Tecniche e frazionamenti in radioterapia: nuovi orizzonti

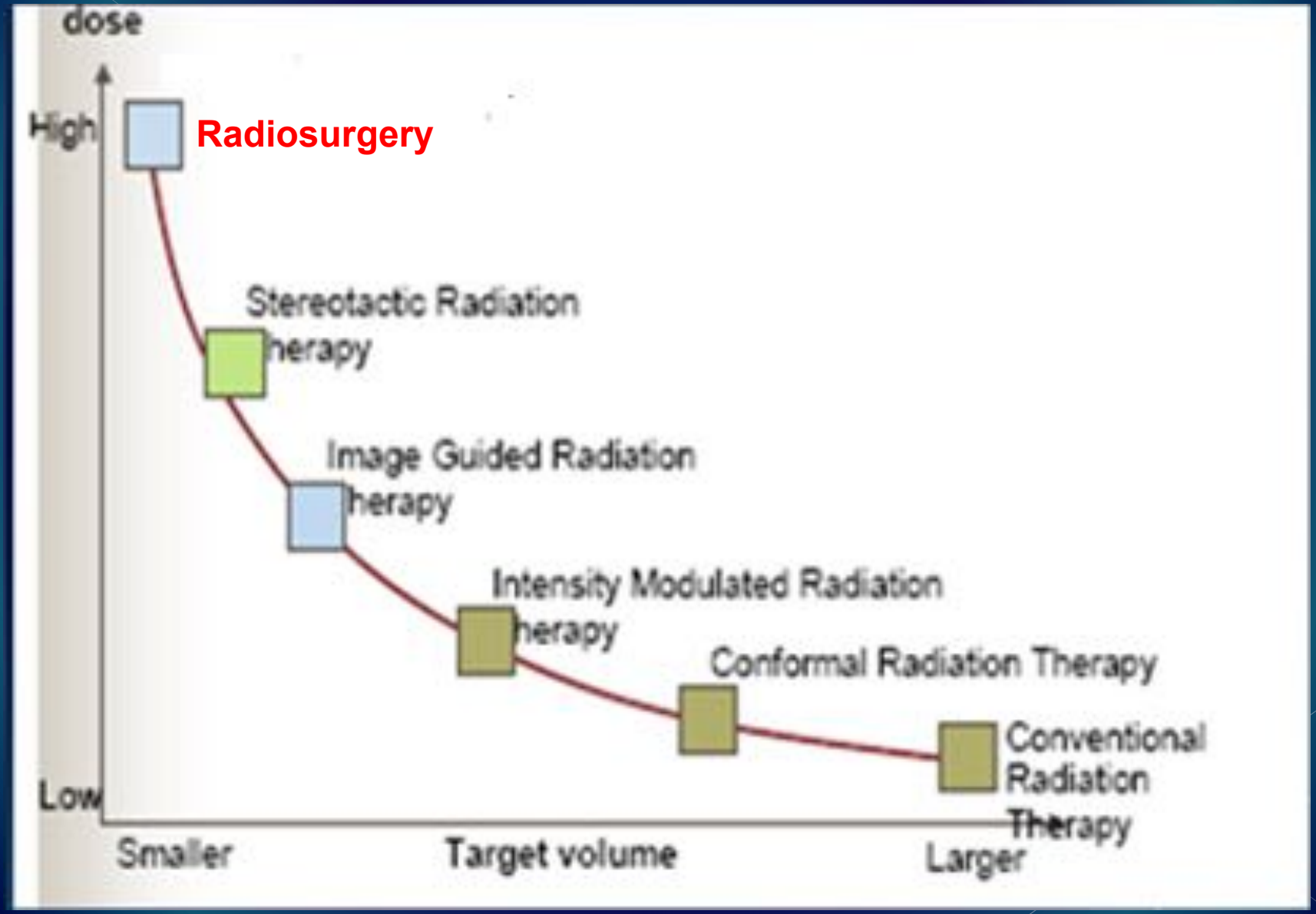
S. Arcangeli

U.O.C. Radioterapia

Azienda Ospedaliera San Camillo – Forlanini

Roma

Evolution in Radiation Oncology



Biochemical outcome from the most relevant dose escalation trials

REFERENCE	No. Pts	Dose/fx size/# fxs	Med F/U (mos)	risk class	% 5-year FFBF(*)
Kuban *et al. 2008 [22]*	150	70Gy/2Gy/35 fx	116	L-I-H	87
	151	78Gy/2Gy/39 fx	116	L-I-H	88
Dearnaley *et al. 2007 [23]*	421	64Gy/2Gy/32 fx	64	L-I-H	60
	422	74Gy/2Gy/37 fx	63	L-I-H	71
Al-Mamgani *et al. 2010 [24]*	331	68Gy/2Gy/34 fx	70	L-I-H	51
	333	78Gy/2Gy/39 fx	70	L-I-H	63
Kuban *et al 2003 [26]*	1087	67Gy/2Gy/33.5 fx	65	L-I-H	36
		78Gy/2Gy/39 fx	65	L-I-H	45
Zelefky *et al. 2008 [25]*	358	70.2 Gy/1.8 Gy/39 fx	79	L-I-H	61
	471	75.6 Gy/1.8 Gy/42 fx	79	L-I-H	74
	741	81 Gy/1.8 Gy/45 fx	79	L-I-H	85
	477	86.4 Gy/1.8 Gy/48 fx	79	L-I-H	82

Abbreviations: L= low risk; I=intermediate risk; H =high risk; FFBF=freedom from biochemical failure. (*) Average of FFBF of patients with/without ADT

ASTRO Online CME

CLINICAL INVESTIGATION Prostate

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.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zietman et al.	0,363	0,164	0,805	-3,280	0,001
Dutch	0,619	0,399	0,959	-2,821	0,005
Shipley et al.	1,069	0,511	2,237	0,233	0,816
Sathya et al.	0,273	0,094	0,799	-3,115	0,002
	0,604	0,477	0,765	-5,487	0,000

Meta-analysis regarding biochemical failure for all subgroups. CI = confidence interval.

…but at the expense and inconvenience of delivering a large number of fractions, often > 40!

Hypofractionation for PCa

- **FASTER** Less distressing for elderly population with Pca

- **CHEAPER** - Reduced treatment costs
  - Shorter waiting lists

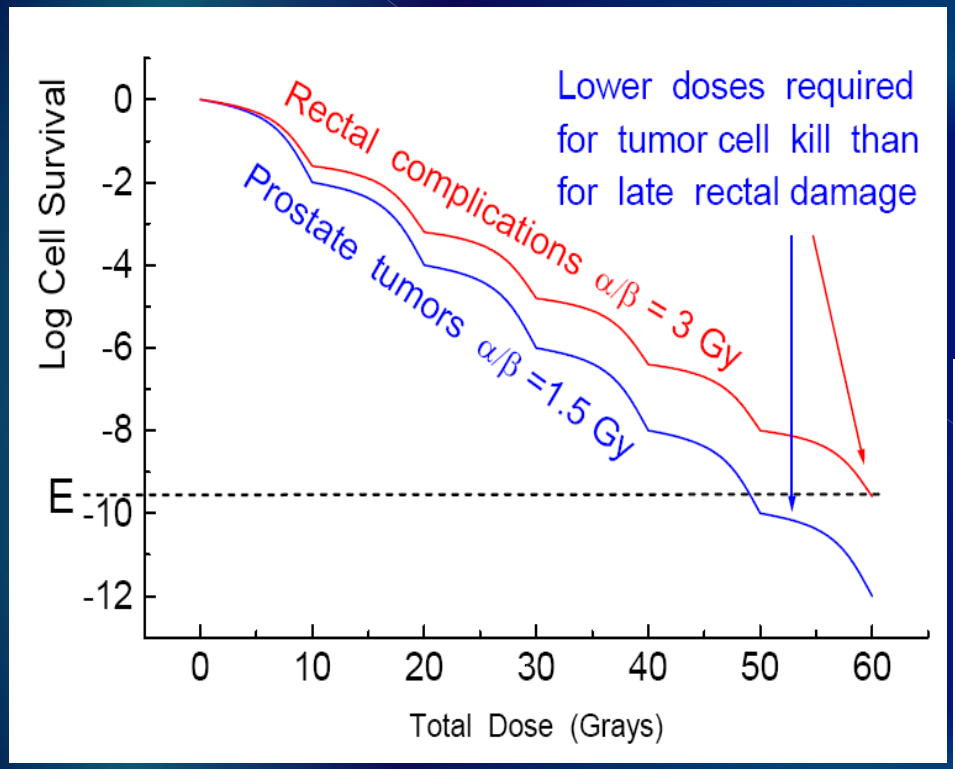
- **BETTER** Biologically worths → unusual radiobiology of PCa

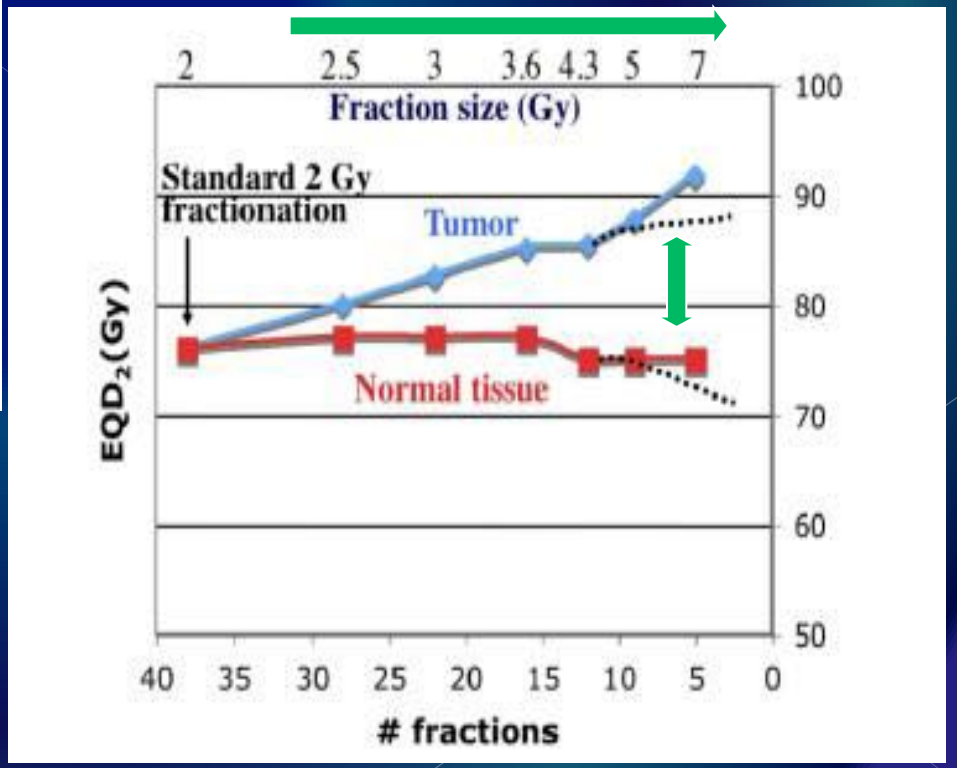
Unusual Radiobiology of PCa

Tumour type	T_{pot} (days)	T_d (days)	Radiobiological/clinical properties	Treatment indication
Head and neck	4.5 (1.8–5.9) Rew et al. [6]	45 Rew et al. [6]	– Rapid regrowth during treatment – High hypoxic content	Hyperfractionation Accelerated radiotherapy
Prostate	28 (16–61) Haustermans et al. [7]	1100 Lee et al. [8]	– Slow proliferation – Very low α/β ratio	Hypofractionation
Glioblastoma	3.9–7.5 Hlatky et al. [9] 2.3–13.3 Nakajima et al. [10]	3.3–29.2 Nakajima et al. [10]	– High hypoxic content – Poor differentiation; radioresistance – High proliferation	Hyperfractionation Accelerated radiotherapy Hyperfractionation
Breast	10.4 (8.2–12.5) Rew et al. [6]	82 Spratt et al. [11] 44–295 Peer et al. [12]	– Age-dependent proliferation – α/β ratio similar to the normal tissue one	Hypofractionation Accelerated radiotherapy
Lung (non-small cell lung cancer – NSCLC)	7.1 Shimomatsuya et al. [13] 8.2 Shibamoto et al. [14]	46 Sharouni et al. [15] 67.5 Arai et al. [16] 81 Lindell et al. [17]	– Small volume doubling time – Rapid regrowth during treatment – NCSLC higher radioresistance than other histologic types	Hyperfractionation Accelerated radiotherapy

Cancer Treatment Reviews 36 (2010)

Hypofractionation & Therapeutic Ratio





Ritter et al Cancer J 2009

How Best Can Hypofractionation Be Explored in a Clinical Setting?

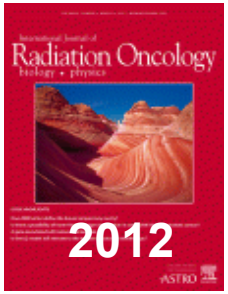
Two approaches:

1) Normal tissue de-escalation of total dose while maintaining constant predicted tumour control.

2) Tumour biological dose escalation with constant predicted normal tissue late effects.

Ritter, Sem Rad Onc 2008

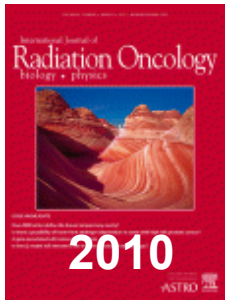
Is α/β ratio really low in PCa?



CLINICAL INVESTIGATION **Genitourinary Cancer**

DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: α/β = 1.4 (0.9–2.2) GY

RAYMOND MIRALBELL, M.D.,*† STEPHEN A. ROBERTS, PH.D.,‡ EDUARDO ZUBIZARRETA, M.D.,§ AND JOLYON H. HENDRY, PH.D.‖



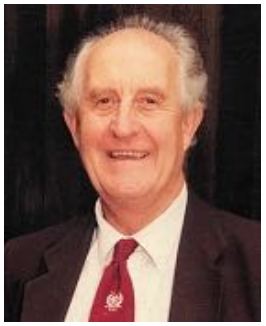
CLINICAL INVESTIGATION **Prostate**

CONFIRMATION OF A LOW α/β RATIO FOR PROSTATE CANCER TREATED BY EXTERNAL BEAM RADIATION THERAPY ALONE USING A POST-TREATMENT REPEATED-MEASURES MODEL FOR PSA DYNAMICS

CÉCILE PROUST-LIMA, PH.D.,*† JEREMY M. G. TAYLOR, PH.D.,‡§ SOLÈNE SÉCHER, PH.D.,*† HOWARD SANDLER, M.D.,‖ LARRY KESTIN, M.D.,¶ TOM PICKLES, M.D.,# KYOUNGWHA BAE, PH.D.,** ROGER ALLISON, F.R.A.N.Z.C.R.,†† AND SCOTT WILLIAMS, M.D., F.R.A.N.Z.C.R.‡‡

Hypofractionation for PCa

"Hypofractionation for prostate cancer is biologically the best strategy" provided the α/β ratio for prostate tumors (~1,5) is less than α/β ratio for late complication (~3 for rectum)"



"If αβ ratio of tumor is the same or less than that of the critical normal tissue, then a larger dose per fraction (hypofractionation) is preferred."


Rules
&
Procedures

Rules for Hypofractionation 1.

Calculate LQ BED & NTD for your new Total Dose = n x d.

Then BED = Total Dose x RE, where RE = (1 + $\frac{d}{\alpha/\beta}$)

Using $\alpha/\beta = 3$ Gy

- **NTD = BED / (RE for 2Gy) = BED / (1+ 2/3) = BED / 1.667 :**

  For prostate tumor BED / (1+2/1.5) = BED / 2.333

Courtesy of J. Fowler

Rules for Hypofractionation 2.

If Late NTD >70 Gy, or BED_3 >117 Gy, look up Rectal constraints, so late complic's not >2 bleeding

Rectal Vol or Area Tol. vs Dose

(100% = 100 sq cm approx)

Dose(Gy)	Area or Vol (%)
60	35 or 41 %
70	22 or 26 %
75.6	11 or 13 %
78	3 or 4 %
80	~2%

Courtesy of J. Fowler

Rules for Hypofractionation 3.

Acute mucosal reactions could become dose-limiting if overall times too short.

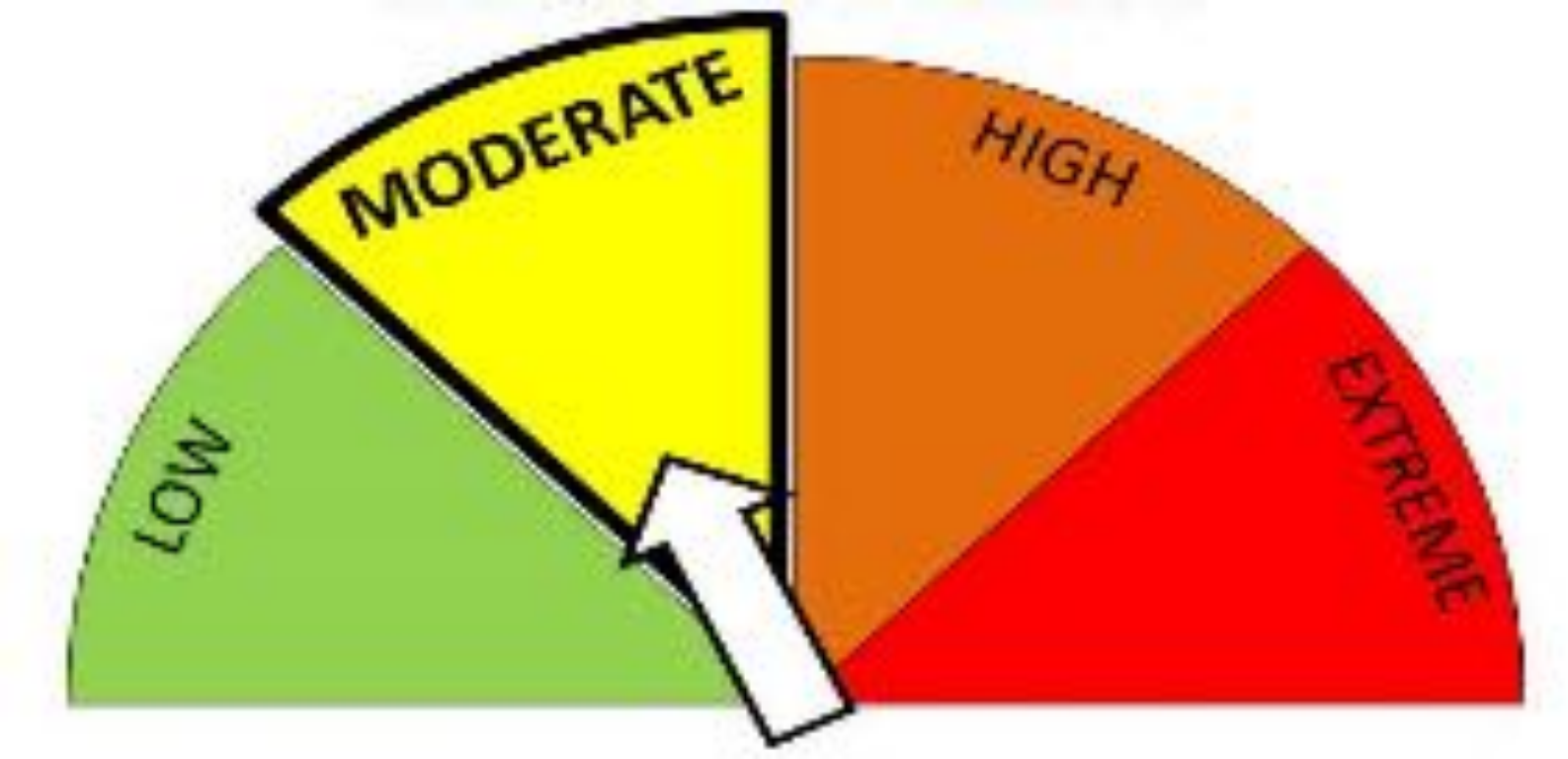
Acute Mucosal Reactions modelled by assuming $\alpha/\beta = 10$Gy, Tk = 7 days, Tp = 2.5 days
Fowler, Harari, Leborgne R&O 2003; 69: 161-8

If BED exceeds 59 – 63 Gy_{10} = 49 – 52.5 Gy NTD, Too hot in oral mucosa, now confirmed as reliable. And in rectal mucosa? Seems to work also.

Consider using alternate treatment days etc.

Courtesy of J. Fowler

Clinical Data
Moderate Hypofractionation for Pca



NON Randomized Trials

Author	Pts	Fractionation Schedule	RT Technique	NTD2/1.5	NTD2/3	Median FUP	% bRFS	>G2 GI	>G2 GU
Fontayne 2012	102 LIH	56 Gy/3.5 Gy/16 f	IMRT	77 Gy	70.4 Gy	47 mo	94	1%	2%
Thomson 2012	30 H 30 H	60 Gy/3 Gy/20 f 57 Gy/2.85 Gy/20 f	IMRT	77.1 Gy 70.8 Gy	72 Gy 66.7 Gy	84 mo	50 58	0 0	0 0
Zilli 2011	82 LIH	56 Gy/4 Gy/14 f	IMRT	88 Gy	78.4 Gy	48 mo	77.5-91.3	1%	0
Ritter 2011	100 LI 100 LI 100 LI	64.7 Gy/2.94 Gy/22 f 58.1 Gy/3.63 Gy/16 f 51.6 Gy/4.3 Gy/12 f	IMRT/TOMO	82.1 Gy 85.1 Gy 85.5 Gy	76.9 Gy 77 Gy 75.3 Gy	56 mo 37 mo 28 mo	91.5 96.1 98.7	3%	0
Faria 2011	89 I	66 Gy/3 Gy/22 f	3D CRT	85 Gy	79.2 Gy	51 mo	95.4	2%	7%
Leborgne 2009	52 LIH 87 LIH	60 Gy/3 Gy/20 f 63 Gy/3.15 Gy/20 f	3D CRT	77.1 Gy 83.7 Gy	72 Gy 77.5 Gy	49 mo	85-96	5.5%	5.6%
Kupelian 2007	770 LIH	70 Gy/2.5 Gy/28 f	IMRT	80 Gy	77 Gy	45 mo	72-94	1.3%	0.1%
Martin 2007	92 LIH	60 Gy/3 Gy/20 f	IMRT	77.1 Gy	72 Gy	38 mo	97	1%	0

Randomized Trials

Trial	Pts	Fractionation Schedule	RT Technique	NTD2/1.5	NTD2/3	Median FUP	% 5y-bRFS
CANADA *JCO 2005*	470 T1-2 466 T1-2	66 Gy/2 Gy/33 f 52.5 Gy/2.62 Gy/20f	2D-3D CRT	66 Gy 62 Gy	66 Gy 59 Gy	47.5 mo	52.9 59.9
AUSTRALIA *IJROBP 2011*	109 T1-2 108 T1-2	64 Gy/2 Gy/32 f 55 Gy/2.75 Gy/20 f	2D-3D CRT	64 Gy 66.8 Gy	64 Gy 63.3 Gy	62.5 mo	56 57
USA *IJROBP 2010*	102 LI 102 LI	75.6 Gy/1.8 Gy/42 f 72 Gy/2.4 Gy/30 f	IMRT	71.3 Gy 80.2 Gy	72.6 Gy 77.8 Gy	40 mo	92 96
USA *IJROBP 2011*	152 LIH 151 LIH	76 Gy/2 Gy/38 f 70.2 Gy/2.7 Gy/26 f	IMRT	76 Gy 84.2 Gy	76 Gy 80 Gy	60 mo	85.6 86.1
UK *Lancet Oncol 2012*	153 LI 153 LI 151 LI	74 Gy/2 Gy/37 f 60 Gy/3 Gy/20 f 57 Gy/3 Gy/19 f	IMRT	74 Gy 77.1 Gy 73.3 Gy	74 Gy 72 Gy 68.4 Gy	50.5 mo	-
ITALY *IJROBP 2012*	85 H 83 H	80 Gy/2Gy/40 f 62 Gy/3.1 Gy/20 f	3D CRT	80 Gy 81.5 Gy	80 Gy 74 Gy	70 mo	74 85

Randomized Trials

Trial	Pts	RT Technique	NTD2/1.5	NTD2/3	Median FUP	%GI	%GU
CANADA *JCO 2005*	470 T1-2 466 T1-2	2D-3D CRT	66 Gy 62 Gy	66 Gy 59 Gy	47.5 mo	G3 1.3 G3 1.3	G3 1.9 G3 1.9
AUSTRALIA *IJROBP 2011*	109 T1-2 108 T1-2	2D-3D CRT	64 Gy 66.8 Gy	64 Gy 63.3 Gy	62.5 mo	similar in both groups	
USA *IJROBP 2010*	102 LI 102 LI	IMRT	71.3 Gy 80.2 Gy	72.6 Gy 77.8 Gy	40 mo	G3 1 G3 3	G3 1 G3 0
USA *IJROBP 2011*	152 LIH 151 LIH	IMRT	76 Gy 84.2 Gy	76 Gy 80 Gy	60 mo	≥ G2 4.1 ≥ G2 5.9	≥ G2 8.9 ≥ G2 13.8
UK *Lancet Oncol 2012*	153 LI 153 LI 151 LI	IMRT	74 Gy 77.1 Gy 73.3 Gy	74 Gy 72 Gy 68.4 Gy	50.5 mo	≥ G2 4.3 ≥ G2 3.6 ≥ G2 1.4	≥ G2 2.2 ≥ G2 2.2 ≥ G2 0
ITALY *IJROBP 2012*	85 H 83 H	3D CRT	80 Gy 81.5 Gy	80 Gy 74 Gy	70 mo	≥ G2 17 ≥ G2 16	≥ G2 14 ≥ G2 11

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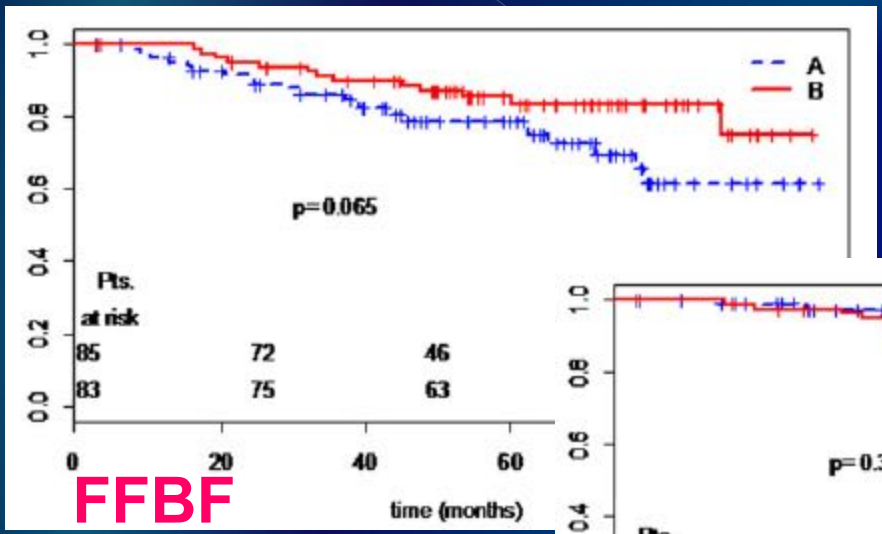
2012

Clinical Investigation

Updated Results and Patterns of Failure in a Randomized Hypofractionation Trial for High-risk Prostate Cancer



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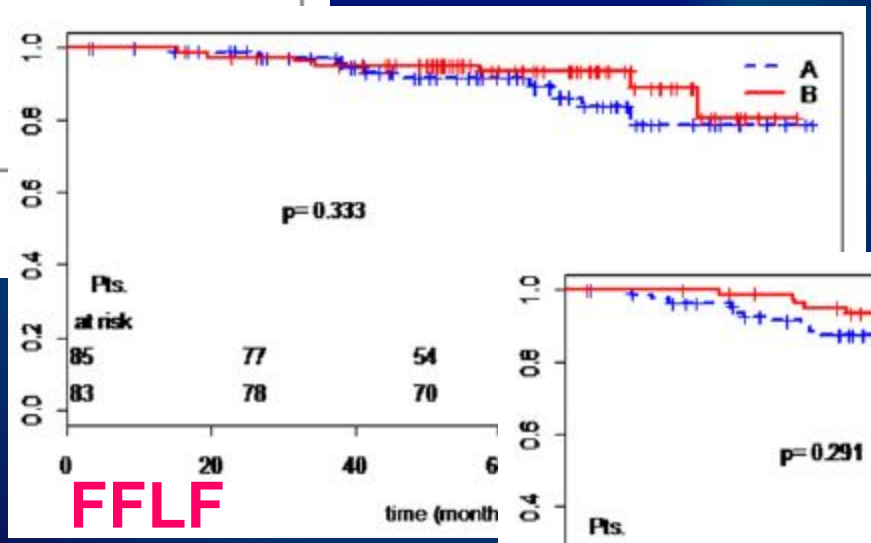

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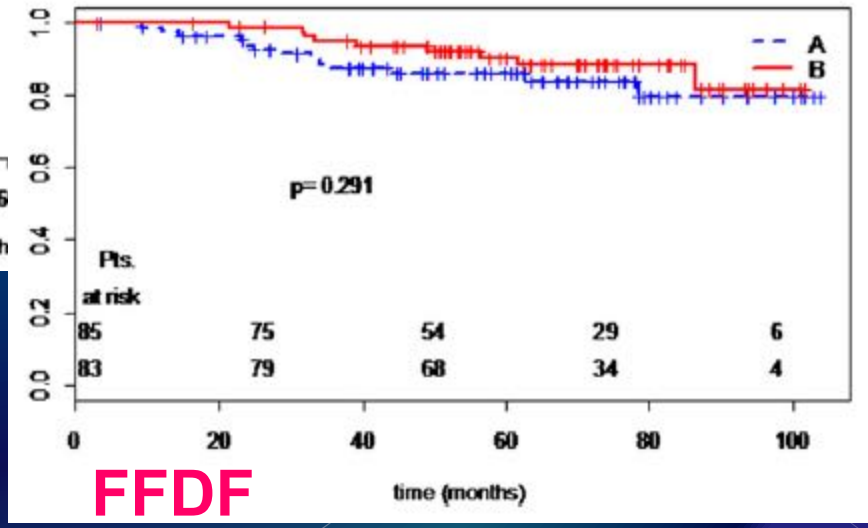

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Clinical Investigation

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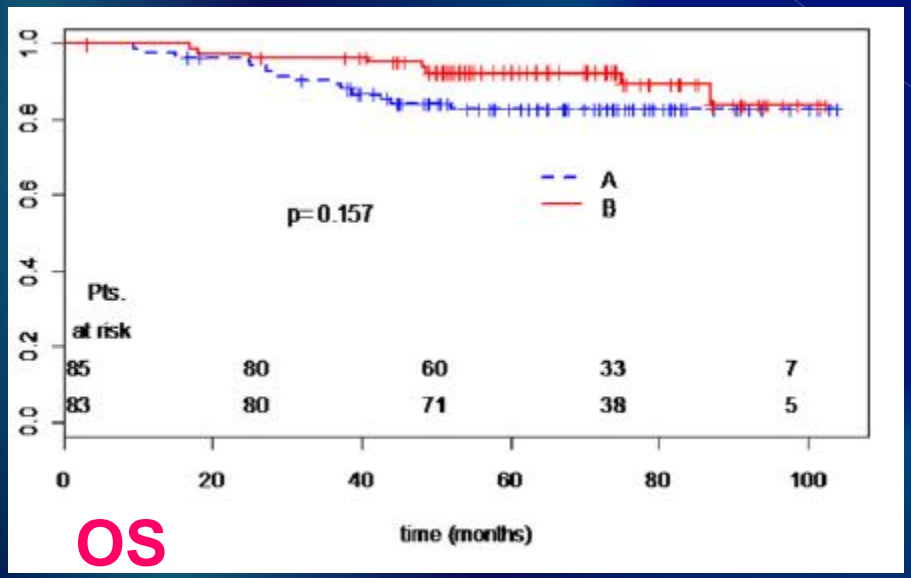

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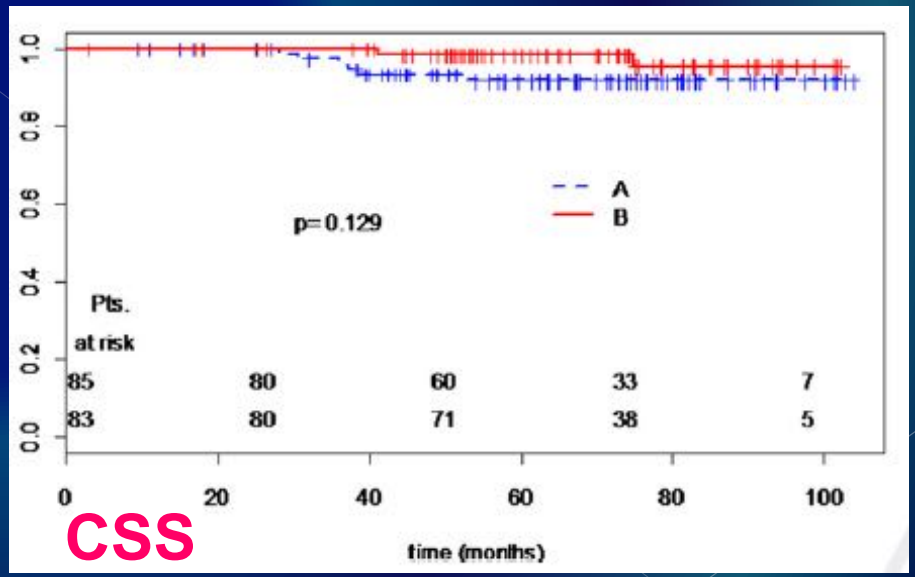

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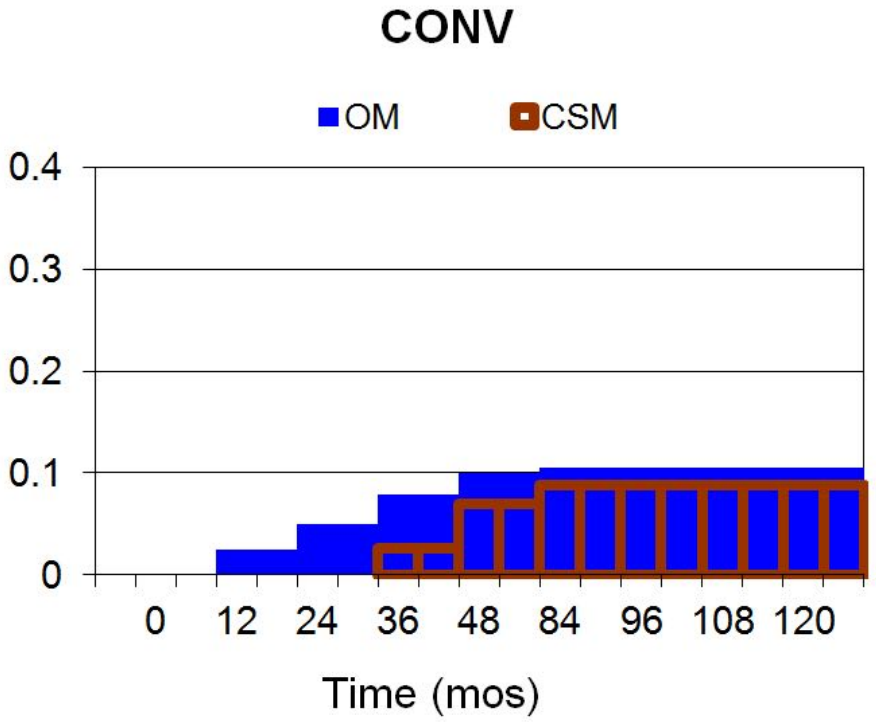

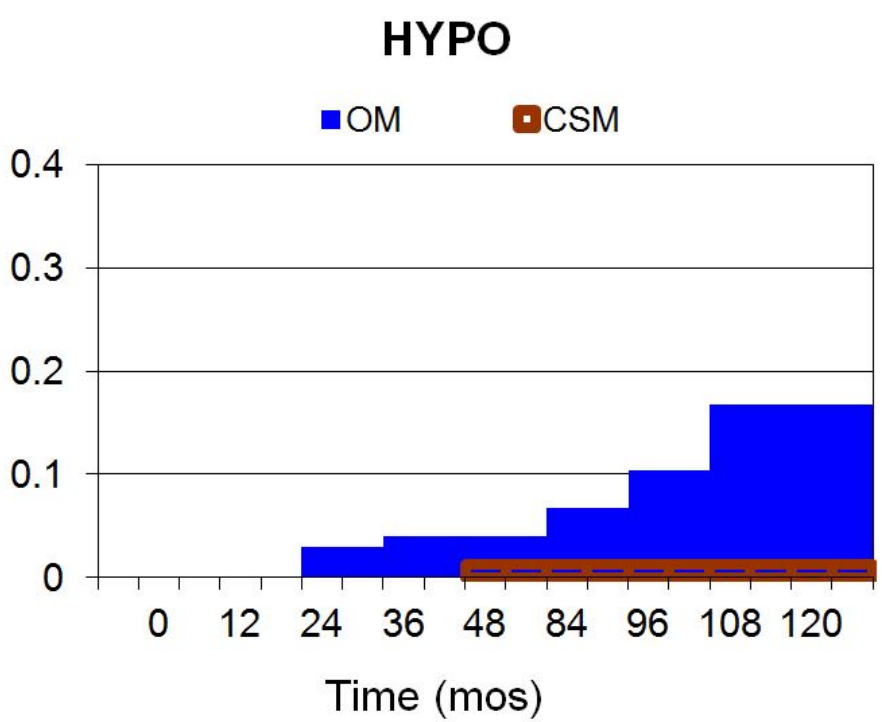

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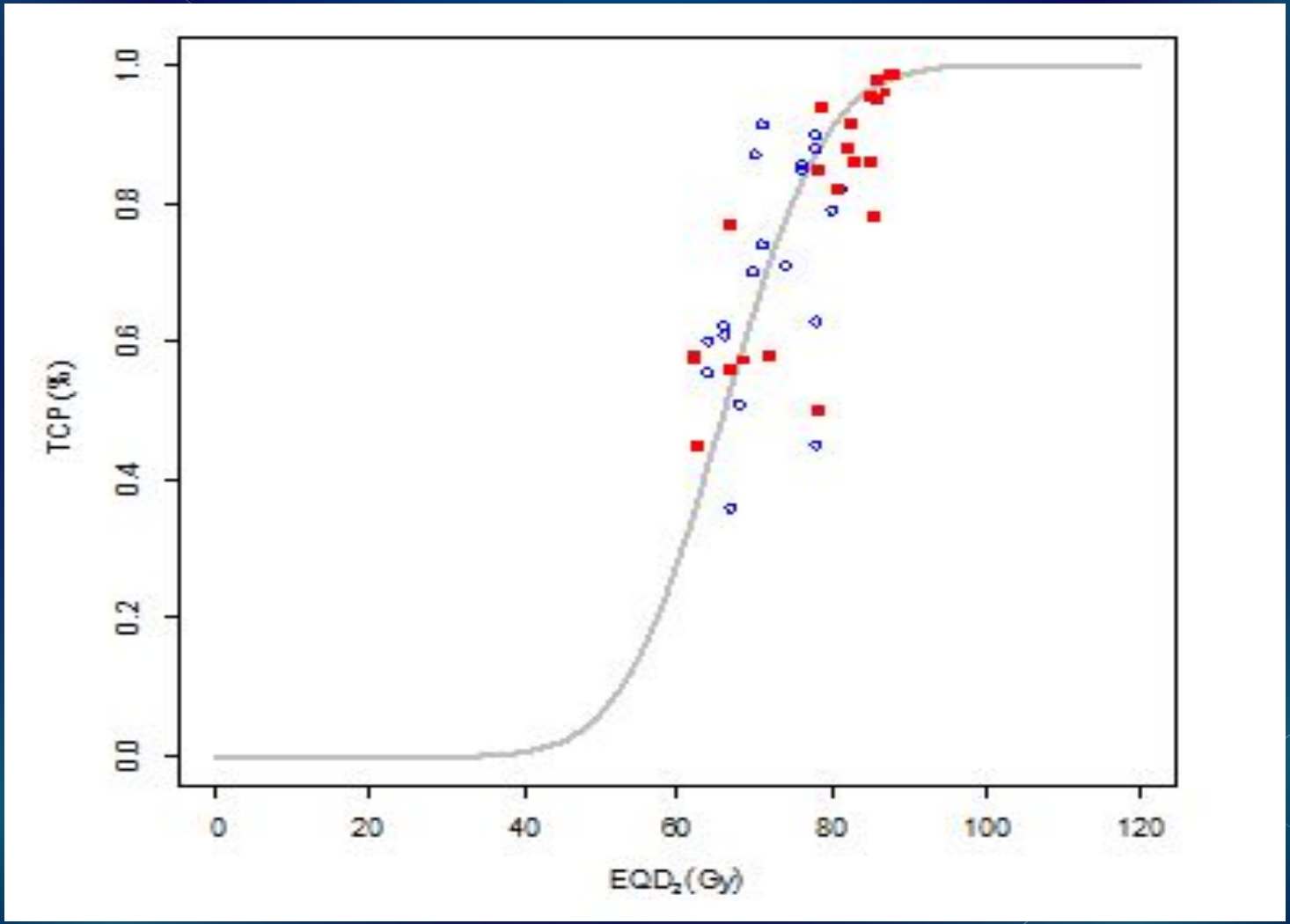
Clinical Investigation

Updated Results and Patterns of Failure in a Randomized Hypofractionation Trial for High-risk Prostate Cancer

- methodology employing 3D rather than IMRT: attractive in the context of expecting hypofx to radiobiologically improve the therapeutic ratio

- support the issue that apha/beta for PCa is truly low even for high risk disease

Dose response curve of the 5-y bRFS vs equivalent dose at 2Gy/fraction (EQD2) assuming an α/β of 1.5Gy for PCa



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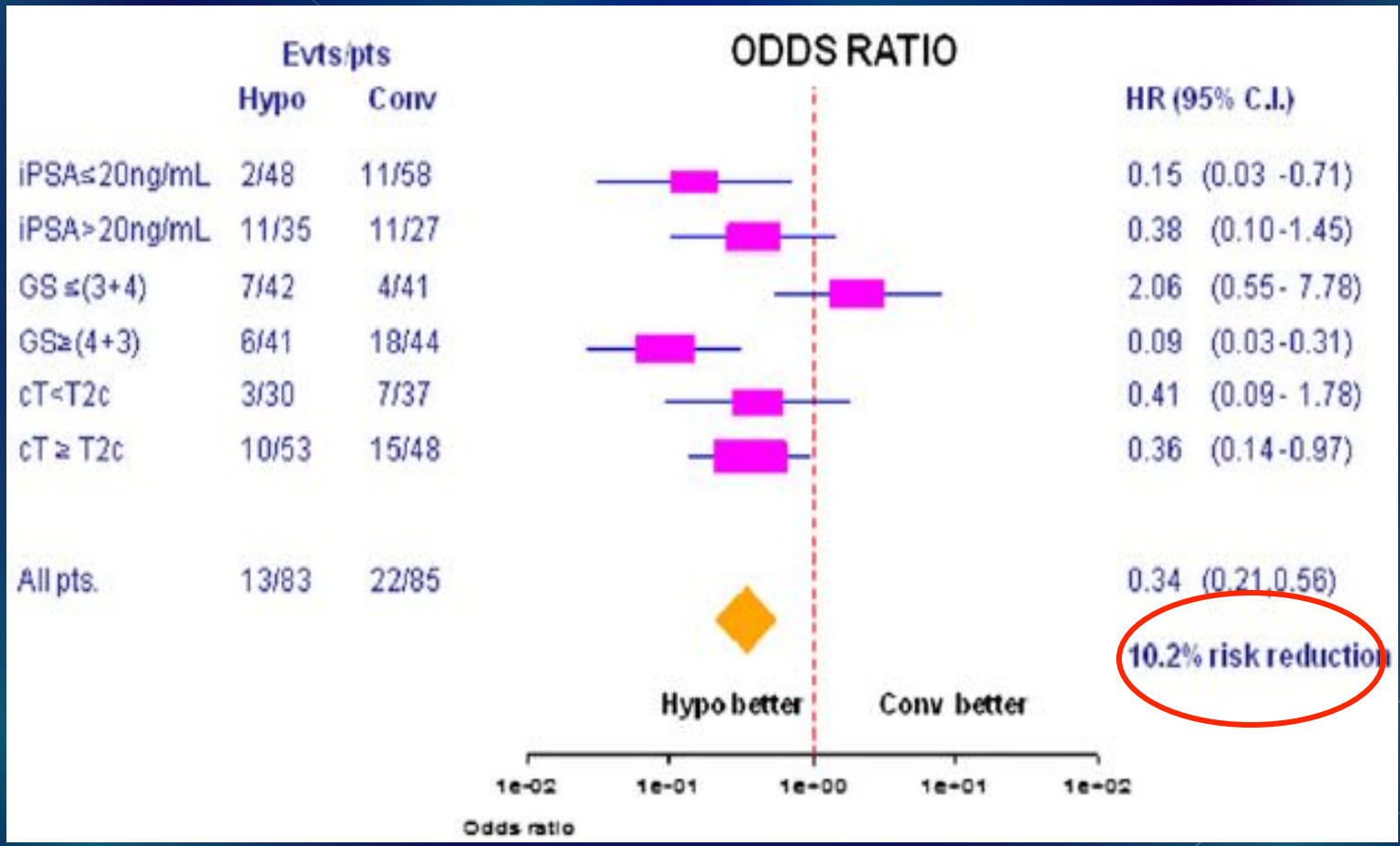


Forest Plot of HRs for BF

Ongoing Trials

Author	Eligible pts: risk classes	Sample size	Fractionation	OTT (weeks)
MRC UK	Low-/ Intermediate-	2,100	70 Gy (2 Gy x 35 fx) *vs.* 57 Gy (3 Gy x 29 fx) 60 Gy (3 Gy x 30 fx)	8 *vs.* 5
NCIC	Intermediate-	1,204	78 Gy (2 Gy x 38 fx) *vs.* 60 Gy (3 Gy x 20 fx)	8 *vs.* 5
RTOG 0415	Low-	1,067	73.8 Gy (1.8 Gy x 41 fx) *vs.* 70 (2.5 Gy x 30 fx)	8 *vs.* 5.5

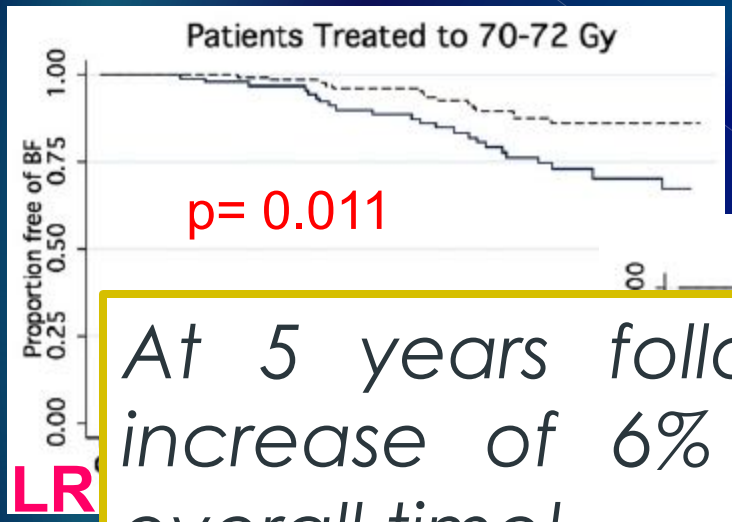
Open Issues

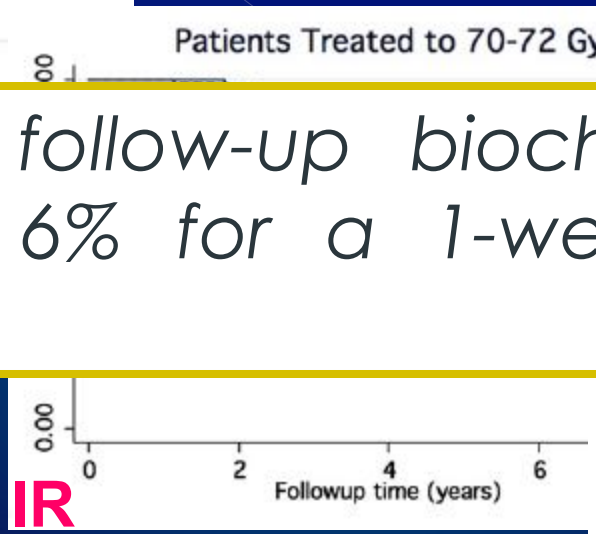
- Tumor Hypoxia
  - May decrease the efficacy of hypofractionation (Carlson *et al. IJROBP 2011)*
- Hormonal Therapy
- Time factor for PCa

Prostate radiotherapy

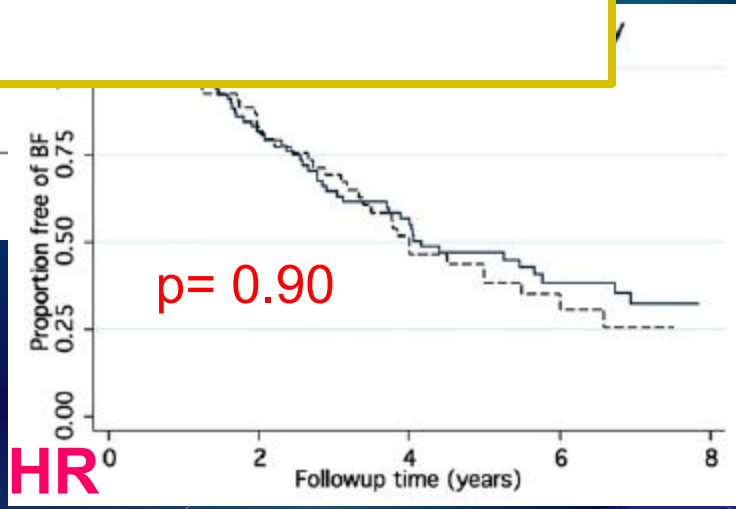
The role of overall treatment time in the outcome of radiotherapy of prostate cancer: An analysis of biochemical failure in 4839 men treated between 1987 and 1995

Howard D. Thames [a,*], Deborah Kuban [b], Larry B. Levy [b], Eric M. Horwitz [c], Patrick Kupelian [d], Alvaro Martinez [e], Jeffrey Michalski [f], Thomas Pisansky [g], Howard Sandler [h], William Shipley [i], Michael Zelefsky [j], Anthony Zietman [i]





At 5 years follow-up biochemical failures increase of 6% for a 1-week increase in overall time!



Editorial

Fractionation in prostate cancer – Is it time after all?

Michael Baumann [a,*], Tobias Hölscher [a], Jim Denham [b]

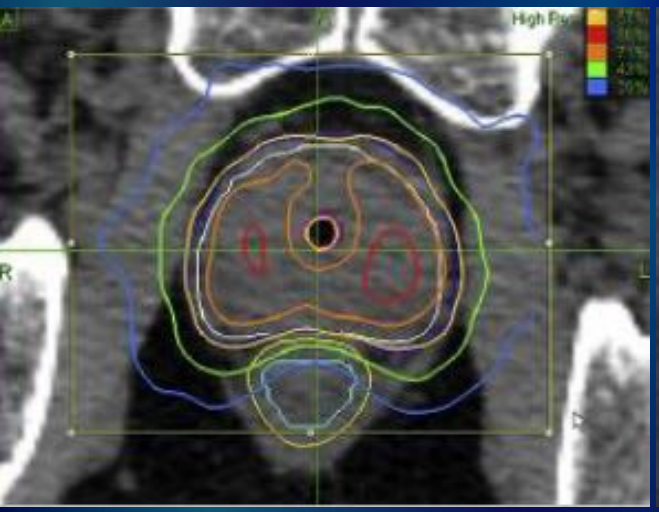
In the belief that no time factor exists, randomized hypofractionation trials have not only increased fraction size but have reduced overall treatment time too in their experimental arms → two variables have been changed at once !

1. If the experimental (hypofractionation) arms of these trials produce better local tumour control, then it will be unclear whether this was achieved by hypofractionation or by reducing overall time.
2. If these experimental regimens produce greater delayed rectal injury then it will not be clear whether hypofractionation was responsible or whether an increase in early reactions due to over rapid RDA is responsible.

Clinical Data
Extreme Hypofractionation for PCa

SBRT for PCa = Virtual Prostate Brachytherapy

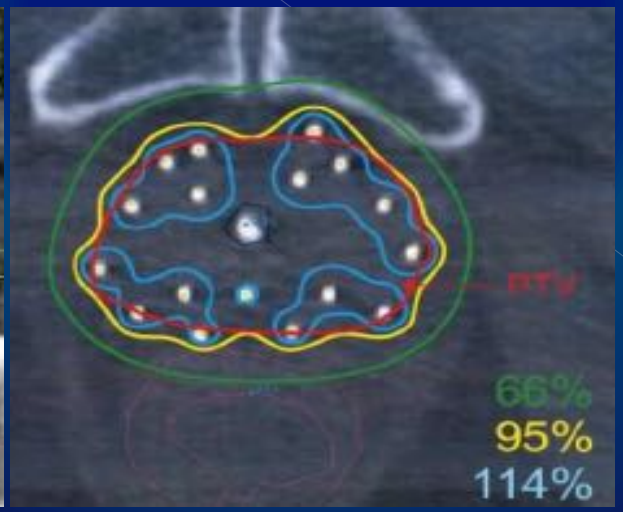
- Non-invasive procedure
- Similar dose distributions “peripheral loading”
- Similar toxicity profile (urinary toxicity)



SBRT: 4 x 9.5 Gy = 38 Gy

Cyberknife®: 45-90min/fx

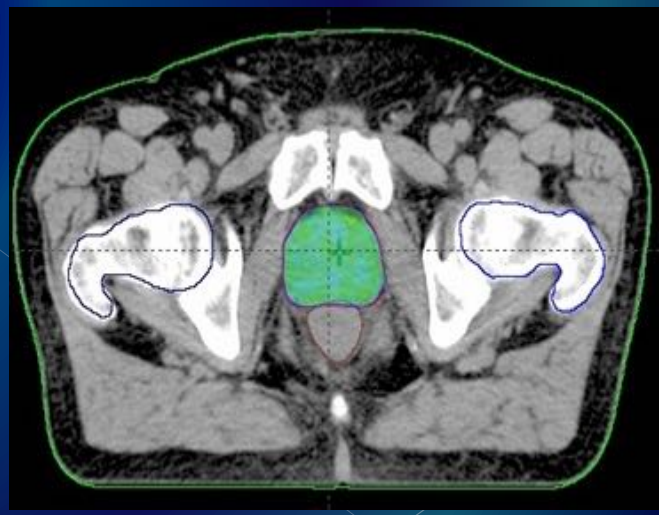
Fuller et al.: IJROBP; 70, 2008



EBRT+HDR-BT46Gy + 2 x 9.5Gy

Zwahlen et al.:

Brachytherapy; 9, 2009



SBRT-10X FFF: 5 x 7Gy = 35 Gy

TrueBeam®: 2 min/fx

Alongi et al.: ESTRO 2013

SBRT for PCa

RTOG®
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RTOG 0938

A RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED RADIOTHERAPY FOR FAVORABLE RISK PROSTATE CANCER

Primary Objective:
To demonstrate that 1-year health-related quality of life (HRQOL) for at least one hypofractionated arm is not significantly lower than baseline as measured by the Bowel and Urinary domains of the Expanded Prostate Cancer Index Composite (EPIC) instrument

36.25 Gy in 5 fx (2 wks) vs 51.6 Gy in 12 fx (2.5 wks)

Hypofractionation Trials: Schedules and NTD2

Study	Treatment	# of patients	Risk group(s)	Median follow-up (months)	Late Grade 3 GU Toxicity	Late Grade 3 GI Toxicity	FFBF
GANTRY-BASED SYSTEMS							
Madsen et al.	33.5 Gy in 5 fx	40	low	41	None	None	90% 4-years actuarial
Boike et al.	45-50 Gy in 5 fx #	45	low & int	30, 18, 12	4%	2% plus 1 Grade 4	100%
Mantz et al.	40 Gy in 5 fx #	80	low	36	None	None	100%
CYBERKNIFE							
King et al.	36.25 Gy in 5 fx ‡	67	low	32	3.5%	None	97%
Friedland et al.	35 Gy in 5 fx	112	low, int, & high	24	< 1%	None	98%
Katz et al.	35 – 36.25 Gy in 5 fx	304	low, int & high	48	2%	None	97, 93, 75% 4-year actuarial
Freeman et al.	7-7.25 Gy in 5 fx	41	low	60	< 1%	None	93% 5-year actuarial
Bolzicco et al.	35 Gy in 5 fx	46	low, int	20	None	2%	100%
Jabbari et al.	38 Gy in 4 fx †	38	low & int	18	5%	None	100%
McBride et al.	36.25-37.5 Gy in 5 fx	45	low	44	< 1%	None	100%
Fuller et al.	38 Gy in 4 fx †	54	low & int	36	4%	None	98%
Kang et al.	32-36 Gy in 4 fx	44	low, int & high	40	None	None	100%, 100%, 90.9%

SBRT for PCa: Features

Very large dose per fractions

Highly focused RT beams

Image Guidance
(allowing minimal
CTV-PTV margin)

Special devices
to minimize toxicity
(SpaceOAR)

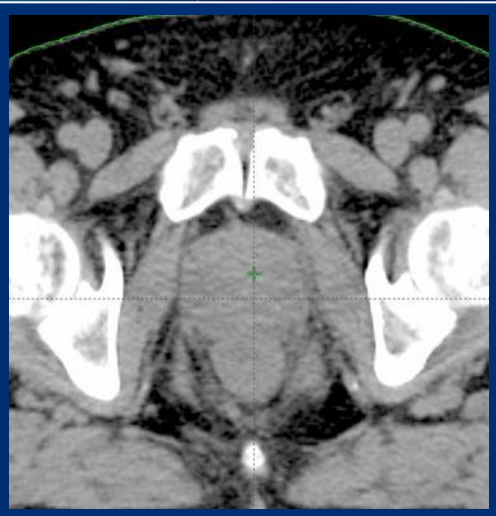
PHASE I-II STUDY OF HIGH DOSE SBRT FOR LOW – INTERMEDIATE RISK PROSTATE CANCER

				NTD2 for an α/β (Gy) value of			
n. of fractions	fraction size (Gy)	Total dose (Gy)	weeks of treatment	1,5	3	10	BED_{10} (Gy)
5	7	35,0	1,5	85,0	70,0	49,6	56,7

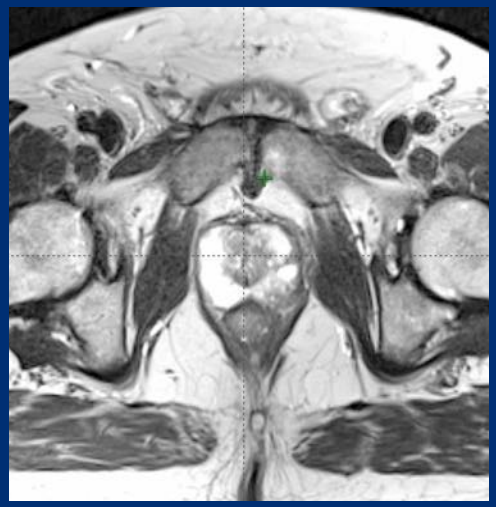
NTD_2 OK for controlling low and intermediate risk disease and late tox

Humanitas Protocol

Imaging and target definition

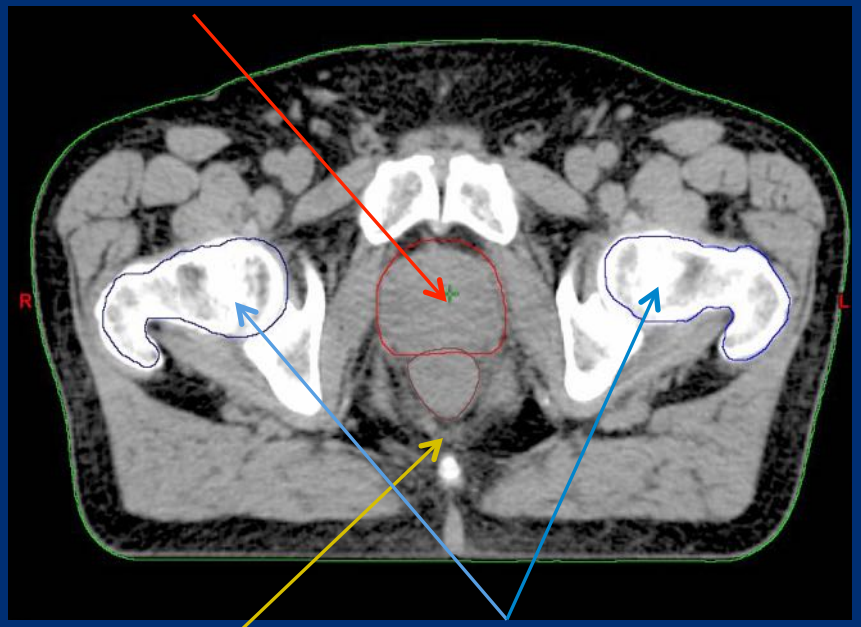


CT



MRI

Prostate

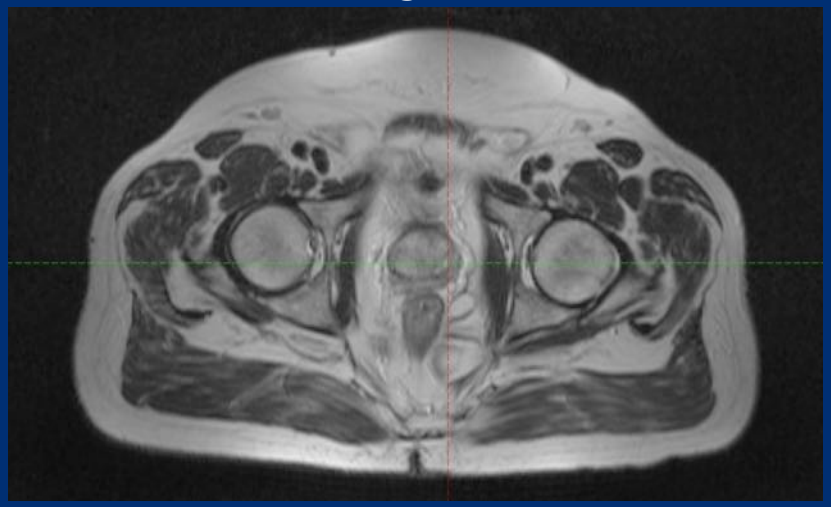


Rectum

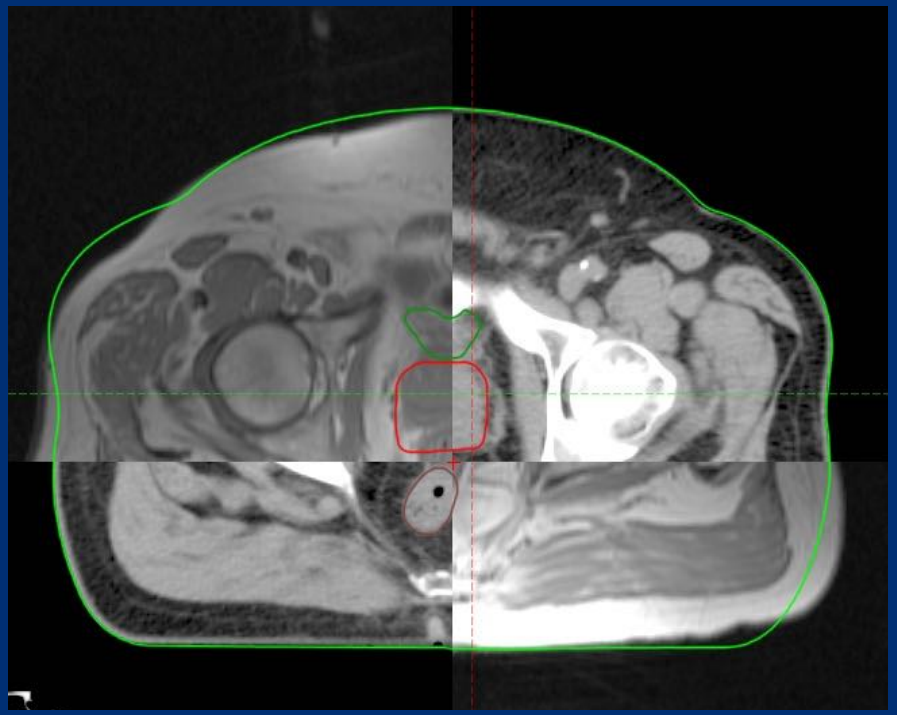
Femoral Heads

Imaging and target definition

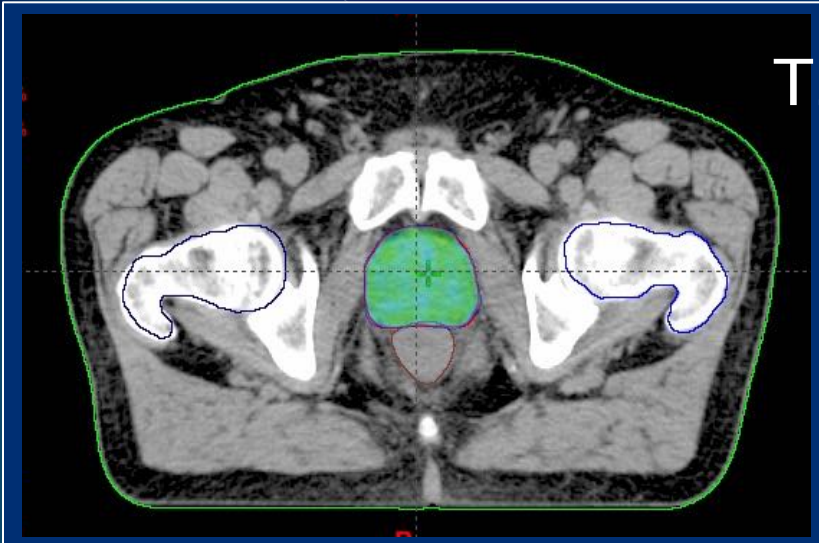
CT



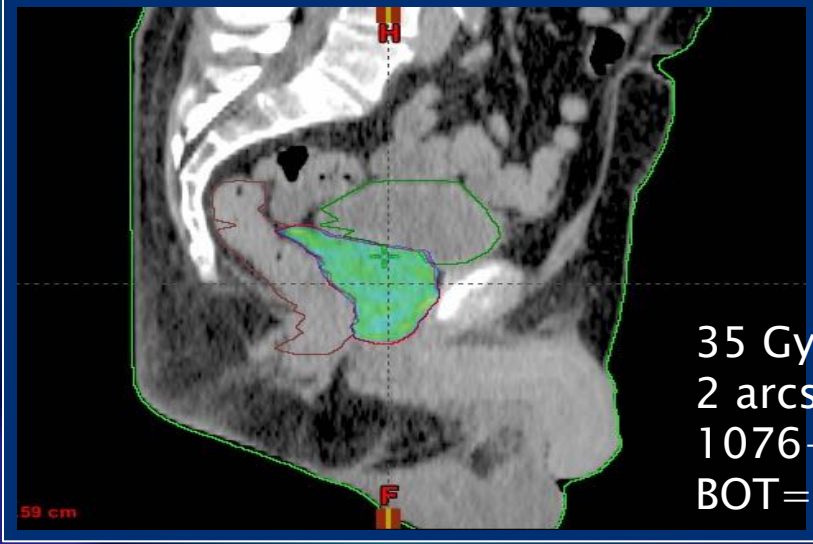
MRI



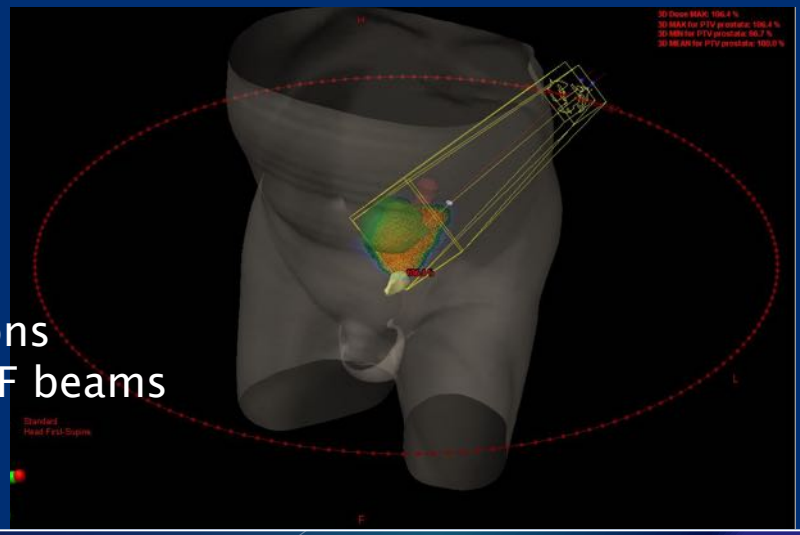
Planning



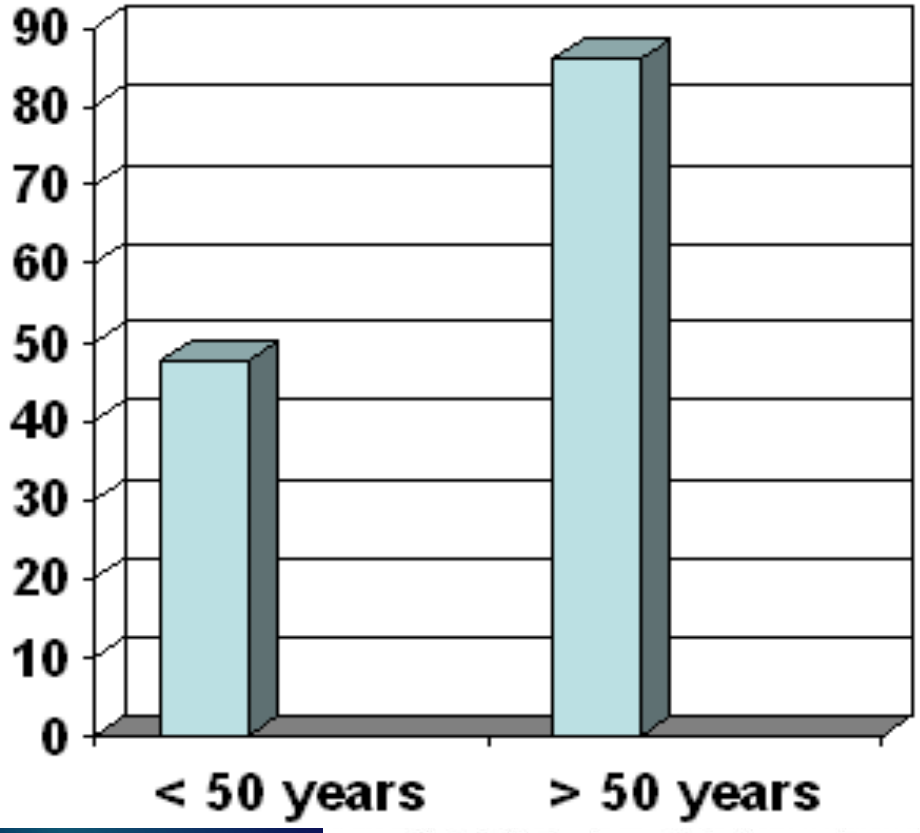
T2, iPSA 8,
GS 3+4



35 Gy in 5 fractions
2 arcs with 10 FFF beams
1076+1094 MU
BOT=121sec



Calcifications as surrogates of fiducials



ES FOR PROSTATE LOCALIZATION
OTHERAPY

M. LARSEN, B.SC.,* LISA M. BRUCE, B.SC.,*
* AND MILLER S. MACPHERSON, PH.D.*‡

a, ON, Canada; † Department of Radiation Oncology,
l, University Health Network, Toronto, ON, Canada

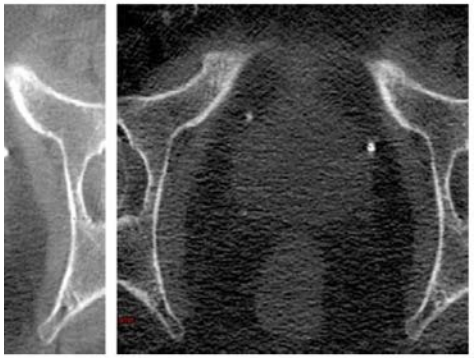


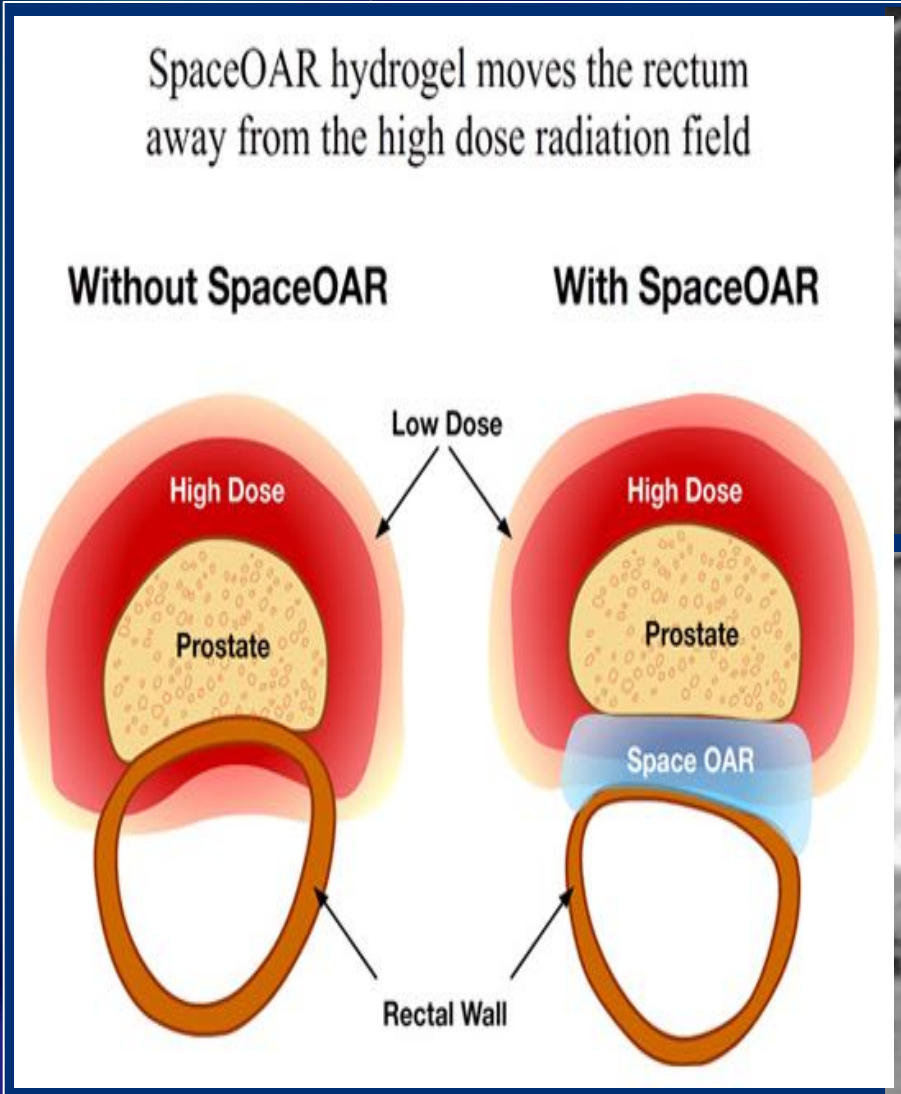
Fig. 2. Calcifications shown on (A) planning computed tomography (CT) scan, (B) cone beam CT scan with standard

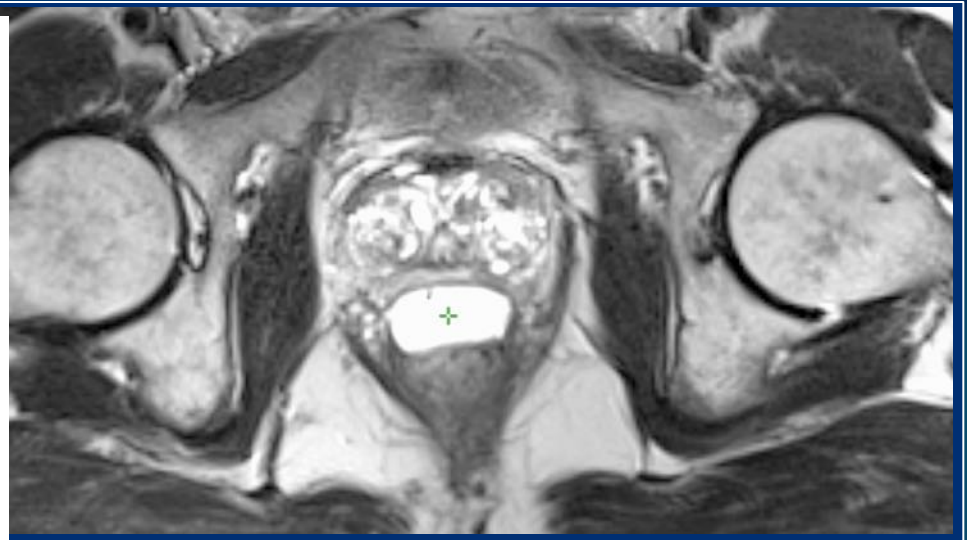
….Calcifications could be reliable markers of prostate position and allow for precise image guided with low-imaging dose

Treatment verification

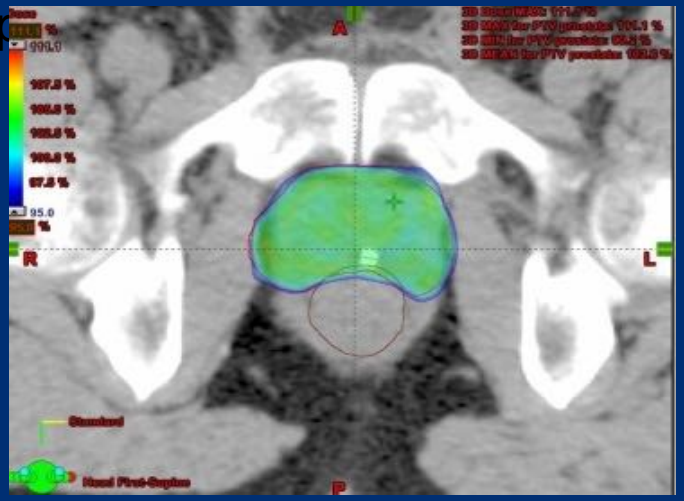
Use of calcifications for repositioning

Space OAR

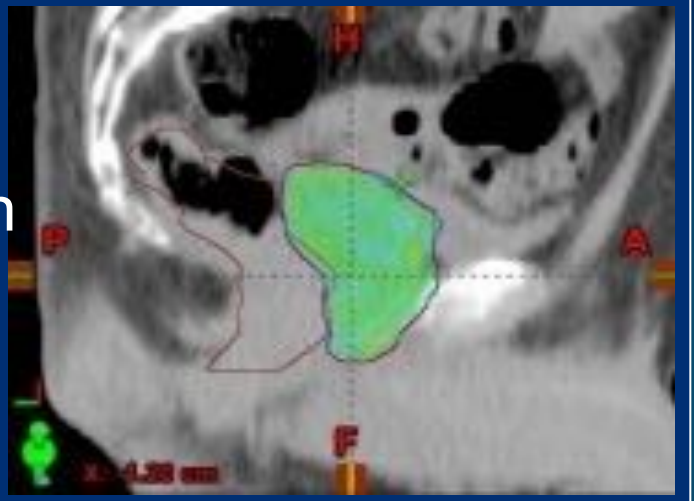

SpaceOAR hydrogel moves the rectum away from the high dose radiation field
Without SpaceOAR
With SpaceOAR
Low Dose
High Dose
Prostate
High Dose
Prostate
Space OAR
Rectal Wall



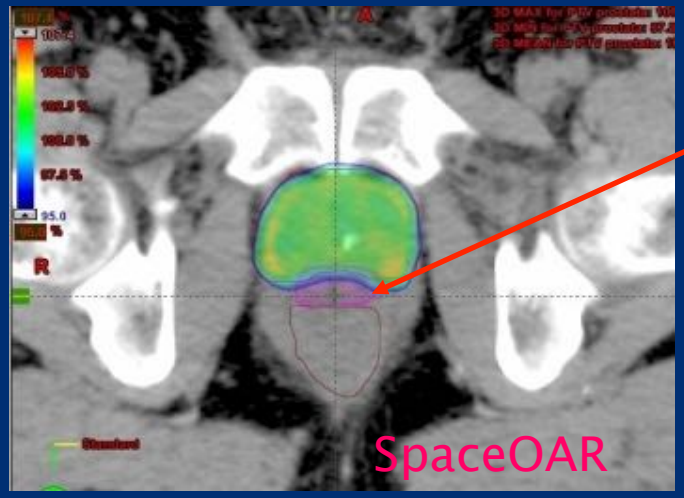
Space OAR



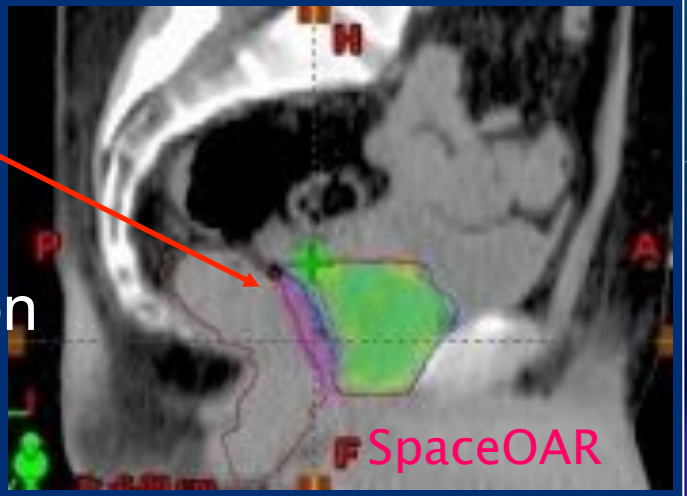
pre- gel injection



Anterior rectal wall sparing

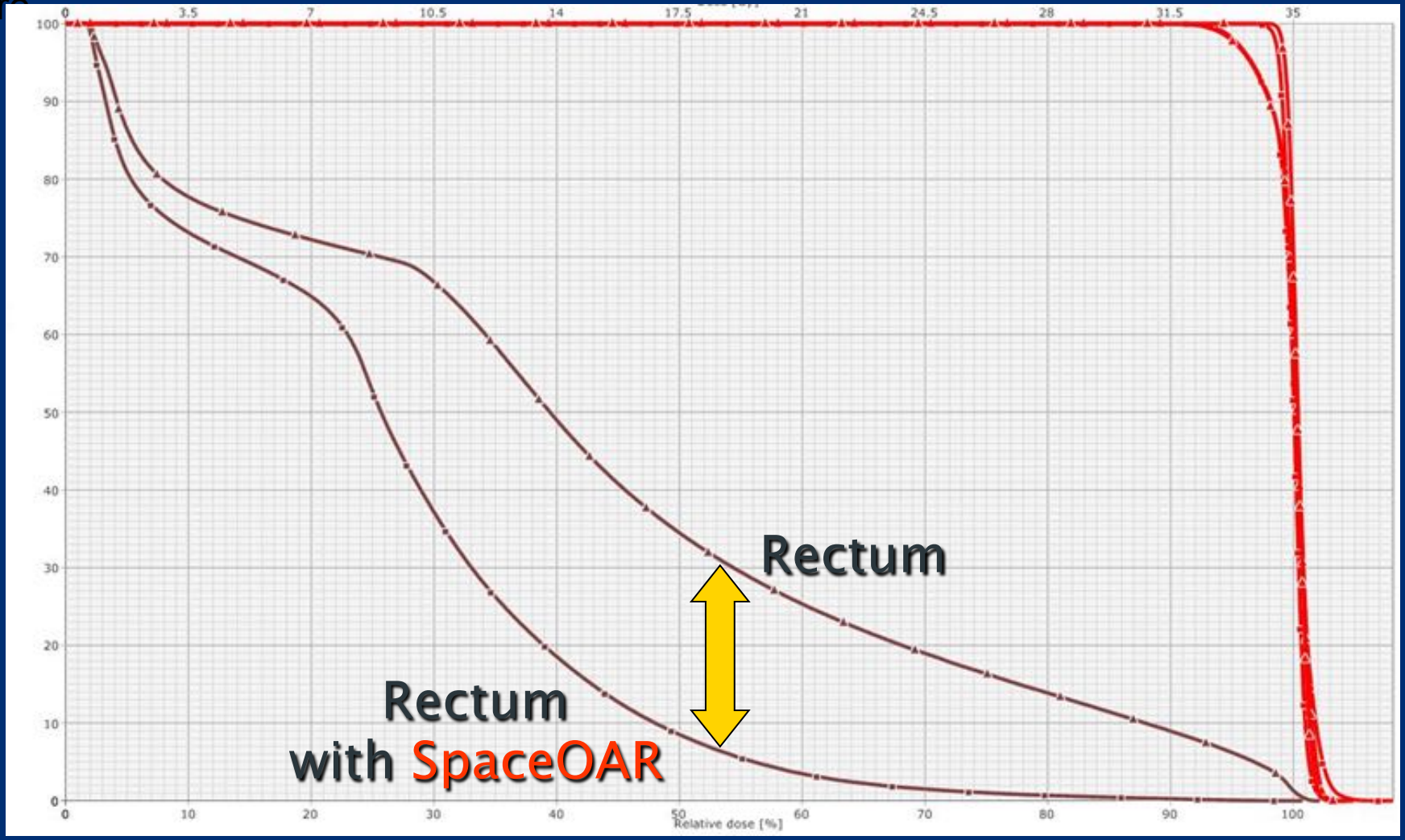


post- gel injection



Space OAR

pro



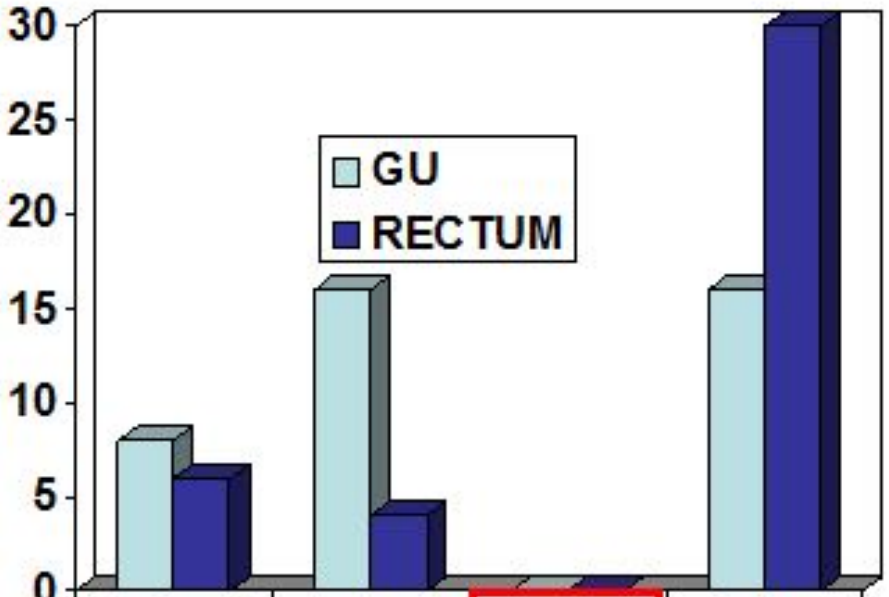
Patients Characteristics

N. of patients	40
Recruitment	Feb 2012–Jan 2013
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 [days]	230 [40-360]
N. of patients with SpaceOAR ™	9

Alongi et al. ESTRO 2013

Acute Toxicity

- Dose: 35 Gy in 5 fractions
- Median follow-up: 230 days
- SpaceOAR: 9 pts

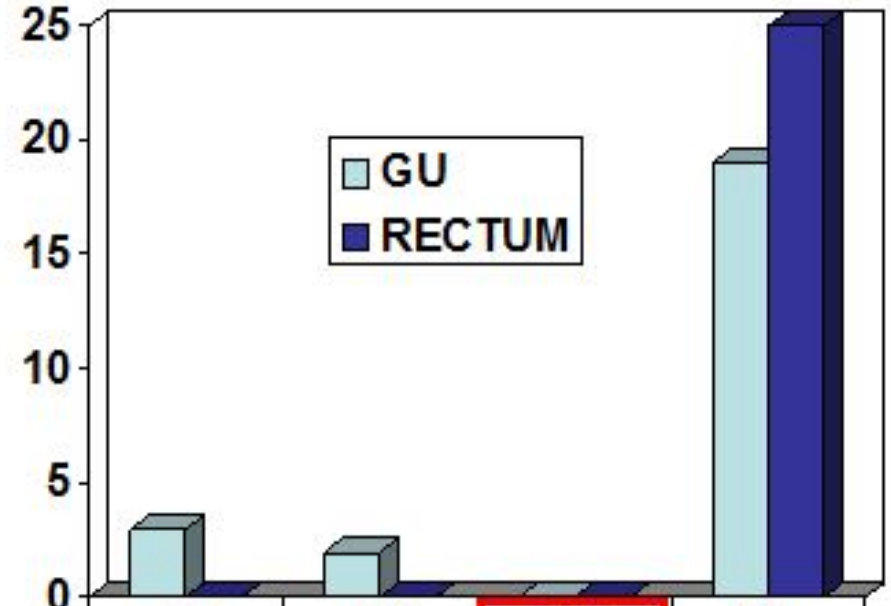


	G1	G2	G3	G0
GU	8	16	0	16
RECTUM	6	4	0	30

Alongi et al. ESTRO 2013

Late Toxicity

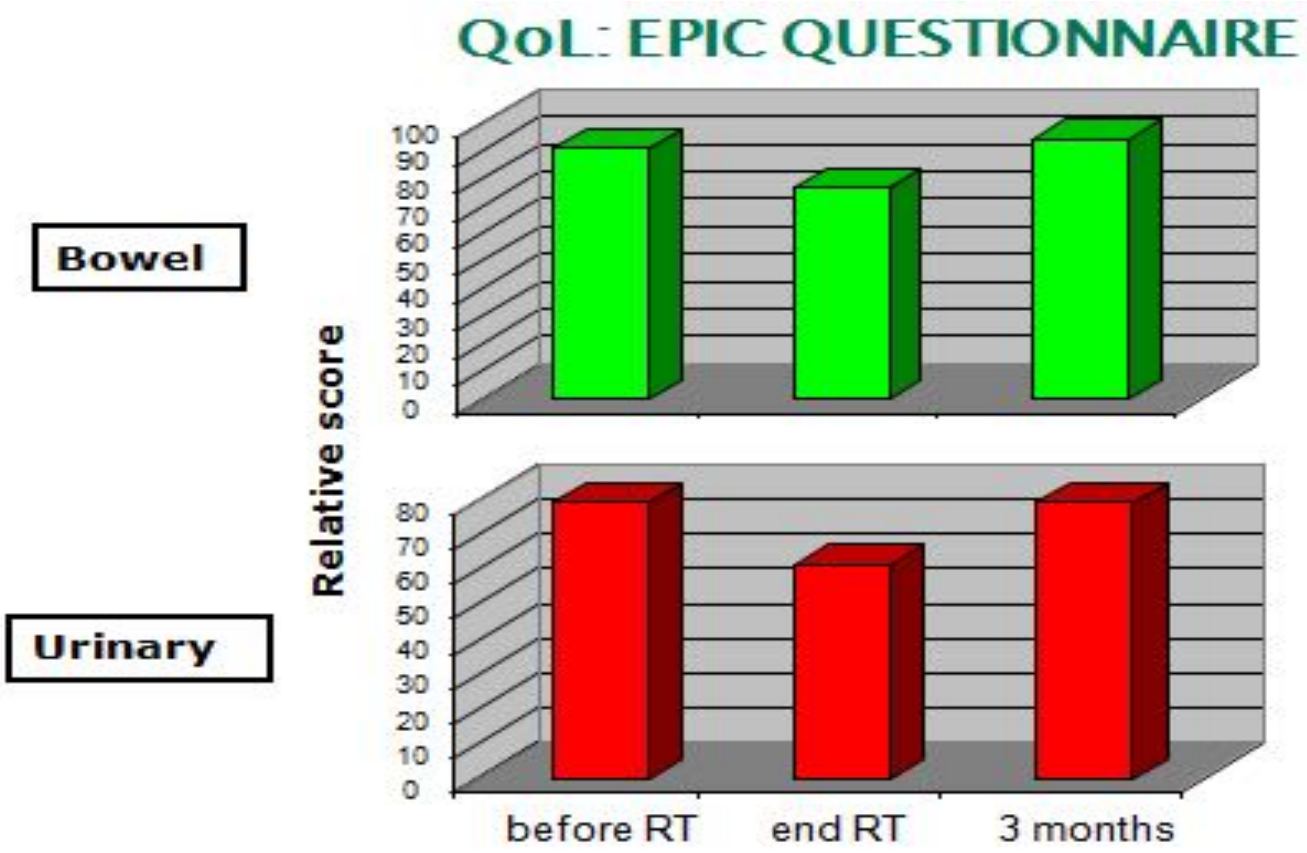
Late toxicity
(>6 months) was evaluable in 25/40 trial patients.



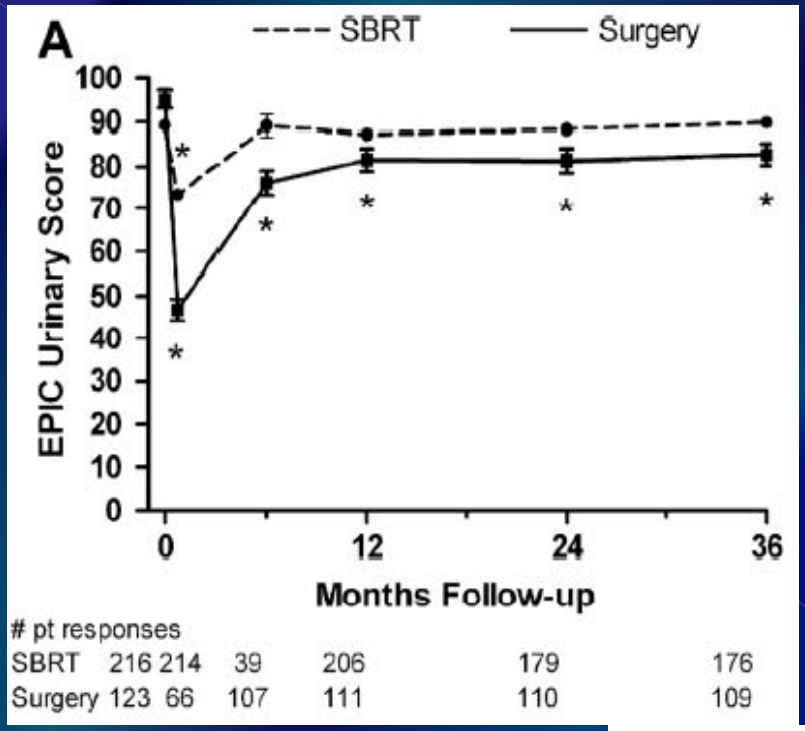
	G1	G2	G3	G0
GU	3	2	0	19
RECTUM	0	0	0	25

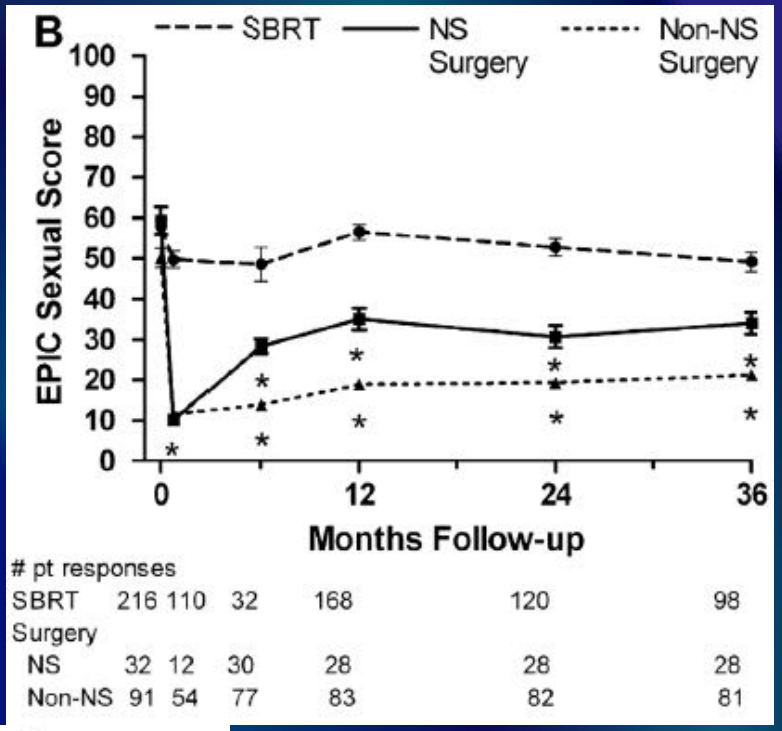
Alongi et al. ESTRO 2013

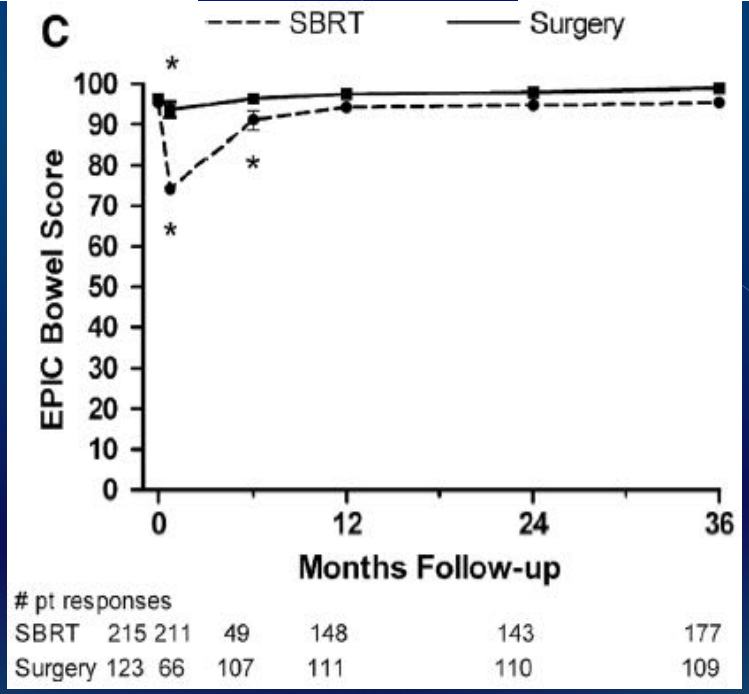
Quality of Life



Alongi et al. ESTRO 2013







Katz et al.
RO 2012, 7:194

Open Issues

- Rationale mainly depending upon the extrapolation from results obtained by the moderate hypofractionation which have not yet been fully established)

- Uncertainties on the validity of the linear quadratic model for predicting the tumour response to large dose fractions

SBRT for PCa

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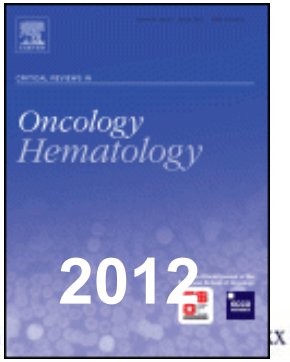
Critical Reviews in Oncology Hematology xx (2012) xxx–xxx



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Will SBRT replace conventional radiotherapy in patients with low-intermediate risk prostate cancer? A review

Stefano Arcangeli*, Marta Scorsetti, Filippo Alongi

Radiotherapy and Radiosurgery department, Istituto Clinico Humanitas, Humanitas Cancer Center, Rozzano, Milano, Italy

Accepted 23 November 2011

“For prostate tumors, hypofractionation is not only biologically best, it is ethically wrong not to use it for the patients’ best chance of cure”.

COMMENT ON “MAGICAL PROTONS?” EDITORIAL BY GOITEIN (INT J RADIAT ONCOL BIOL PHYS 2008;70:654–656)