Ipofrazionamento spinto: l'esperienza con CyberKnife

Cristina Baiocchi

U.O. di Radioterapia Oncologica
Ospedale San Bortolo ULSS 6, Vicenza

CyberKnife®

-Linac compatto 6MV montato su robot a 6 DOF

-Collimatore IRIS

-800 MU/MIN

-Sistema stereotassico guidato da immagini intrafrazione

-Geometria non complanare

-Operatività non isocentrica

-Radiochirurgia intra- ed extra- cranica

-Tracking dei movimenti

Accuray Incorporated, Sunnyvale,CA,USA

Confronto con altri sistemi IGRT

Dalla letteratura alcuni dati su errori geometrici su fantocci

ExacTrac	*errore medio residuo totale dopo fusione <= 1,5 mm +/- 0,7 mm* *(Hacker F. et all MP 2006 33(6)): 2066* *altri lavori 0.7 mm +/- 0,5 mm IJROBF 2006,66:S244* *~ 1mm*
Cyberknife	*Errore max 0.53 ± 0.16 mm Christos Antypas et al 2008 Phys. Med. Biol. 53 4697-4718* *- 0.80 ± 0.05 mm P.Desai et all - Med. Phys. Volume 33, Issue 6, pp. 2082-2082 (June 2006)*
ConeBeam	Errore coincidenza MV/KV ~0,25 mm; accettato +/-2mm J. P. Bissonet et al QA for IG-Tecn. AAPM Org.
Tomotherapy	*± 1.0 mm Phys. Med. Biol. 49 (2004) 2933–2953*

Tutte le apparecchiature ~ 1mm

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Stanford University School of Medicine
300 Pasteur Drive
Stanford, CA 94305, USA

CyberKnife Radiotherapy For Localized Prostate Cancer: Rationale And Technical Feasibility

www.tcrt.org

Christopher R. King, Ph.D., M.D.[1*]
Joerg Lehmann, Ph.D.[1]
John R. Adler, M.D.[2]
Jenny Hai, Ph.D.[1]

The CyberKnife can produce superior DVHs for sparing of rectum and bladder and excellent DVHs for target coverage compared with IMRT, and possesses dose heterogeneities to the same degree **as** IMRT plans.

King R et al. Technol Cancer Res Treat (2003)

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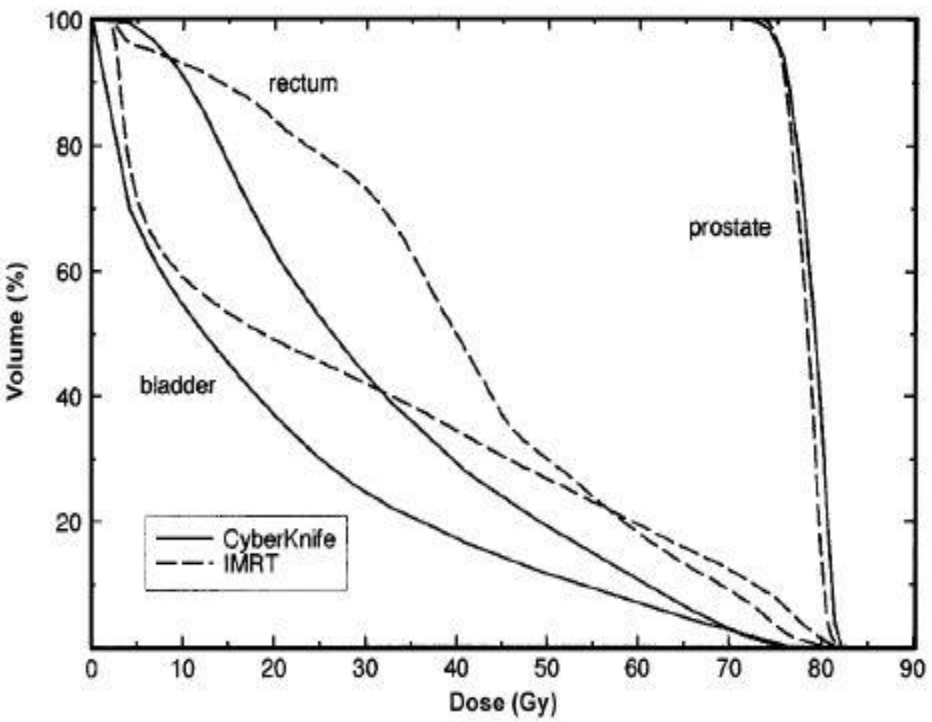

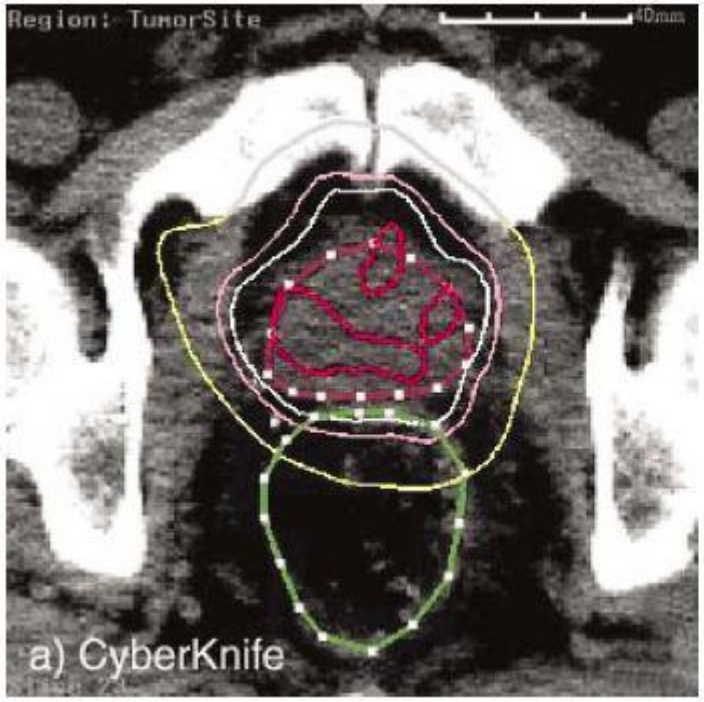

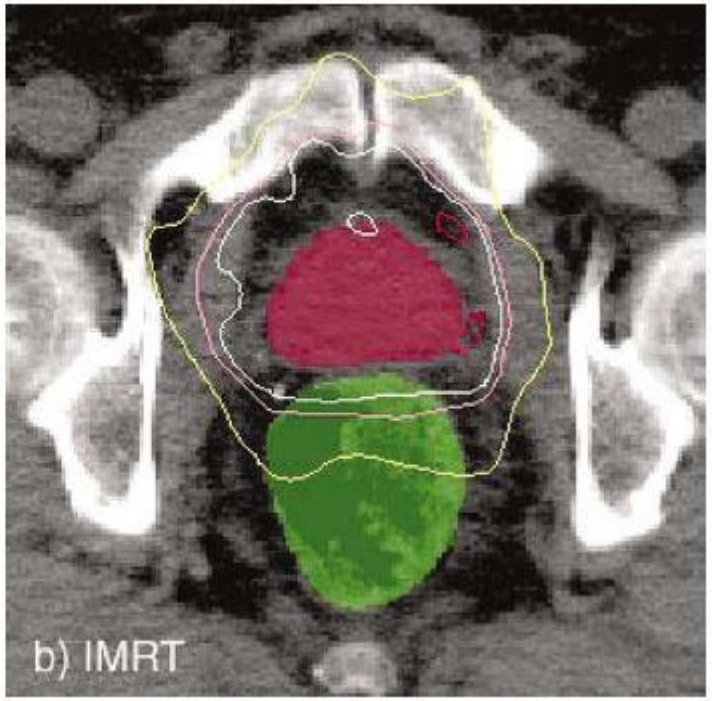

King R et al. Technol Cancer Res Treat (2003)

International Journal of Radiation Oncology biology • physics
Official Journal of the American Society for Radiation Oncology ASTRO

Dose Gradient Near Target and Normal Structure Interface for Non-isocentric Cyberknife and Isocentric Intensity-modulated Body Radiotherapy of Prostate Cancer

S. Hossain, P. Xia, K. Huang, M. Descovich, C. Chuang, A.R. Gottschalk, M. Roach, L. Ma
University of California San Francisco, San Francisco, CA

Purpose/Objective(s): Treatment planning quality between non-isocentric CyberKnife and isocentric intensity modulation treatments was studied for hypofractionated prostate body radiotherapy (SBRT). In particular, dose gradient across the target and the critical structures such as rectum and bladder was characterized.

Results: We found that all the plans satisfied the dose-volume constraints with CK plans showing significantly better conformity than IMRT plans at a relative higher dose inhomogeneity. The volumes of rectum and bladder receiving low dose were also lower for CK as compared with IMRT, however. The average conformal index (CI), the ratio of the prescription isodose volume and the CTV volume, was 1.18±0.08 for CK plans versus 1.44 ± 0.11 for IMRT. The average homogeneity index (HI), the ratio of maximum dose and the prescribed dose to the CTV, was 1.45 ± 0.12 for CK plans versus 1.28 ± 0.06 for IMRT. The average percent dose fall-off were found to be (2.9 ± 0.8)% per mm (CK) and (3.1 ± 1.0)% per mm (IMRT) along the anterior direction, (3.8 ± 1.6)% per mm (CK) and (3.2 ± 1.9)% per mm (IMRT) along the posterior direction, and (3.6 ± 0.4)% (CK) and (3.6 ± 0.4)% (IMRT) along all directions respectively.

Hossain S.et al. Radiation Oncology (2010)

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Technology in Cancer Research and Treatment
ISSN 1533-0346
Volume 5, Number 4, August (2006)

Image-Guided Radiosurgical Ablation of Intra- and Extra-Cranial Lesions

www.tcrt.org

Pantaleo Romanelli, M.D.[1,2,*]
David W. Schaal, Ph.D.[2]
John R. Adler, M.D.[2]

Cyberknife(SBRT) è una forma specifica di RT stereotassica con caretteristiche che ben si adattano alla SBRT del carcinoma prostatico perchè, includendo fasci non-complanari e il "real time tracking" dei movimenti prostatici, permette l'erogazione di dosi altamente conformate ed ipofrazionate.

Romanelli et al. Technol Cancer Res Treat (2006)

Ad oggi 13 studi di fase II e 1 retrospettivo

	Analysis type	N	Risk Group	Media (range) Initial PSA, ng/ml	Protocol
Choi et al., 2007	Prospective, P2	44	Low, Intermediate, High	-	32 Gy (4 x 8 Gy) 36 Gy (4 x 9 Gy)
Fuller et al., 2008	Prospective, P2	10	Low, Intermediate	6.9 (1.3–11.45)	38 Gy (4 x 9 Gy)
Friedland et al. 2009	Prospective, P2	112	Low, Intermediate	5.2 (1.1–17.2)	35 Gy (5 x 7 Gy)
Meier et al. 2009	Prospective, P2	29	Low, Intermediate	<20	36.25 Gy (5 x 7.25 Gy)
Aluwini et al. 2010	Prospective, P2	10	Low, Intermediate	8.3 (1.3–13.6)	38 Gy (4 x 9.5 Gy)
Mc Bride et al. 2011	Prospective, P2	45	Low	4.9 (1.4–9.4)	36.25 Gy (5 x 7.25 Gy) 37.5 Gy (5 x 7.5 Gy)
Freeman et al. 2011	Prospective, P2	41	Low	5.4 (3–7.8)	36.25 Gy (5 x 7.25 Gy)
Kang et al. 2011	Retrospective	44	Low, Intermediate, High	15.5 (1.7-437)	32 GY (4 x 8 Gy) 34 Gy (4 x 8.5 Gy) 36 Gy (4 x 9 Gy)
King et al. 2012	Prospective, P2	67	Low	<10	36.25 Gy (5 x7.25 Gy)
Bolzicco et al. 2013	Prospective, P2	100	Low, Intermediate, High	7.58	35 Gy (5 x 7 Gy)
Chen et al. 2013	Prospective, P2	100	Low, Intermediate, High	6.2 (1.9-31.6)	36.25 Gy (5 x 7.25 Gy) 36.25 Gy (5 x 7.25 Gy)
Katz et al. 2014	Prospective, P2	477	Low, Intermediate, High	11.5	35 Gy (5 x 7 Gy) 36.25 Gy (5 x 7.25 Gy)
Lee et al. 2014	Prospective, P2	29	Low, Intermediate, High	7.96 (0.1-24)	35 Gy (5 x 7 Gy)
Chao et al. 2015	Prospective, P2	21	Low, Intermediate, High	13.5 (4.5-124)	37.5 Gy (5 x 7.5 Gy)

Schemi di trattamento

	Protocol
Choi et al., 2007	32 Gy (4 x 8 Gy) 36 Gy (4 x 9 Gy)
Fuller et al., 2008	38 Gy (4 x 9 Gy)
Friedland et al. 2009	35 Gy (5 x 7 Gy)
Meier et al. 2009	36.25 Gy (5 x 7.25 Gy)
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Lee et al. 2014	35 Gy (5 x 7 Gy)
Chao et al. 2015	37.5 Gy (5 x 7.5 Gy)

Schema più usato 35-36.25 Gy in 5 frazioni
(BED = 200-211 Gy)

International Journal of
Radiation Oncology
biology • physics
Official Journal of the American Society for Radiation Oncology
ASTRO

Evaluation of Biologically Equivalent Dose Escalation, Clinical Outcome, and Toxicity in Prostate Cancer Radiation Therapy: A Meta-Analysis of 12,000 Patients From 40 Institutions

N.G. Zaorsky, M.D. Hurwitz, S.W. Keith, A.P. Dicker, and R.B. Den;
Thomas Jefferson University, Philadelphia, PA

Purpose/Objective(s): For prostate cancer, the role of dose-escalation (DE) to a biologically equivalent dose (BED) of 200 Gy (at an α/β of 1.5) using conventionally fractionated external beam radiation therapy (CFRT) has been established to improve rates of freedom from biochemical failure (FFBF) vs CFRT with BEDs 200 Gy with high dose rate brachytherapy (HDR-BT) has been postulated to further improve outcomes. The purpose of this study was to determine if increasing BED > 200 Gy with HDR-BT is correlated with outcomes or toxicities.

Conclusions: An increase in the BED to 200 Gy (at α/β of 1.5) was associated with increased disease control. Doses above 200 Gy did not result in clinical benefit.

Zaorsky N.G. et al. Radiation Oncology (2013)

bPFS

	Median follow-up,months	Risk Group	Median PSA, ng/mL	bPFS rate, %
Choi et al., 2007	13	Low, Intermediate, High	-	78.3
Fuller et al., 2008	4	Low, Intermediate	0.97	-
Friedland et al. 2009	24	Low, Intermediate	0.6	97.4
Meier et al. 2009	18	Low, Intermediate	0.4	100
Aluwini et al. 2010	5,1	Low, Intermediate	1.6	100
Mc Bride et al. 2011	44,5	Low	0.2	97.7
Freeman et al. 2011	60	Low	0.35	92.7
Kang et al. 2011	40	Low, Intermediate, High	0.1	L(100), I(100), H(90.9)
King et al. 2012	32,4	Low	-	94
Bolzicco et al. 2013	36	Low, Intermediate, High	0.45	94.4 at 3 years
Chen et al. 2013	27,9	Low, Intermediate, High	0.49	99 at 2 years
Katz et al. 2014	60	Low, Intermediate, High	0.14	L(97), I(90.7), h (77.1)
Lee et al. 2014	41	Low, Intermediate, High	0.329	85.6 at 4 years
Chao et al. 2015	36	Low, Intermediate, High	0.04	I (100), H+VH (82) at 3 years

bPFS

frontiers in ONCOLOGY

ORIGINAL RESEARCH ARTICLE
published: 02 September 2014
doi: 10.3389/fonc.2014.00240

Stereotactic body radiotherapy as treatment for organ confined low- and intermediate-risk prostate carcinoma, a 7-year study

Alan Jay Katz[1]* and Josephine Kang[1,2]

[1] *Flushing Radiation Oncology Services, Flushing, NY, USA*
[2] *Department of Medicine, NYU Langone Medical Center, New York, NY, USA*

Methods: Four hundred seventy-seven patients with prostate cancer received CyberKnife SBRT. The median age was 68.6 years and the median PSA was 5.3 ng/mL. Three hundred twenty-four patients were low-risk (PSA <10 ng/mL and Gleason <7), 153 were intermediate-risk (PSA 10–20 ng/mL or Gleason = 7). Androgen deprivation therapy was administered to 51 patients for up to 6 months. One hundred fifty-four patients received 35 Gy delivered in five daily fractions; the remaining patients received a total dose of 36.25 Gy in five daily fractions. Biochemical failure was assessed using the phoenix criterion.

Katz et al et al. Frontiers in Oncology (2014)

bPFS

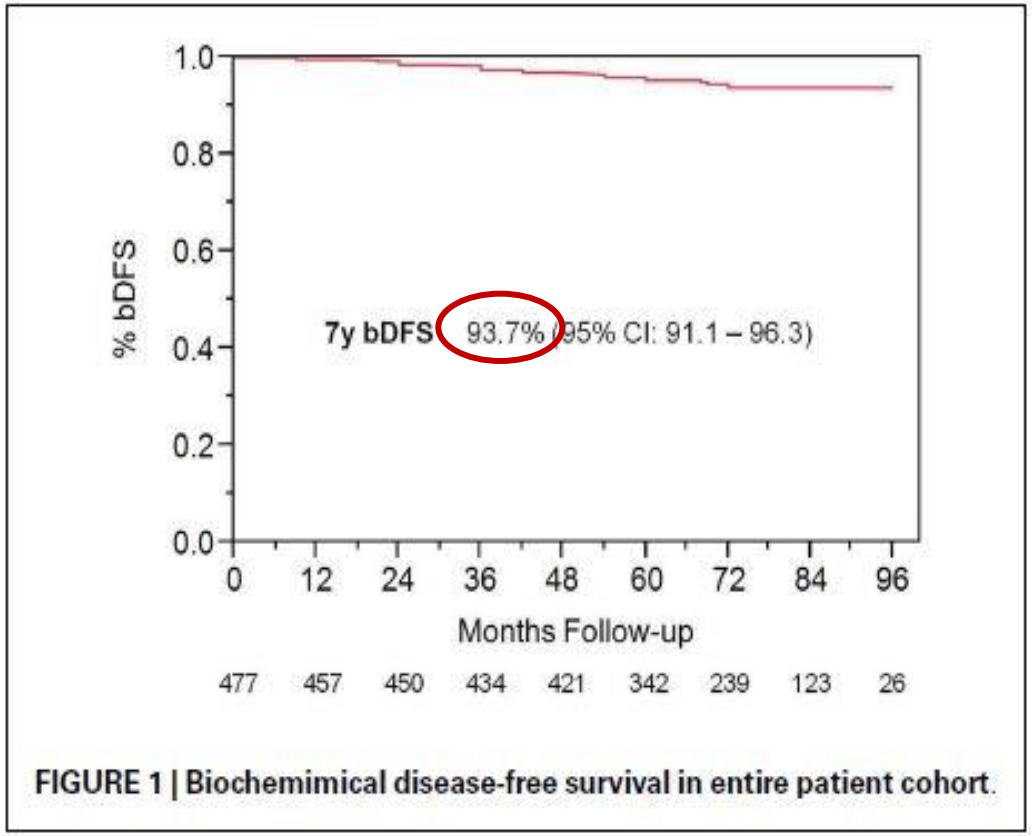


FIGURE 1 | Biochemimical disease-free survival in entire patient cohort.

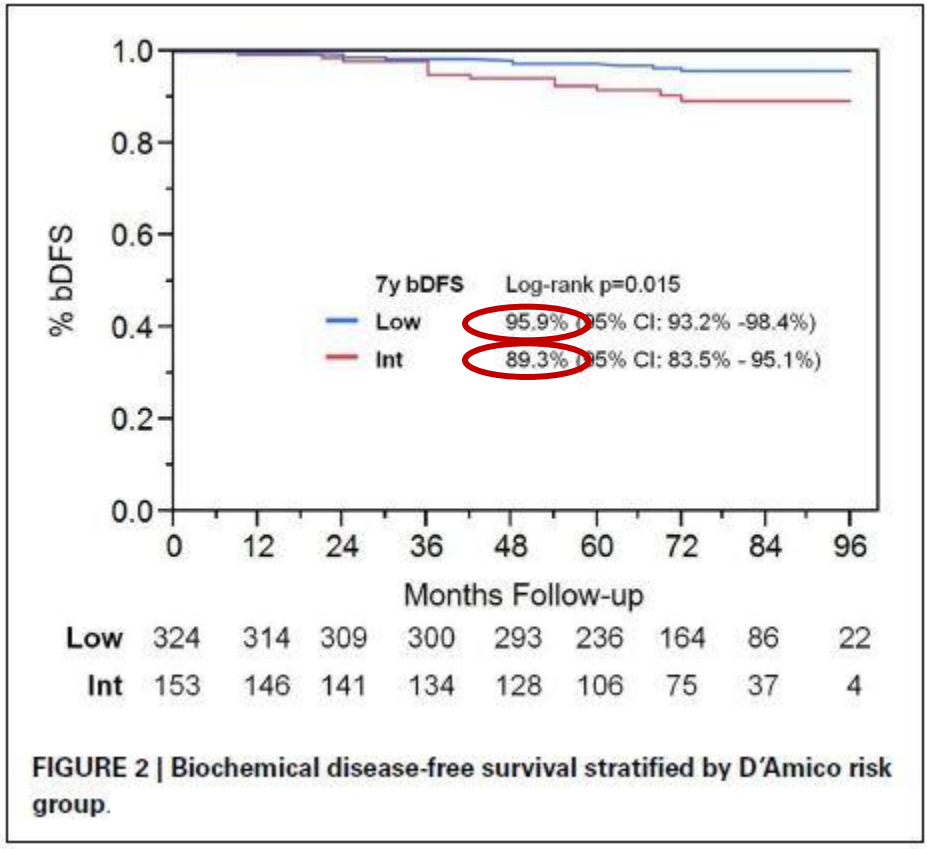


FIGURE 2 | Biochemical disease-free survival stratified by D'Amico risk group.

Katz et al et al. Frontiers in Oncology (2014)

bPFS

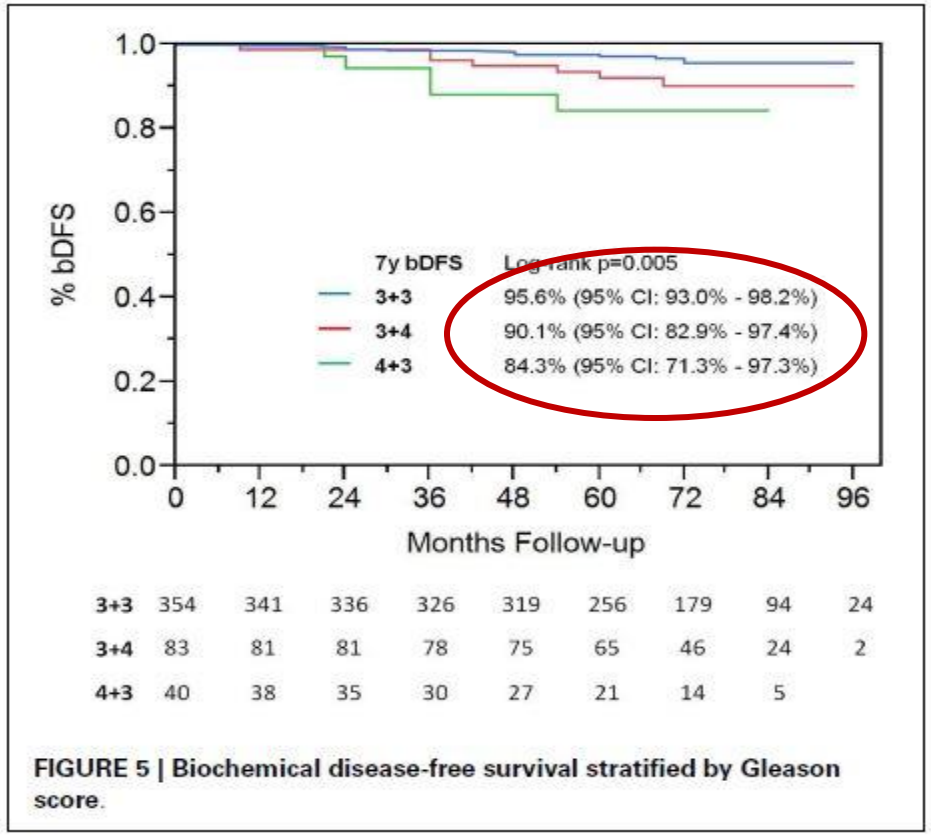


FIGURE 5 | Biochemical disease-free survival stratified by Gleason score.

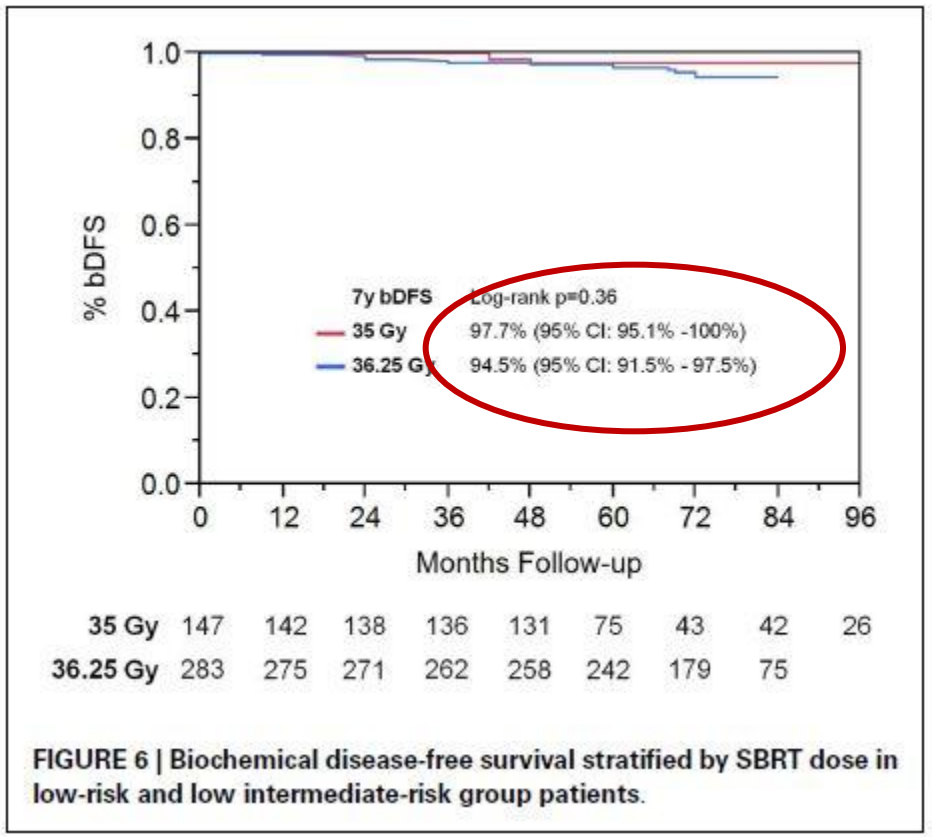


FIGURE 6 | Biochemical disease-free survival stratified by SBRT dose in low-risk and low intermediate-risk group patients.

Katz et al et al. Frontiers in Oncology (2014)

Tossicità

	Acute toxicities			Late toxicities		
	rT	uT	Sexual toxicity	rT	uT	Sexual tocxicity
Choi et al., 2007	32% G1/2	39% G1/2	-	0%	0%	-
Fuller et al., 2008	60% G1/2	60% G1/2	-	-	-	-
Friedland et al. 2009	Rectal urgency	Dysuria	-	1% G3	0%	18% ED
Meier et al. 2009	NA	NA	-	-	-	-
Aluwini et al. 2010	20% G1/2 + 10% G3	50% G1	-	-	-	-
Mc Bride et al. 2011	38% G1/2	78% G1/2	-	14% G1/2 + 5% G3	34% G1/2	-
Freeman et al. 2011	G1/2	G1/2	-	15.5% G1/2	32% G1/2 + 2.5% G3	-
Kang et al. 2011	44% G1/G2	25% G1/ G2	-	16% G1/G2	14% G1/G2	-
King et al. 2012	NA	NA	-	-	-	-
Bolzicco et al. 2013	46% G1/2	45% G1/2	-	2.2% G2	8.8% G1/2 + 2.2% G3	-
Chen et al. 2013	48% G1/G2	21% G1/G2	-	43% G1/G2	11% G1	-
Katz et al. 2014	NA	NA	-	11% G2 + 7% G3	14% G2	-
Lee et al. 2014	34% G1/G2	27% G1/G2	-	10% G1/G2 + 3% G3	3% G1	-
Chao et al. 2015	58% G1/G2	7% G1/G2	-	23% G1/G2	0% G1/G2	-

-Tossicità rettale
Acuta G1/G2= 9-80%
Tardiva G1/G2=0-48%

-Tossicità urinaria
Acuta G1/G2 = 13-78% , G3 = 5%
Tardiva G1/G2 = 0-65% , G3 = 0,5-5%

-Disfunzione erettile
Tardiva = 13-18%

Ripresa di malattia

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 889–897, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.11.031

CLINICAL INVESTIGATION **Genitourinary Cancer**

ROBOTIC IMAGE-GUIDED STEREOTACTIC RADIOTHERAPY, FOR ISOLATED RECURRENT PRIMARY, LYMPH NODE OR METASTATIC PROSTATE CANCER

Barbara Alicja Jereczek-Fossa, M.D., Ph.D.,*† Giancarlo Beltramo, M.D.,‡ Laura Fariselli, M.D.,§ Cristiana Fodor, M.Sc.,* Luigi Santoro, M.Sc.,‖ Andrea Vavassori, M.D.,* Dario Zerini, M.D.,* Federica Gherardi, M.D.,*† Carmen Ascione, M.D.,*¶ Isa Bossi-Zanetti, M.D.,*† Roberta Mauro, M.D.,*† Achille Bregantin, M.Sc.,‡ Livia Corinna Bianchi, M.D.,‡ Ottavio De Cobelli, M.D.,# and Roberto Orecchia, M.D.*†

30 months b PFS rate of 42,6%

Jereczek-Fossa. et al. Radiation Oncology (2012)

La nostra esperienza

Da Giugno 2006

BMC Urology

RESEARCH ARTICLE Open Access

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

Criteri di inclusione:
Ca prostatico organo confinato
Conferma bioptica della malattia
Nessun segno di ostruzione severa

Bolzicco et al. BMC Urology (2013)

La nostra esperienza

Eta media 72 aa (52-82)

ECOG performance status 0-1

Conferma bioptica della malattia (media di 10 prelievi)

Table 1 Cyberknife®-SBRT: clinical characteristics of 100 patients

T Stage	**Patients**
T1c	44 (44%)
T2a-b	29 (29%)
(T2a, 10 pts)	
(T2b, 19 pts)	
T2c	27 (27%)
Gleason score	
<6 (2+2, 2+3, 3+2)	8 (8%)
6 (3+3)	76 (76%)
>7 (3+4 11 pts, 4+3 4 pts, 5+5 1 pt)	16 (16%)
PSA	
at diagnosis	**ng/ml**
All patients	7.72 ng/ml
SBRT (71 pts)	6.48 ng/ml
SBRT+ADT (29 pts)	10.77 ng/ml
Pre-treatment	**ng/ml**
All patients	5.03 ng/ml
SBRT (71 pts)	6.31 ng/ml
SBRT+ADT (29 pts)	1.90 ng/ml
Risk category	**Patients**
Low (PSA <10, GS 6, T1c, T2a)	41 (41%)
Intermediate (PSA >10, GS 7 or T2b-c)	42 (42%)
High (PSA >20, GS 8–10, 2 Int. risk features)	17 (17%)
Prostate volume (medium 33 cc)	
≤ 33 cc	51 (51%)
> 33 cc	49 (49%)
TURP before SBRT (1–16 years)	7 (7%)
ADT	
Before SBRT (median 6 months)	8 (27%)
Concomitant and after SBRT (median 12 months)	21 (73%)

SBRT = Stereotactic Body Radiation Therapy.
ADT = Androgen Deprivation Therapy.
TURP = Transurethral resection of the prostate.

Bolzicco et al. BMC Urology (2013)

La nostra esperienza

- 4 Gold fiducials

-TC(da 1mm) di centratura 10-15 gg dopo l'impianto

-SBRT con Cyberknife 6MV (600-800 MU/min)
Tracking dei fiducials ogni 30-40 sec

-CTV (prostata e 1/3 delle s.v.)

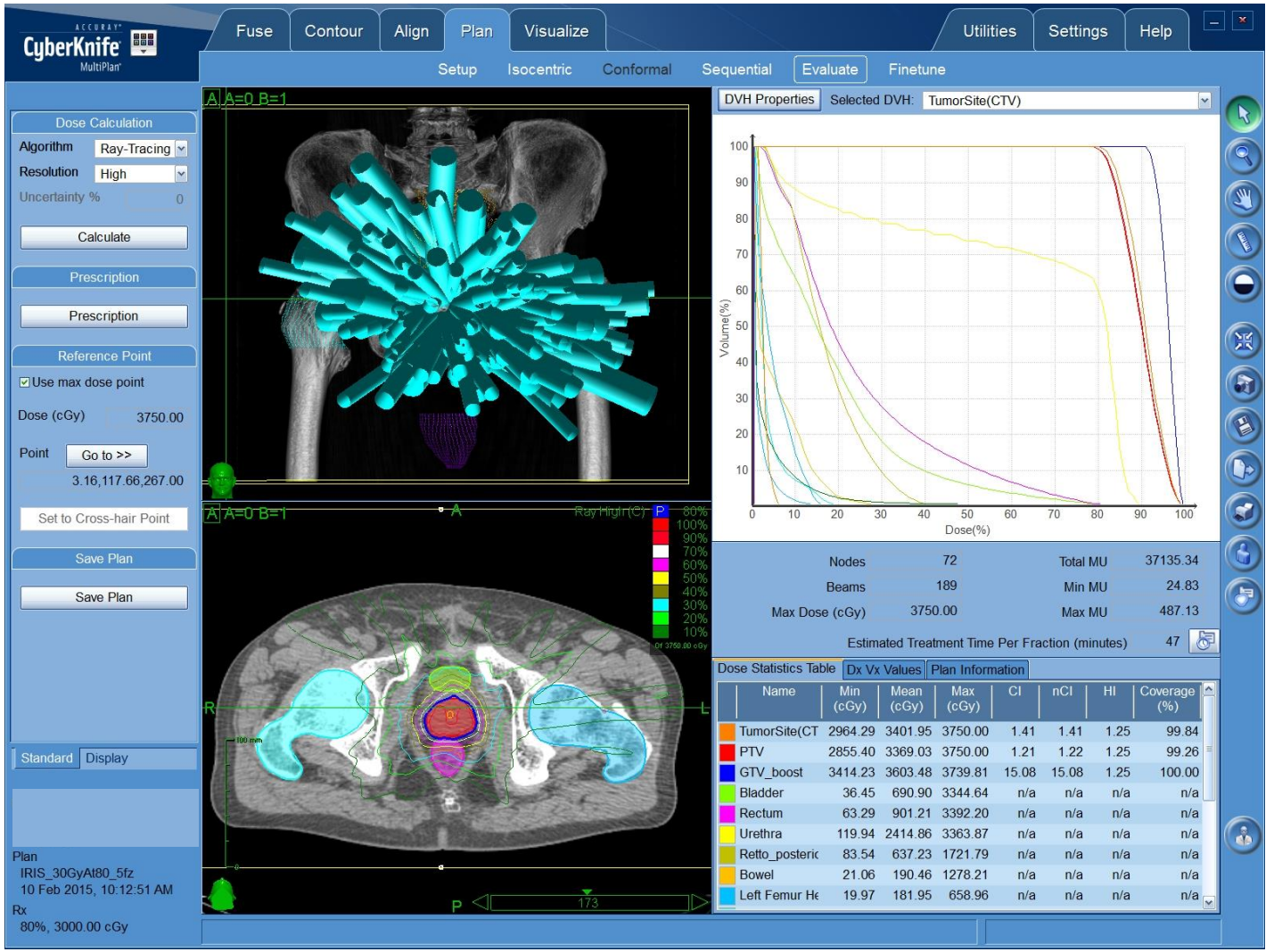
-5mm di margine per il PTV (3mm posteriormente)

-35 Gy/5f al 80% dell'isodose

-Pianificazione con Multiplan CyberKife

Bolzicco et al. BMC Urology (2013)

La nostra esperienza



OAR

-Retto Dmax 38Gy ≤ 5%

-Vescica Dmax 40Gy ≤ 5%

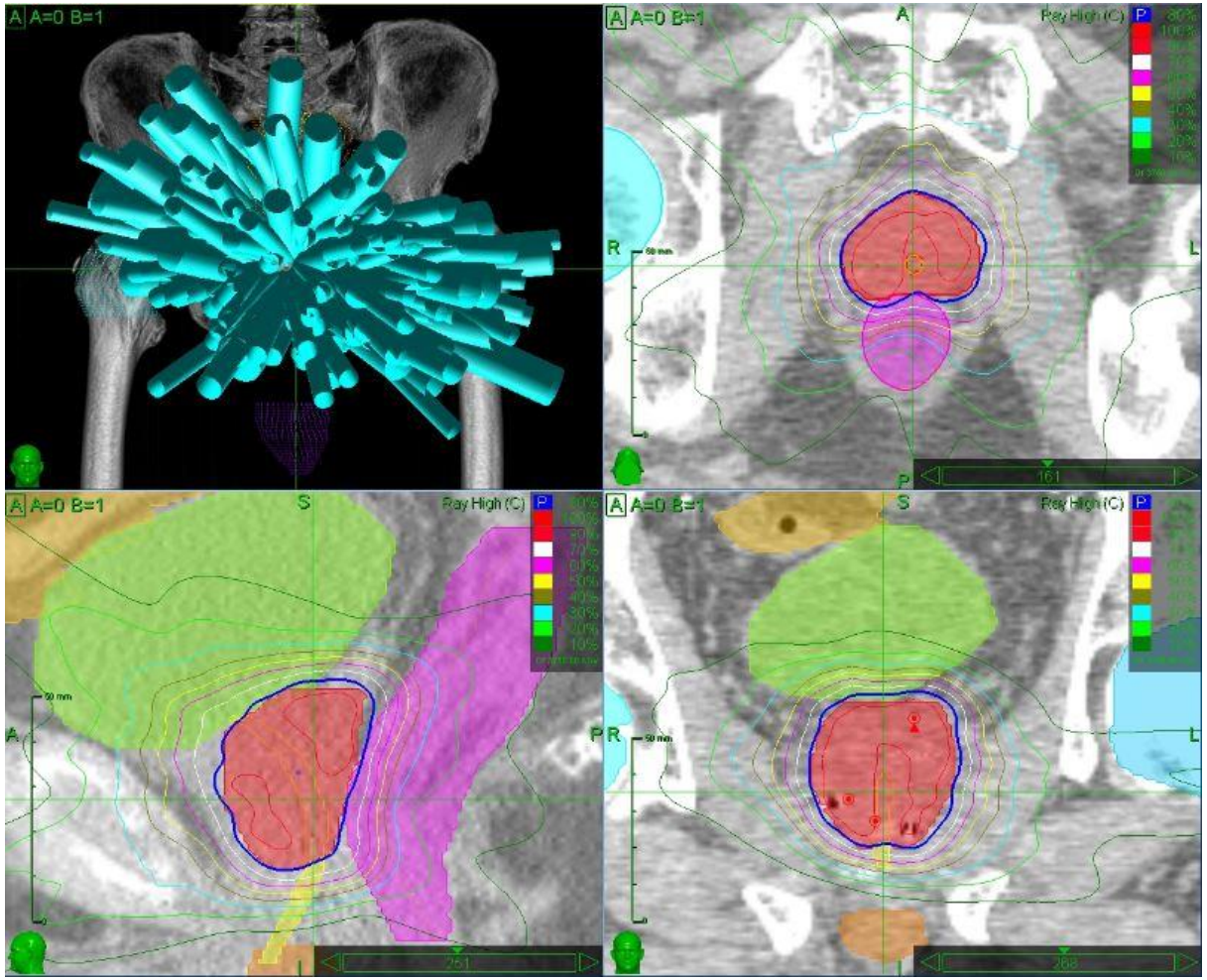
-Uretra Dmax 40Gy ≤ 5%

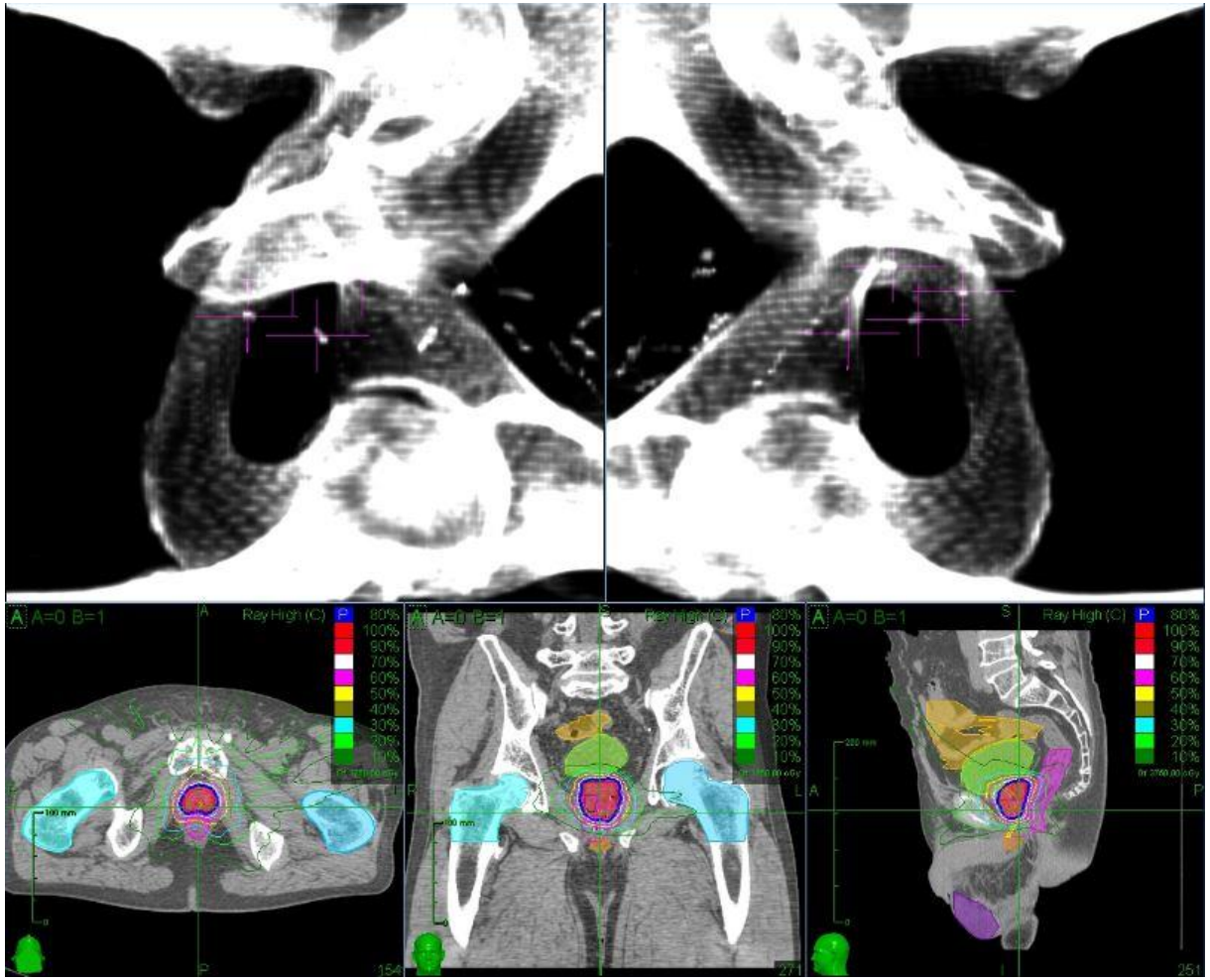
-Bulbo Dmax 29Gy ≤ 25%

-Teste femorali Dmax 25Gy ≤ 25%

Bolzicco et al. BMC Urology (2013)

La nostra esperienza





La nostra esperienza

-Follow up medio di 36 mesi (range 6-76 mesi)

-La tossicità acuta valutata dopo 10gg ,1-3-6 mesi

-La tossicità tardiva valutata dal 6° mese in poi

-RTOG acute/late morbidity scales

Bolzicco et al. BMC Urology (2013)

La nostra esperienza

Valutazione della tossicita' acuta e tardiva

	RTOG grade			
Acute (62 pts)	I	II	III	IV
Urinary	34%	12%	-	-
Rectal	27%	18%		
Late (9 pts)				
Urinary	4%	3%	1%	
Rectal	2%	1%	-	-

SBRT = Stereotactic Body Radiation Therapy.
RTOG Grade= toxicity based on Radiation Therapy Oncology Group.

Bolzicco et al. BMC Urology (2013)

La nostra esperienza

Valutazione del PSA response

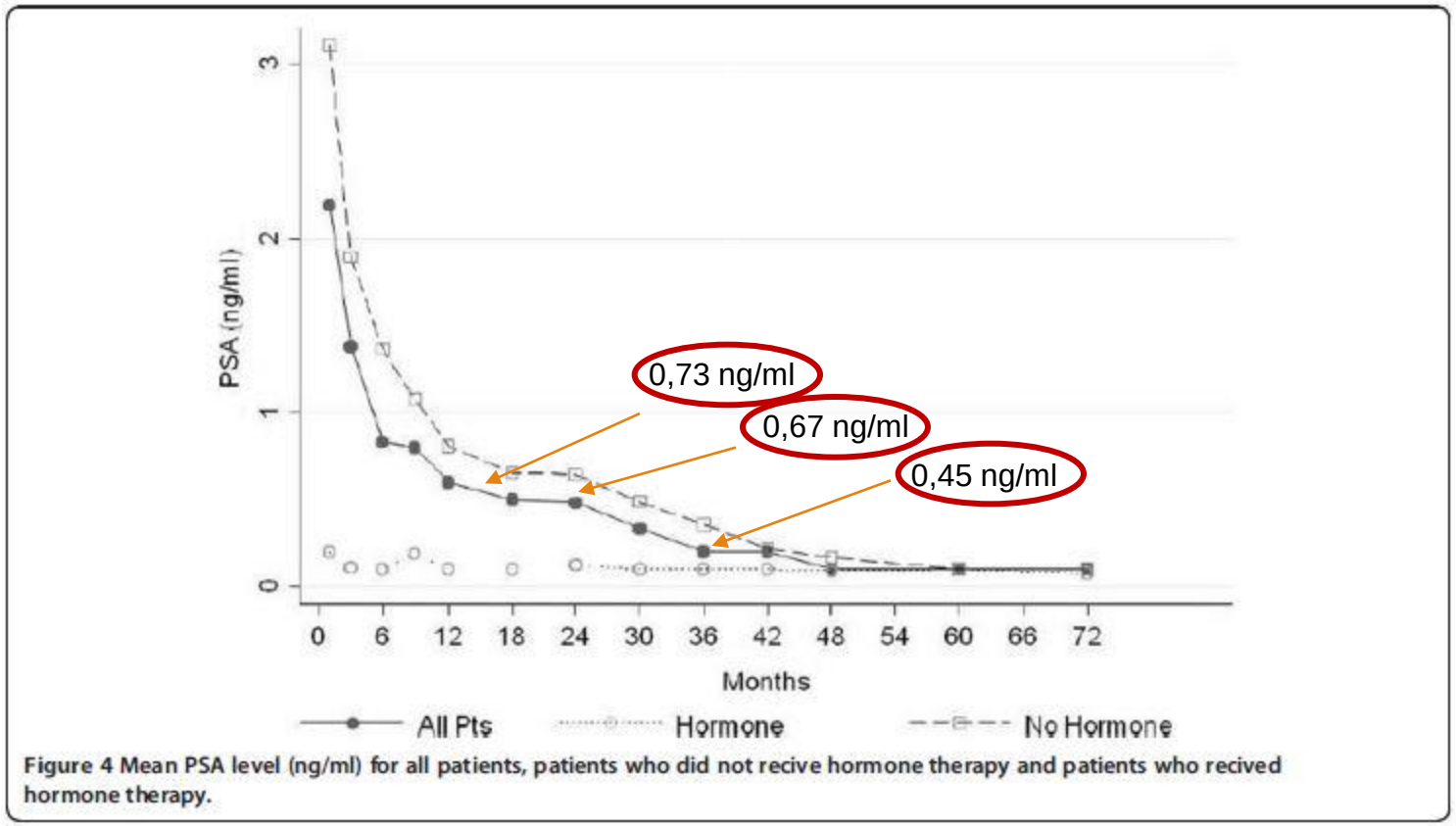


Figure 4 Mean PSA level (ng/ml) for all patients, patients who did not recive hormone therapy and patients who recived hormone therapy.

A 2 anni, nessuna differenza tra i pazienti a basso rischio e quelli a rischio intermedio/alto con PSA medio di 0,44 e 0,50 ng/ml rispettivamente

Table 3 CyberKnife® 71 SBRT-monotherapy patients

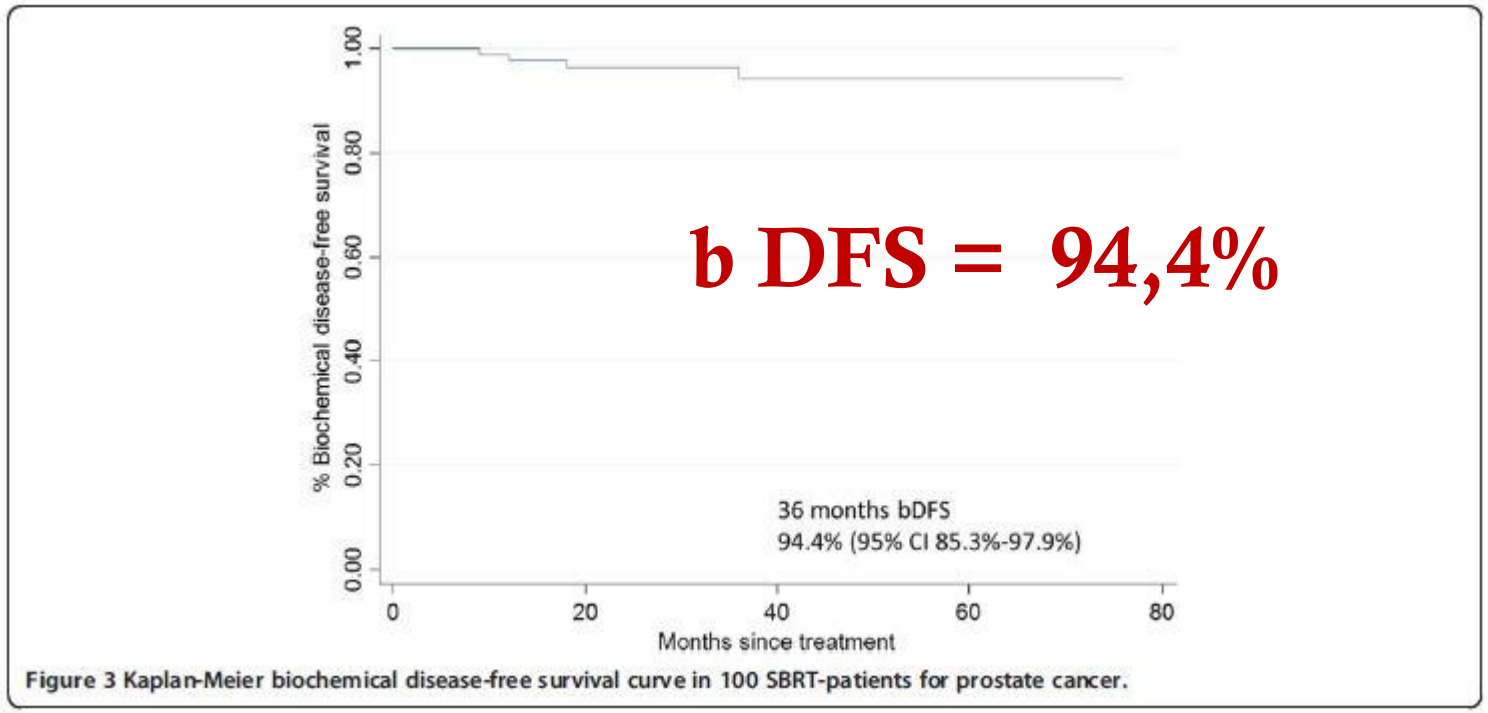
	Patients	ng/ml	months
PSA Bounce	12%	medium value 1.08	medium 23 (18–30)

SBRT = Stereotactic Body Radiation Therapy, Bounce= a PSA rise and a subsequent decline of nadir.

Bolzicco et al. BMC Urology (2013)

La nostra esperienza

Valutazione del PSA response



b DFS = 94,4%

Figure 3 Kaplan-Meier biochemical disease-free survival curve in 100 SBRT-patients for prostate cancer.

4 pazienti con recidiva biochimica di malattia

3 rischio intermedio, 1 alto rischio

1 recidiva locale, 2 linfonodali, 1 ossea

Tutti sottoposti a ADT o CT

3 years PFS = 96%

5 years PFS = 93%

Bolzicco et al. BMC Urology (2013)

Conclusioni

-La Cyberknife SBRT ha un eccellente controllo biochimico a lungo termine sul carcinoma prostatico organo confinato

-L'impatto clinico di questa tecnica deve essere ancora confermato da futuri trials di fase III

Conclusioni
2 studi di fase III
(in corso)

PACE TRIAL

(Prostate Advances in Comparative Evidence-low/intermediate risk)

- **Prostatectomia radicale**
- **IMRT (78 Gy in 39 sedute)**
- **SBRT (36.25 Gy in 5 sedute/38 Gy in 4 sedute)**

HYPO-RT-PC

(Hypofractionated radiotherapy of intermediate risk localized prostate cancer Swedish trial)

- **IMRT (78 Gy in 39 sedute)**
- **SBRT (42.7 Gy/7 sedute)**

Take Home message

-La bRFS a lungo termine dopo CK-SBRT è paragonabile a tutti gli altri tipi di trattamento radicale per i pazienti a rischio basso ed intermedio

-In nessun gruppo di rischio è stato dimostrato un beneficio dall'associazione di ADT.

-Fino ad oggi non è consigliata l'escalation di dose, almeno per i pazienti a basso/intermedio rischio, poichè non è stata dimostrata alcuna correlazione tra dose e risposta, se lo schema di trattamento è di 35-40 Gy in 5 frazioni