Ipofrazionamento nel carcinoma prostatico

Patrocinio

Ospedale "S. Giovanni Calibita" Fatebenefratelli

IPOFRAZIONAMENTO E TECNICHE INNOVATIVE

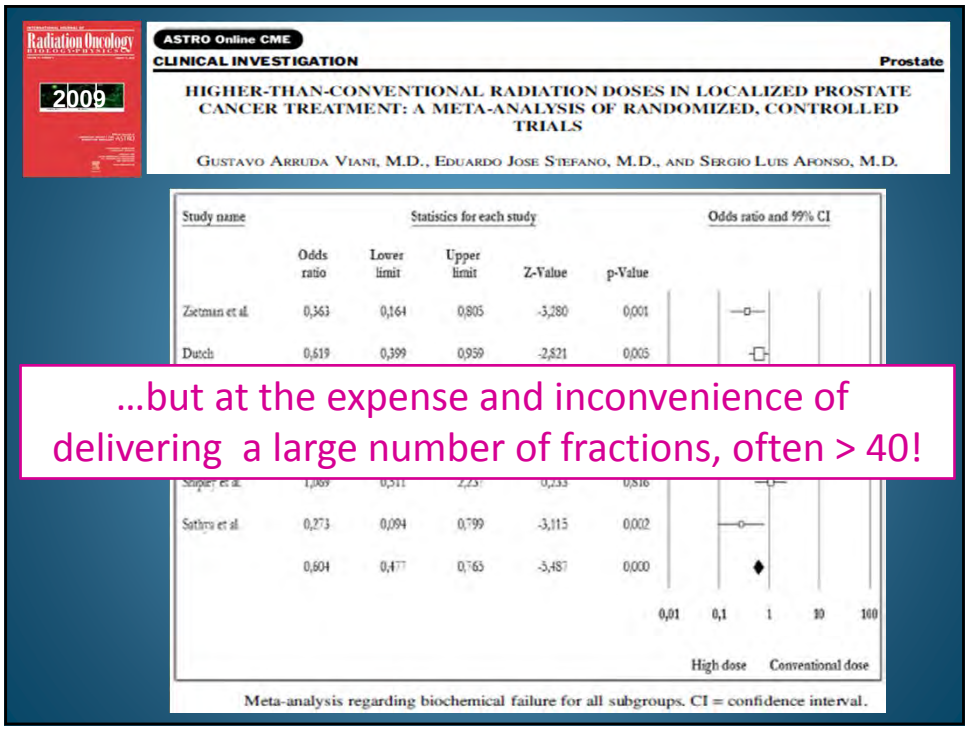
29 Aprile 2014

S. Arcangeli
U.O.C. Radioterapia

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



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

Hypofractionation for PCa

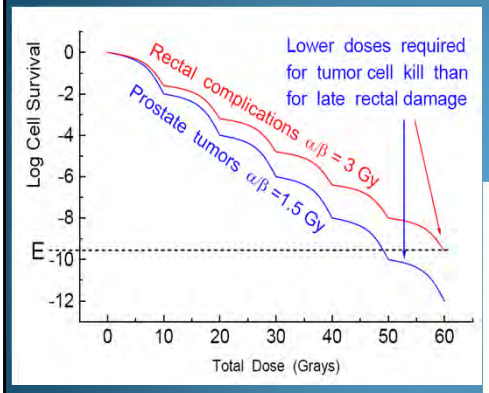
- **FASTER** Less distressing for elderly population with PCa
- **CHEAPER** - Reduced treatment costs
  - Shorter waiting lists
- **BETTER** (?) Biologically works → unusual radiobiology of PCa

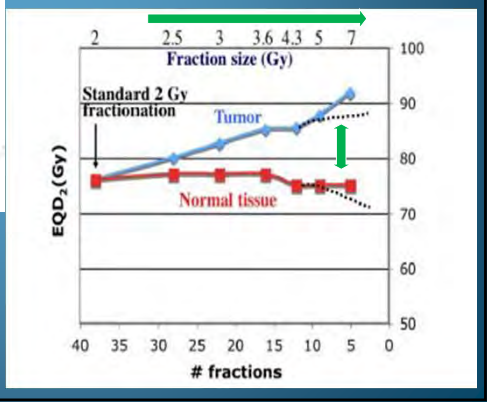
Unusual Radiobiology of PCa

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

Prostate alpha/beta revisited – an analysis of clinical results from 14 168 patients

ALEXANDRU DASU[1,2] & IULIANA TOMA-DASU[3]

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

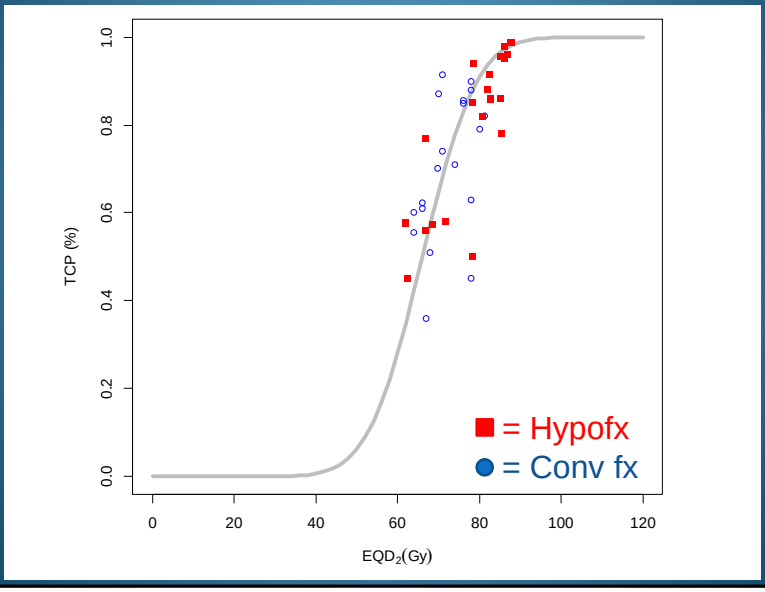
RAYMOND MIRALBELL, M.D.,*† STEPHEN A. ROBERTS, PH.D.,‡ EDUARDO ZUBIZARRETA, M.D.,§ AND JOLYON H. HENDRY, PH.D.‖

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.‡‡

Dose response curve of the 5-y FFBF versus EQD2 with α/β 1.5Gy for PCa

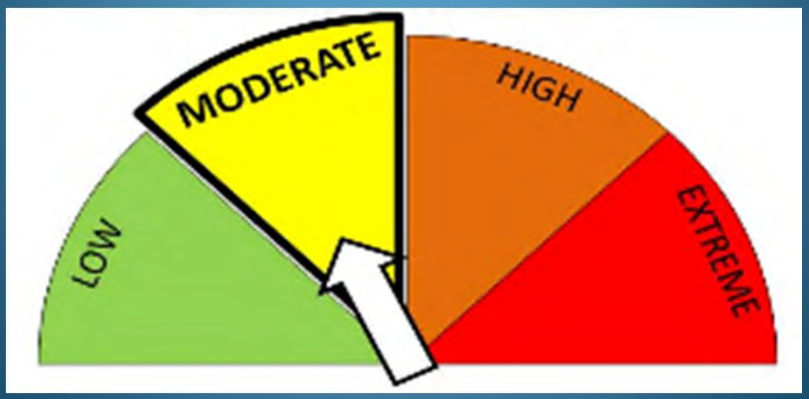


Hypofractionation for PCa

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

Moderate Hypofractionation (2.4-4 Gy per fraction) 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

"OLD" Randomized Trials

No assumptions about the α/β ratio of PCa

Trial	Pts	Schedule	RT	NTD2 1.5 (Gy)	NTD2 3 (Gy)	Median FUP	% 5y-bRFS	% GI	% GU
CANADA* *JCO 2005*	470 T1-2 466 T1-2	66 Gy/2 Gy/33 f 52.5 Gy/2.62 Gy/20f	2D-3D	66 62	66 59	68.5 mo	47 40	1.9 G3	1.3 G3
AUSTRALIA° *IJROBP 2011*	109 T1-2 108 T1-2	64 Gy/2 Gy/32 f 55 Gy/2.75 Gy/20 f	70% 2D	64 66.8	64 63.3	90 mo	34 53	similar	

* hypothesis: BF in the hypofractionated arm no worse than the conventional arm by 7.5%

° hypothesis: to detect a 20% difference in mild late tox in favour of hypofx arm

"MODERN"Randomized Trials

Explicit assumptions about the α/β ratio of PCa

Trial	Pts	Schedule	RT	NTD2 1.5 (Gy)	NTD2 3 (Gy)	Median FUP	% 5y-bRFS	%GI	%GU
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 80.2	72.6 77.8	40 mo	92 96	≥ G2 5.1 ≥ G2 10	≥ G2 16.5 ≥ G2 15.8
ITALY *IJROBP 2012*	85 H 83 H	80 Gy/2Gy/40 f 62 Gy/3.1 Gy/20 f	3D	80 81.5	80 74	70 mo	74 85	≥ G2 17 ≥ G2 16	≥ G2 14 ≥ G2 11
USA *JCO 2013*	152 LIH 151 LIH	76 Gy/2 Gy/38 f 70.2 Gy/2.7 Gy/26 f	IMRT	76 84.2	76 80	68.4 mo	78.6 76.7	≥ G2 22.5 ≥ G2 18.1	≥ G2 13.4 ≥ G2 21.5

"MODERN" Randomized Trials

Assumption of α/β ratio of PCa = 1.5 Gy

Trial	Pts	Schedule	RT	NTD2 1.5 (Gy)	NTD2 3 (Gy)	Median FUP	% 5y-bRFS	%GI	%GU
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 80.2	72.6 77.8	40 mo	92 96	≥ G2 5.1 ≥ G2 10	≥ G2 16.5 ≥ G2 15.8

+ 9 Gy + 5 Gy

P = 0.23 P = 0.11 P = 0.07

REJECTED

HYPOTHESIS

[illegible] difference in biochemical failure at 5 –y in [illegible] of hypo arm

"MODERN" Randomized Trials

Assumption of α/β ratio of PCa = 1.5 Gy

Trial	Pts	Schedule	RT	NTD2 1.5 (Gy)	NTD2 3 (Gy)	Median FUP	% 5y-bRFS	%GI	%GU
ITALY *IJROBP 2012*	85 H 83 H	80 Gy/2Gy/40 f 62 Gy/3.1 Gy/20 f	3D	80 81.5	80 74	70 mo	79 85	≥ G2 17 ≥ G2 16	≥ G2 14 ≥ G2 11

- 6 Gy

P = 0.065 P = 0.571 P = 0.093

REJECTED

HYPOTHESIS

[illegible] result in similar disease control and fe[illegible] than a half) late complications

"MODERN" Randomized Trials

Assumption of α/β ratio of PCa = 1.5 Gy

Trial	Pts	Schedule	RT	NTD2 1.5 (Gy)	NTD2 3 (Gy)	Median FUP	% 5y-bRFS	%GI	%GU
USA *JCO 2013*	152 LIH 151 LIH	76 Gy/2 Gy/38 f 70.2 Gy/2.7 Gy/26 f	IMRT	76 84.2	76 80	68.4 mo	78.6 76.7	≥ G2 22.5 ≥ G2 18.1	≥ G2 13.4 ≥ G2 21.5

+ 8 Gy + 4 Gy

P = 0.745 P = 0.39 P = 0.16

REJECTED

HYPOTHESIS

t hypofx would improve FFBF from 70% to 85% –y, without increasing late complic's

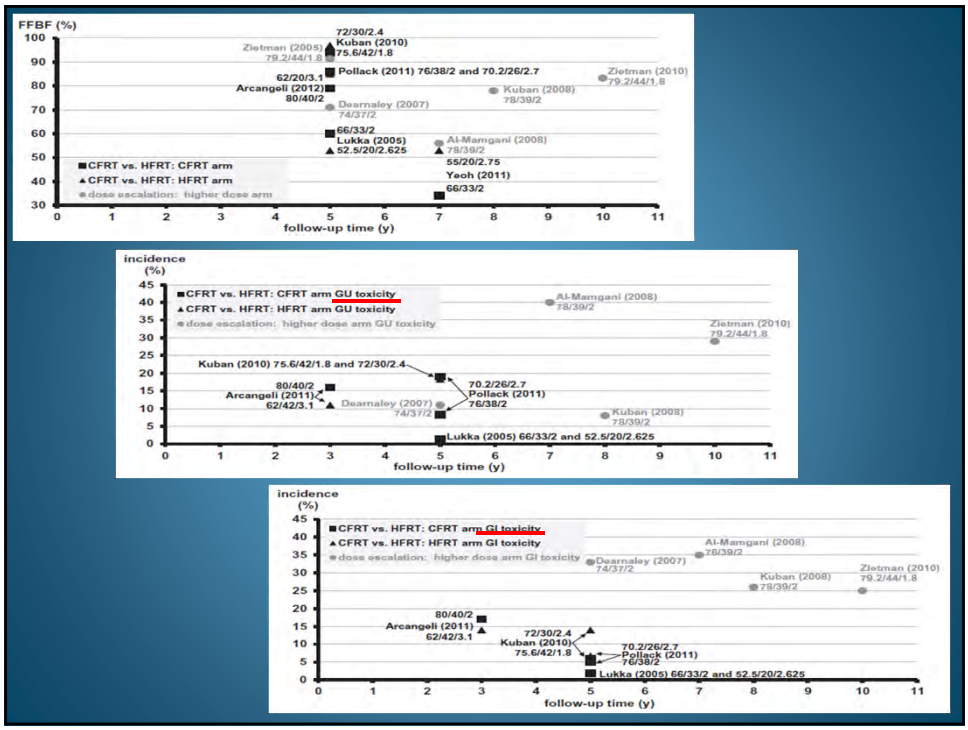
"MODERN" Randomized Trials

Moderate Hypofractionation: Contemporary Superiority Trials

Study (Author)	Sample Size	ADT (%)	Median Follow-up	Randomization Arms	Toxicity	Efficacy
Regina Elena (Arcangeli)	168	100	5.8 years	80 Gy/2 Gy 62 Gy/3.1 Gy	NS	NS
FCCC (Pollack)	303	45	5.5 years	76 Gy/2 Gy 70.2 Gy/2.7 Gy	Hypofractionation: worse GU effects if IPSS ≥ 12	NS
MDACC (Kuban)	204	21	4.7 years	75.6 Gy/1.8 Gy 72 Gy/2.4 Gy	NS	NS

Abbreviations: ADT, androgen deprivation therapy; FCCC, Fox Chase Cancer Center; GU, genitourinary; MDACC, MD Anderson Cancer Center; NS, no significant difference.

Statistical insignificance in a superiority study does not imply that treatments are equivalent, only that the data are insufficient to conclude that the treatments are different


FFBF (%)
follow-up time (y)
CFRT vs. HFRT: CFRT arm
CFRT vs. HFRT: HFRT arm
dose escalation: higher dose arm
72/30/2.4
Kuban (2010)
75.6/42/1.8
Zietman (2005)
79.2/44/1.8
Pollack (2011) 76/38/2 and 70.2/26/2.7
62/20/3.1
Arcangeli (2012)
80/40/2
Dearnaley (2007)
74/37/2
Kuban (2008)
78/39/2
Zietman (2010)
79.2/44/1.8
66/33/2
Lukka (2005)
52.5/20/2.625
Al-Mamgani (2008)
78/39/2
55/20/2.75
Yeoh (2011)
66/33/2
incidence
(%)
CFRT vs. HFRT: CFRT arm GU toxicity
CFRT vs. HFRT: HFRT arm GU toxicity
dose escalation: higher dose arm GU toxicity
Kuban (2010) 75.6/42/1.8 and 72/30/2.4
80/40/2
Arcangeli (2011)
62/42/3.1
70.2/26/2.7
Pollack (2011)
76/38/2
Lukka (2005) 66/33/2 and 52.5/20/2.625
CFRT vs. HFRT: CFRT arm GI toxicity
CFRT vs. HFRT: HFRT arm GI toxicity
dose escalation: higher dose arm GI toxicity


Evidences from
"MODERN"
Randomized Trials
Evidences from Large
RetrospectiveTrials

Multi-institutional Non-Inferiority Trials

Moderate Hypofractionation: Ongoing Noninferiority Trials

Study (Group)	Sample Size	Risk Group	Randomization Arms
CHHiP (MRC)	3216	Intermediate/ low	74 Gy/2 Gy 57 Gy/3 Gy 60 Gy/3 Gy
0415 (RTOG)	1067	Low	73.8 Gy/1.8 Gy 70 Gy/2.5 Gy
PROFIT (OCOG)	1204	Intermediate	78 Gy/2 Gy 60 Gy/3 Gy

Abbreviations: CHHiP, conventional or hypofractionated high-dose intensity-modulated radiotherapy in prostate cancer; MRC, Medical Research Council; OCOG, Ontario Clinical Oncology Group; PROFIT, Prostate Fractionated Irradiation Trial; RTOG, Radiation Therapy Oncology Group.

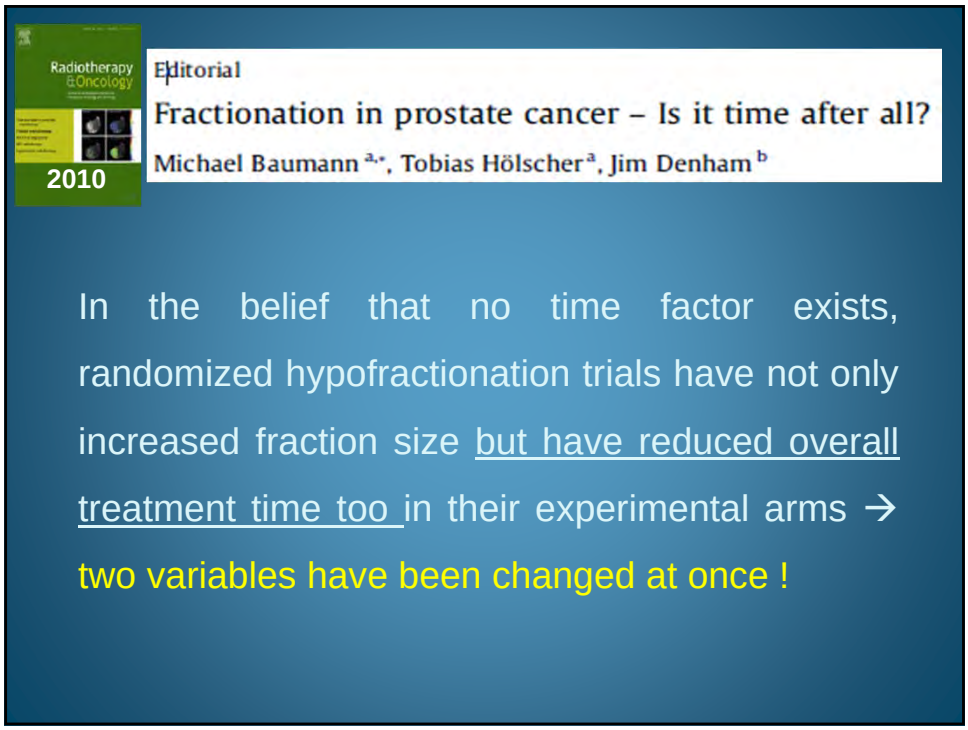
Non-Inferiority Trials

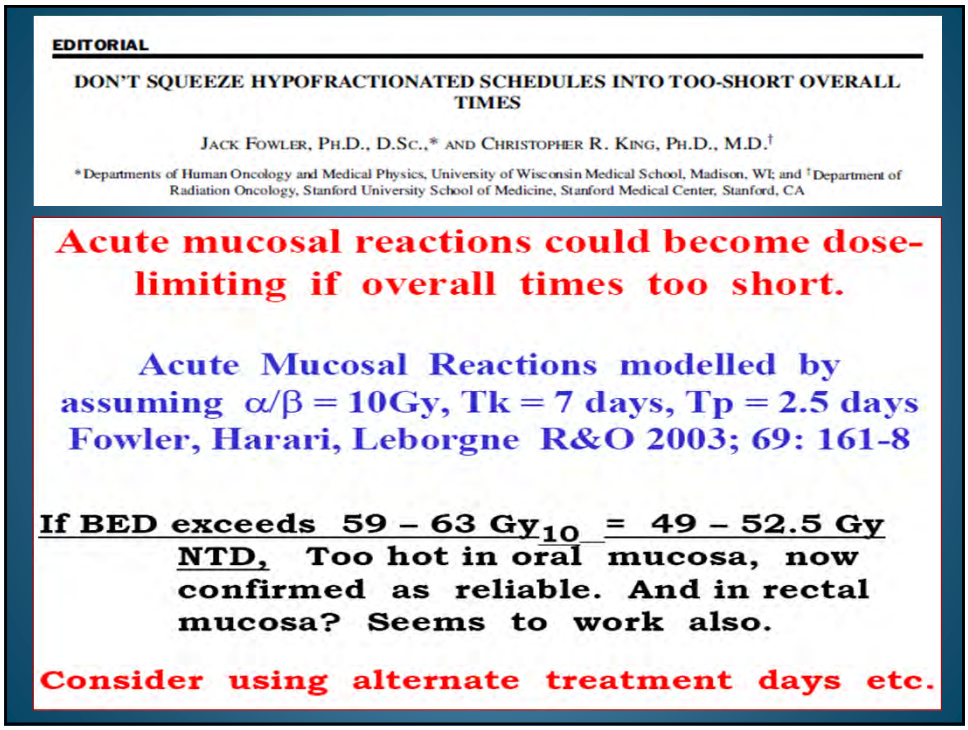
Assumption of α/β ratio of PCa = 1.5-2.5 Gy

Trial	Pts	Schedule	RT	NTD2 1.5/2.5 (Gy)	NTD2 3 (Gy)	Median FUP	% 5y-bRFS	%GI	%GU
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	I M R T	74 77.1 73.3	74 72 68.4	50.5 mo	-	≥ G2 4.3 ≥ G2 3.6 ≥ G2 1.4 ***P = NS***	≥ G2 2.2 ≥ G2 2.2 ≥ G2 0

HYPOTHESIS

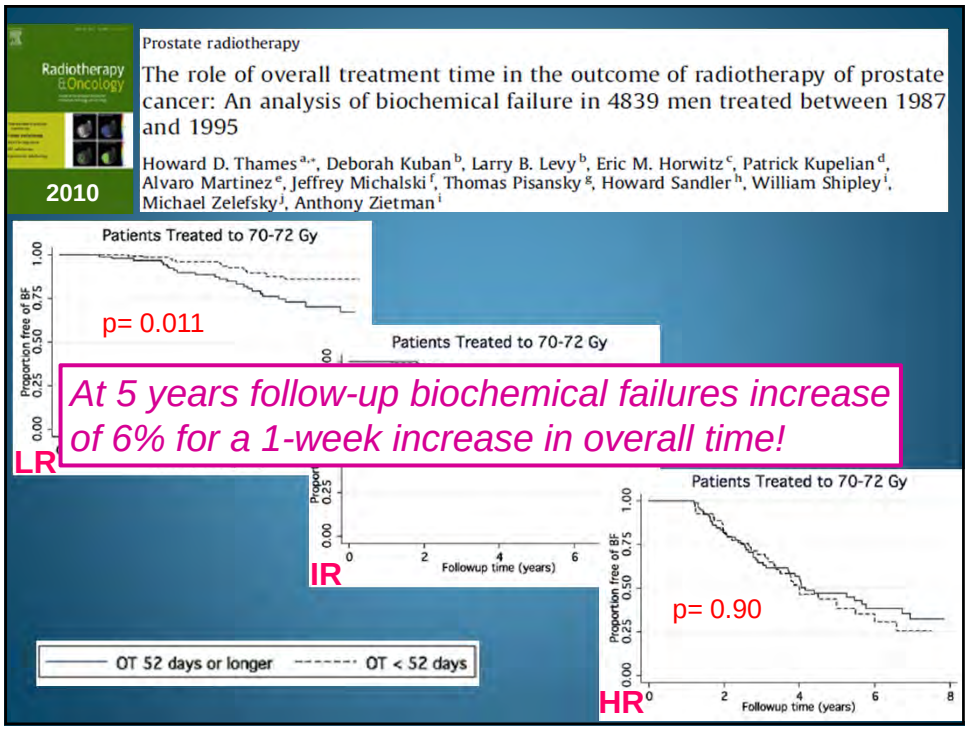
non-inferiority margin set at 6%


Radiotherapy & Oncology
2010
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 !


EDITORIAL
DON'T SQUEEZE HYPOFRACTIONATED SCHEDULES INTO TOO-SHORT OVERALL TIMES
JACK FOWLER, PH.D., D.SC.,* AND CHRISTOPHER R. KING, PH.D., M.D.†
*Departments of Human Oncology and Medical Physics, University of Wisconsin Medical School, Madison, WI; and †Department of Radiation Oncology, Stanford University School of Medicine, Stanford Medical Center, Stanford, CA
Acute mucosal reactions could become dose-limiting if overall times too short.
Acute Mucosal Reactions modelled by assuming α/β = 10Gy, Tk = 7 days, Tp = 2.5 days
Fowler, Harari, Leborgne R&O 2003; 69: 161-8
If BED exceeds 59 – 63 Gy10 = 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.

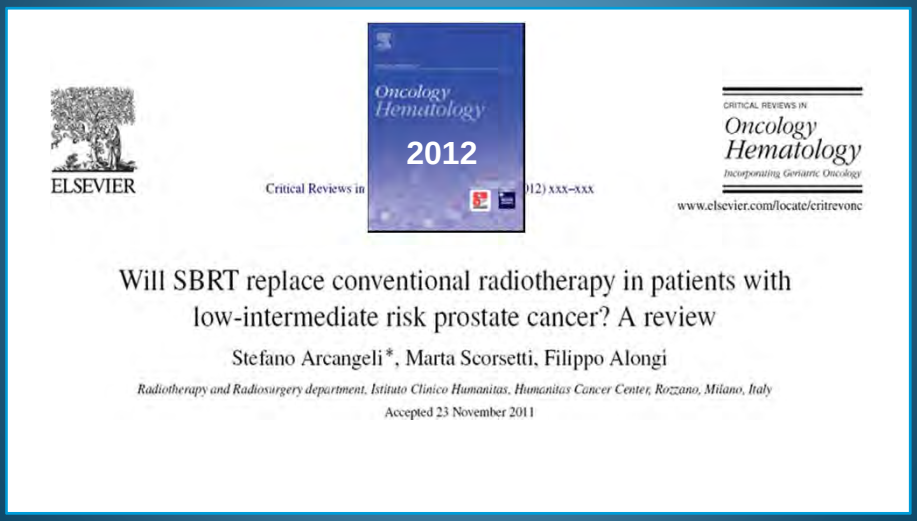
Acute Tox – All Randomized Trials

Trial	RT	Schedule	BED 10 (Gy)	OTT weeks	%GI	%GU
CANADA *JCO 2005*	2D-3D	66 Gy/2 Gy/33 f 52.5 Gy/2.62 Gy/20f	48.7 49.6	6.5 4	G3 2.6 G3 4.1	G3 5 G3 9
AUSTRALIA *IJROBP 2006*	2D-3D	64 Gy/2 Gy/32 f 55 Gy/2.75 Gy/20 f	46.3 53.5	6.5 4	*"almost doubled"* –	
USA *IJROBP 2010*	IMRT	75.6 Gy/1.8 Gy/42 f 72 Gy/2.4 Gy/30 f	47.6 61.6	8.5 6	–	
ITALY *IJROBP 2010*	3D	80 Gy/2Gy/40 f 62 Gy/3.1 Gy/20 f	73.8 59	8 5	≥ G2 20 ≥ G2 31 *P = 0.01*	≥ G2 35 ≥ G2 41 *P = 0.07*
USA *IJROBP 2006*	IMRT	76 Gy/2 Gy/38 f 70.2 Gy/2.7 Gy/26 f	54 64.2	7.7 5.5	≥ G2 8 ≥ G2 18	≥ G2 56 ≥ G2 48
				"slightly more" P = NS		



Extreme Hypofractionation (6.5-10 Gy per fraction) for PCa

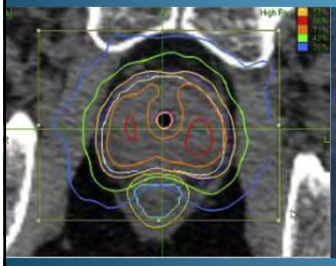
SBRT for PCa



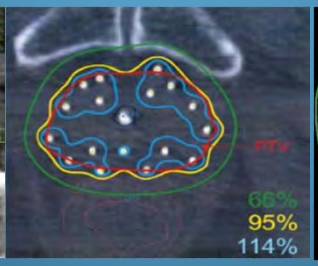
Sir Laurence Olivier (Hamlet, 1948) was treated in 1967 for prostate cancer with a hypofractionated 6-fraction protocol, reported no major sequelae, and lived a further 22 years

SBRT for PCa = Virtual Prostate Brachytherapy

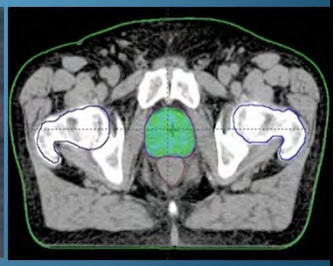
- Non-invasive procedure
- Similar dose distributions "peripheral loading"
- Similar toxicity profile (urinary toxicity)



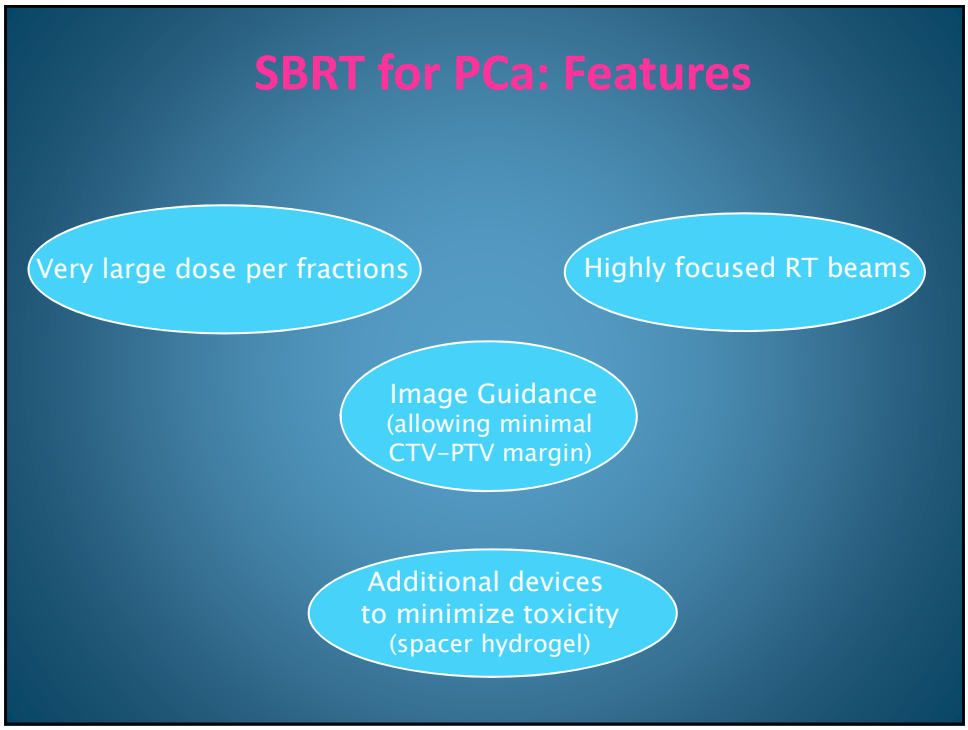
SBRT: 4 x 9.5 Gy = 38 Gy
Cyberknife®: 45-90min/fx
Fuller et al.: IJROBP; 70, 2008



EBRT+HDR-BT46Gy + 2 x 9.5Gy
Zwahlen et al.:
Brachytherapy; 9, 2009

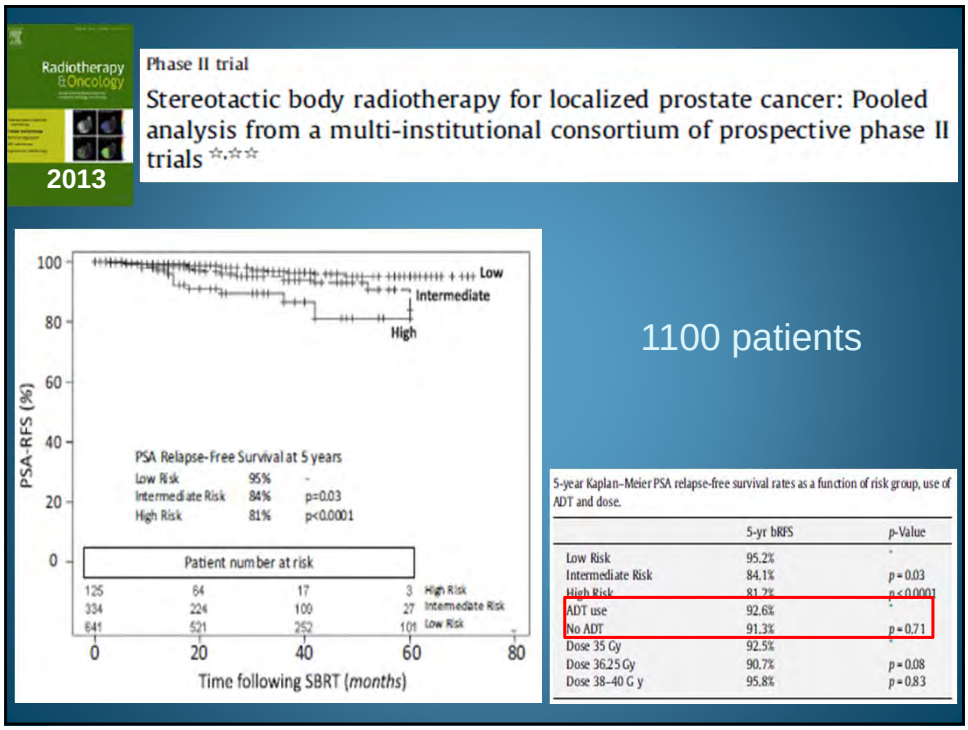


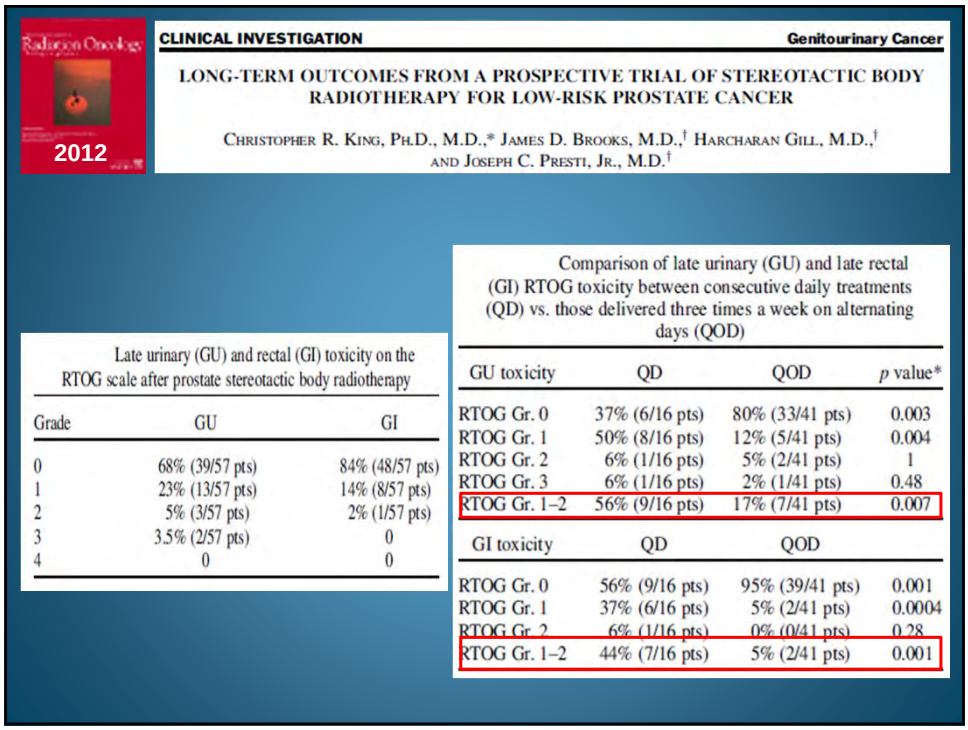
SBRT-10X FFF: 5 x 7Gy = 35 Gy
TrueBeam®: 2 min/fx
Alongi et al.: ESTRO 2013



Outcomes of Phase I-II SBRT Trials

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%


Radiotherapy & Oncology
2013
Phase II trial
Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆,☆☆
PSA-RFS (%)
Low
Intermediate
High
PSA Relapse-Free Survival at 5 years
Low Risk 95%
Intermediate Risk 84% p=0.03
High Risk 81% p<0.0001
Patient number at risk
125 64 17 3 High Risk
334 224 100 27 Intermediate Risk
641 521 252 101 Low Risk
Time following SBRT (months)
1100 patients
5-year Kaplan–Meier PSA relapse-free survival rates as a function of risk group, use of ADT and dose.
5-yr bRFS
p-Value
Low Risk 95.2%
Intermediate Risk 84.1% p = 0.03
High Risk 81.2% p < 0.0001
ADT use 92.6%
No ADT 91.3% p = 0.71
Dose 35 Gy 92.5%
Dose 36.25 Gy 90.7% p = 0.08
Dose 38–40 G y 95.8% p = 0.83


Radiation Oncology
2012
CLINICAL INVESTIGATION
Genitourinary Cancer
LONG-TERM OUTCOMES FROM A PROSPECTIVE TRIAL OF STEREOTACTIC BODY RADIOTHERAPY FOR LOW-RISK PROSTATE CANCER
CHRISTOPHER R. KING, PH.D., M.D.,* JAMES D. BROOKS, M.D.,† HARCHARAN GILL, M.D.,† AND JOSEPH C. PRESTI, JR., M.D.†
Late urinary (GU) and rectal (GI) toxicity on the RTOG scale after prostate stereotactic body radiotherapy
Grade GU GI
0 68% (39/57 pts) 84% (48/57 pts)
1 23% (13/57 pts) 14% (8/57 pts)
2 5% (3/57 pts) 2% (1/57 pts)
3 3.5% (2/57 pts) 0
4 0 0
Comparison of late urinary (GU) and late rectal (GI) RTOG toxicity between consecutive daily treatments (QD) vs. those delivered three times a week on alternating days (QOD)
GU toxicity QD QOD p value*
RTOG Gr. 0 37% (6/16 pts) 80% (33/41 pts) 0.003
RTOG Gr. 1 50% (8/16 pts) 12% (5/41 pts) 0.004
RTOG Gr. 2 6% (1/16 pts) 5% (2/41 pts) 1
RTOG Gr. 3 6% (1/16 pts) 2% (1/41 pts) 0.48
RTOG Gr. 1–2 56% (9/16 pts) 17% (7/41 pts) 0.007
GI toxicity QD QOD
RTOG Gr. 0 56% (9/16 pts) 95% (39/41 pts) 0.001
RTOG Gr. 1 37% (6/16 pts) 5% (2/41 pts) 0.0004
RTOG Gr. 2 6% (1/16 pts) 0% (0/41 pts) 0.28
RTOG Gr. 1–2 44% (7/16 pts) 5% (2/41 pts) 0.001

RADIATION ONCOLOGY
RESEARCH Open Access

Hypofractionated SBRT versus conventionally fractionated EBRT for prostate cancer: comparison of PSA slope and nadir

2014

Mekhail Anwar*, Vivian Weinberg, Albert J Chang, I-Chow Hsu, Mack Roach III and Alexander Gottschalk

Results (all patients)

		SBRT	CF-EBRT	p-value
	Through year			
PSA Measurements #				
Mean (range)	1	3.9 (2 – 6)	4.1 (3 – 11)	
	2	5.8 (4 – 9)	5.6 (3 – 15)	
	3	7.6 (5 – 11)	7.3 (3 – 21)	
Nadir PSA (ng/mL)				
Median (range)	1	0.70 (0 – 2.5)	1.00 (0 – 8.5)	
	2	0.40 (0 – 1.4)	0.72 (0 – 2.7)	p = 0.0005*
	3	0.24 (0.1 – 1.4)	0.60 (0 – 2.2)	p = 0.002*
Time to Nadir PSA (mos.)				
Median (range)	1	12.0 (2.7 – 15.0)	11.5 (1.2 – 15.0)	
	2	21.0 (2.7 – 26.9)	18.0 (1.2 – 26.9)	
	3	32.3 (2.7 – 41.6)	28.6 (1.0 – 41.1)	p = 0.004^
Rate of PSA change: ng/mL/month				
Median slope (range)	1	−0.09 (−0.88, 0.04)	−0.09 (−0.60, 0.06)	
	2	−0.06 (−0.38, 0.01)	−0.04 (−0.65, 0.05)	p = 0.04*
	3	−0.05 (−0.19, 0.00)	−0.02 (−0.38, 0.04)	p = 0.006*

Radiotherapy & Oncology
2013

Prostate radiotherapy

Prostate stereotactic ablative body radiotherapy using a standard linear accelerator: Toxicity, biochemical, and pathological outcomes

Andrew Loblaw[a,b,d,*,1], Patrick Cheung[a,b,1], Laura D'Alimonte[a,d], Andrea Deabreu[d], Alexandre Mamedov[d], Liying Zhang[a], Colin Tang[e], Harvey Quon[f], Suneil Jain[g], Geordi Pang[a,d], Robert Nam[c,d]

ABSTRACT

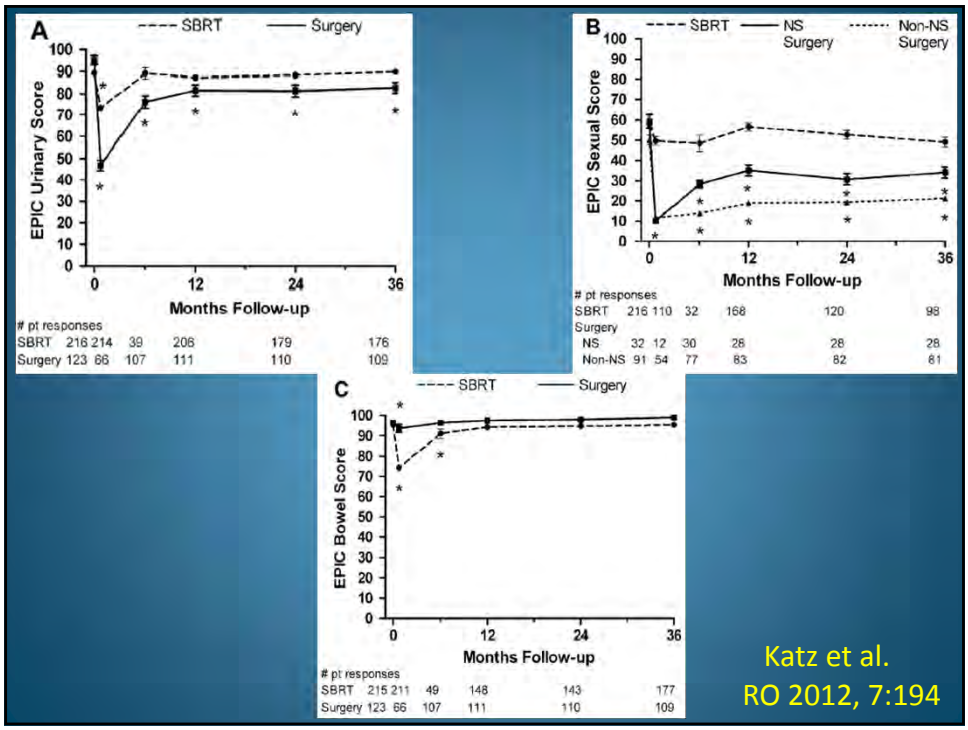
Background and purpose: Biological dose escalation through stereotactic ablative radiotherapy (SABR) holds promise of improved patient convenience, system capacity and tumor control with decreased cost and side effects. The objectives are to report the toxicities, biochemical and pathologic outcomes of this prospective study.

Materials and methods: A phase I/II study was performed where low risk localized prostate cancer received SABR 35 Gy in 5 fractions, once weekly on standard linear accelerators. Common Terminology Criteria for Adverse Events v3.0 and Radiation Therapy Oncology Group late morbidity scores were used to assess acute and late toxicities, respectively. Biochemical control (BC) was defined by the Phoenix definition.

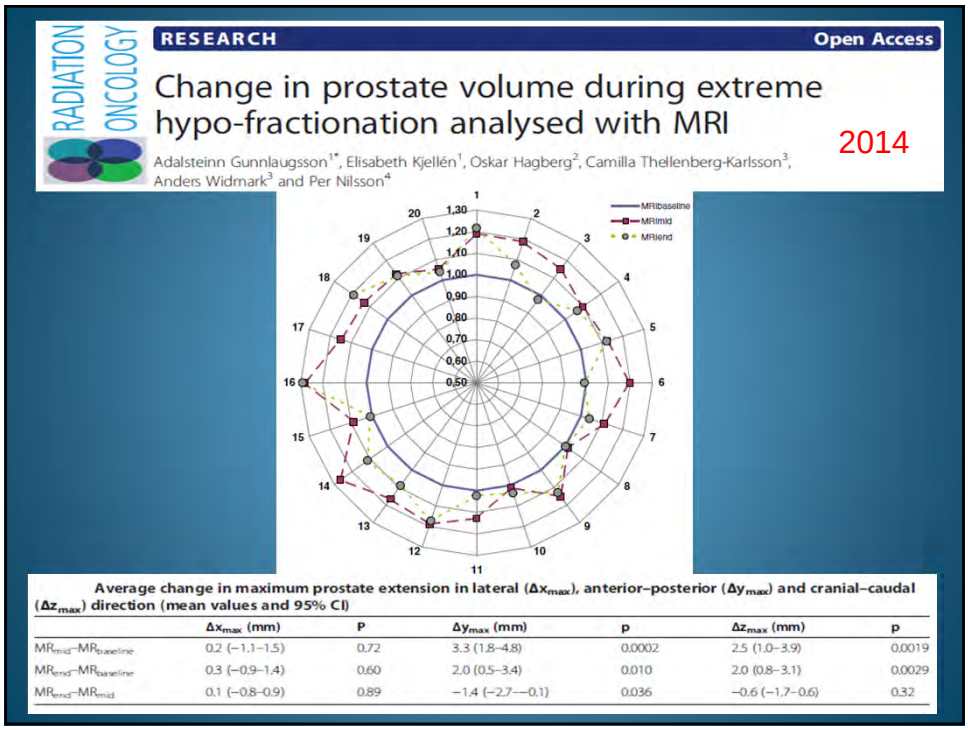
Results: As of May 2012, 84 patients have completed treatment with a median follow-up of 55 months (range 13–68 months). Median age was 67 years and median PSA was 5.3 ng/ml. The following toxicities were observed: acute grade 3+: 0% gastrointestinal (GI), 1% genitourinary (GU), 0% fatigue; late grade 3+: 1% GI, 1% GU. Ninety-six percent were biopsy negative post-treatment. The 5-year BC was 98%.

Conclusions: This novel technique employing standard linear accelerators to deliver an extreme hypofractionated schedule of radiotherapy is feasible, well tolerated and shows excellent pathologic and biochemical control.

 Radiotherapy and Oncology 107 (2013) 153–158



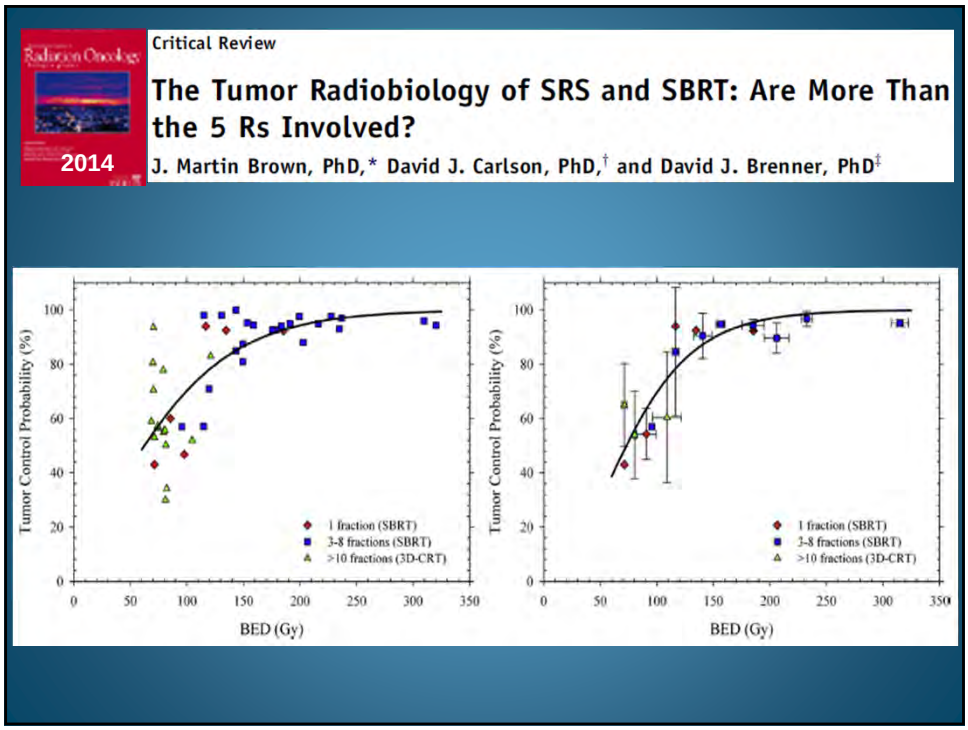
Katz et al.
RO 2012, 7:194

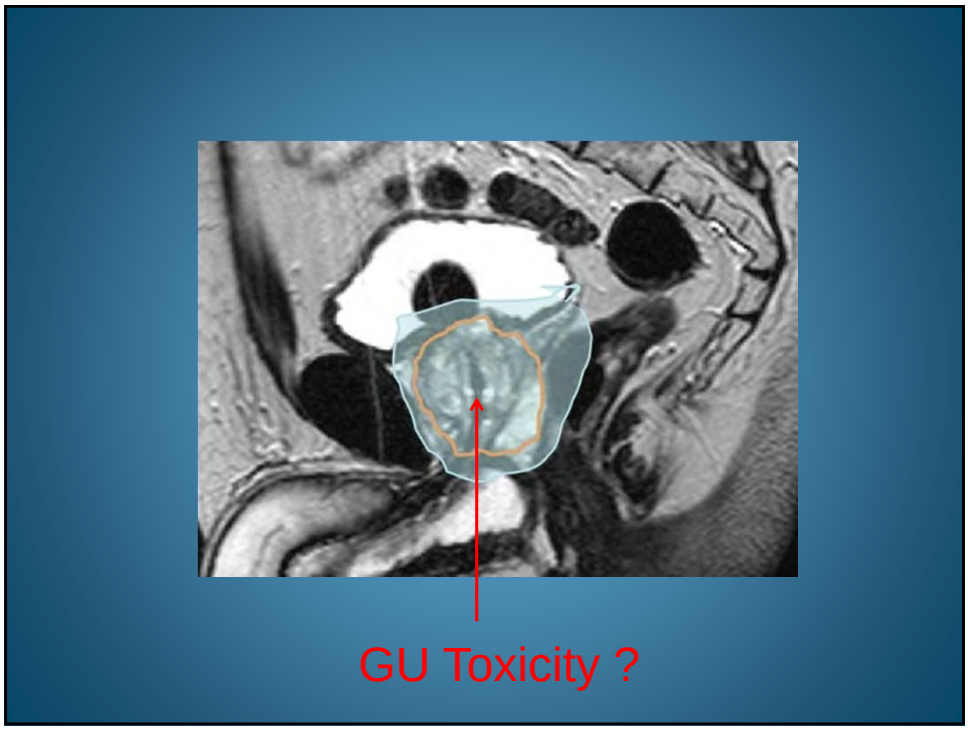


2014

Average change in maximum prostate extension in lateral (Δx_{max}), anterior–posterior (Δy_{max}) and cranial–caudal (Δz_{max}) direction (mean values and 95% CI)

	Δx_{max} (mm)	p	Δy_{max} (mm)	p	Δz_{max} (mm)	p
MR_{mid}–$MR_{baseline}$	0.2 (−1.1–1.5)	0.72	3.3 (1.8–4.8)	0.0002	2.5 (1.0–3.9)	0.0019
MR_{end}–$MR_{baseline}$	0.3 (−0.9–1.4)	0.60	2.0 (0.5–3.4)	0.010	2.0 (0.8–3.1)	0.0029
MR_{end}–MR_{mid}	0.1 (−0.8–0.9)	0.89	−1.4 (−2.7—0.1)	0.036	−0.6 (−1.7–0.6)	0.32


Critical Review
The Tumor Radiobiology of SRS and SBRT: Are More Than the 5 Rs Involved?
J. Martin Brown, PhD,* David J. Carlson, PhD,† and David J. Brenner, PhD‡
2014
Tumor Control Probability (%)
BED (Gy)
1 fraction (SBRT)
3-8 fractions (SBRT)
>10 fractions (3D-CRT)

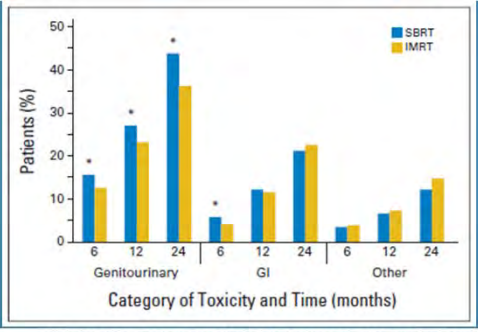

GU Toxicity ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

current issue

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross



Adjusted Random Effects Logit Model of Subcategories of Genitourinary Toxicity

Toxicity	Duration of Follow-Up: 6 Months OR*	6 Months P†	12 Months OR*	12 Months P†	24 Months OR*	24 Months P†
Diagnostic procedures to investigate incontinence or obstruction	**1.80**	**< .001**	**1.64**	**< .001**	**2.23**	**< .001**
Urethritis, urethral strictures, and bladder outlet obstruction	1.25	.14	**1.45**	**.002**	**1.78**	**< .001**
Therapeutic procedures to correct urinary incontinence	0.71	.22	1.00	1.00	1.33	.09
Other genitourinary toxicity	0.77	.45	1.14	.58	0.73	.23
Infections	1.01	.99	2.30	.11	2.42	.15
Erectile dysfunction	1.46	.03	1.15	.28	1.13	.35

SBRT for PCa
Open Issues

- **Optimal duration of treatment**
  Every day/Every other day?
- **Late toxicicy**
  Accurate evaluation of long term tolerance and toxicity, >of the urethra, an unavoidable organ at risk in the irradiation of prostate cancer
- **Patients selection**
  Mostly low and intermediate risk patients

SBRT ongoing randomized trials

ClinicalTrials.gov

Prostate Accurately Targeted Radiotherapy Investigation of Overall Treatment Time (PATRIOT)

Arms	Assigned Interventions
Experimental: Short treatment time (11 days)	Radiation: Image-guided radiotherapy 40 Gy / 5 fractions / 11 days
Experimental: Long treatment time (29 days)	Radiation: Image-guided radiotherapy 40 Gy / 5 fractions / 29 days

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0938

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

Arms	Assigned Interventions
Experimental: Arm I Patients undergo intensity-modulated radiation therapy (IMRT) twice a week for approximately 2½ weeks (36.25 Gy total).	Radiation: hypofractionated radiation therapy Given twice a week for 2½ weeks (36.25 fractions)
Experimental: Arm II Patients undergo IMRT once a day, 5 days a week, for approximately 2½ weeks (51.6 Gy total).	Radiation: hypofractionated radiation therapy Given twice a week for 2½ weeks (36.25 fractions)

SBRT ongoing randomized trials

ClinicalTrials.gov

Prostate Advances in Comparative Evidence (PACE)

Arms	Assigned Interventions
Active Comparator: Laparoscopic prostatectomy vs CyberKnife prostate SBRT Patients for whom surgery is considered will be randomized to laparoscopic prostatectomy (manual laparoscopic prostatectomy or da Vinci prostatectomy) or CyberKnife prostate SBRT.	Other: CyberKnife prostate SBRT delivered by the CyberKnife in 36.25Gy in 5 fractions or 38Gy in 4 fractions CyberKnife prostate SBRT delivered by the CyberKnife in 36.25Gy in 5 fractions or 38Gy in 4 fractions.
Active Comparator: Conventionally fractionated RT vs CyberKnife prostate SBRT Patients for whom surgery is not considered or who refuse surgery will be randomized to either conventionally fractionated radiotherapy or CyberKnife SBRT.	Other: CyberKnife prostate SBRT delivered by the CyberKnife in 36.25Gy in 5 fractions or 38Gy in 4 fractions CyberKnife prostate SBRT delivered by the CyberKnife in 36.25Gy in 5 fractions or 38Gy in 4 fractions.

Phase III study of HYPOfractionated RadioTherapy of intermediate risk localised Prostate Cancer

Interventions	Fractionation schedule and treatment durations: Conventional arm: radiotherapy is given daily (5 days/week) with 39 fractions of 2.0 Gy, i.e. total 78.0 Gy. The total treatment time is 53 - 55 days. Maximum allowed treatment days are 65. Hypofractionated arm: radiotherapy is given working-days with 7 fractions of 6.1 Gy, i.e. total 42.7 Gy. The total treatment time is 15 - 19 days. Treatment is given every other weekday, always including two weekends.

Ci sono soltanto due possibili conclusioni: se il risultato conferma le ipotesi, allora hai appena fatto una misura; se il risultato è contrario alle ipotesi, allora hai fatto una scoperta.

E. Fermi