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Cyberknife for Prostate Cancer

Mohamed S. Zaghloul, MD

Children's Cancer Hospital, Egypt (CCHE)
and
National Cancer Institute, Cairo University

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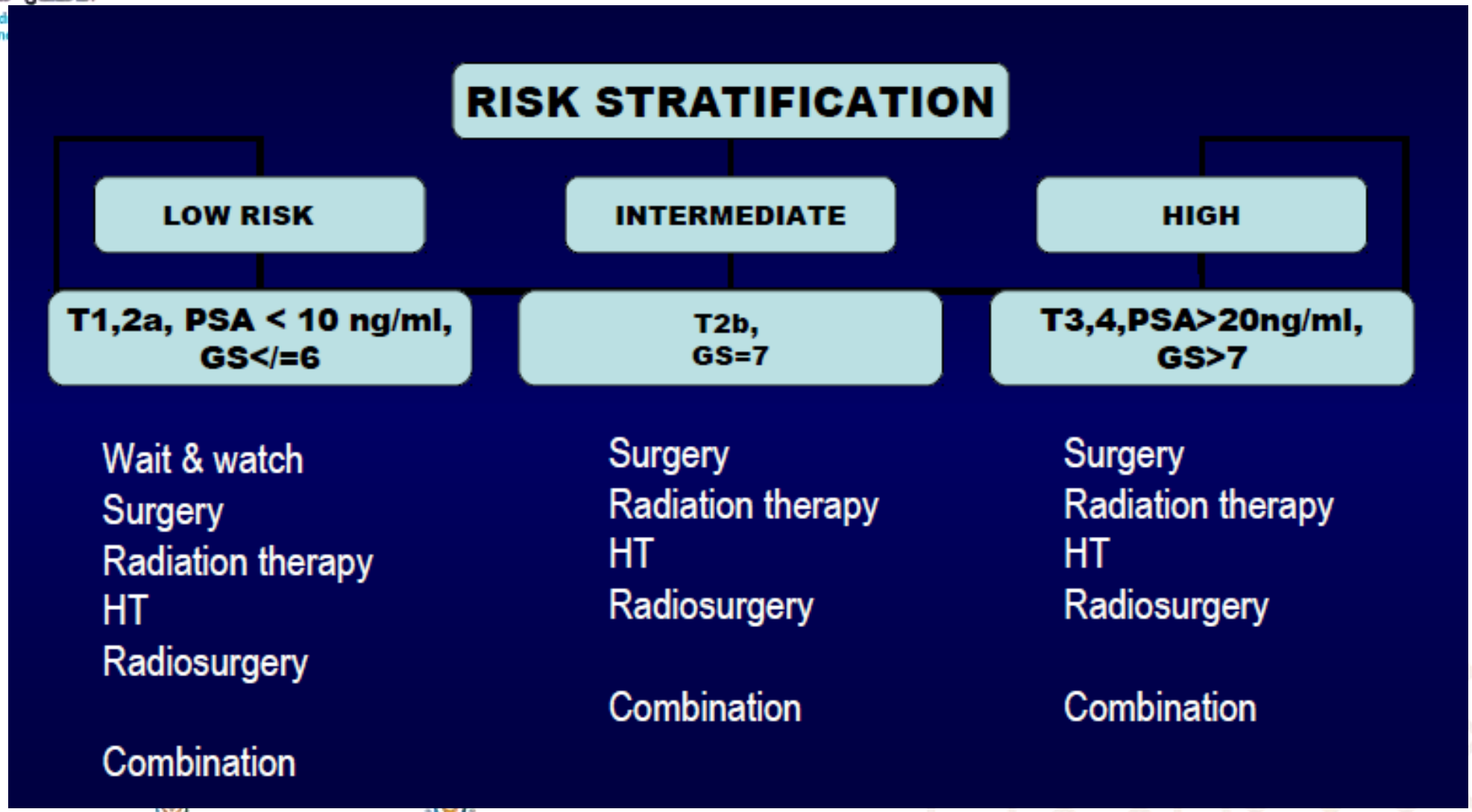
Prostate Cancer

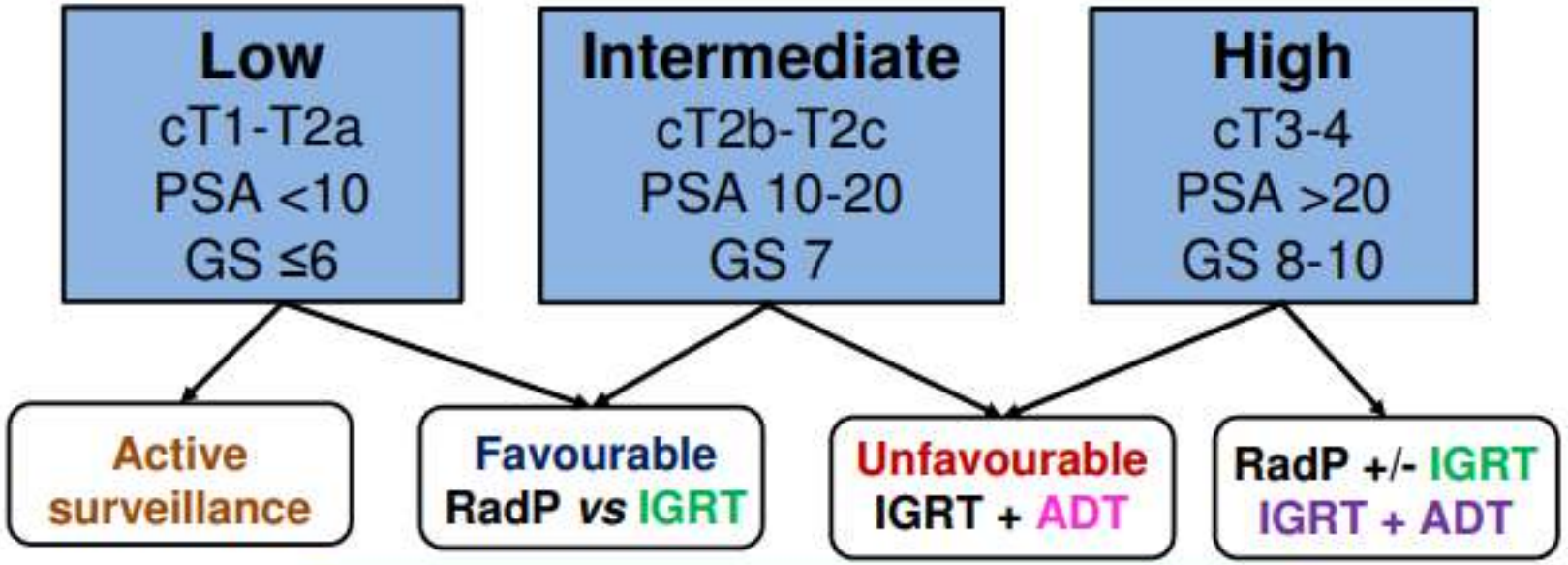
- Most prevalent malignancy in males in western community
- 2nd MC cause of mortality in the west
- In recent years, more early prostate cancer patients are diagnosed with prostate cancer
- Prostate cancer is slow growing tumour, risk of bone metastasis is high in 'high risk' group patient

Incidence of pelvic LN metastasis at diagnosis

Study	T1a,b	T1c	T2a	T2b,c	T3
Pisansky	12/457 (2.6%)	15/456 (3.3%)	130/1206 (10.8%)	81/320 (25%)	-
Petros & Catalona	2/61 (3.3%)		33/425 (7.8%)		0
Sands	6/127 (5%)		41/243 (16.9%)		95/199 (47.7%)
Van Poppel	2/40(5%)		18/199 (9%)		25/46 (54%)
Hanks	1/21(5%)		38/135(28%)		48/95(50%)


RISK STRATIFICATION
LOW RISK
INTERMEDIATE
HIGH
T1,2a, PSA < 10 ng/ml, GS</=6
T2b, GS=7
T3,4,PSA>20ng/ml, GS>7
Wait & watch
Surgery
Radiation therapy
HT
Radiosurgery
Combination
Surgery
Radiation therapy
HT
Radiosurgery
Combination
Surgery
Radiation therapy
HT
Radiosurgery
Combination

Treatment of Prostate Cancer



NCCN Zumsteg-Spratt critieria (Eur Urol, 2013)

Sub-stratification for IR-PCa

- ≥50% +ve biopsy cores
- Primary GG 4
- ≥2 NCCN IRF – cT2b,c; GS 7; PSA 10-20 ng/ml

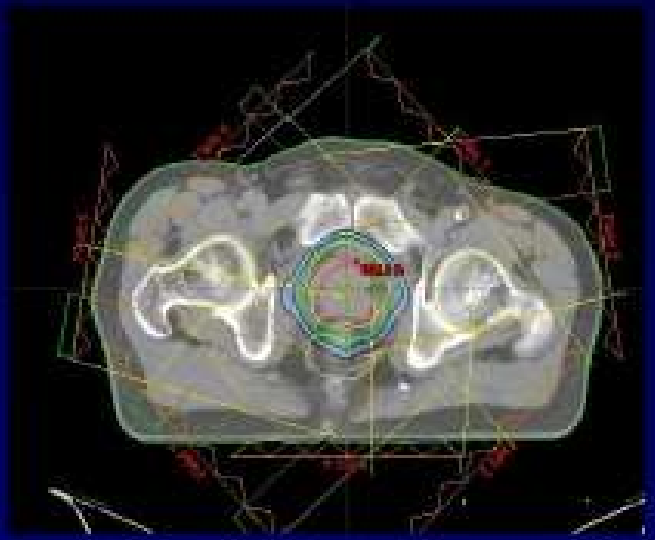
Radiotherapy

Radiation techniques:

2D Planning

Conformal Radiation therapy

- 3D-CRT
- IMRT
- SBRT



Target volume:

CTV – prostate with capsule + SV

T1 & small T2 with less PSA less GS only prostate is sufficient.

PTV – 1 cm margin.

Inclusion of pelvic lymph nodes still controversial

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1

Original Position of Prostate during treatment planning

Planned treatment area

2

Movement of anatomy during treatment

3

Without tracking prostate movement, there can be unwanted radiation to healthy tissue

Planned treatment area

Unwanted radiation to rectum and bladder

4

The CyberKnife System adjusts to movement of the anatomy, keeping the radiation only on the intended target

Adjusted treatment area

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Prostate Cancer: Hypofractionation studies

Author	*Study*	*Patient criteria*	*Study details*	*Results*
Martin	Prospect ive PMH	N= 92 June 2001- Mar 2004	60 Gy /20 fr/ 4 wks IMRT, FU: 38 mo	3 yr PSA relapse free was 76%. RTOG Gr ≥3 GI toxicity in 1 patient
Kupelian	Clevelan d Clinic	N= 770 1998-2005	70 Gy, 2 5-Gy/fr/ 5 wks. FU: 45 mo	5 yr PSA relapse free of low, intermediate and high-risk disease was 95%, 85%, and 68%, respectively.
Livsey	Retrospe clive Manches ter	N– 705 men T1-T4 disease 1995 -1998	Conformal RT (50 Gy/16fr/ 22 days) Median FU: 48 months	Favourable, intermediate, poor prognostic groups biochemical control was 82%, 56%, and 39%. RTOG Gr ≥2 GI and bowel toxicity was 5% and 9%.
Lukka	Randomi zed NCI Canada	N= 936 Mar 1995- Dec1998	Long arm: 66 Gy/33 fr 45 days Short arm: 52.5 Gy/20 fr 28 days	5 yrs, PSA relapse free survival was 52.95% in long and 59.95% in short arm. GI toxicity higher with short arm (11% vs 7%)
Isuji	Chiba Japan	N=201 June 1995-Feb 2004	Three clinical trials	RTOG Gr ≥2 GI toxicity. 5-yr PSA relapse-free survival 83.2% without any local recurrence.

Dose escalation improves local control

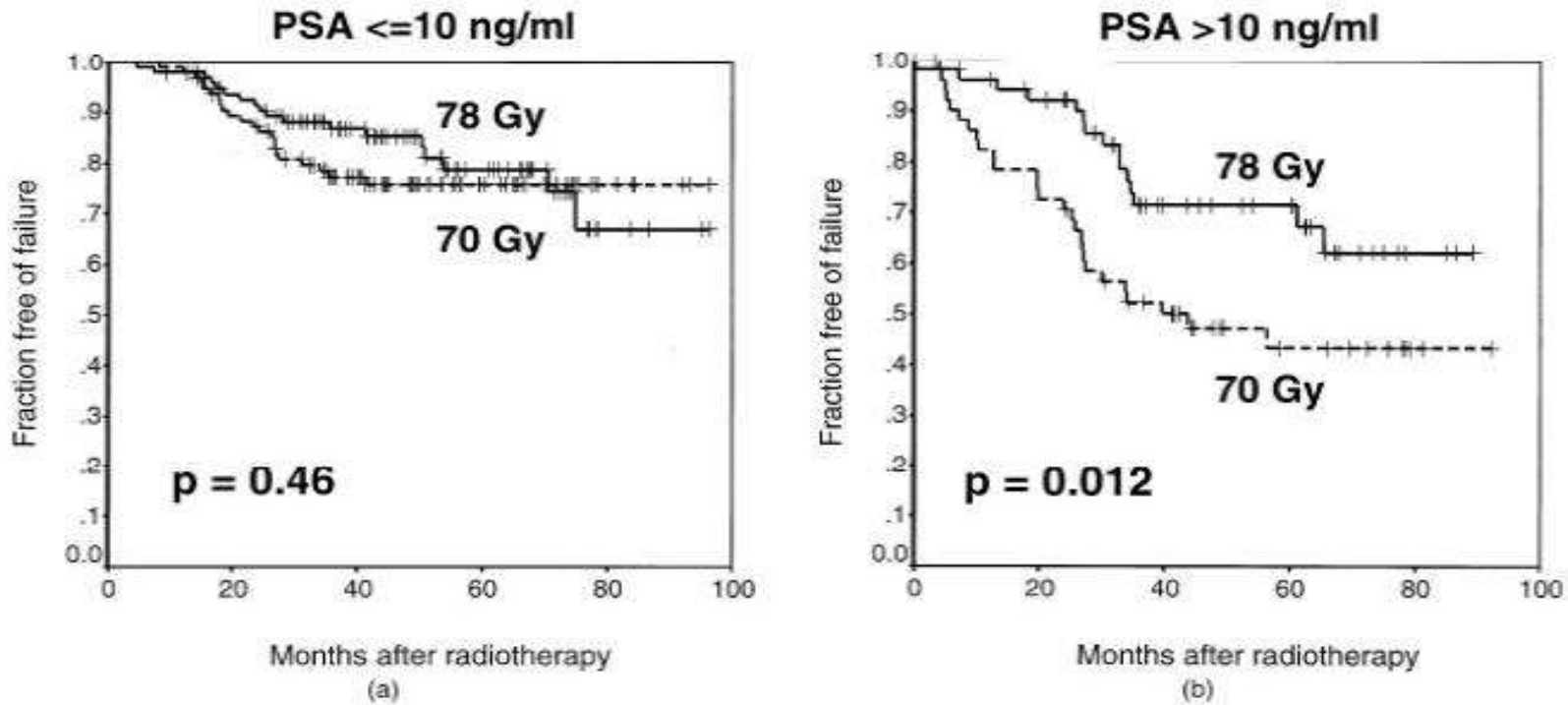


Fig. 2. Kaplan–Meier FFF curves for patients with pretreatment PSA (a) ≤10 ng/mL and (b) >10 ng/mL by dose randomization (70 Gy vs. 78 Gy).

Dose escalation : IMRT

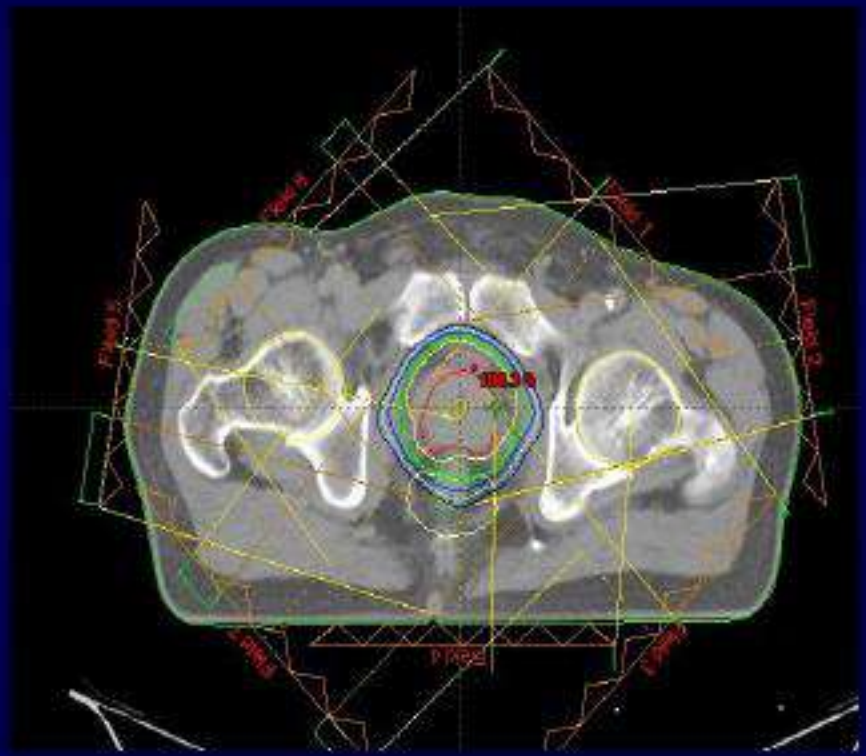
Intensity modulated radiation therapy

76- 81 Gy at 2 Gy/# dose delivered

Dose to target higher

Rectal & Bladder dose is high

High acute reactions



FRACTIONATION

CONVENTIONAL FRACTIONATION
versus
HYPOFRACTIONATION
versus
STEREOTACTIC BODY RADIOSURGERY (SBRT) or SABR

Number of fractions

1 5 ~35 45

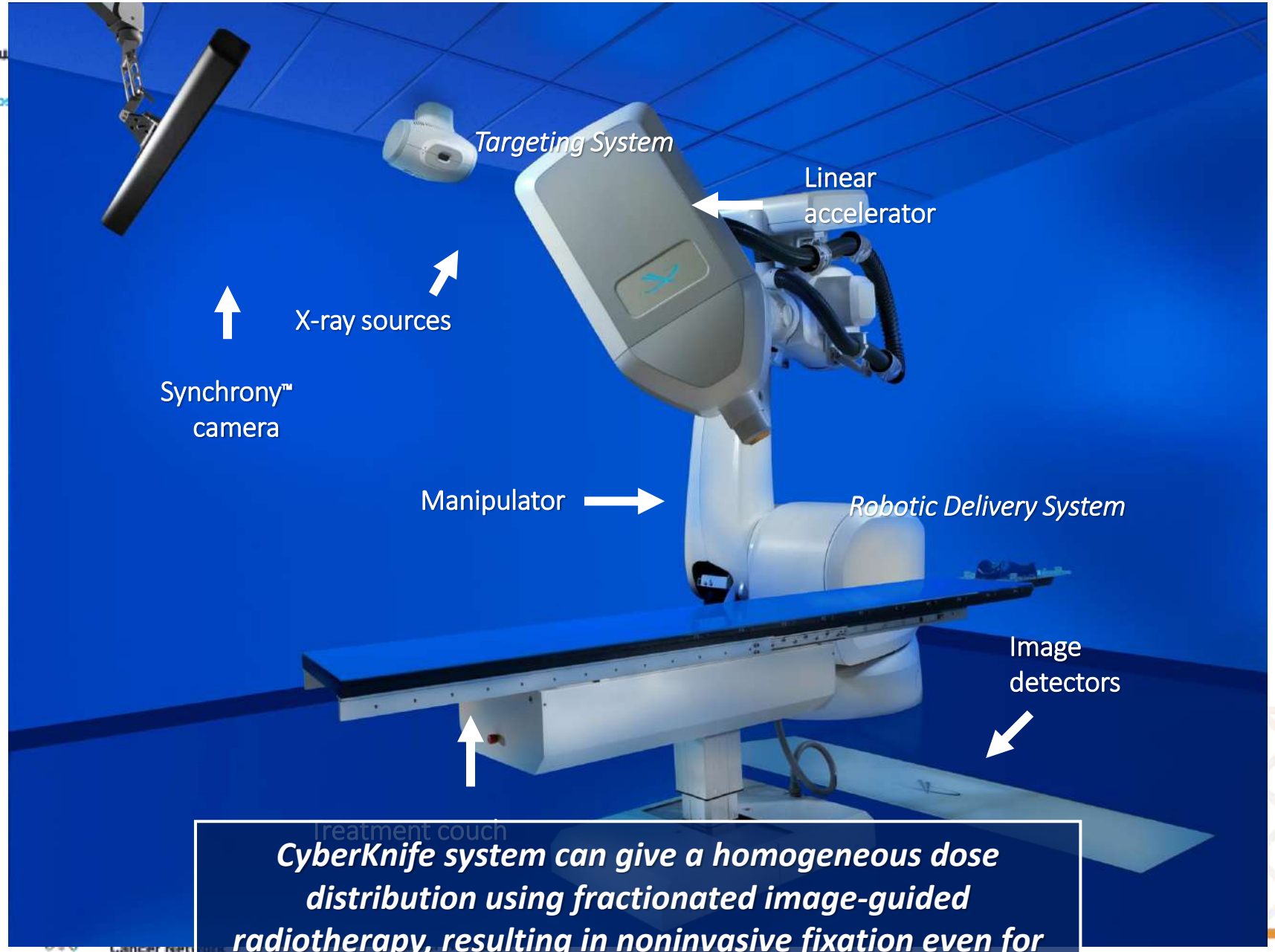
"EXTREME"
"AGGRESSIVE"
"ULTRA HIGH DOSE"

"PROFOUND"

"MILD"
"MODERATE"
"CONSERVATIVE"

Prostate Cancer: Ultra-hypofractionation studies

Author	*Study*	*Patient criteria*	*Study details*	*Results*
King	Prospective	N=41 Stanford	SBRT (CyberKnife) 36.25 Gy/ 5 fr/ 1 week Median FU: 33 months	Biochemical control 100% At 12 months, 78% achieved PSA nadir RTOG Gr ≥3 rectal toxicity 4.8%
Friedland	Prospective	N=112 Naples Feb2005-Dec 2006	SBRT (CyberKnife) RT dose: 35-36 Gy/5 fr Median FU: 24 months	3 patients had failure (two local and one distant failure). 82% no erectile dysfunction



CyberKnife system can give a homogeneous dose distribution using fractionated image-guided radiotherapy, resulting in noninvasive fixation even for other than cranial lesions

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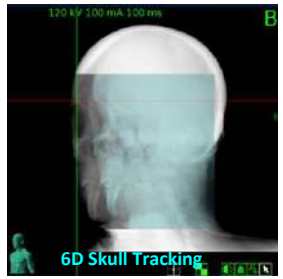
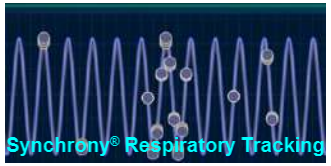
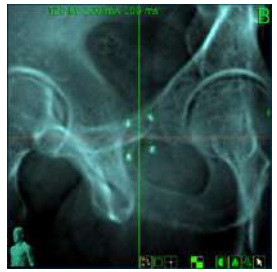
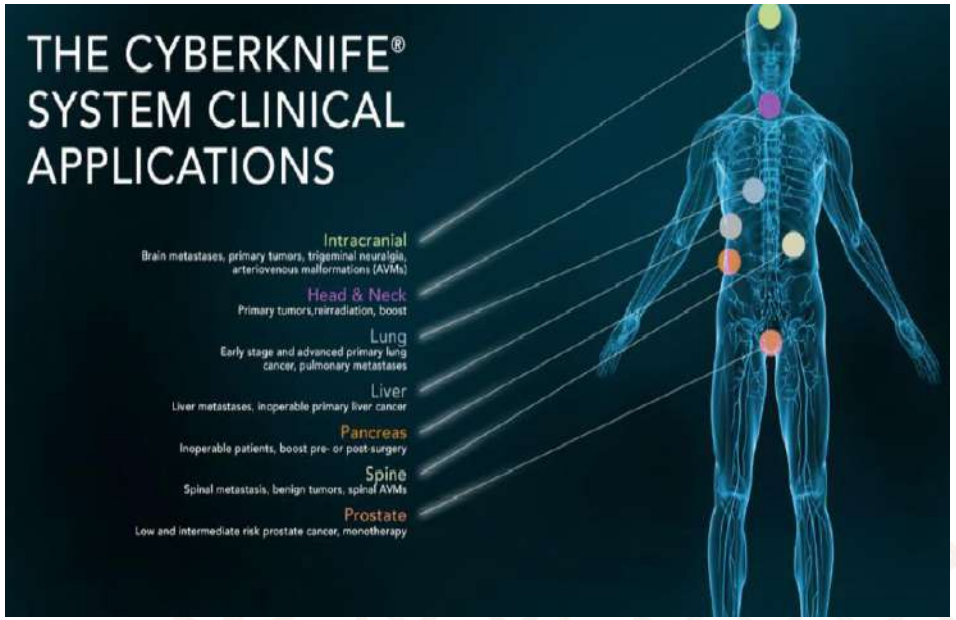
Full body Radiosurgery (SRS) and SBRT







Fiducial Tracking



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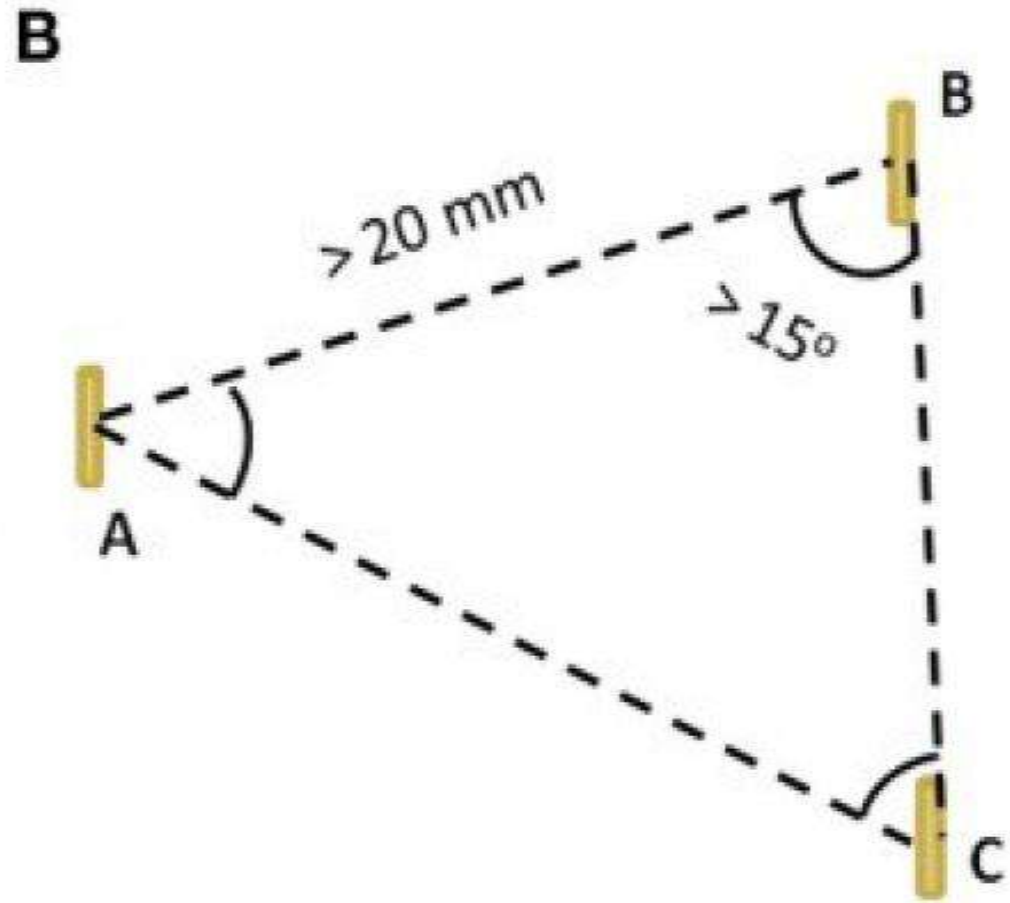
How is the technology different?

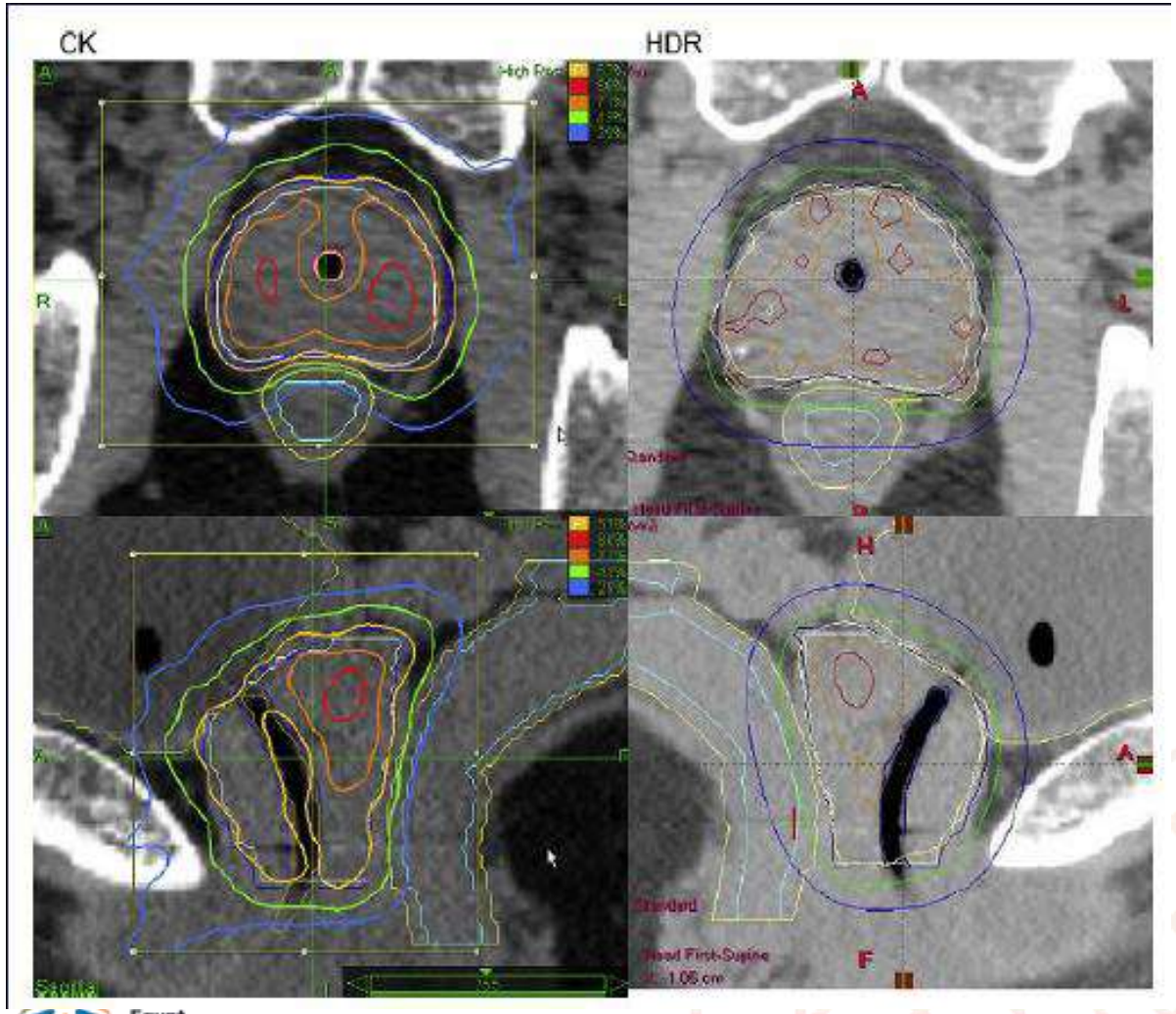
- Advanced interactive robotics (Linac & Couch).
- Real-time imaging.
- Dynamic automated motion tracking.
- Flexible and accurate linac multiple-beam radiation delivery.
- Robotic couch for more automated and accurate radiation dose delivery.

FIDUCIAL TRACKING

- The fiducial tracking system enables tracking extracranial tumors by tracking implanted fiducial markers. Fiducial traking mode correlates fiducial location in reference DRR images with live x-ray images to extract fiducial location.Fiducial tracking mode allow tracking and treating tumours.

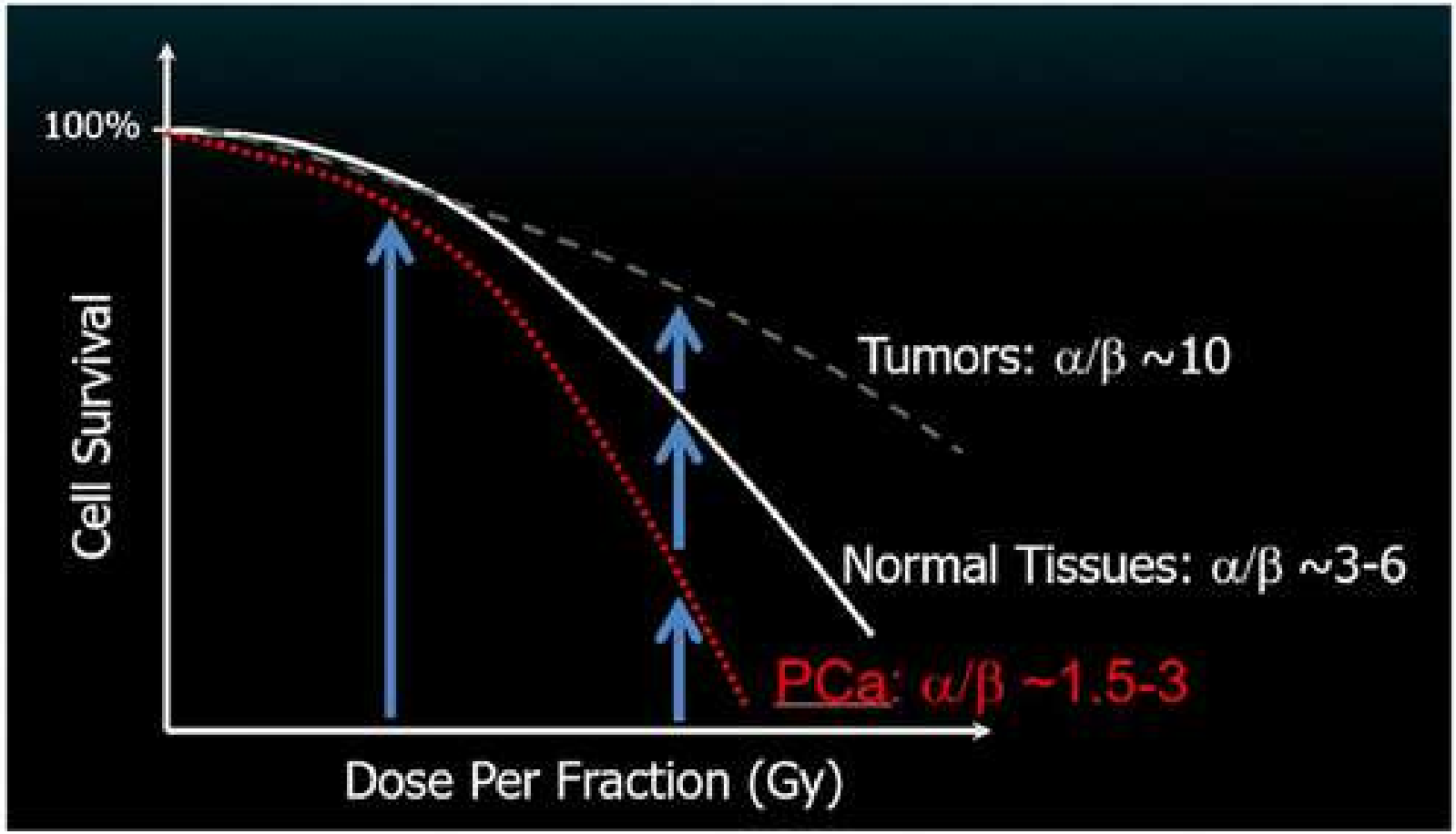

B
B
> 20 mm
> 15°
A
C

Isodose distribution in Cyberknife



Fullar et al, Int J Radiat Oncol Biol Phys. 2008

Hossain et al. Int J Radiat Oncol Biol Phys. 2010



SBRT DOSE SCHEDULES

Dose ranges:	BED (α/β=2)	
6.70 x 5 = 33.5 Gy	146	Madsen IJROBP 2007
7.25 x 5 = 36.25 Gy	168	King IJROBP 2009 King IJROBP 2011 Friedland TCRT 2009 Katz BMC Urol 2010 Wiegner IJROBP 2010 Bolzicco TCRT 2010 Aluwini J Endourol 2010 Freeman RO 2010 Townsend AJCO 2011 Kang Tumori 2011 Jabbari IJROBP 2011 Chen RO 2013
7.5 x 5 = 37.5 Gy	178	
9.0 x 4 = 36.0 Gy	198	Fuller IJROBP 2008
8.0 x 5 = 40.0 Gy	200	King RO 2013 Meier TCR 2014 Mantz FO 2014
9.0 x 5 = 45.0 Gy	248	Kim IJROBP 2014
9.5 x 5 = 47.5 Gy	273	
10.0 x 5 = 50.0 Gy	300	
24 x 1 = 24 Gy	312	Greco, Lisbon

BED equivalent to LDR or HDR prostate RT

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Comparable Late Toxicity

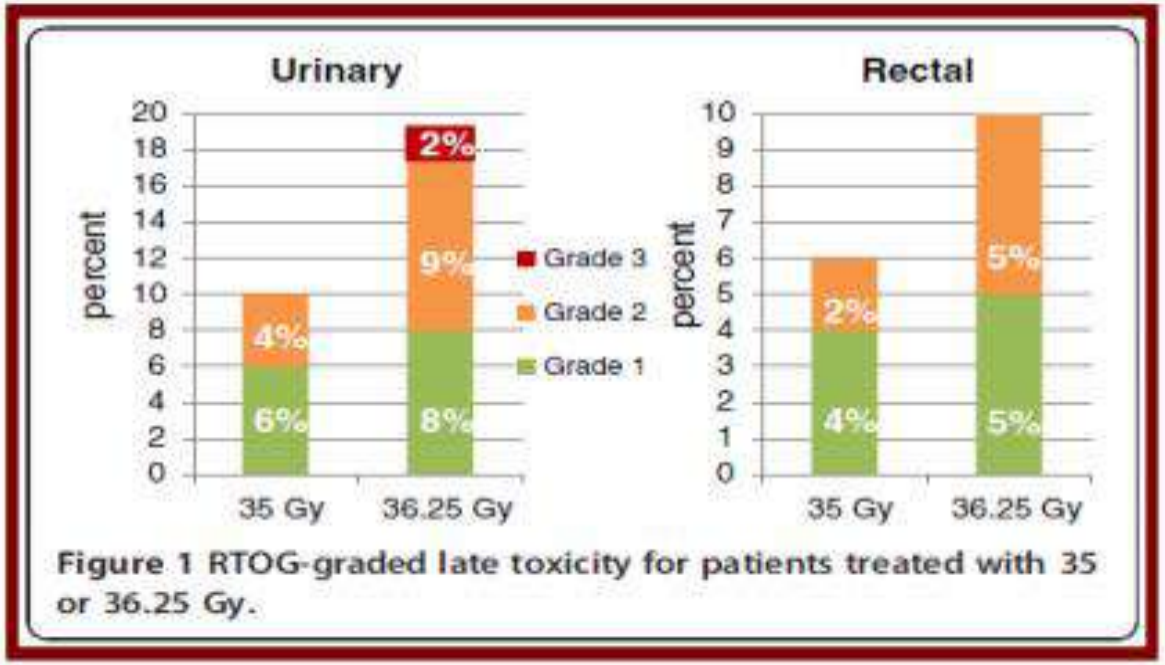

Figure 1 RTOG-graded late toxicity for patients treated with 35 or 36.25 Gy.

Table 3. Comparison of late urinary (GU) and rectal (GI) toxicity on the RTOG scale from the dose-escalation arm of randomized trials and intensity-modulated radiotherapy–based hypofractionated studies

Series	*n*	Dose/no. fx and median FU	GI Gr. 2	GI Gr. 3	GI Gr. 4	GU Gr. 2	GU Gr. 3	GU Gr. 4
Dutch†	333	78/39 and 4.2 yr	27%	5%	0%	26%	13%	0%
MDA‡	151	78/39 and 8.7 yr	19%	7%	0%	7%	3%	0%
MGH§	196	79.2/44 and 8.9 yr	24%	1%	0%	27%	2%	0%
RTOI¶	422	74/37 and 5.2 yr	20%	6%	0%	4%	4%	0%
Kupelian‖	770	70/28 and 3.7 yr	3.1%	1.3%	0.1%	5.1%	0.1%	0%
Martin**	92	60/20 and 3.2 yr	4%	NR	0%	3%	NR	0%
Coote††	60	60/20 and 2 yr*	4%	NR	0%	4.2%	1.6%	0%
Lock‡‡	66	63.2/20 and 3 yr	25%	3.1%	1.5%	14.1%	4.7%	0%

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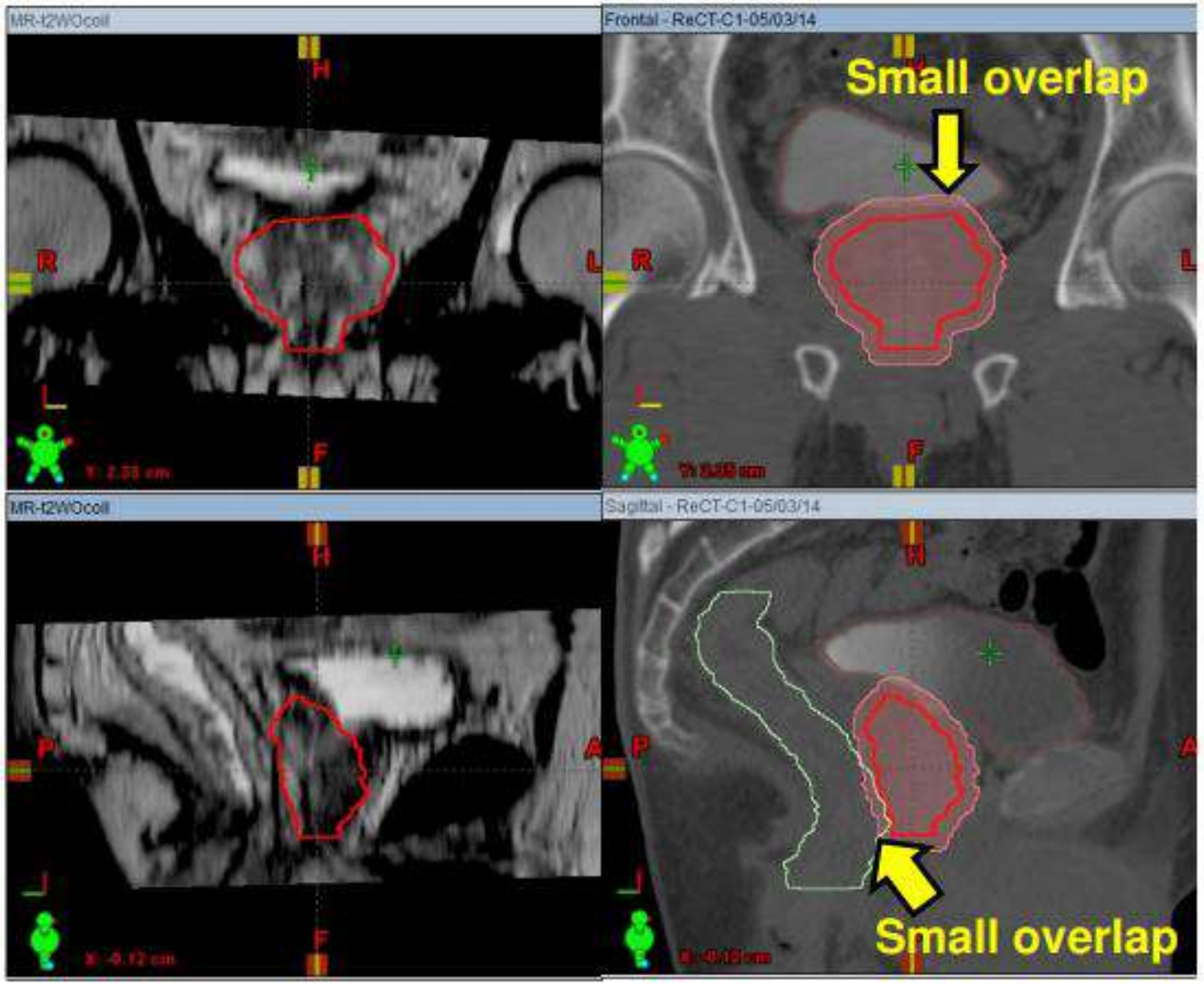
Target Contouring



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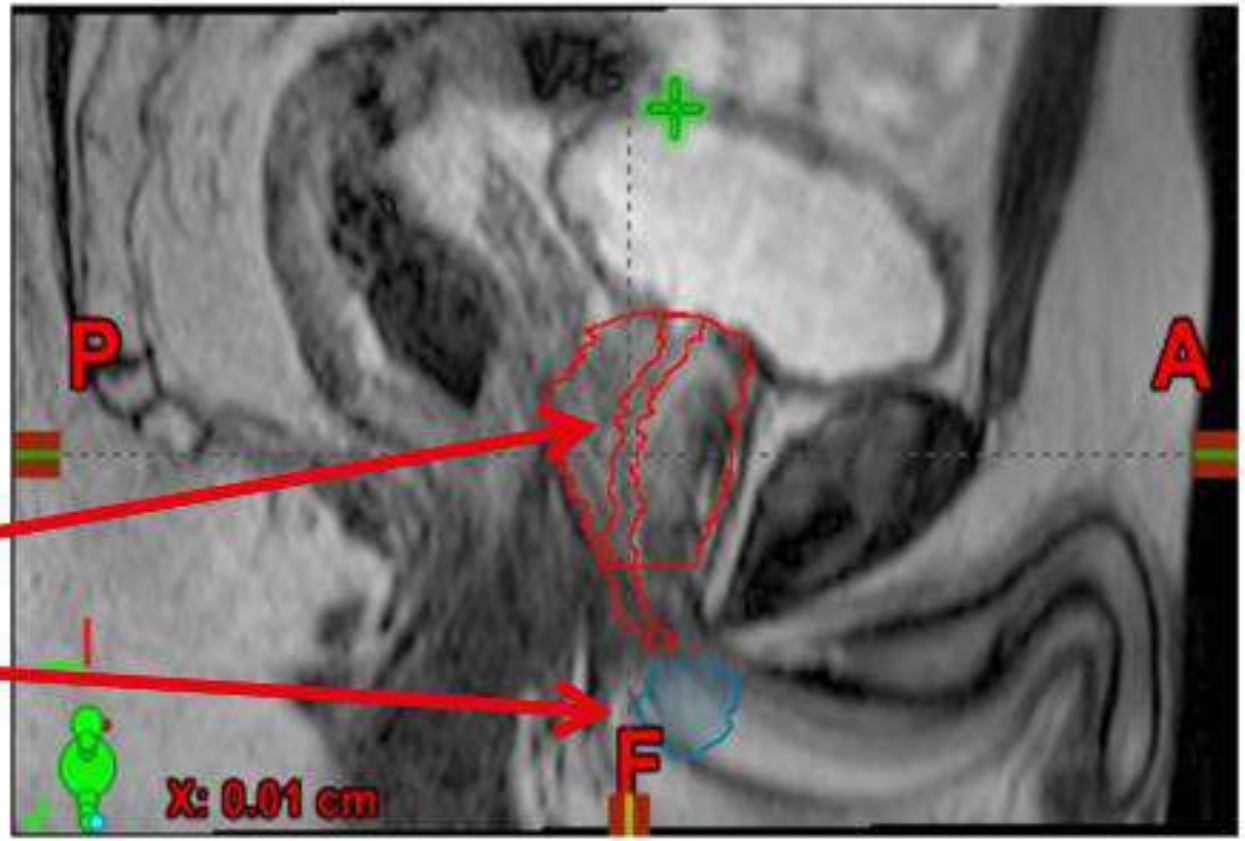
Target Contouring

- ❑Rectum
- ❑Bladder
- ❑Fem heads
- ❑Urethra
- ❑Penile bulb



RT options for Prostate Cancer Treatment

	CyberKnife	HDR	LDR	IMRT	3-D CRT	Proton
Continual image guidance throughout treatment	✔	✔	✔			
Non-invasive	✔			✔	✔	✔
Treatment time – 5 treatments or less	✔	✔				
Does not require anesthesia	✔			✔	✔	✔
Does not require operative procedure	✔			✔	✔	✔

Fullar et al, Int J Radiat Oncol Biol Phys. 2008

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Cyberknife Vs Brachytherapy

Table 1. PTV statistics: Prescription dose 38 Gy/four fractions

	CyberKnife actual	High-dose-rate simulated	*p* (paired *t* test)
Isodose prescription (%)	56 (49–67)	N/A	
PTV V100* (%)	96.5 (95.6–99.2)	96.0 (93.4–99.1)	–
PTV V125 (%)	44.0 (28.4–55.5)	67.5 (53.3–75.5)	<0.001
PTV V150 (%)	8.5 (0.3–20.5)	37.8 (25.4–45.6)	<0.001
PTV D90 (Gy)	39.8 (39.3–40.9)	41.3 (39.6–43.9)	.002

Fullar et al, Int J Radiat Oncol Biol Phys. 2008

Cyberknife Vs Brachytherapy

Table 3. Rectal wall and mucosa statistics

	CyberKnife actual	High-dose-rate simulated	*p* (paired *t*-test)
Rectal wall V80 (ml)	1.3 (0.3–4.0)	2.4 (0.6–6.0)	0.06
Rectal wall Dmax (Gy)	37.3 (34.7–38.0)	37.5 (34.6–43.3)	Not significant
Rectal wall D1 (Gy)	33.3 (29.6–34.7)	34.7 (30.5–37.2)	0.02
Rectal wall D10 (Gy)	23.2 (20.0–25.6)	25.7 (20.7–30.7)	0.002
Rectal wall D25 (Gy)	15.8 (13–18.7)	19.4 (13.7–24.5)	<0.001
Rectal mucosa V80 (ml)	0.0 (0.0–0.7)	0.1 (0.0–2.3)	Not significant
Rectal mucosa Dmax (Gy)	29.0 (25.3–33.5)	31.4 (27.4–35.0)	0.04
Rectal mucosa D1 (Gy)	25.9 Gy (22.1–30.2)	29.0 Gy (24.8–33.6)	0.001
Rectal mucosa D10	19.5 (16.3–22.7)	23.8 (18.5–28.9)	<0.001
Rectal mucosa D25 (Gy)	14.2 (11.7–17.3)	19.4 (13.6–23.8)	<0.001

Fullar et al, Int J Radiat Oncol Biol Phys. 2008

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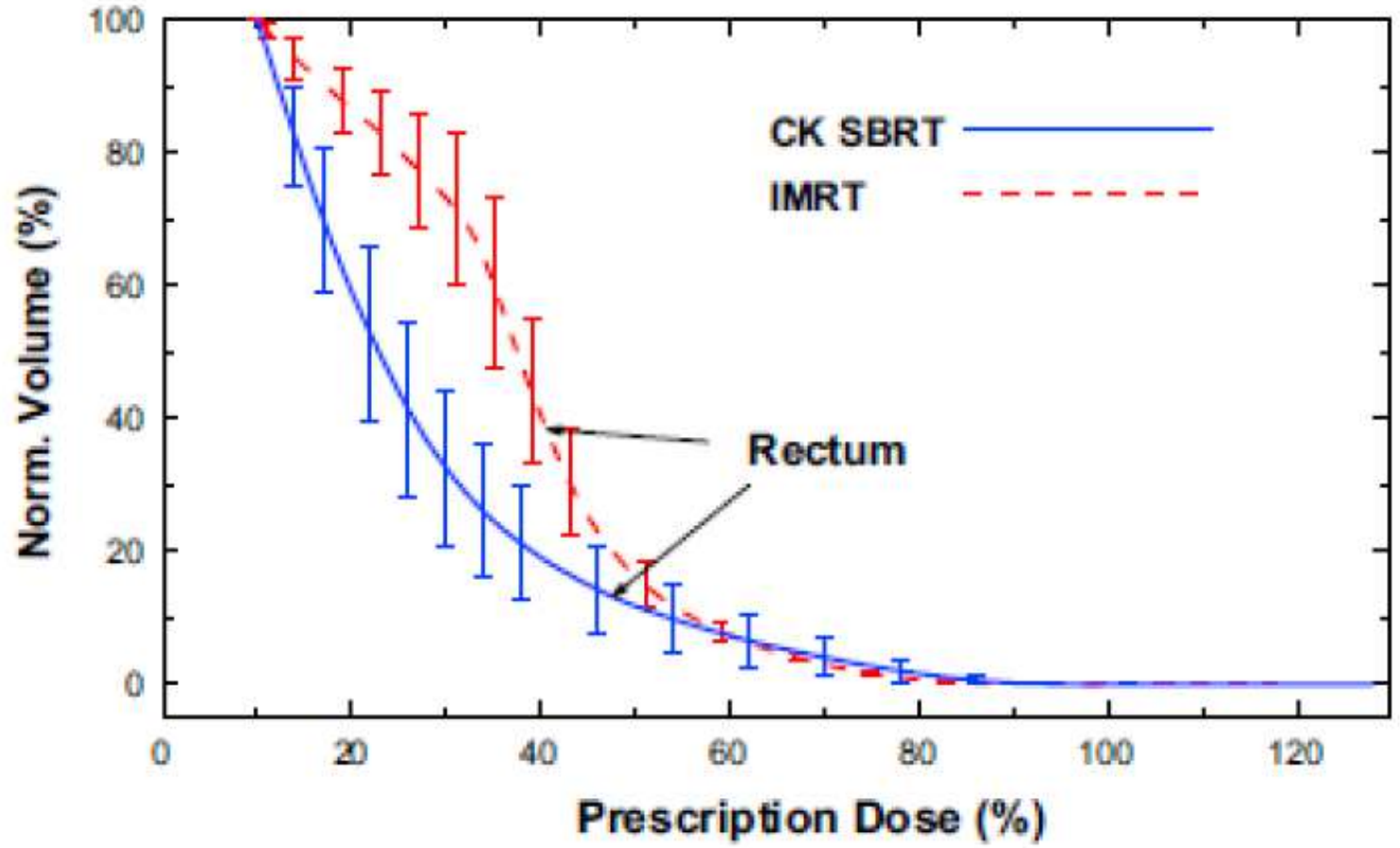
Cyberknife Vs IMRT

Structure	$V_{x\%}$	CK SBRT	IMRT	*p*
CTV				
	$V_{95\%}$	98.41 ± 0.87	98.09 ± 0.35	.27
	$V_{100\%}$	95.09 ± 0.62	95.46 ± 0.34	.12
	$V_{125\%}$	7.04 ± 4.63	3.52 ± 4.51	.08
Bladder				
	$V_{30\%}$	46.71 ± 7.72	50.31 ± 8.32	.24
	$V_{40\%}$	27.57 ± 8.33	31.56 ± 6.63	.06
	$V_{50\%}$	15.99 ± 7.12	18.28 ± 4.35	.19
	$V_{60\%}$	9.05 ± 5.01	9.72 ± 2.34	.62
	$V_{75\%}$	3.34 ± 2.15	2.58 ± 0.64	.24
	$V_{80\%}$	2.13 ± 1.44	1.33 ± 0.35	.11
Rectum				
	$V_{30\%}$	32.59 ± 11.82	73.29 ± 10.61	<.01
	$V_{40\%}$	19.19 ± 7.96	44.26 ± 10.91	<.01
	$V_{50\%}$	11.83 ± 5.87	16.32 ± 3.88	.11
	$V_{60\%}$	7.41 ± 4.22	7.42 ± 1.33	.99
	$V_{75\%}$	2.79 ± 2.02	1.74 ± 0.35	.18
	$V_{80\%}$	1.35 ± 0.48	0.29 ± 0.10	.11

Hossain et al, Int J Radiat Oncol Biol Phys. 2010

Cyberknife Vs IMRT: Rectal dose distribution



CI & HI in different techniques

Table 1. Conformity index and homogeneity index values for each patient for CK SBRT and simulated IMRT plans

		CI			HI		
Pt. No.	Volume (cm^3)	CK SBRT	IMRT	ΔCI%	CK SBRT	IMRT	ΔHI%
1	138.0	1.13	1.24	−8.87	1.33	1.18	12.71
2	95.6	1.31	1.41	−7.09	1.35	1.31	3.05
3	67.3	1.11	1.58	−29.75	1.39	1.38	0.72
4	64.0	1.11	1.52	−26.97	1.67	1.30	28.46
5	41.7	1.13	1.41	−19.86	1.39	1.27	9.45
6	40.0	1.16	1.54	−24.68	1.41	1.30	8.46
7	36.2	1.20	1.35	−11.11	1.49	1.20	24.17
8	28.0	1.30	1.45	−10.34	1.56	1.27	22.83
Mean	60.9	1.18	1.44	−17.33	1.45	1.28	13.73
SD	37.1	0.08	0.11	9.03	0.12	0.06	10.28
p		<.01		.01			

Hossain et al, Int J Radiat Oncol Biol Phys. 2010

	Treatment Option	Late Toxicity ‡‡ (Grade 3 or higher)	Disease Free Survival
External Beam Radiation Therapy (EBRT)	3-D CRT ‡	3-13%	84-97% (5-year)
	IMRT	0-8%	81% (10-year, low risk); 78% (10-year, intermediate risk); 62% (10-year, high risk)
	Proton	Not Reported	73% (10-years)
Stereotactic Body Radiation Therapy (SBRT)	**CyberKnife**	**0-2%**	**93% (5-years)**
Brachytherapy†	HDR	0-3%	89% (5-years)
	LDR	0-3%	88% (5-years)

Cyberknife Results for Prostate Cancer

Summary of published CyberKnife prostate treatment results with a median follow-up of more than 12 months.

Study	Median Follow-up (months)	PSA Freedom from Relapse (%)	Grade 3+ Late Urinary Toxicity	Grade 3+Late Bowel Toxicity	Erectile Function Preservation Rate
King *et al.* (8)	33	100%	5%	0%	40%*
Friedland *et al.* (9)	24	97%	0%	0%	82%
Katz *et al.* (10)	30	100%	0%	0%	87%
	17	98%	0.5%	0%	

*Wiegner *et al.* median 35.5 months follow-up.

Katz. Technology in Cancer Research and Treatment, 2010

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Dose level for prostate cancer treatment using cyberknife

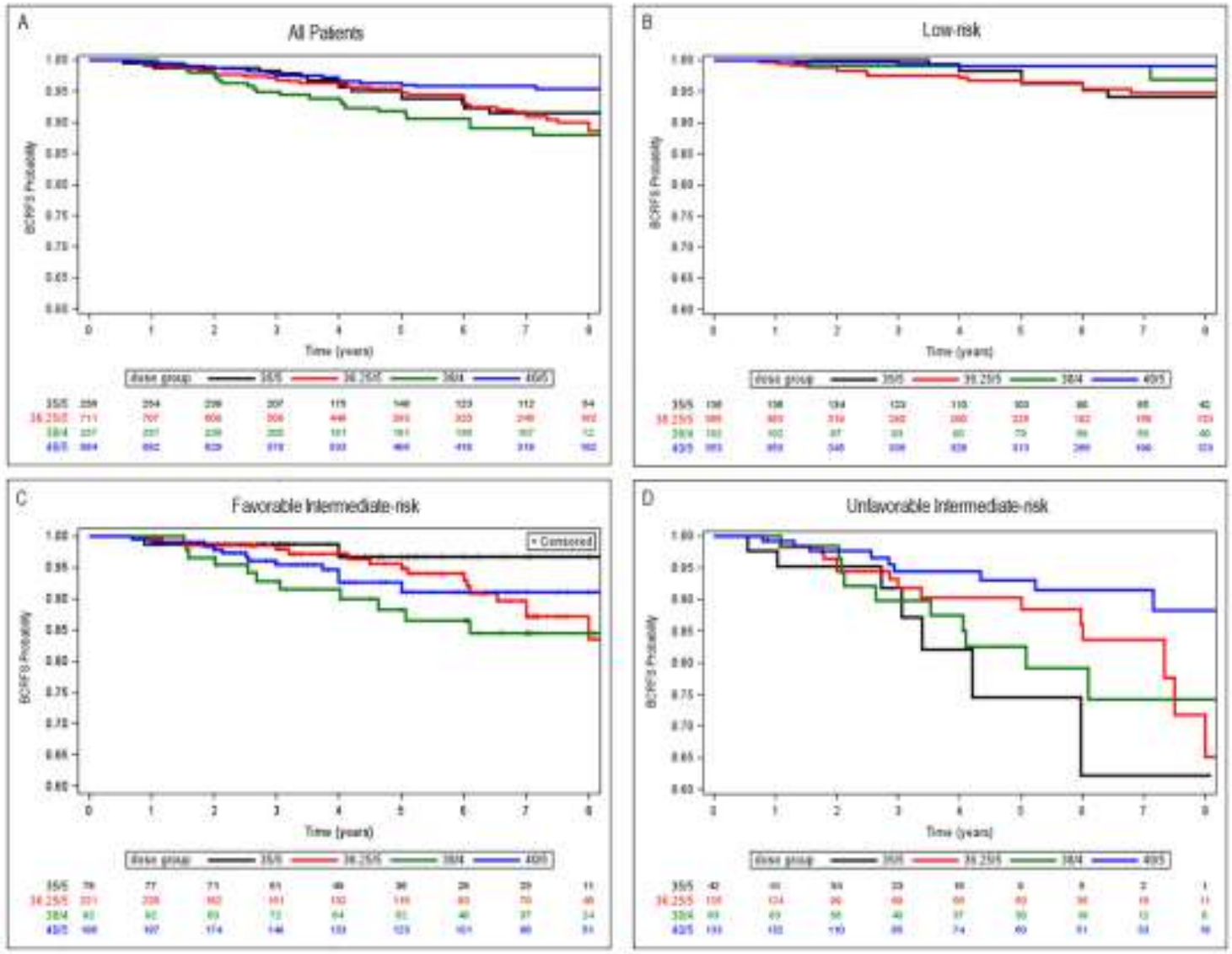

Fig. 2. Kaplan–Meier curves for biochemical recurrence-free survival (BCRFS) for (A) all patients, (B) low-risk disease, (C) favorable intermediate-risk disease, and (D) unfavorable intermediate-risk disease, treated with one of four SBRT dose regimens without neoadjuvant/concurrent androgen deprivation therapy.

Levin-Epstein et al. Radiotherapy & Oncology, 2021

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Dose level for prostate cancer treatment using cyberknife

Between-regimen comparisons for biochemical recurrence-free survival.

Dose group comparison	Hazard ratio (95% CI)	*p*-value
36.25/5 vs. 35/5	1.16 (0.66–2.05)	0.60
40/5 vs. 35/5	**0.49 (0.26–0.92)**	**0.026**
40/5 vs. 36.25/5	**0.42 (0.26–0.69)**	**0.0005**
40/5 vs. 38/4	**0.55 (0.31–0.97)**	**0.037**
38/4 vs. 35/5	0.90 (0.47–1.72)	0.75
38/4 vs. 36.25/5	0.77 (0.46–1.30)	0.33

CI: confidence interval; 36.25/5: "36.25 Gy in 5 fractions".

Levin-Epstein et al. Radiotherapy & Oncology, 2021

Normal Tissue Constraint

Structure	Constraint	Revised Constraint
Rectum	V36Gy < 1cc	
Bowel	V30Gy < 1cc	
Bladder	V37Gy < 5-10cc	V37Gy < 2cc
Penile bulb	D50 < 29.5Gy	
Prostatic urethra*	D20 < 47Gy	D20 < 42Gy
Membranous urethra*	D50 < 37Gy	
Neurovascular bundles*	D50 < 38Gy	D50 < 37.5Gy
Testes	no beams may traverse	

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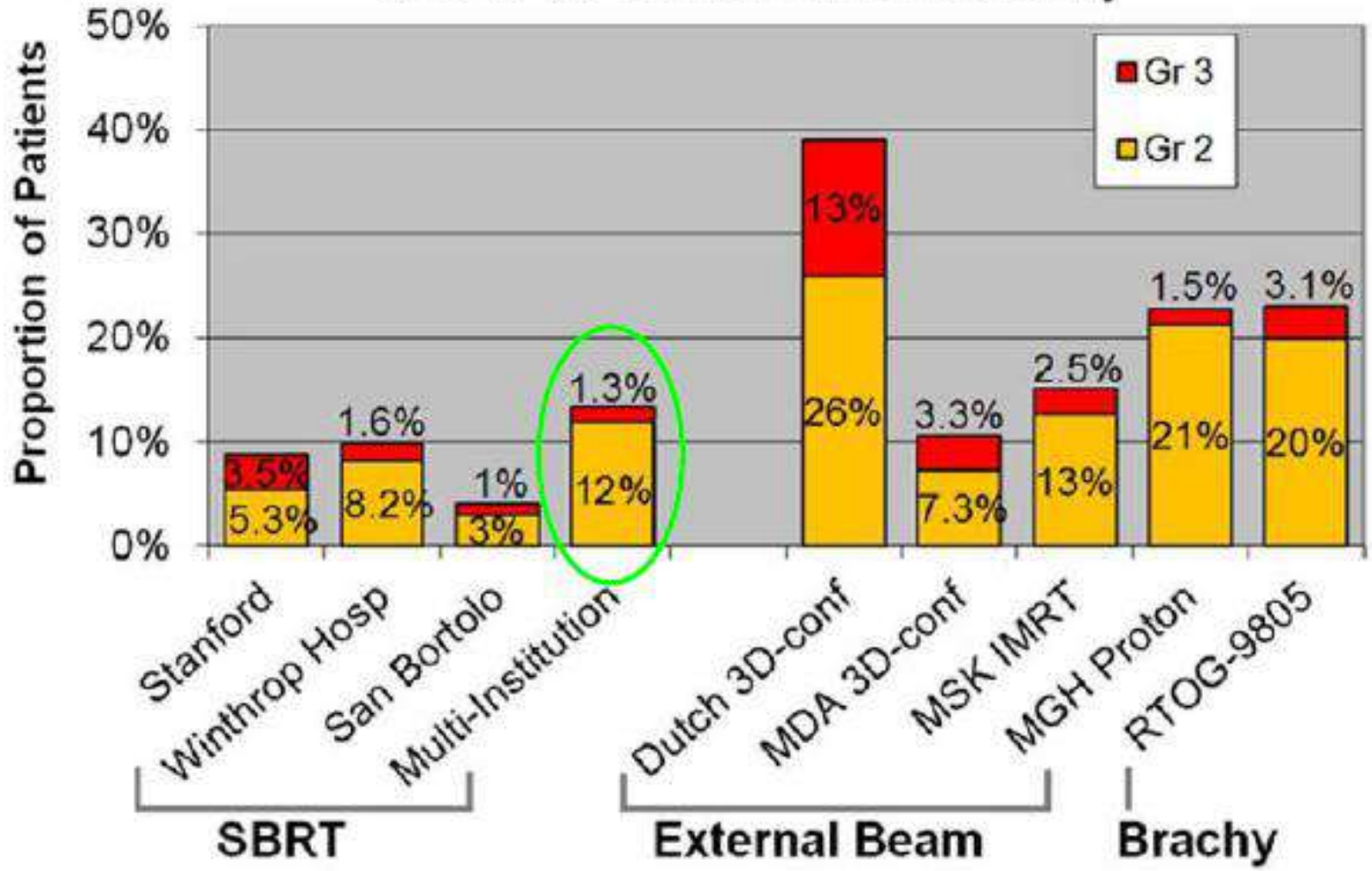
Late Urinary Toxicity
SBRT *vs* EBRT & LDR Brachy



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Children's Cancer Hospital Foundation - Egypt
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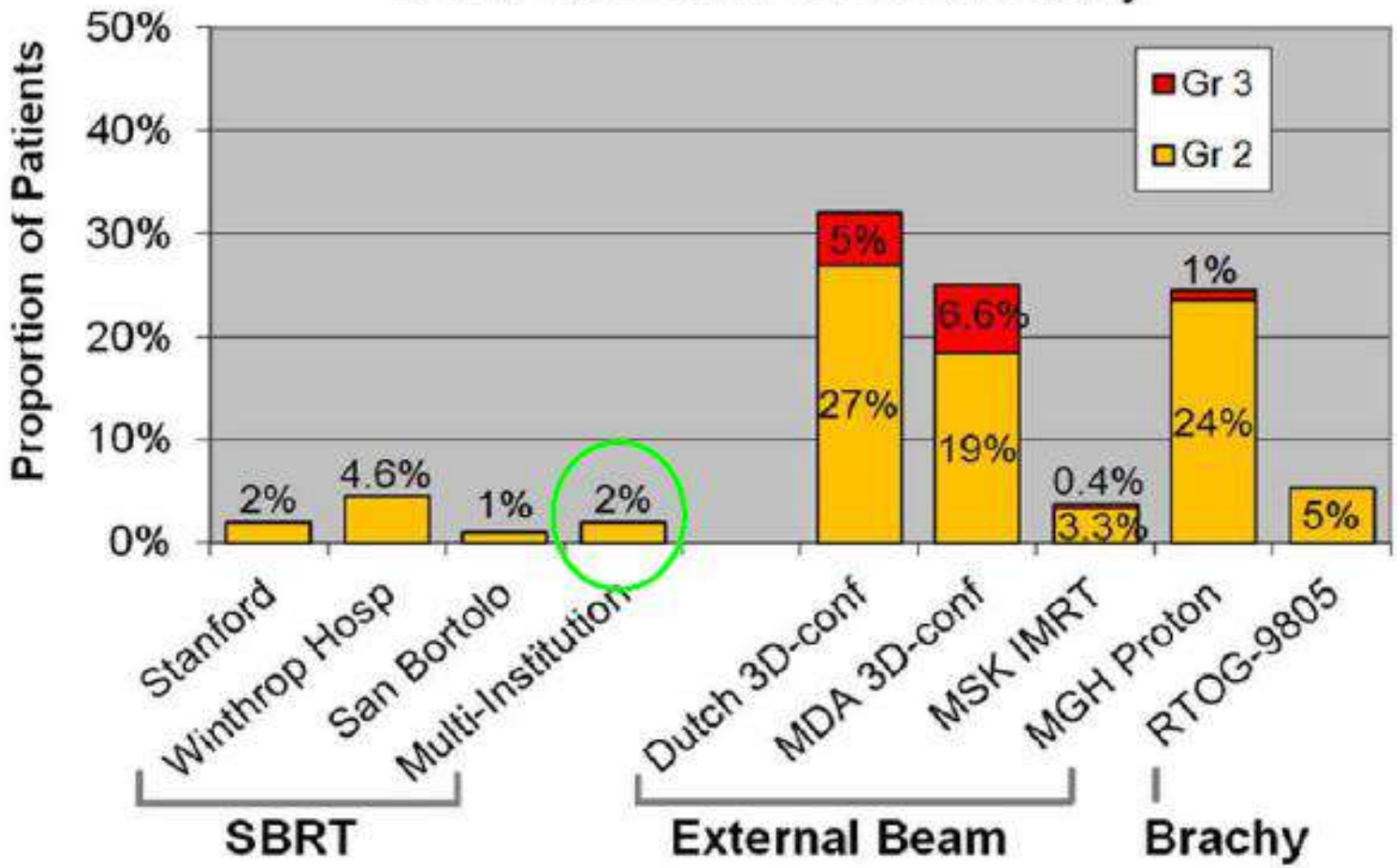
Late GI Toxicity

SBRT *vs* EBRT & LDR Brachy



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Limitations of Cyberknife

- No posterior (under couch) shooting.
- More complex planning
- Long treatment time.
- Significant QA required prior to treatment to ensure that the robotic arm acts as expected.

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Conclusion

- Using the CyberKnife® platform, dose-escalated prostate SBRT is safe, with a low rate of serious side effects.
- QOL outcomes show a brief acute effect on GI & GU QOL; Urinary irritative symptoms at 1 year resolve
- 5-year biochemical relapse rates following SBRT are very favorable compared to historical data
- CyberKnife® SBRT is a suitable option for low- and intermediate-risk prostate cancer, and may be preferable to other treatment approaches.

Thank you