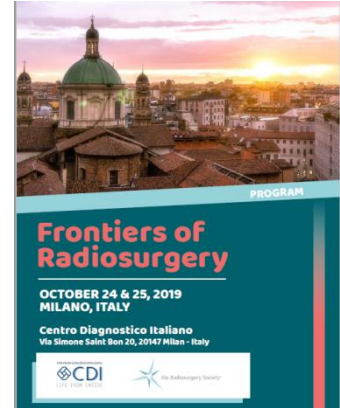


Evaluation of outcomes after stereotactic Hypofractionated radiotherapy for prostate



G. Beltramo, I. Bossi Zanetti, A. Bergantin, A.S. Martinotti, I. Radaelli,
P. Bonfanti, C. Spadavecchia, F. Moretti, L.C. Bianchi

Centro Diagnostico Italiano Milano

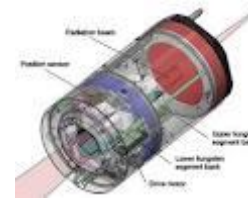


G 3

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.‡

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



At the beginning

Right now

Phase I/II Ultrahypofractionation Trials: Schedules and Equivalent Total Doses in 2-Gy Fractions

Fractionation (tot.does/fx size/#fx)	Total Dose Equivalent in 2Gy Fractions (NTD ₂)		No. of PTS	Institution	References
	Alpha/Beta = 1.5 (tumor)	Alpha/Beta = 3 (late effects)			
33.5 Gy/6.7 Gy/5 fx	78 Gy	64.9 Gy	40	Virginia Mason	Madsen et al ³⁶
36.25 Gy/7.25 Gy/5 fx	90.6 Gy	74.3 Gy	23 (ongoing)	Stanford	Pawlicki et al ³⁷
42.7 Gy/6.1 Gy/7 fx	92.7 Gy	77.7 Gy	105	Umea	Widmark (personal communication, 2008)
35 Gy/7 Gy/5 fx	85.1 Gy	70 Gy	30 (ongoing)	University of Toronto	Tang et al ³⁸
47.5 Gy/9.5 Gy/5 fx	149 Gy*	118 Gy	15	UTSW, Dallas	Timmerman (personal communication, 2008)
50 Gy/10 Gy/5 fx	164 Gy	130 Gy	10 (ongoing)		
52.5 Gy/10.5 Gy/5 fx	180 Gy	142 Gy	—		

* NTD doses based on linear-quadratic modeling may overpredict NTDs for large fractions, as in the UTSW trial.

Radiobiology of prostate cancer

Equivalent dose in 2 Gy

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

$$9.5 \times 4 = 38 \text{ Gy}$$

Prostate Ca
(α/β) = 1.5

119.4 Gy

Late effects
(α/β) = 3

95 Gy

Acute effects
(α/β) = 10

61.8 Gy

Radiobiology of prostate cancer

Equivalent dose in 2 Gy

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

What if we're wrong?

Prostate Ca
 $(\alpha/\beta) = 10$

61.8 Gy

Late effects
 $(\alpha/\beta) = 3$

95 Gy

Acute effects
 $(\alpha/\beta) = 10$

61.8 Gy

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(July 2007 – June 2016)

217 patients

Median follow up 72 months (range 12-120)

Median Age: 75 Years (range 52 - 86)

PSA at diagnosis: mean 8.51 ng/ml (range 1.75 – 51.13 ng.ml)

Risk Assessment Criteria: :

- Low: 116 pts (53%)
- Int: 60 pts (28%)
- High: 41 pts (19%)

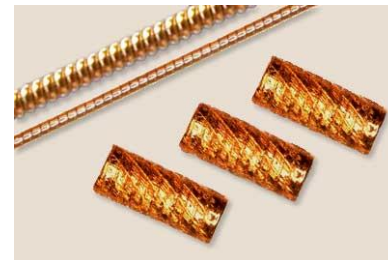
Gleason Score:

- = 6: 145 pts
- = 7: 46 pts
- > 7: 27 pts

Hormone Treatment: NO: 200 pts YES: 17 pts

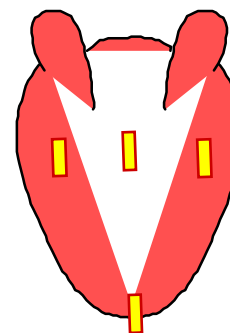
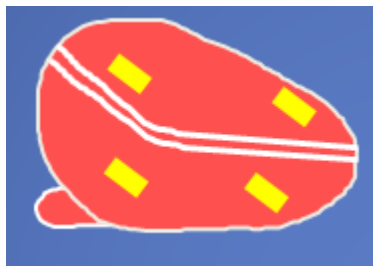
Prostate Volume: mean 75.6 cc (range 37.03 - 163.16)

Fiducial marker



- Insertion under TRUS guidance
- 4 for “triangulation” (spatial coordination)

sagittal



posterior

REAL-TIME INTRAFRACTIONAL MOTION TRACKING

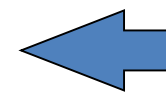
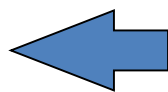
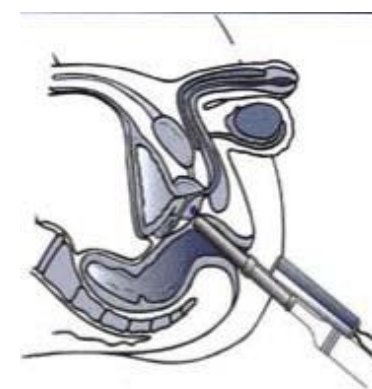
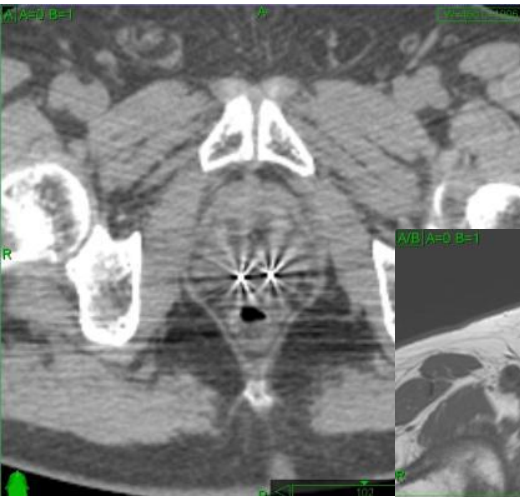
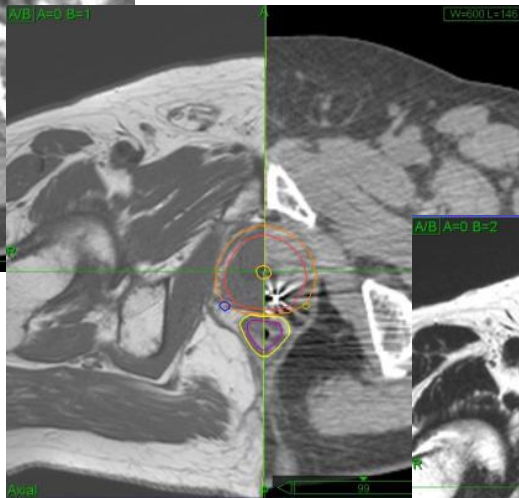


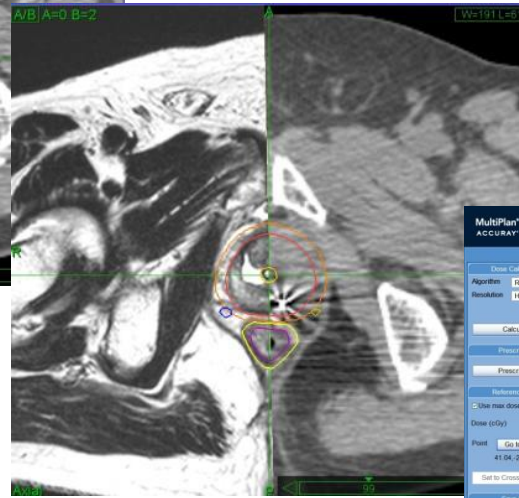
Image guidance facilitates targetting



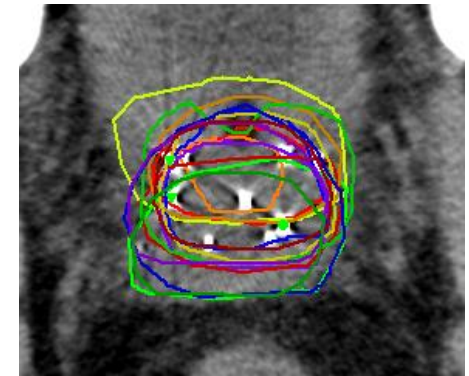
TC



T1 MR1



T2 MRI



Inter observer variability
 Who is correct?

TC - MRI image Fusion

Use CT for geometric accuracy
 Use MRI for target delineation

Organ at Risk	Min (cGy)	Max (cGy)	Mean (cGy)	CP (%)	CP (%)	CP (%)	CP (%)	CP (%)
Prostate	3377.73	3949.55	4545.45	1.82	1.63	1.30	99.1	
PTV	3359.61	3984.09	4545.45	1.21	1.23	1.20	99.4	
Bladder	215.14	1831.39	3545.82	na	na	na	na	na
Rectum	90.05	878.46	2051.49	na	na	na	na	na
Urethra	418.78	2652.42	3723.08	na	na	na	na	na
Left Femoral Head	131.15	400.20	750.03	na	na	na	na	na
Right Femoral Hd	118.96	402.03	773.08	na	na	na	na	na
Rectum Vnd	105.57	854.96	2052.29	na	na	na	na	na
Bladder wall	200.30	1655.41	3238.67	na	na	na	na	na
Skin	43.23	194.83	4545.45	na	na	na	na	na

Cyberknife stereotactic radiosurgery Constraints for low and intermediate risk prostate cancer

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 intermediate risk Group)

- ❖ Maximum rectal wall dose of 100% of the prescription dose (38 Gy)
- ❖ Maximum rectal mucosa dose of 75% of the prescription dose (28.5 Gy)
- ❖ Maximum urethra dose of 120% of the prescription dose (45.6 Gy)
- ❖ Maximum bladder dose of 120% of the prescription dose (45.6 Gy)

Erectile Function

- ❖ Neurovascular Bundle and penile bulb D_{90} , D_{50} , D_{10} , D_{max} , V_{100} and V_{50} will be carried for possible dosimetry-morbidity correlation but no specific dosimetry constraint will be applied –

ACTIVE CLINICAL STUDY Low and Intermediate Risk Prostate Cancer: HDR Brachytherapy Emulation	
STUDY	Prospective Evaluation of CyberKnife® Radiosurgery of Low and Intermediate Risk Prostate Cancer: Emulating HDR Brachytherapy
PRINCIPLE INVESTIGATOR	Don Fuller, M.D. (San Diego CyberKnife Center, San Diego, CA) Chad Lee, Ph.D. (San Diego CyberKnife Center, San Diego, CA)
SPONSOR	Accuray Incorporated
PRIMARY AIMS	1. To assess acute and late gastrointestinal and genitourinary toxicities following CyberKnife® Stereotactic Radiosurgical treatment of prostate cancer in low and intermediate risk patients
SECONDARY AIMS	1. To assess clinical response rates by PSA monitoring, overall survival and Gleason-specific survival 2. To assess quality of life in this population following treatment 3. To assess economic implications of treatment with CyberKnife® Radiosurgery
PATIENT POPULATION	Early stage organ confined prostate cancer Low Risk: Stage T1b-T2a and Gleason 2-6 and PSA<10 Intermediate Risk: Stage T2b and Gleason 2-6 and PSA<10 Stage T1b-T2a and Gleason 2-6 and PSA<20 Stage T1b-T2a and Gleason 7 and PSA<10
METHODS	Primary treatment of organ confined prostate cancer by CyberKnife Radiosurgery 9.5 Gy x 4 fractions with an HDR dose distribution within the prostate
PARTICIPATING CENTERS	San Diego CyberKnife Center, San Diego, CA (PI) Participating sites TBD

SCHEMA

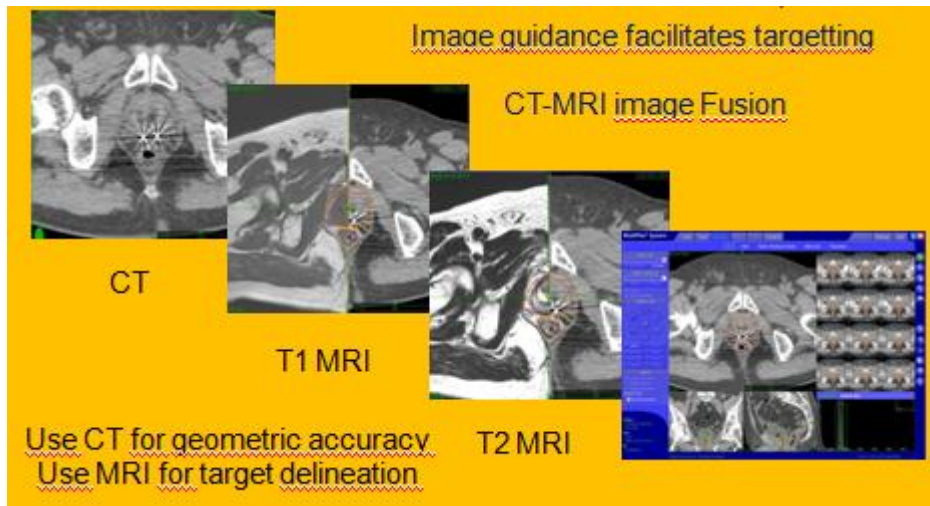




Virtual HDR CyberKnife SBRT for localized prostatic carcinoma: 5-year disease-free survival and toxicity observations

Donald Blake Fuller^{1*}, John Naitoh² and George Mardirossian¹

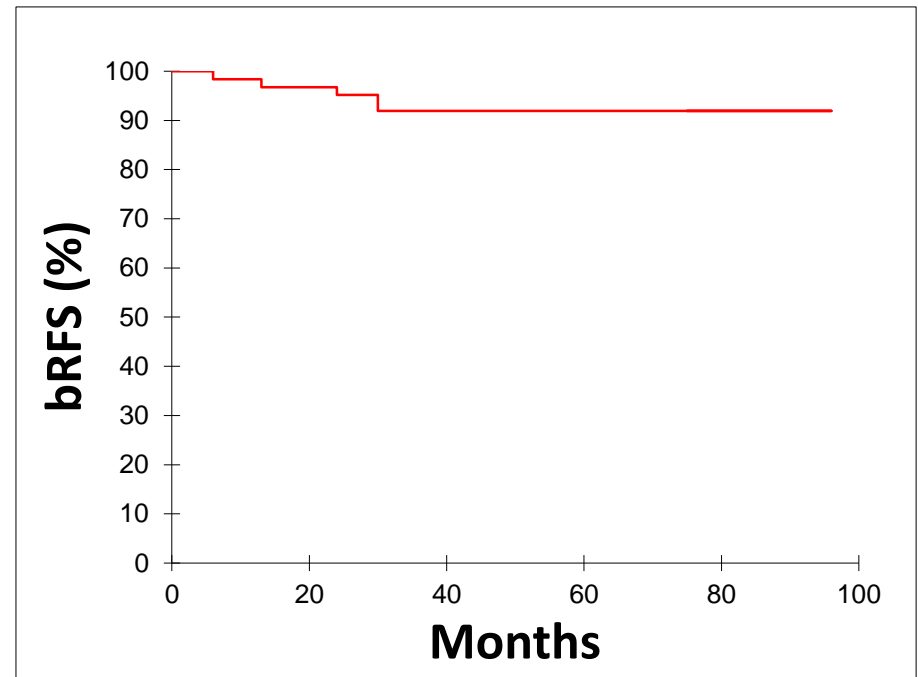
The planning target volume (PTV) for all cases included the prostate as defined by our prostate MRI imaging protocol, three- dimensionally co-registered with prostate CT imaging, matching fiducial to fiducial, and a **2-mm volume expansion** in all directions, **except posteriorly** where the prostate abutted the rectum, where **the margin expansion** was reduced to **zero** based on reports that prostate cancer does not invade posteriorly in the mid- line beyond Denonvilliers' fascia



Villers A, McNeal JE, Freiha FS, Boccon-Gibod L, Stamey TA. Invasion of Denonvilliers' fascia in radical prostatectomy specimens. *J Urol* (1993) **149(4):793–8**.

Centro Diagnostico Italiano : preliminary results

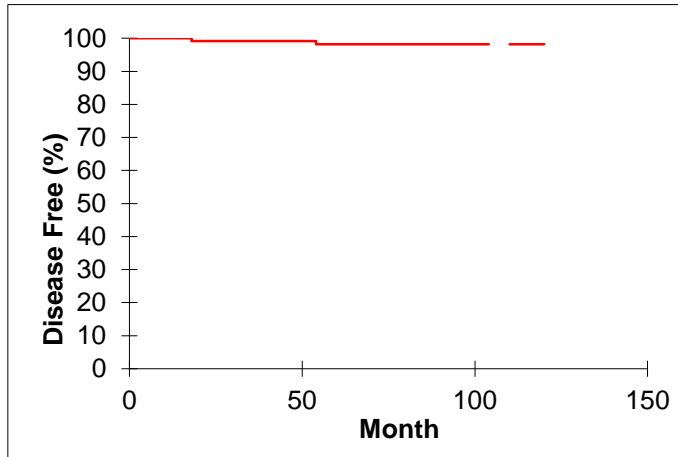
38 Gy in 4 Fractions



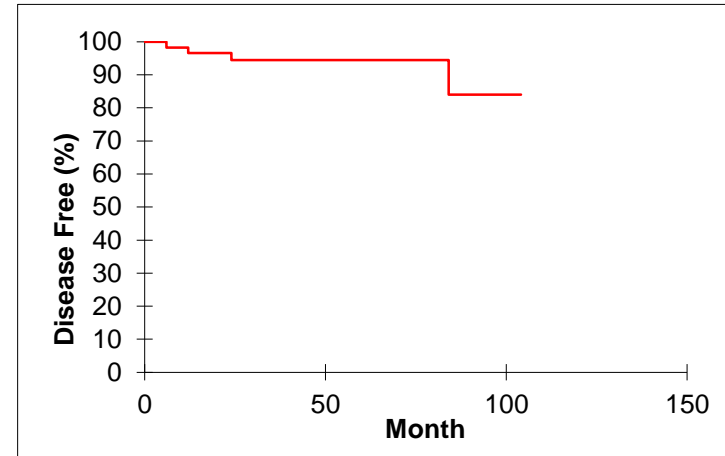
Median follow-up: 72 months (12-120)

The 6-years actuarial PSA relapse free survival rate is **94.4% (CI: 90.8%-98.2%)** with 98.2% for low risk, 94.5% for intermediate – risk and 85.6% for high risk respectively.

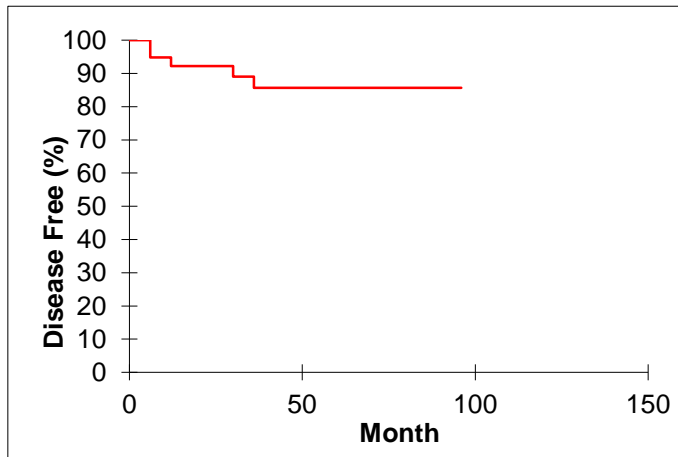
Centro Diagnostico Italiano : preliminary results



Brfs 98.2% (IC 95.6 – 100) Low risk



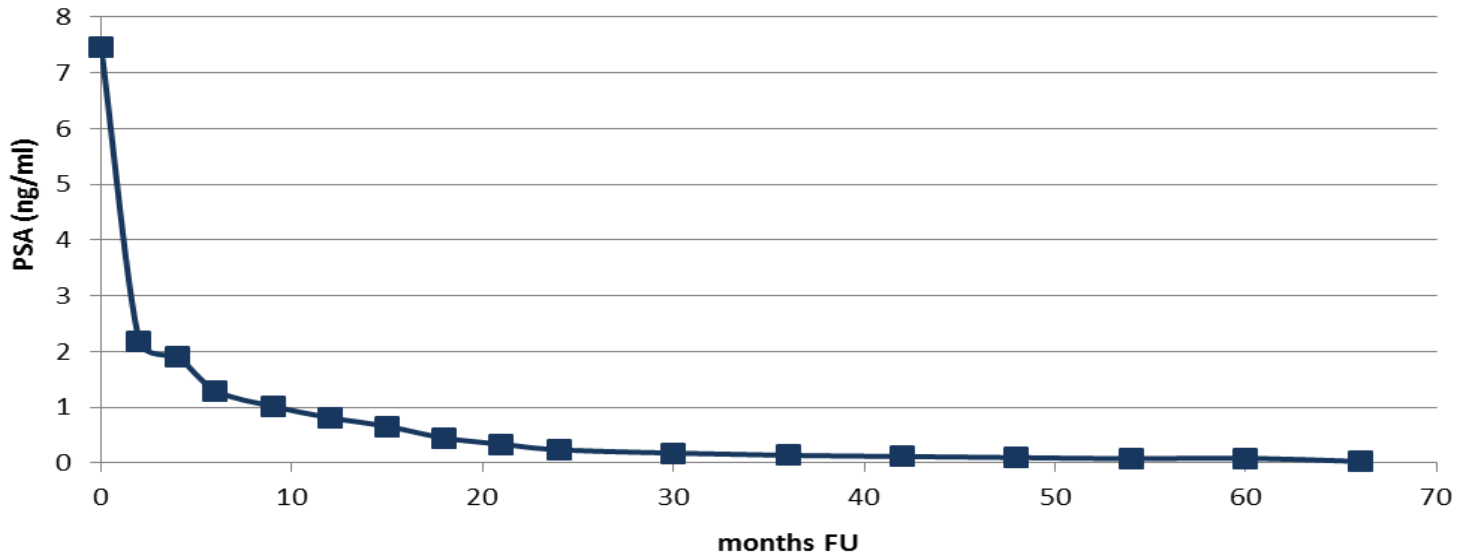
Brfs 94.5% (IC 87.9 – 100) Intermediate Risk



Brfs 85.6% (IC 71.6-99.6) High Risk

All patients are alive except for 23 that died of unrelated causes.
One patient died for bone metastases

Cdi Cyberknife center: Preliminary Results



Median PSA nadir 0.07 ng.ml

The patterns of PSA response show a gradual decline with a psa nadir below 1.0 ng.ml, 12 months after the Ck treatment

Centro Diagnostico Italiano : preliminary results

Toxicity

Early

RTOG/EORTC Grade	0	I-II	III	IV
Urinary	116(53.5%)	101 (46.5%)	-	-
Rectal	172(79.3%)	44 (20.3%)	1 (0.5%)	-

Late

RTOG/EORTC Grade	0	I-II	III	IV
Urinary	170(78.3%)	39 (18%)	7 (3%)	1(0.5%)
Rectal	15 (95%)	10 (5%)	-	-

Stereotactic body radiation therapy for prostate cancer—a review

Waqar Haque¹, E. Brian Butler², Bin S. Teh²

Study	Number of patients	Radiation therapy device	Study type	Median follow up time (months)	Dose and fractionation	Actuarial FFBF	RTOG/CTCAE late GI toxicity ≥ grade 3 (%)	RTOG/CTCAE late GU toxicity ≥ grade 3 (%)
King <i>et al.</i> (25)	1,100 (641 L, 334 I, 125 H)	Robotic arm	Phase II	36	35–40 Gy in 5 fx	5 years: 93% (95% L, 84% I, 81% H)	NR	NR
Katz <i>et al.</i> (26)	477 (324 L, 153 I)	Robotic arm	Retrospective	72	35–36.3 Gy in 5 fx	7 years: 93.7% (95.9% L, 89.3% I)	0	1.70
Meier <i>et al.</i> (27)	309 (172 L, 137 I)	Robotic arm	Phase II	61	40 Gy in 5 fx	5 years: 87.1% (97.3% L, 97.1% I)	0	2
Bernetch <i>et al.</i> (28)	142 (61 L, 63 I, 18 H)	Robotic arm	Retrospective	38	35–37.5 Gy in 5 fx	5 years: 92.7% (94.4% L, 94.2% I, 83.9% H)	0	2
Friedland <i>et al.</i> (29)	112	Robotic arm	Retrospective	24	35–36 Gy in 5 fx	97% FFBF (actuarial value not reported)	1	0
Mantz <i>et al.</i> (30)	102 (L)	Gantry	Retrospective	48	40 Gy in 5 fx	5 years: 100%	0	0
Bolzicco <i>et al.</i> (31)	100 (41 L, 42 I, 17 H)	Robotic arm	Prospective, single institution	36	35 Gy in 5 fx	3 years: 94.4%	0	1
Hannan <i>et al.</i> (32)	91 (33 L, 58 I)	Gantry	Phase I-II	54	45–50 Gy in 5 fx	5 years: 98.6% (100% L, 98% I)	6.80	6
D'Agostino <i>et al.</i> (33)	90 (53 L, 37 I)	Gantry	Phase II	27	35 Gy in 5 fx	100% FFBF for L, 94.5% FFBF for I (actuarial not reported)	0	0
Loblaw <i>et al.</i> (34)	84 (L)	Gantry	Phase I-II	55	35 Gy in 5 fx	5 years: 98%	1	1
Fuller <i>et al.</i> (35)	79 (40 L, 39 I)	Robotic arm	Retrospective	60	38 Gy in 4 fx	5 years: 100% L, 92% I	0	6
Rucinska <i>et al.</i> (36)	68 (7L, 61 I)	Gantry	Prospective, single institution	24	33.5 Gy in 5 fx	100% FFBF (actuarial value not reported)	0	0
McBride <i>et al.</i> (37)	45 (L)	Robotic arm	Phase I	44.5	36.3–37.5 in 5 fx	3 years: 97.7%	4.40	2.20
Lee <i>et al.</i> (38)	45 (6 L, 26 I, 13 H)	Robotic arm	Retrospective	63	36 Gy in 5 fx	5 years: 89.7%	0	4.40
Kang <i>et al.</i> (39)	44 (5 L, 28 I, 11 H)	Robotic arm	Retrospective	40	34–36 Gy in 4 fx	5 years: 100% L, 100% I, 90.8% H	0	0
Madsen <i>et al.</i> (40)	40 (L)	Gantry	Phase I/II	41	33.5 in 5 fx	4 years: 90%	0	0

- **Cyberknife SBRT represents a non invasive method for the definitive treatment of localized prostate cancer.**
- **Biochemical control results at 6 years and early and late toxicity in line with the literature, not inferior to IMRT hypofractionated treatments.**
- **A longer follow-up is necessary to evaluate and validate the trend of clinical outcomes and late toxicity.**