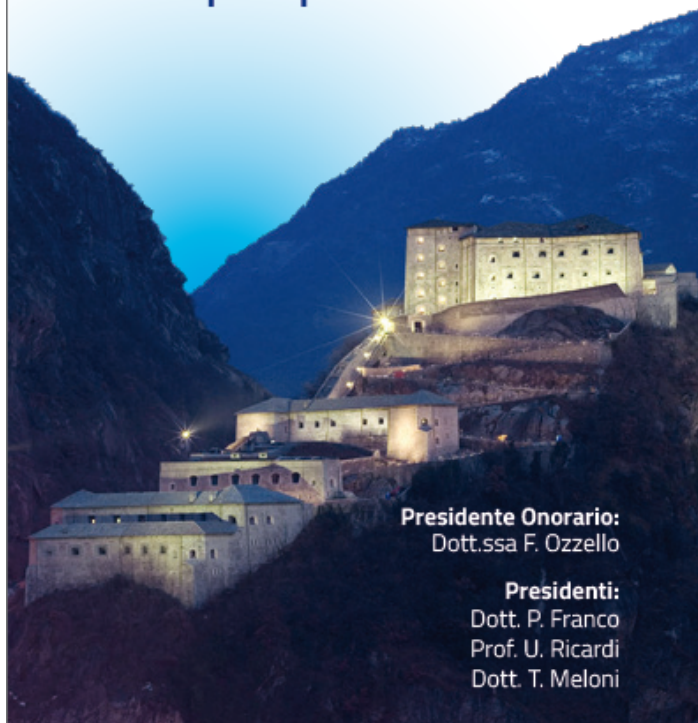




Associazione
Italiana
Radioterapia
Oncologica

IV CONGRESSO AIRO PIEMONTE/VALLE D'AOSTA/LIGURIA

Il carcinoma prostatico:
tra multidisciplinarietà e
nuove prospettive



Presidente Onorario:
Dott.ssa F. Ozzello

Presidenti:
Dott. P. Franco
Prof. U. Ricardi
Dott. T. Meloni

FORTE DI BARD • VALLE D'AOSTA
14 dicembre **2013**

Nuovi approcci radioterapici al carcinoma prostatico Radioterapia stereotassica

S.Barra

Radioterapia Infantile e tecniche speciali



IRCCS Azienda Ospedaliera Universitaria San Martino - IST



CLINICAL INVESTIGATION

Genitourinary Cancer

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

RAYMOND MIRALBELL, M.D.,*[†] STEPHEN A. ROBERTS, PH.D.,[‡] EDUARDO ZUBIZARRETA, M.D.,[§]
AND JOLYON H. HENDRY, PH.D.^{||}



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Revue générale

Le rapport alpha/bêta revisité à l'heure de l'hypofractionnement

Alpha/beta ratio revisited in the era of hypofractionation

C. Hennequin^{a,*}, B. Dubray^{c,d}



Based on the assumption that the fractionation sensitivity of prostate cancer cells is characterized by a low α/β ratio in the range of 0.8 to 2.2 Gy, delivering treatment fractions higher than the standard 2-Gy/fraction may be radiobiologically and therapeutically effective.



Urology. 1990 Aug;36(2):107-11.

Carcinoma of prostate treated by radical external beam radiotherapy using hypofractionation. Twenty-two years' experience (1962-1984).

Lloyd-Davies RW, Collins CD, Swan AV.

Department of Urology, St. Thomas' Hospital, London, England.

The survival of **209** patients with apparently localized carcinoma of the prostate treated by radical external beam radiotherapy is reported, noting the influence of age, stage of the disease at presentation, initial histology, previous surgery, and dose of radiotherapy given. From this it is seen that the development of a six-fraction (**36 Gy/ 6Gy/6 fx**) regimen given over a period of three weeks leads to excellent results whether assessed as a local response or by survival curves and to the economical use of scarce resources, but, even more important, is less wearing for patients than conventional daily fractionation and with no major early or late morbidity recorded up to October 1986.

Analysis	LE	n.	Risk group	median initialPSA	Protocol
----------	----	----	------------	-------------------	----------

Choi 2007	P	2b	44	Low Intermediate High	-	32 (4 x 8) 36 (4 x 9)	
Fuller 2008	P	2b	10	<p>Classificazione delle evidenze</p> <p>Ia Evidenze da meta-analisi o trias controllati e randomizzati</p> <p>Ib Evidenze da almeno un trial controllato e randomizzato</p> <p>Ila Evidenze da almeno uno studio controllo non randomizzato</p> <p>Ilb Evidenze da almeno uno studio di altro disegno qualitativo sperimentale</p> <p>III evidenze da uno studio descrittivo, come studio comparativo, studi di correlazione e studi caso controllo</p> <p>IV evidenze prodotte da report di comitati di esperti o opinioni od esperienze di cliniche autorevoli</p> <p>Grading delle raccomandazioni</p> <p>A basate su evidenze di categoria I</p> <p>B basate su evidenze di categoria II, o estrapolate da evidenze di categoria I</p> <p>C basate su evidenze di categoria III o estrapolate da evidenze di categoria I o II</p> <p>D basate su evidenze di categoria I, II o III</p>			
King 2009	P	2b	41				
Friedland 2009	P	2b	112				
Meier 2009	P	2b	29				
Aluwini 2010	P	2b	10				
Katz 2013	P	2b	304				5)
Bolzicco 2013	P	2b	100				
Mc Bride 2011	P	2b	45				(7.5)
Freeman 2011	P	2b	41				
Katz 2011	P	1b	82				5)
Kang 2011	R	3	44				(4 X
King 2012	P	2b	67				Low
Chen 2013	P		100	Low, Intermediate, High	6.9	35 (5 x 7) 36.25 (5 x 7.25)	
Alongi 2013	P		40	Low, Intermediate	6.25	35(5x7)	



CLINICAL INVESTIGATION

Prostate

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.‡

*Sections of Radiation Oncology and †Urology, Virginia Mason Medical Center, Seattle, WA; ‡Emeritus, Department of Human Oncology, Medical School, University of Wisconsin, Madison, WI

Int. J. Radiation Oncology Biol. Phys., Vol. 67, No. 4, pp. 1099–1105, 2007



A 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 (α/β ratio of 1.5 Gy). noncoplanar conformal fields and daily stereotactic localization of implanted fiducials were used for Treatment. **40 patients** **The median follow-up is 41 months** (range, 21–60 months). Acute Toxicity: Grade 1–2 was 48.5% (GU) and 39% (GI); Grade 3 1/40 GU toxicity. Late Grade 1–2 toxicity was 45% (GU) and 37% (GI). No late Grade 3 or higher toxicity was reported. **Median time to PSA nadir was 18 months** with the majority of nadirs **less than 1.0 ng/mL**. The actuarial 48-month biochemical freedom from relapse is **70%**





CLINICAL INVESTIGATION

Prostate

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.†

Departments of *Radiation Oncology and †Urology, Division of Urologic Oncology,
Stanford University School of Medicine, Stanford, CA

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 4, pp. 1043–1048, 2009

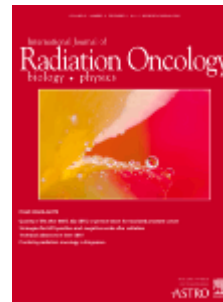


41 low-risk prostate cancer patients received **36.25 Gy** in five fractions of **7.25 Gy** with image-guided SBRT alone using the **CyberKnife**. The median follow-up was 33 months. There were no RTOG Grade 4 acute or late rectal/urinary complications. There were 2 patients with RTOG Grade 3 late urinary toxicity and none with RTOG Grade 3 rectal complications. **A reduced rate of severe rectal toxicities was observed with every-other-day vs. 5 consecutive days treatment regimen (0% vs. 38%, p = 0.0035)**. A benign PSA bounce (median, 0.4 ng/mL) was observed in 12 patients (29%) occurring at 18 months (median) after treatment. Of 32 patients with 12 months minimum follow-up, 25 patients (78%) achieved a **PSA nadir < 0.4 ng/ml**. A PSA decline to progressively lower nadirs up to 3 years after treatment was observed.



CLINICAL INVESTIGATION

Prostate



**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.,†
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Departments of *Radiation Oncology and †Urology, Division of Urologic Oncology,
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Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 4, pp. 1043–1048, 2009

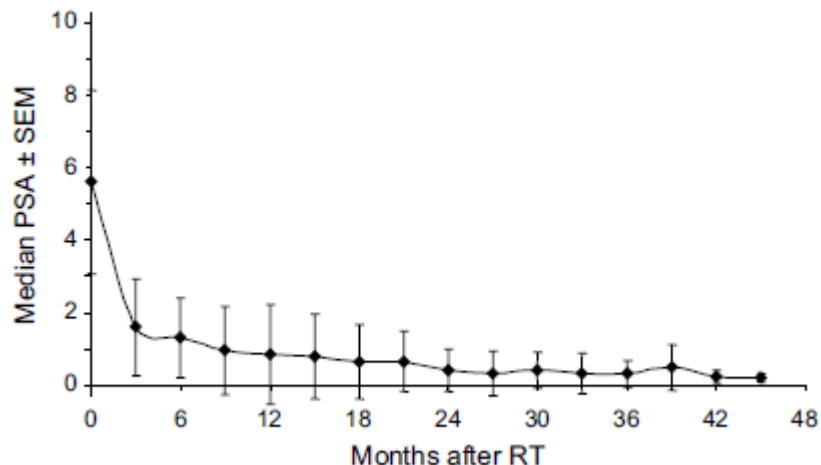


Table 1. Proportion of patients achieving a given PSA nadir threshold as a function of time after SBRT

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%



Chen et al. *Radiation Oncology* 2013, 8:58
<http://www.ro-journal.com/content/8/1/58>



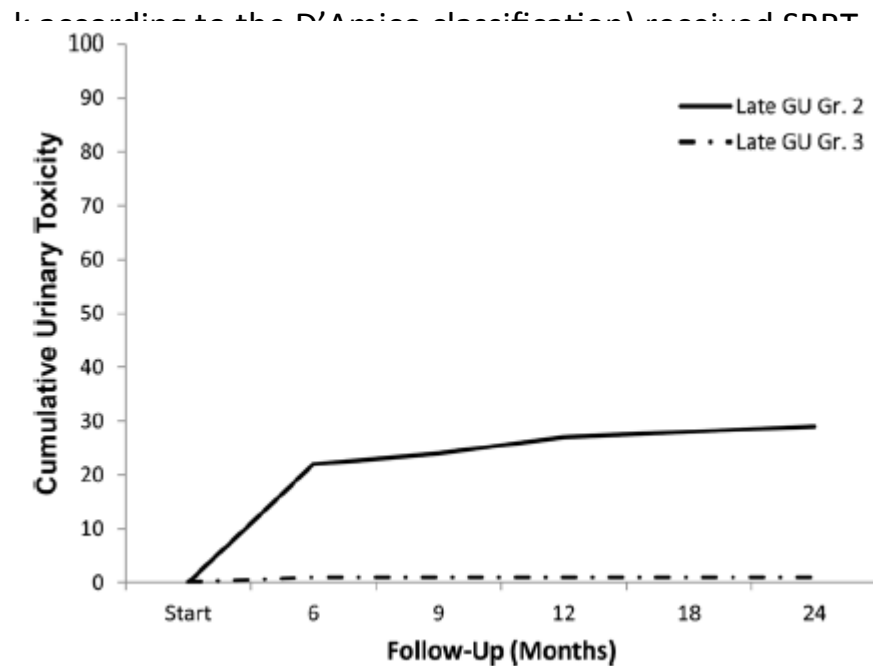
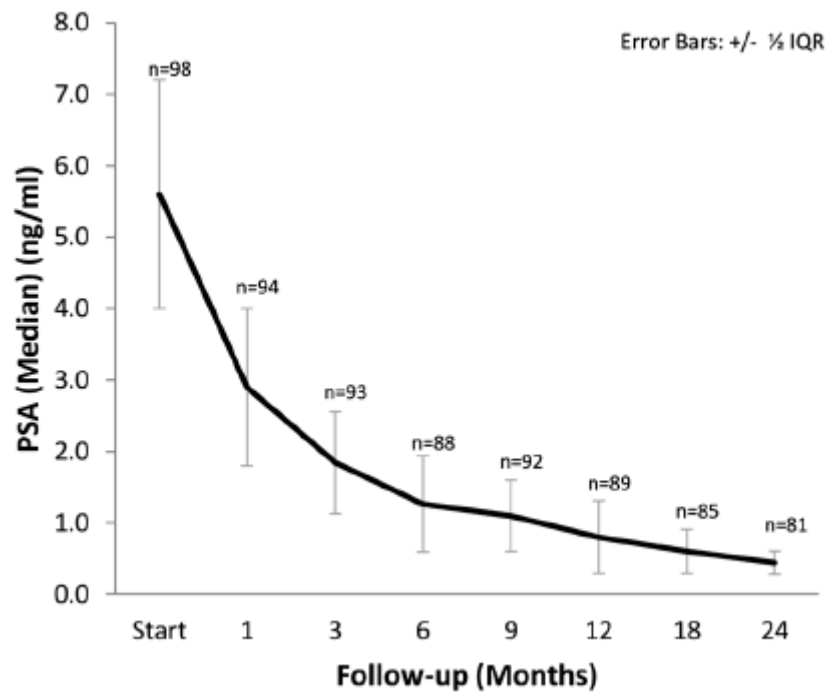
RESEARCH

Open Access

Stereotactic Body Radiation Therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience

Leonard N Chen^{1†}, Simeng Suy^{1†}, Sunghae Uhm¹, Eric K Oermann¹, Andrew W Ju¹, Viola Chen¹, Heather N Hanscom¹, Sarah Laing¹, Joy S Kim¹, Siyuan Lei¹, Gerald P Batipps², Keith Kowalczyk², Gaurav Bandi², John Pahira², Kevin G McGeagh², Brian T Collins¹, Pranay Krishnan³, Nancy A Dawson⁴, Kathryn L Taylor⁴, Anatoly Dritschilo¹, John H Lynch² and Sean P Collins^{1*}

¹Department of Radiation Medicine, Georgetown University Hospital





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



RESEARCH

Open Access

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

Istituto Clinico Humanitas Cancer Center, Radiotherapy and Radiosurgery,

40 patients (26/40 were low-risk and 14/40 were intermediate risk). The schedule was **35 Gy in 5** alternative days. SBRT was delivered with RapidArc VMAT, **Median follow-up was 11 months** (range: 5–16). Acute Toxicities were as follow: Rectum **G0**: 30/40 cases (75%); **G1**: 6/40 (15%); **G2**: 4/40 (10%). Genito-urinary: **G0**: 16/40 (40%); **G1**: 8/40 (20%); **G2**: 16/34 (40%). In two G2 urinary retention cases, intermittent catheter was needed. No acute G3 or greater toxicity was found.



Bolzico et al. *BMC Urology* 2013, 13:49
http://www.biomedcentral.com/1471-2490/13/49



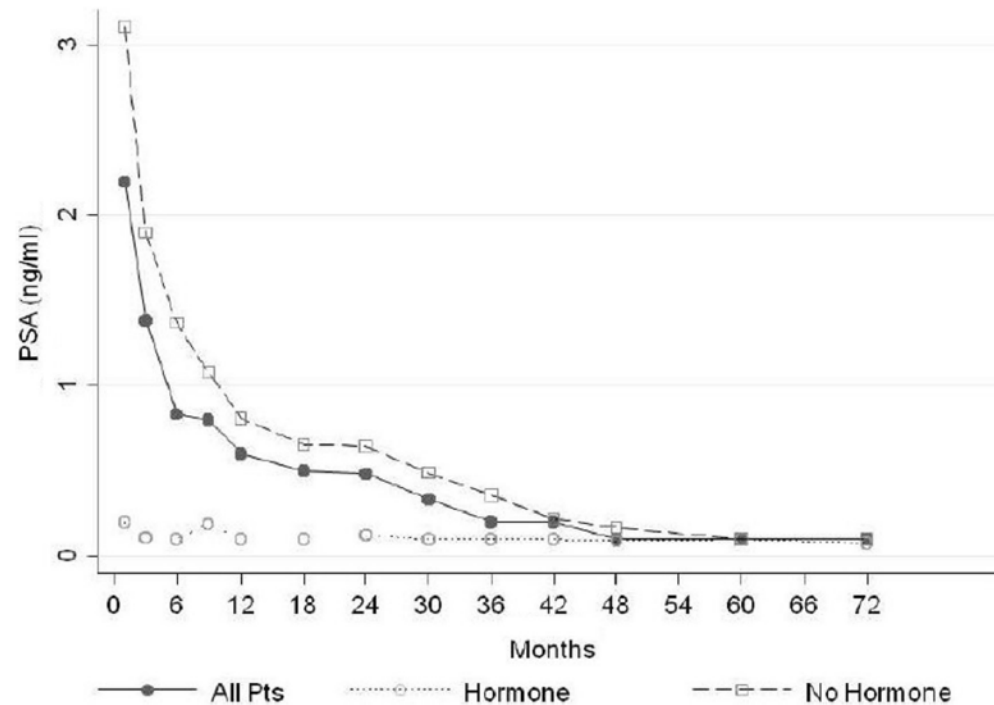
RESEARCH ARTICLE

Open Access

A single-center study of 100 consecutive patients with localized prostate cancer treated with stereotactic body radiotherapy

Giampaolo Bolzico^{1†}, Maria Silvia Favretto^{1†}, Ninfa Satariano^{3†}, Enrico Scremin^{2†}, Carmelo Tambone^{2†} and Andrea Tasca^{2†}

100 patients in five months respectively 1, 2, and 1 gast



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Katz et al. *Radiation Oncology* 2013, **8**:118
<http://www.ro-journal.com/content/8/1/118>

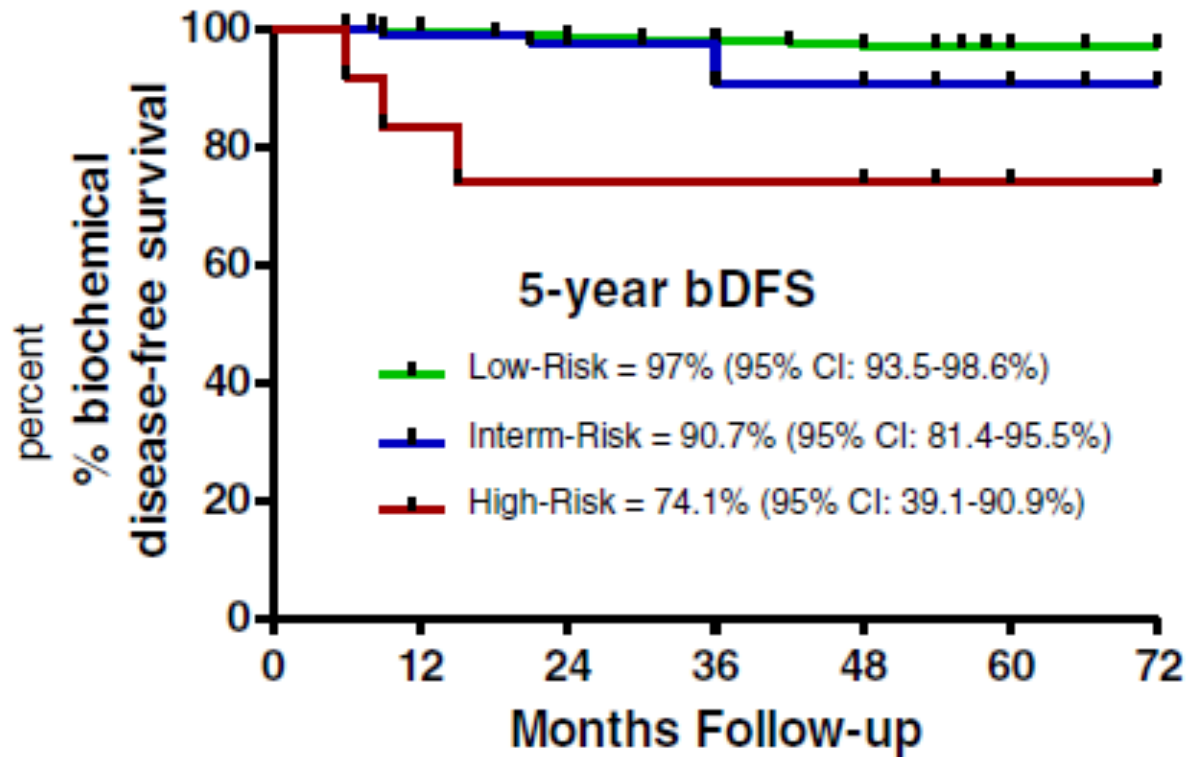


RESEARCH

Open Access

Stereotactic body radiotherapy for localized prostate cancer: disease control and quality of life

BIOCHEMICAL CONTROL



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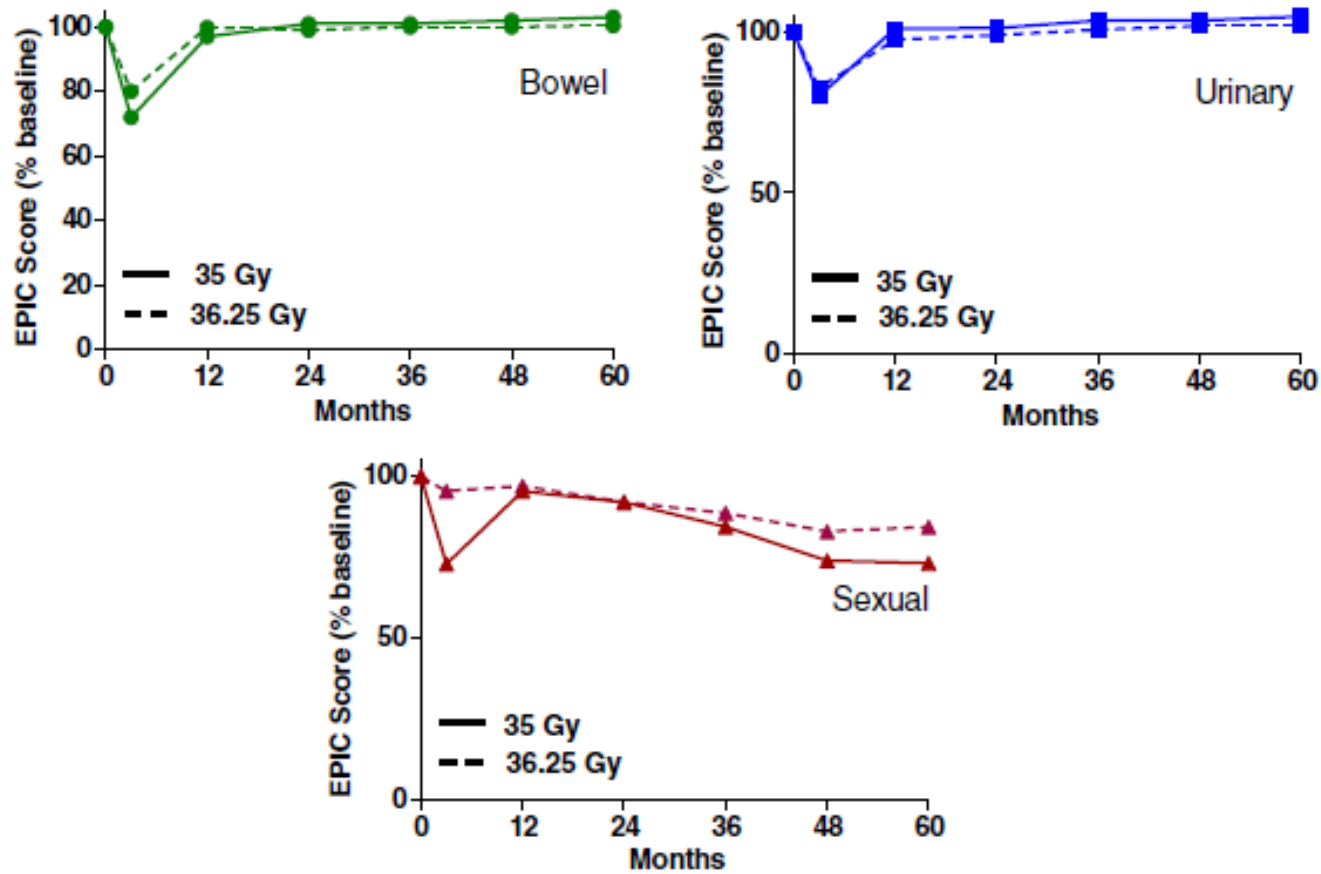
10

RESEARCH

Open Access

Stereotactic body radiotherapy for localized

EPIC QUALITY of LIFE





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Radiotherapy and Oncology xxx (2013) xxx–xxx



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original article

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

5-year Kaplan–Meier PSA relapse-free survival rates as a function of risk group, use of ADT and dose.

	5-yr bRFS	<i>p</i> -Value
Low Risk	95.2%	*
Intermediate Risk	84.1%	<i>p</i> = 0.03
High Risk	81.2%	<i>p</i> < 0.0001
ADT use	92.6%	*
No ADT	91.3%	<i>p</i> = 0.71
Dose 35 Gy	92.5%	*
Dose 36.25 Gy	90.7%	<i>p</i> = 0.08
Dose 38–40 G y	95.8%	<i>p</i> = 0.83

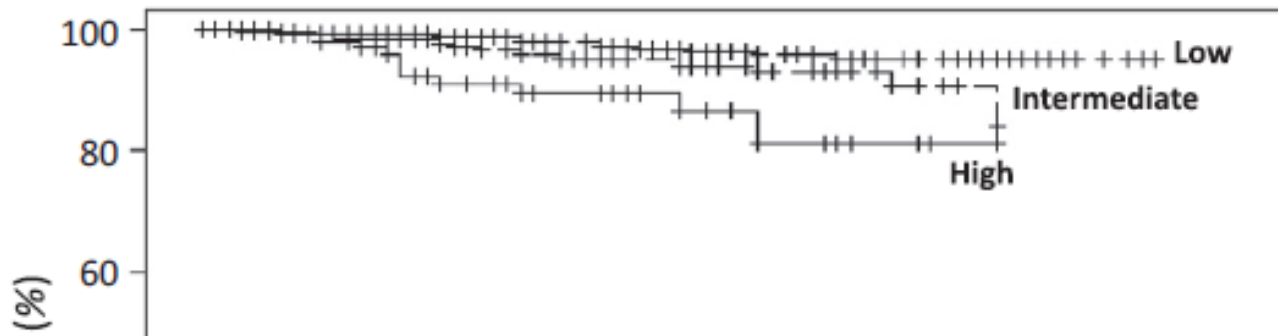
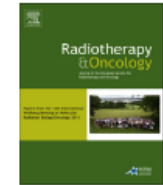


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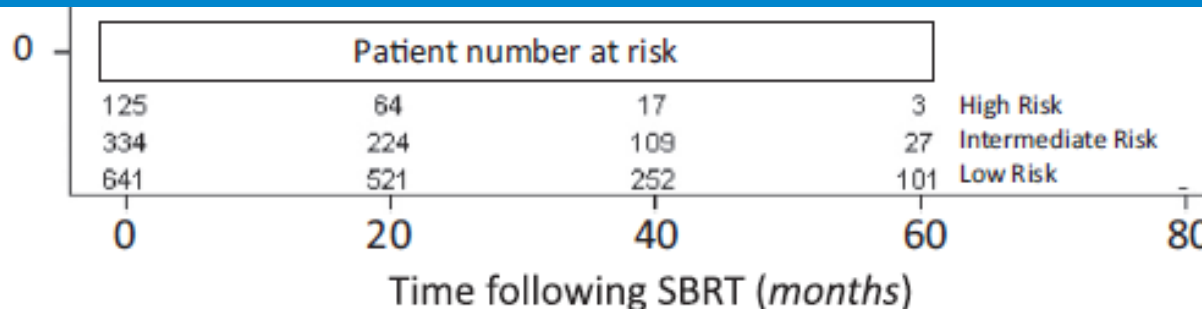
Radiotherapy and Oncology xxx (2013) xxx–xxx



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Radiotherapy and Oncology
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The 5-year biochemical relapse free survival (bRFS) rate was 95% for GS ≤6
 83% for GS =7 p = 0.001
 78% for GS ≥8





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Radiotherapy and Oncology xxx (2013) xxx–xxx



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Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com



Original article

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

^a Department of Radiation Oncology, UCLA, Los Angeles, CA; ^b Naples Radiation Oncology, Naples, Florida; ^c Department of Radiation Oncology, Beth Israel Deaconess, Boston, MA; ^d Radiosurgery Medical Group, San Diego, CA, United States; ^e Division of Radiation Oncology, San Bortolo Hospital, Vicenza, Italy; ^f Department of Radiation Oncology, Georgetown University, Washington DC; ^g Department of Radiation Oncology, Swedish Medical Center, Seattle, WA; and ^h Flushing Radiation Oncology, Flushing, NY, United States

Conclusion: 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



	Acute		Late		
	rectal	urinary	rectal	urinary	erectile dysfunction
Choi 2007	32% G1/2	39% G1/2	0%	0%	
Fuller. 2008	60% G1/2	60% G1/2			
King 2009	48% G1/2 + 5% G3	58% G1/2 + 16% G3	48% G1/2	65% G1/2 + 5% G3	
Friedland 2009	<i>Rectal urgency</i>	<i>Dysuria</i>	1% G3	0%	18%
Aluwini. 2010	20% G1/2 + 10% G3	50% G1			
Katz 2010	80% G1/2	76% G1/2	9% G1/2	9% G1/2, + 0.5% G3	13%
Bolzicco 2013	48.8% G1/2	46.6% G1/2	2.2% G2	8.8% G1/2 + 2.2% G3	
Mc Bride. 2011	38% G1/2	78% G1/2	14% G1/2 + 5% G3	34% G1/2	
Freeman 2011			15.5% G1/2	32% G1/2 + 2.5% G3	
Katz. 2011			11%	12% G1/2	
Kang 2011	9% G2	13.5% G2	11.4% G2	7% G2	
King. 2012			16% G1/2	28% G1/2 + 3.5% G3	

Endpoints .

1. Tossicità acuta e tardiva (Scala CTCAE- RTOG/EORTC)
2. Valutazione della sopravvivenza libera da recidiva biochimica e/o clinica
3. Valutazione della tossicità soggettiva urinaria e rettale con questionario EPIC

PROM

Biologic Equivalent Dose (BED)

ST- Genova

$$BED = D [1+ d / (\alpha/\beta)]$$

Frazionamento D/d/n.fx	BED con $\alpha/\beta=4$ Gy per tessuti a risposta tardiva**	BED con $\alpha/\beta=3$ Gy per tessuti a risposta tardiva	BED con $\alpha/\beta=1.5$ Gy per carcinomi a risposta tardiva(prostata)	BED con $\alpha/\beta=10$ Gy per tessuti a risposta acuta(mucose)
76 Gy/2Gy/38 fx	114	126	177	91.2
78 Gy/2/40 fx	117	130	182	93.6
70.2/2.6/27 fx *	115	131	191	88.45
40 Gy/8Gy/5 fx	120	146	253	72
38.5 Gy/7.7Gy/5 fx	112	137	236	68,1
37.5 Gy/7.5/5fx	107	131	225	65.6
36.25Gy/7.25Gy/5fx (presente trial)	102	124	211	62.53



I volumi di interesse sono così definiti:
GTV(gross tumor volume) : prostata
CTV (clinical tumor volume) : espansione di 3 mm del GTV
anteriormente, lateralmente e cranio-caudalmente e un 1 mm
di espansione posteriormente.
PTV (planning tumor volume) : espansione di 2 mm del CTV

Retto: $V_{36.25 \text{ Gy}} < 1\text{cc}$, $V_{36.25 \text{ Gy}}(100\%) < 5\%$, $V_{32.6 \text{ Gy}}(90\%) < 10\%$, $V_{29 \text{ Gy}}(80\%) < 20\%$, $V_{18.12 \text{ Gy}}(50\%) < 50\%$

Vescica: $V_{36 \text{ Gy}} \leq 1\text{cc}$, $V_{18.12 \text{ Gy}}(50\%) < 40\%$, $V_{36.25 \text{ Gy}}(100\%) \leq 10\%$

Bulbo penieno: $V_{29.5 \text{ Gy}} < 50\%$

Anse intestinali fuori dal PTV $\leq 10\%$ della dose di prescrizione

Teste femorali $V_{14.5 \text{ Gy}}(40\%) \leq 5\%$



Contouring ROIs Plan Settings Beam Angles Optimization Fractionation
 Contouring ROIs Plan Settings Beam Angles Optimization Fractionation

Presets ▾
 Lines
 Gy %

38.8 Gy
 36.3 Gy
 34.4 Gy
 32.6 Gy
 29.0 Gy
 25.4 Gy
 18.1 Gy
 10.9 Gy
 Edit

Target

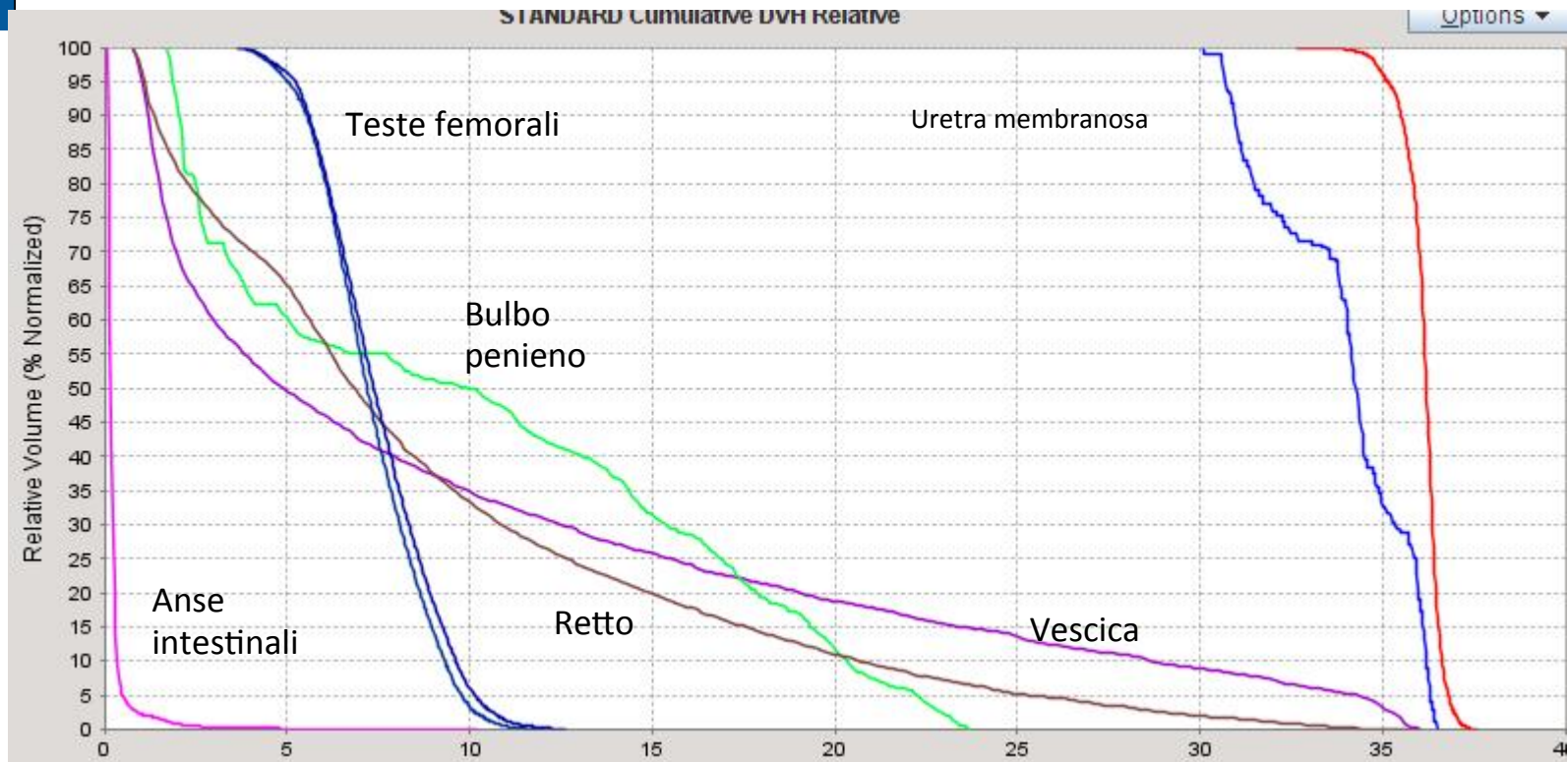
Name		
PTV	<input checked="" type="checkbox"/>	■
Ptv+vesc	<input type="checkbox"/>	■
PTV+Retto	<input type="checkbox"/>	■

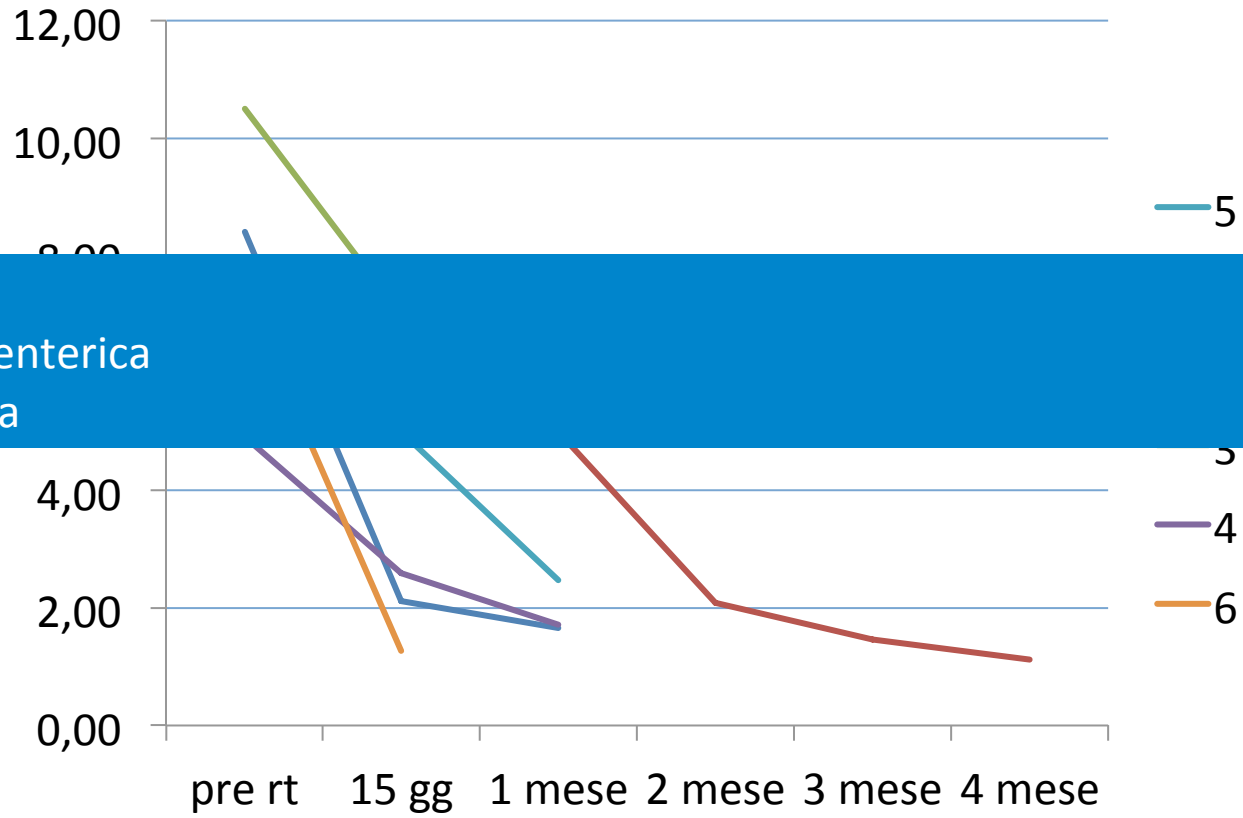
Regions at Risk

Name		
Bladder, NOS	<input checked="" type="checkbox"/>	■
Body	<input type="checkbox"/>	■
Bowel	<input checked="" type="checkbox"/>	■
Bulbo penieno	<input type="checkbox"/>	■
Rectum, NOS	<input checked="" type="checkbox"/>	■
Ring_1	<input type="checkbox"/>	■
V.S.	<input type="checkbox"/>	■
prostata	<input type="checkbox"/>	■
ring_2	<input type="checkbox"/>	■
testa femore dx	<input checked="" type="checkbox"/>	■
testa femore sn	<input checked="" type="checkbox"/>	■
uretra membrano	<input type="checkbox"/>	■

Coronal
 Options ▾

GH
 R L
 F
 122
 133
 HFS HFS HFS





Tossicità
Acuta gastroenterica
Acuta urinaria



Conclusioni



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Semin Radiat Oncol24:35-42 2014

Seminars in
**RADIATION
ONCOLOGY**

Comparative Effectiveness Research in Radiation Oncology: Stereotactic Radiosurgery, Hypofractionation, and Brachytherapy

Sanjay Aneja, MD,^{*,†,‡} and James B. Yu, MD^{*,†,‡}

**extreme hypofractionation is safe and effective,
RS is delivered with fewer visits
there is strong evidence it is less expensive than IMRT for prostate cancer**

**follow-up for most studies has been relatively short
cost-effectiveness RS/IMRT
Randomized clinical trials
long-term follow-up is needed to evaluate biological endpoints such: disease-free survival,
metastasis-free and overall survival.**



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ONCOLOGY GROUP

A Randomized Phase II Trial of Hypofractionated Radiotherapy for Favorable Risk Prostate Cancer



S
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Gy over two s)*
4.3 Gy over days)*

- DISEASE**
- Histolo
 - History
 - registrat
 - Histological evaluation of prostate biopsy with assignment of a Gleason score to the biopsy material; .Gleason scores 2-6 within 180 days of randomization
 - Clinical stage T1-2a (AJCC 7th edition) within 90 days of randomization
 - Prostate-specific antigen (PSA) < 10 ng/mL within 60 days prior to registration;
 - PSA should not be obtained within 10 days after prostate biopsy
 - No evidence of distant metastases
 - No regional lymph node involvement
- domization
prior to



	lat	long	vert	roll	lat	long	vert	roll
1	0.2	0.7	8.7	-1.1	0.1	0.7	9.7	1.1
2	-3.3	0.3	11.2	0.7	-5	2.1	9.3	1
3	-0.7	-3.7	10.5	1	-2.7	-4.7	10.5	1
4	1.5	4.2	8.7	0.2	1.5	4.7	7.4	0.2
5	3.3	2.3	8.7	0.7	3.5	2.3	8.7	0.7



CLINICAL INVESTIGATION

Prostate

HYPOFRACTIONATED CONFORMAL RADIOTHERAPY IN CARCINOMA OF THE PROSTATE: FIVE-YEAR OUTCOME ANALYSIS

JACQUELINE E. LIVSEY, F.R.C.R.,* RICHARD A. COWAN, F.R.C.R.,* JAMES P. WYLIE, F.R.C.R.,*
RIC SWINDELL, M.Sc.,† GRAHAM READ, F.R.C.R.,‡ VINCENT S. KHOO, F.R.A.C.R.,§ AND
JOHN P. LOGUE, F.R.C.R.*

Departments of *Clinical Oncology and †Medical Statistics, and ‡Academic Department of Radiation Oncology, Christie Hospital NHS Trust, Manchester, England; †Department of Clinical Oncology, Royal Preston Hospital, Preston, England

Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 5, pp. 1254–1259, 2003



The outcome for **705** men with T1–T4, N0, M0

Radiotherapy was delivered to a planning target volume (prostate plus all/base of the seminal vesicles dependent on risk criteria with a 1-cm margin) with a 4-field conformal technique to a dose of **50 Gy /3.3 Gy/ 16** daily fractions over 22 days.

When patients were grouped into good (*n* 181), intermediate (*n* 247), or poor (*n* 277) prognostic groups, the bNED was, respectively, **82%, 56%, and 39%**. Radiation Therapy Oncology Group **Grade >2** bowel toxicity was **5%** and bladder **9%**.