THE BRISTOL CANCER INSTITUTE

University Hospitals Bristol NHS
NHS Foundation Trust

LDR or HDR Brachytherapy for low risk disease

Amit Bahl

Consultant Clinical Oncologist

The Bristol Cancer Institute, UK

Prostate cancer brachytherapy and the two faces of Janus

LDR

HDR

In ancient Roman religion and myth, **Janus** is the god of beginnings, gates, transitions, time, doorways, passages, and endings. He is usually depicted as ***having two faces***, since he looks to the future and to the past.

NCCN brachytherapy guidelines - brachytherapy

LDR

- Permanent low-dose rate (LDR) brachytherapy as monotherapy is indicated for patients with low-risk cancers.
- For intermediate-risk cancers consider combining brachytherapy with EBRT (40-50 Gy) ± 4-6 mo neoadjuvant/concomittant/adjuvant ADT.
- Patients with high-risk cancers may be treated with a combination of EBRT (40-50 Gy) and brachytherapy ± 4-6 mo neoadjuvant/concomitant/adjuvant ADT.
- Patients with a very large prostate or very small prostate, symptoms of bladder outlet obstruction (high IPSS), or a previous transurethral resection of the prostate (TURP) are more difficult to implant and may sufler increased risk of side effects.
- Neoadjuvant androgen deprivation therapy may be used to shrink the prostate to an acceptable size.

HDR Brachy in Ca Prostate

- HDR Boost
  - NICE approved
  - Usually for high-risk patients
- HDR Monotherapy
  - Increasing evidence
  - Low to intermediate risk patients
- HDR Salvage
- Focal HDR BRT

LDR vs. HDR Brachytherapy

LDR

1. Limited prostatic volume (<55 cc).
2. Probability of non symmetric distribution with 'hot' & 'cold' spots.
3. Risk of radiation exposure to physicians & staff.
4. Seeds are permanently inserted in the prostate with risk of radiation exposure to others.
5. High cost of seeds.
6. Chance for seed migration.
7. Low dose radiation.
8. Prolonged acute urinary & bowel side effects & increased late complications.

HDR

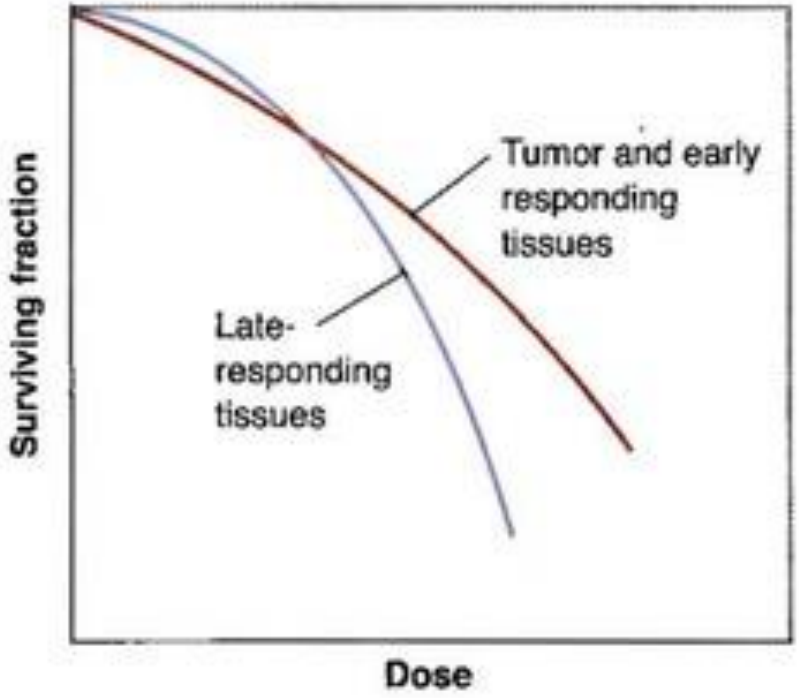
1. Treat small & large prostates.
2. Uniform radiation distribution throughout the whole prostate.
3. No radioactivity exposure.
4. No radioactive material left in the prostate.
5. Cost effective.
6. No seed migration.
7. High intensity radiation.
8. Short acute side effects & appreciable decrease of late complications.

Seeds LDR brachytherapy

Advantages over HDR

- Large worldwide clinical experience and long-term data available,
- Patient and MD convenience,
- High patient turnover in OR,
- Ideal for patients with pre-existing ED or comorbidities precluding prolonged bedrest,
- Ideal for patients with AUA scores of $\leq$12.

Radiobiology



The low alpha/beta ratio (estimated 1.2–4) means that the large fraction sizes used in HDR have a relatively high biological effectiveness for prostate cancer (15–17).

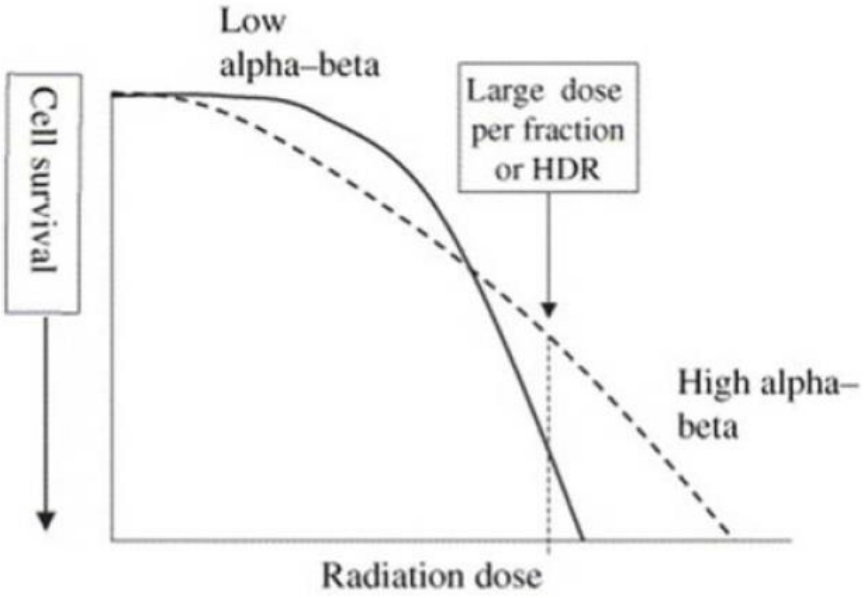


Figure 1. Idealised cell survival curves of a tissue with a low α/β ratio (solid line) and one with a high α/β ratio (dashed). A higher dose per fraction or high dose rate (HDR) brachytherapy will result in lower cell survival for tissues with a lower α/β ratio.

Rationale

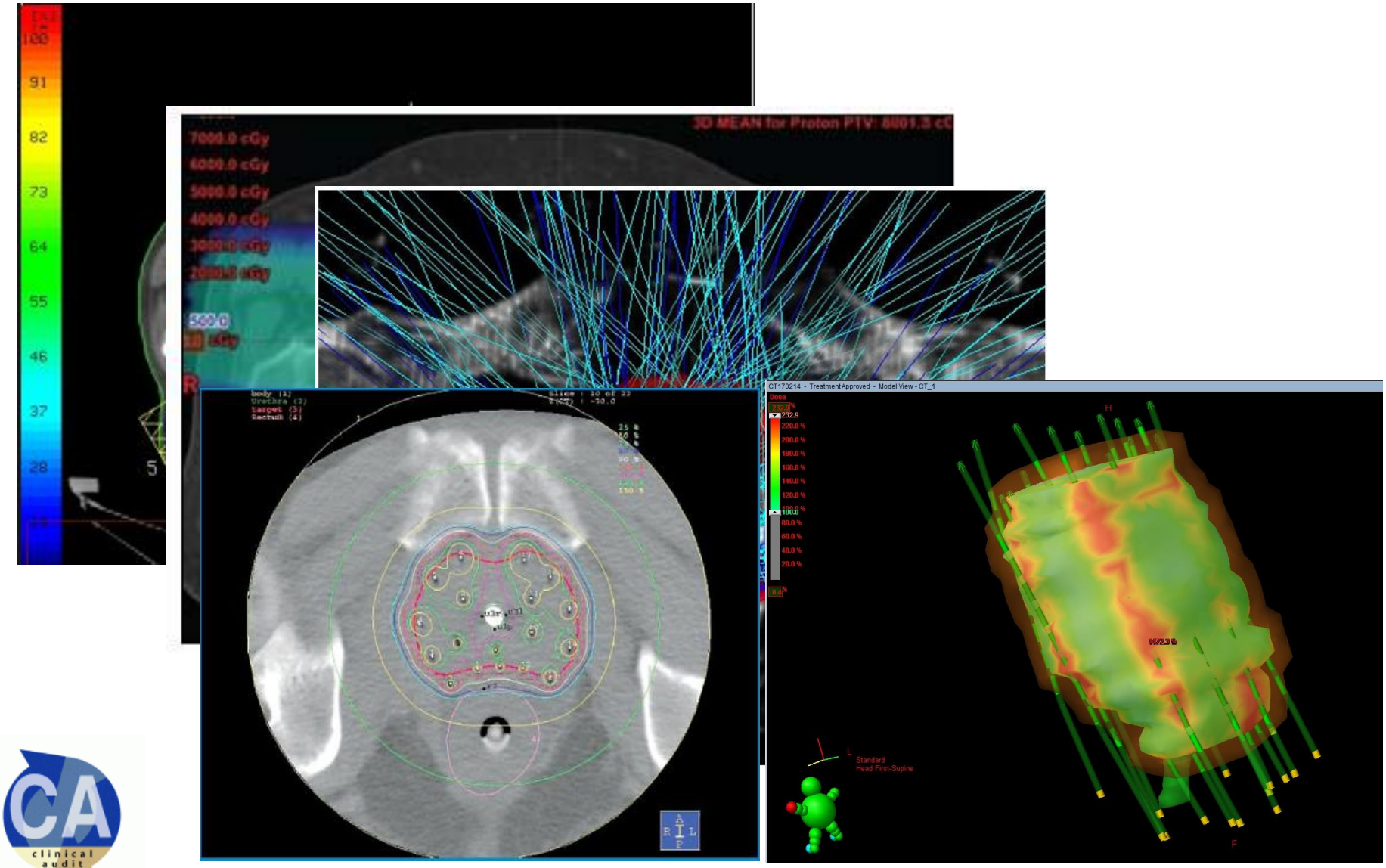
Table 1. Comparison of biologically equivalent doses (BEDs) as total doses at 2 Gy per fraction for different dose fractionation regimens

Dose schedule	BED_{10} (early responding tissues)	$BED_{1.5}$ (late responding tissue/prostate cancer)
EBRT alone schedule (hypofractionation)		
55 Gy in 20 daily fractions	70.1	155.8
EBRT+HDR brachytherapy boost		
44 Gy in 22 daily fractions	52.8	102.7
17 Gy in two fractions	31.5	113.3
Total dose	84.3	216.0
EBRT alone schedule (conventional)		
74 Gy in 37 daily fractions	87.3	162.8

EBRT, external beam radiation therapy; HDR, high dose rate.

EBRT REGIME			HDR Monotherapy REGIME		
Prescribed Dose	74	Gy	Prescribed Dose	19	Gy
No of #	37	#	No of #	1	#
Dose/#	2	Gy	Dose/#	19	Gy
BED10	87.3	Gy10	BED10	55.1	Gy10
BED5	103.6	Gy5	BED5	91.2	Gy5
BED3	123.3	Gy3	BED3	139.9	Gy3
BED1.5	162.8	Gy1.5	BED1.5	259.6	Gy1.5

Ultimate conformal Treatment



Advantages of HDR BRT

- Image guidance – accuracy of needle placements
- Allows dose optimisation
- Avoids uncertainty of intra-fraction motion
- Short treatment duration
- Less problems with radioprotection
- Single source delivers treatment to large pt numbers and for different tumour sites – cost effective

HDR Monotherapy

- One off treatment similar to surgery
- Discharge after overnight stay and back to normal within few days
- Can avoid ADT in low to intermediate risk patients
- Principle as for LDR monotherapy
- Not suitable for high risk disease due to concerns about treating microscopic disease

HDR Monotherapy-Efficacy

Author	Dose/#	Risk grp	bRFS (%)	LC (%)	DFS (%)	OS (%)	Toxicity (Gr3: %)
Yoshioka et al 1995 N=112 **5Yr FU**	48Gy/8#/ 4d 54Gy/9# /5d ADT allowed	HR>50%	LR-85% IR-93% HR-79%	97	87	96	GU: 6
Demanes/ Martinez et al 1996 **10Yr FU**	46Gy/6# 24% had ADT	LR-288 IR-160	97.8	99	99	77	GU: 4.7 GI: No

- QoL evaluated in 51 pts treated with 45.5Gy/7#/5d
- FACT-P : physical & wellbeing scores took 12 wks to return to baseline
- Social & Family wellbeing took 1yr to normalize
- IPSS score ↑ & IIEF score ↓ @ 2 wks and normalized by 12wks

Komiyama et al, Int J Urol 2013

HDR Monotherapy - Evidence

High-dose-rate monotherapy disease control

First author	Year	*N*	Dose × fractions	Years median fu	Local control (%)	PSA-PFS low (%)	PSA-PFS interm. (%)	PSA-PFS high (%)	DMFS (%)	CSS (%)	OS (%)
Barkati	2012	79	10–11.5 Gy × 3	3.3	99		88	n/a	n/a	n/a	n/a
Demanes	2010	157	7 Gy × 6	5.2	99		97	n/a	99	99	95
Ghadjar	2009	36	9.5 Gy × 4	3	n/a	100	100	n/a	n/a	n/a	n/a
Hoskins	2012	55	8.5–9 Gy × 4	4.5	n/a	n/a	95	87	n/a	n/a	n/a
		109	10.5 Gy × 3	3							
Komiya	2013	51	6.5 Gy × 7	1.5	n/a		96		n/a	n/a	n/a
Mark	2010	317	7.5 Gy × 6	8	n/a		88		n/a	n/a	n/a
Martinez	2010	141	9.5 Gy × 4	5.2	99	97		n/a	99	99	95
Prada	2012	40	19 Gy × 1	1.6	100	100	88	n/a	98	98	98
Rogers	2012	284	6 Gy × 6	3	100	n/a	94	n/a	99	100	98
Yoshioka	2011	111	6 Gy × 9	5.4	97	85	93	79	n/a	87	96
Zamboglou	2013	492	9.5 Gy × 4	4.4	n/a	95	93	93	n/a	n/a	97.5
		225	11.5 Gy × 3								

fu = followup; PSA = prostate-specific antigen; PSA-PFS = PSA progression-free survival, biochemical control (ASTRO or nadir +2); interm. = intermediate; n/a = not applicable; DMFS = distant metastases-free survival; CSS = cause-specific survival; OS = overall survival.

- ***Demanes et al, Brachytherapy 2014***

How many # of HDR are ideal?

Multiple HDR fractions

- Inconvenient to patient
  - Needles either remain in between fractions or multiple insertions require repeat anaesthesia
  - Needles may become displaced between fractions requiring re-positioning
- Inconvenient to treating team
  - Time consuming
    - Multiple insertions
    - Multiple plans
  - Cost

Benefits of single fraction treatment

- For the patient
  - More comfortable
  - Shorter treatment time with max. 1 overnight stay
  - No variation in needle position meaning more accurate treatment
- For the Health Service
  - Cost-effectiveness: better utilisation of hospital resources
    - Beds & Staff
    - Eliminates need for repeat CT and plan adjustment between fractions
- For the Normal Tissues
  - Radiobiology – as discussed

Ultra-Hypofractionation

Author	Dose/#/ FU	Toxicity
Ghilezan et al USA ***IJROBP 2011***	N=50: 24Gy/2# N=50: 27Gy/2# 17m	No difference in tox, all <5% GU freq/urgency – 16%, resolved by 6m 3 m FU with 19Gy/SXT – No >Gr3 GU/GI toxicity
Prada et al Spain ***Brachytherapy 2012***	N=29 LR, N=11 IR 19Gy/SXT 19m	35% had ADT bRFS: 100% LR and 88% IR All toxicity <Gr3 No GI toxicity & sexual preservation – 89%
Hoskin et al UK ***Radiother Oncol 2013***	N=115: 24Gy/2# N=24: 19Gy/SXT N=20: 20Gy/SXT	IPSS score worse with 20Gy/SXT, but back to baseline by 12 weeks Grade 3 GU toxicity in <9% of patients overall No Grade 4 GU, No Grade 3 or 4 GI complications Recatheterization rates 7-29%

Safety & Tolerability

	Dysuria (%)	Freq/ Urgency (%)	Rectal pain (%)	Chronic freq/ urgency (%)	Stricture (%)	Potency prservation (%)	
HDR	36	54	6	32	8	83	
LDR	67	92	20	56	3	55	

HDR: n=65, 38Gy/4# & LDR: n=84, Palladium
bRFS: 97%

Grills et al, J Urol 2004

N=197, 34Gy/4#
Acute tox: Gr3GU- 3-7%; Gr4GU- 0-4%, No GI toxicity
Late tox: Gr3GU- 3-16%, stricture rate: 3-7%, GI tox – 1%

Hoskin et al, IJROBP 2012

QoL Probability

Medicine is a science of uncertainty and an art of probability.

(William Osler)

IMPORTANT VARIABLES IN PROSTATE CANCER TREATMENT

URINARY FUNCTION
- Irrito-Obstructive
- Incontinence

RECTAL -BOWEL FUNCTION

ERECTILE FUNCTION

VITALITY (Hormone therapy)

	emotional, cognitive, social, ***Symptoms*** ***, Economic problems***
	ctional, physic, social-family
	and relationship with others, physical ***h, vitality, limitations due the physical*** ***ental health***
EORTC-QLQ-PR25	Urinary, Digestive, Sexual, Sympt rel to treatment
FACT-P	Urinary, Digestive, Sexual
UCLA-PCI	Urinary, Digestive, Sexual
EPIC	***Urinary, Digestive, Sexual, Hormones and Vitality***
IPSS	Urinary (Obstruction)
ICS Male Cuestionnaire	Urinary (Incontinence)
BMSFI	Sexual
CSFQ	Sexual
IIEF	Sexual

- lity
- W

Quality of life with HDR

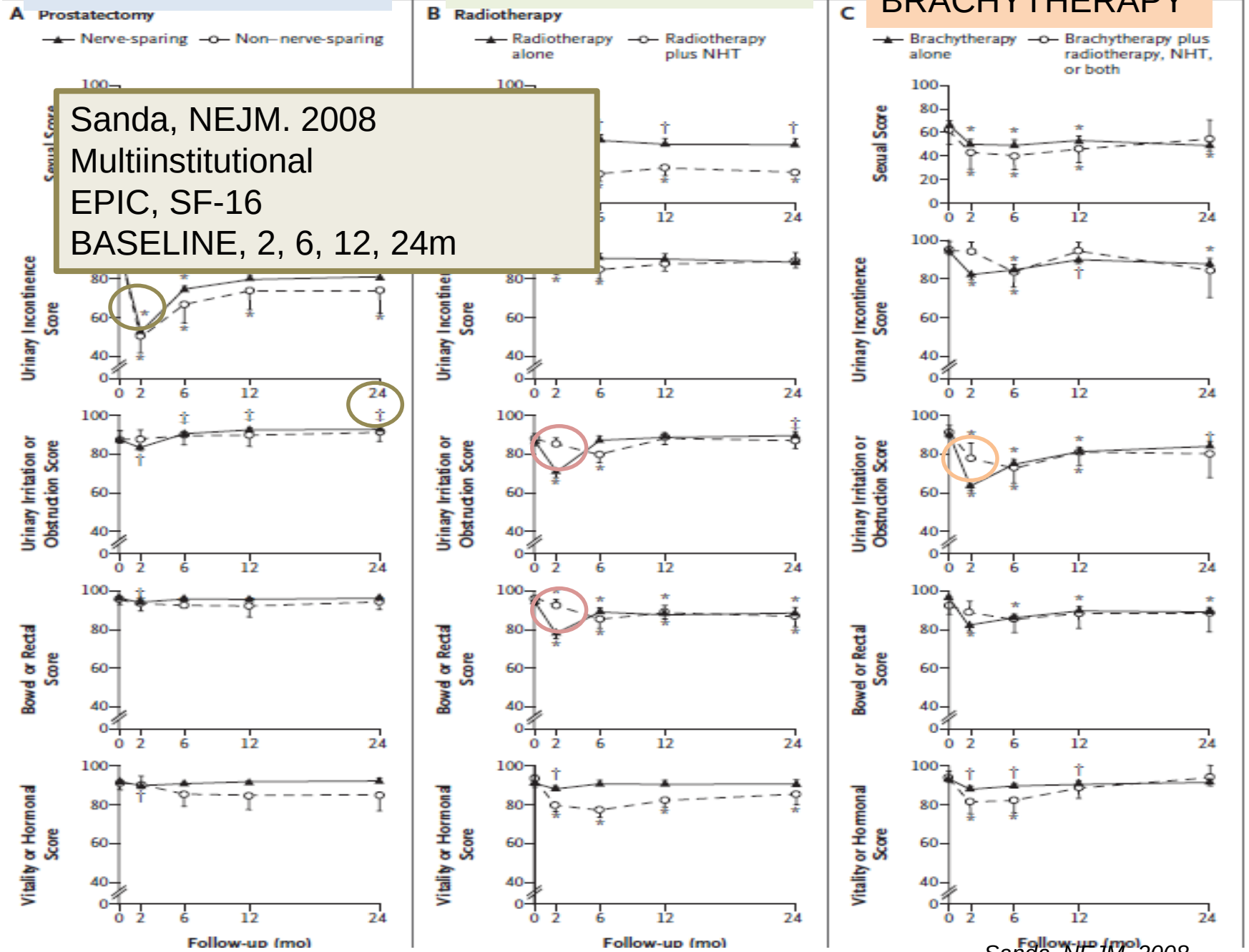
- Physician-reported morbidity may underestimate adverse HRQOL effects when compared with patient-reported data (urinary, bowel & sexual effects).
- HRQOL assessed (mean FU of 5.3 years) for 168 men who were treated with RP or brachytherapy
  Response rate was 88.4%.
- There was no difference in bowel or hormonal domains for RP or brachytherapy, but patients treated with BRT significantly scored better in urinary, sexual domains, and in patient satisfaction

  – ***Crook et al, JCO 2011***

PROSTATECTOMY

EBRT

BRACHYTHERAPY

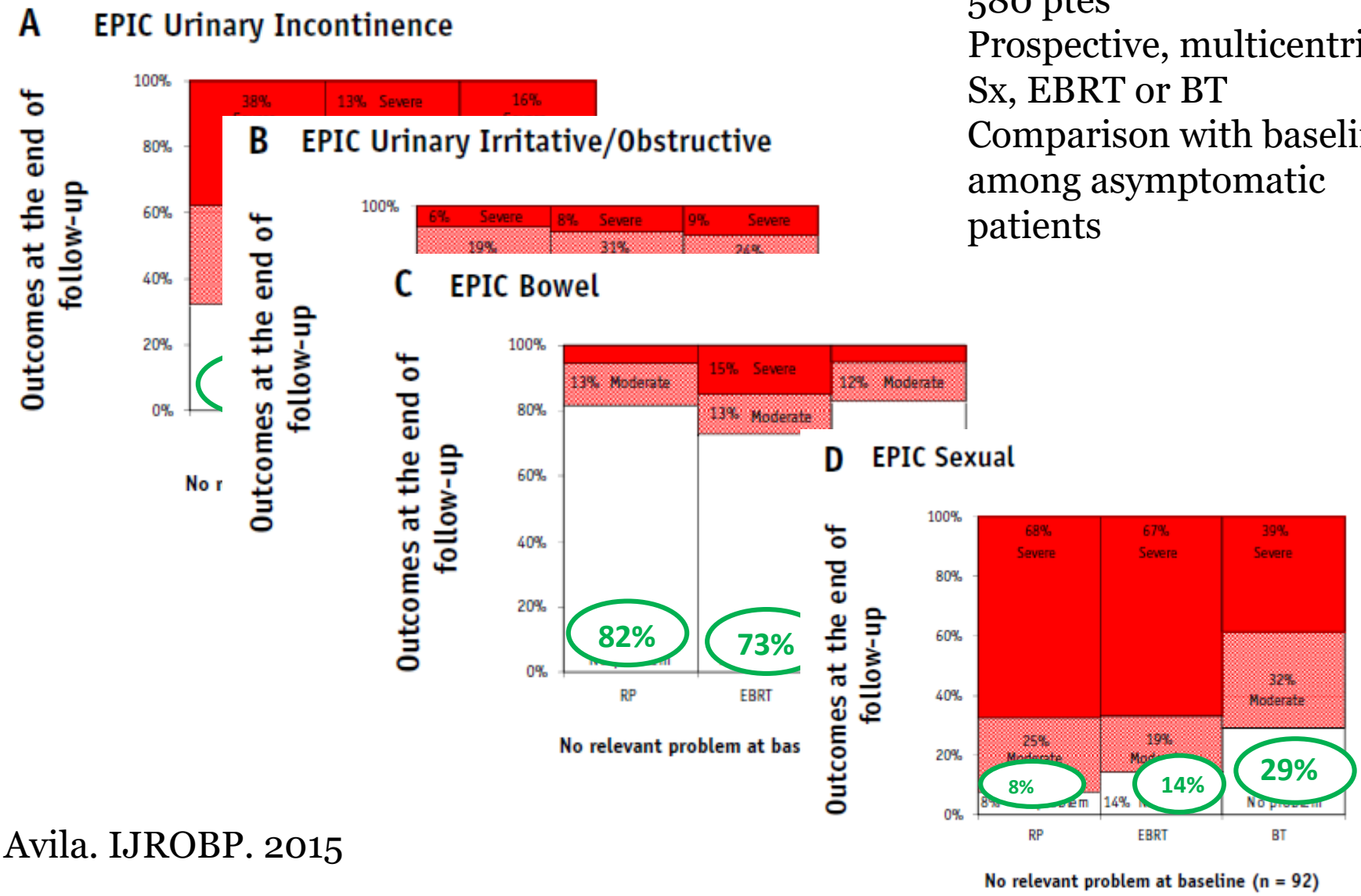


Sanda, NEJM. 2008
Multiinstitutional
EPIC, SF-16
BASELINE, 2, 6, 12, 24m

Sanda. NEJM. 2008

QoL- Severity-Probability

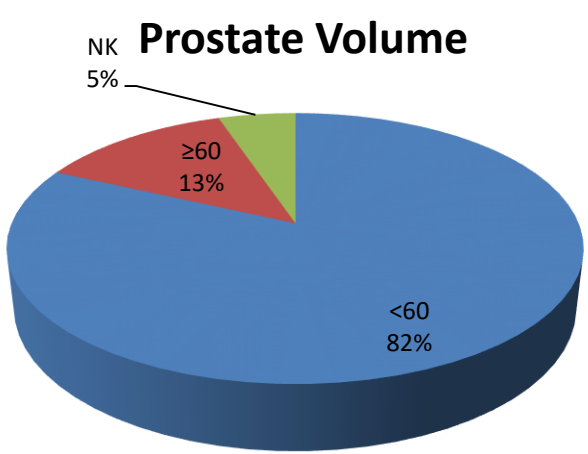
5 y follow-up
580 ptes
Prospective, multicentric
Sx, EBRT or BT
Comparison with baseline among asymptomatic patients

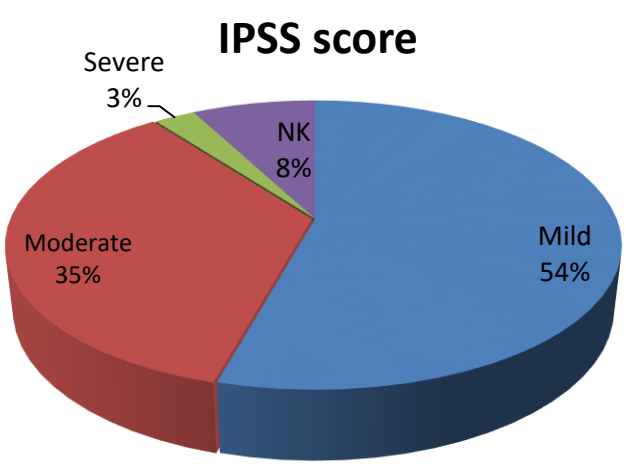


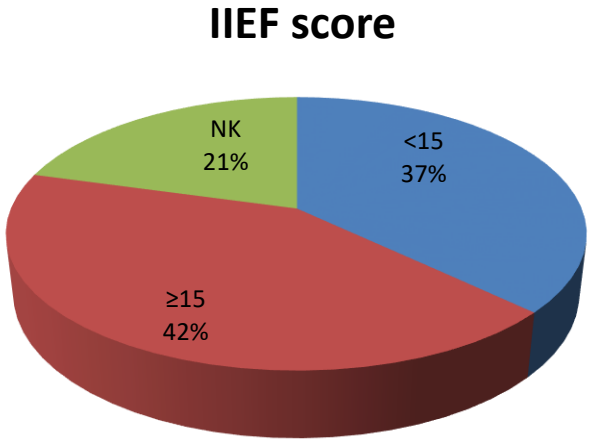
Avila. IJROBP. 2015

BRISTOL EXPERIENCE

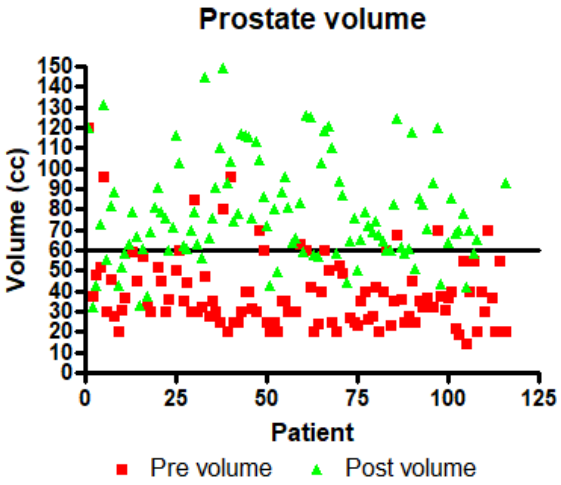
Results: Patient characteristics

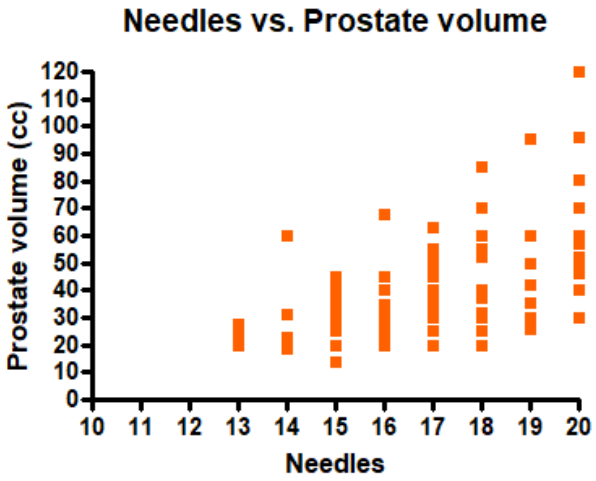


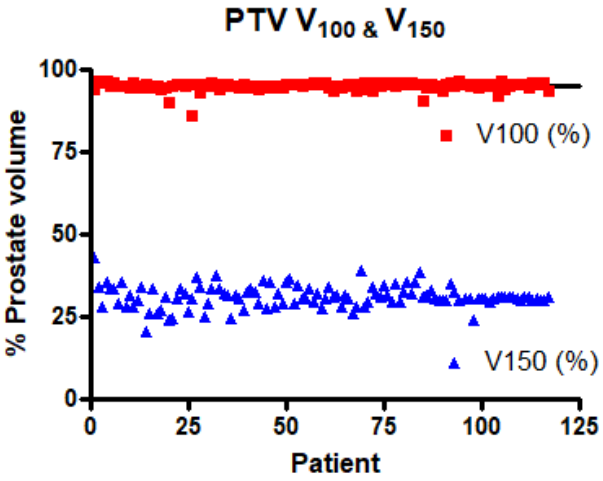




- A range of volumes were implanted (14–120 cc, median: 35), using a median of 17 needles (range:13–20).





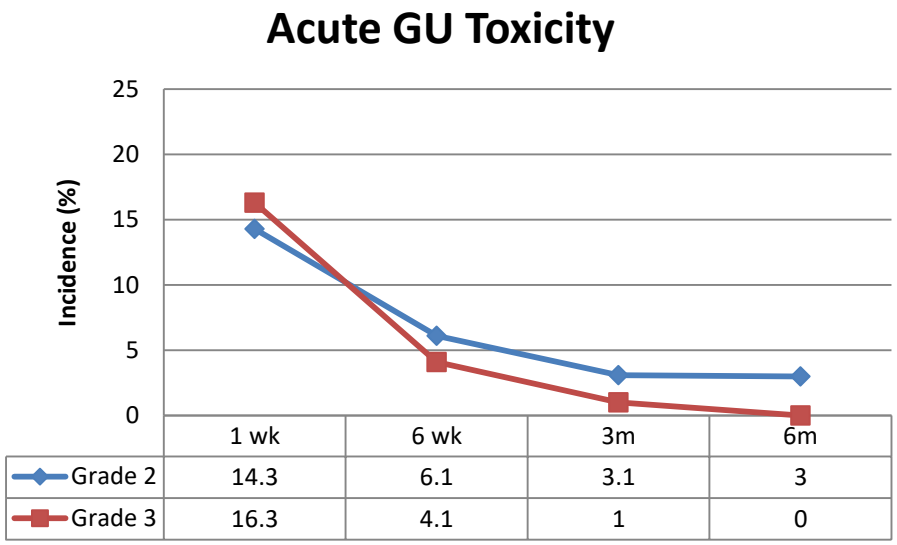


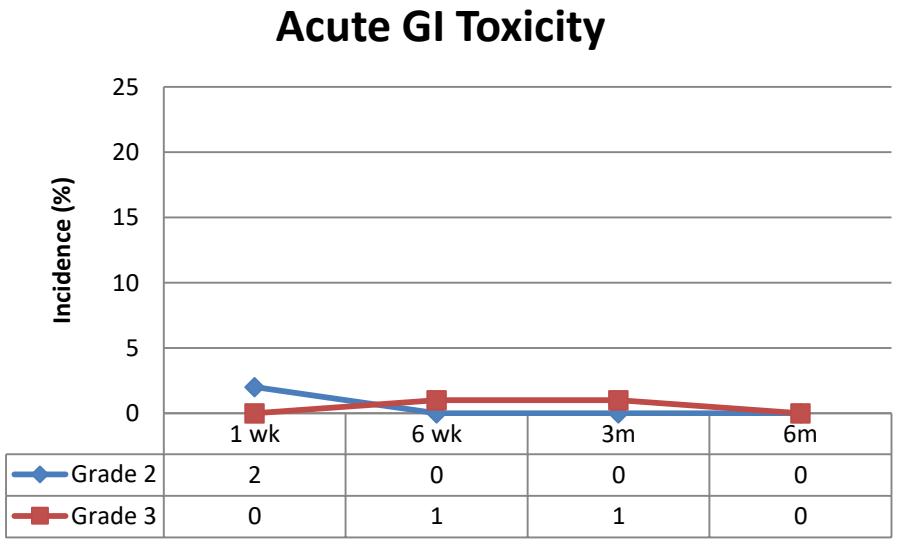
Results

- The median FU was 18.5 months (1-48.2m).
- All patients were discharged home within 24hours, with 15 patients (13%) requiring re-catheterisation.

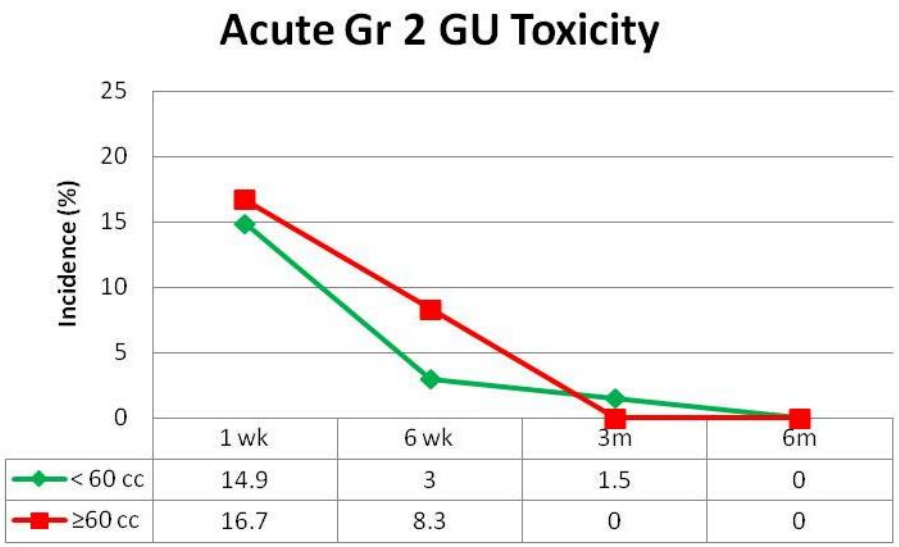
Results: Acute Toxicity

- The incidence of acute GU and GI toxicity were Gr2:14.3% & 2%, Gr3: 16.3% & 1%, respectively at week 1, which decreased to Gr2: 3.1% & 0%, Gr3: 1% & 1% by 3months PT.

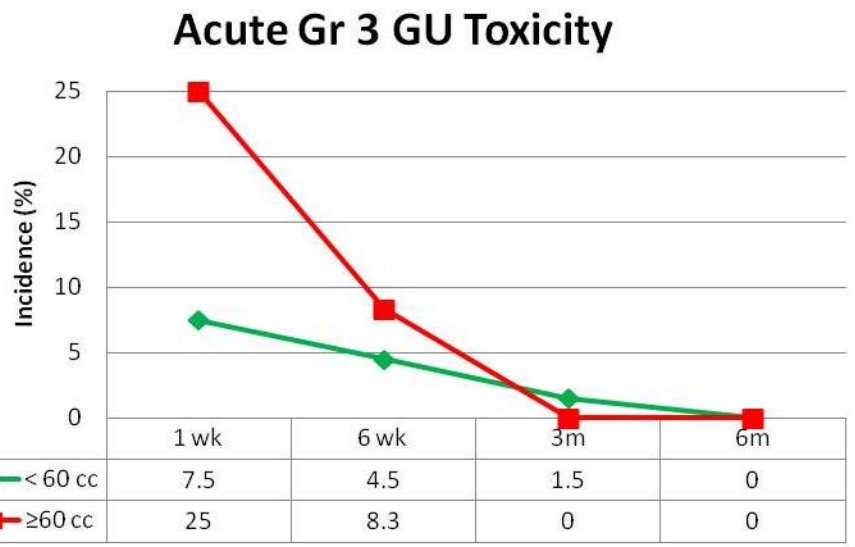




Results: Acute Toxicity



	1 wk	6 wk	3m	6m
< 60 cc	14.9	3	1.5	0
≥60 cc	16.7	8.3	0	0



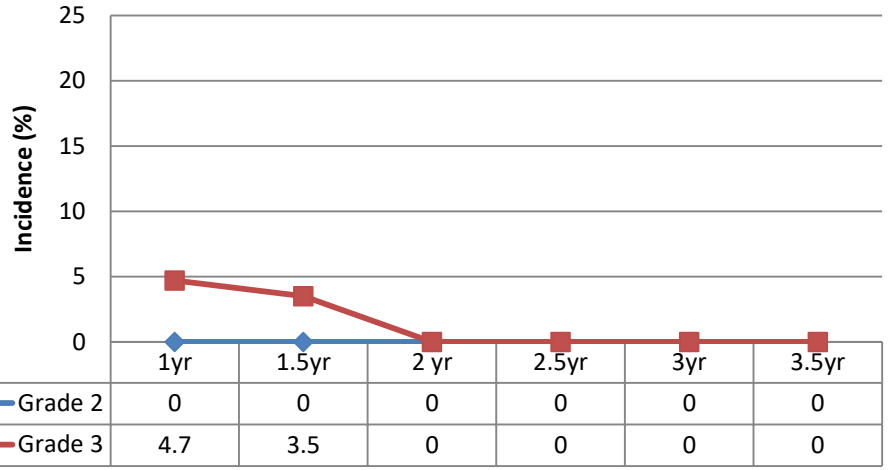
	1 wk	6 wk	3m	6m
< 60 cc	7.5	4.5	1.5	0
≥60 cc	25	8.3	0	0

- Toxicity rates did not differ significantly in patients with volume <60cc as compared to those with volume ≥ 60cc.

Results: Late Toxicity

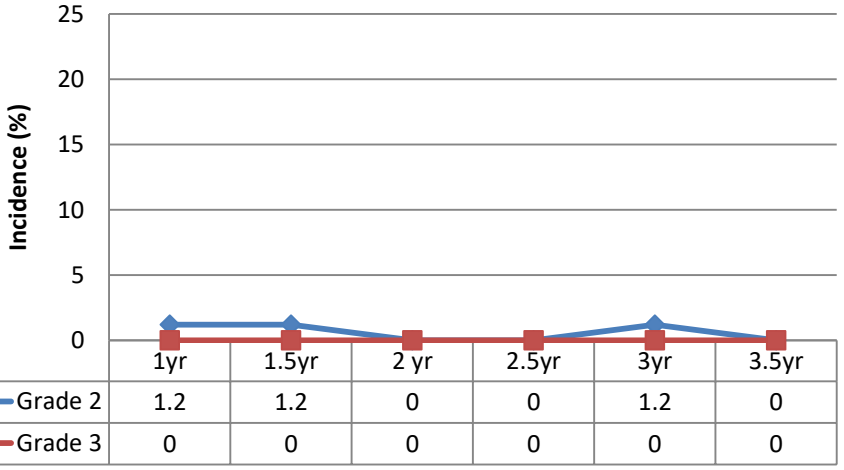
- Chronic GU and GI toxicity were Gr2: 0% & 1.2%, Gr3: 4.7% & 0%, respectively at 1 year, but none had any toxicity at 3.5 yrs PT.

Chronic GU Toxicity



	1yr	1.5yr	2 yr	2.5yr	3yr	3.5yr
Grade 2	0	0	0	0	0	0
Grade 3	4.7	3.5	0	0	0	0

Chronic GI Toxicity



	1yr	1.5yr	2 yr	2.5yr	3yr	3.5yr
Grade 2	1.2	1.2	0	0	1.2	0
Grade 3	0	0	0	0	0	0

Results: Outcomes

- Four patients experienced a biochemical failure, giving a cumulative incidence estimate of 3.4% at 1.5 year.
- Out of these 4, 2 had salvage prostatectomy and 2 developed metastatic disease.

Literature comparison

Authors	Gland Vol (cc)	Median FU	Acute GU tox		Late GU tox		Comments
			Gr2	Gr3	Gr2	Gr3	
Prada et al N=60	38	72m	0%	0%	0%	0%	No GI tox (rectal spacer) 2.5% recatheterisation No PTV margin
Hoskin et al N=24	-		0%	9%	-	-	8% recatheterisation 80% had ADT No Gr3 GI tox
Morton et al, N= 87	35	20m	31%	1.1%	3%	0%	6% recatheterisation No GI toxicity 0-2mm PTV margin
Krauss et al N=58	34.8	36m	12%	0%	10%	0%	1.7% chronic Gr2 GI tox No PTV margin
Our study N=116	35	16m	3%	0%	0%	0%	3mm PTV margin 13% recatheterisation No chr Gr3 GI tox

Conclusions

- Both LDR and HDR brachytherapy are safe, with favourable toxicity profile
- Biochemical control rates are promising
- It is possible to implant volumes higher than 60cc with HDR
- Brachytherapy remains the Ultimate Conformal Radiotherapy and the trials with various novel forms of external radiotherapy to mimic the brachytherapy conformality only confirms that…..
  - *'Imitation is the best form of flattery'*