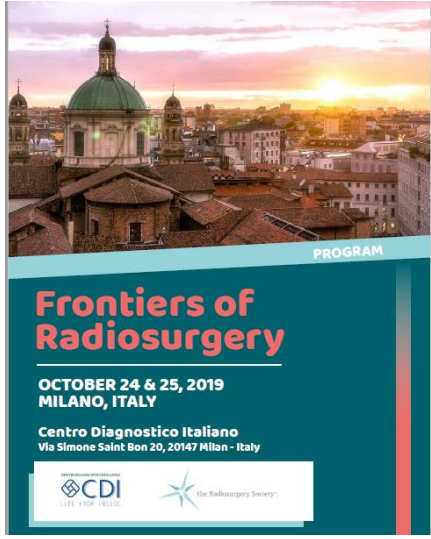
CENTRODIAGNOSTICOITALIANO

CDI

LIFE FROM INSIDE

SBRT for prostate cancer



G. Beltramo

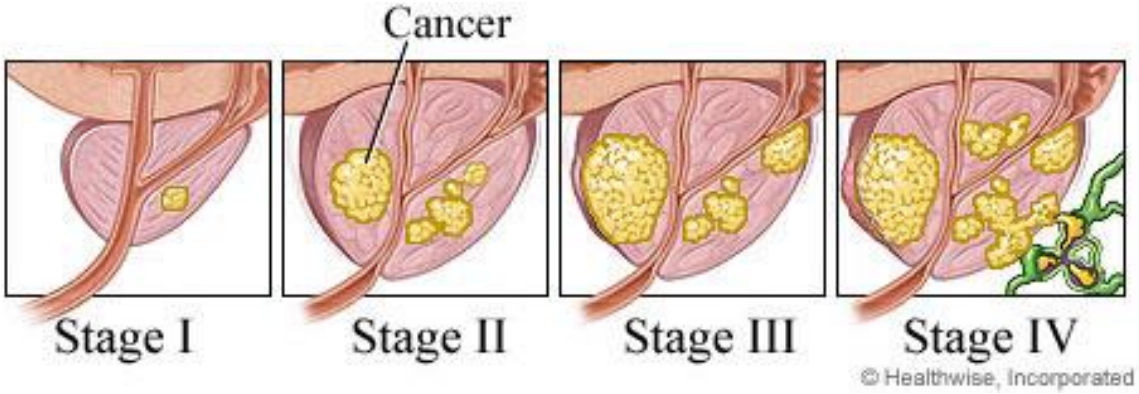
Centro Diagnostico Italiano, Milano

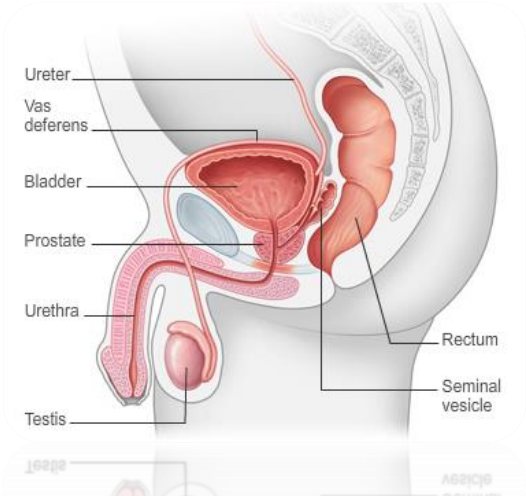
Milano 24-25 ottobre 2019

The challenge of preserving the surrounding organs

❖Prostate cancer is usually a slowly growing tumor and several patients are longer survival

❖The routine implementation of prostate specific antigen (PSA) has resulted in a raising number of new cases of patients with a remarkable drop in the median age at diagnosis (Ninety-five percent diagnosed between 45 and 89 years.)
Most are asymptomatic



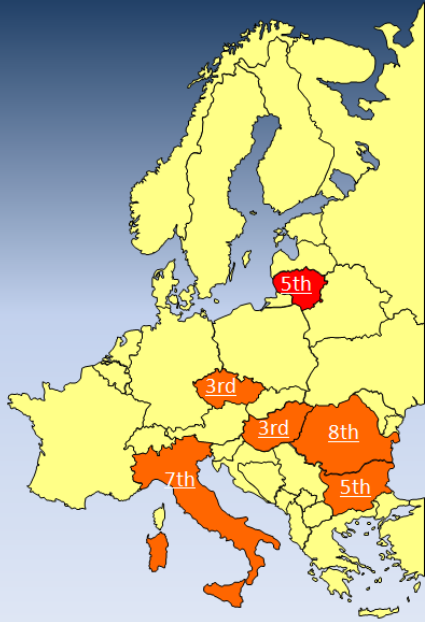


Incidence and mortality

Prostate cancer is the most common cancer in men; is estimated that in the United States, every Year over 220,000 patients are diagnosed

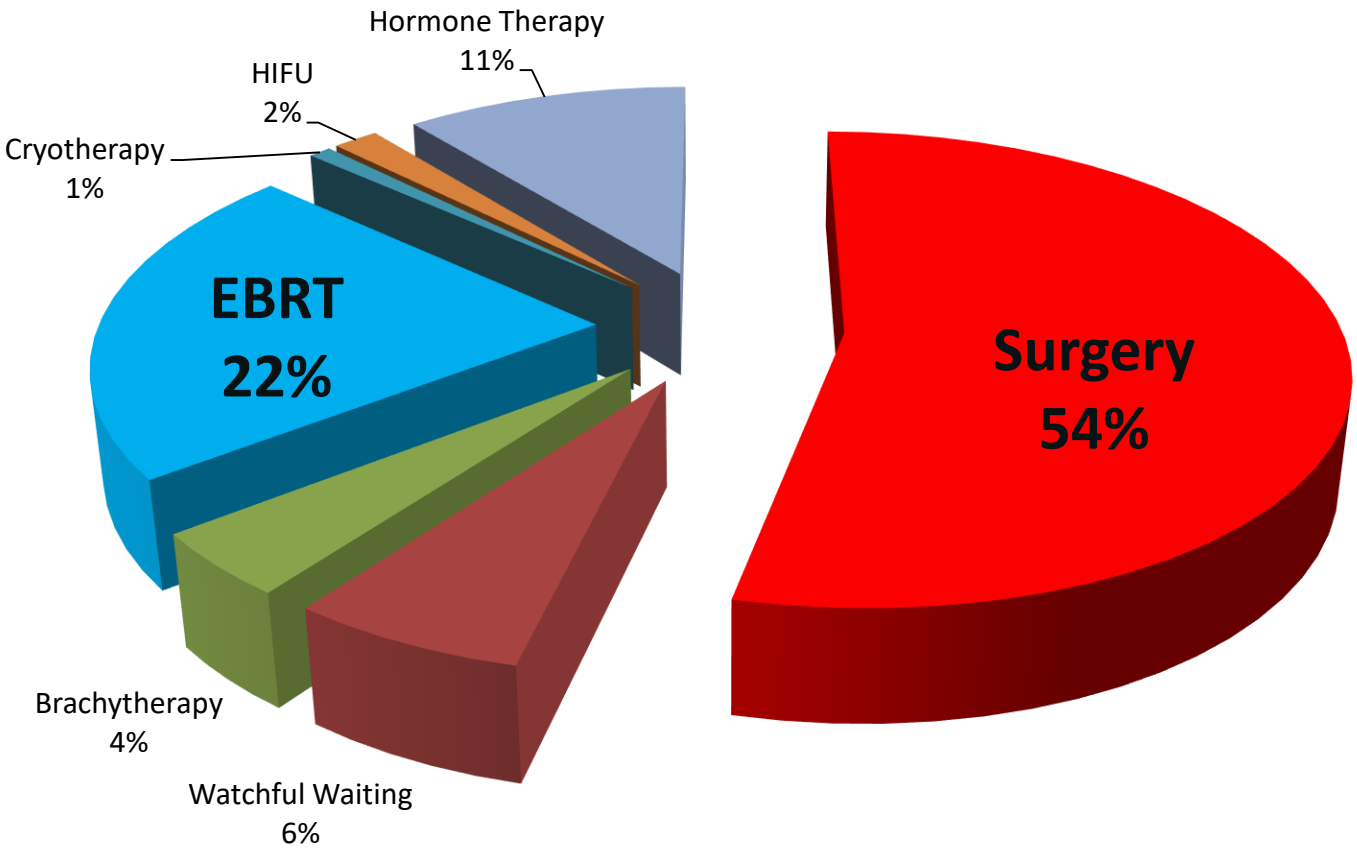
Is the second most common cause of cancer-related mortality in males (about 28.000 for year)

Country	Incidence (2008)
Bulgaria	3825
Czech Republic	5551
Hungaria	2686
Italy	40016
Lithuania	1697
Romania	3740



Legend:
- "5th": prostate's rank in cancer mortality
- Mortality by prostate cancer
  - more than 30%
  - between 30% and 15%

HOW LOW-INTERM. RISK PROSTATE PATIENTS ARE TREATED IN EUROPE?



More therapeutic options with different toxicity

Int J Radiat Oncol Biol Phys.

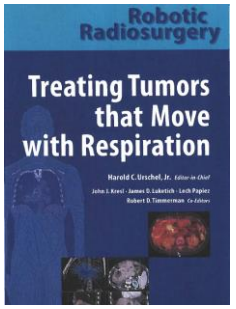
1995 Dec 1;33(5):1311-20.

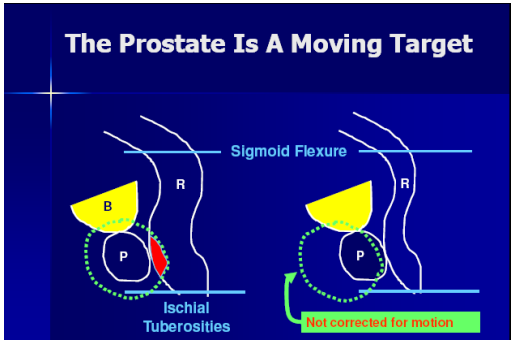
● *Treatment Verification*

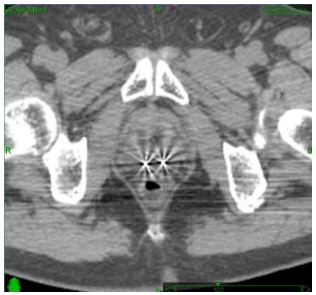
QUANTIFICATION OF ORGAN MOTION DURING CONFORMAL RADIOTHERAPY OF THE PROSTATE BY THREE DIMENSIONAL IMAGE REGISTRATION

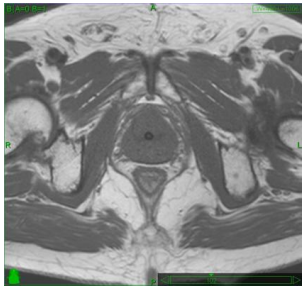
MARCEL VAN HERK, PH.D., ALLISON BRUCE, M.D., A. P. GUUS KROES, M.S., TAREK SHOUMAN, M.D., PH.D., ADRIAAN TOUW, R.T.T. AND JOOS V. LEBESQUE, M.D., PH.D.

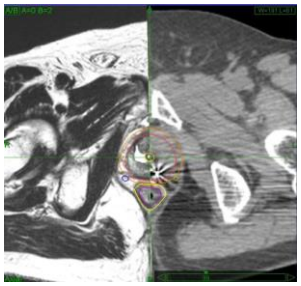
Radiotherapy Department, The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis), Amsterdam, The Netherlands

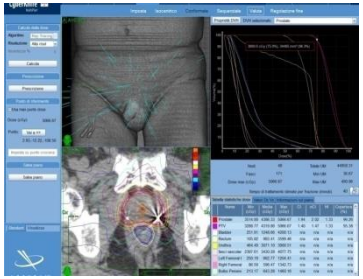






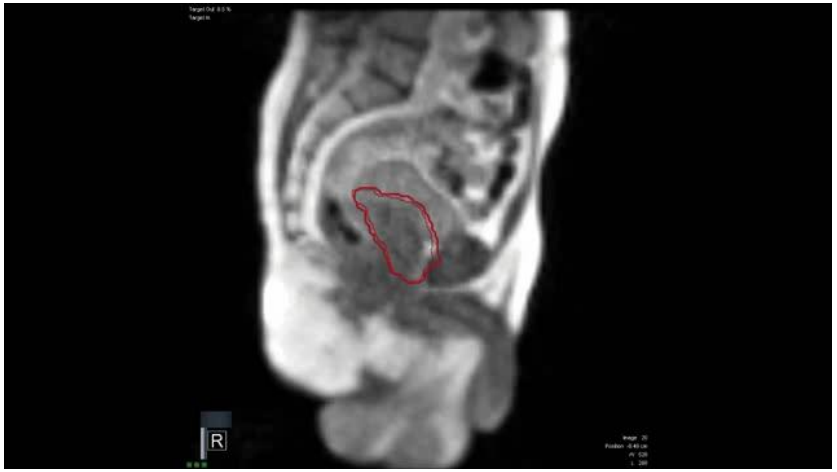






The surgeon point of view

The radiation oncologist point of view



Illusion or reality

H. Herrmann · Y. Seppenwoolde · D. Georg · J. Widder
Dept of Radiotherapy, Medical University of Vienna, Vienna, Austria

Der Radiologe
Published online: 25 July 2019

Image guidance: past and future of radiotherapy

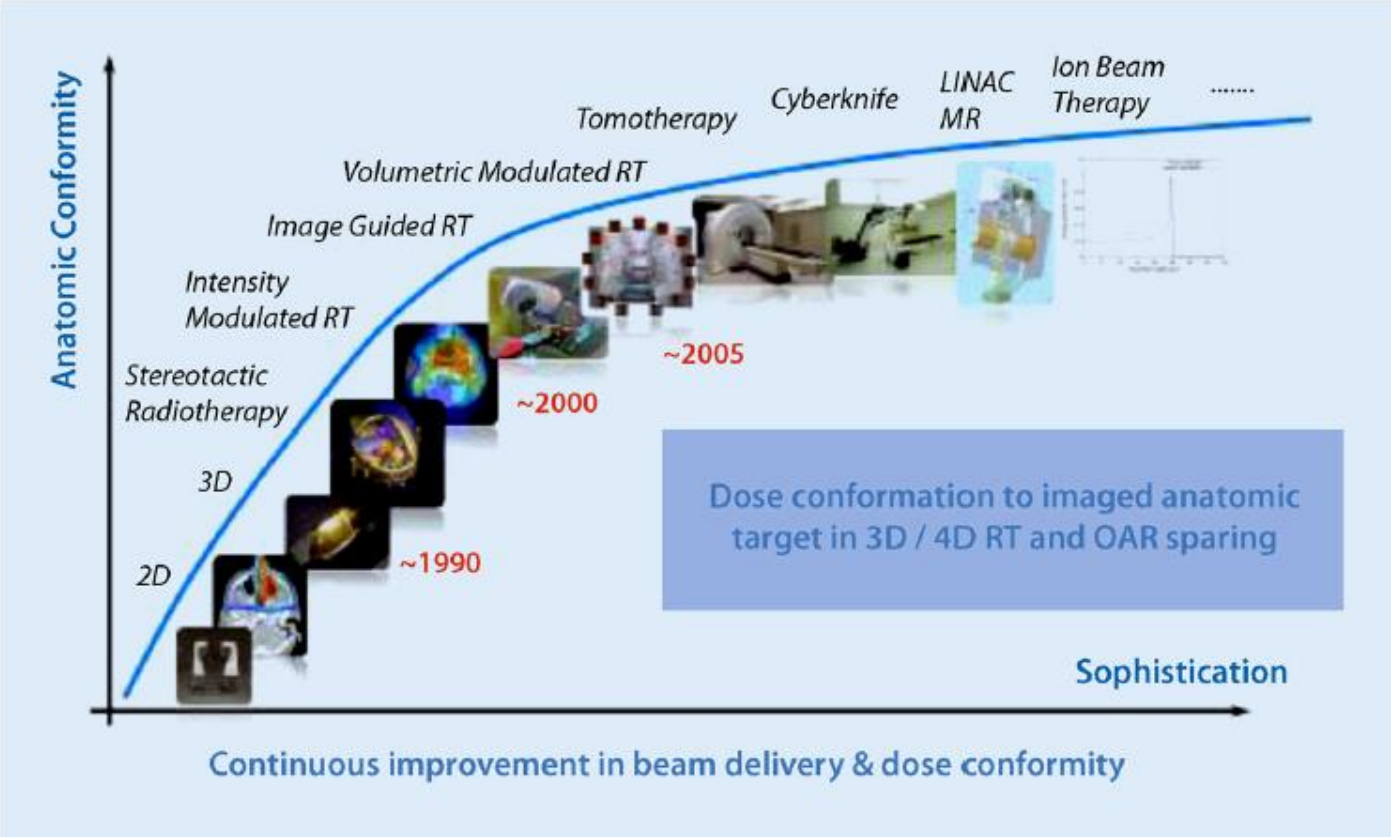
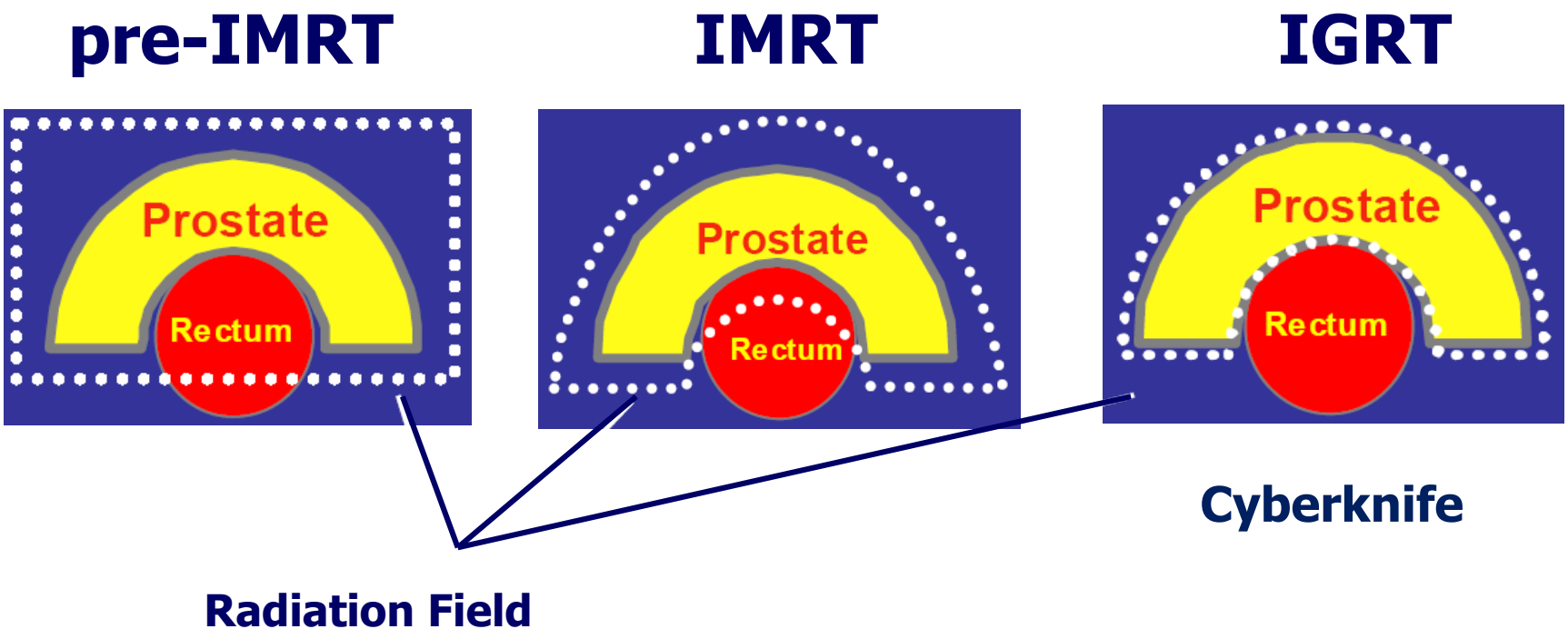


Image guidance has been playing a decisive role throughout the history of radiotherapy

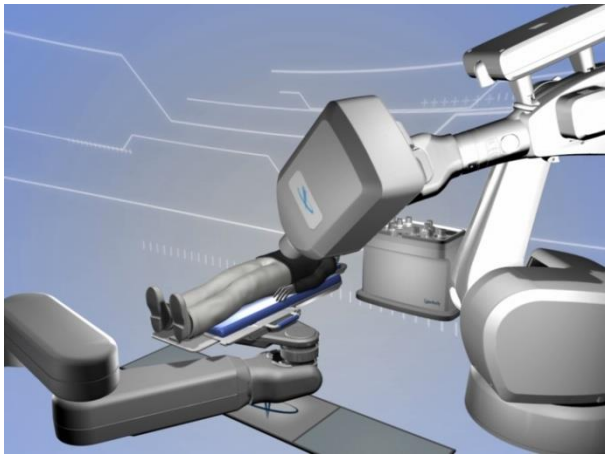
Radiation therapy technique

Best Evidence: dose escalation can be accomplished by improving the physichal delivery of the radiation

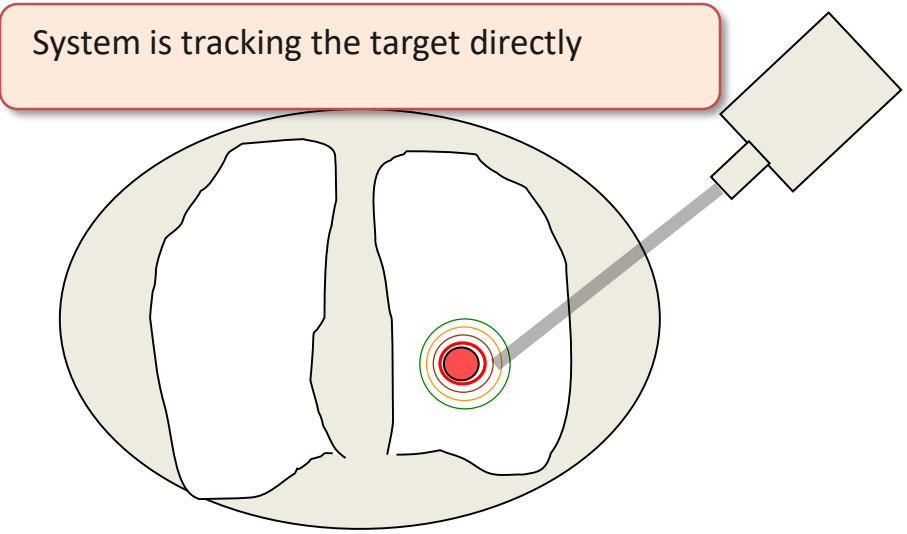


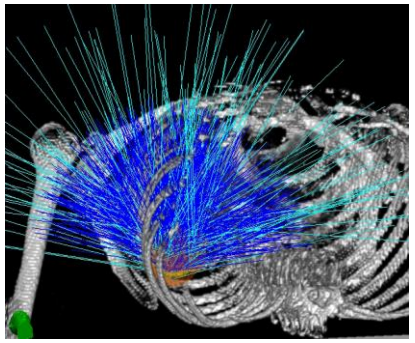
Efforts to achieve greater precision in prostate organ targeting in order to reduce the dose to the adjacent rectum and bladder have risen from new technological advancements

Cyber Knife
A New Reality

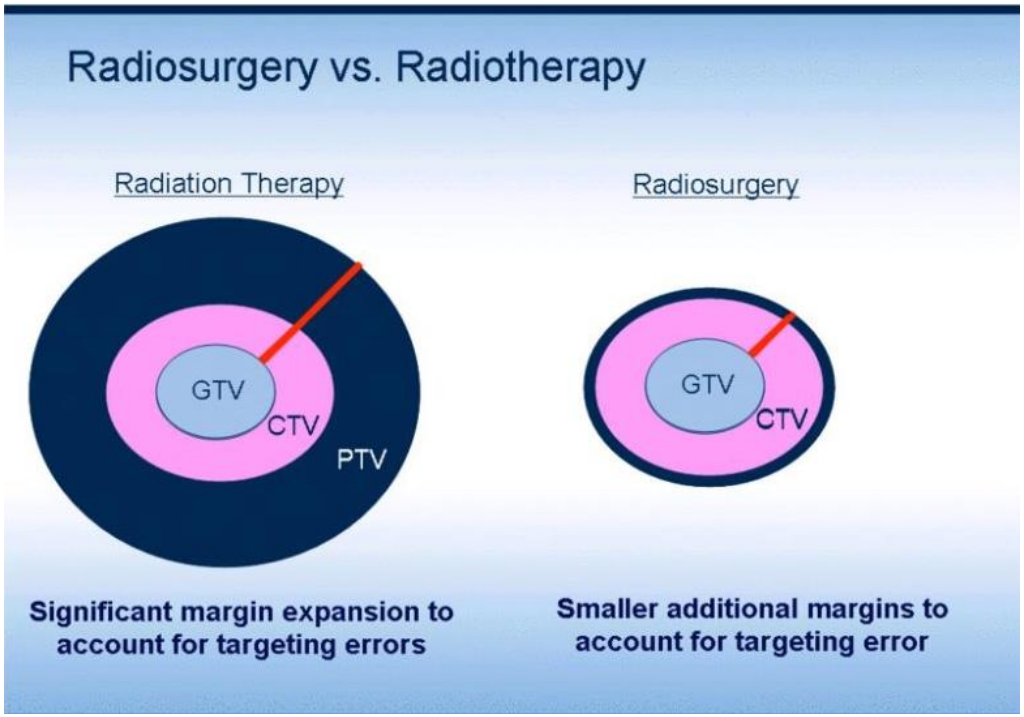


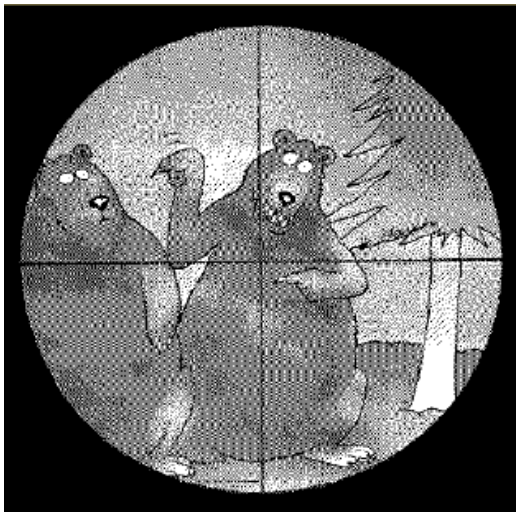
The robotic-based radiosurgery system is able to track the neoplastic target using intrafractional orthogonal kilovoltage images taken every 15–30 seconds, and can make adjustments for any intrafraction motion during treatment





Cyberknife Radiosurgery : clinical rationale





Accuracy and Precision

Reduced Side Effects

Technological advances such as Cyberknife combined with optimum immobilization and organ localization may allow refinements in dose delivery precision to achieve the goal of minimal margins around the target structure while permitting dose acceleration

Prelude to a New Therapeutic Paradigm: The Clinical Transition from Intracranial to Extracranial Stereotactic Radiation Therapy

Ingmar Lax and Henric Blomgren

- Stereotactic Radiosurgery was a term coined by Leksell

- Describes an approach utilizing:
-multiple convergent beams
-precise localization with stereotactic coordinate system
-single fraction treatment

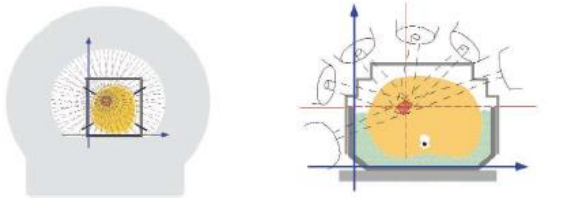


FIGURE 1. The left panel shows a schematic drawing of intracranial stereotactic radiosurgery with the Gamma Knife (Elekta, Norcross, GA). The stereotactic frame is fixed with screws into the skull. The right panel shows a schematic drawing of extracranial stereotactic radiation therapy with linear accelerator. The patient is fixed in the stereotactic body frame.

Stereotactic Body Radiation Therapy (SBRT) has been defined in an ASTRO practice guideline as an emerging non invasive radiotherapy procedure allowing the delivery of high ablative doses of radiation to the target with a high degree of precision while sparing the surrounding normal tissue with surprisingly minimal morbidity

ELSEVIER

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

0360-3016/01/$–see front matter

PII S0360-3016(01)01607-8

BIOLOGY CONTRIBUTION

IS α/β FOR PROSTATE TUMORS REALLY LOW?

JACK FOWLER, D.SC., PH.D.,* RICK CHAPPELL, PH.D.,† AND MARK RITTER, M.D., PH.D.*

Departments of *Human Oncology and †Biostatistics, University of Wisconsin-Madison, Madison, WI

Ref	α/β (Gy)	95% Confidence interval
Brenner and Hall [8]	1.5	[0.8,2.2]
Arcangeli 2010	–0.45	[–1.31, 0.41]*
Leborgne 2011[10]	1.86	[0.7, 5.1]
Lukka 2005[11]	2.02	[–1.03, 5.07]*
Valdagni 2005	7.44	[–13.97, 28.86]*
Yeoh 2011[12]	0.13	[–1.06, 1.31]*
Vogelius 2013 [13]	–0.07	[–0.73 – 0.59]
Williams 2007 [14]	2.6	[0.9, 4.8]
Fowler 2001 [15]	1.49	[1.25, 1.76]
Brenner 2002 [16]	1.2	[0.03, 4.1]

Acta Oncologica, 2005; 44: 265–276

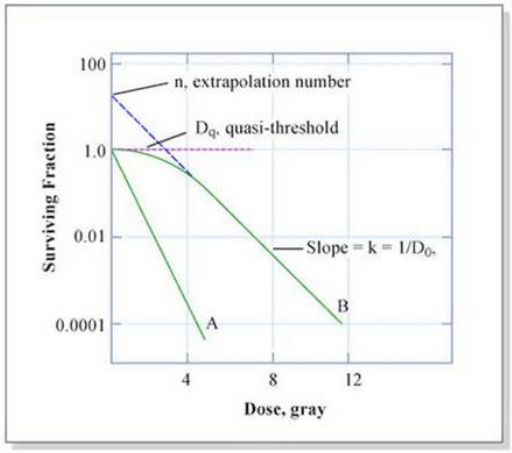
Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

The radiobiology of prostate cancer including new aspects of fractionated radiotherapy

JACK F. FOWLER

The alpha-beta ratio is a parameter that describes the response of organs to radiation.



- Recent analyses of clinical tumor control data have argued for a low alpha/beta ratio for prostate cancer on the order of 1-3 Gy

Clinical Oncology

Original Article

Normal Tissue Radiosensitivity – How Important Is It?

The smaller the alpha-beta ratio, the more responsive the organ is to a larger fraction size while conversely, the larger the alpha-beta ratio, the more sensitive the organ is to fractionation.

Tumour Review

Extreme hypofractionation for early prostate cancer: Biology meets technology

Berardino De Bari [a], Stefano Arcangeli [b], Delia Ciardo [c,*], Rosario Mazzola [d], Filippo Alongi [d], Elvio G. Russi [e], Riccardo Santoni [f], Stefano M. Magrini [g], Barbara A. Jereczek-Fossa [c,h], on the behalf of the Italian Association of Radiation Oncology (AIRO)

[a] Division of Radiation Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
[b] Division of Radiation Oncology, San Camillo-Forlanini Hospitals, Rome, Italy
[c] Division of Radiation Oncology, European Institute of Oncology, Milan, Italy
[d] Division of Radiation Oncology, Sacro Cuore Don Calabria Cancer Care Center, Negrar-Verona, Italy
[e] S.C. di Radioterapia Oncologica, Azienda ospedaliera S. Croce e Carle, Cuneo, Italy
[f] Università di Roma, Tor Vergata, U.O.C. di Radioterapia, Policlinico Tor Vergata, Roma, Italy
[g] Istituto del Radio "O. Alberti", Spedali Civili, Università di Brescia, Brescia, Italy
[h] Department of Oncology and Hemato-oncology, University of Milan, Milan, Italy

Hypofractionation in Prostate Cancer: Radiobiological Basis and Clinical Appliance

M. Mangoni,[1] I. Desideri,[1] B. Detti,[1] P. Bonomo,[1] D. Greto,[1] F. Paiar,[1] G. Simontacchi,[1] I. Meattini,[1] S. Scoccianti,[1] T. Masoni,[1] C. Ciabatti,[1] A. Turkaj,[1] S. Serni,[2] A. Minervini,[2] M. Gacci,[2] M. Carini,[2] and L. Livi[1]

Acta Oncologica, 2005; 44: 265–276

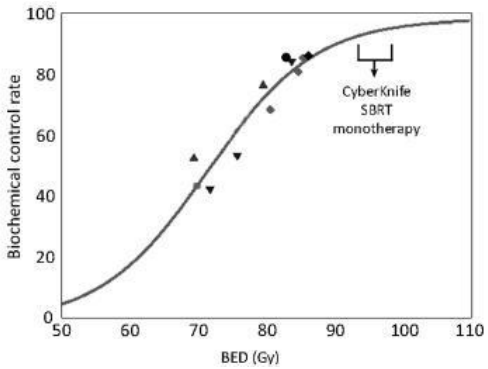
REVIEW ARTICLE

The radiobiology of prostate cancer including new aspects of fractionated radiotherapy

JACK F. FOWLER

For patients with prostate cancer, hypofractionation would have a greater increase of biologically equivalent dose (BED) to the tumor than the normal tissue, improving the therapeutic ratio

During the last decades, tremendous advances in pre-treatment imaging, treatment-planning, delivery and verification, combined with mature results from moderately hypofractionated randomized controlled trials reassuring on the sensitivity of PC to larger fraction sizes, have implemented the opportunity of using fewer large dose per fraction delivered in a short treatment duration.
Beyond the obvious advantages in terms of patient convenience and health economics, the unique radiobiology of PC along with the evidence that dose-escalation yields better outcomes seems to favour this strategy, widely known asstereotactic body radiation therapy (SABR).



WHAT HYPOFRACTIONATED PROTOCOLS SHOULD BE TESTED FOR PROSTATE CANCER?

JACK F. FOWLER, D.SC., PH.D.,* MARK A. RITTER, M.D., PH.D.,* RICK J. CHAPPELL, PH.D.,† AND DAVID J. BRENNER, D.SC., PH.D.‡

- SF = $\exp(\alpha d - \beta d^2)$
- n fractions of dose d $(SF)^n$
- SF (fractions of d) = SF (at 2 Gy fractions)
- Dose in 2 Gy/fraction = Dose in d Gy/fraction

$$EQ_2 = D_d \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Equivalent dose in 2 Gy

Table 2. Doses for Prostate Stereotactic Body Radiotherapy.

	35 Gy in 5 Fractions		36.25 Gy in 5 Fractions		40 Gy in 5 Fractions		50 Gy in 5 Fractions	
α/β Ratio	BED	EQD2	BED	EQD2	BED	EQD2	BED	EQD2
1	280	93	299	100	360	120	550	183
1.5	198	85	211	91	253	109	383	164
2	158	79	168	84	200	100	300	150
3	117	70	124	74	147	88	217	130
10	60	50	63	52	72	60	100	83

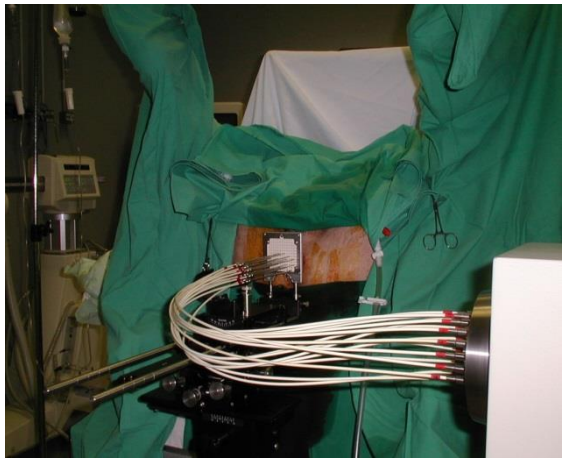
Int.J.Radiation.Oncology Biol Phys. Vol 56, 2003

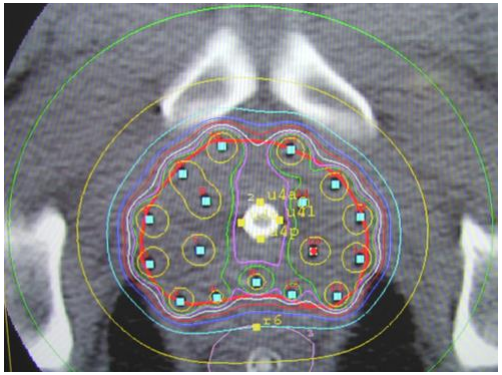
High dose-rate brachytherapy in the treatment of prostate cancer

Lucas C. Mendez and Gerard C. Morton

Author	N	Dose (Gy)/no. of fractions	Median FU (yrs)	Late Grade 3 toxicity (%)		Biochemical DFS (%)		
				GU	GI	Low	Intermediate	High
Yoshioka (55)	190	48/8	7.6	1	1	–	93	81
		54/9						
		45.5/7						
Hauswald (56)	448	42–43.5/6	6.5	5	0	99	95	–
Rogers (57)	284	39/6	2.7	1	0	–	94	–
Demanes (58)	157	42/6	5.2	3	0	97	–	–
Patel (59)	190	43.5/6	6.2	4	0	–	90	–
Zamboglou (60)	492	38/4	5–7.7	6	1	95	93	93
Barkati (61)	79	30–34.5/3	3.3	9	0	85	85	–
Strouthos (62)	450	34.5/3	4.7	1	0	96	96	92
Kukielka (63)	77	45/3	4.7	1	0	97	97	–
Jawad (64)	319	38/4	5.5	6	0	98	98	–
	79	24/2	3.5	0	0	92	92	
	96	27/2	2.9	8	0	100	100	
Hoskin (65)	30	34/4	5	3–16	1	–	99	91
	25	36/4	4.5					
	109	31.5/3	3					
Hoskin (66)	106	31.5/3	9	11	1	–	91	91
	138	26/2	5.25	2	0		93	93
	50	19–20/1	4.1	2	0		94	94
Krauss (67)	63	19/1	2.9	0	0		93 (3 yrs)	–
Prada (68)	60	19/1	6	0	0		66 (6 yrs)	–

Dose fractionation, late genito-urinary (GU) and Gastrointestinal (GI) toxicity, and biochemical disease-free survival (DFS) by risk groupings in HDR monotherapy series.





Brachytherapy prostate cancer treatment

Transl Androl Urol. 2018 Jun; 7(3): 357–370.

Radical External Beam Radiotherapy for Localised Carcinoma of the Prostate using a Hypofractionation Technique

C. D. Collins, R. W. Lloyd-Davies and A. V. Swan

Departments of Radiotherapy and Oncology and Urology St Thomas' Hospital, and Department of Public Health Medicine, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London SE1 7EH, UK

Clinical Oncology

Hypofractionated EBRT was first used for management of prostate cancer in the United Kingdom in the 1960s.

From 1964–1984, 233 patients were treated to 36 Gy in 6 fractions using a 2-dimenstional technique with acceptable clinical outcomes and toxicity

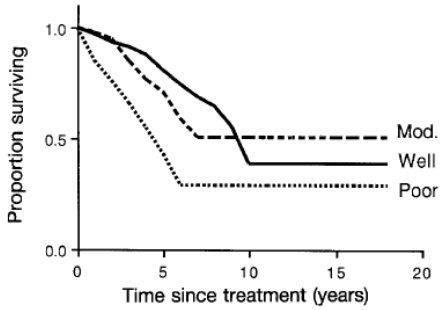


Fig. 4. Life table survival curves by histological grade.

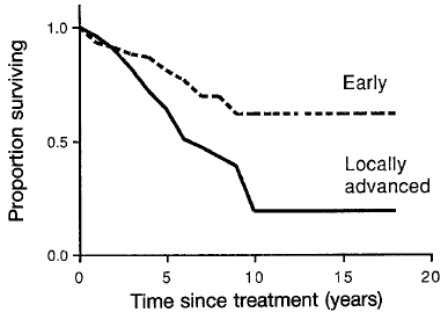


Fig. 6. Life table survival curves by stage.

Table 2. Survival figures

	Ed	STH
Whole group		
5 year	60%	(62%)
10 year	31.5%	(37%)
By stages 5 year		
T_1+T_2	78.9%	(77%)
T_3+T_4	41.0%	(51%)

Late Morbidity

Up to October 1986 there had been no long-term urological or bowel morbidity apart from the development of rectal strictures in two patients, one in 1965 and one in 1971 when larger fields of irradiation were used than normally planned.

Early Morbidity

At the end of treatment the majority of patients developed some frequency of micturition and tenesmus, which settled within a period of two to three weeks with the appropriate medication

Clinical Oncology (1991) 3:127-132

STEREOTACTIC HYPOFRACTIONATED ACCURATE RADIOTHERAPY OF THE PROSTATE (SHARP), 33.5 GY IN FIVE FRACTIONS FOR LOCALIZED DISEASE: FIRST CLINICAL TRIAL RESULTS

Berit L. Madsen, M.D.,* R. Alex Hsi, M.D.,* Huong T. Pham, M.D.,*
Jack F. Fowler, D.Sc., Ph.D.,† Laura Esagui, C.M.D.,* and John Corman, M.D.‡

Phase I/II trial of SHARP performed for localized prostate cancer using 33.5 Gy in 5 fractions, calculated to be biologically equivalent to 78 Gy in 2 Gy fractions (alpha/beta ratio of 1.5 Gy).

RTOG Acute Toxicity

Grade	Genitourinary	Gastrointestinal
0	19 (49%)	24 (61%)
1	11 (28%)	10 (26%)
2	8 (20.5%)	5 (13%)
≥3	1	0

RTOG Late Toxicity

Grade	Genitourinary	Gastrointestinal
0	22 (55%)	25 (62.5%)
1	10 (25%)	12 (30%)
2	8 (20%)	3 (7.5%)
≥3	0	0

Median time to PSA nadir was 18 months with the majority of nadirs less than 1.0 ng/mL.

Virginia Mason Medical Center, Seattle

The actuarial 48-month biochemical freedom from relapse was 70%

Int.J.Radiation.Oncology Biol Phys. Vol 67. 2007

STEREOTACTIC BODY RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: INTERIM RESULTS OF A PROSPECTIVE PHASE II CLINICAL TRIAL

CHRISTOPHER R. KING, PH.D., M.D.,* JAMES D. BROOKS, M.D.,† HARCHARAN GILL, M.D.,† TODD PAWLICKI, PH.D.,* CRISTIAN COTRUTZ, PH.D.,* AND JOSEPH C. PRESTI, JR., M.D.†

Patient characteristics

41 patients	March 03 – December 06
Age	Median 66 yrs (48 – 82)
Psa	median 5.6 (0.7-12.2)
Biopsy Gs	3+3 (28 pts); 3+4 (13 pts)
T-stage	T1c (28 pts); T2a (12 pts); T2b (1 pt)
Cyberknife treatment Schema	5 x 7.25 Gy (36.25 Gy) BED: 95 Gy
Follow up	Median 33 months (6 – 45)

Stanford University School of Medicine

Int. J. Radiation Oncology Biol. Phys., pp. 1–6, 2008

STEREOTACTIC BODY RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: INTERIM RESULTS OF A PROSPECTIVE PHASE II CLINICAL TRIAL

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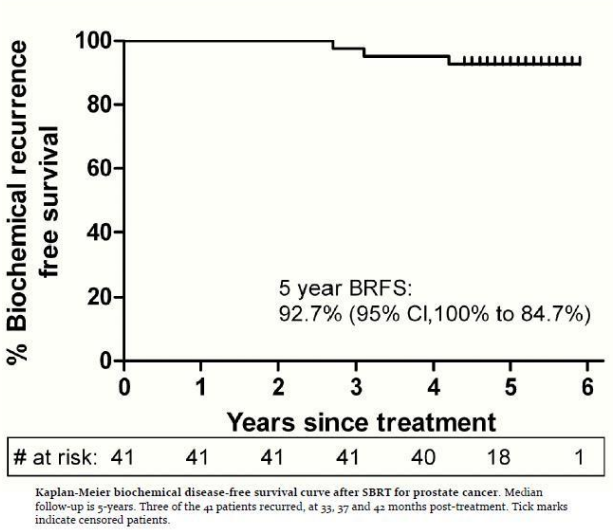
TODD PAWLICKI, PH.D.,* CRISTIAN COTRUTZ, PH.D.,* AND JOSEPH C. PRESTI, JR., M.D.†

Stanford University School of Medicine

Toxicity

- No RTOG grade 3 rectal toxicity
- One RTOG grade 3 urinary toxicity (dysuria)
- No incontinence reported

RTOG Grade	I	II	III	IV
Urinary	25% (10/41)	7% (3/41)	2.5% (1/41)	0%
Rectal	13% (6/41)	2.5% (1/41)	0%	0%



Kaplan-Meier biochemical disease-free survival curve after SBRT for prostate cancer. Median follow-up is 5-years. Three of the 41 patients recurred, at 33, 37 and 42 months post-treatment. Tick marks indicate censored patients.

PSA nadir	% achieving PSA nadir by follow-up time: At 1 y (32 patients)	At 2 y (17 patients)	At 3 y (15 patients)
≤1 ng/mL	53%	70%	93%
≤0.6 ng/mL	31%	70%	87%
≤0.4 ng/mL	19%	53%	67%
≤0.2 ng/mL	9%	6%	40%

Int. J. Radiation Oncology Biol. Phys., pp. 1–6, 2008

Phase II trial

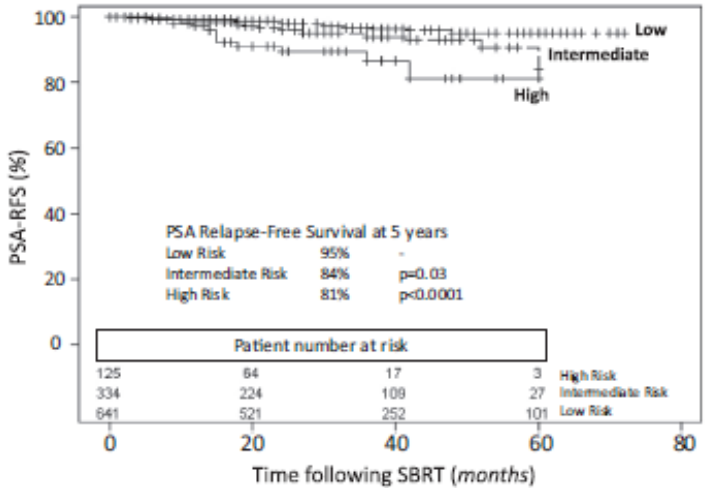
Stereotactic body radiotherapy for localized prostate cancer: Pooled analysis from a multi-institutional consortium of prospective phase II trials ☆,☆☆

Christopher R. King [a,*], Debra Freeman [b], Irving Kaplan [c], Donald Fuller [d], Giampaolo Bolzicco [e], Sean Collins [f], Robert Meier [g], Jason Wang [a], Patrick Kupelian [a], Michael Steinberg [a], Alan Katz [h]

Radiother Oncol. 2013 Nov;109(2):217-21

Patient and treatment characteristics ($n = 1100$[†]).

Risk group	N (%)	35 Gy	36.25 Gy	38–40 Gy	ADT use	FU[*]
Low	641 (58%)	254 (40%[‡])	319 (50%)	68 (11%)	50 (8%)	36
Intermediate	334 (30%)	108 (32%)	188 (56%)	38 (11%)	49 (15%)	30.5
High	125 (11%)	23 (18%)	82 (66%)	20 (16%)	48 (38%)	23
Total	1100	385 (35%)	589 (54%)	126 (11%)	147 (14%)	



The 5-years biochemical relapse free survival rate was 93%

PSA relapse-free survival rates after SBRT compare favorably with other definitive treatments for low and intermediate risk patients. The current evidence supports consideration of SBRT among the therapeutic options for these patients.

Stereotactic body radiation therapy for low and intermediate risk prostate cancer—Results from a multi-institutional clinical trial☆

Raquibul Hannan [a], Vasu Tumati [a], Xian-Jin Xie [b], L. Chinsoo Cho [c], Brian D. Kavanagh [d], Jeffrey Brindle [e], David Raben [d], Akash Nanda [f], Susan Cooley [a], D.W. Nathan Kim [h], David Pistenmaa [i], Yair Lotan [g], Robert Timmerman [a,*]

University of Texas Southwestern Medical Center, USA

EJC EUROPEAN JOURNAL OF CANCER

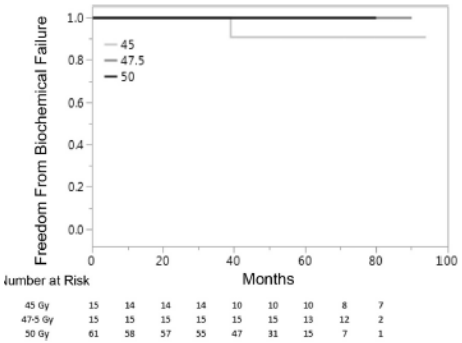
May 2016 Volume 59, Pages 142–151

Eligible patients included men with prostate adenocarcinoma with Gleason score 6 with PSA ≤ 20 or Gleason 7 with PSA ≤ 15 and clinical stage ≤ T2b. For the phase I portion of the study patients in cohorts of 15 received 45, 47.5, or 50 Gray (Gy) in five fractions. Since the maximally tolerated dose was not met in the phase I study, an additional 47 patients received 50 Gy in five fractions in the phase II study.

doses greater than 47.5 Gy in five fractions led to increased severe late toxicity.

Patient characteristics.

Characteristic	45 Gy		47.5 Gy		50 Gy		Phase II		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Number of patients	15	16.5%	15	16.5%	14	15.4%	47	51.6%	91	100.0%
Follow up, months										
Median	74		72		66		47.5		54	
Range	4–94		1–90		3–73		1–64		1–90	
Age, years										
Median	67		67		67		65		66	
Range	55–82		58–76		53–78		52–80		53–80	
Prostate size cm^3										
Median	31		38		30		35		33	
Range	19–60		17–52		17–55		12–59		12–59	
AUA score										
Median	4.5		4		7		5		5	
Range	0–15		0–13		2–12		5–14		0–15	
PSA										
Median	6.4		5.7		4.5		5.3		5.4	
Range	3.3–12.4		1.3–11.5		0.2–7.9		0.73–16.2		0.2–16.2	
T-stage										
T1c	11	73.3%	13	86.7%	8	57.1%	31	66.0%	63	69.2%
T2a	1	6.7%	1	6.7%	4	28.6%	14	29.8%	20	22.0%
T2b	3	20.0%	1	6.7%	2	14.3%	3	6.4%	8	8.8%
Gleason										
6 (3 + 3)	4	26.7%	8	53.3%	9	64.3%	22	46.8%	43	47.3%
7 (3 + 4)	8	53.3%	5	33.3%	3	21.4%	17	36.2%	33	36.3%
7 (4 + 3)	3	20.0%	2	13.3%	2	14.3%	8	17.0%	15	16.5%
ADT use										
Yes	4	26.7%	2	13.3%	4	28.6%	5	10.6%	15	16.5%
No	11	73.3%	13	86.7%	10	71.4%	42	89.4%	76	83.5%
NCCN risk										
Low	3	20.0%	8	53.3%	7	50.0%	15	31.9%	33	36.3%
Intermediate	12	80.0%	7	46.7%	7	50.0%	32	68.1%	58	63.7%
Treatment site										
A	14	93.3%	8	53.3%	9	64.3%	27	57.4%	58	63.7%
B	1	6.7%	4	26.7%	4	28.6%	11	23.4%	20	22.0%
C	0	0.0%	3	20.0%	1	7.1%	0	0.0%	4	4.4%
D	0	0.0%	0	0.0%	0	0.0%	7	14.9%	7	7.7%
E	0	0.0%	0	0.0%	0	0.0%	2	4.3%	2	2.2%



Cumulative acute and late GU and GI toxicities by dose levels.

Grade	45 Gy								47.5 Gy								50 Gy							
	Genitourinary				Gastrointestinal				Genitourinary				Gastrointestinal				Genitourinary				Gastrointestinal			
	Acute		Late		Acute		Late		Acute		Late		Acute		Late		Acute		Late		Acute		Late	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0	8	53·3%	8	53·3%	8	53·3%	14	93·3%	6	40·0%	9	60·0%	7	46·7%	9	60·0%	13	21·3%	28	45·9%	21	34·4%	39	63·9%
I	2	13·3%	4	26·7%	6	40·0%	1	6·7%	8	53·3%	1	6·7%	4	26·7%	5	33·3%	34	55·7%	17	27·9%	24	39·3%	5	8·2%
II	5	33·3%	3	20·0%	1	6·7%	0	0·0%	1	6·7%	4	26·7%	4	26·7%	1	6·7%	14	23·0%	12	19·7%	14	23·0%	11	18·0%
III	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	1	6·7%	0	0.0%	0	0·0%	0	0·0%	3	4·9%	1	1·6%	4	6·6%
IV	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0.0%	0	0·0%	0	0·0%	1	1·6%	1	1·6%	2	3·3%
V	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0.0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%	0	0·0%

Stereotactic body radiation therapy (SBRT) for high-risk prostate cancer: Where are we now?

Alejandro Gonzalez-Motta MD [a,b,*], Mack Roach III MD FACR FASTRO [c]

practical radiation oncology
pro
www.practicalradonc.org

Author, y, origin	No. patients (HR patients)	HR definition	Dose	Median FU (y)	ADT/duration	Toxicity (scale used)
Kang 2011, Korea[31]	44 (29)	D'Amico	8 Gy ×4, 8.5 Gy ×4 or 9 Gy ×4	3.3	Yes/24 mo	Acute: GU and GI grade 2: 25%. Late GU and GI 2: 14% [b]
Bolzicco 2013, Italy[27]	100 (17)	NCCN	7 Gy ×5	3	8 HR patients received/NS	Acute: GU and GI grade 2: 12% and 18%. Late GU grade 3: 1% [c]
Chen 2013, USA[28]	100 (8)	D'Amico	7-7.25 Gy ×5	2.3	"Most" received 3-6 mo/2 HR patients 2-3 y	2-y actuarial GU and GI grade ≥2 (31%) and (1%). 21% late GU flare [b]
King 2013, USA[33]	1100 (125)	D'Amico	7-8 Gy ×5	3	38% of HR patients/ 4 mo	NS
Lee 2014, Korea[36]	45 (13)	NCCN	7.2 Gy ×5	5.3	Yes/NS	Acute: GU and GI grade 2: 4% and 4%. Late GU and GI grade 2: 4% and 4% [b]
Janowski 2014, USA[30]	57 (9)	D'Amico	7-7.25 Gy ×5	2.9	Yes/NS	2-y actuarial grade ≥2 GU and GI: 49% and 1.8% [b]
Davis 2015, Radiosurgery Society[29]	437 (33)	NCCN 2015	7-9.5 Gy ×4-5	1.6	15 HR patients received ADT/NS	Late grade 2 GU: 8%. Late grade 2 proctitis: 2% [b]
Fan 2015, Taiwan[38]	31 (16)	NCCN	7.5 Gy ×5	3	82% HR/NS	No grade ≥3. 7 patients acute GU grade 2. 2 patients late GU grade 2 [b]
Rana 2015, USA[39]	102 (8)	D'Amico	5-8 Gy ×5	4.3	8.9% of patients/4 mo	Late grade 2 GU and GI: 9.9% and 3% [c]
Ricco 2016, USA[37, d]	270 (A1: 32)	NCCN 2015	7-7.5 Gy ×5	4.1	27% of all SBRT patients/NS	No late GU and GI grade 3 [c]
Katz 2016, USA[32]	515 (38)	NCCN 1.2016	7-7.25 Gy ×5	7	Yes/NS	Acute: GU and GI grade 2: <5%; Late GU and GI grade 2: 9% and 4%. Late GU grade 3: 1.7% [c]
Kotecha 2016, USA[35]	24 (13)	NCCN	7.25 and 10 Gy ×5 to LDPTV and HDPTV SIB	2	Yes/NS	Acute GU grade 2: 38%. Late GU and GI grade 2: 4% and 8% [b]
Koskela 2017, Finland[34]	218 (111)	D'Amico	7-7.25 Gy ×5	2	88.3% of HR/48% of HR patients ADT ≥24 mo	No acute GU and GI grade 3 Intermediate-term GU and GI grade 3: 1.8 and 0.9% [b]

Outcomes HR patients [a]	Comments and conclusions
5-y bDFS: 90.9%	Short FU, small number of patients. EQD2: 87-108 Gy, Urethral avoidance used. T3: 22% patients
3-y bDFS: 94% (all patients)	Short FU. Duration of ADT not reported. Urethral catheter for planning and treatment. 12% of bounce. Favorable HR patients
2-y-bDFS: 99% (all patients)	Short FU. 79% of patients with a pretreatment SHIM score ≥10 conserved potency beyond 2 y. Late urinary flare could be related to urethral dose; urethral sparing not used
5-y bDFS: 81%	No difference in patients with ADT vs no ADT. Median nPSA 0.2 at 3 y. Better bDFS with dose ≥36.25. Short FU. No T stage specified
5-y bDFS: 89.7% (all patients)	GS ≥8: 17.8%, cT3 ≥13.3%, 68%: 70-79 y of age. No specific bDFS for HR patients
2-y bDFS: 98% (all patients)	Only 15.7% HR. Short FU. Prostate volume ≥50 mL. At 2-y median PSA: 0.4
2-y bDFS: 90% but with PSA >20 ng/mL: 62.5%	95% monotherapy. Short FU. No information about use of ADT. Community-based practices. Variable equipment used, different fractionations, planning heterogeneity. Median nPSA 0.3 ng/mL 3 y
3-y bDFS: 82%	Median PSA 0.12 at 12 mo. 45% HR patients. 6% VHR patients
3-y bDFS: 100% (all patients)	24% bounce. Urinary flare after 1 y. T stage and PSA not reported
6-y bDFS for SBRT: 92%. 4-y bDFS for HR and VHR: 95% and 72%	Duration of ADT not reported. Acute toxicity grades 1 and 2 not reported. Authors conclude SBRT "alternative" to IMRT. Monotherapy. Few HR and VHR patients
8-y bDFS: 65% for HR. Favorable unfavorable intermediate 7-y bDFS ~93% and 68%	Author concluded ADT could be of less benefit with SBRT. Only T1-T2a, 32 patients GS ≥8. Author concluded SBRT "equivalent" conventional EBRT. Longest FU but few HR patients
2-y bDFS: 95.8% for all patients. 2 HR patients biochemical failures	SIB. Only 13 HR patients. Patients T ≥3:1. GS ≥8: 12 patients. Short FU. High acute toxicity grade 2 (38%)
23-mo bDFS: 92.8%	Short FU. Long ADT for HR patients. All grade 3 toxicity was in ≥36.25 Gy patients. 51% patients HR. 32% locally advanced (T3-4). GS ≥8: 13%, PSA >20: 15%. Median nPSA: 0.2 at 9-12 mo

The evidence for SBRT in HR patients in this review is based on observational studies with relatively few patients and short follow-up (level III evidence). Based on these data and the principles surrounding treatment, SBRT boost should ideally be validated in clinical trials.

SBRT monotherapy should be used cautiously in highly selected HR patients outside of a clinical trial.

Practical Radiation Oncology (2018) 8, 185–202

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

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

RADIATION ONCOLOGY

	CK	EBRT
# Evaluable patients		
Total	43	75
# Follow up from end of RT		
Thru Year 1	43	42
Thru Year 2	38	62
Thru Year 3	27	68
# with PSA follow-up for all 3 intervals	26	37
Median age at RT (yrs) (range)	69.0 (51 – 83)	69.8 (55 – 82)
Gleason score:		
3 + 3	24 (56%)	59 (79%)
3 + 4	19 (44%)	16 (21%)
Pretreatment PSA (ng/mL)		
Median (range)	6.2 (2.0 – 13.5)	5.9 (0.1 – 16.7)
# >10.0 ng/mL	10 (23%)	19 (25%)
Years of RT	2006 – 2011	1997 – 2006
Median follow-up (mos.) (range)	29.3 (12 – 75)	62.1 (15 – 156)

	Through year	SBRT	CF-EBRT	p-value
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*

SBRT (Cyberknife): 9.5 x 4 dft: 38 Gy VS EBRT: 72-78Gy

Patients treated with SBRT experienced a lower PSA nadir and tended to a continuously greater rate of decline of PSA for duration 2, 3 and 4 years than CF-EBRT.

The improved PSA kinetics of SBRT leaded to favorable BCF-free survival.

Anwar et al. Radiation Oncology 2014, 9:42

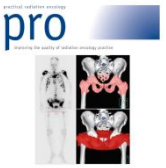
Original article

Prostate-specific antigen kinetics following hypofractionated stereotactic body radiotherapy versus conventionally fractionated external beam radiotherapy for low- and intermediate-risk prostate cancer

Seok Ho Lee, Hun Jung Kim ✉, Woo Chul Kim

Volume 12, Issue 4
December 2016
Pages 388-395

SBRT and HDR brachytherapy produce lower PSA nadirs and different PSA decay patterns than conventionally fractionated IMRT in patients with low- or intermediate-risk prostate cancer.



Kishan AU[1], Wang PC[2], Upadhyaya SK[3], Hauswald H[4], Demanes DJ[2], Nickols NG[5], Kamrava M[2], Sadeghi A[6], Kupelian PA[2], Steinberg ML[2], Prionas ND[7], Buyyounouski MK[7], King CR[2].

Pract Radiat Oncol. 2016 Jul-Aug;6(4):268-75. doi: 10.1016/j.prro.2015.11.002. Epub 2015 Nov 10.

Int J Radiat Oncol Biol Phys. 2019 Nov 1;105(3):628-636. doi: 10.1016/j.ijrobp.2019.06.2539. Epub 2019 Jul 2.

Multi-Institutional Analysis of Prostate-Specific Antigen Kinetics After Stereotactic Body Radiation Therapy.

Jiang NY[1], Dang AT[1], Yuan Y[1], Chu FI[1], Shabsovich D[1], King CR[1], Collins SP[2], Aghdam N[2], Suy S[2], Mantz CA[3], Miszczyk L[4], Napieralska A[4], Namysl-Kaletka A[4], Bagshaw H[5], Prionas N[5], Buyyounouski MK[5], Jackson WC[6], Spratt DE[6], Nickols NG[1], Steinberg ML[1], Kupelian PA[1], Kishan AU[7].

Stereotactic body radiation therapy produce lower nPSAs than IMRT

In turn, lower nPSAs are associated with reduced incidence of, and longer time to, biochemical failure.

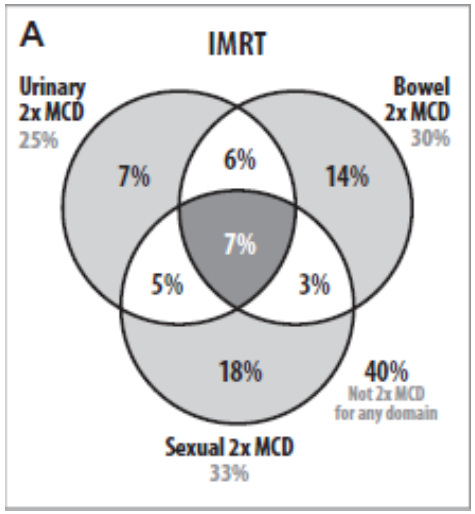
Because nPSA is a validated predictor of long-term outcome, these data not only suggest a distinct radiobiological effect with SBRT , but also predict for clinical outcomes that might equal or surpass those of IMRT.

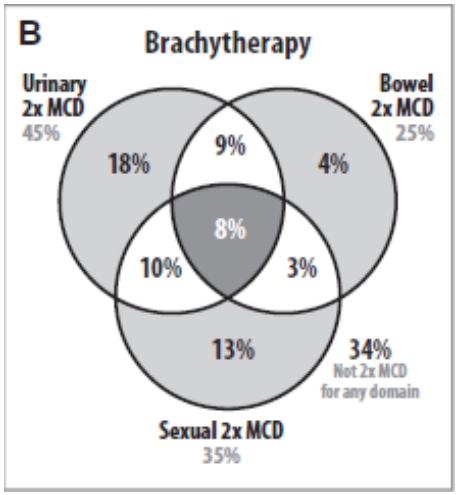
Original article

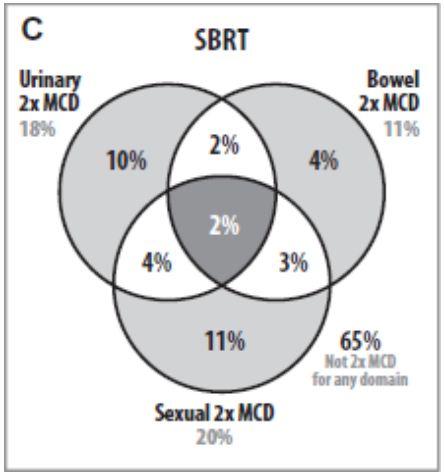
Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy

Joseph R. Evans [a,1], Shuang Zhao [a,1], Stephanie Daignault [b], Martin G. Sanda [c], Jeff Michalski [d], Howard M. Sandler [e], Deborah A. Kuban [f], Jay Ciezki [g], Irving D. Kaplan [h], Anthony L. Zietman [i], Larry Hembroff [j], Felix Y. Feng [a], Simeng Suy [k], Ted A. Skolarus [l,m], Patrick W. McLaughlin [a], John T. Wei [l], Rodney L. Dunn [l], Steven E. Finkelstein [n], Constantine A. Mantz [n], Sean P. Collins [k], Daniel A. Hamstra [a,*], and the PROSTQA Study Consortium

The EPIC-26 and SF-12 surveys were collected at baseline, 1–2 months, 6 ,12, and 24 months







	IMRT	Brachy therapy	SBRT
Urinary	25%	45%	18%
Bowel	30%	25%	11%
Sexual	33%	35%	20%

Radiother Oncol. 2015 Aug;116(2):179-84. doi: 10.1016/j.radonc.2015.07.016. 11.

Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies

William C. Jackson, MD,* Jessica Silva, BS,* Holly E. Hartman, MS,† Robert T. Dess, MD,* Amar U. Kishan, MD,‡ Whitney H. Beeler, MD,* Laila A. Gharzai, MD,* Elizabeth M. Jaworski, MD,* Rohit Mehra, MD,§ Jason W.D. Hearn, MD,* Todd M. Morgan, MD,‖ Simpa S. Salami, MD,‖ Matthew R. Cooperberg, MD, MPH,¶ Brandon A. Mahal, MD,# Payal D. Soni, MD,* Samuel Kaffenberger, MD,‖ Paul L. Nguyen, MD,# Neil Desai, MD,** Felix Y. Feng, MD,†† Zachary S. Zumsteg, MD,‡‡ and Daniel E. Spratt, MD*

International Journal of Radiation Oncology biology • physics

University of Michigan, Ann Arbor

A systematic search leveraging Medline via PubMed and EMBASE for original articles published between January 1990 and January 2018 was performed.

All prospective series assessing curative-intent prostate SBRT for localized prostate cancer reporting bRFS, physician-reported toxicity, and patient-reported quality of life with a minimum of 1-year follow-up were included.

Table 1 Summary trial and patient characteristics

	Trial level n (%) or median (range)	Patient level* n (%) or mean (range)
Trials and prospective series (n)	38	6116
Phase 1	1	45
Phase 1/2	4	245
Phase 2	15	1,536
Phase 3	2	638
Prospective	14	1,472
Registry	2	2,180
Patients (n)	6116	6116
Fractions	5 (4-9)	5 (4-9)
Dose per fraction	7.25 Gy (5-10 Gy)	7.4 Gy (5-10 Gy)
Average follow-up†	30 mo (12-115 mo)	39 mo (12-115 mo)
Average age‡	68 y (63-77 y)	68 y (63-77 y)
Clinical stage, n (%)§		
T1	28 (88)	67%
T2	28 (88)	31%
T3	6 (19)	2%
T4	1 (3)	0%
Pre-SBRT PSA‖	6.8 ng/mL (4.7-72 ng/mL)	7.5 ng/mL (4.7-72 ng/mL)
NCCN risk group (V4.2018)		
Low	34 (92)	2745 (45)
Intermediate	29 (78)	2901 (47)
High	15 (38)	470 (8)
ADT receipt with SBRT¶	19 trials	654 (15%)
Number reporting bRFS	33 (87)	5778 (95)
Number reporting acute or late toxicity	37 (97)	6044 (99)
Number reporting HRQOL	25 (66)	3973 (65)
Number using EPIC-26	16 (42)	3293 (54)
Number reporting AUA IPSS	13 (34)	2399 (39)

Thirty-eight unique prospective series were identified comprising 6116 patients.

Int J Radiation Oncol Biol Phys, Vol. 104, No. 4, pp. 778e789, 2019

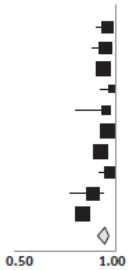
Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies

William C. Jackson, MD,* Jessica Silva, BS,* Holly E. Hartman, MS,† Robert T. Dess, MD,* Amar U. Kishan, MD,‡ Whitney H. Beeler, MD,* Laila A. Gharzai, MD,* Elizabeth M. Jaworski, MD,* Rohit Mehra, MD,§ Jason W.D. Hearn, MD,* Todd M. Morgan, MD,‖ Simpa S. Salami, MD,‖ Matthew R. Cooperberg, MD, MPH,¶ Brandon A. Mahal, MD,# Payal D. Soni, MD,* Samuel Kaffenberger, MD,‖ Paul L. Nguyen, MD,# Neil Desai, MD,** Felix Y. Feng, MD,†† Zachary S. Zumsteg, MD,‡‡ and Daniel E. Spratt, MD*

International Journal of Radiation Oncology biology • physics

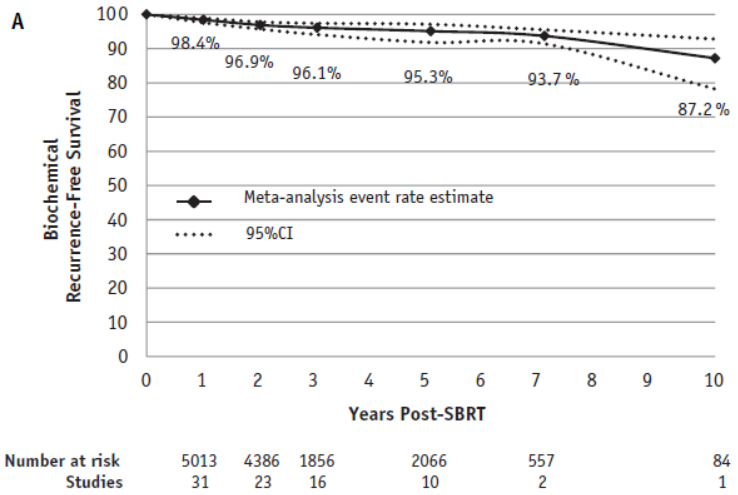
Study name	Sample Size	Risk Group (%) Low	Int	High	Statistics for each study Event rate	Lower limit	Upper limit
Loblaw DA et al	84	100	0	0	0.975	0.908	0.994
Zimmermann M et al.	80	100	0	0	0.960	0.887	0.987
Katz AJ et al.	477	68	32	0	0.950	0.926	0.966
Mantz C et al.	102	67	33	0	0.995	0.927	1.000
Alayed Y et al.	30	60	37	3	0.967	0.798	0.995
Meier R et al.	309	56	44	0	0.970	0.944	0.984
Fuller DB et al.	259	43	57	0	0.935	0.898	0.959
Boike TP et al.	91	36	64	0	0.986	0.925	0.998
Lee SW et al.	45	13	58	29	0.897	0.769	0.958
Widmark A et al.	589	0	89	11	0.837	0.805	0.865
Overall	**2066**				**0.953**	**0.913**	**0.975**

Event rate and 95% CI



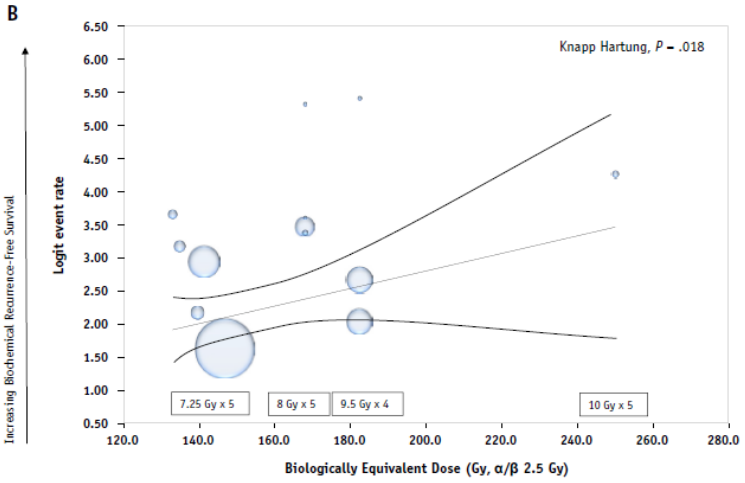
I-squared 87.96
Q -value 74.9
P -value < .001

Meta-analysis using random effects model of 5-year brfs



Overall, 5- and 7-year bRFS rates were 95.3% (95% confidence interval [CI], 91.3%-97.5%) and 93.7% (95% CI, 91.4%-95.5%), respectively

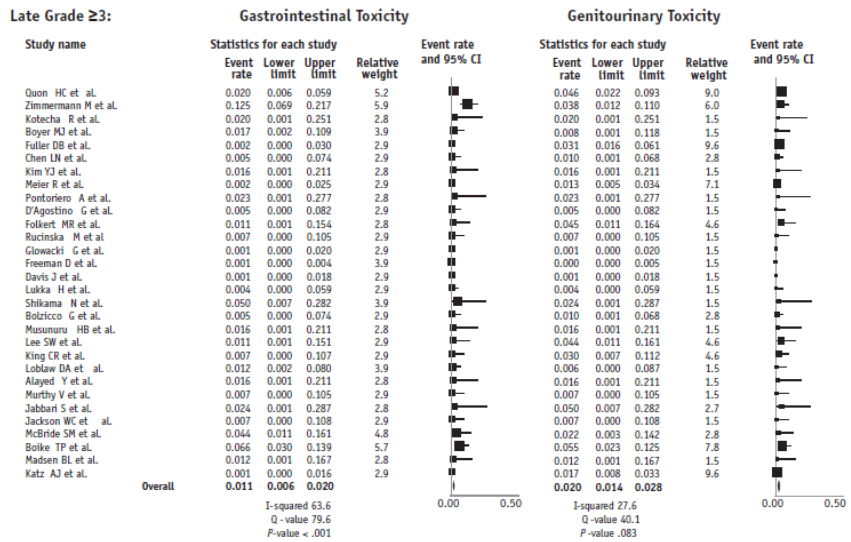
Increasing dose of SBRT was associated with improved biochemical control (P = .018)



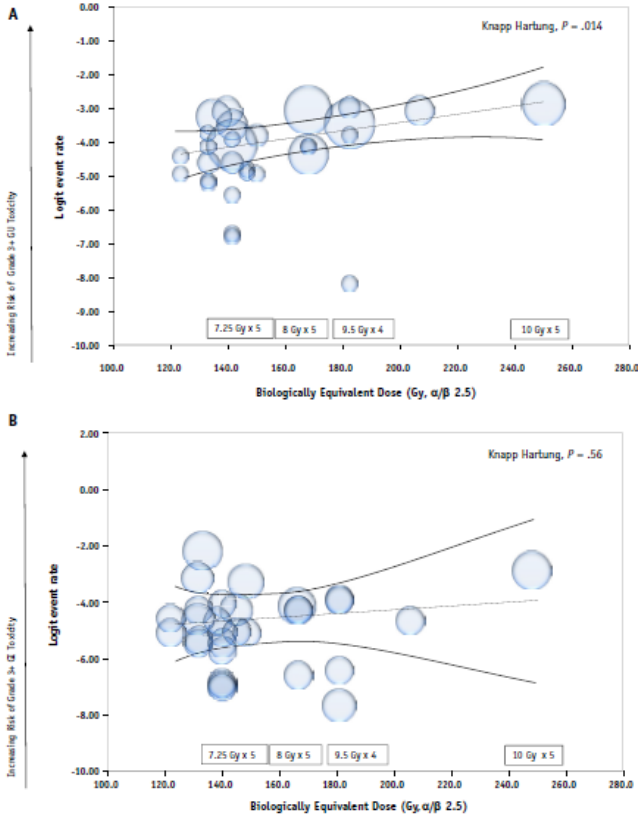
Int J Radiation Oncol Biol Phys, Vol. 104, No. 4, pp. 778e789, 2019

Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies

William C. Jackson, MD,* Jessica Silva, BS,* Holly E. Hartman, MS,† Robert T. Dess, MD,* Amar U. Kishan, MD,‡ Whitney H. Beeler, MD,* Laila A. Gharzai, MD,* Elizabeth M. Jaworski, MD,* Rohit Mehra, MD,§ Jason W.D. Hearn, MD,* Todd M. Morgan, MD,‖ Simpa S. Salami, MD,‖ Matthew R. Cooperberg, MD, MPH,¶ Brandon A. Mahal, MD,# Payal D. Soni, MD,* Samuel Kaffenberger, MD,‖ Paul L. Nguyen, MD,# Neil Desai, MD,** Felix Y. Feng, MD,†† Zachary S. Zumsteg, MD,‡‡ and Daniel E. Spratt, MD*



Late meta-analysis using random effects model of late grade 3 gi and gu toxicity



Prostate SBRT has substantial prospective evidence supporting its use, with favorable tumor control, patient-reported quality of life, and levels of toxicity demonstrated. SBRT has sufficient evidence to be supported as a standard treatment option for localized prostate cancer while ongoing trials assess its potential superiority.

Estimated late grade 3 genitourinary and gastrointestinal toxicity rates were 2.0% (95% CI, 1.4%- 2.8%) and 1.1% (95% CI, 0.6%-2.0%)

Increasing dose of SBRT was associated with improved worse late grade 3 GU toxicity (P = .014).

Int J Radiation Oncol Biol Phys, Vol. 104, No. 4, pp. 778e789, 2019

A Younger Man With Localized Prostate Cancer Asks, "Which Type of Radiation Is Right for Me?"

Justin E. Bekelman, *Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

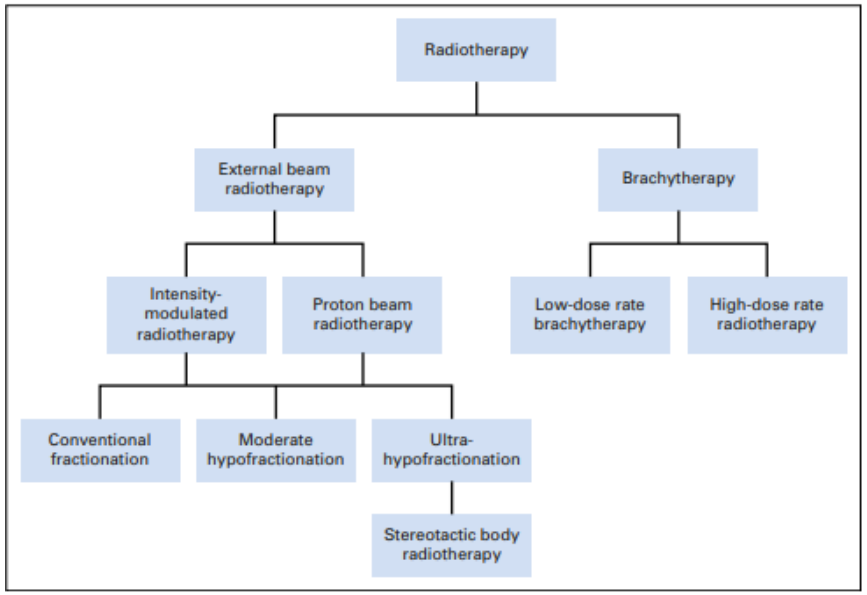


Table 1. Description of Radiotherapy Treatment Options

Radiotherapy Option	Description	Additional Information
IMRT	Typically multiple x-ray radiation beams tightly conform the high radiation dose region (the therapeutic dose region) to the prostate and seminal vesicles. IMRT deposits low and intermediate radiation dose to normal tissues in the pelvis.	IMRT can also be delivered using volumetric arc therapy, helical tomotherapy, or robotic arm approaches.
PBT	Typically two proton radiation beams tightly conform the high radiation dose region (the therapeutic dose region) to the prostate and seminal vesicles. PBT deposits low and intermediate radiation dose to normal tissues in the pelvis as the beams course through the hips to the prostate but reduces or eliminates low and intermediate radiation dose to normal tissues in the anterior and posterior pelvis.	PBT can be delivered using scattering or scanning technologies.
SBRT	A type of ultrafractionation that typically uses IMRT delivered with 5 large daily radiation doses.	Both IMRT and PBT can be delivered as conventional fractionation (daily treatment of up to 7.5-8.5 weeks), moderate hypofractionation (daily treatment of up to 4-5.5 weeks), or ultrafractionation (daily treatment of up to 2.5 weeks).
BRT	Radioactive pellets (low-dose rate) or temporary catheters (high-dose rate) that are implanted in the prostate based on image guidance to produce a tightly conformal high radiation dose region around the prostate. BRT eliminates the low or intermediate radiation dose to the pelvis characteristic of the external beam radiation techniques (PBT and IMRT).	

Abbreviations: BRT, brachytherapy; IMRT, intensity-modulated radiotherapy; PBT, proton beam radiotherapy; SBRT, stereotactic body radiotherapy.

Treatment comparison

Treatment option	5 yr. bDFS
• Prostatectomy	76-92%
• IMRT	69-89%
• LDR brachy	83-88%
• HDR brachy	90-92%
• SBRT*	93%

*current study

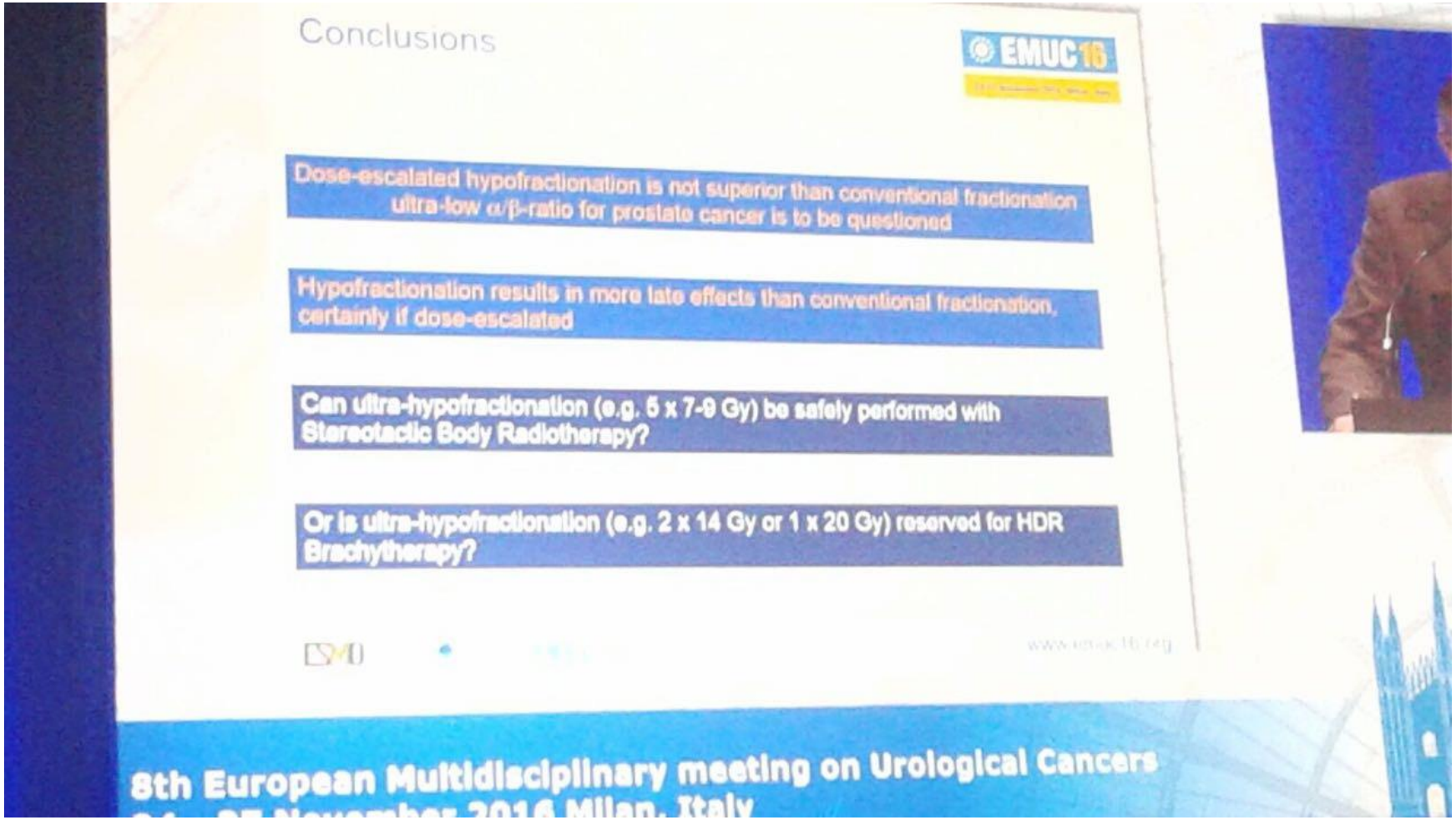
From Cyberknife User's Meeting. San Francisco 2011

Radiotherapy treatment options

VOLUME 36 · NUMBER 18 · JUNE 20, 2018

JOURNAL OF CLINICAL ONCOLOGY

Report of the 8 th European Myltidisciplinary Conference on Urological Cancer



Milano 24-27 Novembre 2016

Prostate cancer and hypofractionation: really a new standard of care?

Christian Carrie, Ronan Tanguy

No benefit either on relapse free survival or failure rate was observed and the difference is observed on the side effects rate. Despite the use of IMRT for 95% of cases and the use of fiducial markers for daily image guidance (not performed in the CHHiP trial), the cumulative incidence of grade 2 or worse is significantly higher in the hypofractionated arm as well as the overall grade 3 or worse genitourinary toxic side effects (19% *vs. 13%): conclusions of authors are as clear as those drawn by Dearnaley but opposite: hypofractionated radiotherapy cannot be regarded as a standard of care.*

Hypofractionated regimens for prostate cancer has never been demonstrated as superior as conventional arm and toxicity have always been the limiting factors

We could consider this regimen as an option: **perhaps** for small prostate volume, at least intermediate risk group in order to not expose low risk patient to exceed of toxicity and without intent to increase the biological efficiency but only with the aim to shorten the overall treatment time and decrease the overall cost of treatment.

Transl Androl Urol 2016;5(6):966-967

Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial

Lancet Oncol ;

Luca Incrocci, Ruud CWortel*, Wendimagegn Ghidey Alemayehu, Shafak Aluwini, Erik Schimmel, Stijn Krol, Peter-Paul van der Toorn, Hanja de Jager, Wilma Heemsbergen, Ben Heijmen, Floris Pos*

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

David Dearnaley, Isabel Syndikus, Helen Mossop, Vincent Khoo, Alison Birtle, David Bloomfield, John Graham, Peter Kirkbride, John Logue, Zafar Malik, Julian Money-Kyrle, Joe M O'Sullivan, Miguel Panades, Chris Parker, Helen Patterson, Christopher Scrase, John Staffurth, Andrew Stockdale, Jean Tremlett, Margaret Bidmead, Helen Mayles, Olivia Naismith, Chris South, Annie Gao, Clare Cruickshank, Shama Hassan, Julia Pugh, Clare Griffin, Emma Hall, on behalf of the CHHiP Investigators*

ORIGINAL REPORTS | Rapid Communication

Randomized Phase III Noninferiority Study Comparing Two Radiotherapy Fractionation Schedules in Patients With Low-Risk Prostate Cancer

W. Robert Lee , James J. Dignam, Mahul B. Amin, Deborah W. Bruner, Daniel Low, Gregory P. Swanson, Amit B. Shah, David P. D'Souza, Jeff M. Michalski, Ian S. Dayes, Samantha A. Seaward, William A. Hall, Paul L. Nguyen, Thomas M. Pisansky, Sergio L. Faria, Yuhchyau Chen, Bridget F. Koontz, Rebecca Paulus, Howard M. Sandler

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

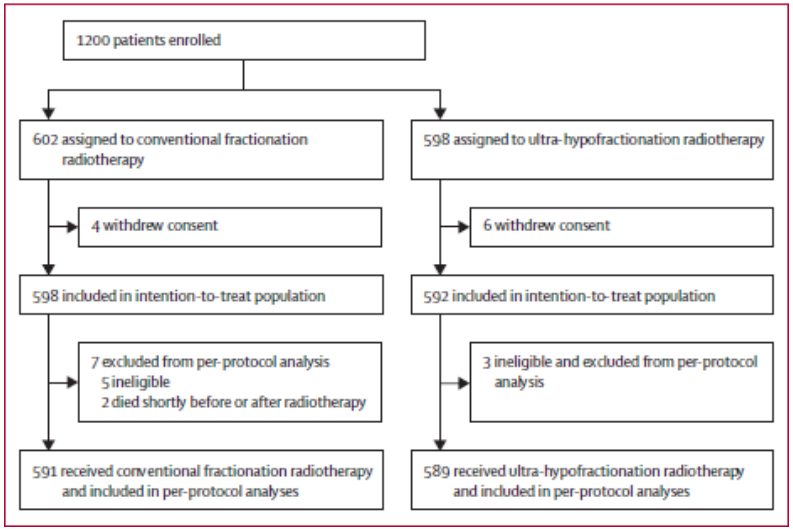
Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson

A open-label, randomised, phase 3 non-inferiority trial done in 12 centres in Sweden and Denmark, that recruited 1200 men up to 75 years of age with intermediate-to-high-risk prostate cancer and a WHO performance status between 0 and 2.

Patients were randomly assigned to ultra-hypofractionation (42·7 Gy in seven fractions, 3 days per week for 2·5 weeks)

Or

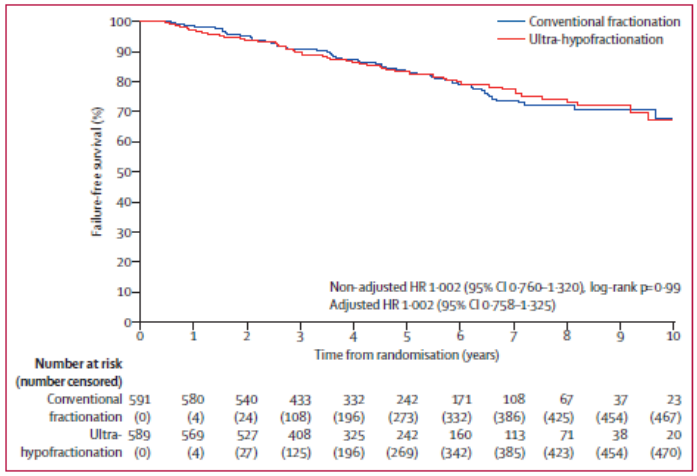
conventional fractionated radiotherapy (78·0 Gy in 39 fractions, 5 days per week for 8 weeks).



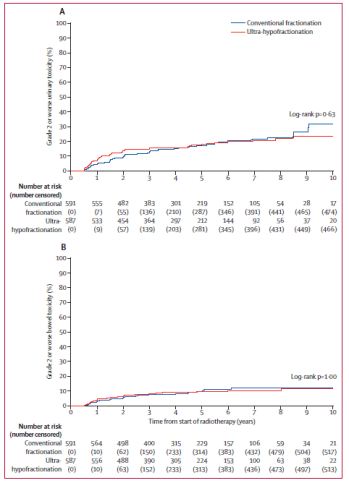
The lancet.com Vol 394 August 3, 2019

Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Anders Widmark, Adalsteinn Gunnlaugsson, Lars Beckman, Camilla Thellenberg-Karlsson, Morten Hoyer, Magnus Lagerlund, Jon Kindblom, Claes Ginman, Bengt Johansson, Kirsten Björnlinger, Mihajl Seke, Måns Agrup, Per Fransson, Björn Tavelin, David Norman, Björn Zackrisson, Harald Anderson, Elisabeth Kjellén, Lars Franzén, Per Nilsson



Failure-free survival



Cumulative incidence of physician-reported acute urinary and bowel toxicity of grade 2 or worse

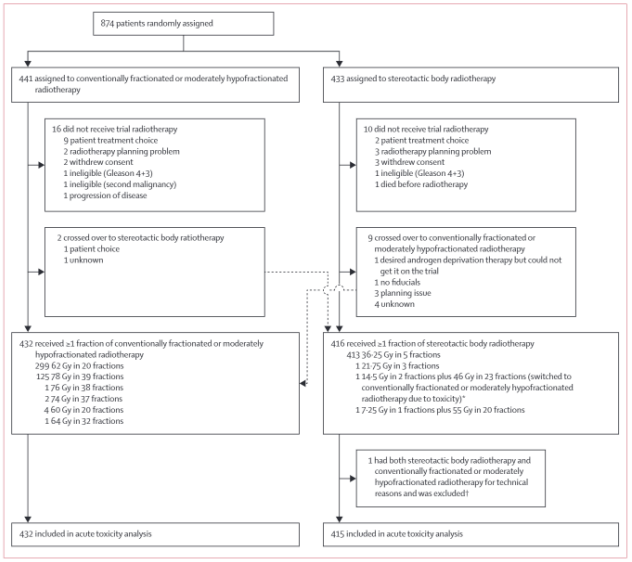
ultra-hypofractionation is non-inferior to standard fractionated radiotherapy in terms of failure-free survival.

Due to the short overall treatment time for ultra-hypofractionation, both physician-recorded and patient-reported acute toxicity was more intense compared with conventional fractionation.
However, late toxicity was similar in both treatment arms.

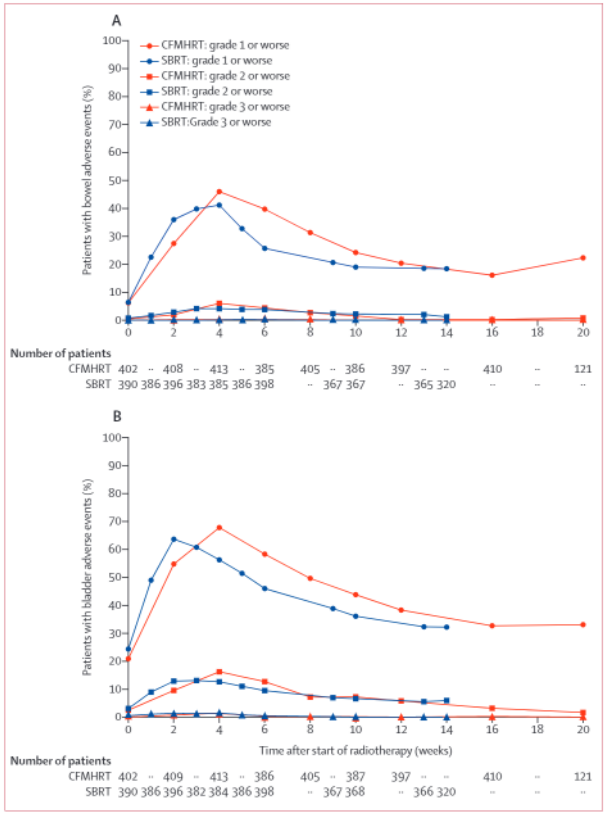
The lancet.com Vol 394 August 3, 2019

Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial

Douglas H Brand, Alison C Tree*, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu, Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, Philip Camilleri, Kiran Kancherla, John Frew, Andrew Chan, Ian S Dayes, Daniel Henderson, Stephanie Brown, Clare Cruickshank, Stephanie Burnett, Aileen Duffton, Clare Griffin, Victoria Hinder, Kirsty Morrison, Olivia Naismith, Emma Hall, Nicholas van As, on behalf of the PACE Trial Investigators*



Trial design



RTOG GI and GU acute toxicity

	Conventionally fractionated or moderately hypofractionated radiotherapy (n=432)				Stereotactic body radiotherapy (n=415)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	264 (61%)	49 (11%)	4 (1%)	0	219 (53%)	42 (10%)	1 (<1%)	0
Genitourinary	254 (59%)	111 (26%)	6 (1%)	1 (<1%)	236 (57%)	86 (21%)	8 (2%)	2 (<1%)

Data are n (%). No death due to adverse events were reported.

Table 2: **Radiation Therapy Oncology Group adverse events**

Similar acute toxicity for ultra-hypofractionation compared with standard fractionation

The lancet.com September 17, 2019

Stereotactic Body Radiotherapy for Primary Prostate Cancer

Gargi Kothari, MBBS,[1,2] Andrew Loblaw, MD,[3] Alison C. Tree, MD,[1] Nicholas J. van As, MD,[1] Drew Moghanaki, MD, MPH,[4] Simon S. Lo, MD,[5] Piet Ost, MD,[6] and Shankar Siva, PhD[2,7]

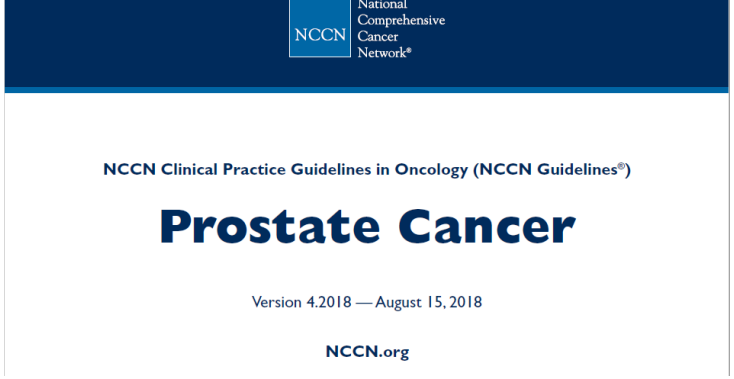
Stereotactic body **radiotherapy**, which is a form of extreme **hypofractionation**, delivered with high precision and conformality typically over 1 to 5 fractions, offers a more contemporary approach with several **advantages** including being non-invasive, cost-effective, convenient for **patients**, and potentially improving outcomes

What hypofractionated protocols should be used for prostate cancer ?

Which patients benefit from SBRT ?

Forthcoming randomized trials will allow us to better compare SBRT outcomes with alternative treatment modalities, as well as optimize radiotherapy dose, schedule, and volumes.

Technology in Cancer Research & Treatment Volume 17: 1-13 ª 2018



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2018
Prostate Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF RADIATION THERAPY

Definitive Radiation Therapy General Principles

- Highly conformal RT techniques should be used to treat localized prostate cancer.
- Photon or proton beam radiation are both effective at achieving highly conformal radiotherapy with acceptable and similar biochemical control and long-term side effect profiles (See Discussion).
- Brachytherapy boost, when added to EBRT plus ADT in men with NCCN intermediate and high/very high risk prostate cancer, has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials, but with higher toxicity.
- Ideally, the accuracy of treatment should be verified by daily prostate localization, with any of the following: techniques of IGRT using CT, ultrasound, implanted fiducials, or electromagnetic targeting/tracking. Endorectal balloons may be used to improve prostate immobilization. Perirectal spacer materials may be employed when the previously mentioned techniques are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic geometry or other patient related factors, such as medication usage and/or comorbid conditions. Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo perirectal spacer implantation.
- Various fractionation and dose regimens can be considered depending on the clinical scenario (See Table 1). Dose escalation has been proven to achieve the best biochemical control in men with intermediate and high risk disease.
- SBRT is acceptable in practices with appropriate technology, physics and clinical expertise.
- Biologically effective dose (BED) modeling with the linear-quadratic equation may not be accurate for extremely hypofractionated (SBRT/SABR) radiation.

Definitive Radiation Therapy by Risk Group

- Very low risk
  - Men with NCCN very low risk prostate cancer are encouraged to pursue active surveillance.
- Low Risk
  - Prophylactic lymph node radiation should NOT be performed routinely. ADT or antiandrogen therapy should NOT be used routinely
- Favorable Intermediate Risk
  - Prophylactic lymph node radiation is not performed routinely, and ADT or antiandrogen therapy is not used routinely. Prophylactic lymph node radiation and/or ADT use is reasonable if additional risk assessments suggest aggressive tumor behavior.
- Unfavorable Intermediate Risk
  - Prophylactic nodal radiation can be considered if additional risk assessments suggest aggressive tumor behavior. ADT should be used unless additional risk assessments suggest less-aggressive tumor behavior or if medically contraindicated. The duration of ADT can be reduced when combined with EBRT and brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT can be considered when delivering longer courses of EBRT would present medical or social hardship.
- High Risk
  - Prophylactic nodal radiation can be considered. ADT is required unless medically contraindicated. The duration of ADT may be reduced when EBRT is combined with brachytherapy. Brachytherapy combined with ADT (without EBRT), or SBRT combined with ADT, can be considered when delivering longer courses of EBRT would present a medical or

Clinical Oncology 26 (2014) 4–9

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Stereotactic Body Radiotherapy in Prostate Cancer: Is Rapidarc a Better Solution than Cyberknife?

N.D. MacDougall *†, C. Dean *†, R. Muirhead ‡

(a) Novalis Tx (b) TrueBeam (c) Elekta Axesse

(d) Elekta Synergy (e) Cyberknife (f) TomoTherapy

Cancer Radiother. 2019 Oct;23(6-7):651-657. doi: 10.1016/j.canrad.2019.06.009. Epub 2019 Aug 22.

[Stereotactic ablative body radiotherapy: Which machine for which therapeutic indication? A focus on prostate cancer].

[Article in French]

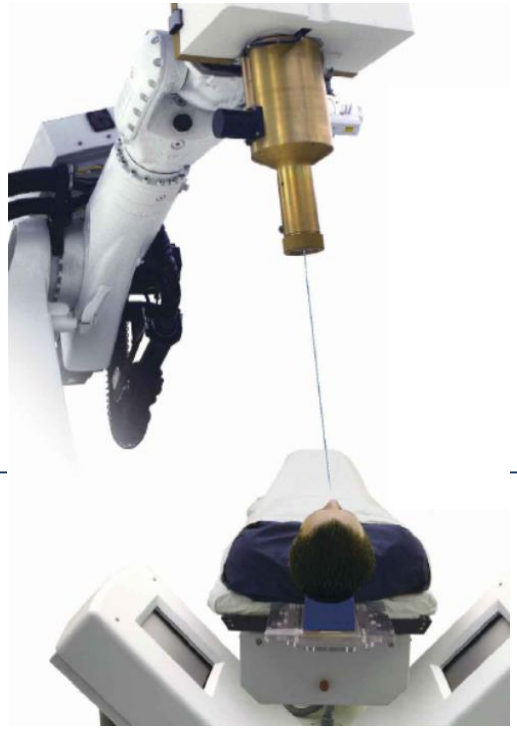
Lapierre A[1], Horn S[2], Créhange G[3], Enachescu C[2], Latorzeff I[4], Supiot S[5], Sargos P[6], Hennequin C[7], Chapet O[2].

STEREOTACTIC BODY RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER: INTERIM RESULTS OF A PROSPECTIVE PHASE II CLINICAL TRIAL

CHRISTOPHER R. KING, PH.D., M.D.,* JAMES D. BROOKS, M.D.,† HARCHARAN GILL, M.D.,† TODD PAWLICKI, PH.D.,* CRISTIAN COTRUTZ, PH.D.,* AND JOSEPH C. PRESTI, JR., M.D.†

Minimum PTV prescription dose coverage of 95%

(A 5 mm volume expansion in all direction, except posteriorly 3 mm,
With 1 cm extension in SV in intermedie and high risk Group)



G 3

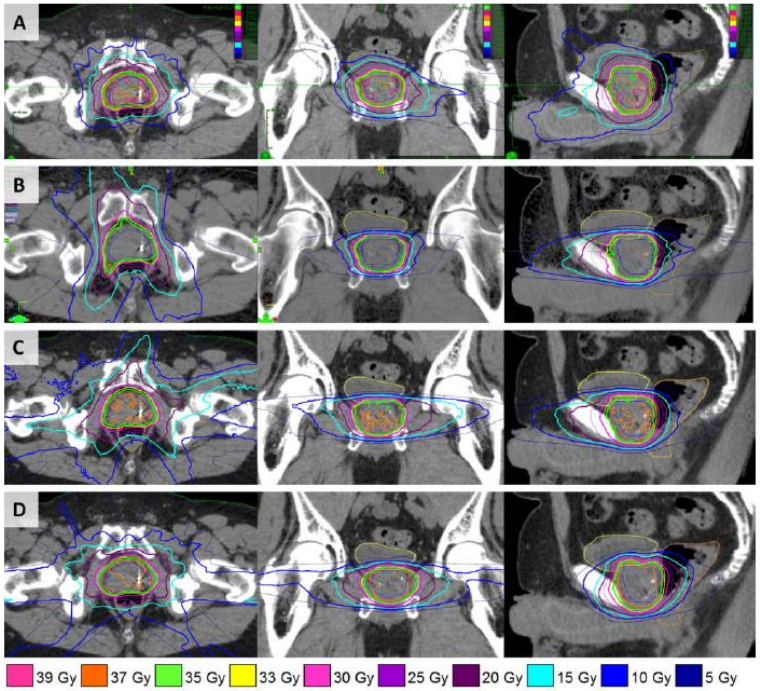
Set of Circular Collimators

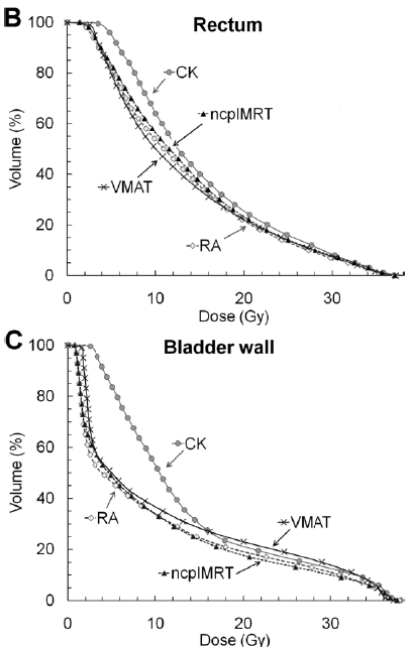
Int. J. Radiation Oncology Biol. Phys., pp. 1–6, 2008

Dosimetric Comparison and Evaluation of 4 Stereotactic Body Radiotherapy Techniques for the Treatment of Prostate Cancer

Jan Seppälä, PhD[1], Sami Suilamo, PhLic[2], Mikko Tenhunen, PhD[3], Liisa Sailas, MD[4], Heli Virsunen, MD[1], Erna Kaleva, PhD[3,5], and Jani Keyriläinen, PhD[2,3]

The dosimetric properties were relatively similar. The comparison of the delivery systems in clinical practice should focus on factors such as dose delivery accuracies, beam-on and delivery times, and the compensation of inter- and intrafractional positional errors.





The major differences between the techniques were mainly related to dose delivery characteristics of the CK system, resulting in higher maximum doses in the target and larger low dose volumes in the studied OARs

	Rectum	Bladder Wall	Penile Bulb	Femoral Heads	Normal Tissue
Minimum constraints	$D_{max} < 38$ Gy $D1cm^3 < 36$ Gy $D20cm^3 < 25$ Gy $V18Gy < 50\%$	$D_{max} < 38$ Gy $D5cm^3 < 37.5$ Gy $D15cm^3 < 18.3$ Gy	$D3cm^3 < 30$ Gy	$D10cm^3 < 30$ Gy	$CI \leq 1.25$
Ambition constraints	$D4cm^3 < 32$ Gy $D20cm^3 < 16$ Gy	$D2cm^3 < 36.25$ Gy $D4cm^3 < 32.62$ Gy $D10cm^3 < 18.12$ Gy	$D10cm^3 < 18$ Gy	$D4cm^3 < 18$ Gy	$CI \leq 1.15$

Technology in Cancer Research & Treatment
2017, Vol. 16(2) 238–245

EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer

Axel Heidenreich[a,,†], Patrick J. Bastian[b], Joaquim Bellmunt[c], Michel Bolla[d], Steven Joniau[e], Theodor van der Kwast[f], Malcolm Mason[g], Vsevolod Matveev[h], Thomas Wiegel[i], Filiberto Zattoni[j], Nicolas Mottet[k,‡]*

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016 Prostate Cancer

NCCN Guidelines Index
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Discussion

SYSTEMIC THERAPY FOR PROGRESSIVE CASTRATION-NAIVE DISEASE

M0 →
- Orchiectomy
- or
- LHRH agonist ± antiandrogen[l,v]
- or
- LHRH antagonist[l,v]
- or
- Observation[t]

M1 →
- Orchiectomy
- or
- LHRH agonist ± antiandrogen[l,v] ≥7 days to prevent testosterone flare
- or
- LHRH agonist + antiandrogen[l,v]
- or
- LHRH antagonist[l,v]
- or
- Continuous ADT[l,v] and docetaxel 75 mg/m^2 with or without prednisone for 6 cycles[w]

→ Progression[u,x]

Progression[u,x] → Studies negative for distant metastases → See Systemic Therapy For M0 CRPC (PROS-10)

Progression[u,x] → Studies positive for distant metastases → Consider biopsy if small cell suspected

- Not small cell → See Systemic Therapy For M1 CRPC (PROS-11)
- Small cell →
  - Cisplatin/etoposide[y,z]
  - or
  - Carboplatin/etoposide[y,z]
  - or
  - Docetaxel/carboplatin[y,z]
  - or
  - Clinical trial

In current practice systemic hormonal therapy (androgen deprivation, ADT) or a combination of ADT with chemotherapy is almost always the only approach proposed to the patient

EUROPEAN UROLOGY 6 5 (2 0 1 4) 4 6 7 – 4 7 9

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.

Department of Radiation Oncology, Marilia School of Medicine, São Paulo, Brazil

- There is now convincing evidence that biochemical control is improved with higher cumulative doses of radiation

- Significant differences in late rectal toxicity were seen between HDRT and CDRT groups

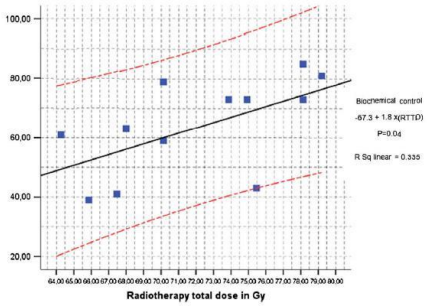

Table 2. Gastrointestinal and genitourinary late toxicity in the trials included in the meta-analysis

	GI *		GU*	
Study (reference)/toxicity criteria	High dose	Conventional	High dose	Conventional
Zietman *et al.* (23)/RTOG scale	43% G1	36% G1	43% G1	43% G1
	17% G2	8% G2	20% G2	18% G2
	1% G3	1% G3	1% G3	2% G3
Dutch (25)/RTOG/EORTC	32% G≥2	27% G≥2	39% G≥2	41% G≥2
	5% G≥3	4% G≥3	13% G≥3	12% G≥3
MRC RT01 (27)/RTOG scale	60% G≥1	58% G≥1	26% G≥1	22% G≥1
	33% G≥2	24% G≥2	11% G≥2	8% G≥2
	10% G≥3	6% G≥3	4% G≥3	2% G≥3
M. D. Anderson (22)/RTOG/EORTC	42% G1	66% G1	35% G1	21% G1
	28% G2	42% G2	7% G2	11% G2
	10% G3	3% G3	7% G3	5% G3
GETUG (28)/RTOG modified	57% G1	42% G1	65% G1	67% G1
	43% G2	28% G2	46% G2	48% G2
	3% G3	10% G3	11% G3	8% G3
Sathya *et al.* (24)/CTC scale	3.9% G3 or G4	1.9% G3 or G4	13.7% G3 or G4	3.8% G3 or G4
Shipley *et al.* (26)/RTOG scale	27% G≥2	9% G≥2	14% G≥2	6% G≥2

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0360-3016/08/$–see front matter

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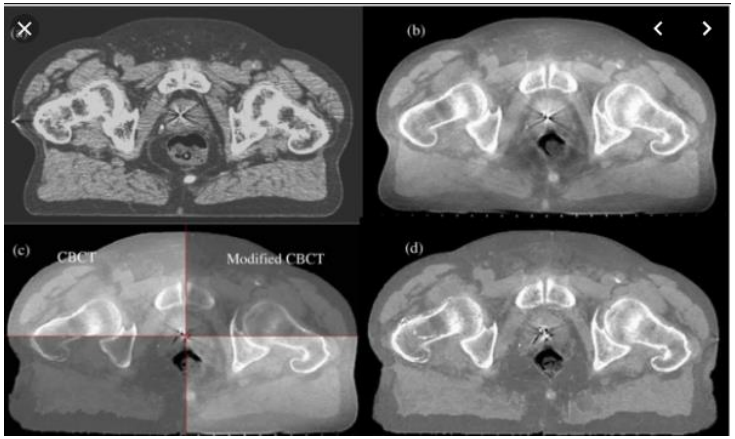
PHYSICS CONTRIBUTION

INTRAFRACTIONAL MOTION OF THE PROSTATE DURING HYPOFRACTIONATED RADIOTHERAPY

YAOQIN XIE, PH.D.,* DAVID DJAJAPUTRA, PH.D.,* CHRISTOPHER R. KING, PH.D., M.D.,* SABBIR HOSSAIN, PH.D.,† LIJUN MA, PH.D.,† AND LEI XING, PH.D.*



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Original Article

Intra-fraction Motion during Extreme Hypofractionated Radiotherapy of the Prostate using Pre- and Post-treatment Imaging☆

H. Quon *†, D.A. Loblaw *†, P.C.F. Cheung *†, L. Holden †, C. Tang *†, G. Pang *†, G. Morton *†, A. Mamedov †, A. Deabreu †

	Prostate Movement Threshold				
Sampling interval	1 mm	2 mm	3 mm	4 mm	5 mm
30	10.5%	4.4%	2.3%	1.9%	1.2%
60	19.0%	7.5%	4.2%	3.2%	1.9%
90	30.2%	10.8%	6.6%	3.5%	2.6%
120	39.3%	13.8%	8.4%	4.9%	2.8%

Margins calculated using Van Herk's formula

Dimension	Standard deviation of systematic errors (mm)	Standard deviation of random errors (mm)	Margin (mm)
Left–right	0.2	1.3	1.4
Superior–inferior	1.2	2.0	4.4
Anterior–posterior	1.4	2.4	5.2

When real-time imaging is not available, some authors advocate repeating an IGRT procedure every 5 minutes

The advantage of Cyberknife tracking sistem is the ability *to verify real time tumor position during treatment delivery and to adjust* beam delivery moving the robotic arm for optimal radiation therapy treatment outcomes

X-ray Sources

Linear Accelerator

ROBOTIC DELIVERY SYSTEM

IMAGING SYSTEM

Manipulator

TARGETING SOFTWARE

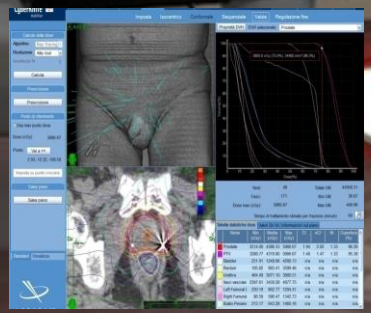


Image Detectors

System is tracking the target directly

J Korean Med Sci. 2018 Apr 2;33(14):e107
https://doi.org/10.3346/jkms.2018.33.e107
eISSN 1598-6357·pISSN 1011-8934

JKMS

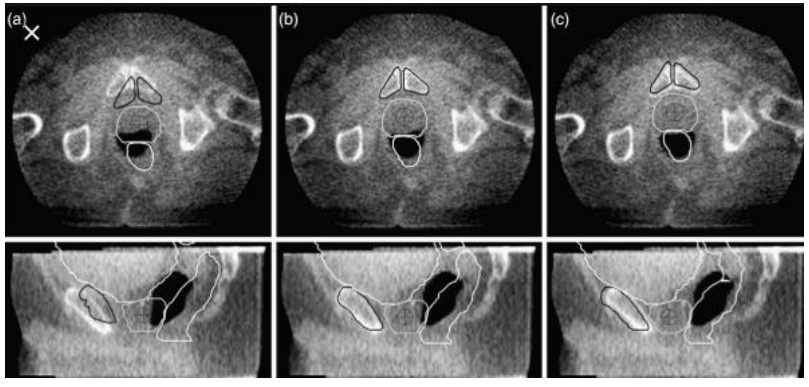
Original Article
Oncology & Hematology

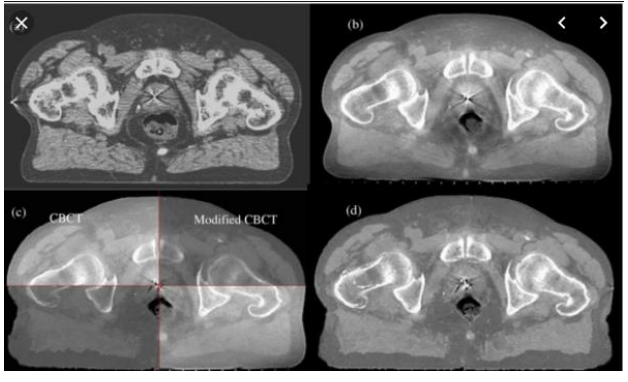
Check for updates

Analysis of Motion-dependent Clinical Outcome of Tumor Tracking Stereotactic Body Radiotherapy for Prostate Cancer

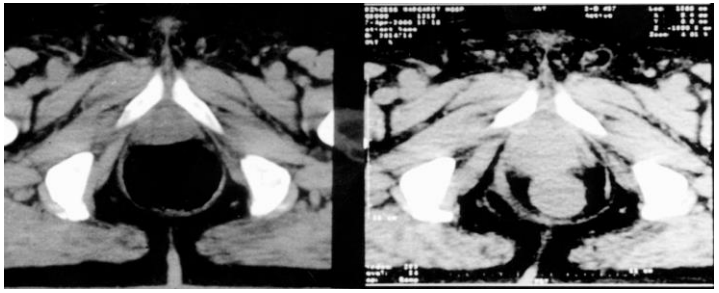
During Treatment with SBRT ,in addition to sophisticated treatment planning and treatment delivery systems, image guided radiation therapy (IGRT) is an essential component of ensuring accurate treatment

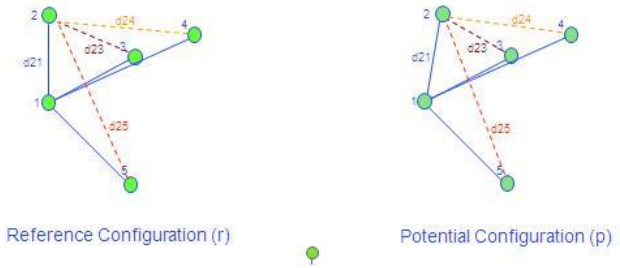
SBRT procedures require images be taken of the prostate prior to each treatment, which can performed using the gantry linear accelerator using a gantry-mounted cone beam computed tomography (CBCT) scan as on devices made by Varian, Elekta, or Novalis TxTM, CT on rails, or radiofrequency transponders, such as the Calypso® (Varian; CA, USA) real-time tracking device, that are additionally able to provide intrafraction image guidance





Cyberknife prostate tracking



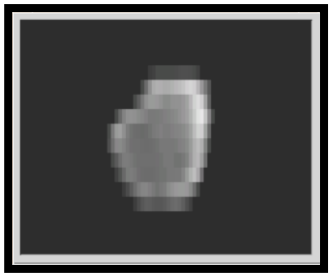


True-Beam

Rapid Arc

Advanced in Technology: IGRT - ready Machines

Cyber Knife



IGRT

VMAT

Helical Tomo therapy

Serial Tomo therapy