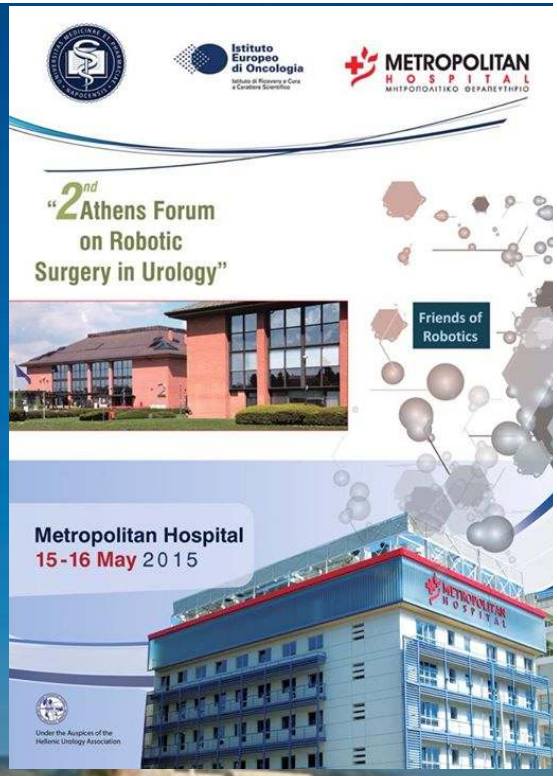
Radiation therapy: hypofractioning escalation



Agnese Cecconi MD, PhD

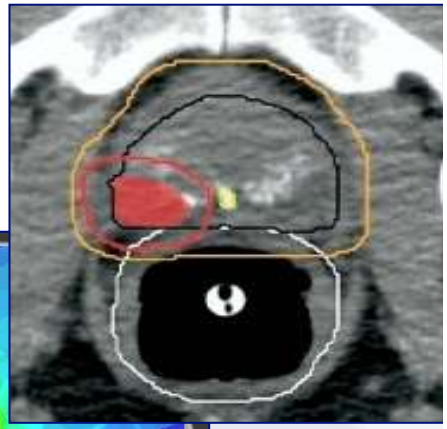
European Institute of Oncology, Milan, Italy
University of Milan, Italy

High precision radiotherapy…

Steps of radiotherapy treatment planning and techniques

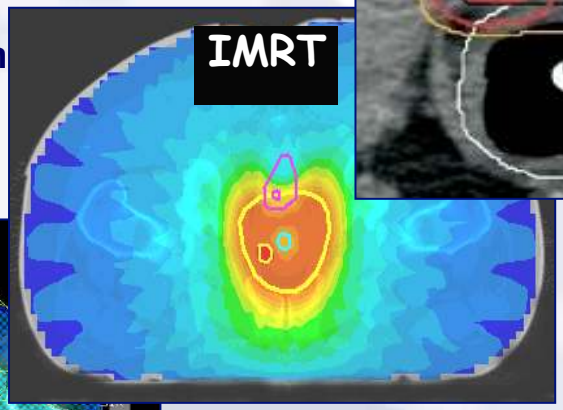
To deliver high dose in the small target or in a dominant lesion

> 90 Gy?



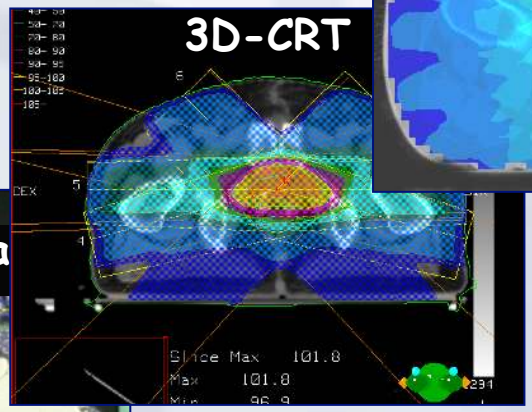
90 Gy

IMRT



80 Gy

3D-CRT

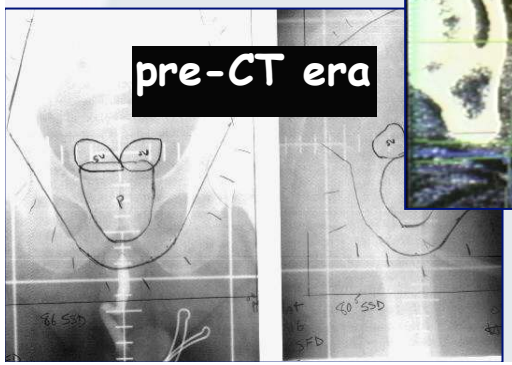


70 Gy

post-CT era

60 Gy

pre-CT era



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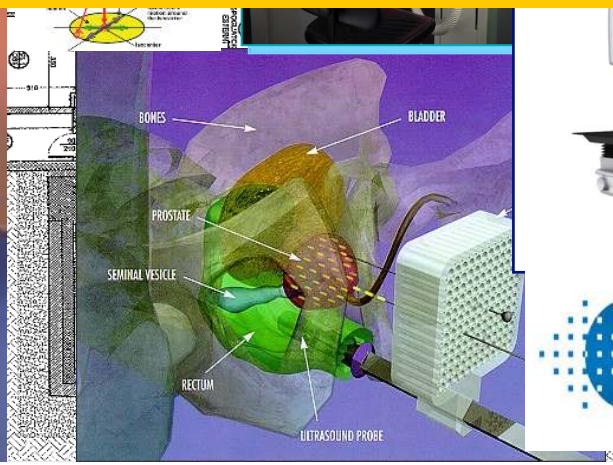
High precision mini-invasive and robotic radiotherapy

- The increased conformality of SBRT and the potential improvement in therapeutic ratio mean that gaining the benefits of further dose escalation, without the associated increase in toxicity may be possible.
- This represents an opportunity to extend the progress made with moderate hypofractionation.



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Radical external beam radiotherapy for localised carcinoma of the prostate using a hypofractionation technique.

Collins CD, Lloyd-Davies RW, Swan AV.

Department of Radiotherapy and Oncology, St Thomas' Hospital, London, UK.

Clin Oncol (R Coll Radiol). 1991 May;3(3):127-32

…the first report of extreme hypofractionation (4-8 fr) was in England 1960-1980.

36 Gy in 6 fractions (prior to CT era)

- The pts had good clinical response (prior to Psa era): with overall survival curves similar to the unaffected population
- Very low toxicity

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Dose escalation…why ???

EFFECT OF INCREASING RADIATION DOSES ON LOCAL AND DISTANT FAILURES IN PATIENTS WITH LOCALIZED PROSTATE CANCER

PATRICK A. KUPELIAN, M.D.,* JAY CIEZKI, M.D.,† CHANDANA A. REDDY, M.S.,†
ERIC A. KLEIN, M.D.,‡ AND ARUL MAHADEVAN, M.D.†

*Department of Radiation Oncology, M.D. Anderson Cancer Center Orlando, Orlando, FL;
†Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH; and
‡Glickman Urological and Kidney Institute, Cleveland Clinic Foundation, Cleveland, OH

Table 1. Distribution of pretreatment and treatment parameters by radiation dose group

Variable	<72 Gy	≥72 but <82 Gy	≥82 Gy	p
Clinical T stage				0.003
T1-T2	512 (93)	199 (93)	152 (100)	
T3	40 (7)	16 (7)	0 (0)	
iPSA level (ng/mL)				<0.001
≤4	50 (9)	14 (7)	13 (8)	
>4 to ≤10	233 (42)	135 (63)	112 (74)	
>10 to ≤20	147 (27)	50 (23)	26 (17)	
>20	122 (22)	16 (7)	1 (1)	
bGS				<0.001
2–6	350 (63)	149 (69)	122 (80)	
7–10	202 (37)	66 (31)	30 (20)	
Risk group				<0.001
Low	161 (29)	96 (45)	99 (65)	
Intermediate	134 (24)	51 (24)	43 (28)	
High	257 (47)	68 (31)	10 (7)	
Total	552 (100)	215 (100)	152 (100)	

Abbreviations: iPSA = pretreatment prostate-specific antigen; bGS = biopsy Gleason score.

Data presented as number of patients, with percentages in parentheses.

⬇ dose for OAR +

⬆ dose for target

= ↑ bNED

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 1, pp. 16–22, 2008

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Dose escalation…why ???

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.

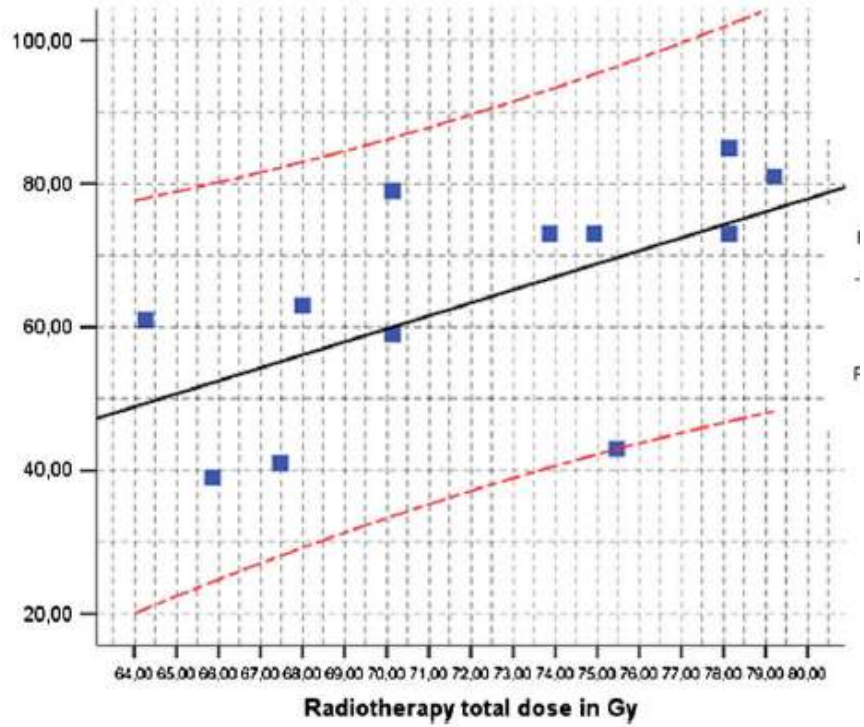

Fig. 10. Meta-regression analysis for biochemical control as a function of the radiotherapy total dose for all subgroups present in six trials. RTTD = radiotherapy total dose.

1° Meta-analysis

Increase of 1.8% in PSA control

For 1 Gy dose delivered

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 5, pp. 1405–1418, 2009

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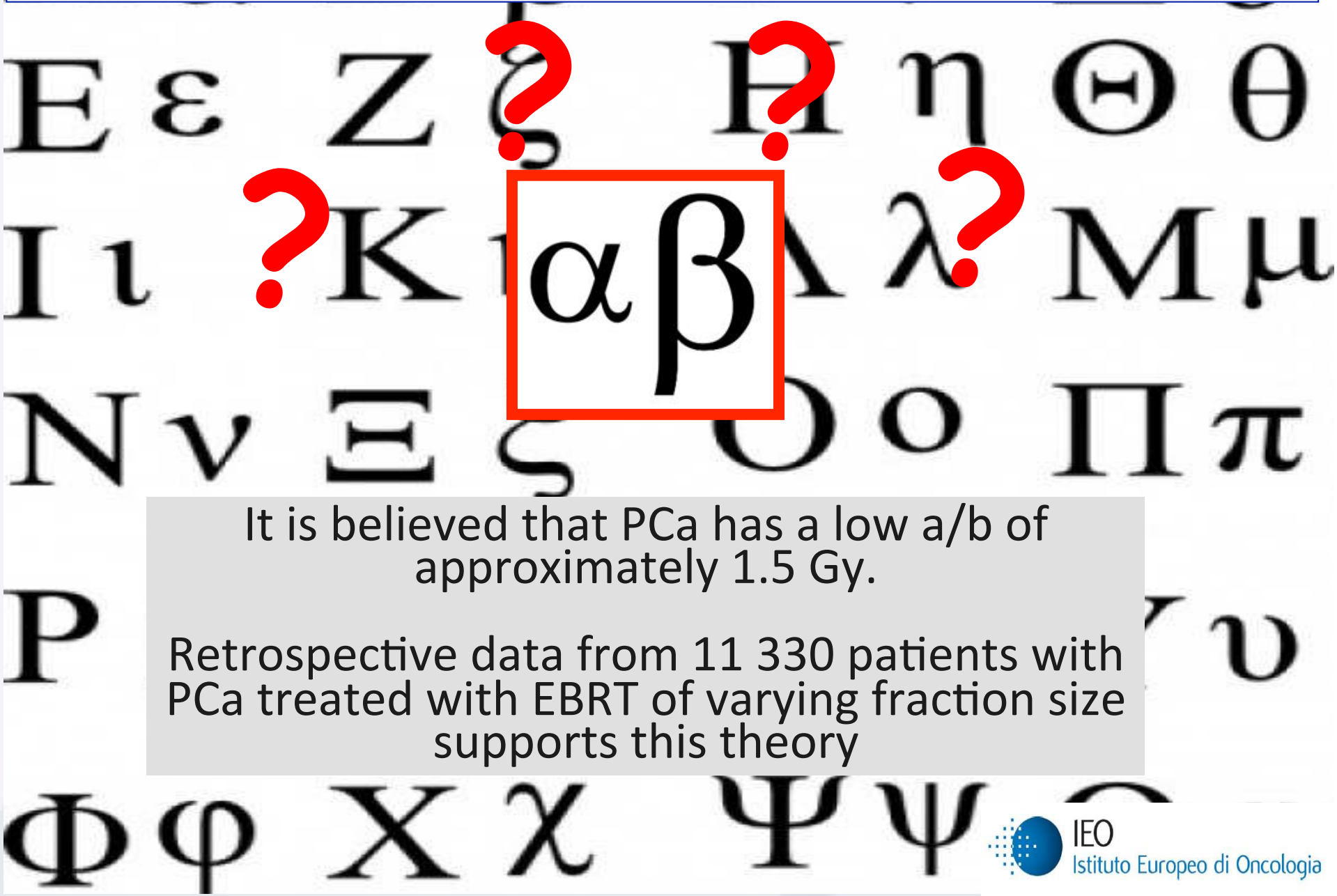
Dose escalation…How ???



It is believed that PCa has a low a/b of approximately 1.5 Gy.

Retrospective data from 11 330 patients with PCa treated with EBRT of varying fraction size supports this theory

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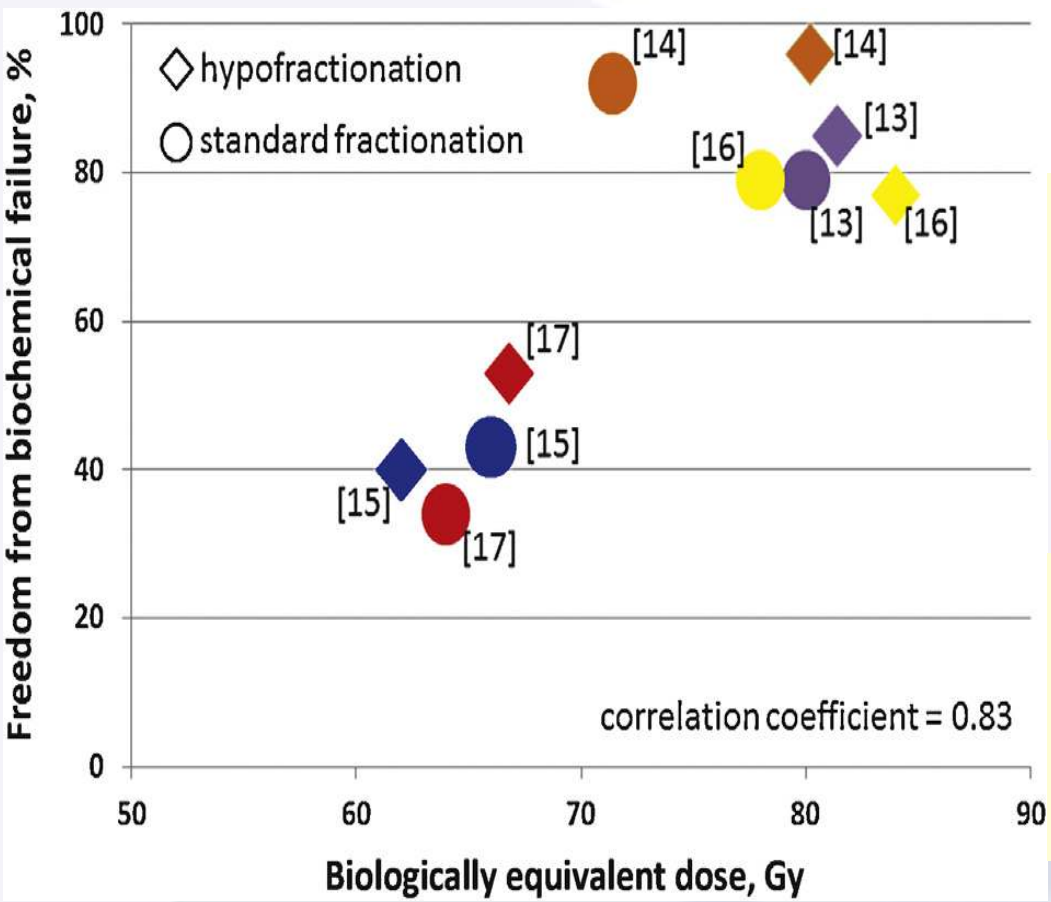

For slowly proliferating cells, high doses per fraction may be more effective because immediate cell death is instigated due to the high number of DNA double-strand breaks caused by each fraction.

A slow proliferation rate results in a high reparation ability of radiation damage over time, such standard fractionation given in small increments over a long time period may be suboptimal for PCa for which a high total dose is required for effective control.

hypofractionation for PCa has the advantages of increased convenience for the patient and a lower cost burden for the health care system

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Table 1 – Phase 3 randomized trials of moderate hypofractionation for intact prostate cancer

Study	Median FU, mo	Risk, GS, or NCCN	Technique	Regimen	BED, Gy	*n*	Outcome	Toxicity
							4,3 – 7,5 years	
Lukka et al. [15]	68	60% GS ≤6 31% GS 7 9% GS 8–10	3DCRT No IGRT	52.5 Gy/20 fx	62	466	5 yr FFBF 40% (NS)	Gr ≥3 2% (NS)
				66 Gy/33 fx	66	470	5 yr FFBF 43%	Gr ≥3 1%
Yeoh et al. [17]	90	n.s.	2D/3DCRT No IGRT	55 Gy/20 fx	66.8	108	7.5 yr FFBF 53% ($p < 0.05$)	Late GU; HR: 1.58 (95% CI, 1.01–2.47) favoring hypofractionation
				64 Gy/32 fx	64	109	7.5 yr FFBF 34%	
Dearnaley et al. [18]	51	n.s.	3D/IMRT No IGRT 3–6 mo ADT	57 Gy/19 fx	73.4	151	n.s.	Gr ≥2 GU 0% (NS) Gr ≥2 GI 1% (NS)
				60 Gy/20 fx	77	153		Gr ≥2 GU 2% Gr ≥2 GI 4%
				74 Gy/37 fx	74	153		Gr ≥2 GU 2% Gr ≥2 GI 4%
Kuban et al. [14]; Hoffman et al. [19]	60	28% low 71% intermediate 1% high	IMRT IGRT 21% ADT	72 Gy/30 fx	80.2	102	5 yr FFBF 96% (NS)	5 yr Gr ≥2 GU 16% (NS) 5 yr Gr ≥2 GI 10% (NS)
				75.6 Gy/42 fx	71.4	101	5 yr FFBF 92%	5 yr Gr ≥2 GU 17% 5 yr Gr ≥2 GI 5%
Arcangeli et al. [12,13]	70	26% GS ≤7 74% GS >7	3DCRT No IGRT 100% 9 mo ADT	62 Gy/20 fx	81.4	83	5 yr FFBF 85% ($p = 0.065$) *p ss for GS ≥4 + 3	3 yr Gr ≥2 GU 16% (NS) 3 yr Gr ≥2 GI 17% (NS)
				80 Gy/40 fx	80	85	5 yr FFBF 79%	3 yr Gr ≥2 GU 11% 3 yr Gr ≥2GI 14%
Pollack et al. [16]	68	34% GS ≤6 47% GS 7 19% GS 8–10	IMRT IGRT	70.2 Gy/26 fx	84	151	5 yr BCDF 23% (NS)	5 yr Gr ≥2 GU 13% ($p = 0.16$) 5 yr Gr ≥2 GI 9% (NS)
				78 Gy/36 fx	78	152	5 yr BCDF 21%	5 yr Gr ≥2 GU 13% 5 yr Gr ≥2 GI 9%

Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial

Shafak Aluwini, Floris Pos, Erik Schimmel, Emile van Lin, Stijn Krol, Peter Paul van der To
Wendimagegn Ghidey Alemayehu, Ben Heijmen, Luca Incrocci

Lancet Oncol 2015; 16: 274–83

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial

David Dearnaley, Isabel Syndikus, Georges Sumo, Margaret Bidmead, David Bloomfield, Catharine Clark, Annie Gao, Shama Hassan, Alan Horwich, Robert Huddart, Vincent Khoo, Peter Kirkbride, Helen Mayles, Philip Mayles, Olivia Naismith, Chris Parker, Helen Patterson, Martin Russell, Christopher Scrase, Chris South, John Staffurth, Emma Hall

Lancet, January 2012

A Dutch group (HYPRO study; ISRCTN 85138529) 820 patients

64,6 Gy in 19 fractions (hypofractionation) vs 78 Gy in 39 fractions (standard fractionation)

UK study (CHHiP study; ISRCTN 97182923) has completed recruitment of 3200 men comparing

60 Gy in 20, 57 Gy in 19 , 74 Gy in 37 fractions

- pre-treatment symptoms were a major risk factor for genitourinary side-effects
- acute gastrointestinal toxicity was increased with hypofractionation

longer follow up is needed to establish whether the association will hold true for short-term effects after modest hypofractionation

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Moderate Hypo: Take home message

Conventional fractionation *Vs* Moderate Hypofractionation

- IMRT and IGRT may be useful in limiting overall toxicity
- Higher doses and > BED improve BCR
- No difference in overall outcome, distant disease survival
- Late toxicity appears to be similar (the volume of rectum receiving high dose may be a predictor of late tox: Vr receiving 64,6 Gy >20% → risk of G2 tox)
- Late urinary symptoms: not different from baseline
- Erectile function decreases 24 months after

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Extreme Hypofractionation

Table 2 – Prospective studies of extreme hypofractionation for intact prostate with at least 50 participants

	n	Median FU, mo	Risk, NCCN	Technique	Regimen	BED, Gy	Outcome	Toxicity
							18 mo-4,6 years	
Aluwini et al. [46]	162	28	Low/intermediate	n.s.	38 Gy/4 fx	119.6	3 yr BC 98%	Gr 2 GU 15% Gr 2 GI 3%
Bolzicco et al. [27]	100	36	41% low 42% intermediate	Robotic IGRT	35 Gy/5 fx 29% ADT	85	BC 96%	Gr 1/2/3 GU 4%/3%/1% Gr 1/2/3 GI 2%/1%
Chen et al. [47								≥2 GU 31% ≥2 GI 1%
D'Alimonte et al. [48]								3 GU 5/1% 3 GI 5/1%
Fuller et al. [39								U 2% 44%) 0% 11%)
Katz and Kang								GU 9% GI 4%
King et al. [34]								GU 7% GI 12%
Loblaw et al. [2								≥2 GU 5% ≥2 GI 7%
Meier et al. [38								U 10%
					No ADT			Gr 2 GI 2%
Menkarios et al. [29]	80	33	100% low	IMRT/IGRT	45 Gy/5 fx	135	3 yr BC 97%	Gr ≥2 GU 14% Gr ≥2 GI 16%
Ouon et al. [50]	84	18	100% low	IMRT/IGRT	35 Gy/5 fx	85	n.s.	Gr 2 GU 2% Gr 2 GI 5%

- In general for low and selected intermediate risk pts
- Early decrease in urinary and bowel QOL before returning to baseline by 2y after treatment
- Erectile dysfunction remains a permanent late effect
- Nonconsecutive days may reduce late tox
- < 50% of V rectum → 4,8 Gy/fr

Printed by Antonio Cioffi on 11/24/2014 11:10:05 AM. For personal use only. Not approved for distribution. Copyright © 2014 National Comprehensive

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Prostate Cancer Updates

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

Primary External Beam Radiation Therapy

- Highly conformal RT techniques should be used to treat prostate cancer.
- Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate (± seminal vesicles for part of the therapy) are appropriate for patients with low-risk cancers. For patients with intermediate- or high-risk disease, doses up to 81.0 Gy provide improved PSA-assessed disease control.
- Moderately hypofractionated image-guided IMRT regimens (2.4–4 Gy per fraction over 4–6 weeks) have been tested in randomized trials reporting similar efficacy and toxicity to conventionally fractionated IMRT. They can be considered as an alternative to conventionally fractionated regimens when clinically indicated.
- Extremely hypofractionated image-guided IMRT/SBRT regimens (6.5 Gy per fraction or greater) are an emerging treatment modality with single institutional and pooled reports of similar efficacy and toxicity to conventionally fractionated regimens. They can be considered as a cautious alternative to conventionally fractionated regimens at clinics with appropriate technology, physics, and clinical expertise.

ADT.

- Patients with low-risk cancer should not receive pelvic lymph node irradiation or ADT.
- The accuracy of treatment should be improved by attention to daily prostate localization, with techniques of IGRT using CT, ultrasound,
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate are more difficult to implant and may suffer increased risk of side effects. Neoadjuvant ADT may be used to shrink the prostate to an acceptable size; however, increased toxicity would be expected from ADT and prostate size may not decline.
- Post-implant dosimetry must be performed to document the quality of the implant.
- The recommended prescribed doses for LDR monotherapy are 145 Gy for Iodine-125 and 125 Gy for Palladium-103. The corresponding boost doses after 40 to 50 Gy EBRT are 110 Gy and 90 to 100 Gy, respectively.
- High-dose rate (HDR) brachytherapy can be used alone or in combination with EBRT (40–50 Gy) instead of LDR. Commonly used boost regimens include 9.5 to 11.5 Gy x 2 fractions, 5.5 to 7.5 Gy x 3 fractions, and 4.0 to 6.0 Gy x 4 fractions. A commonly used regimen for HDR treatment alone includes 13.5 Gy x 2 fractions.
- Permanent LDR or temporary HDR brachytherapy can be used as treatment for a local recurrence following EBRT or primary brachytherapy. Radiation dose depends on the original primary external beam dose and ranges from 100 to 110 Gy for LDR and 9 to 12 Gy x 2 fractions for HDR.

Continued on next page

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Clinical Oncology xxx (2015) 1–10

Overview

Stereotactic Body Radiotherapy for Prostate Cancer

D.R. Henderson, A.C. Tree, N.J. van As

Academic Uro-oncology Department, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

Table 1
Studies of stereotactic body radiotherapy for localised prostate cancer

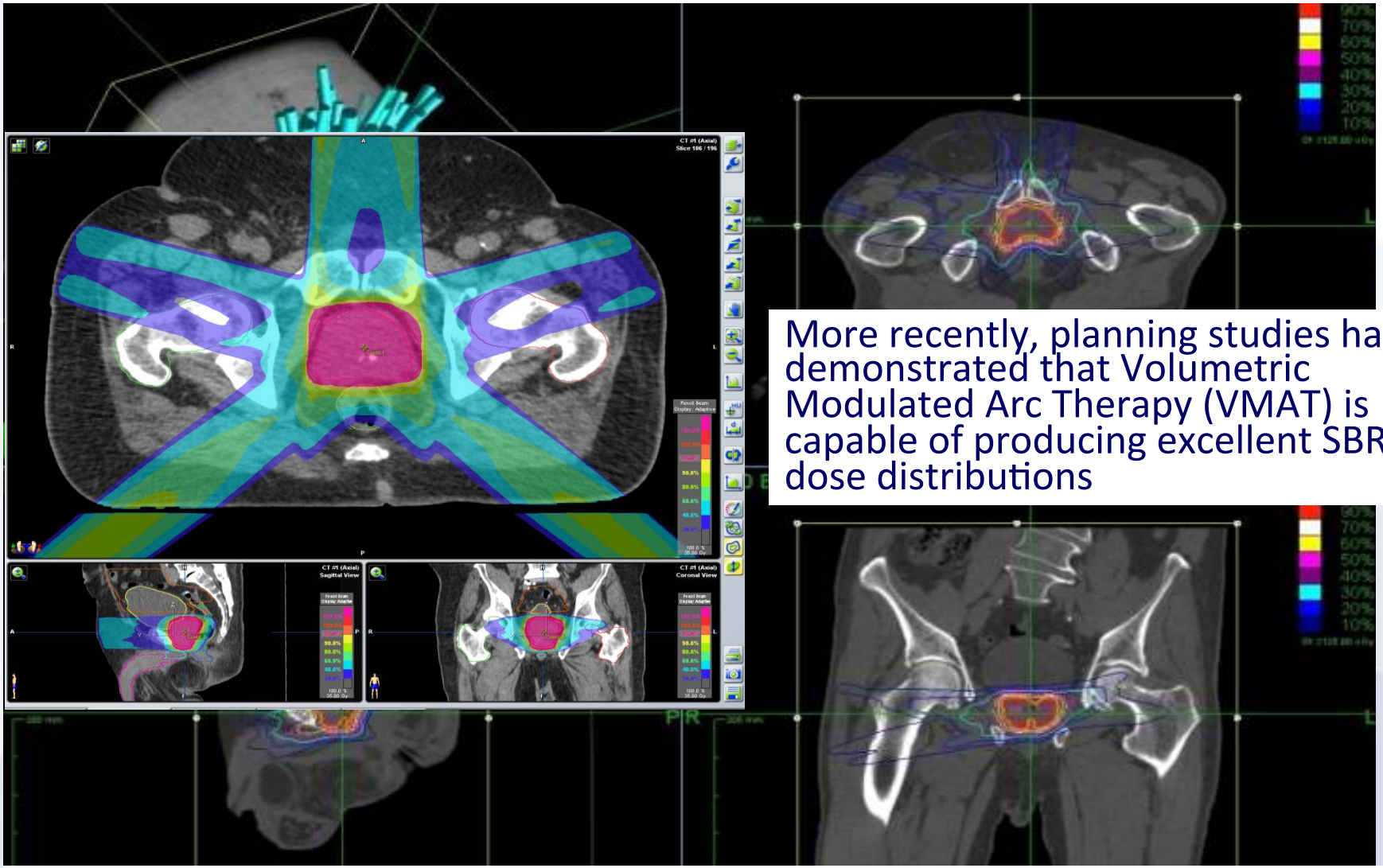
Reference	No. of patients	Technique	Image guidance	Dose	Schedule	ADT	Follow up (median)	bRFS	Acute urinary toxicity	Late urinary toxicity	Acute rectal toxicity	Late rectal toxicity
[26]	40	IMRT	Fiducials	33.5 Gy/5#	Daily	None	41.0 mo	90%	20% G2 1 patient G3	20% G2 No G3+	13% G2 No G3+	8% G2 No G3+
[37]	67	RRS	Fiducials	36.25 Gy/5#	Alt days	None	32.4 mo	94%	NR	5% G2 3.5% (n = 2) G3	NR	2% G2 No G3+
[47]	100	RRS	Fiducials	36.25 Gy/5#	Alt days	11%	27.6 mo	99%	35% G2 No G3+	31% G2 1 patient G3	5% G2 No G3+	1% G2 No G3+
[36]	100	RRS	Fiducials	35.0 Gy/5#	Daily	29%	36.0 mo	95%	12% G2 No G3+	3% G2 1 patient G3	18% G2 No G3+	1% G2 No G3+
[38]	304	RRS	Fiducials	36.25 Gy/5#	Daily	19%	60.0 mo	74–97%*	5% G2 No G3+	9% G2 2% G3	4% G2 No G3+	5% G2 No G3+
[39]	83	RRS	Fiducials	36.25 Gy/5#	Daily	33%	31.0 mo	95%	19% G2 4% G3	29% G2 3% G3	4% G2 No G3+	4% G2 No G3+
[25]	84	IMRT	Fiducials	35.0 Gy/5#	Weekly	1%	55.0 mo	98%	19% G2 1 patient G3	5% G2 No G3+	10% G3 No G3+	7% G2 1 patient G4: "fistula-in-ano"
[30]	40	VMAT FFF	CBCT	35.0 Gy/5#	Alt days	25%	11.0 mo	NR	40% G2 No G3+	None	10% G2 No G3+	2% G2 No G3+
[27,50]	91	IMRT or Tomo	Fiducials	45.0–50.0 Gy/5#	Alt days	18%	24.5 mo	NR	21% G2 No G3+	8% G2 4% G3	19% G2 2% G3+	23% G2 G4: 5 patients required diverting colostomy
[48]	51	RRS	Fiducials	36.25 Gy/5#	Alt days	18%	14.5 mo	NR	22% G2 4% G3	NR	14% G2 No G3+	NR

NR, not reported; ADT, androgen deprivation therapy; VM… …graphy; FFF, flattening filter free system; Tomo, Tomotherapy® … …hemical relapse free survival.

* 74% for high risk patients.

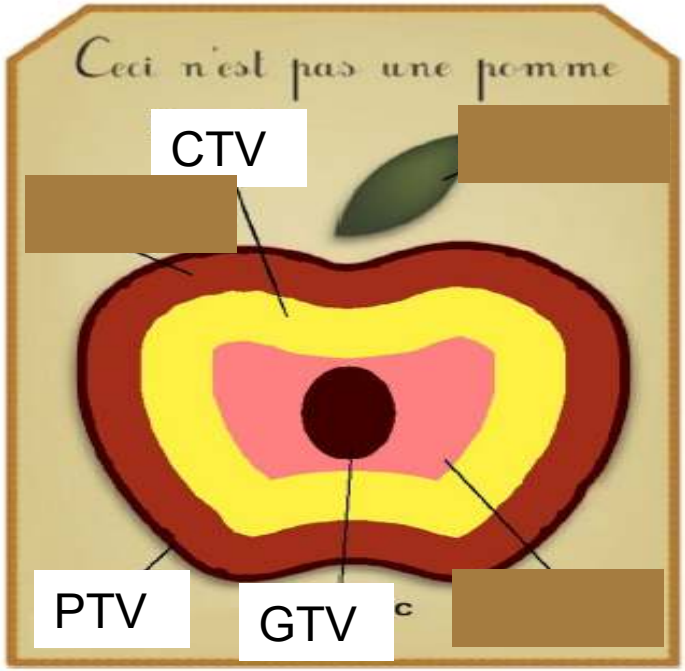
All reported series have used doses of 35 - 36 Gy in five fractions, given daily or on alternate days.

The majority of clinical evidence comes from treatments using the Cyberknife robotic radiosurgery (RRS) system (Accuray Incorporated)



More recently, planning studies have demonstrated that Volumetric Modulated Arc Therapy (VMAT) is capable of producing excellent SBRT dose distributions

The CBCT approach is appealing due to its non-invasive nature and ability to define soft tissue changes (such as those due to bladder and rectal filling) which cannot be appreciated with fiducial guidance. *Moseley et al*. have reported equivalent accuracy to fiducial markers



A reduction in PTV allowed delivery of higher radiation dose without increasing toxicity

Recomandations for therapy planning

By reducing rectal gas and faeces, dietary protocols may also help in reducing prostate motion and CBCT artefact

With regard to margins, the majority of studies have used

PTV margins of 5 mm with 3 mm posteriorly

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HOW WE TREAT PROSTATE CANCER?

EXTREME HYPOFRATIONATION: Rectal Damage??

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Genitourinary Cancer

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,* Alana Christie, MS,‡ Yair Lotan, MD,§ David Pistenmaa, MD,* Brian D. Kavanagh, MD,‖ Akash Nanda, MD, PhD,¶ Patrick Kueplian, MD,# Jeffrey Brindle, MD,** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,‖ Xian-Jin Xie, PhD,‡ and Robert D. Timmerman, MD*

*Departments of *Radiation Oncology and §Urology, ‡Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas; †Department of Radiation Oncology, University of Minnesota, Minneapolis, Minnesota; ‖Department of Radiation Oncology, University of Colorado, Denver, Colorado; ¶Department of Radiation Oncology, University of Florida Health Cancer Center at Orlando Health, Orlando, Florida; #Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, California; and **Prairie Lakes Hospital, Watertown, South Dakota*

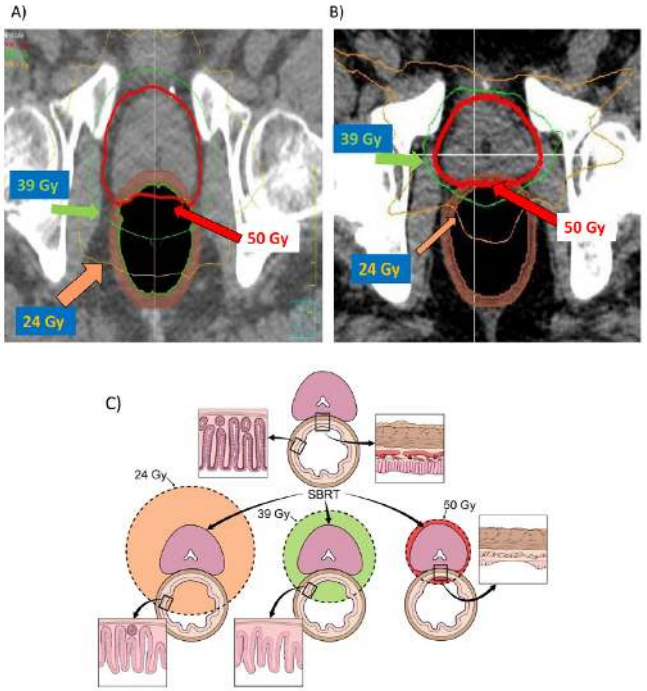


Fig. 2. Representative treatment plans of patients treated to 50 Gy in 5 fractions, with (A) grade 2 acute and grade 3 delayed rectal toxicity, and (B) grade 1 acute/delayed rectal toxicity only. (C) Representation of biologic consequence of rectal wall irradiated to 24 Gy, 39 Gy, and 50 Gy.

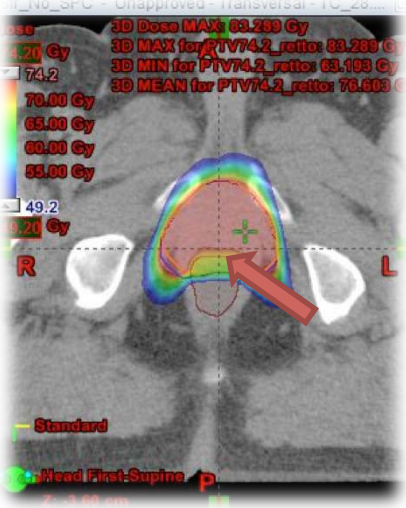
One potential strategy is to distance the anterior rectum from the prostate, to reduce dose to the rectum, such as that afforded by injectable rectal spacers (26-29). These spacers would likely be particularly effective at reducing the high dose associated with vascular/stromal injury and will likely lead to significant reduction of HGDRT.

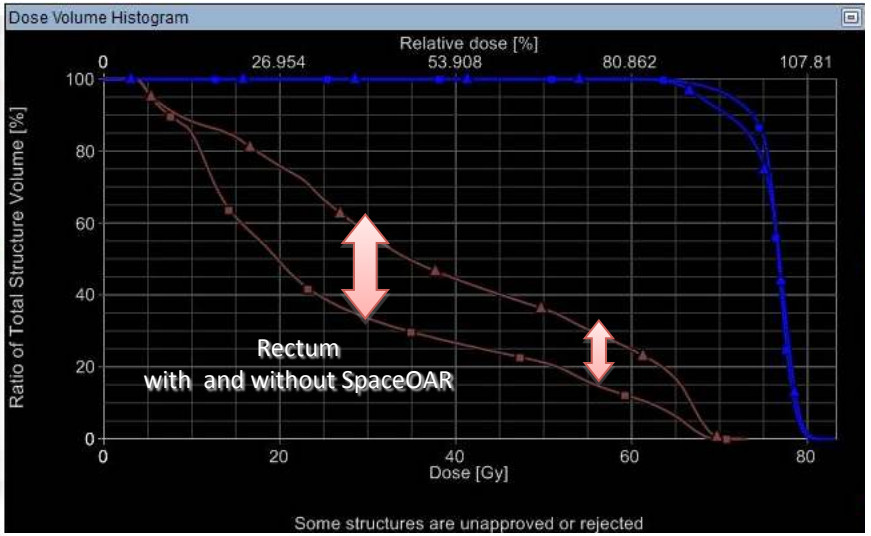
Courtesy by Dr. Alongi (radiotherapy, Sacro Cuore Don Calabria Negrar)

3RD ESTRO FORUM
24 - 28 April 2015
Barcelona, Spain

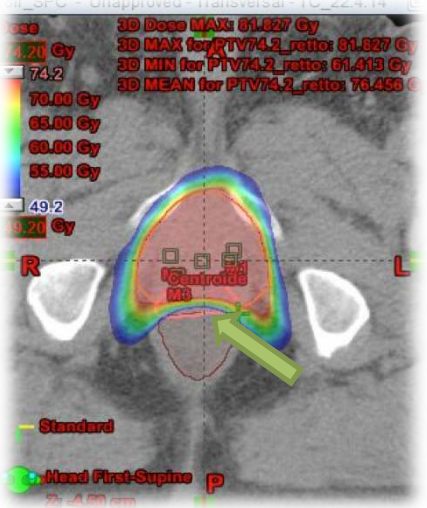
USEFUL OF SPACEOAR™ IN MODERATE HYPOFRACTIONATION:

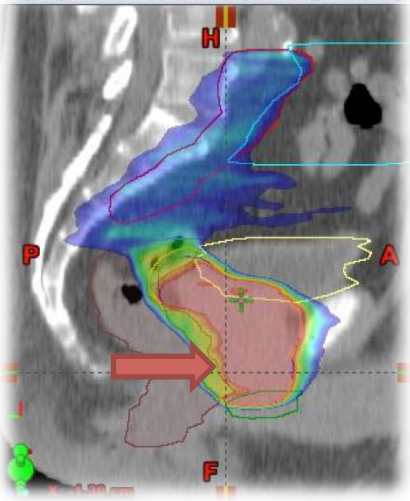
NO SPACER





SPACER

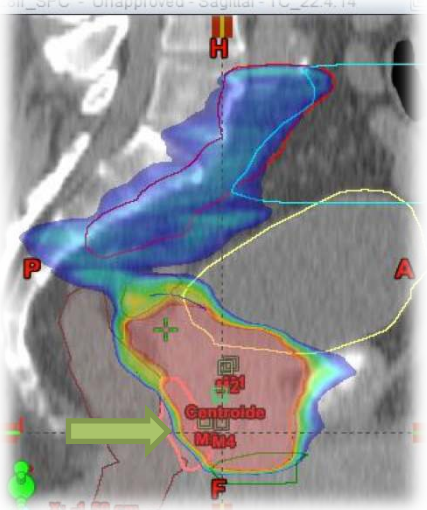




MODERATE HYPOFRATIONATION
PLAN COMPARISON WITHOUT AND WITH SPACEOAR

NO HIGH DOSE
IN ANTERIOR RECTAL WALL

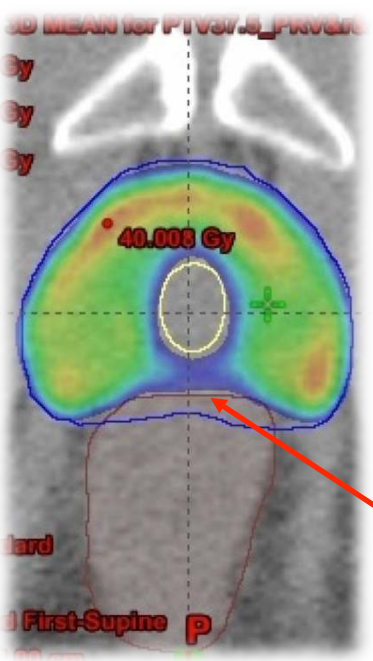
NO NEED OF REDUCTION OF DOSE IN THE OVERLAP BETWEEN RECTUM AND PROSTATE PTV

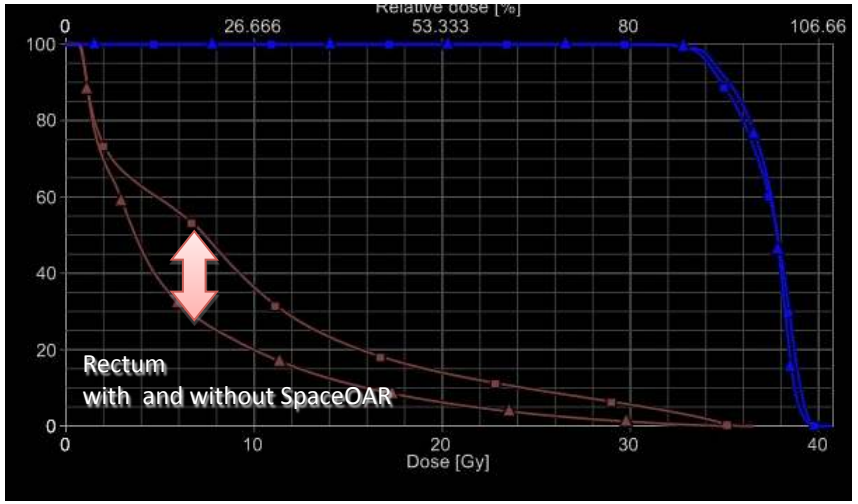


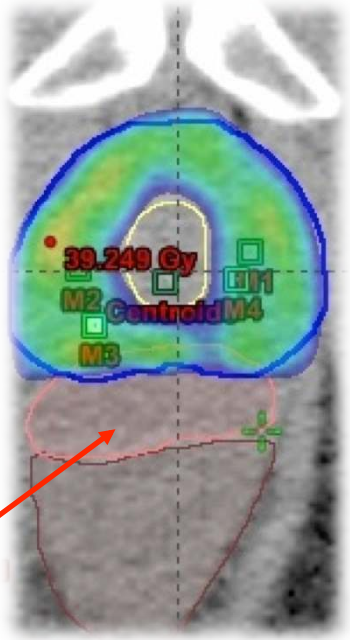
Courtesy by Dr. Alongi (radiotherapy, Sacro Cuore Don Calabria Negrar)

USEFUL OF SPACEOAR™ IN EXTREME HYPOFRACTIONATION:

SPACEOAR™ PROTOCOL: *37.5 Gy in 5 fraction, urethral sparing*







NO SPACEOAR
Dose Distribution
Isodose 95%

Anterior
Rectal wall

SPACEOAR
Dose distribution
Isodose 95%

Courtesy by Dr. Alongi (radiotherapy, Sacro Cuore Don Calabria Negrar)

HOW DO WE TREAT PROSTATE CANCER?

Alongi *et al. Radiation Oncology* 2013, **8**:171
http://www.ro-journal.com/content/8/1/171

RADIATION ONCOLOGY

RESEARCH Open Access

Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: preliminary report of a phase II study

Filippo Alongi[1,4*], Luca Cozzi[2], Stefano Arcangeli[1], Cristina Iftode[1], Tiziana Comito[1], Elisa Villa[1], Francesca Lobefalo[1], Pierina Navarria[1], Giacomo Reggiori[1], Pietro Mancosu[1], Elena Clerici[1], Antonella Fogliata[2], Stefano Tomatis[1], Gianluigi Taverna[3], Pierpaolo Graziotti[3] and Marta Scorsetti[1]

35 Gy in 5 fractions

Table 1 Patient characteristics

N. of patients	40
Median Age [year]	70 [56, 80]
Median Initial PSA [ng/mL]	6.25 [0.50, 13.43]
Median Gleason Score	6 [6,7]
NCCN Low Risk Class	26
NCCN Intermediate Risk Class	14
Median F-UP [months]	10 [3-14]
N. of patients with SpaceOAR™	8

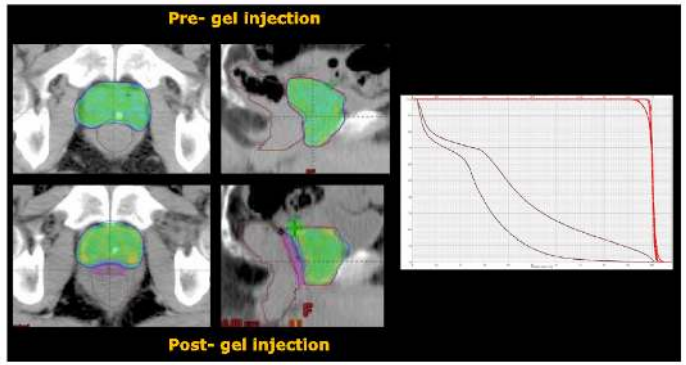


Figure 2 The potential dosimetric role of SpaceOAR™ gel implantation: dose distribution and DVH for a study patient where double CT scan and double planning was performed. Data are shown for CTV, PTV and rectum. No differences were observed for the target volumes while remarkable difference was observed in this case for the rectum.

Courtesy by Dr. Alongi (radiotherapy, Sacro Cuore Don Calabria Negrar)

IMPACT OF SPACER IN SBRT: PLANNING COMPARISON

Study analysis of the first 11 patient

Planning Results

Firstly, by comparing plans *Spacer* vs. *NoSpacer*, spacer insertion significantly improved rectal dose sparing for [V_{18Gy}%(p =.0003); V_{28Gy}%: (p =.00005); V_{32Gy}%: (p =.0006)]. Target dose coverage also was improved, in terms of D98% (p =.003); and PTV33.2Gy (p =.005)

TABLE: p-values, from *t*-test in normal characters, or from Wilcoxon test in italic characters, from five comparisons of ten parameters ($D_{98\%}$, $D_{50\%}$, $PTV_{33.2Gy}$, PTV_{35Gy}, V^{r}_{18Gy}, V^{r}_{28Gy}, V^{r}_{32Gy}, V^{rw}_{18Gy}, V^{rw}_{28Gy}, V^{rw}_{32Gy}) computed from 11 plans per group (*Spacer*, *NoSpacer*).

	$D_{98\%}$	$D_{50\%}$	$PTV_{33.2}$	PTV_{35}	V^{r}_{32Gy}	V^{r}_{28Gy}	V^{r}_{18Gy}	V^{rw}_{32Gy}	V^{rw}_{28Gy}	V^{rw}_{18Gy}
Spacer vs. *NoSpacer*	.003	.110	*.005*	.060	*.0006*	$5x10^{-5}$	.0003	$2x10^{-5}$	$3x10^{-5}$	.0005

Courtesy by Dr. Alongi (radiotherapy, Sacro Cuore Don Calabria Negrar)

Ruggieri R et al. Submitted 2015

Ongoing

Prostate Advances in Comparative Evidence (PACE)

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2015 by Royal Marsden NHS Foundation Trust

Sponsor:
Royal Marsden NHS Foundation Trust

Collaborator:
The Institute of Cancer Research, Sutton, Surrey, UK

Information provided by (Responsible Party):
Royal Marsden NHS Foundation Trust

ClinicalTrials.gov Identifier:
NCT01584258

First received: April 22, 2012
Last updated: April 7, 2015
Last verified: April 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Tracking Information	
First Received Date ICMJE	April 22, 2012
Last Updated Date	April 7, 2015
Start Date ICMJE	April 2012
Estimated Primary Completion Date	September 2021 (final data collection date for primary outcome measure)

low and intermediate risk patients who are
suitable for prostatectomy
Between laparoscopic surgery and SBRT
those unsuitable or who do not want a prostatectomy are randomised between

image-guided IMRT (78 Gy in 39 fractions) and SBRT.

SBRT is given to a dose of 36.25 Gy in 5 fractions, daily or on alternate days

Image guidance is fiducial-based and ADT is not given

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The SPARC Trial: Stereotactic Prostate Ablative Radiotherapy Using Cyberknife

This study is currently recruiting participants. (see Contacts and Locations)

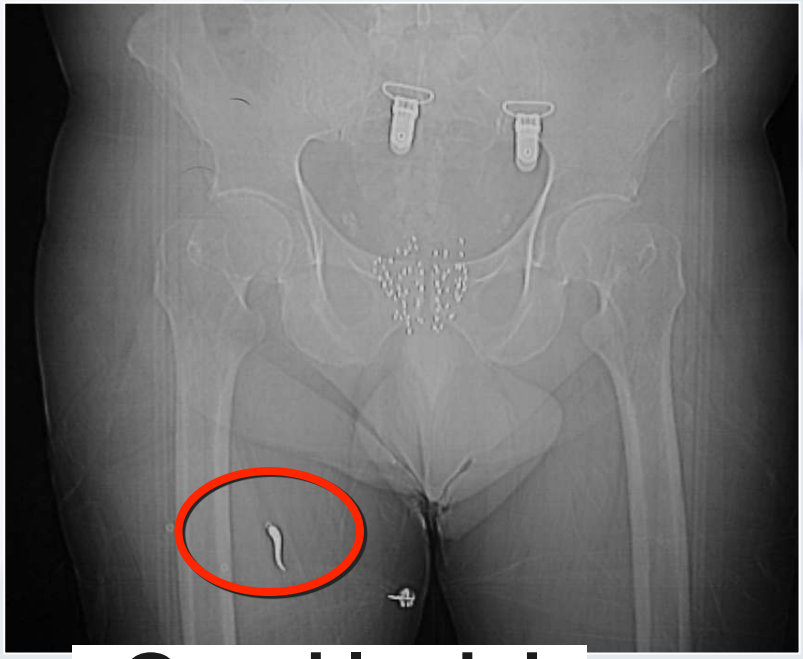
Verified May 2014 by Royal Marsden NHS Foundation Trust

Sponsor:
Royal Marsden NHS Foundation Trust

Information provided by (Responsible Party):
Royal Marsden NHS Foundation Trust

Estimated Enrollment:	20
Study Start Date:	June 2013
Estimated Study Completion Date:	December 2018
Estimated Primary Completion Date:	December 2015 (Final data collection date for primary outcome measure)

Experimental: Treatment Radiotherapy	Radiation: Radiotherapy Stereotactic body radiotherapy (SBRT) to the whole prostate (36.25 Gy in 5 fractions) with a focal boost (47.5 Gy in 5 fractions) to the MRI-defined dominant tumour nodule. Other Name: Cyberknife



Good luck !

Detailed Description:

Aim To assess if a focal boost can be delivered to the dominant tumour nodule alongside 36.25 Gy in 5 fractions to the whole prostate gland.

Primary end-point: Acute toxicity (Radiation Therapy Oncology Group (RTOG), International prostate symptom score (IPSS))

Secondary end-points: Prostate specific antigen (PSA) nadir and 2-year biochemical control Late toxicity (IPSS, RTOG, International index of erectile function (IIEF-5)) Quality of life (EQ5D scale)

Inclusion criteria

- Prostate cancer patients with any of the following:
- PSA>20
- Gleason grade 4+3 or higher
- Stage T3a
- Exclusion criteria
- Nodal or metastatic disease
- PSA>40
- Stage T3b or higher

Study interventions

This is a phase II study which will recruit 20 patients. A dose of 36.25 Gy in 5 fractions will be delivered to the whole prostate with a simultaneous integrated boost up to 47.5 Gy in 5 fractions or to the highest dose possible within dose constraints. The boost volume will be defined on the multiparametric magnetic resonance scan by the specialist radiologist.

"Give me five"

EIO protocol with Vero Brainlab

Prostata in sede: Out-trial VERO (casi selezionati, consenso informato specifico)

Volume	Dose/fr	Num fr	Dtot	**NTD** (α/β=1,5Gy) d/fr 2Gy	**BED** (α/β=1,5Gy)
PTVprostata	6,5	5	32,5	74,3	173
	7	5	35	85	198

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Report doses for each patient

	Valori raccomandati per dose/frazione 6,5 Gy-7 Gy		Valori dal piano di cura	Valori raccomandati per dose/ frazione 7,5-7,25 Gy	Valori dal piano di cura
Retto V= _____cc	$V_{100\%}$ <5 %		%	$V_{100\%}$ <5 %	%
	$V_{50\%}$ < 50%		%	$V_{50\%}$ < 50%	%
	$V_{80\%}$ < 20%		%	$V_{80\%}$ < 20%	%
	$V_{90\%}$ < 10%		%	$V_{90\%}$ < 10%	%
	$V_{100\%}$ < 5%		%	$V_{28\ Gy}$ < 1 cc	cc
Parete ant. del retto				D_{max}<105% Se possible D_{max}<100%	%
Parete post del retto/canale anale				D_{max}<45%	%
	$V_{100\%}$ < 5%		%	$V_{100\%}$ < 5%	%
	6,5 Gy	7 Gy		$V_{25\ Gy}$ < 5 cc	
Pene	V_{30Gy} < 1cc	V_{34Gy} < 1cc	cc	V_{34Gy} < 1cc	cc
Testicoli	$D_{0,01cc}$ < 3Gy	$D_{0,01cc}$ < 4Gy	Gy	$D_{0,01cc}$ < 4Gy	Gy
Cauda equina	D_{max} < 22Gy	D_{max} < 23,5Gy	Gy	D_{max}<23 Gy (4,5 Gy/fraz.)	Gy
	D_{10cc}<20Gy	D_{10cc}<21,5Gy	Gy	$V_{20,8Gy}$ < 10 cc	cc

Rectum dose/fr: **V50% < 50%**
V80% < 20%
V90% <10%
V100% <5%

Posterior part of the rectum Dmax< 45%

Anterior part of the rectum Dmax< 85% or Dmax <31 Gy

Boike TP et al. Phase I Dose-Escalation Study of Stereotactic Body Radiation Therapy for Low- and Intermediate-RiskProstate Cancer. J Clin Oncol 2011;29:2020-2026.

King CH et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate Int. J. Radiat Oncol Biol. Phys.2012, 82: 877–882,

Katz AJ et al. Stereotactic body radiotherapy for organ confined prostate cancer. BMC Urology 2010, 10:1

Arcangeli S et al. Will SBRT replace conventional radiotherapy in patients with low-intermediate risk prostate cancer? A review. Critical Reviews in Oncology/Hematology 2012; 84: 101–108

Freeman DE et al. Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol 2011, 6:3.

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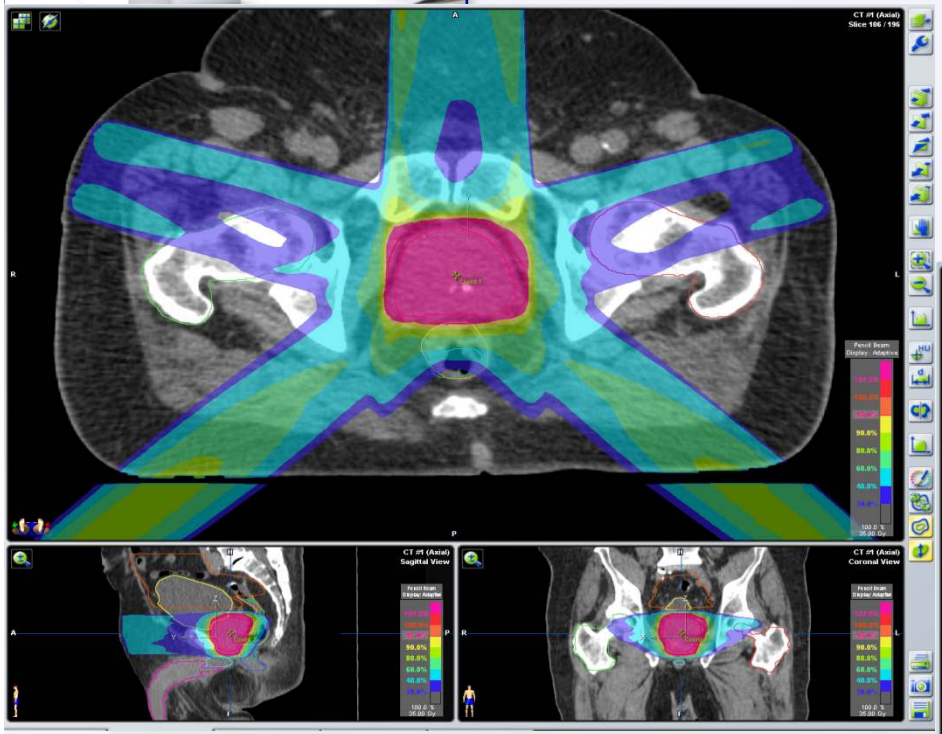
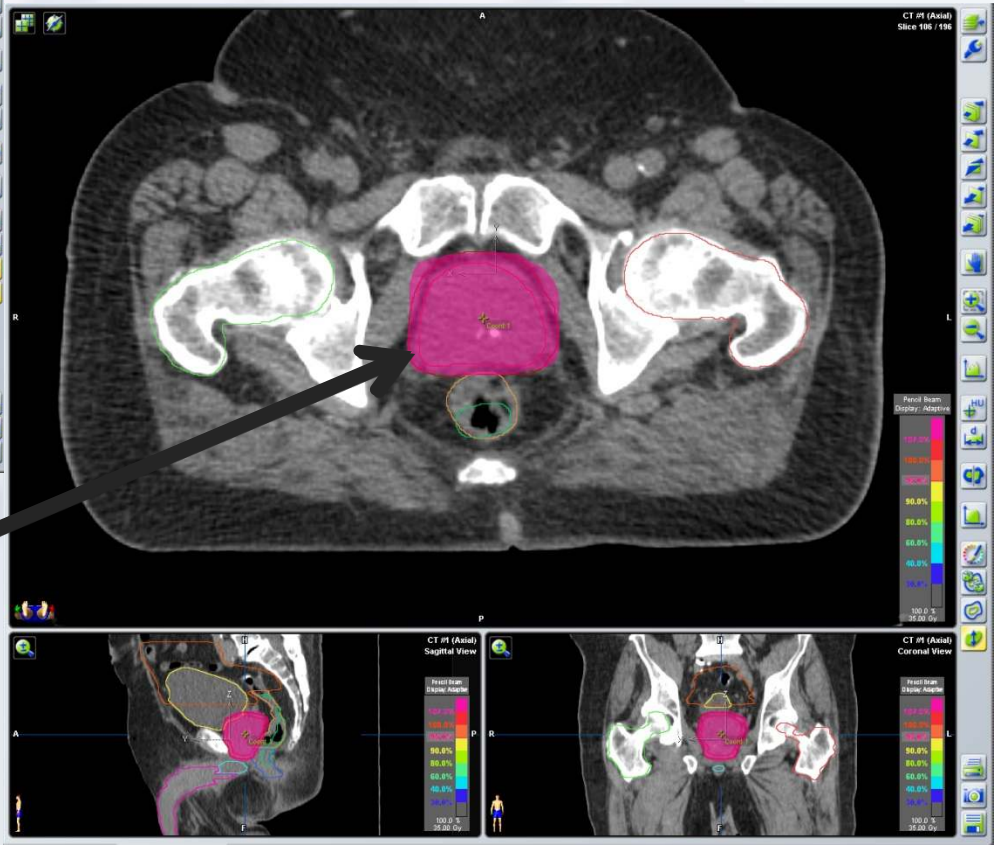
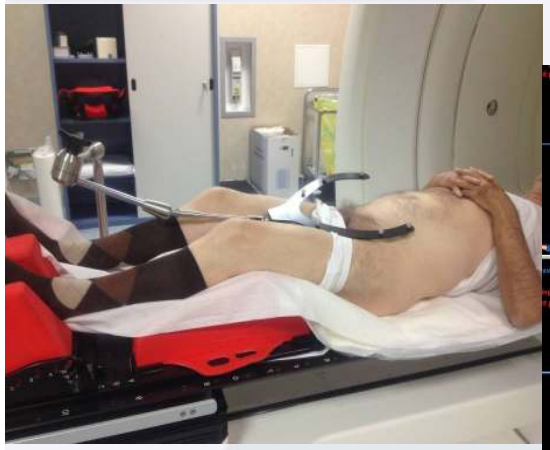
Prostate cancer

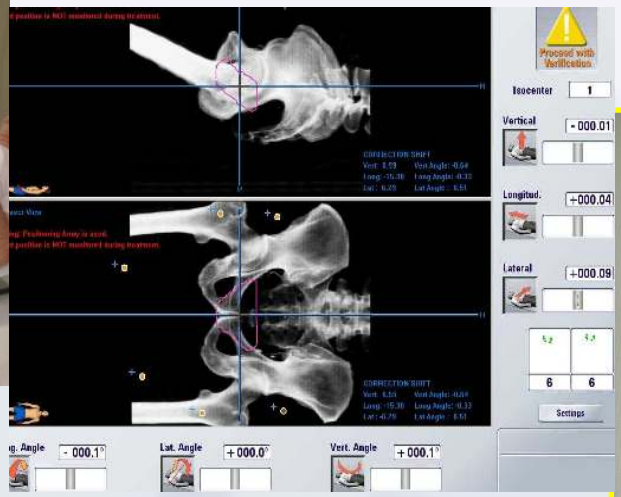


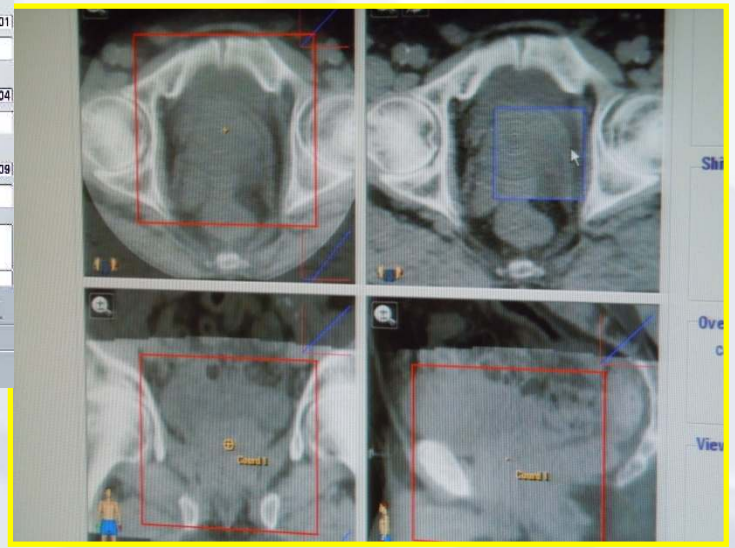


CTV-PTV : 5/3 mm (post)

Prostate cancer







1. Daily ExacTrac (positioning array or surface markers)

2. Daily IGRT with CBCT

Just couple of minutes, imaging dose 1.9 cGy

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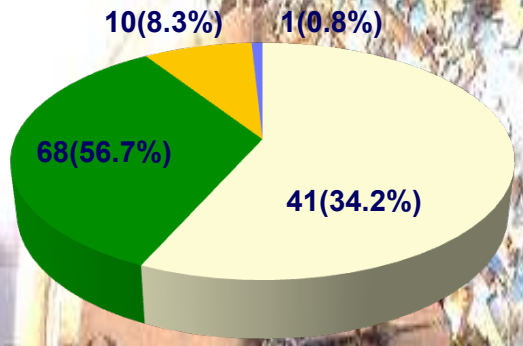
Our experience EIO: OUT TRIAL

- 120 pts from April 2012 to October 2014
- risk categories : low (T1-T2a, PSA <10 ng/ml, Gleason score <7) or intermediate (T2b or T2c, PSA between 10 and 20 ng/ml, Gleason score of 7)
- personalized indication for high risk pts (PSA > 20 ng/ml, Gleason score> 7) prostate volume <100 cc
- ADT 29%
- IG-IMRT with CBCT on alternate days
- 32,5-35 Gy/5 fr

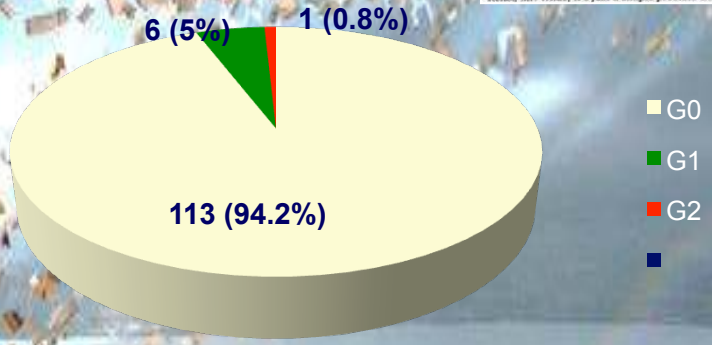
BC rate after a mean follow up of 8 months was 99,2%

ACUTE TOXICITY
(according to EORTC/RTOG)

Acute tox GU



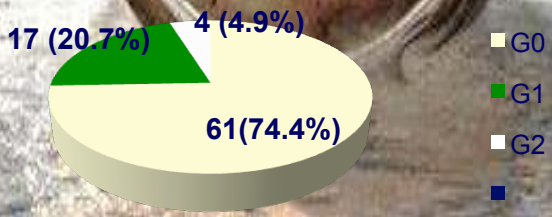
Acute tox GI



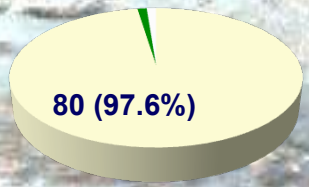
LATE TOXICITY
(according to EORTC/RTOG)

82 patients with f.-up > 6 months
8 months
(range 3 – 24)

Late tox GU



Late tox GI



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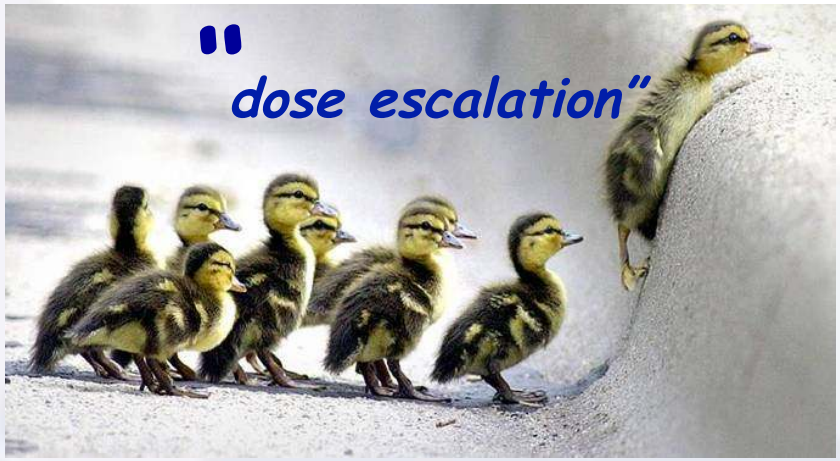
Take home message

IMRT and dose escalation (doses > 80 Gy) is mandatory for curative RT for prostate cancer



SBRT and hypofractionated regimen for localized prostate cancer has yet to be fully validated:

Moderate 2,5-4 Gy/fr to 50-70 Gy

Extreme 5-10 Gy/fr to 35-50 Gy

Hypo for Pca has advantages of increased convenience for the pts and lower cost

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Take home message

Longer follow-up is needed to confirm durable biochemical control rate and low late toxicity profiles

Early efficacy data is also promising, the majority of treated patients having low or intermediate risk disease.

SBRT has been delivered successfully using both RRS and IMRT (IGRT with CBCT)

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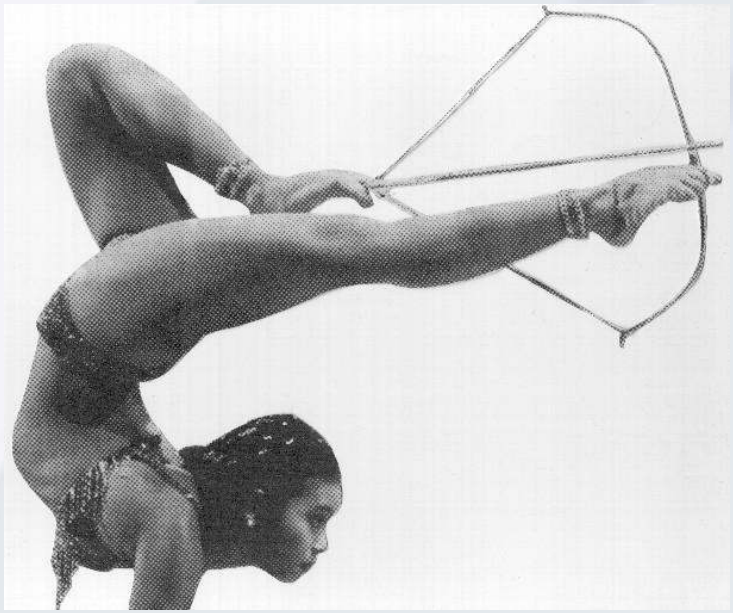
“If you can't see it, you can't hit it,

and if you can't hit it, you can't cure it”

(credited to the Canadian medical physicist Harold Johns)

Thank you for your attention



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