casi nel centro Italia (2005)
- 4853 nuovi casi nelle regioni Lazio, Abruzzo e Molise (2005)

TABELLA II - Classi di rischio NCCN

Rischio molto basso

- T1c
- Gleason score <6
- PSA <10 ng/mL
- Meno di tre frustoli agobioptici positivi, con adenocarcinoma della prostata riscontrato in meno del 50% in ogni frustolo
- PSA density <0.15 ng/mL/g

Rischio basso

- T1-T2a
- Gleason score <6
- PSA <10 ng/mL

Rischio intermedio

- T2b-T2c o
- Gleason score 7 o
- PSA 10-20 ng/mL

Rischio alto

- T3a o
- Gleason score 8-10 o
- PSA >20 ng/mL

Molto alto

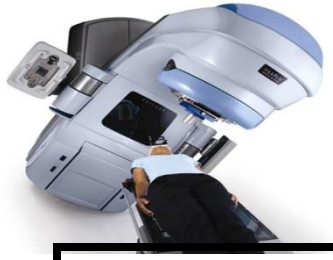
- T3b - T4 o
- Pattern primario di Gleason 5 o
- Più di quattro frustoli con Gleason score 8-10

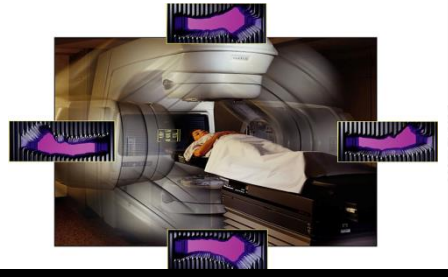
Prostatectomia radicale

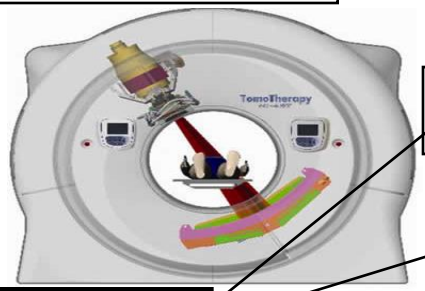
"Nerve sparing"

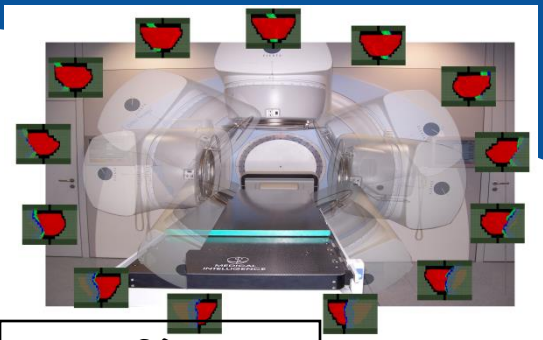
Prostatectomia laparoscopica
Chirurgia robotica

o









3D

IMRT

RT conformazionale

Proton

IGRT

High dose conformal

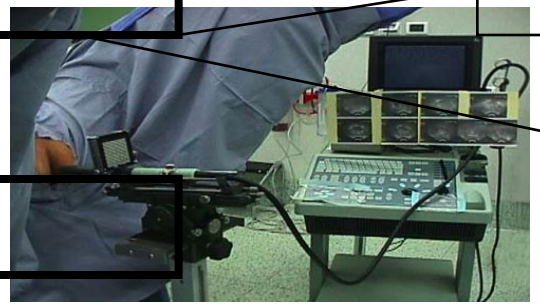
o

Dose escalation

Ipofx

BRT

HDR



LDR

HIFU

o

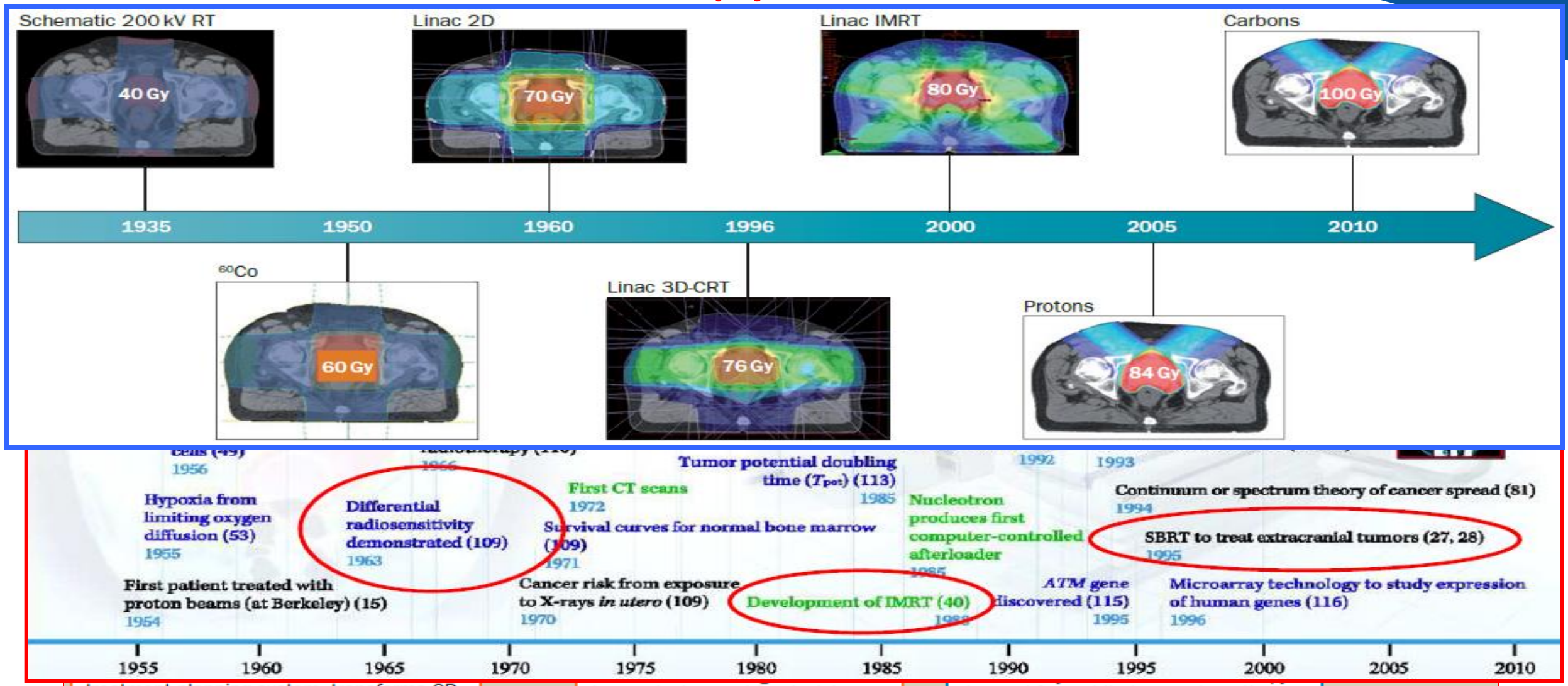
RITA

BRT/RT esterna

Crioterapia

+/- OT

Evolution of Radiotherapy



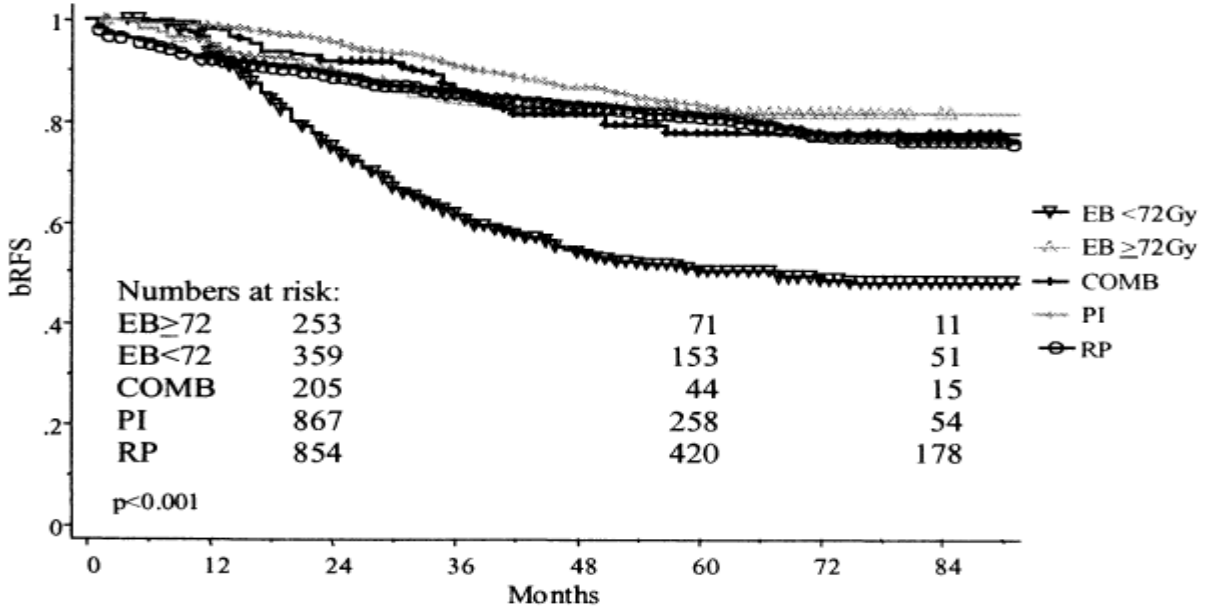
treatment planning system, transforms 2D external-beam radiotherapy to 3D conformal radiotherapy

increasingly used for decision making in 3D conformal radiotherapy planning

is used for mobile tumour targeting enabling robotic image-guided technology to track targets in real time

Cancer Res 2009; 69: (2), 2009

Thariat, J *et al. Nat. Rev. Clin. Oncol.* 10, 2013



2991 pts	# pt.	bNED @ 7 yy
Prostatectomy	1034	76%
3D-CRT < 72 Gy (median 68.4 Gy)	484	48%
3D-CRT ≥ 72 Gy (median 78 Gy)	301	81%
BRT (^{103}Pd or ^{125}I)	950	75%
Comb: RT + BRT	222	77%

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 1, pp. 25–33, 2004

0360-3016/04/$–see front matter
ELSEVIER
doi:10.1016/S0360-3016(03)00784-3

CLINICAL INVESTIGATION **Prostate**

RADICAL PROSTATECTOMY, EXTERNAL BEAM RADIOTHERAPY <72 Gy, EXTERNAL BEAM RADIOTHERAPY ≥72 Gy, PERMANENT SEED IMPLANTATION, OR COMBINED SEEDS/EXTERNAL BEAM RADIOTHERAPY FOR STAGE T1–T2 PROSTATE CANCER

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*Department of Radiation Oncology, M. D. Anderson Cancer Center Orlando, Orlando, FL; †Department of Radiation Oncology, Memorial Sloan-Kettering at Mercy Medical Center, Rockville Centre, NY; ‡Department of Radiation Oncology and the Urological Institute, Cleveland Clinic Foundation, Cleveland, OH

Purpose: To review the biochemical relapse-free survival (bRFS) rates after treatment with permanent seed implantation (PI), external beam radiotherapy (EBRT) <72 Gy (EBRT <72), EBRT ≥72 Gy (EBRT ≥72), combined seeds and EBRT (COMB), or radical prostatectomy (RP) for clinical Stage T1-T2 localized prostate cancer treated between 1990 and 1998.

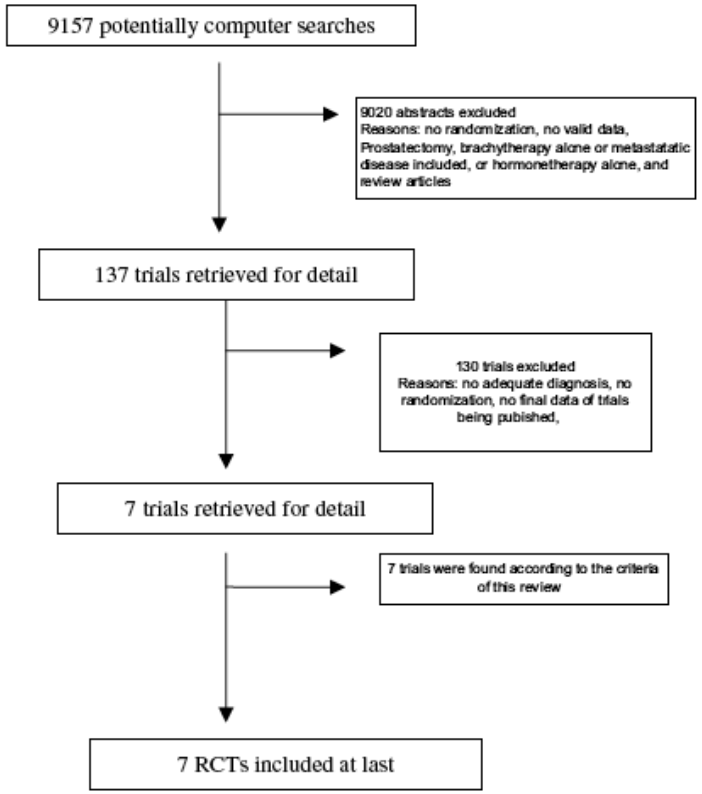
Methods and Materials: The study population comprised 2991 consecutive patients treated at the Cleveland Clinic Foundation or Memorial Sloan Kettering at Mercy Medical Center. All cases had pretreatment prostate-specific antigen (iPSA) levels and biopsy Gleason scores (bGSs). Neoadjuvant androgen deprivation for ≤6 months was given in 622 cases (21%). No adjuvant therapy was given after local therapy. RP was used for 1034 patients (35%), EBRT <72 for 484 (16%), EBRT ≥72 for 301 (10%), PI for 950 (32%), and COMB for 222 patients (7%). The RP, EBRT <72, EBRT ≥72, and 154 PI patients were treated at Cleveland Clinic Foundation. The median radiation doses in EBRT <72 and EBRT ≥72 case was 68.4 and 78.0 Gy, respectively. The median follow-up time for all cases was 56 months (range 12–145). The median follow-up time for RP, EBRT <72, EBRT ≥72, PI, and COMB was 66, 75, 49, 47, and 46 months, respectively. Biochemical relapse was defined as PSA levels >0.2 for RP cases and three consecutive rising PSA levels (American Society for Therapeutic Radiology Oncology consensus definition) for all other cases. A multivariate analysis for factors affecting the bRFS rates was performed using the following variables: clinical T stage, iPSA, bGS, androgen deprivation, year of treatment, and treatment modality. The multivariate analysis was repeated excluding the EBRT <72 cases.

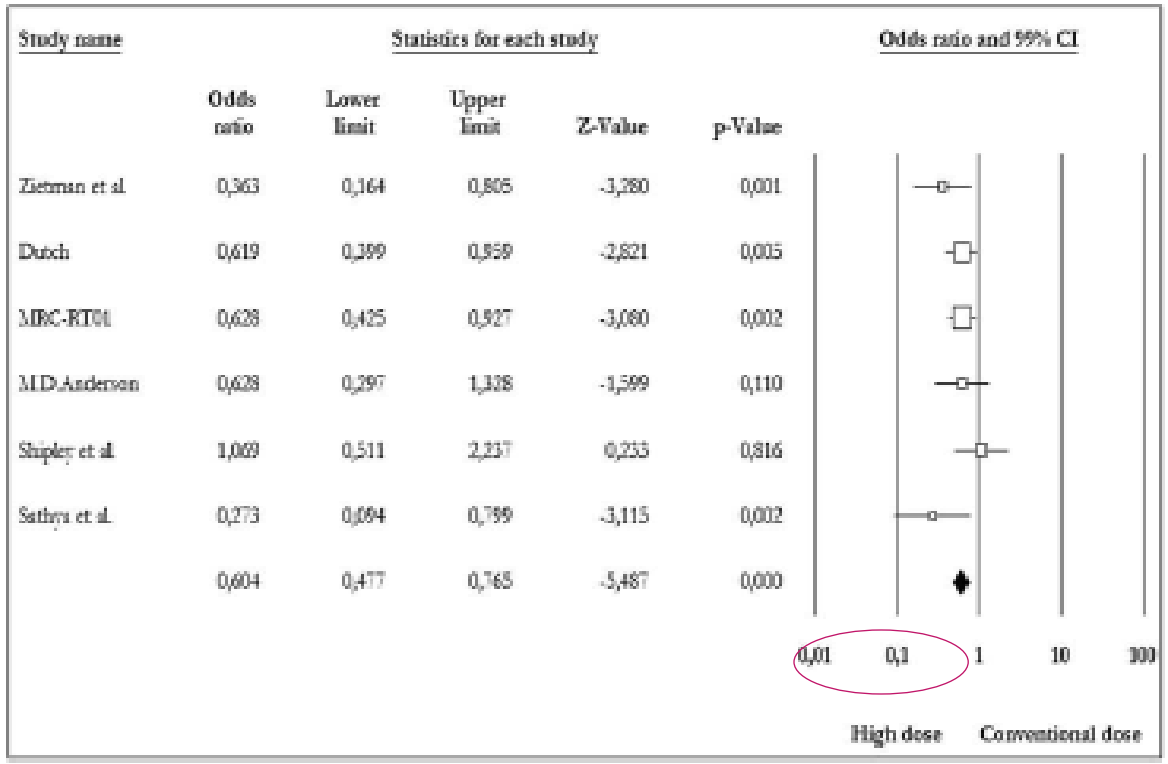
Results: The 5-year bRFS rate for RP, EBRT <72, EBRT ≥72, PI, and COMB was 81%, 51%, 81%, 83%, and 77%, respectively (p <0.001). The 7-year bRFS rate for RP, EBRT <72, EBRT ≥72, PI, and COMB was 76%, 48%, 81%, 75%, and 77%, respectively. Multivariate analysis, including all cases, showed iPSA (p <0.001), bGS (p <0.001), year of therapy (p <0.001), and treatment modality (p <0.001) to be independent predictors of relapse. Because EBRT <72 cases had distinctly worse outcomes, the analysis was repeated after excluding these cases to discern any differences among the other modalities. The multivariate analysis excluding the EBRT <72 cases revealed iPSA (p <0.001), bGS (p <0.001), and year of therapy (p = 0.001) to be the only independent predictors of relapse. Treatment modality (p = 0.95), clinical T stage (p = 0.09), and androgen deprivation (p = 0.56) were not independent predictors for failure.

Conclusion: The biochemical failure rates were similar among PI, high-dose (≥72 Gy) EBRT, COMB, and RP for localized prostate cancer. The outcomes were significantly worse for low-dose (<72 Gy) EBRT.

HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

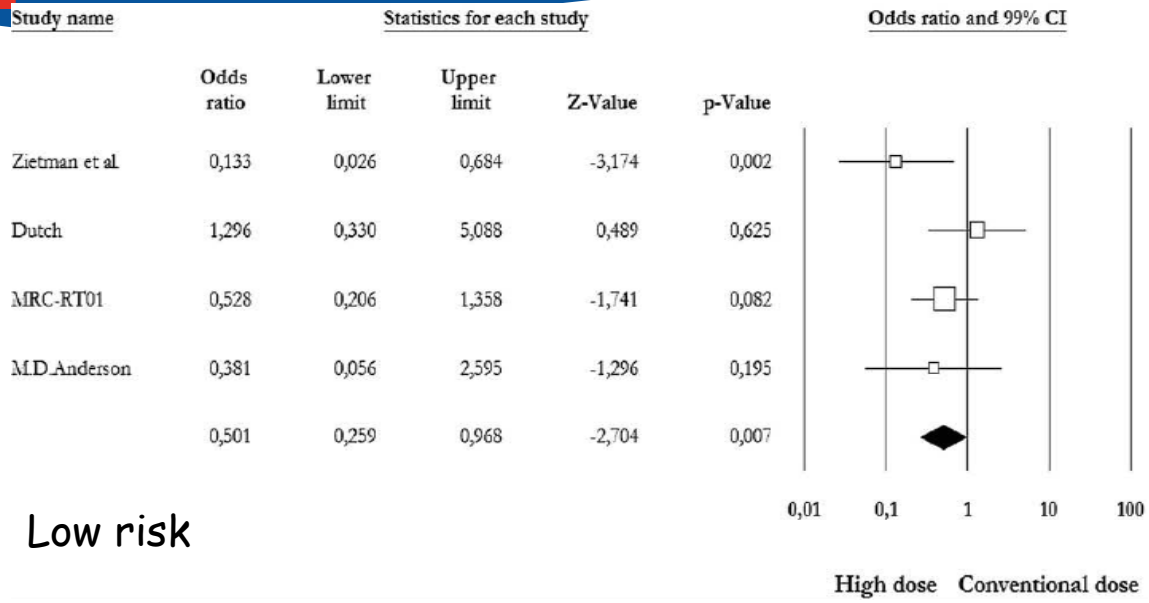
GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.



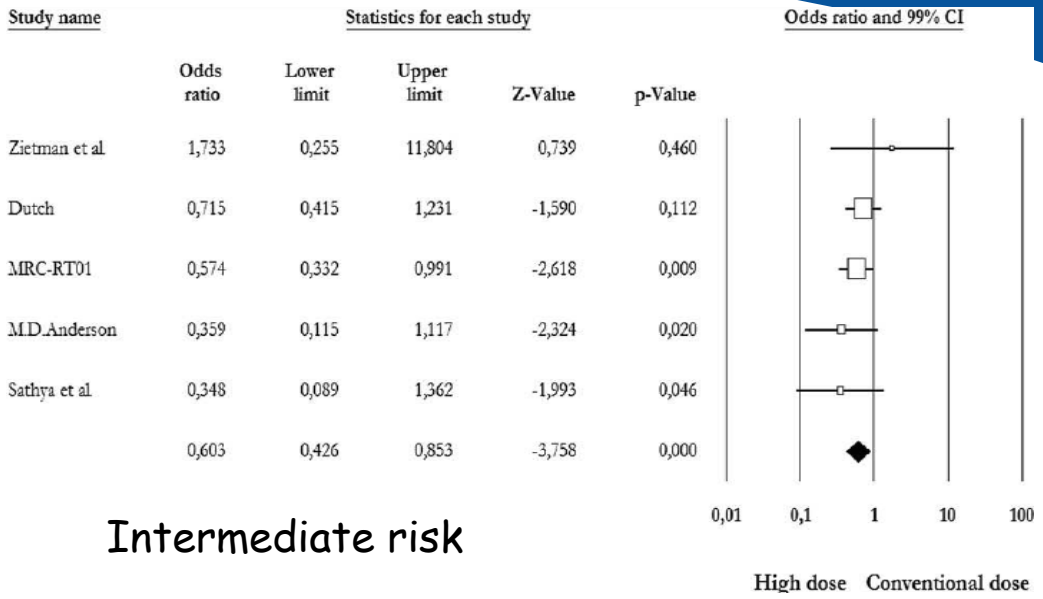


Meta-analysis regarding biochemical failure for all subgroups.

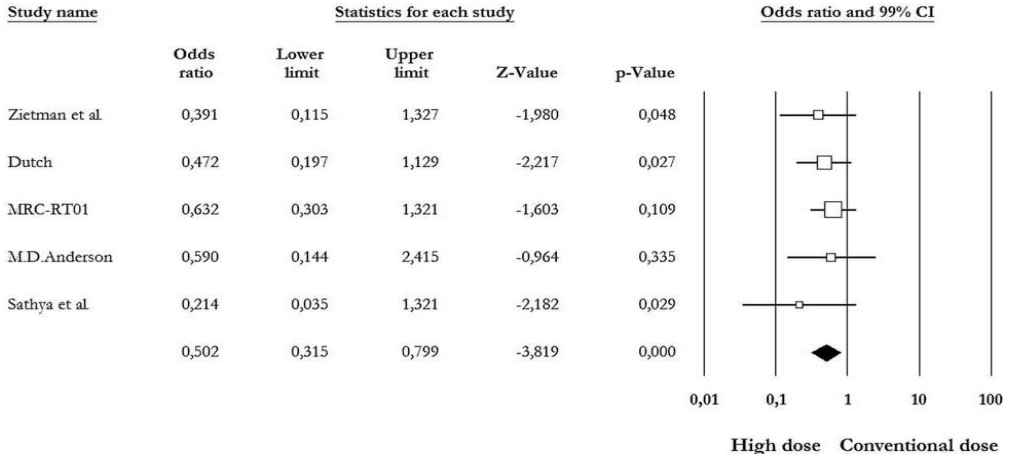
7 RCTs included (2812 pts):
Zietman et al
Dutch
MRC RT01
M.D. Anderson
Shipley et al
Sathya et al
GETUG



Low risk



Intermediate risk



High risk

Conclusion

HDRT significant reduce BF in low, int, high risk.
Across a range 64 to 79.2 Gy in localized prostate cancer BC is linear.
Incresing total dose reduces the risk of BF by 1.8% for each 1 Gy increase.
Hypothetically the RT dose of approximately 86.5, 90.4 and 95.5 Gy would need to be delivered to low, int and high risk for 100% BC rate
HDRT > risk of G≥2 RTOG bowel toxicity with HDRT.
GU adverse effects: ns.

Table 6.3.1: Randomised trials on dose escalation in localised PCa

Trial	n	PCa condition	Radiotherapy Dose	Follow-up	Outcome	Results
MD Anderson 2011 [410]	301	T1-T3, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	70 vs.78 Gy	Median 9 yr	Disease specific mortality (DSM) vs. other cause of death	High risk/PSA > 10 16 % DSM @ 70 Gy 4% DSM @ 78 Gy (p = 0.05) Higher risk 15% DSM @ 70 Gy 2% DSM @ 78 Gy (p = 0.03)
PROG 95-09 2010 [411]	393	T1b-T2b PSA 15 ng/mL 75% GS < 6	70.2 vs.79.2 Gy including proton boost 19.8 vs. 28.8 Gy	Median 8.9 yr. for survivors	10-year ASTRO BCF	All patients: 32% BF @ 70.2 Gy 17% BF @ 79.2 Gy (p < 0.0001) Low-risk patients: 28% BF @ 70.2 Gy 7% BF @ 79.2 Gy (p < 0.0001)
MRC RT01 2014 [407]	843	T1b-T3a, N0, M0 PSA < 50 ng/mL neoadjuvant HT	64 vs. 74 Gy	Median 10 yr.	BFS; OS	43% BFS @ 64 Gy 55% BFS @ 74 Gy (p = 0.0003) 71% OS both groups (p = 0.96)

Dutch RCT 2014 [419]	664	T1b-T4 143 pts. with (neo)adjuvant HT	68 vs. 78 Gy	Median 110 mo.	Freedom biochemical (Phoenix) and/or clinical failure (FFF) @ 10 yr.	43% FFF @ 68 Gy 49% FFF @ 78 Gy (p = 0.045)
French GETUG 06 2011 [414]	306	T1b-T3a, N0, M0 PSA < 50 ng/mL	70 vs. 80 Gy	Median 61 mo.	BCF (ASTRO)	39% BF @ 70 Gy 28% BF @ 80 Gy
Retrospective NCDB study 2015 [420]	16,714	intermediate risk 73% T ≤ 2a 76% GS ≤ 7a	< 75.6 Gy vs. ≥ 75.6 Gy 49% HT	Median 85-86 mo.	OS	Propensity adjusted HR: 0.84 favouring dose escalation (p < 0. 001)
	13,538	high risk 40% T ≥ 2b 67% GS ≥ 7b	< 75.6 Gy vs. ≥ 75.6 Gy 77% HT			Propensity adjusted HR: 0.82 favouring dose escalation (p < 0.001)

DOSE ESCALATION REQUIRES MARGIN REDUCTION

1. Target identification
2. Set-up variability
3. Organ motion (prostate, organs at risk)

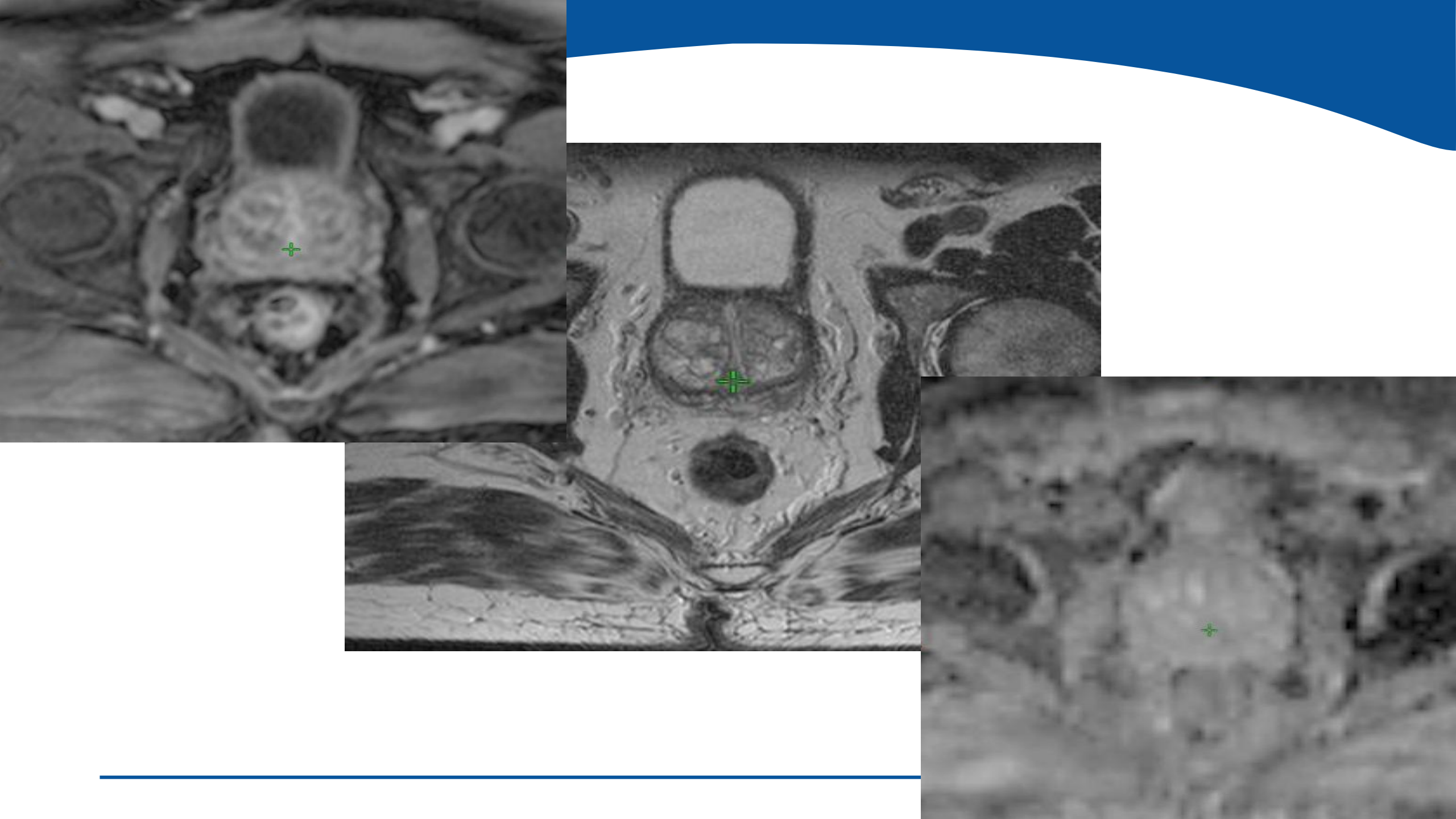
DOSE ESCALATION REQUIRES HIGH PRECISION RT

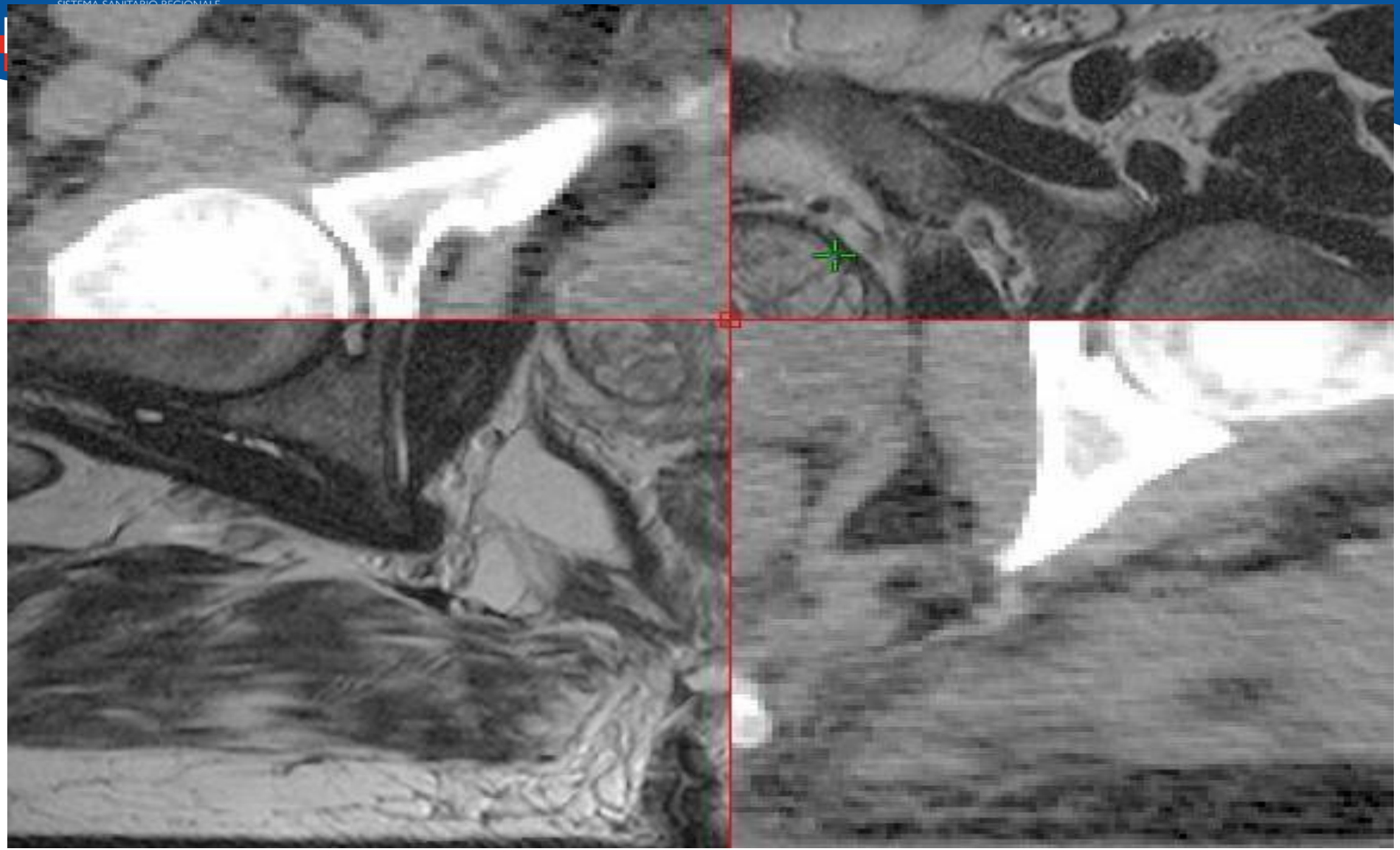
The first step:
3D conformal RT (3D-CRT)

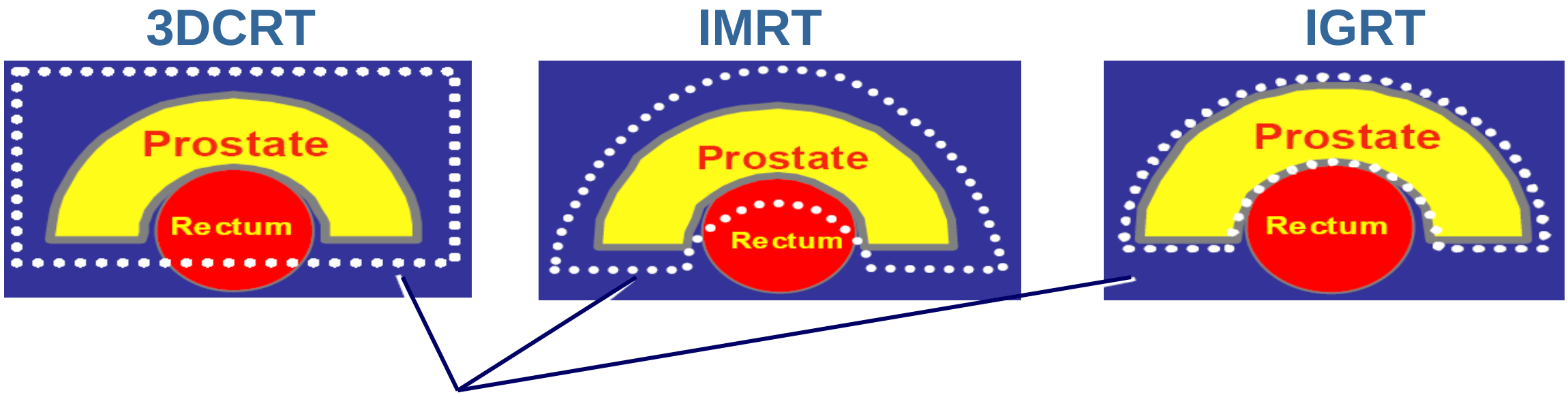
Recent innovations:
Dynamic arcs
Non coplanar technique
IMAT
IMRT
IGRT
Tomotherapy
Cyberknife, Rapidarc, Truebeam.....

Fusion TC-RM


Transversal - CT_1
A
R
L
P
1
2
3
4
Standard
Head First-Supine
Z: -4.25 cm
MR-T2
A
R
L
P
1
2
3
4
Standard
Head First-Supine

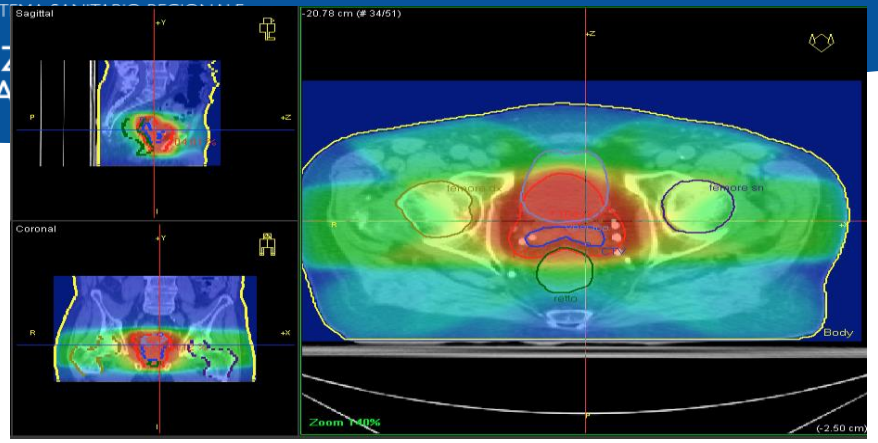




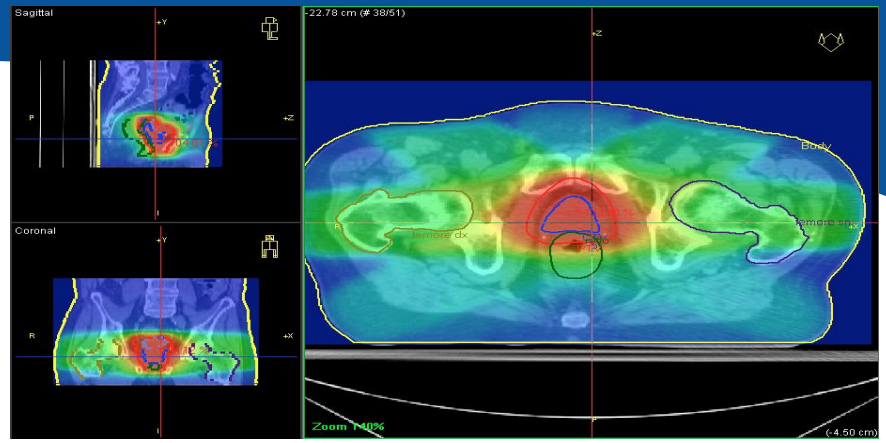


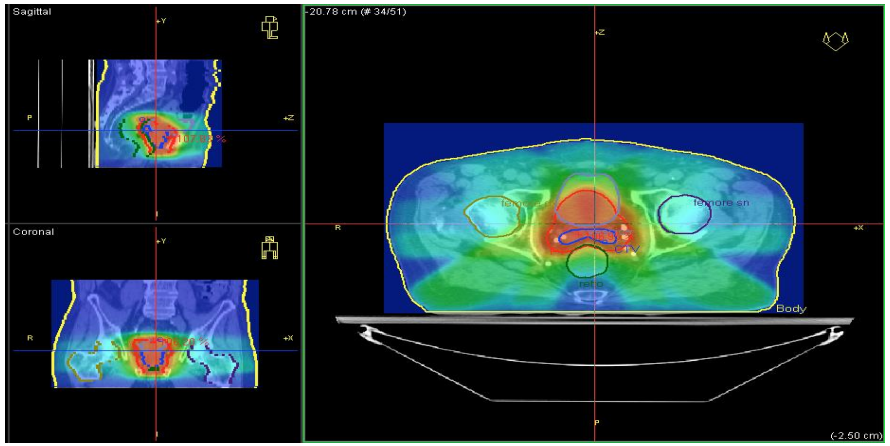
Improved Outcomes

Reduced Side Effects

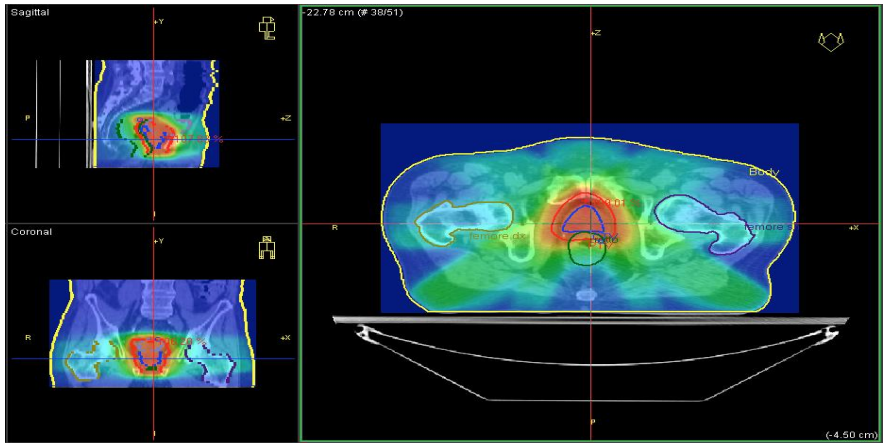


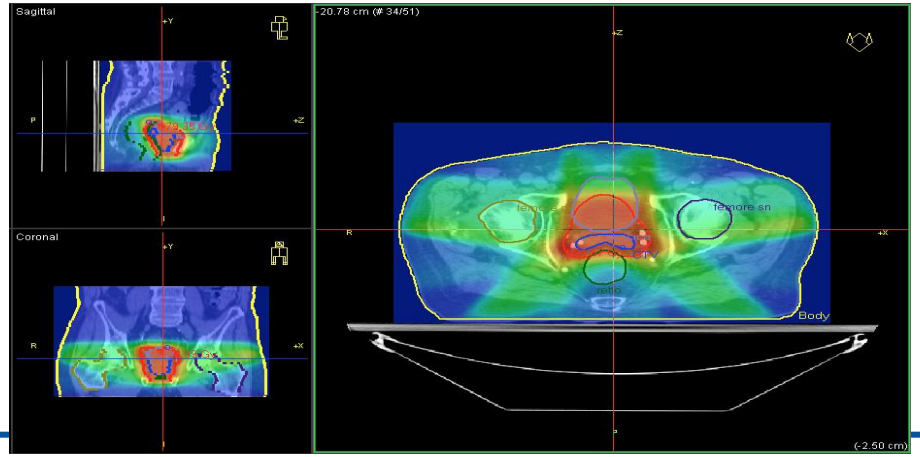
3DCRT
7F



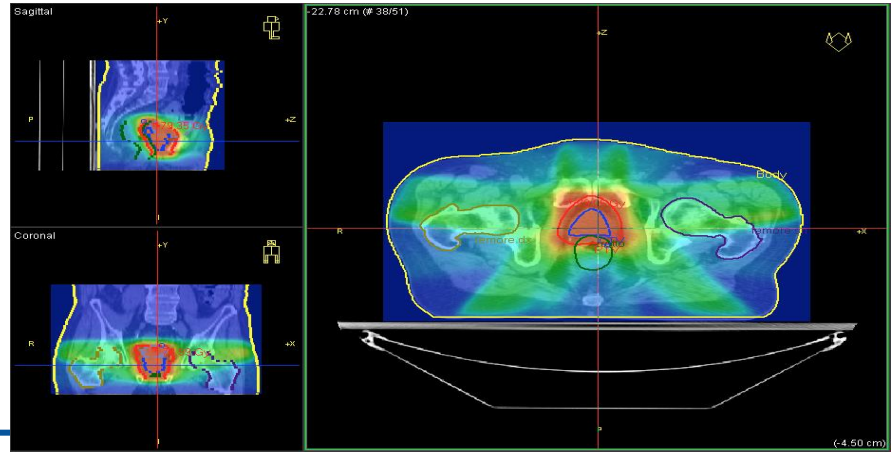


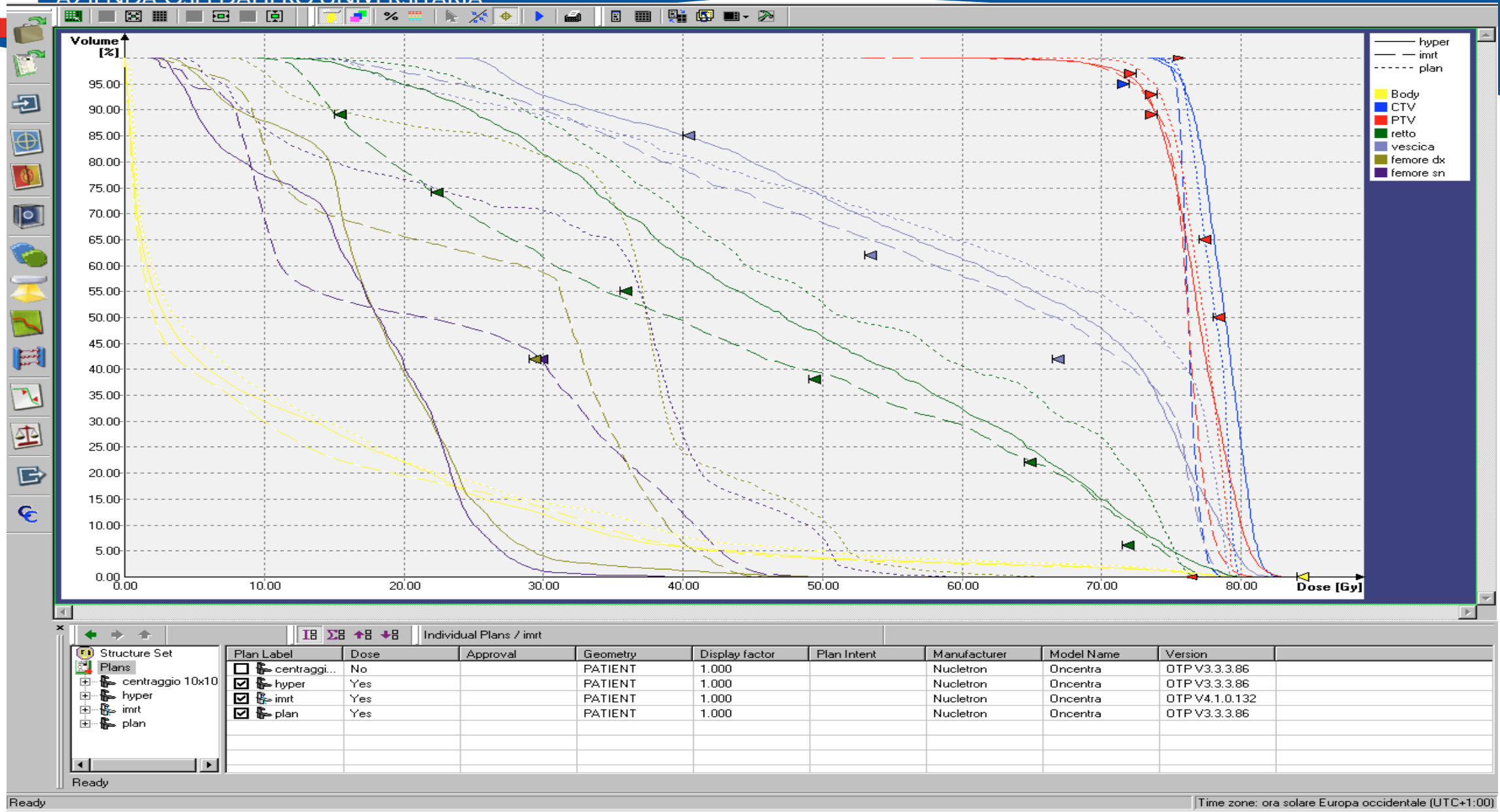
3DCRT
17F
("hyper")



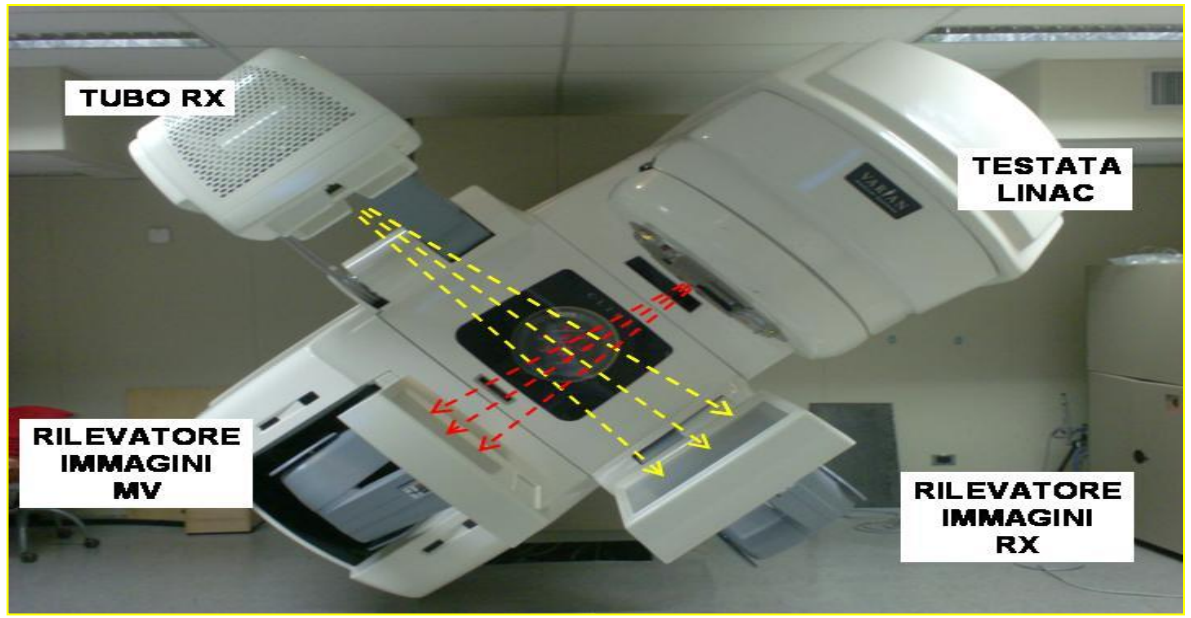


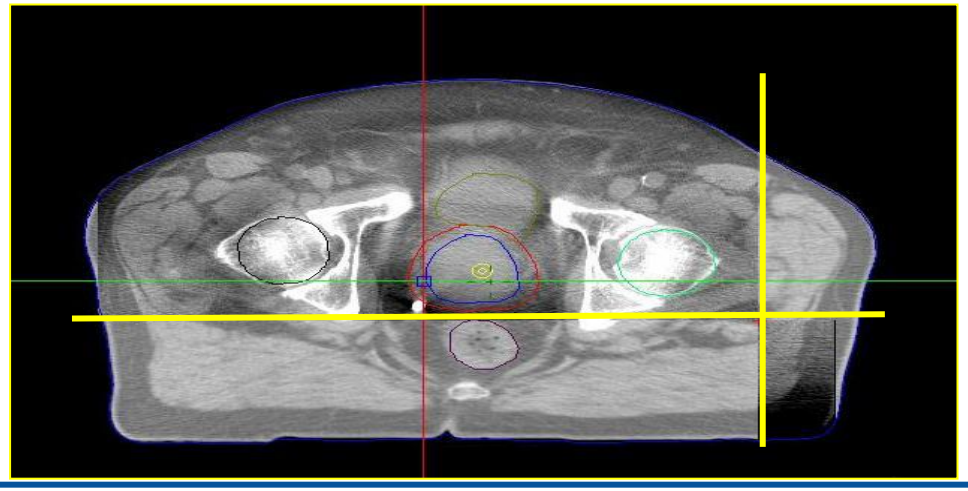
IMRT

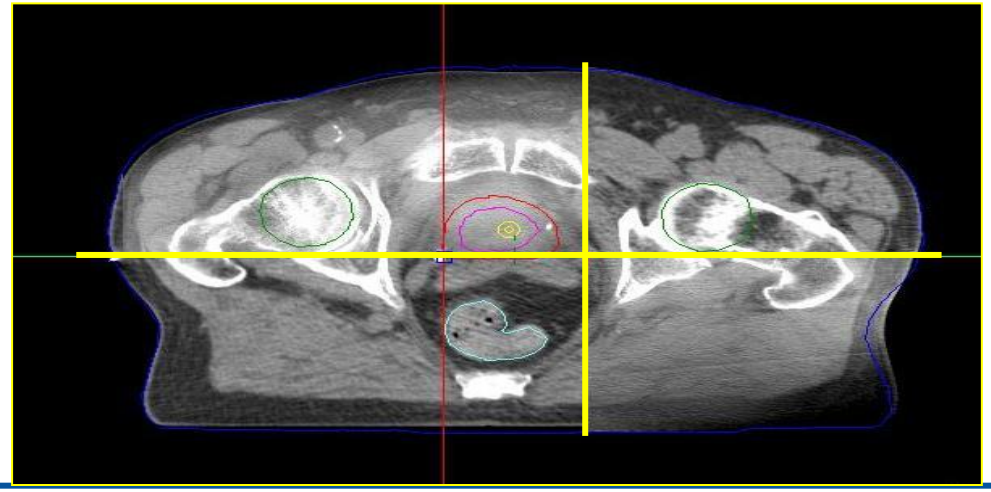



Volume [%]
95.00
90.00
85.00
80.00
75.00
70.00
65.00
60.00
55.00
50.00
45.00
40.00
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
0.00
10.00
20.00
30.00
40.00
50.00
60.00
70.00
80.00
Dose [Gy]
hyper
imrt
plan
Body
CTV
PTV
retto
vescica
femore dx
femore sn
Individual Plans / imrt
Structure Set
Plans
centraggio 10x10
hyper
imrt
plan
Plan Label | Dose | Approval | Geometry | Display factor | Plan Intent | Manufacturer | Model Name | Version
centraggi... | No | | PATIENT | 1.000 | | Nucletron | Oncentra | OTP V3.3.3.86
hyper | Yes | | PATIENT | 1.000 | | Nucletron | Oncentra | OTP V3.3.3.86
imrt | Yes | | PATIENT | 1.000 | | Nucletron | Oncentra | OTP V4.1.0.132
plan | Yes | | PATIENT | 1.000 | | Nucletron | Oncentra | OTP V3.3.3.86
Ready
Ready
Time zone: ora solare Europa occidentale (UTC+1:00)

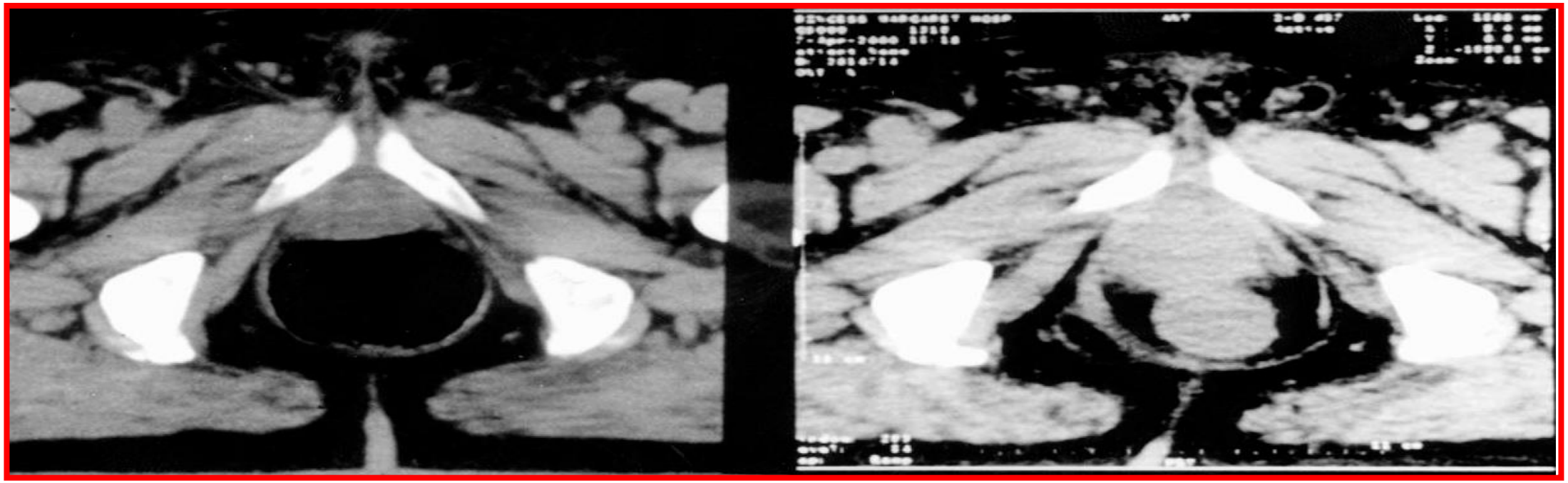
IGRT (image guided radiation therapy)



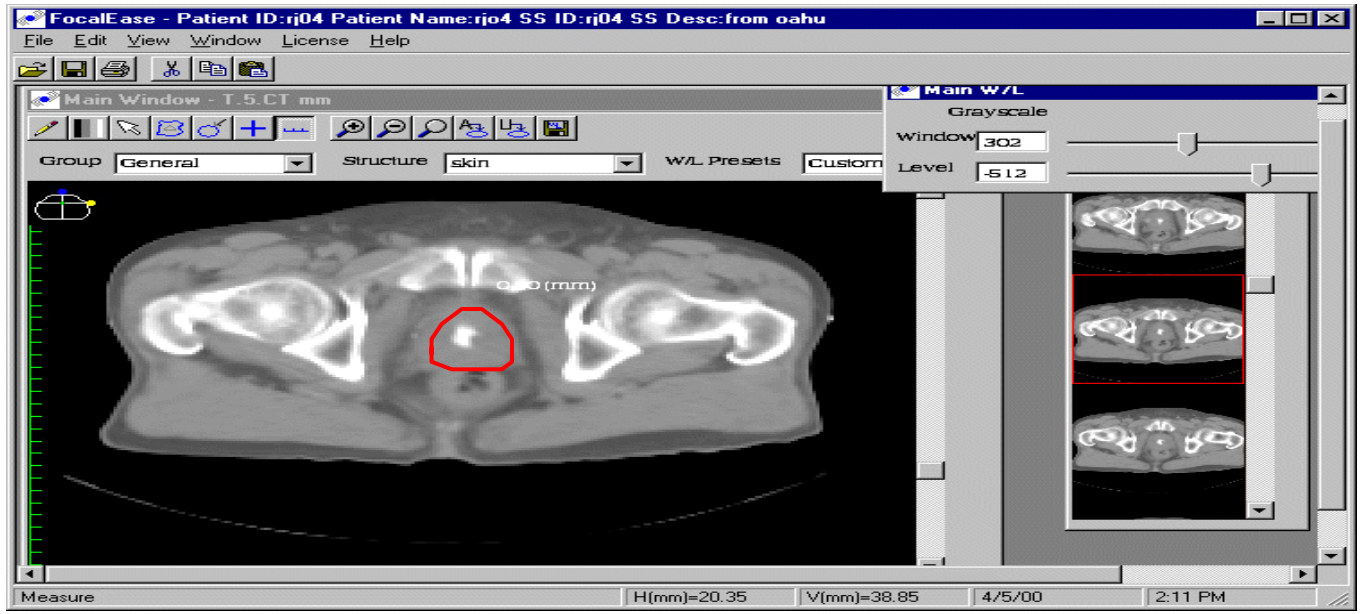




Organ Motion



Organ motion



Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 965–973, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.11.032

CLINICAL INVESTIGATION **Prostate**

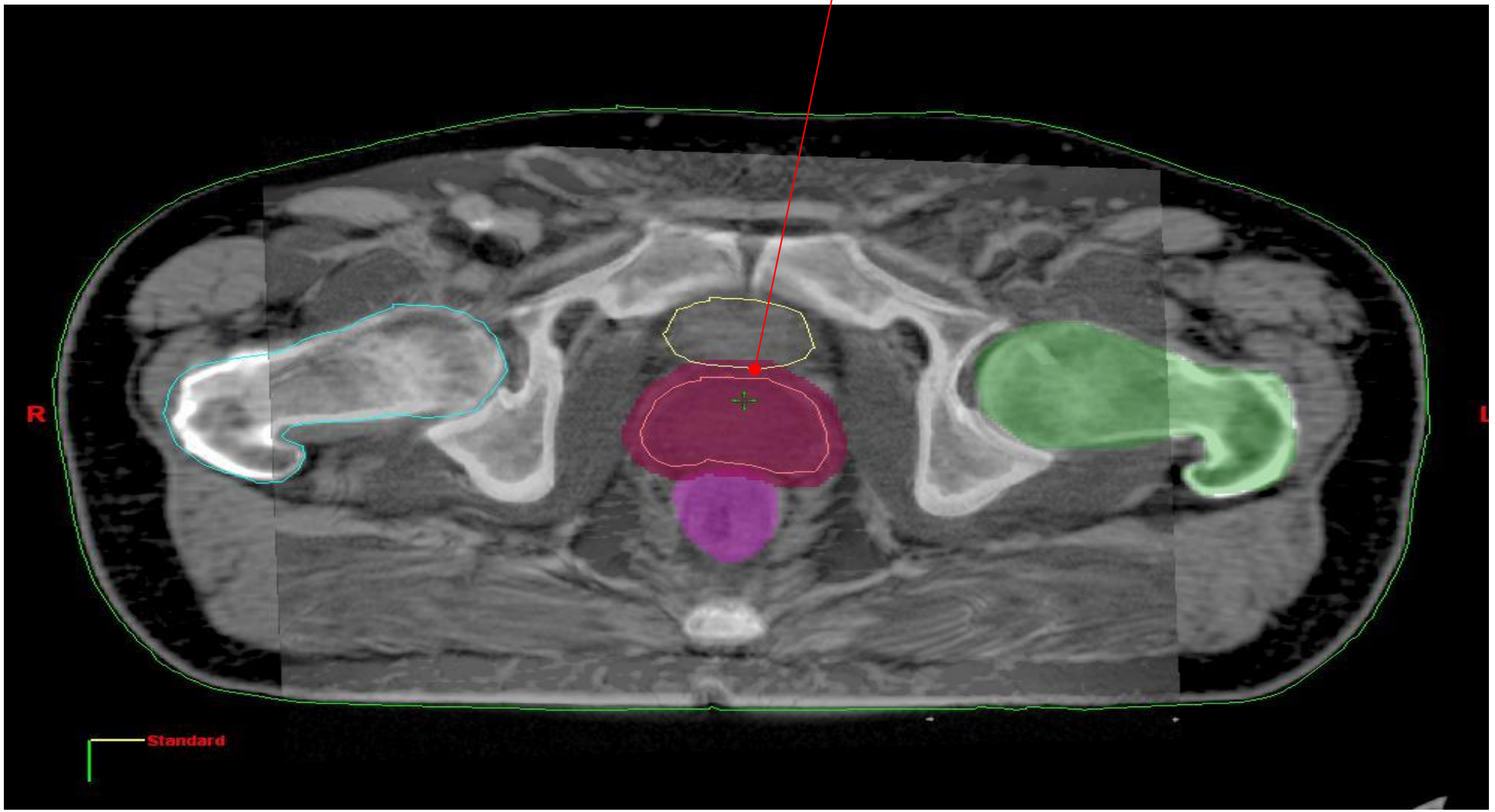
INCREASED RISK OF BIOCHEMICAL AND LOCAL FAILURE IN PATIENTS WITH DISTENDED RECTUM ON THE PLANNING CT FOR PROSTATE CANCER RADIOTHERAPY

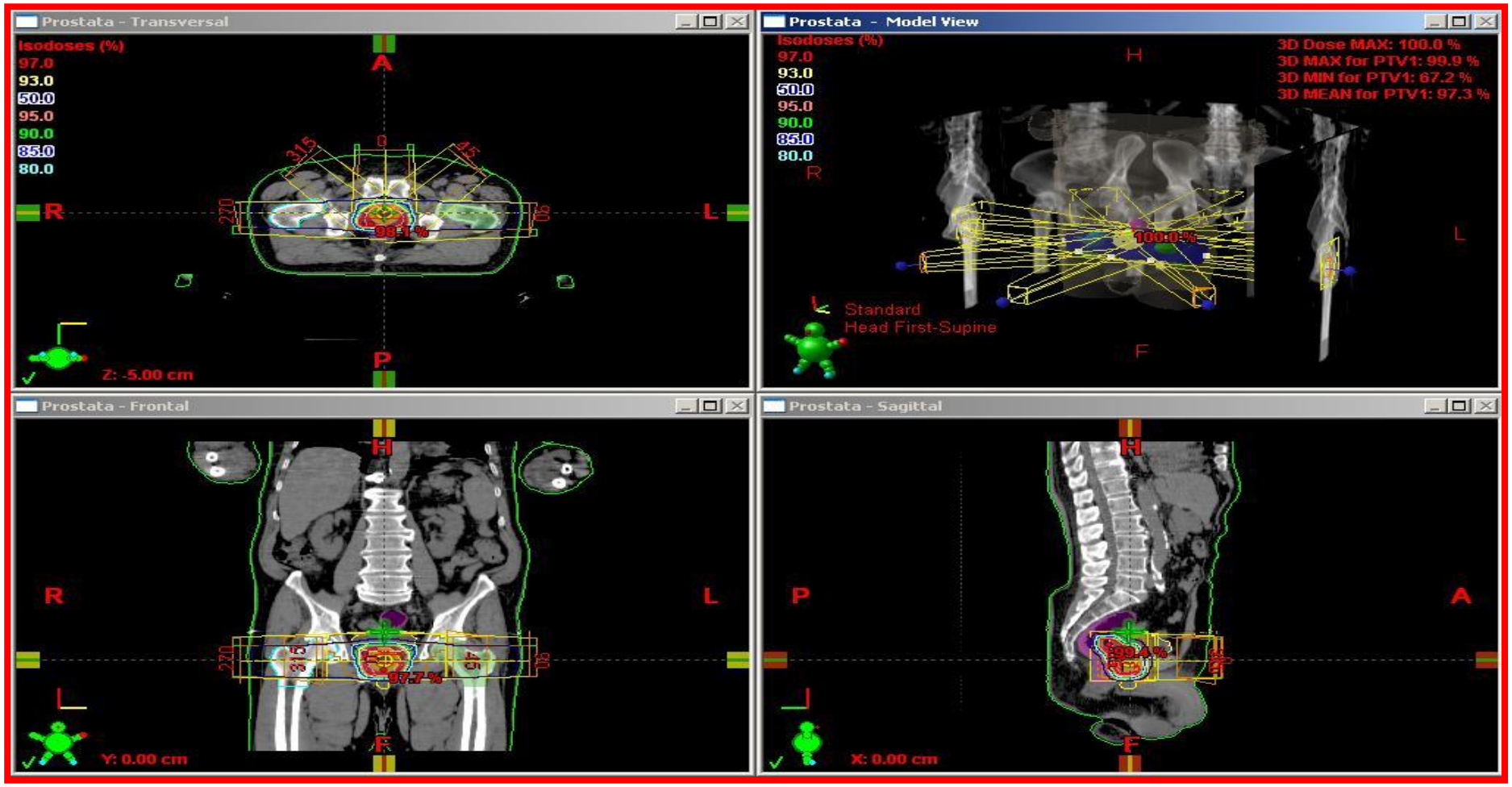
RENAUD DE CREVOISIER, M.D.,* SUSAN L. TUCKER, PH.D.,† LEI DONG, PH.D.,‡ RADHE MOHAN, PH.D.,‡ REX CHEUNG, M.D., PH.D.,* JAMES D. COX, M.D.,* AND DEBORAH A. KUBAN, M.D.*

Departments of *Radiation Oncology, †Biostatistics and Applied Mathematics, and ‡Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, TX

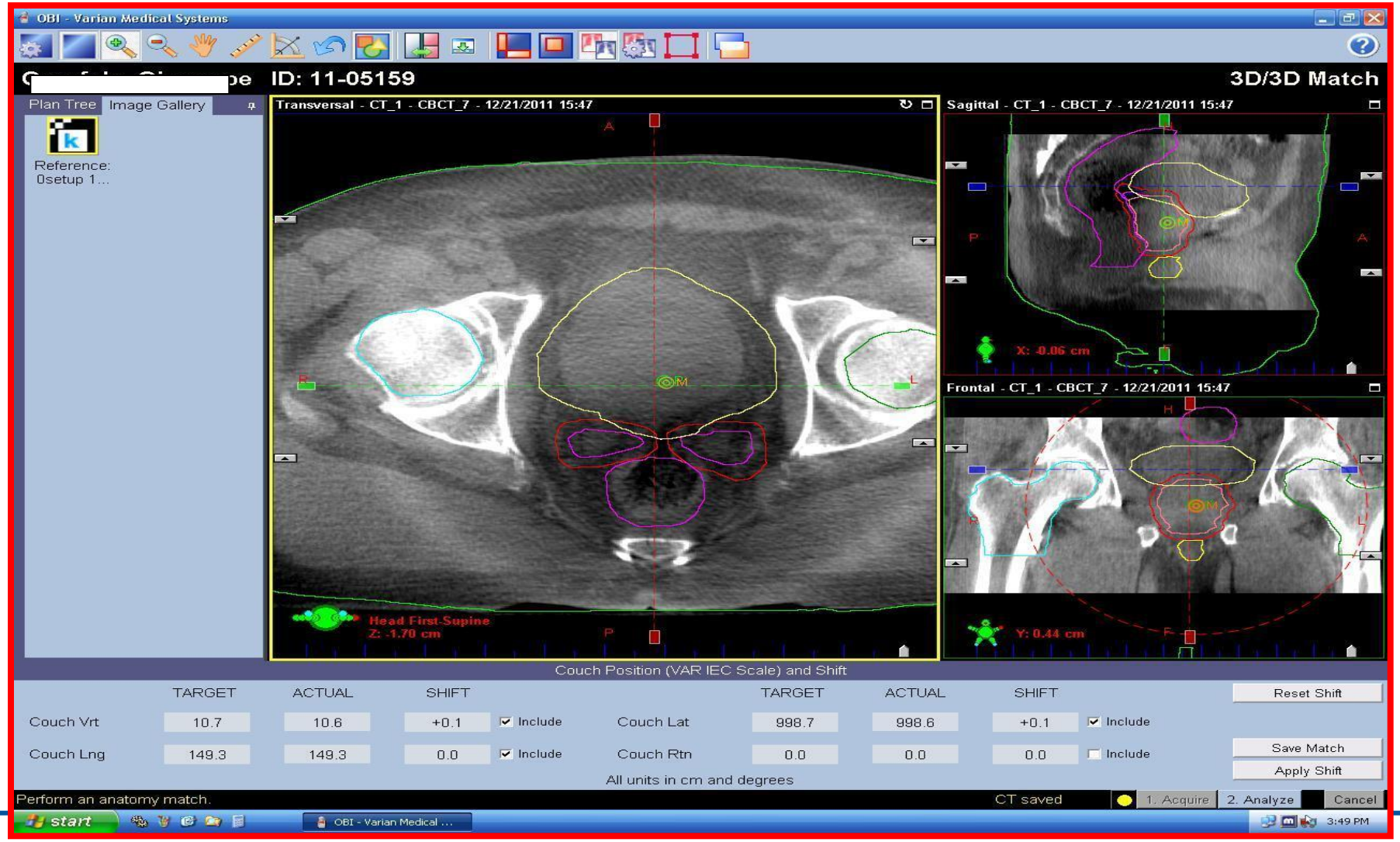
PTV: 60 Gy in 20 fr. on prostate and 1 cm the proximal seminal vescicles

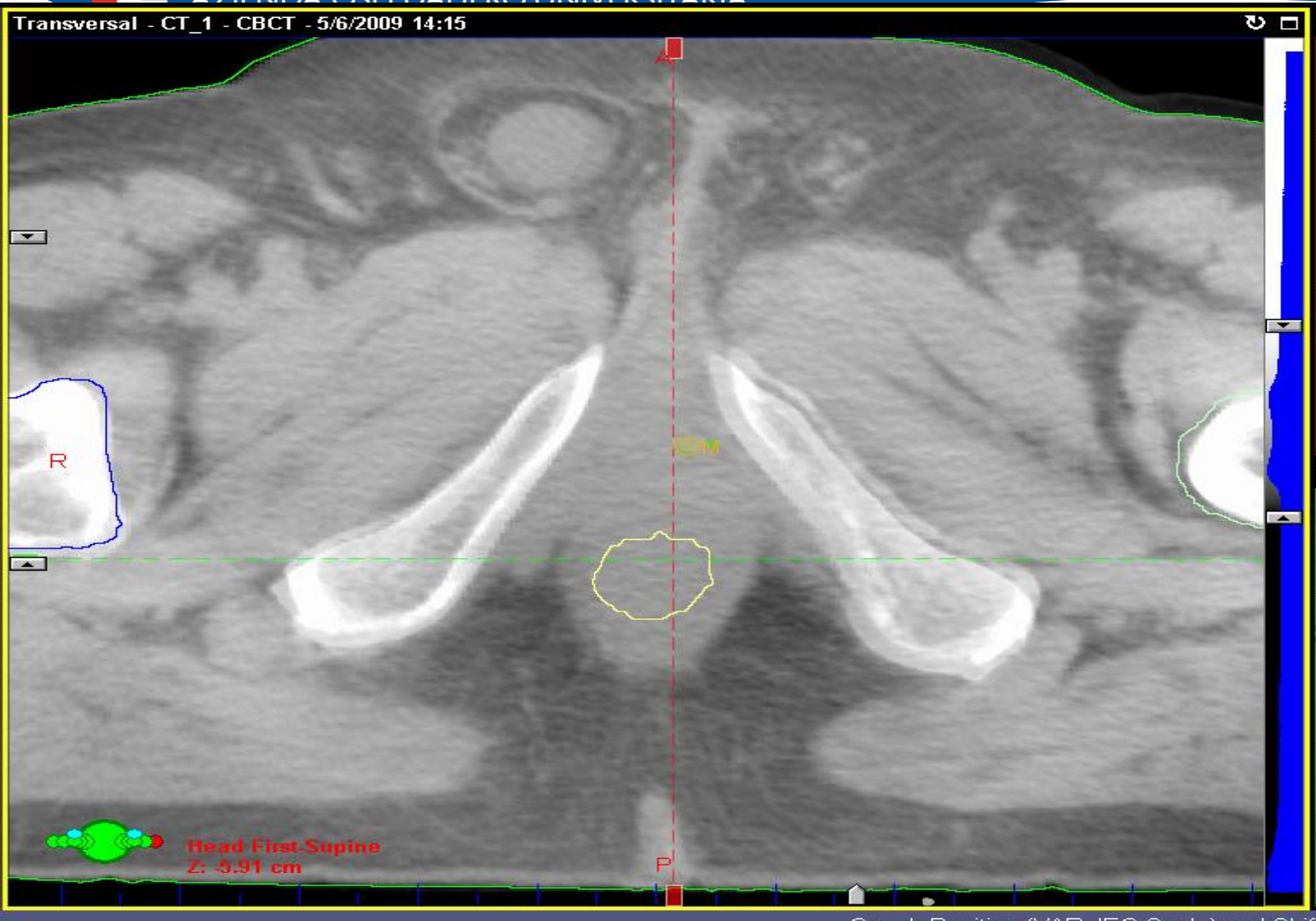
Margin from CTV to PTV was 5 mm in all directions

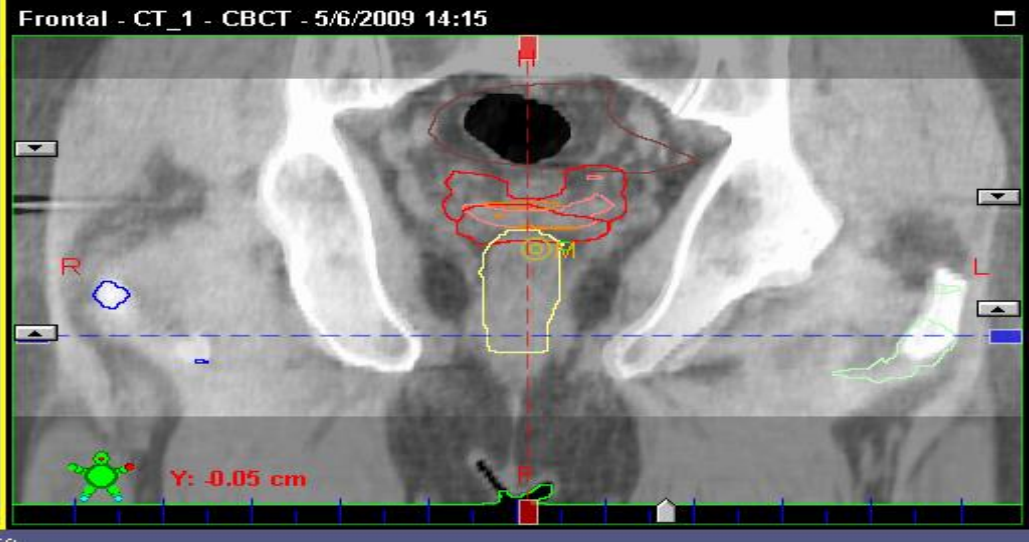



Prostata - Transversal
Isodoses (%)
97.0
93.0
50.0
95.0
90.0
85.0
80.0
A
R
L
P
315
0
45
270
90
98.1 %
Z: -5.00 cm
Prostata - Model View
Isodoses (%)
97.0
93.0
50.0
95.0
90.0
85.0
80.0
H
R
L
F
3D Dose MAX: 100.0 %
3D MAX for PTV1: 99.9 %
3D MIN for PTV1: 67.2 %
3D MEAN for PTV1: 97.3 %
100.0 %
Standard
Head First-Supine
Prostata - Frontal
H
R
L
F
315
45
270
90
97.7 %
Y: 0.00 cm
Prostata - Sagittal
H
P
A
F
99.4 %
X: 0.00 cm

Daily cone beam CT (IGRT)







Couch Position (VAR_IEC Scale) and Shift

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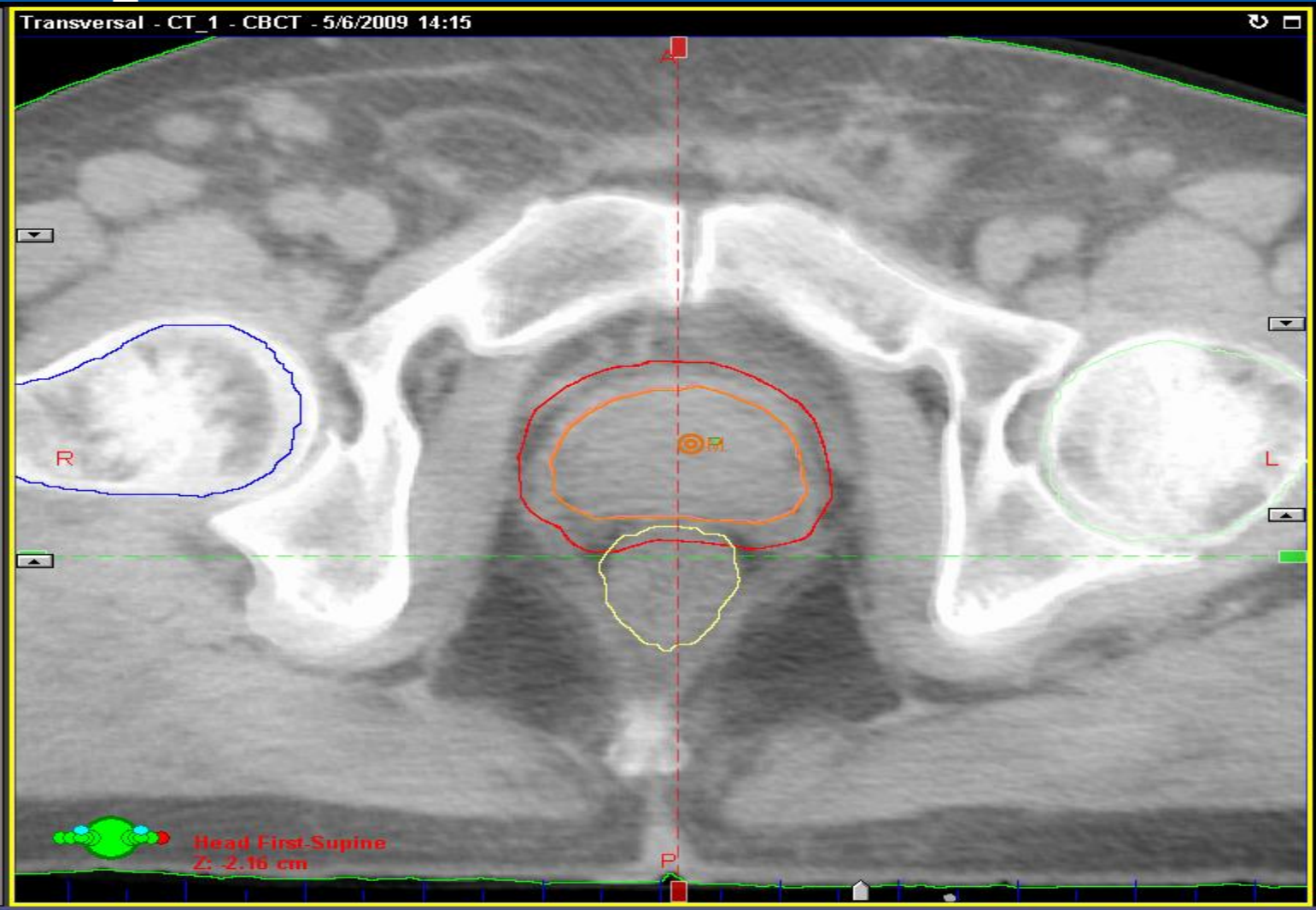
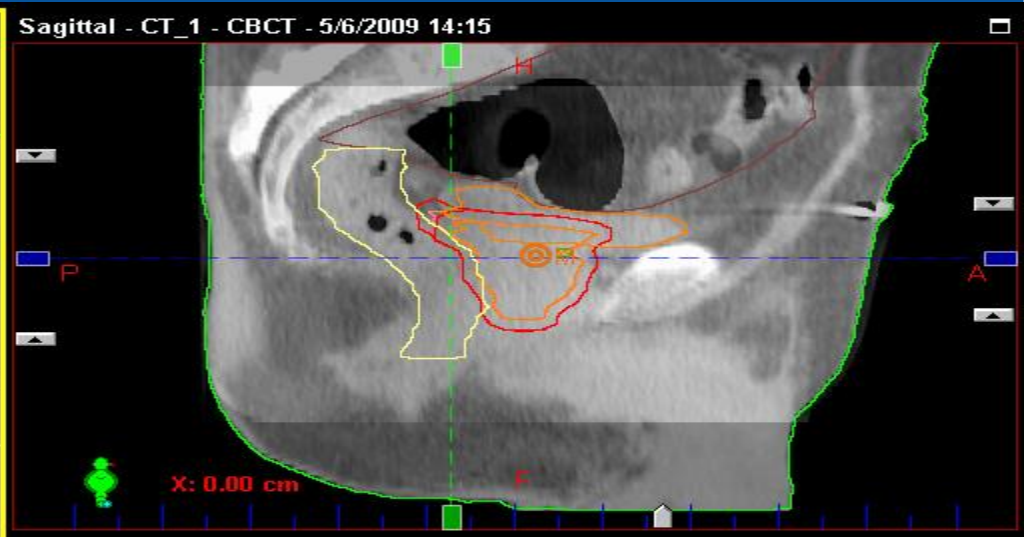
Couch Lng	144.0	144.0	0.0	☑ Include	Couch Rtn	0.0	0.0	0.0	☐ Include

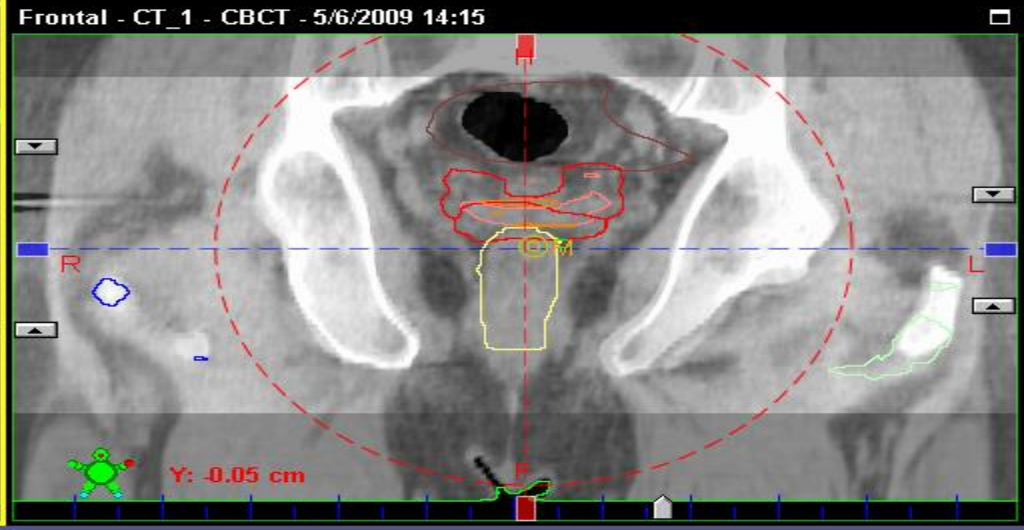
All units in cm and degrees

Reset Shift
Save Match
Apply Shift

Perform the anatomy match
CT saved
1. Acquire
2. Analyze
Cancel







Couch Position (VAR_IEC Scale) and Shift

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Couch Lng	144.0	144.0	0.0	☑ Include	Couch Rtn	0.0	0.0	0.0	☐ Include

All units in cm and degrees

Reset Shift

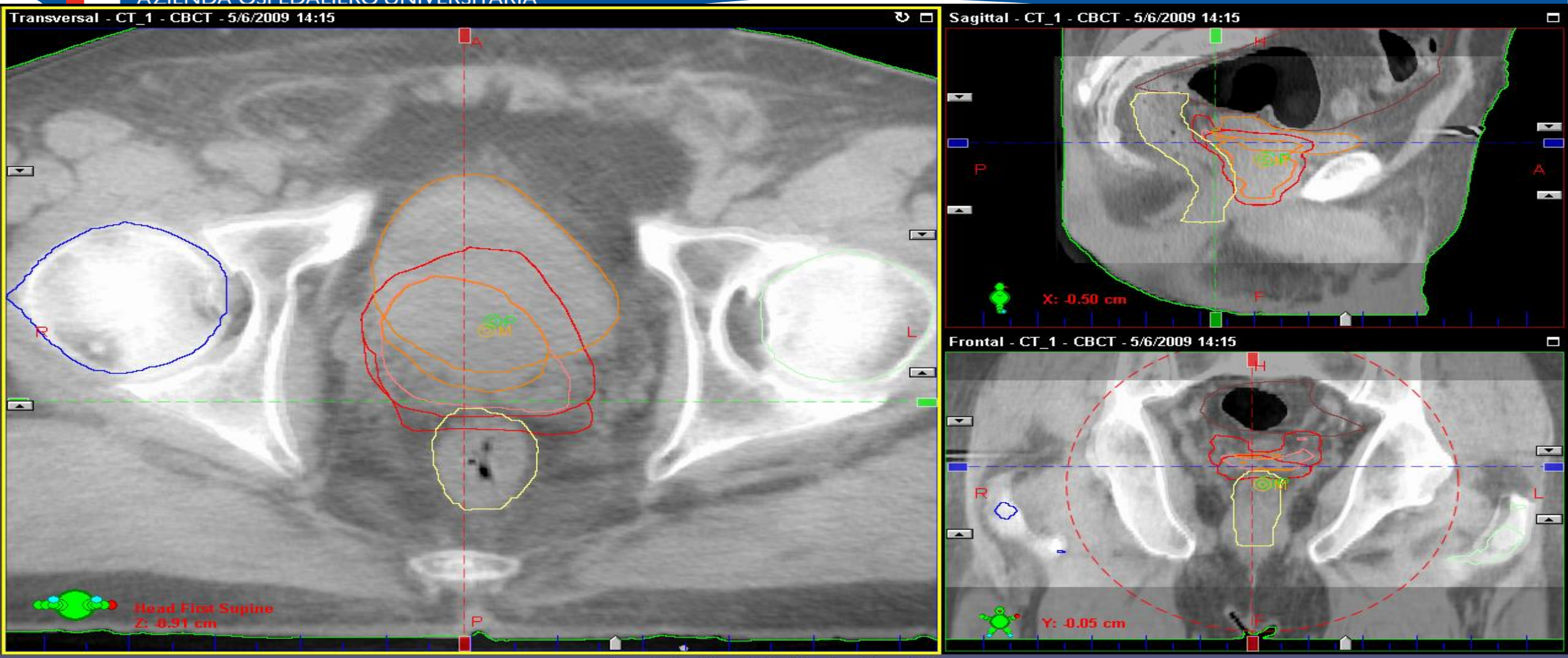
Save Match

Apply Shift

Perform the anatomy match

CT saved

1. Acquire | 2. Analyze | Cancel



Couch Position (VAR_IEC Scale) and Shift

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Couch Lng	143.9	144.0	-0.1	☑ Include	Couch Rtn	0.0	0.0	0.0	☐ Include

All units in cm and degrees

Reset Shift
Save Match
Apply Shift

Perform the anatomy match
CT saved
1. Acquire
2. Analyze
Cancel

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Seminars in
RADIATION
ONCOLOGY

Optimization of the Radiation Management of High-Risk Prostate Cancer

Paul L. Nguyen, MD

Table Summary of Highlighted Trials for Unfavorable Risk Disease

Risk Group	Trial	Arms	Result
Intermediate or high	RTOG 94-08[38]	66 Gy ± 4 mo ADT	ADT improves OS
Intermediate or high	DFCI 95-096[21]	70 Gy ± 6 mo ADT	ADT improves OS in healthy men
Intermediate or high	ASCENDE-RT[31]	ADT + (78 vs 46 Gy + LDR)	Brachy boost improves PFS
Intermediate or high	RTOG 94-13[25]	(AAT vs NHT) and (WP vs PO)	No definite benefit to treating pelvis
Intermediate or high	GETUG-01[26]	WP vs PO RT. ADT optional	No benefit to treating pelvis
High risk	TROG 96.01[9]	66 Gy + 0, 3, and 6 mo ADT	6 but not 3 mo ADT improves OS
High risk	RTOG 86-10[8]	65-70 Gy ± 4 mo ADT	ADT improves CSS
High or locally adv	EORTC 22863[7]	70 Gy ± 3 years ADT	ADT improves OS
High or locally adv	RTOG 92-02[11]	65-70 Gy + 4 vs 28 mo ADT	Longer ADT improves CSS
High or locally adv	EORTC 22961[10]	70 Gy + 6 vs 36 mo ADT	Longer ADT improves OS
High or locally adv	DART 01/05[14]	76-82 Gy + 4 vs 28 mo ADT	Longer ADT improves OS
High or locally adv	RTOG 05-21[33]	75.6 Gy + ADT ± Docetaxel	Docetaxel improves OS on 1-sided *P*
High or locally adv	PCS IV[12]	74 Gy + 18 vs 36 mo ADT	No difference yet. Further FU needed
High or locally adv	NCIC PR3[6]	ADT ± 70 Gy	RT improves OS
High or locally adv	SPGC-7[5]	ADT ± 70 Gy	RT improves OS

CSS, cancer-specific survival; FU, follow up; OS, overall survival; RT, radiation therapy.

Table 6.3.3: Studies of use and duration of androgen deprivation therapy in combination with radiotherapy for prostate cancer

Trial	TNM stage	n	Trial	ADT	RT	Effect on OS
EORTC 22863, 2010 [451]	T1-2 poorly differentiated and M0, or T3-4 N0-1 M0	415	EBRT ± ADT	LHRH agonist for 3 yr. (adjuvant)	70 Gy RT	Significant benefit at ten yr. for combined treatment (HR: 0.60, 95%, CI: 0.45-0.80, p = 0.0004).
RTOG 85-31, 2005 [452]	T3 or N1 M0	977	EBRT ± ADT	Orchiectomy or LHRH agonist 15% RP	65-70 Gy RT	Significant benefit for combined treatment (p = 0.002) seems to be mostly caused by patients with GS 7-10
Granfors, *et al.* 2006 [458]	T3 N0-1 M0	91	EBRT ± ADT	Orchiectomy	65 Gy RT	Significant benefit (p = 0.02 p = 0.03), mainly caused by LN-positive tumours
D'Amico, *et al.* 2008 [454]	T2 N0 M0 (localised unfavourable risk)	206	EBRT ± ADT	LHRH agonist plus flutamide for 6 mo.	70 Gy 3D-CRT	Significant benefit (HR: 0·55, 95% CI: 0.34-0.90, p = 0.01) that may pertain only to men with no, or minimal, comorbidity TROG 96-01
Denham, *et al.* 2011 [455]	T2b-4 N0 M0	802	Neoadjuvant ADT duration	Goserelin plus flutamide 3 or 6 mo. before, plus concomitant suppression	66 Gy 3D-CRT	No significant difference in OS reported; benefit in PCa-specific survival (HR: 0·56; 95% CI: 0.32-0.98, p = 0.04) (10 yr.: HR: 0.84, 0.65-1.08; p = 0.18)
RTOG 94-13, 2007 [459]	T1c-4 N0-1 M0	1292	ADT timing comparison	2 mo. neoadjuvant plus concomitant vs. 4 mo. adjuvant suppression	Whole pelvic RT vs. prostate only; 70.2 Gy	No significant difference between neoadjuvant plus concomitant vs. adjuvant androgen suppression therapy groups (interaction suspected)
RTOG 86-10, 2008 [453]	T2-4 N0-1	456	EBRT ± ADT	Goserelin plus flutamide 2 mo. before, plus concomitant therapy	65-70 Gy RT	No significant difference at 10 yr.
RTOG 92-02, 2008 [456]	T2c-4 N0-1 M0	1554	Short vs. prolonged ADT	LHRH agonist given for 2 years as adjuvant after 4 mo. as neoadjuvant	65-70 Gy RT	p = 0.73 p = 0.36 overall; significant benefit (p = 0.044) (p = 0.0061) in subset with GS 8-10

EORTC 22961, 2009 [416]	T1c-2ab N1 M0, T2c-4 N0-1 M0	970	Short vs. prolonged ADT	LHRH agonist for 6 mo. vs. 3 yr.	70 Gy 3D-CRT	Better result with 3-year treatment than with 6 mo. (3.8% improvement in survival at 5 yr.)
Pisansky, *et al*. 2014 [457]	intermediate risk (94% T1-T2, 6% T3-4)	1579	Short vs. prolonged ADT	LHRH antagonist 8 + 8 vs. 8 + 28 wk	70.2 Gy 2D/ 3D	67 vs. 68% p = 0.62, confirms 8 + 8 weeks LHRH as a standard
SPCG-7/ SFUO-3, 2014 [460]	T1b-2 Grade 2-3, T3 N0 M0	875	ADT ± EBRT	LHRH agonist for 3 mo plus continuous flutamide	70 Gy 3D-CRT vs. no RT	18.9% (30.7%) vs. 8.3% (12.4%) cancer specific mortality at 10 (15) yr. favouring combined treatment (HR: 0.35; p < 0.0001 for 15 yr. results) NCIC CTG PR.3/MRC
PRO7/ SWOG, 2014, 2015 [461, 462]	T3-4 (88%), PSA > 20 ng/ mL (64%), GLS 8-10 (36%) N0 M0	1205	ADT ± EBRT	Continuous LHRH agonist	65-70 Gy 3D-CRT vs. no RT	10 yr. OS = 49% vs. 55% favouring combined treatment (HR: 0.7, p < 0.001)
Mottet, *et al*. 2012 [463]	T3-4 N0 M0	273 264	ADT ± EBRT	LHRH agonist for 3 yr.	70 Gy 3D-CRT vs. no RT	Significant reduction of clinical progression; 5 yr. OS 71.4% vs. 71.5%

TABELLA - Grado di raccomandazione SIGN e forza della raccomandazione clinica

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	*Dose escalation* è raccomandata in tutti i pazienti con malattia non metastatica (qualora siano disponibili 3DCRT e/o IMRT, e siano rispettati *constraints* DVH).	Positiva forte
A	L'associazione terapia ormonale e radioterapia è raccomandata in tutti i pazienti con malattia di rischio intermedio, soprattutto se intermedio sfavorevole (4-6 mesi) e alto (2-3 anni).	Positiva forte
A	L'associazione terapia ormonale e radioterapia non è raccomandata nei pazienti con malattia di rischio basso.	Negativa forte

Hypofractionated Radiotherapy

Technological developments and the possibility of obtaining highly selective irradiation techniques, have recently renewed the clinical interest for these treatment modalities, not only in terms of palliation only, but also in the context of **therapeutic strategies targeted to the increase in local control** of the disease and, consequently, the **final result** of the treatment.

The use of large dose fractions reducing the weekly (fewer than five fractions) and overall number is currently know as 'hypofractionation'; the use of high dose fractions is generally associated with a reduction of the final dose.

Hypofractionation: radiobiological rationale and clinical implications

- **Higher dose per fraction**

Potential dose escalation with a higher BED: Theoretical advantage on local tumor control

- **Reduced overall treatment time**

Reduce tumor cell repopulation
Overall treatment time is reduced to 1 to 2 weeks Improved patient convenience and reduced cost (Avoidance of waiting list;reduce demand on RT resources)

- **Concerns of a disproportionate increase in late normal tissue toxicity**

(α/β ratio of tumor and normal tissues)

Int. J. Radiation Oncology Biol. Phys., Vol. 50, No. 4, pp. 1021–1031, 2001

0360-3016/01/$–see front matter

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BIOLOGY CONTRIBUTION

IS α/β FOR PROSTATE TUMORS REALLY LOW?

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JOURNAL OF CLINICAL ONCOLOGY

EDITORIAL

Prostate Cancer and the Hypofractionation Hypothesis

W. Robert Lee, *Duke University School of Medicine, Durham, NC*

Review Article

Hypofractionated External-Beam Radiotherap
Prostate Cancer

L. Chinsoo Cho,[1] Robert Timmerman,[2] and Brian Kavan

Review Article

Hypofractionation in Prostate Cancer:
Radiobiological Basis and Clinical Appliance

M. Mangoni,[1] I. Desideri,[1] B. Detti,[1] P. Bonomo,[1] D.
G. Simontacchi,[1] I. Meattini,[1] S. Scoccianti,[1] T. M
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50134 Firenze, Italy
[2] Urology Unit, Department of Experimental

Review Article

Hypofractionated radiation therapy for prostate cancer: biologic and technical considerations

Nicholas J Sanfilippo, Benjamin T Cooper

REVIEW ARTICLE

The radiobiology of prostate cancer including new aspects of fractionat radiotherapy

JACK
wisconsin University, Department of Human Oncology, University of Wisconsin-Madison,

Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 4, pp. 1093–1104, 2003

0360-3016/03/$–see front matter
doi:10.1016/S0360-3016(03)00132-9

CLINICAL INVESTIGATION

WHAT HYPOFRACTIONATED PROTOCOLS SHOULD BE TESTED FOR PROSTATE CANCER?

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Rationale, conduct, and outcome using hypofractionated radiotherapy in prostate cancer

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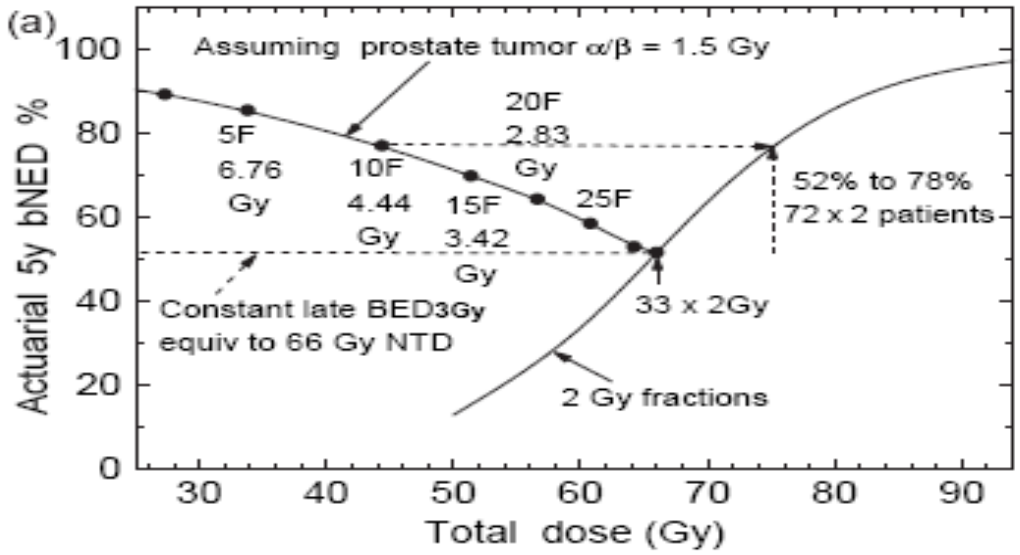
Unlike most cancers, the α/β ratio of the prostatic carcinoma is probably lower than that of the healthy organs around the gland, although there is no agreement as to how low this α/β really is.

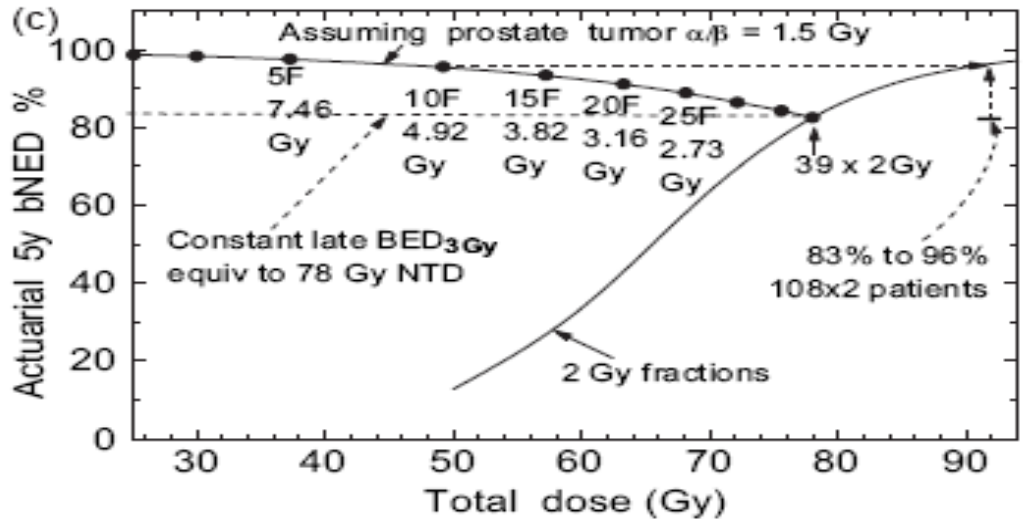
This peculiarity implies that, theoretically, a hypofractionated schedule would increase the therapeutic gain of radiotherapy

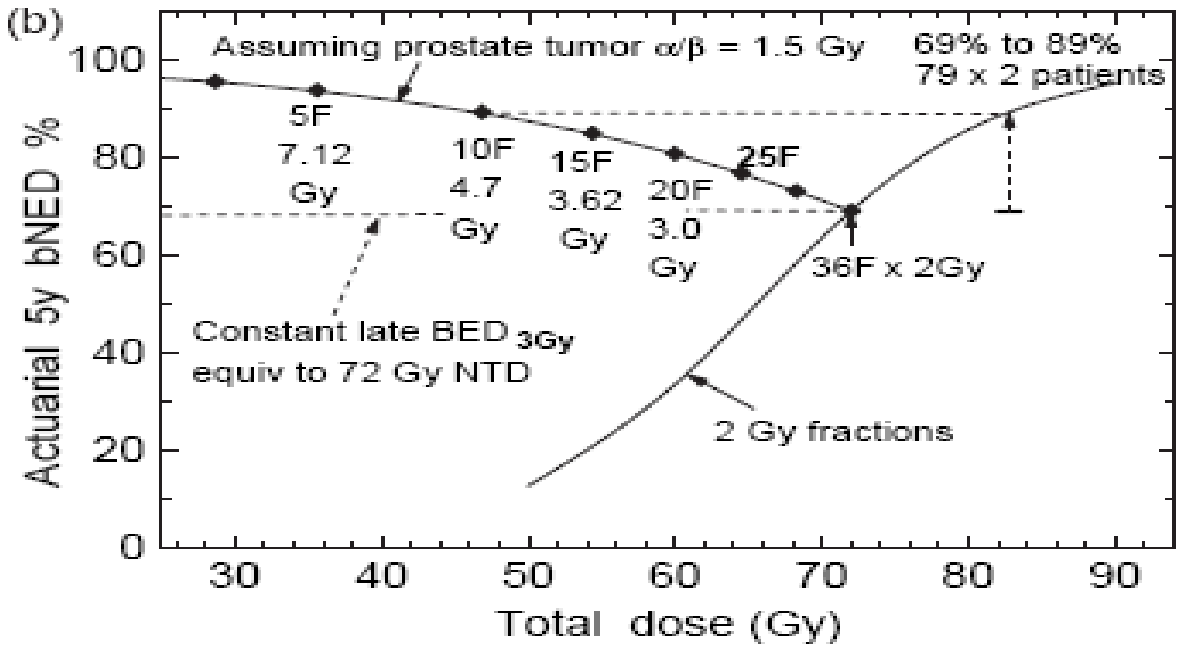
	Median	Range
Larynx	4 days	2–19 days
Tongue	4–6	2–16
Mouth, cheek	3.4	2–15
Esophagus	5	2.5–20
Ca. cervix	5	3–20
Rectum	5	3–18
Prostate	42	15– >70
Breast	14	3–70

Vocal cord	~9.9 Gy	Harrison et al. 1988
Oropharynx	13–19	Rezvani et al. 1993
Larynx	25–35	Maciejewski et al 1988
Larynx	50–infinity	Chappell & Fowler 1995
Larynx	50–infinity	Roberts & Hendry 1998
Only a few types of tumor have low values of α/β:		
Malig. melanoma	0.6 Gy	Bentzen et al. 1989
Prostate Ca.	1.5	Brenner & Hall 1999
Prostate Ca.	1.49	Fowler et al. 2001
Prostate Ca.	1.2	Brenner . . . Martinez 2002
Rhabdomyosarcoma	2.8	Timmerman 2002

Early reactions	α/β (Gy)	Late reactions	α/β (Gy)
Skin	9–12	Kidney	2–2.4
Jejunum	6–10	Rectum	2.5–5
Colon	9–11	Lung	2.7–4
Testis	12–13	Bladder	3–7
Mucosa	9–10	CNS: brain,spinal cord	1.8–2.2







Fowler JF, Ritter MA, Chappel RJ, Brenner JD Int J Radiat Oncol Biol Phys 2003.

Table 1 | Superiority randomized controlled trials of moderately hypofractionated radiotherapy for organ-confined prostate cancer

Study	Patients (*n*) and disease characteristics	Schedule (total dose, *n* of fractions)	Technique	NTD2/1.5*	NTD2/3*	Median follow-up period (months)	Biochemical-recurrence-free survival	Late gastrointestinal toxicity	Late genitourinary toxicity
Lukka *et al.* (2005)[16]	• 470 T1–2 • 466 T1–2	• 66 Gy, 33 • 52.5 Gy, 20	2D	• 66 Gy • 62 Gy	• 66 Gy • 59 Gy	68.5	• 47% • 40%	≥G3: 1.9% (both schedules)	≥G3: 1.3% (both schedules)
Yeoh *et al.* (2011)[17]	• 109 T1–2 • 108 T1–2	• 64 Gy, 32 • 55 Gy, 20	2D and 3D	• 64 Gy • 66.8 Gy	• 64 Gy • 63.3 Gy	90	• 34% • 53%	NR	NR‡
Kuban *et al.* (2010)[18]	• 102 L–I • 102 L–I	• 75.6 Gy, 42 • 72 Gy, 30	IMRT	• 71.3 Gy • 80.2 Gy	• 72.6 Gy • 77.8 Gy	40	• 92% • 96%	• ≥G2: 5.1% • ≥G2: 10%	• ≥G2: 16.5% • ≥G2: 15.8%
Pollack *et al.* (2013)[19]	• 153 L–I–H • 154 L–I–H	• 76 Gy, 38 • 70.2 Gy, 26	IMRT	• 76 Gy • 84.2 Gy	• 76 Gy • 80 Gy	68.4	• 79% • 77%	• ≥G2: 22.5% • ≥G2: 18.1%	• ≥G2: 13.4% • ≥G2: 21.5%
Arcangeli *et al.* (2012)[20]	• 85 H • 83 H	• 80 Gy, 40 • 62 Gy, 20	3D	• 80 Gy • 81.5 Gy	• 80 Gy • 74 Gy	70	• 74% • 85%	• ≥G2: 17% • ≥G2: 16%	• ≥G2: 14% • ≥G2: 11%

2D, 2D-volume imaging; 3D, 3D-conformal radiotherapy; G2, grade 2; G3, grade 3; H, high-risk disease; I, intermediate-risk disease; IMRT, intensity-modulated radiotherapy; L, low-risk disease; NR, not reported; NTD, normalized total dose; T1–2, tumour stage 1–2. *NTD at 2 Gy per fraction using an α/β ratio of 1.5 Gy or 3 Gy to estimate the tumoricidal radiation dose for prostate cancer or late effects of radiation on dose-limiting normal tissues, respectively. ‡Late ≥G3 genitourinary toxicity differed between groups, favouring the group receiving 55 Gy in 20 fractions (HR 1.58, 95% CI 1.01–2.47).

Table 2 | Noninferiority randomized controlled trials of moderately hypofractionated radiotherapy for organ-confined prostate cancer

Study (completion date)	Patients (*n*) and disease characteristics	Schedule (total dose, *n* of fractions)	Technique	NTD2/1.5*	NTD2/3*	Median follow-up period (months)	Biochemical-recurrence-free survival	Late gastrointestinal toxicity	Late genitourinary toxicity
CHHiP (2015)[31]	3,216 L-I-H	• 74 Gy, 37 • 60 Gy, 20 • 57 Gy, 19	IMRT	• 74 Gy • 77.1 Gy • 73.3 Gy	• 74 Gy • 72 Gy • 68.4 Gy	62.4	• 88% • 91%‡ • 86%	• ≥G2 1.3% • ≥G2 2.3% • ≥G2 2%	• ≥G2 13.5% • ≥G2 13.2% • ≥G2 11.2%
HYPRO (2016)[30]	820 I-H	• 78 Gy, 39 • 64.6 Gy, 19	3D and IMRT	• 78 Gy • 90.4 Gy	• 78 Gy • 82.7 Gy	60	• 77% • 80%§	• ≥G2 18% • ≥G2 22%	• ≥G2 39% • ≥G2 41%
RTOG 0415 (2016)[29]	1,097 L	• 73.8 Gy, 41 • 70 Gy, 28	3D and IMRT	• 69.6 Gy • 80 Gy	• 70.8 Gy • 77 Gy	69.6	• 85.3% • 86.3%‖	• ≥G3 2.6% • ≥G3 4.1%	• ≥G3 2.3% • ≥G3 3.5%
PROFIT (ongoing)[24]	1,204 I	• 78 Gy, 39 • 60 Gy, 20	3D and IMRT	• 78 Gy • 77.1 Gy	• 78 Gy • 72 Gy	NA	NA	NA	NA

3D, 3D-conformal radiotherapy; G2, grade 2; G3, grade 3; H, high-risk disease; I, intermediate-risk disease; IMRT, intensity-modulated radiotherapy; L, low-risk disease; NA, not available; NTD, normalized total dose. *NTD at 2 Gy per fraction using an α/β ratio of 1.5 Gy or 3 Gy to estimate the tumoricidal radiation dose for prostate cancer or late effects of radiation on dose-limiting normal tissues, respectively. ‡60 Gy in 20 fractions not inferior to 74 Gy in 37 fractions (HR 0.83, 90% CI 0.68–1.02); HR 1.208 was set to claim noninferiority. §64.6 Gy in 19 fractions not inferior to 78 Gy in 39 fractions (HR 0.86, 90% CI 0.63–1.16). ‖70 Gy in 28 fractions not inferior to 73.8Gy in 41fractions (HR 0.85, 95% CI 0.64–1.14); HR <1.52 was set to claim noninferiority.

Hegemann et al. Radiation Oncology 2014, 9:275
http://www.ro-journal.com/content/9/1/275

RADIATION ONCOLOGY

REVIEW Open Access

Hypofractionated radiotherapy for prostate cancer

Nina-Sophie Hegemann[1], Matthias Guckenberger[2], Claus Belka[1], Ute Ganswindt[1], Farkhad Manapov[1] and Minglun Li[1*]

Abstract

In the last few years, hypofractionated external beam radiotherapy has gained increasing popularity for prostate cancer treatment, since sufficient evidence exists that prostate cancer has a low α/β ratio, lower than the one of the surrounding organs at risk and thus there is a potential therapeutic benefit of using larger fractionated single doses. Apart from the therapeutic rationale there are advantages such as saving treatment time and medical resources and thereby improving patient's convenience. While older trials showed unsatisfactory results in both standard and hypofractionated arm due to insufficient radiation doses and non-standard contouring of target volumes, contemporary randomized studies have reported on encouraging results of tumor control mostly without an increase of relevant side effects, especially late toxicity. Aim of this review is to give a detailed analysis of relevant, recently published clinical trials with special focus on rationale for hypofractionation and different therapy settings.

Hegemann et al. Radiation Oncology 2014, 9:275
http://www.ro-journal.com/content/9/1/275

Table 1 Hypofractionated primary radiotherapy for prostate cancer

Institution	Number of patients	Fractionation (total dose/singel dose/fractions)	EQD for tumor α/β-ratio 1.4Gy	EQD for normal tissue α/β-ratio 3Gy	Follow-up	Acute GU toxicitiy	Late GU toxicity	Acute GI toxicity	Late GI toxicity	Therapeutic outcomes
Rome, Italy [14]	168 pat.	Arm I: 80Gy/2Gy/40 fractions; Arm II: 62Gy/3.1Gy/20 fractions, 4x/week	82.1Gy	74.2Gy	70 months	Arm I: 40% ≥ II° GI, Arm II: 47% ≥ II° GI.	Arm I: 16% ≥ II° GI, Arm II: 11% ≥ II° GI.	Arm I: 21% = II° GI, Arm II: 35% = II° GI.	Arm I: 17% ≥ II° GI, Arm II: 14% ≥ II° GI.	Hypofraction-RT is not inferior to conventional RT, potentially even better for high-risk pat. (IPSA > 20 ng/ml, GS > 7, cT > 2c).
11 UK centres [15]	Arm I: 153 pat. 74Gy; Arm II 153 pat. 60Gy and 151 pat. 57Gy.	Arm I: 74Gy/2Gy/37 fractions; Arm II: 57-60Gy/3Gy/19-20 fractions	73.8/77.6Gy	68.4/72Gy	50.5 months	-	3 pat. (2 - 2%) in 74Gy group, 3 (2 - 2%) in 60Gy group, and 0 in 57Gy group ≥ II° GU.	-	6 pat. (4 - 3%) in Arm I ≥ II° GI RTOG, 5 pat. (3 - 6%) in Arm II, 2 (1 - 4%) in 57Gy group.	-
Fox Chase, Philadelphia [16]	307 pat. (ASTRO Update 2011)	Arm I: 76Gy/2Gy/28 fractions; Arm II: 70.2Gy/2.7Gy/26 fractions	84.7Gy	80Gy	5 years	Arm I: 54% > II°; 2% > III°; Arm II: 40% > II°; 8% > III°.	Arm I: 8.3%; Arm II: 18.3% at 5 years.	Arm I: 8% > II° GI; Arm II: 18% > II° GI.	-	biochemical recurrence 21.5% vs. 21.9% at 5 years
MDACC [17]	101 pat. in CIMRT, 102 pat. in HIMRT arm. For all pat. 28% low-risk, 71% intermed.-risk, 1% high-risk	CIMRT arm: 75.6 Gy/1.8Gy/42 fractions; HIMRT arm: 72Gy/2.4Gy/30 fractions	85,5Gy	81Gy	6 years	-	At 5 years, CIMRT: 15% I°, 14% II°, 1% III°; HIMRT: 10% I°, 15% II°, 0% III°.	-	At 5 years, CIMRT: 17% I°, 4% II°, 1% III°;HIMRT: 26% I°, 9% II°, 2% III°.	-

Ontario, Canada [11]	Arm I: 470, Arm II: 436 pat.	Arm I: 66Gy/2Gy/33 fractions; Arm II: 52.5Gy/ 2.63Gy/20 fractions	62.2Gy	59.1Gy	5.7 years	Arm I: 7% ≥ III° GU, Arm II: 11.4% ≥ III° GU.	Arm I: 1.9% ≥ III° GU, Arm II: 1.9% ≥ III° GU.	Arm I: 2.6% ≥ III° GI, Arm II: 4.1% ≥ III° GI.	Arm I: 1.3% ≥ III° GI, Arm II: 1.3% ≥ III° GI.	at 5 years, BCF in Arm I 53%, in Arm II 60%.
Adelaide, Australia [13]	Arm I: 108 pat.; Arm II: 109 pat.	Arm I: 64Gy/2Gy/32 fractions; Arm II: 55Gy/ 2.75Gy/20 fractions	67.1Gy	63.25Gy	90 months	-	no signif. diff. between 2 groups at 5 years	-	no signif. diff. between 2 groups	biochemical relapse-free survival at 90 months 53% in hypofraction Arm vs. 34% in control Arm.
Vilnius, Lithuania [50]	91 pat. low- and intermed.-risk	Arm I: 74Gy/2Gy/37 fractions; Arm II: 57Gy = 13x3Gy + 4x4.5Gy	84.9Gy	73.8Gy	3 months	Arm I: 21 (47.7%) and Arm II: 9 (19.1%) = II° GU.	-	Arm I: 10 (22.7%) and Arm II: 8 (17%) = II° GI.	-	-
Milan, Italy [51]	337 all cT1-2. 40.9% low-risk; 43.3% intermed-risk; 14.2% high-risk.	70.2Gy/2.7Gy/26 fations	84.7Gy	80Gy	19 months	3.5% ≥ II° GU, 6.2% ≥ III° GU.	10.4% ≥ II° GU, 1.6% ≥ III° GU.	11.3% ≥ II° GI, 1.2% ≥ III° GI.	7.5% ≥ II° GI, 1.3% ≥ III° GI.	-
Cleveland Ohio [18]	770 pat, 34% low-risk, 28% intermed-risk, 38% high-risk .	70Gy/2.5Gy/28 fractions, but mean target dose was 75.3Gy at 2.7Gy.	80.3Gy, 90.8Gy (mean target dose)	77Gy	45 months	48% I°, 18% II°, 1% III° RTOG GU.	4.3% I°, 5.1% II°, 0.1%(1 pat.) III° RTOG GU.	40% I°, 9% II° RTOG GI.	5.9% I°, 3.1% II°, 1.3% III°, 0.1% (1 pat.) IV° RTOG GI.	nadir + 2 ng/ml bRFS at 5 years 83%, and 94%, 83%, 72%.

Table 2 Hypofractionated adjuvant/salvage radiotherapy

Reference	Study design	Institution	Patient collection	Fractionation (total dose/singel dose/fractions)	BQD for tumor α/β ratio 1.4Gy	EQD for normal tissue α/β ratio 3Gy	IMRT	Follow-up	Acute GU toxicitiy	Late GU toxicity	Acute GI toxicity	Late GI toxicity	Therapeutic outcomes
Cozzarini, C. [23]	Prospective phase I-II for adjuvant RT	Milan, Italy	247 patients	65.8Gy/2.35Gy/28 fractions adj. RT for 117 pat.; 71.4-72.8Gy/2.55Gy/28 fractions salvage RT for 80 pat.; 58Gy/2.9Gy/20 fractions for 50 pat. Conventional arm 929 pat. 70.2Gy/1.8Gy/39 fractions	72.6Gy adjuvant RT; 83.0Gy salvage RT; 73.4Gy for the other 50 pat.	α/β ratio = **5Gy** for late GU toxicity! 69.14Gy adjuvant RT; 77.1Gy salvage RT; 65.5Gy for the other 50 pat.	Tomo-RT	68 months median	-	41/247 (16.5%) ≥ III° GU in hypofraction arm; 72/929 (7.7%) in conventional arm	-	-	-
Kruse, T.J. [26]	Retrospective for salvage RT	Madison, Wisconsin	108 patients	65Gy/2.5Gy/26 fractions	74.6Gy	71.5Gy	IMRT	32.4 months median	8 pat. (7%) II° and 1 pat. III° GU RTOG.	16 pat. (15%) II° GU RTOG.	15 pat. (14%) II GI RTOG.	4 (4%) pat. II° GI RTOG.	freedom from biochem. failure at 4 years 67% ± 5.3%.
Ippolito, E. [24]	Prospective phase I for dose-escalation, adjuvant RT	Campobasso, Italy	25 patients	7 pat. 56.8Gy/2.27Gy/25 fractions; 6 pat. 59.7Gy/2.39Gy/25fractions; 6 pat. 61.25Gy/2.45Gy/25fractions; 6 pat. 62.5Gy/2.5Gy/25 fractions	7 pat. 61.3Gy; 6 pat. 66.5Gy; 6 pat. 69.4Gy; 6 pat. 71.7Gy.	7 pat. 59.9Gy; 6 pat. 64.4Gy; 6 pat. 66.8Gy; 6 pat. 68.8Gy.	IMRT	19 months median	9/25 (36%) II° GU.	-	5/25 (20%) II° GI.	-	-
Lee, W. [52]	Retrospective for salvage RT	Manchester	37 patients	50-52.5Gy/2.5-2.63Gy/20 fractions	57.4-62.2Gy	55-59.1Gy	-	30.6 months median	0% II° GU.	16 pat. I° GU, 0 pat. II° GU.	0% II° GI.	4 pat. I° GI, 1 pat. II° GI.	3-year disease-free survival is 74%.

Table 3 Hypofractionated radiotherapy including pelvic nodes

Reference	Study design	Number of patients	Fractionation (total dose/singel dose/fractions)	pelvic RT dose schema	EQD for tumor α/β-ratio 1.4Gy	EQD for normal tissue α/β-ratio 3Gy	Follow-up	Acute GU toxicitiy	Late GU toxicity	Acute GI toxicity	Late GI toxicity
McDonald, A. M. [31]	Retrospective	57 PORT and 31 WPRT	70Gy/2.5Gy/28 fractions	50.4Gy/ 1.8Gy/28 fractions	80.3Gy	77Gy	41 months	18/31(58%) in PORT, 28/57 (49%) in WPRT ≥2°	4/57(7%)in WPRT, 0% in PORT ≥ III°	7/31(23%) in PORT, 23/57 (40%) in WPRT ≥ II°	0% in PORT, 10/57 (18%) in WPRT ≥ I°
McCammon, R. [30]	Retrospective	30	70Gy/2.5Gy/28 fractions	50.4Gy/ 1.8Gy/28 fractions	80.3Gy	77Gy	24 months	36.7% ≥2°	10% ≥ II°	20%	13% ≥ II°
Adkinson, J.B. [29]	Phase I prospective	53	70Gy/2.5Gy/28 fractions	56Gy/ 2Gy/28 fractions	80.3Gy	77Gy	25.4 months	20/53(38%) ≥2°	14/53(27%) ≥ II°	17/53(32%) ≥ II°	4/53(8%) ≥ II°
Pervez, N. [32]	Phase II prospective	60 high-risk	68Gy/2.72Gy/25 fractions	45Gy/ 1.8Gy/25 fractions	82.4Gy	77.8Gy	3 months	34(40%) ≥ II°	-	21(35%) ≥ II°	-
Quon, H. [33]	Prospective phase I-II	97 pat. High-risk	67.5Gy/2.7Gy/25 fractions	45Gy/ 1.8Gy/25 fractions	81.4Gy	77Gy	39 months median	50% I°, 39% II°, 4% III°	9% I°, 5% II°, 3% III°, 1% IV°.	4% pat. 0°, 59% I °, 37% II°	54% pat. 0°, 40% I°, 7% II°
Guckenberg, M. [34]	150 consecutive patients	109 PORT and 41 WPRT	73,9Gy/2,31Gy/32 fx; 76.2Gy/2.31Gy/33 fx.	45Gy/ 1.8Gy/25 fractions	80.6Gy/83.1Gy.	78.5Gy; 80.9Gy.	50 months median	85% pat. I°-II°	22.4% Pat. ≥ II° at 60 months; less than 5% pat. III°.	-	2 pat. ≥III°
Fonteyne, V. [53]	Prospective phase I	31 patients	69.3/2.77Gy/25 fractions	50Gy/ 2.0Gy/25 fractions	85Gy	80Gy	3 months median	14/31 (45%) II°, 3/31 (9.7%) III°	-	14/31 (45%) II° lower GI toxicity	-
Zilli, T. [54]	Prospective trial	78 pat.	50.4Gy/1.8Gy/28 fractions +6x4Gy boost (twice weekly)	50.4Gy/ 1.8Gy/28 fractions	85.2Gy with 1.5Gy alpha/ beta	-	57 months	~1% = III°	5 year sulvival rate without II° GU toxicity 79.1 ± 4.8%	~1% = III°	5 year sulvival rate without II° GI toxicity 84.1 ± 4.5%

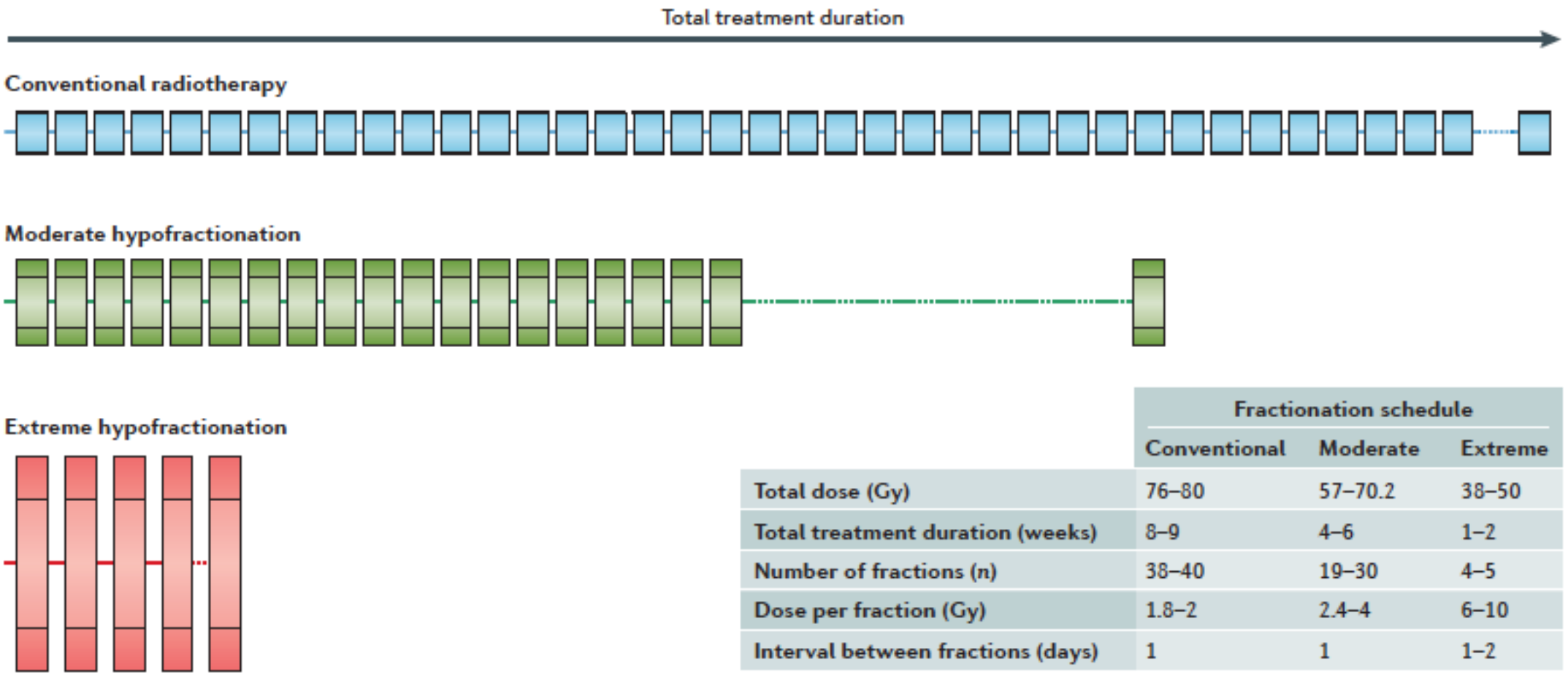
Table 4 Hypofractionated IMRT/IGRT trials

Reference	Study design	Number of patients	Fractionation (total dose/ singel dose/ fractions)	EQD for tumor α/β-ratio 1.4Gy	EQD for normal tussues α/β-ratio 3Gy	IGRT	Follow-up	Acute GU toxicity	Late GU toxicity	Acute GI toxicity	Late GI toxicity	Therapeutic outcomes
Arcangeli, G. [14]	Phase III prospective	168 pat.	Arm I: 80Gy/ 2Gy/40 fractions, ArmII: 62Gy/ 3.1Gy/20 fractions, 4x/week.	82.1Gy	74.2Gy	daily portal imaging	70 months	-	Arm I: 16% ≥ II° GI, Arm II: 11% ≥ I° GI, at 3 years.	-	Arm I: 17% ≥ II° GI, Arm II: 14% ≥ II° GI, at 3 years.	Hypofraction-RT is not inferior to conventional RT.
Dearnaley, D. [15]	Phase III prospective	Arm I: 153 pat. 74Gy; Arm II 153 pat. 60Gy and 151 pat. 57Gy.	Arm I: 74Gy/ 2Gy/37 fx; Arm II: 57-60 Gy/3Gy/19-20 fx.	Arm II: 73.8/ 77.6Gy	Arm II: 68.4/ 72Gy	no	50.5 months	-	At 2 years, 3 pat. (2 - 2%) in 74Gy group, 3 (2 - 2%) in 60Gy group, and 0 in 57Gy group ≥ II° GU.	-	At 2 years, 6 pat. (4 - 3%) in Arm I ≥ II° RTOG, 5 pat. (3 - 6%) in 60Gy group, 2 (1 - 4%) in 57Gy group.	-
Pollack, A. [16]	Phase III prospective	307 (ASTRO Update 2011)	Arm I: 76Gy/ 2Gy/28 fx; Arm II: 70.2Gy/ 2.7Gy/26 fx.	Arm II: 84.7Gy	Arm II: 80Gy.	no	5 years	Arm I: 54% > II°; 2% > III°; Arm II: 40% > II°; 8% > III°.	Arm I: 8.3%; Arm II: 18.3% at 5 years	Arm I: 8% ≥ II°; Arm II: 18% ≥ II°	4.5% ≥ II° GI.	biochem. recurrence 21.5% vs. 21.9% at 5 years
McDonald, A.M. [31]	Retrospective	57 PORT and 31 WPRT	70Gy/2.5Gy/ 28 fractions	80.3Gy	77Gy	CBCT daily	41 months	18/31 (58%) in PORT, 28/ 57(49%) in WPRT ≥ II°	4/57(7%)in WPRT, 0% in PORT ≥ III° GU	7/31 (23%) in PORT, 23/57 (40%) in WPRT ≥ II° GI	0% in PORT, 10/57(18%) in WPRT ≥ II° GI	-

Adkinson, J.B. [29]	Phase I prospective	53 pat.	70Gy/2.5Gy/ 28 fractions	80.3Gy	77Gy	yes	25.4 months	20/53 (38%) ≥ II° GU	14/53(27%) ≥ II° GU	17/53 (32%) ≥ II° GI	4/53(8%) ≥ II° GI	biochem. control (nadir +2) 81.2 ± 6.6%
Jereczek-Fossa, B.A. [51]	Prospective longitudinal follow-up	337 pat. cT1-2, 40.9% low-risk; 43.3% intermed-risk; 14.2% high-risk.	70.2Gy/2.7Gy/ 26 fractions	84.7Gy	80Gy	BAT 72%, stereo X-ray 16.4%, CBCT 11.9% pat.	19 months	35% ≥ II° GU, 6.2% ≥ III° GU.	10.4% ≥ II° GU, 1.6% ≥ III° GU.	11.3% ≥ II° GI, 1.2% ≥ III° GI.	7.5% ≥ II° GI, 1.3% ≥ III° GI.	-
Kupelian, P. A. [18]	Retrospective	770 pat, 34% low-risk, 28% intermed-risk, 38% high-risk D'Amico criteria.	70Gy/2.5Gy/ 28 fractions, but mean target dose was 75.3Gy at 2.7Gy!	80.3Gy with 1.4Gy α/β-ratio (83.8Gy with 3.5Gy α/β-ratio in publication)	77Gy	IGRT with BAT tranabdominal ultrasound	45 months	33% Pat. 0°, 48% I°, 18% II°, 1% III° RTOG	90.5% pat. 0°, 4.3% I°, 5.1% II°, 0.1%(1 pat.) III° RTOG	51% pat. 0°, 40% I°, 9% II° RTOG	89.6% pat. 0°, 5.9% I°, 3.1% II°, 1.4% ≥ III° RTOG	At 5 years 94%, 83%, 72% for low-/intermed./ high-risk respectively (Nadir + 2 ng/ml)
Quon, H. [33]	Prospective phase I-II	97 pat. High-risk	67.5Gy/2.7Gy/ 25 fractions	81.4Gy	77Gy	IGRT with gold marker	39 months median	8% pat. 0°, 50% I°, 39% II°, 4% III° **CTCAE**	82% pat. 0°, 9% I°, 5% II°, 3% III°, 1% IV°.	4% pat. 0°, 59% I°, 37% II°	54% pat. 0°, 40% I°, and 7% II°	4 year bFFS 90.5%.
Martin, J. [40]	Prospective phase I-II	92 pat., mainly intermed./low risk	60Gy/3Gy/ 20 fractions	77.6Gy	72Gy	IGRT with gold marker	38 months median	32% pat. 0°, 43% I°, 25% II° RTOG	90% pat. 0°, 7% I°, 3% II° RTOG	66% pat. 0°, 22% I°, 11% II°, 1% IV° RTOG	93% pat. 0°, 2% I°, 4% II° RTOG	3 year biochemical control 76%.

SBRT

- Highly focused radiation concentrated on tumors – low dose to surrounding tissue
- Single or hypofx treatments – high dose per treatment
- Very precise delivery – image guidance, immobilization, and other technologies to ensure accuracy
- Historically used mainly for treating intracranial lesions



	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

Figure 1 | **Radiotherapy fractionation schedules for the management of patients with prostate cancer.** Fractionation of a prescribed radiation dose over several treatment sessions is used to protect nonmalignant tissues adjacent to the tumour. Technological developments have improved the precision of radiation delivery, enabling increased fraction doses and shorter treatment schedules without compromising efficacy but increasing patient compliance. Conventionally fractionated radiotherapy is usually delivered in 38–40 sessions of single 1.8–2 Gy fractions, resulting in an 8–9-week treatment duration. In moderate hypofractionation, 19–30 sessions of single 2.4–4 Gy fractions are given over a total of 4–6 weeks. Extremely hypofractionated radiotherapy consists of 4–5 treatment sessions of 6–10 Gy doses each and treatment is usually concluded after 1–2 weeks.

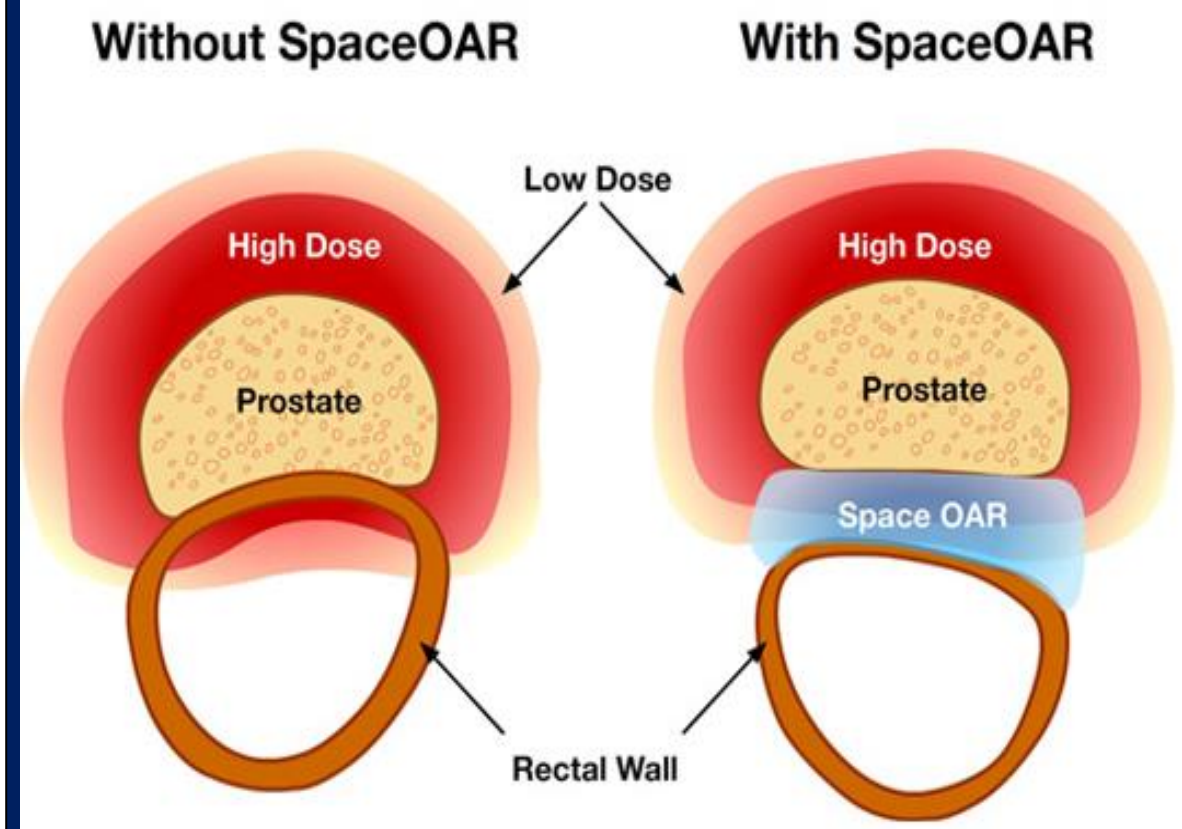
Table 3 | **Phase I–II trials of extremely hypofractionated radiotherapy* for organ-confined prostate cancer**

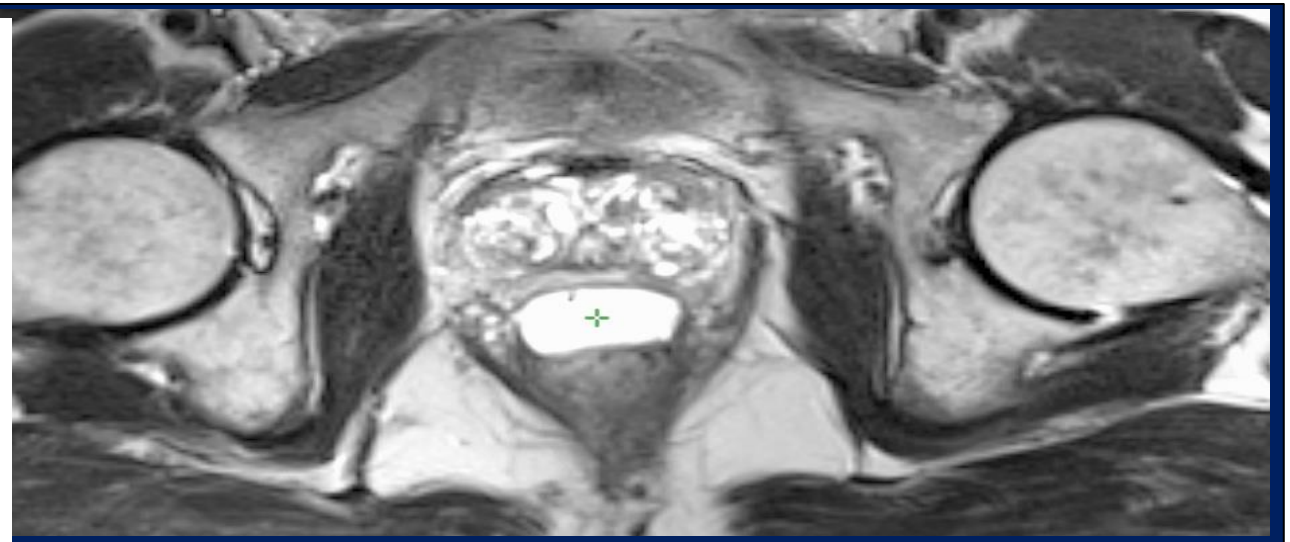
Study	Patients (n) and disease characteristics	Schedule (total dose, n of fractions)	Technique	Median follow-up period (months)	Biochemical-recurrence-free survival	Acute toxicity ≥G3		Late toxicity ≥G3	
						Genitourinary	Gastrointestinal	Genitourinary	Gastrointestinal
Linac-based									
Madsen *et al.* (2007)[36]	40 L–I–H	33.5 Gy, 5	IMRT	41	90%	0%	0%	0%	0%
Aluwini *et al.* (2013)[37]	50 L–I	38 Gy, 4	IMRT and IGRT	23	100%	2%	8%	0%	6%
Loblaw *et al.* (2013)[38]	84 L	35 Gy, 5	IMRT and IGRT	55	98%	0%	1%	1%	1%
Kim *et al.* (2014)[39]	91 L–I	• 45 Gy, 5 • 47.5 Gy, 5 • 50 Gy, 5	IMRT (tomotherapy)	24.5	NR	1.6%	0%	4.9%	4%
Robotic-based									
Fuller *et al.* (2014)[35]	79 L–I	38 Gy, 4	CK	42	• L: 100% • I: 92%	0%	0%	0%	6%
King *et al.* (2012)[40]	67 L	36.25 Gy, 5	CK	32.4	94%	0%	0%	0%	3.5%
Bolzicco *et al.* (2013)[41]	100 L–I–H	35 Gy, 5	CK	36	95%	0%	0%	0%	0%
Chen *et al.* (2013)[42]	100 L–I–H	36.25 Gy, 5	CK	27.6	99%	0%	0%	0%	1%
Oliai *et al.* (2013)[43]	70 L–I–H	• 35 Gy, 5 • 36.25 Gy, 5 • 37.5 Gy, 5	CK	31	• L: 100% • I: 95% • H: 77.1%	0%	4%	0%	3%
Meier *et al.* (2015)[44]	137 I	40 Gy, 5	CK	56	95%	0%	0%	0%	1.5%
Katz *et al.* (2014)[45]	515 L–I–H	35–36.25 Gy, 5	CK	72	• L: 95.8% • I: 89.3% • H: 68.5%	0%	0%	0%	1.7%

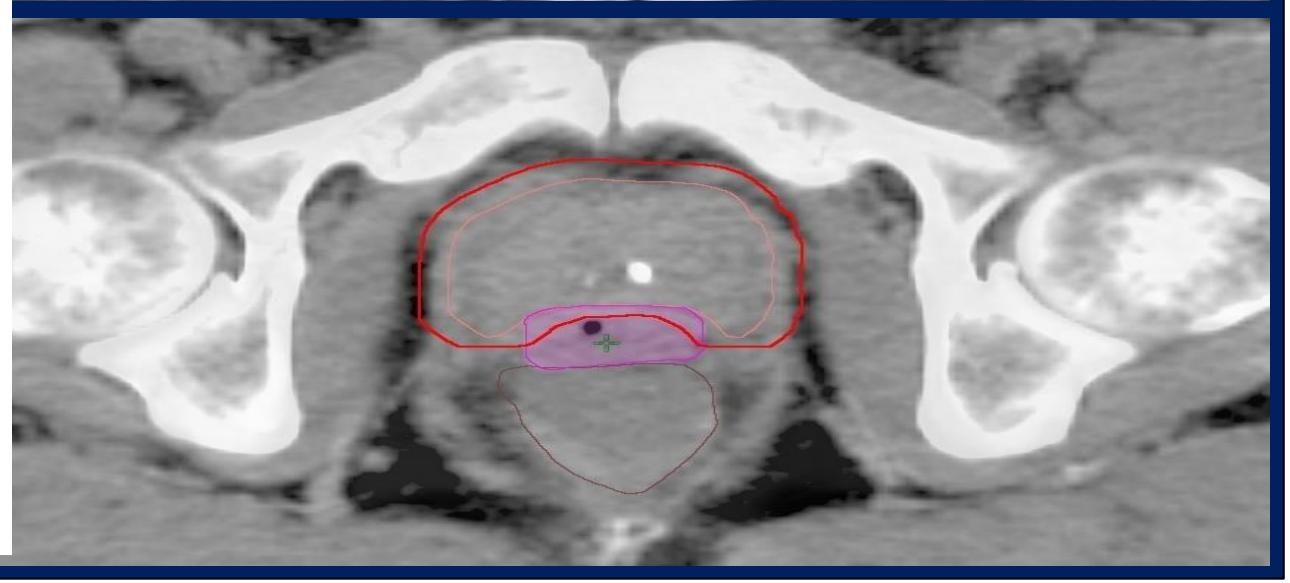
S. Arcangeli – C. Greco
Nature Review Urology, 2016

Space OAR

SpaceOAR hydrogel moves the rectum away from the high dose radiation field







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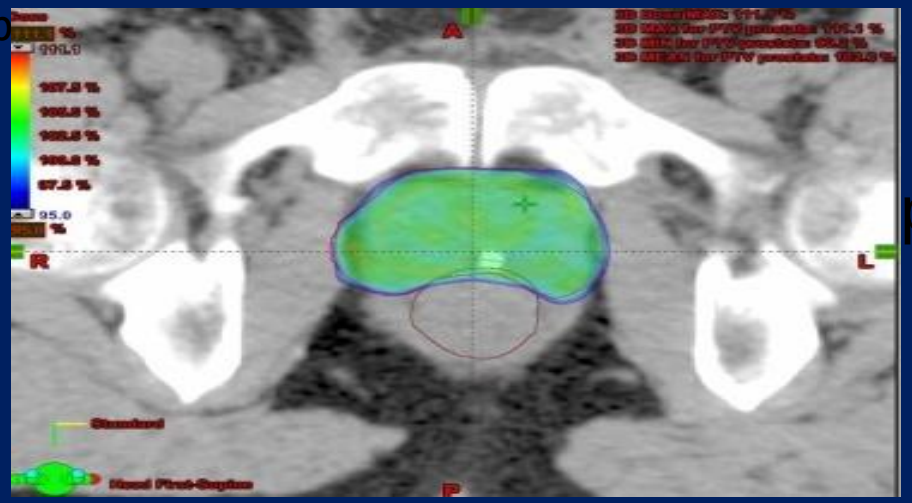
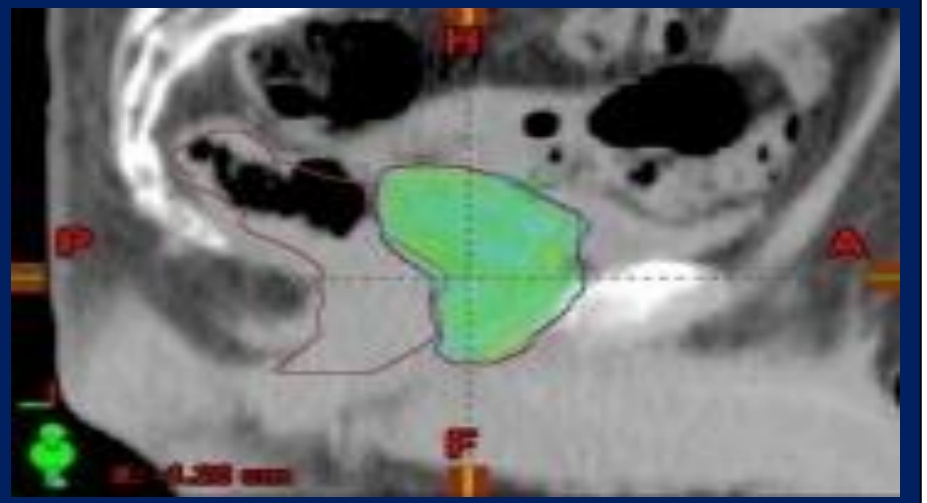
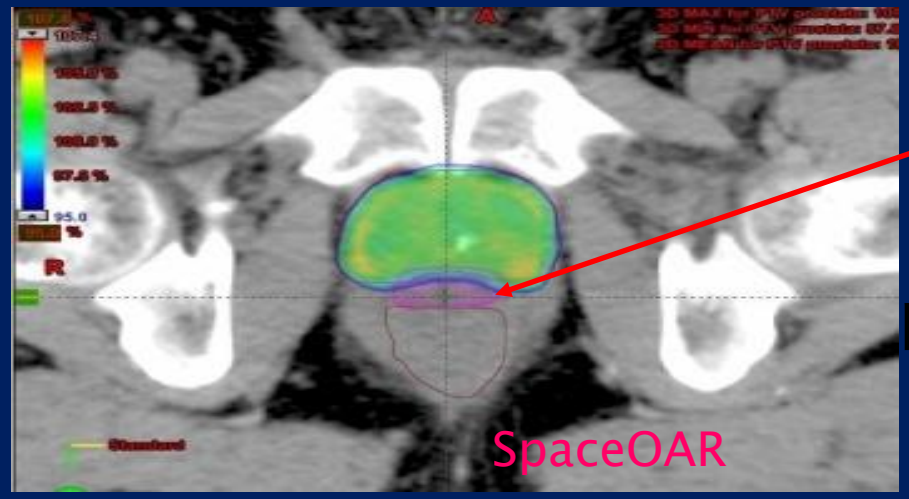


pre- gel injection



Anterior rectal wall sparing



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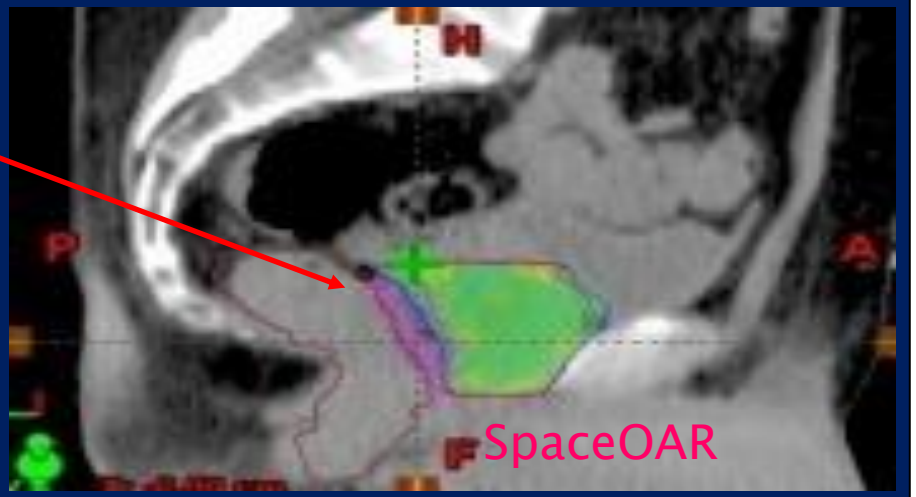

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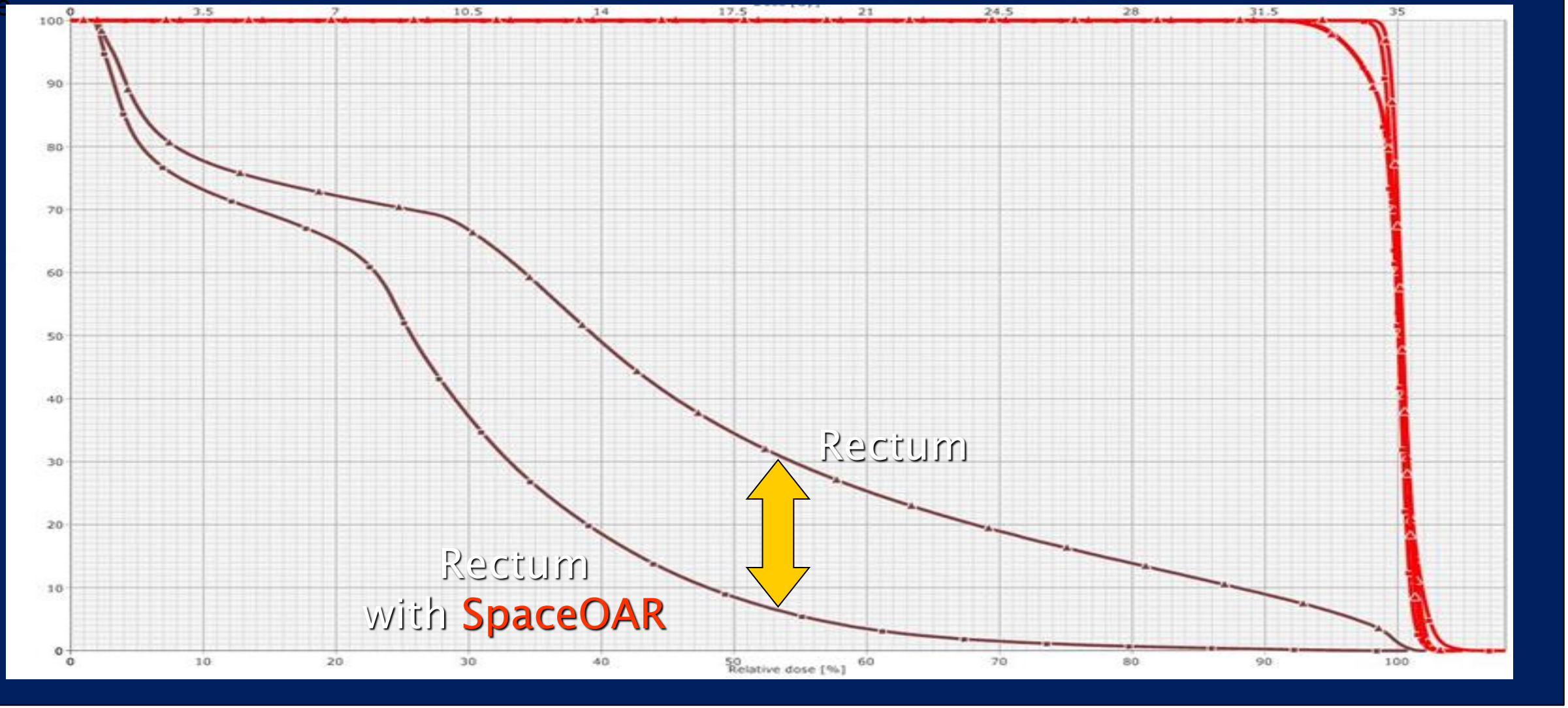


Hypofractionated radiotherapy for organ-confined prostate cancer: is less more?

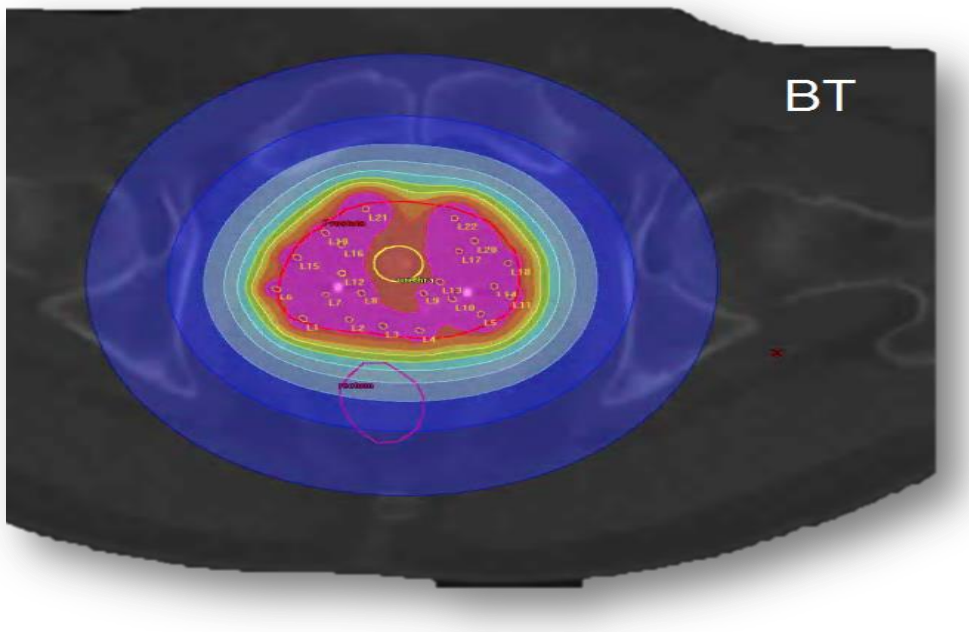
Stefano Arcangeli and Carlo Greco

Abstract | Moderate hypofractionation of radiotherapy is widely considered a viable alternative to conventional fractionation for the treatment of patients with organ-confined prostate cancer, but stereotactic body radiotherapy (SBRT) is rapidly emerging as a novel treatment modality for this disease. Advances in treatment planning, image guidance, target position reproducibility and on-line tracking, coupled with a compelling radiobiological rationale, have promoted SBRT as a safe and effective treatment. Dose escalation to the tumour tissue through a decreased number of radiation fractions improves patient comfort and convenience, as well as treatment cost-effectiveness, compared with conventional radiotherapy regimens. Several clinical trials have investigated moderate and extreme hypofractionation of radiotherapy in patients with prostate cancer. Evidence is accumulating which suggests that the use of moderately hypofractionated radiotherapy can be recommended regardless of cancer risk group. Regimens of extremely hypofractionated radiotherapy have shown very good short-term efficacy and safety outcomes, but appropriately designed trials with extended follow-up monitoring are required to confirm long-term outcomes.

Key points

- Moderate and extreme hypofractionation are alternatives to conventional radiotherapy for organ-confined prostate cancer that were developed following technological advances in radiation delivery and tumour imaging
- In strategies of moderate and extreme hypofractionation, increased radiation doses are administered per treatment session, reducing overall treatment duration and improving patient compliance
- Prostate cancer seems particularly suitable for hypofractionated radiotherapy as these tumours have unique sensitivity to increased radiation dose fractions in comparison with surrounding healthy tissues
- Trials investigating clinical and toxicity outcomes of moderate hypofractionation schedules have sufficient follow-up data to show that efficacy and toxicity of these schedules are similar to those of conventionally fractionated regimens
- Several phase II trials of extremely hypofractionated radiotherapy in men with low-risk or intermediate-risk prostate cancer show excellent short-term outcomes, but extended follow-up monitoring is required to confirm long-term safety
- Extreme hypofractionation schedules are highly cost-effective, despite the need for cutting-edge technologies, but the efficacy and safety of dose escalation and single-dose treatments still need to be confirmed in carefully conducted clinical trials

Brachiterapia



Brachiterapia

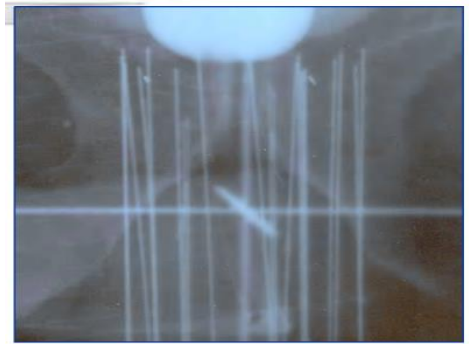
E' una **tecnica radioterapica** conformazionale che consiste nel **posizionare sorgenti radioattive all' interno del tumore** o a contatto con esso per un tempo prestabilito!

La caratteristica fondamentale è
un rapido **"gradiente di dose"** che consente di adattarsi al volume da irradiare, **risparmiando i tessuti sani** circostanti!

Brachiterapia

Impianto permanente
LDR (125 I , 103 Pd) erogazione continua della dose (mesi)

Impianto temporaneo
HDR (192 Ir) erogazione frazionata della dose (minuti)



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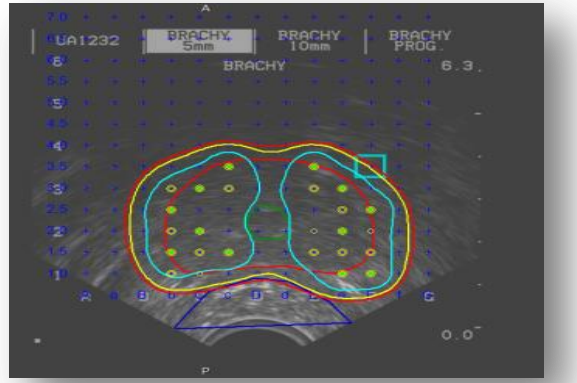


6.3.5 *Low-dose rate and high-dose rate brachytherapy*

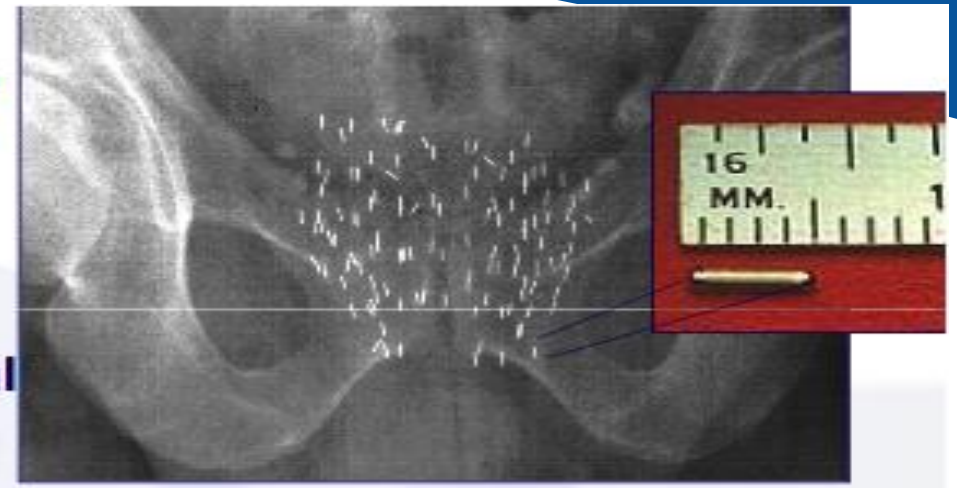
6.3.5.1 *Low-dose rate (LDR) brachytherapy*

There is a consensus on the following eligibility criteria for LDR monotherapy [479]:

- stage cT1b-T2a N0, M0;
- Gleason score 6 with v 50% of biopsy cores involved with cancer or;
- Gleason score 3 + 4 with ≤ 33% of biopsy cores involved with cancer;
- an initial PSA level of ≤ 10 ng/mL;
- a prostate volume of < 50 cm^3;
- an International Prostatic Symptom Score (IPSS) ≤ 12 and maximal flow rate > 15 mL/min on urinary flow tests [408].

	Differences in prostate brachytherapy techniques
Low Dose Rate (LDR)	• Permanent seeds implanted • Uses I-125 (most common), Pd-103 or Cs-131 isotopes • Radiation dose delivered over weeks and months • Acute side effects resolve over months • Radiation protection issues for patient and carers
High Dose Rate (HDR)	• Temporary implantation • Ir-192 isotope introduced through implanted needles or catheters • Radiation dose delivered in minutes • Acute side effects resolve over weeks • No radiation protection issues for patient or carers

ADVANTAGES OF BRT



Patient comfort

- Overnight hospitalization
- Rapid resumption of normal activities
- High satisfaction

Dosimetric advantages

- High intraprostatic dose
- Low critical organ dose

Favorable clinical outcomes

- 10 year biochemical results

Low long-term morbidity

But time consuming, requires training and good logistics

Operator-dependent procedure

Postoperative Radiotherapy

The PSA level → Should become undetectable within 6 weeks of RP, as the prostate tissue has been removed

The American Urological Association (AUA) → biochemical recurrence following radical prostatectomy

↓

initial serum PSA of ≥ 0.2 ng/mL, with a second confirmatory level of > 0.2 ng/mL

Stamey TA, et al *N Engl J Med* 317:909-916,1987
Cookson MS, et al *J Urol* 177: 540-545, 2007

Postoperative Radiotherapy

Risk factors for progression after RP

*STRONGLY **PREDICTIVE** FOR RELAPSE :*

Preoperative factors

- **cGS ≥ 7**
- **clinical stage ≥ cT2**
- **iPSA > 10**

Kupelian 1997
Connolly 2006
Porter 2006

*STRONGLY **RELEATED** TO THE PROBABILITY OF:*
- BIOCHEMICAL RELAPSE
- LOCAL RELAPSE

Histopathological factors

- **pGS ≥ 7**
- **ECE, SV +**
- **SM +, N +**

Blute 1997
Van der Kwast 2007
Bolla 2007

Postoperative Radiotherapy

Predictive factors for **LOCAL RELAPSE**

- Late rising PSA (b-Relapse>1 year after resection) ---
- PSA doubling time >12 months
- PSA VELOCITY (increase within 12 months <0.75 ng/mL)
- GS ≤7 at RP
- SM +
- Negative LN

Pisansky TM, *J Urol;163:845-850,2000*
Stephenson A.J., et al *JCO* 25,(15): 2035-2041,2007

Postoperative Radiotherapy

Predictive factors for **DISTANT RELAPSE**

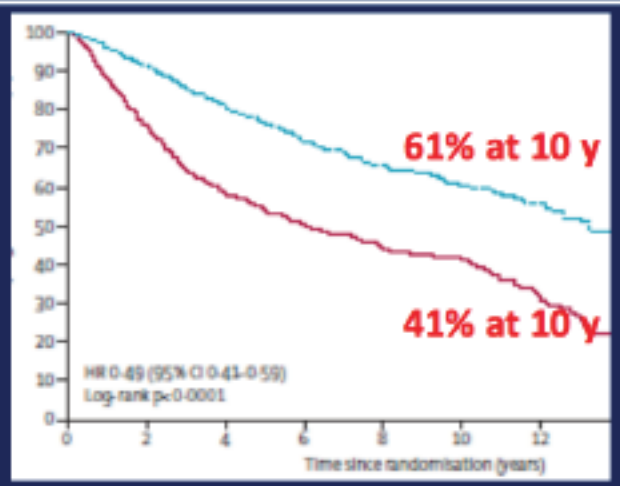
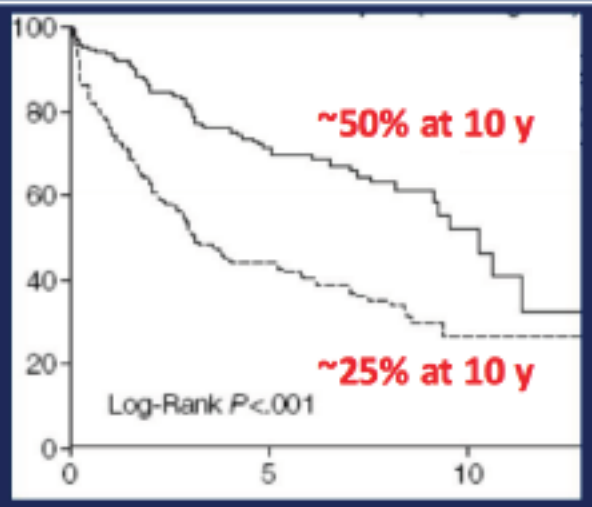
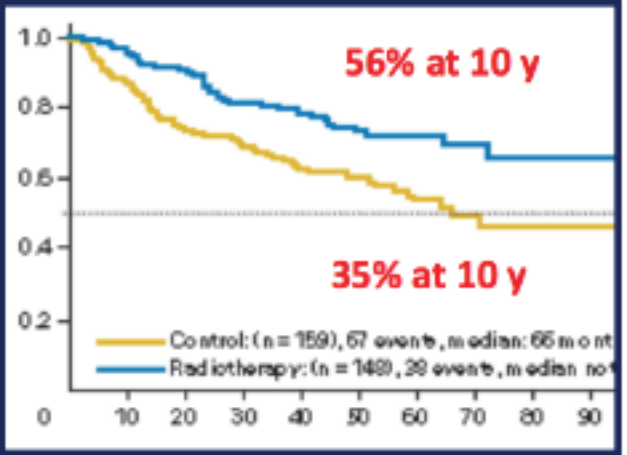
- Short PSA doubling time (<5 mhts)
- GS 8-10 at RP
- SV +
- Positive LN
- PSA pre RT> 2 ng/ml

Ward JF, *Urol, 172:2244–2248,2004*
Stephenson AJ, *Curr Treat Opt Onc* 5:357-365,2004
Pazona JF, *J Urol 174:1282–1286,2005*

Adjuvant Radiotherapy
Randomised Trials

Randomized trial	TNM inclusion criteria	Median age (yr)	No. of patients: RT *vs* observation	RT dose (Gy)	Median follow-up (yr)	bRFS: RT *vs* observation	Metastatic events: RT *vs* observation	OS: RT *vs* observation (yr)
EORTC 22911	pT2N0M0R1 or pT3N0M0 (R0-1)	65	1005 (502 *vs* 503)	60	5	74% *vs* 52% (at 5 yr)	-	-
SWOG ** 8794	pT2N0M0R1 or pT3N0M0 (R0-1)	64.9	425 (214 *vs* 211)	60-64	>12	13.8 *vs* 9.9 yr	93/214 *vs* 114/211 (P = 0.016)	15.2 *vs* 13.3
ARO 96-02/AUO AP 09/95	pT3N0M0 (R0-1)	-	385 (192 *vs* 193)	60	5	72% *vs* 54% (at 5 yr)	-	-

- **Relationship between relapse and risk factors**
- **Adjuvant radiotherapy: increases b-PFS, LC, MFS and OS**
- **Low toxicities and good tolerance**
- **LIMITS 2/3:** **- used 2D RT (higher toxicities vs 3DCRT)**
  - ** included pts with PSA >0,2 ng/ml nowadays considered biochemical relapse

	EORTC 22911	*SWOG 8794*	*ARO 9602*
bNED			
Endpoints (primary)	bPFS, LRF-10 y (7/17) DM (~11), OS-10 y (~78) bPFS: all except age>70 cPFS: age<65, +margins OS: none (worse if >70)	Clinical PFS-10 y (~70/50) On ADT- 5y (10/21) MetFS-15 y (46/38) OS-15 y (47/37)	bPFS bPFS: +margins, PSA>10, pT3a

Adjuvant Radiotherapy

Retrospective Monoinstitutional Trial

-334 pts
-pT3a / pT4 N0M0 (R0-1)

	RT < 70.2 Gy (median 66.6 Gy)	RT ≥ 70.2 Gy (median 70.2 Gy)	*P*
N° pts	153	181	
Median f.u.	38 months	36 months	
5 yrs b-RFS	71%	83%	***p = 0.001***
5 yrs DFS	88%	94%	***p = 0.005***

MULTIVARIATE ANALYSIS : RT ≥ 70.2 Gy INDIPENDENT FACTOR RELEATED TO b-RFS (p = 0.04) and DFS (p = 0.004)

Cozzarini C. et al., *IJROBP, 2009*

Patients who are most likely to benefit from immediate adjuvant radiotherapy are:

1. **Positive surgical margins**
2. **Seminal vesicle invasion**
3. **high grade tumours**
4. **high pre-RP PSA**
5. **detectable PSA >/= 0.2 after RP**

CAVE: extracapsular extension itself is NOT in the list

Salvage radiotherapy for biochemical failure after radical prostatectomy (RP)

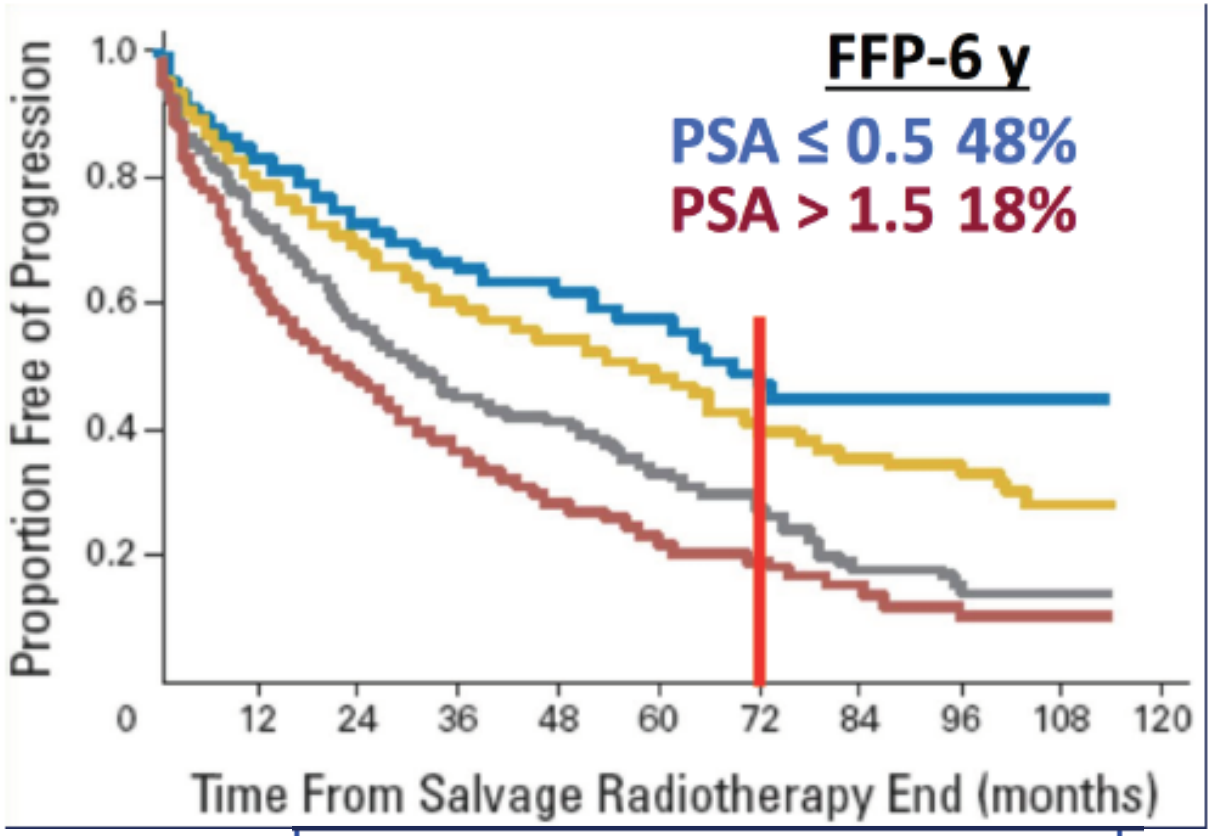
Radiotherapy is administered as salvage therapy in 2 main scenario's:

1. **Delayed rise in PSA after the PSA has dropped to undetectable level**
2. **Persistently detectable PSA after radical prostatectomy (RP)**

Salvage Radiotherapy : Stephenson, 2007

Retrospective Trial

- 1540 pts with b-Relapse
- Primary ENDPOINT: PD after SRT
- Median RT dose: 64,8 Gy
- Median FU: 53 months



FFP depends:

- **Gleason**
- **Pre PSA before RT**
- **LFN involvement**
- **Margin status**
- **PSA DT**
- **ADT use**

Stephenson AJ, et al *JCO* 25:2035-2041,2007

Salvage Radiotherapy: Trock, 2008

Retrospective Trial

- 635 pts with b-Relapse/ Local Relapse
- no SRT (397) vs SRT (160) vs 78 (SRT +OT)
- Primary ENDPOINT: PCSS
- Median dose: 66,4 Gy
- Median FU: 6 years

	RT arm	No RT arm	HR	*p*
10-year PC Specific Survival	86%	62%	0,32	< 0.001

- **The addiction of hormonal therapy to SRT did not improve PCSS**
- The increase PCSS was most marked in men with:
  - PSA doubling time < 6 months
  - Gleason Score of 8 -10

Trock BJ, et al *JAMA* 299:2760-2769,2008

Salvage Radiotherapy : Wiegel, 2009

- 162 Pts between 1997 and 2004 with b-Relapse/Local R
- no OT
- Median dose: 66 Gy
- Median FU: 41.5 months

PREDICTOR FACTORS of **b-PROGRESSION after Salvage RT**

UNIVARIATE ANALYSIS

Detectable PSA after RT	GS (≤6 vs ≥7)	pT stage (≤ T2c vs ≥T3a)	Pre RT PSA ≤0.5 vs >0.5
p<0.00005	*p=0.01*	*p=0.047*	*p=0.031*

Undosable PSA (≤ 0.1) after SRT: most significant independent predictor factor of b-PFS

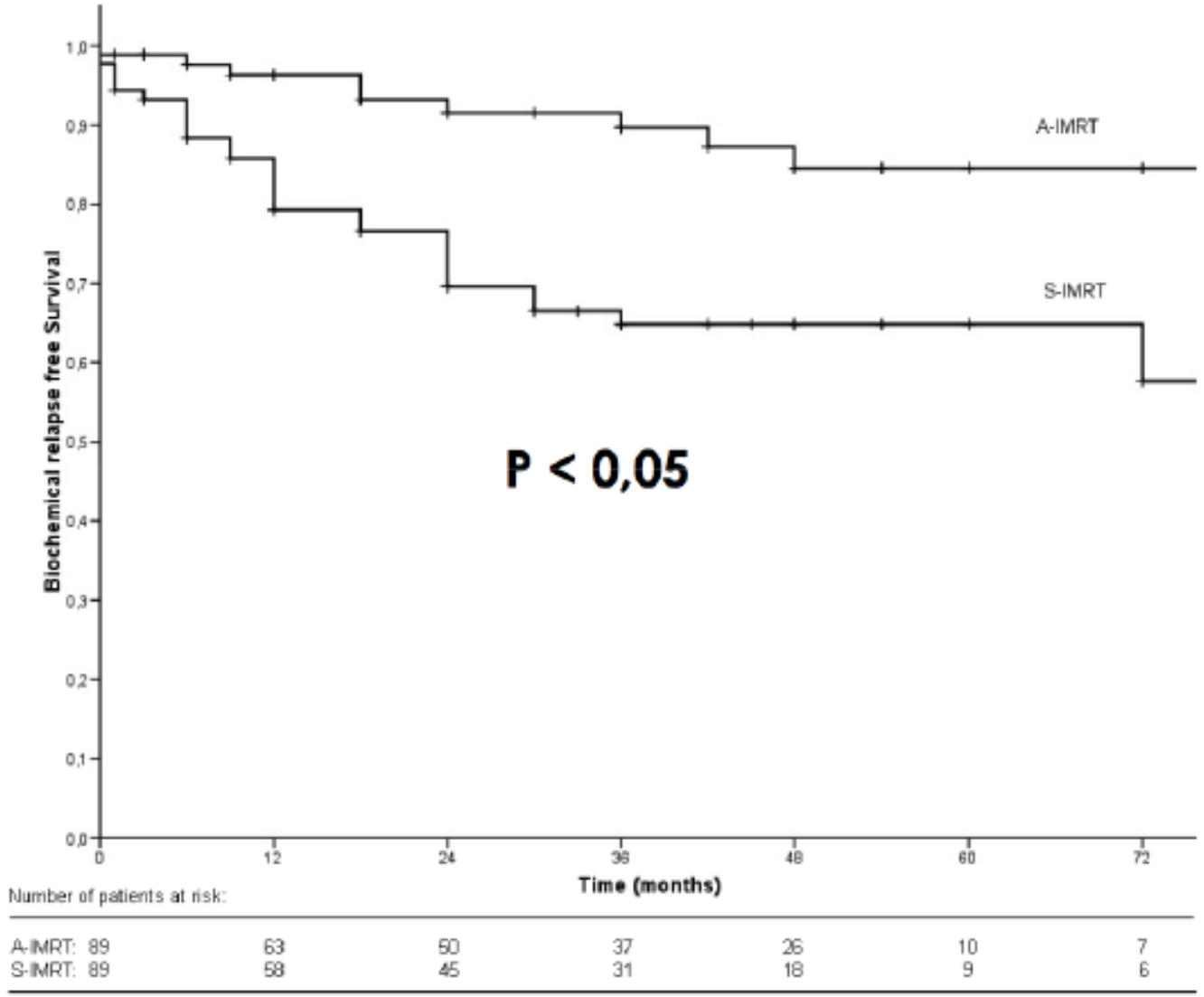
Best patients selection for Salvage RT: low preRT PSA, SM+, low pT

Wiegel T. et al., *IJROBP 73(4):1009–1016,2009*

Ideal patient for salvage....

rischio	No.	Fattori di rischio	opzioni
basso	tutti	Psa postRP azzerato PSA pre RT<0.5 ng/ml Tempo alla rec. Bioch.>2yrs assenza SVI+,pN+,GPS>7	RT
alto	uno	Psa postRP non azzerato PSA pre RT>0.5 ng/ml Tempo alla rec. Bioch.<2yrs SVI+,pN+,GPS>7	RT RT +/- OT OT +/- RT(pN+)

Is salvage RT as efficient as immediate adjuvant RT?



Number of patients at risk:

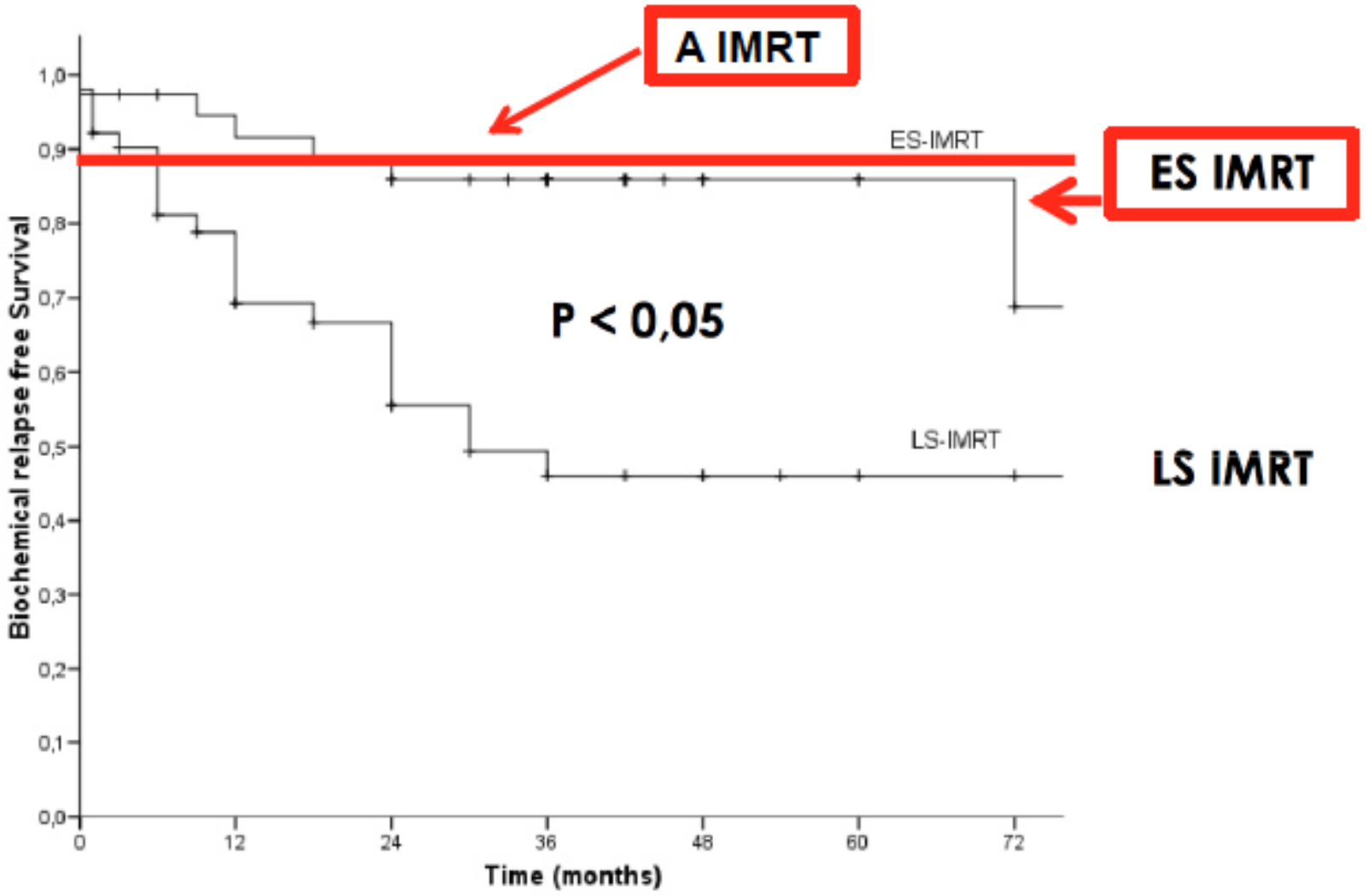
A-IMRT: 89	63	50	37	26	10	7
S-IMRT: 89	58	45	31	18	9	6

A IMRT

S IMRT

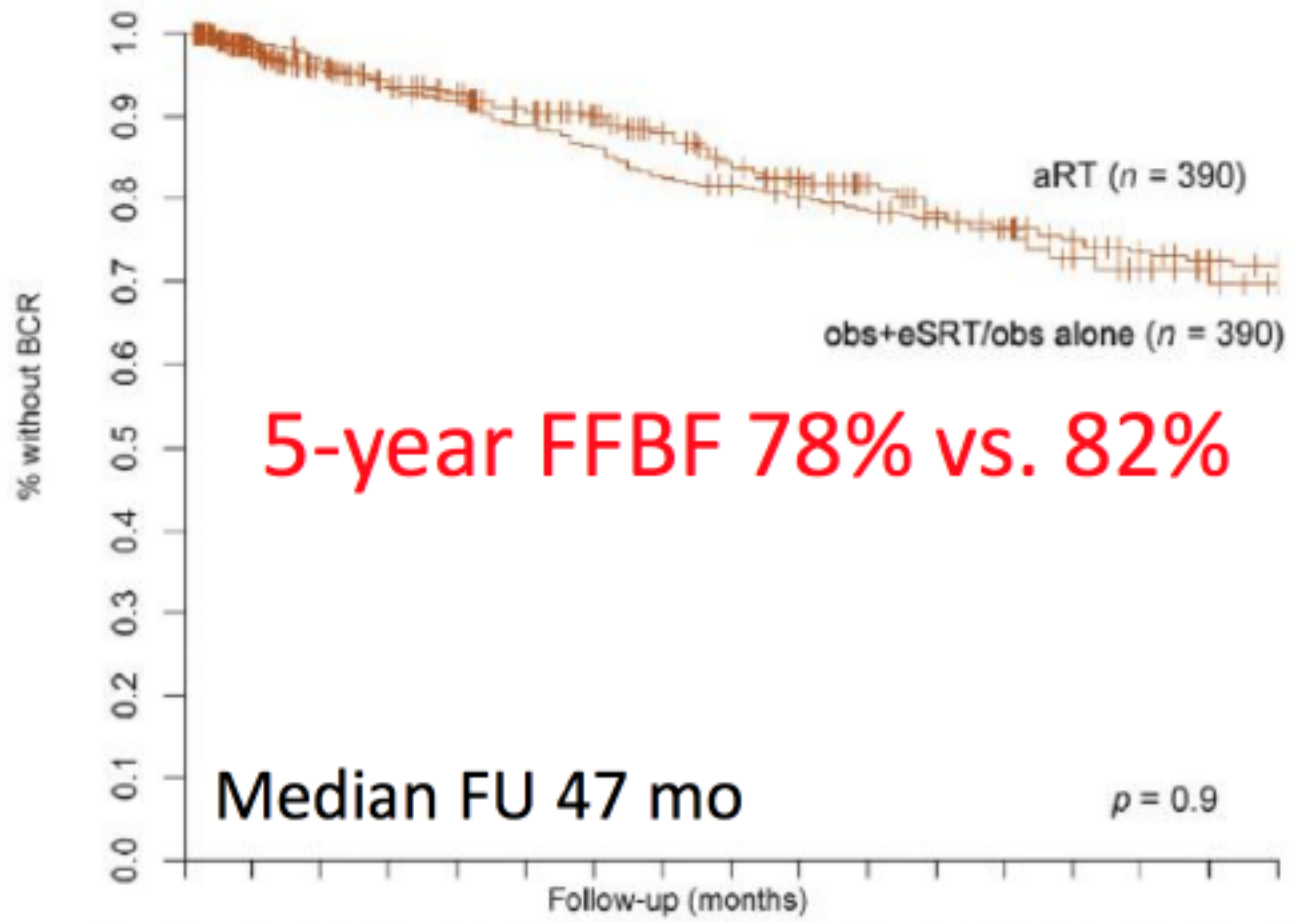
Ost et al. Unpublished data

Is salvage RT as efficient as immediate adjuvant RT?



Ost et al. Unpublished data

Matched-paired analysis of adjuvant and observation with early salvage



- As need 890 pt
- 65Gy to PB, no ADT
- Early salvage≅ ART
- Is accruing

Briganti Eur Urolog 2012

TABELLA - Grado di raccomandazione SIGN e forza della raccomandazione clinica – Radioterapia +/- Terapia ormonale adiuvante

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
A	L'irradiazione della loggia prostatica è raccomandata nei pazienti con stadio patologico pT3-T4N0M0 e/o R1 e con PSA indosabile	Positiva forte
C	Nei pazienti che risultano pN1 dopo prostatectomia radicale R1 può essere proposta RT post-operatoria pelvica immediata ± OT adiuvante	Positiva debole

TABELLA - Grado di raccomandazione SIGN e forza della raccomandazione clinica – Radioterapia di salvataggio

Grado di raccomandazione SIGN	Raccomandazione clinica	Forza della raccomandazione clinica
C	I pazienti con recidiva biochimica dopo prostatectomia radicale dovrebbero ricevere RT di salvataggio sul letto prostatico	Positiva forte
C	I pazienti candidati a SRT dovrebbero ricevere il trattamento radiante di salvataggio con valori di PSA ≤0.5 ng/mL	Positiva forte

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Seminars in RADIATION ONCOLOGY

Postoperative Radiation After Radical Prostatectomy

Eric C. Ko, MD, PhD,[*,†] Anthony L. Michaud, MD, PhD,[*] and Richard K. Valicenti, MD, MA, FASTRO[*]

A total of 3 randomized clinical trials have demonstrated a significant clinical benefit with adjuvant radiation in patients with high-risk prostate cancer after radical prostatectomy, with each showing improved biochemical control outcomes, and one trial (SWOG 8794) also demonstrating increased overall survival. How broadly these results have informed clinical practice has evolved over time, given the widespread availability of ultrasensitive prostate-specific antigen level testing and increased awareness that the high-risk patients are not a uniform cohort. In this review, we discuss the evidence from published and ongoing trials as well as current controversies, focusing on unanswered questions such as when postoperative radiation should be offered and whether the inclusion of androgen-deprivation therapy improves clinical outcomes. The emerging interest in genomic prediction tools and the enhanced sensitivity of novel imaging modalities should offer strategies to improve patient selection, which would help to identify men who may benefit from postoperative radiation while avoiding unnecessary treatment and toxicities in other men.
Semin Radiat Oncol 27:50-66 © 2016 Published by Elsevier Inc.

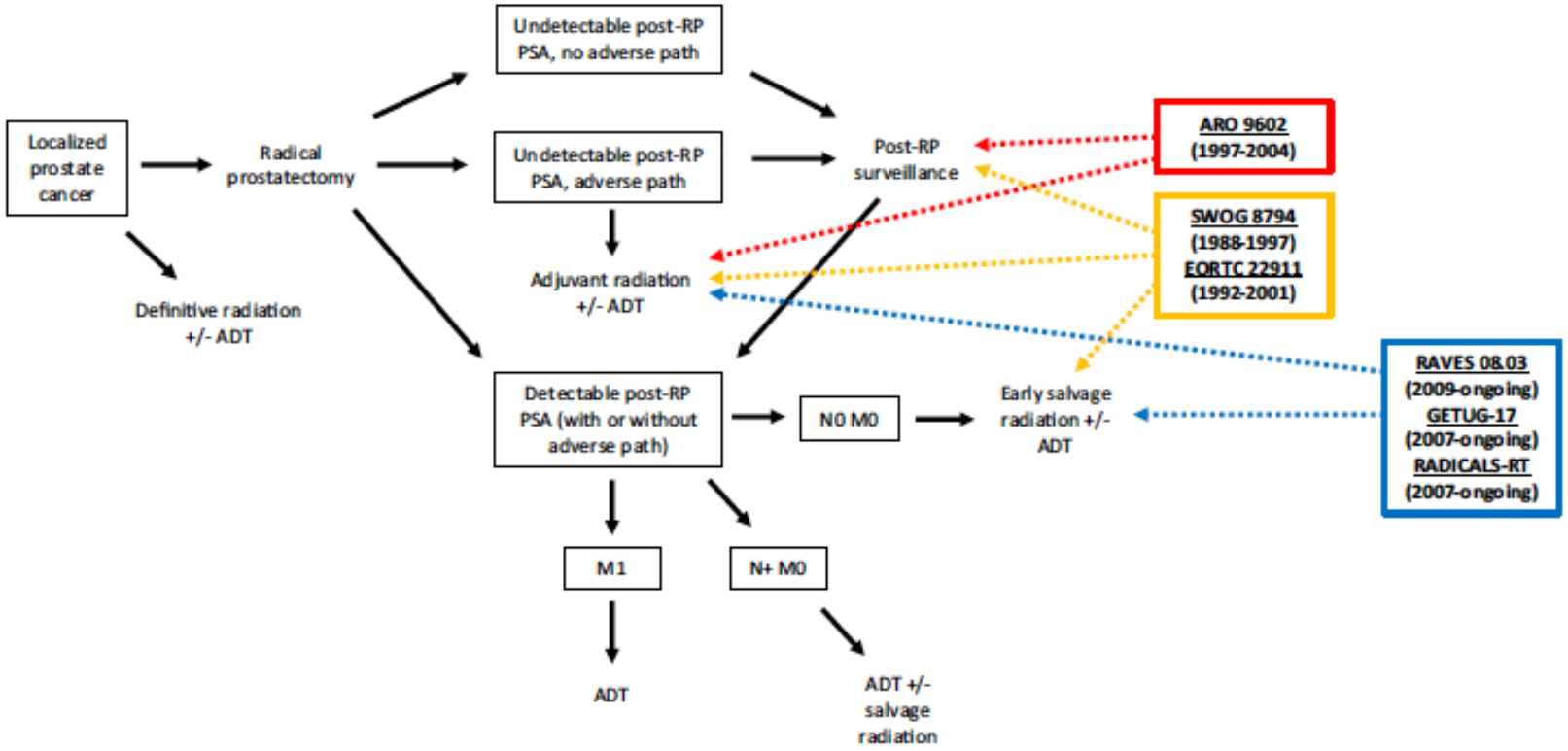

Figure Current management paradigm for patients with prostate cancer after radical prostatectomy. Abbreviations: RADICALS, radiotherapy and androgen deprivation in combination after local surgery; RAVES, radiotherapy-adjuvant vs early salvage. (Color version of figure is available online.)

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"Hit the primary": A paradigm shift in the treatment of metastatic prostate cancer?

Stefano Arcangeli[a,*], Thomas Zilli[b], Berardino De Bari[c,1], Filippo Alongi[d,1]

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Contents

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Definitive treatments of the primary tumour
Local radiotherapy

Table 1
Summary of retrospective studies providing analysis of survival of patients with locally advanced or metastatic prostate cancer according to the treatment received.

Study	Patients	Local treatment (RP or RT)		No local treatment	Median follow up (months)	Outcome remarks
Culp (Culp et al., 2014)	8185	129 (BT)	245 (RP)	7811	16	5y-OS: 52.6%–67.4% vs 22.5%
Fossati (Fossati et al., 2015)	8197	628		7569	36	20% 3y-OS benefit in favor of LT[a]
Zagars (Zagars et al., 2001)	255	72		183	112.8	10y-OS: 67% vs 46%
Verhagen[b] (Verhagen et al., 2010)	7751	4980		2771	–	31% OS benefit in favor of LT
Lin[c] (Lin et al., 2015)	3540	318 (RT)		318	60.2	5y-OS: 71.5% vs 53.2%
Engel (Engel et al., 2010)	938	688		250	67.2	10y-OS: 64% vs 28%

(RP = radical prostatectomy; RT = radiation therapy; BT = brachytherapy, ADT = androgen deprivation therapy; LT = local treatment; cN+ = clinically lymph node-positive; CSM = cancer-specific mortality; OS = overall survival).

[a] Only in a subset of patients with CSM <30%.
[b] Only data from randomized trials in N1 and/or M1 patients have been included.
[c] Only patients with cN+ disease.

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ORIGINAL REPORT

Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer

Chad G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Matthew Koshy, David J. Sher, Usama Mahmood, Ronald C. Chen, Brian F. Chapin, Brian D. Kavanagh, and Thomas J. Pugh

See accompanying editorial on page 2810

Chad. G. Rusthoven, Bernard L. Jones, Thomas W. Flaig, E. David Crawford, Brian D. Kavanagh, and Thomas J. Pugh, University of Colorado School of Medicine, Aurora, CO; Matthew Koshy, University of Illinois at Chicago School of Medicine; Matthew Koshy, The University of Chicago School of Medicine, Chicago, IL; David J. Sher, University of Texas Southwestern, Dallas; Usama Mahmood and Brian F. Chapin University of Texas, MD Anderson Cancer Center, Houston, TX; and Ronald C. Chen University of North Carolina at Chapel Hill, Chapel Hill, NC.

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0732-183X/16/3424w-2835w/$20.00

A B S T R A C T

Purpose
There is growing interest in the role of local therapies, including external beam radiotherapy (RT), for men with metastatic prostate cancer (mPCa). We used the National Cancer Database (NCDB) to evaluate the overall survival (OS) of men with mPCa treated with androgen deprivation (ADT) with and without prostate RT.

Methods
The NCDB was queried for men with newly diagnosed mPCa, all treated with ADT, with complete datasets for RT, surgery, prostate-specific antigen (PSA) level, Gleason score, and Charlson-Deyo comorbidity score. OS was analyzed using the Kaplan-Meier method, log-rank test, Cox proportional hazards models, and propensity score-matched analyses.

Results
From 2004 to 2012, 6,382 men with mPCa were identified, including 538 (8.4%) receiving prostate RT. At a median follow-up of 5.1 years, the addition of prostate RT to ADT was associated with improved OS on univariate ($P < .001$) and multivariate analysis (hazard ratio, 0.624; 95% CI, 0.551 to 0.706; $P < .001$) adjusted for age, year, race, comorbidity score, PSA level, Gleason score, T stage, N stage, chemotherapy administration, treating facility, and insurance status. Propensity score analysis with matched baseline characteristics demonstrated superior median (55 *v* 37 months) and 5-year OS (49% *v* 33%) with prostate RT plus ADT compared with ADT alone ($P < .001$). Landmark analyses limited to long-term survivors of ≥1, ≥3, and ≥5 years demonstrated improved OS with prostate RT in all subsets (all $P < .05$). Secondary analyses comparing the survival outcomes for patients treated with therapeutic dose RT plus ADT versus prostatectomy plus ADT during the same time interval demonstrated no significant differences in OS, whereas both therapies were superior to ADT alone.

Conclusion
In this large contemporary analysis, men with mPCa receiving prostate RT and ADT lived substantially longer than men treated with ADT alone. Prospective trials evaluating local therapies for mPCa are warranted.

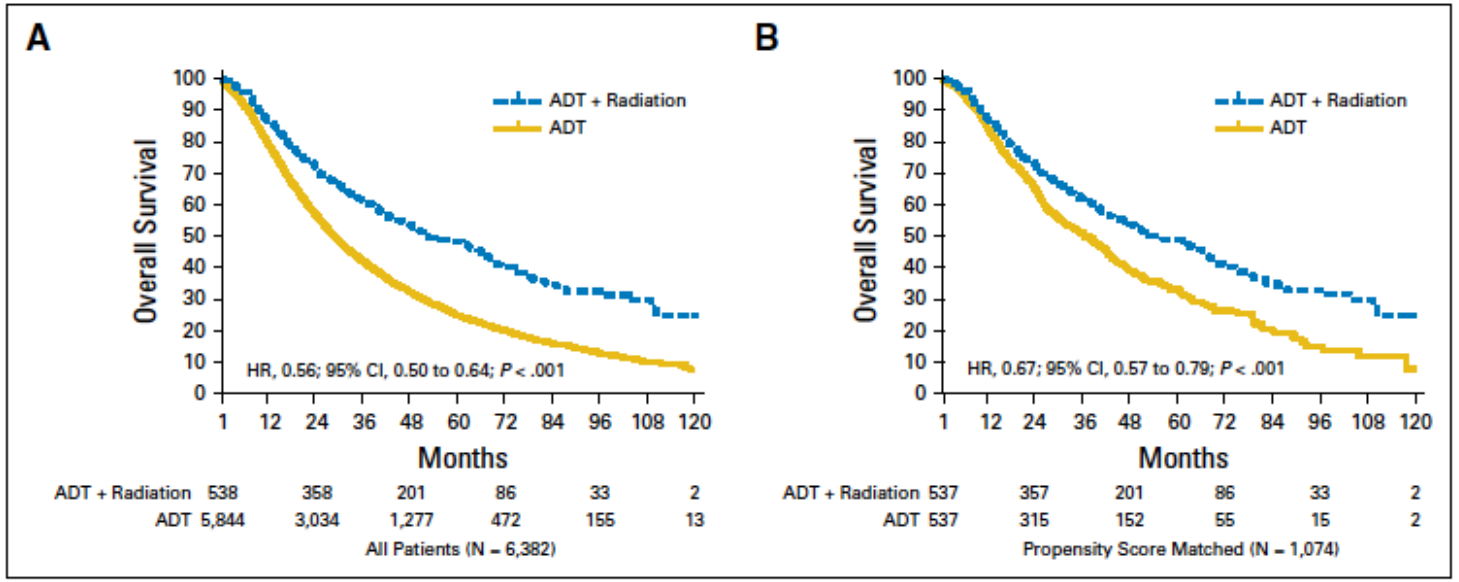

Fig 1. Overall survival for patients with metastatic prostate cancer treated with ADT with and without external beam radiation to the prostate. (A) All patients. (B) Propensity score-matched patients. ADT, androgen deprivation therapy; HR, hazard ratio.

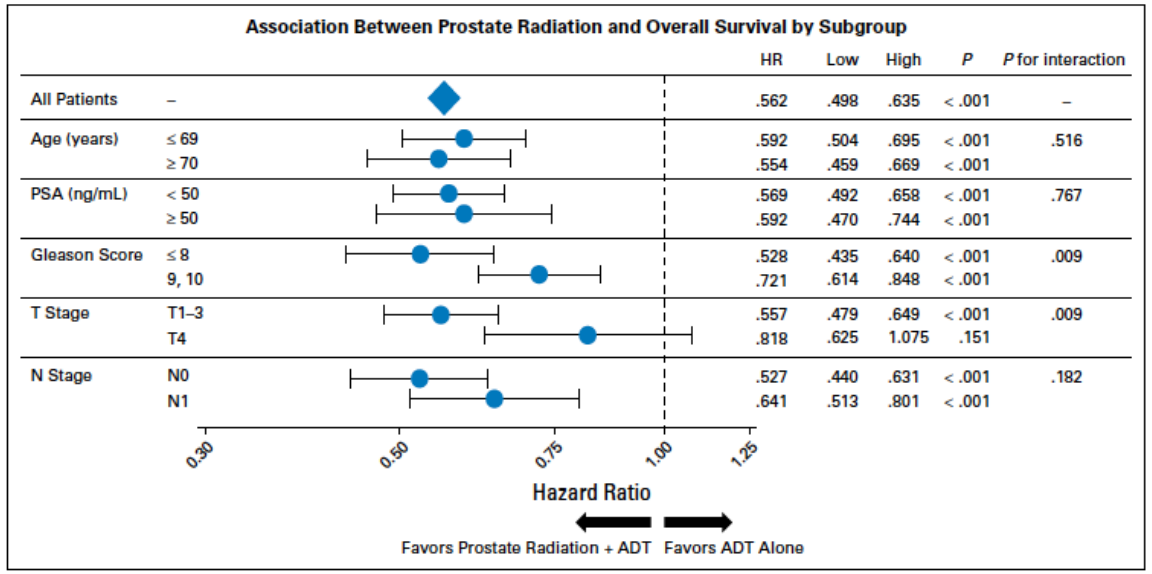

Fig 3. Forest plot of the association between external beam radiation to the prostate and overall survival by subgroup. ADT, androgen deprivation therapy; high, up nit of the 95% confidence interval; HR, unadjusted hazard ratio associated with prostate radiation (ADT alone is the reference, [HR = 1]); low, lower limit of the 9 onfidence interval; N, nodal stage; PSA, prostate-specific antigen; T, tumor stage.

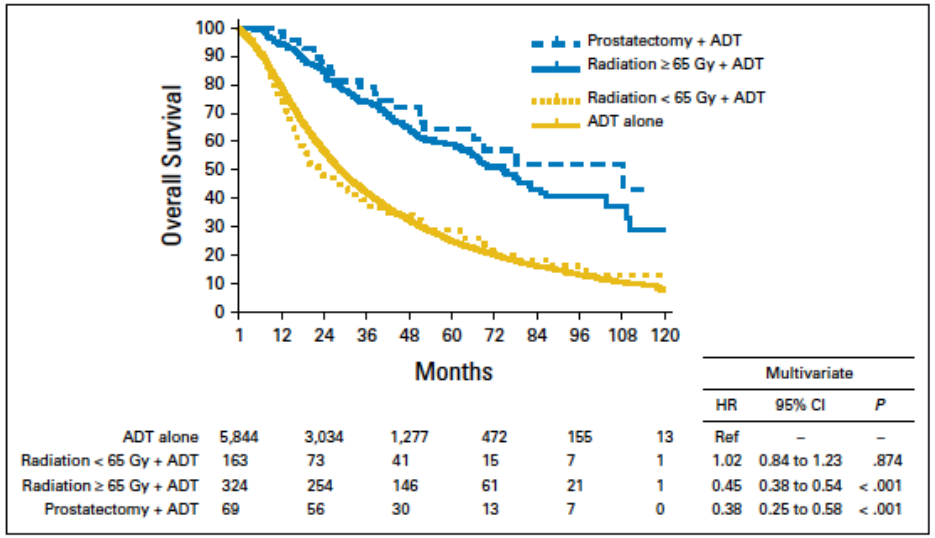

Fig 4. Overall survival analyses including radiation dose and prostatectomy subgroups. Radiation therapy doses are divided into those receiving < 65 Gy and ≥ 65 Gy, as described in Methods. Multivariate analyses are adjusted for identical factors to the primary analysis, as described in Methods. ADT, androgen deprivation therapy; HR, hazard ratio; Ref, reference.

Moreno et al. Radiation Oncology 2014, 9:258
http://www.ro-journal.com/content/9/1/258

RADIATION ONCOLOGY

REVIEW Open Access

Oligometastases in prostate cancer: restaging stage IV cancers and new radiotherapy options

Antonio José Conde Moreno*, Carlos Ferrer Albiach, Rodrigo Muelas Soria, Verónica González Vidal, Raquel García Gómez and María Albert Antequera

Abstract

There are various subgroups of patients with metastatic prostate cancer: polymetastatic, oligometastatic, or oligo-recurrent cancers whose progression follows different courses and for whom there are different treatment options. Knowledge of tumor dissemination pathways and different genetic and epigenetic tumor profiles, as well as their evolution during disease progression, along with new diagnostic and therapeutic advances has allowed us to address these situations with local ablative treatments such as stereotactic body radiation therapy or stereotactic radiosurgery. These treatments provide high rates of local control with low toxicity in metastatic spread for primary cancers including those of pulmonary, digestive, and renal origin, while these types of treatments are still emerging for cancers of prostatic origin. There are several retrospective studies showing the effectiveness of such treatments in prostate cancer metastases, which has led to the emergence of prospective studies on the issue and even some phase II studies intended to prevent or delay systemic treatments such as chemotherapy. Here we collect together and review these past experiences and the studies currently underway. These types of radiotherapy treatments redefine how we approach extracranial metastatic disease and open up new possibilities for combination therapy with new systemic treatment agents.

Keywords: SBRT, SRS, Prostate metastases

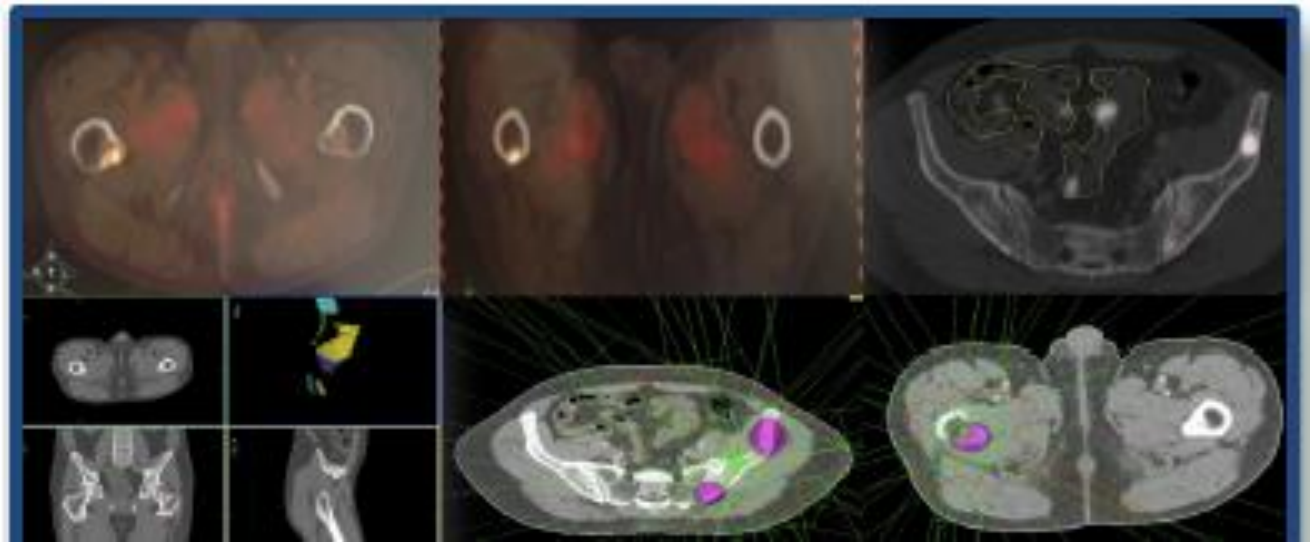

Table 1 Published studies in the literature about ablative and radical radiotherapy in the management of oligometastases

Author	Year of publication	Type of lesions	Treatment received	Results
Casamassine et al [84].	2011	71 patients: - 28 post-prostatectomy - 15 post-radiotherapy - 28 post-prostatectomy and radiotherapy	No ADT	- 13 persistent regression - 2 bone metastases - 8 lymph node recurrences (outside the irradiated áreas)
Muacevic et al. [58].	2011	64 bone metastases	-19 ADT - Mean dose 20,2 Gy (range 16,6-22 Gy) - 8 patients chemotherapy	95% local control
Würschmidt *et al.* [83].	2011	26 patients	Mean dose 75,6 Gy (primary site) and 66,6 Gy (lymph node sites)	- Overall survival at 28 m: 94% - Biochemical relapse free survival (primary site): 83%; 49% (recurrences) - Distant free survival 100% (primary site) and 75% (recurrent)
Ahmed et al. [89].	2013	17 patients (21 lesions)	Mean dose 20 Gy in 1 to 3 fractions	- Local control rates 100% - 2-5 year progresión-free survival 20%
Berkovic et al. [87].	2012	24 patients with biochemical relapse after initial treatment	- SBRT 50 Gy in 10 fractions - None ADT	- 100% 2-year local control -Progr. free survival at 2 years 42% - ADT: median survival free 38 months
Jereczek-Fossa et al. [85].	2012	34 re-irradiated patients: 15 local relapse, 4 anastomosis, 16 nodal and 3 distant metastases (2 retroperitoneal, 1 bone)	23 Gy in 3 fractions in lymph node metastases and 36 Gy in 3 fractions in bone.	- 32 biochemical response - 4 PSA stabilization - 2 PSA progression - 17 disease progression - Progression free survival at 30 m: 42,6%.
Shick et al. [82].	2013	22 oligometastasic patients (55% one lesión)	55% ADT + EBRT (65 Gy)	- Biochemical relapse-free survival at 3 y: 63% - Overall survival 89%
Picchio et al. [45].	2014	83 patients biochemical recurrence after radical primary treatment	No ADT	- 66 patients complete biochemical response - 12 partial biochemical response - 1 stable disease - 15 progression disease

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Seminars in
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ONCOLOGY

Management of Node-Positive and Oligometastatic Prostate Cancer

James R. Broughman, BS,[*,†] and Ronald C. Chen, MD, MPH[*,†,‡]

Historically, stage IV prostate cancer was considered incurable. Although node-positive and oligometastatic prostate cancers are both classified as stage IV, these likely represent distinct clinical groups, and some patients may be curable with aggressive multimodality treatments. There is a lack of randomized evidence, but retrospective studies suggest that radical prostatectomy or radiotherapy may improve survival in these patients. This is an area of great current research interest and prospective randomized trials are needed to help define the optimal treatments for these patients.
Semin Radiat Oncol 27:79-86

Table 4 Studies Evaluating Aggressive Metastasis-Directed Treatment in Patients With Oligometastatic Prostate Cancer

Study	No. of Patients	Treatment	Median Follow-Up (Months)	Metastatic Sites Treated (Nodes/Bone/Visceral)	Outcomes
Schick et al[41]	50	IMRT	31	33/15/2	(3 y) OS: 92%; BRFS: 55%; CFFS: 59%. No grade 3 toxicity
Muacevic et al[46]	40	SBRT	14	0/40/0	(2 y) LC: 95.5%
Decaestecker et al[47]	50	SBRT	25	27/22/1	(2 y) LC: 100%; PFS: 35%. Grade 1 toxicity: 17%; Grade 2 toxicity: 6%
Berkovic et al[48]	24	SBRT	24	11/13/0	(2 y) LC: 100%; PFS: 42%. No grade 3 toxicity

Abbreviations: BRFS, biochemical recurrence-free survival; CFFS, clinical failure–free survival; IMRT, intensity-modulated radiation therapy; LC, local control; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiotherapy.

Table Summary of Biomarkers

Biomarker	Description	Significant Clinical Associations	References
Serum and plasma biomarkers of resistance and response to treatment			
Percentage-free PSA	Ratio of free PSA level to the total serum PSA level	Lower ratio correlated with more aggressive disease. Range of 0.10-0.25 (15%-25%) correlated with both presence of prostate cancer and Gleason grade	16-24
PSA density	Ratio of the total PSA level to the prostate volume (measured on US)	Higher PSA density associated with more aggressive pathologic features; cut point is controversial; linear effect and values more than 0.15 ng/mL^2 have been reported as significantly associated with more aggressive disease	25-33
PSA velocity	Rate of increase in the PSA value over time	Increase greater than 2.0 ng/mL/y was associated with a shorter time to PSA failure and prostate-specific mortality	38
PSA doubling time	Multiple calculation methods, using various PSA acquisition times, see references	Multiple levels reported, ranging from 10-18 months, shorter double time associated with worse outcomes	34-37
PSA nadir level	The lowest PSA level following treatment completion	Range of levels reported; the lower the nadir the better; following SBRT, <0.5 ng/mL appears optimal and following brachytherapy, <0.2 ng/mL	39-48
C-reactive protein	Acute-phase reactant and marker of tissue inflammation	Patients with higher levels respond poorly to EBRT, levels more than 8.6 have been associated with worse cause-specific survival, further validation needed	50,51
PSP94	Beta-microseminoprotein, a nonglycosylated peptide consisting of 94 amino acids	Lower levels of PSP94 are associated with higher Gleason scores	52,53
Macrophage migration inhibitor factor (MIF)	T-cell–derived lymphokine and inhibits the random migration of macrophages	Serum MIF values have been associated with clinical stage, Gleason score, and percentage of positive biopsy cores	54,55
Serum-free testosterone	Testosterone not bound to albumin	Lower levels are associated with higher-grade prostate cancer and larger number of biopsies	56
Urine biomarkers of resistance and response to treatment			
Prostate cancer antigen 3 (PCA3)	Noncoding large-chain RNA and overexpressed in prostate cancer tissue	Useful biomarker indicating the presence of prostate cancer; however, little is known about the correlation between PCA3 and radiation response	58,59
TMPRSS2-ERG	Transmembrane protease, serine 2 fused to ERG erythroblastosis virus E26 oncogene homolog, gene fusion	Presence was associated with clinically significant prostate cancer and Gleason score	60-62
Serine peptidase inhibitor kazal type 1 (SPINK1)	A protein encoded by the SPINK1 gene	Associated with higher rates of recurrence following radical prostatectomy	63
Urinary gene panel	HOXC6, TDRD1, and DLX1	Associated with higher Gleason score and clinically aggressive behavior	70
EN-2	Engrailed-2, expressed in early embryonic development and prostate cancer	Increased urinary levels associated with higher volume of cancer and T stage	66
Urinary exosomes	Urinary 3 gene expression assay	Able to discriminate high from low Gleason score; limited data radiation predicting treatment response	68,69
Prostate parenchymal biomarkers of resistance and response to therapy			
Gleason score	"Gold standard," histologic metric of disease aggressivity	Higher Gleason score associated with worse prostate cancer outcomes	71-77
Numerical cores positive	The number of cores positive on a multiple core biopsy specimen	Increasing number of biopsy cores positive is a predictor of response to radical prostatectomy and radiation	78,79
Ki-67	Cellular marker of proliferation		80-85
p53	Tumor suppressor and cell cycle regulator	Percentage higher than 7.1% is associated with distant metastasis and cause-specific mortality Abnormal p53 expression associated with increased risk of PSA level failure following treatment with radiation therapy	86,87
MDM-2	Oncogene and negative regulator of p53	Overexpression in prostate cancer tissue has been associated with worse outcomes following treatment with radiation therapy	81,88,89
DNA-PKcs	DNA protein kinase catalytic subunits, involved in the formation of a synaptic complex that brings DNA ends together	Nuclear staining of DNA-PKcs is associated with biochemical recurrence in patients treated with external beam radiation therapy	90
Nibrin (NBN)	Component of the MRN double-strand DNA break repair complex	Copy number gain of NBN is associated with biochemical recurrence following radiotherapy but not after surgery	91
BCL-2	Antiapoptotic protein	Associated with biochemical failure after treatment with radiation therapy	92,93
Bax	Proapoptotic protein	Higher expression of Bax associated with worse ourcomes after radiation	94,95
C-myc and PTEN copy number	Alleic loss of PTEN and alleic gain of c-myc	c-MYC gain alone, or combined c-MYC gain and PTEN loss were prognostic for relapse following treatment with EBRT	96
SChLAP1	Long noncoding RNA second chromosome locus	High SChLAP1 is significantly prognostic for metastatic progression	97
PKA	Protein kinase A type 1	High PKA staining associated with worse prostate outcomes	98
Signal transducers and activators of transcription STAT3	Related to the regulation of cell proliferation and oncogenesis.	The activation of STAT3 correlated inversely with the presence of metastatic disease	99
Her-2	Human epidermal growth factor receptor 2	Preliminary data, Her-2 expression may be of prognostic relevance in patients undergoing radiation therapy for prostate cancer	100
EGFR	Epithelial growth factor	Low expression of EGFR in patients treated with radiation therapy is associated with a favorable prognosis	101
VEGF	Vascular endothelial growth factor	High VEGF expression was associated with a risk of treatment failure following radiation therapy	102,103
Hypoxia (including Hif-1A)	Low oxygen concentration (including expression of hypoxia-inducible factor 1A)	Associated with recurrence after treatment with external beam radiation therapy	102-107
Clinically available tissue-based biomarkers			
Cell cycle progression score	RNA signature based on the average expression level of 31 cell cycle progression genes	Predicted biochemical recurrence following treatment with radiation therapy	109,110
Decipher	RNA signature based on expression of 22 genes, identified through unbiased high-throughput approaches	High decipher scores associated with benefit from earlier initiation of postoperative RT (adjuvant vs salvage RT)	111

Abbreviation: EBRT, external beam radiation therapy.