



Optimizing QOL Post SBRT /Strategies to Reduce Toxicity

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Disclosures

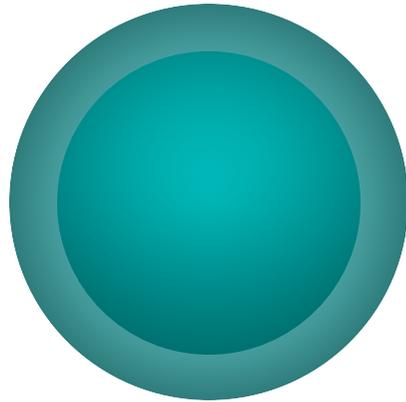
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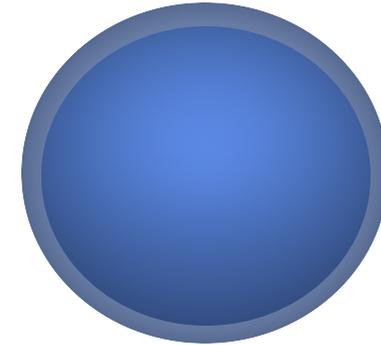
Comparison of IMRT and SBRT

IMRT



- Expand Treated Volume
- More Radiation to Normal Structures
- Limit Total Dose
- Limit Daily Dose

SBRT



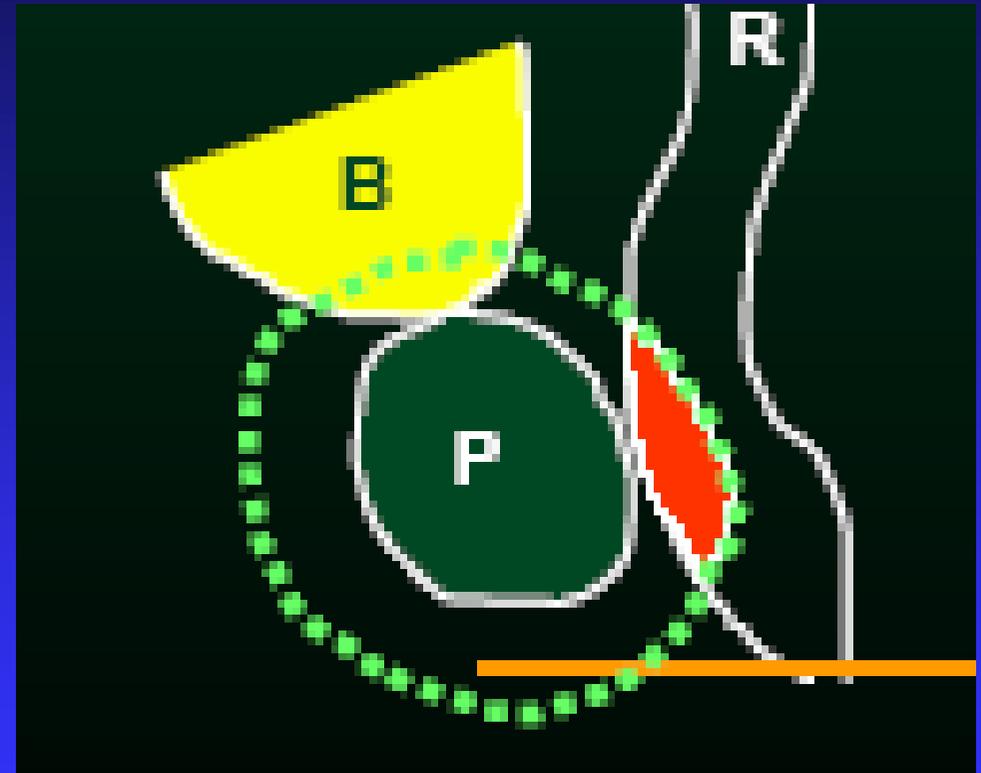
- Smaller Treatment Volume
- Requires Continuous Tracking
- Allows for Higher Total Dose
- Allows for Higher Daily Dose

Continuous Prostate Tracking Allows for Smaller Treatment Margins

□ Robotic SBRT allows for reduced treatment margins

- Posterior 3 mm
- All others 5 mm

□ Reduced treatment margins allow for safer delivery of fewer high dose fractions

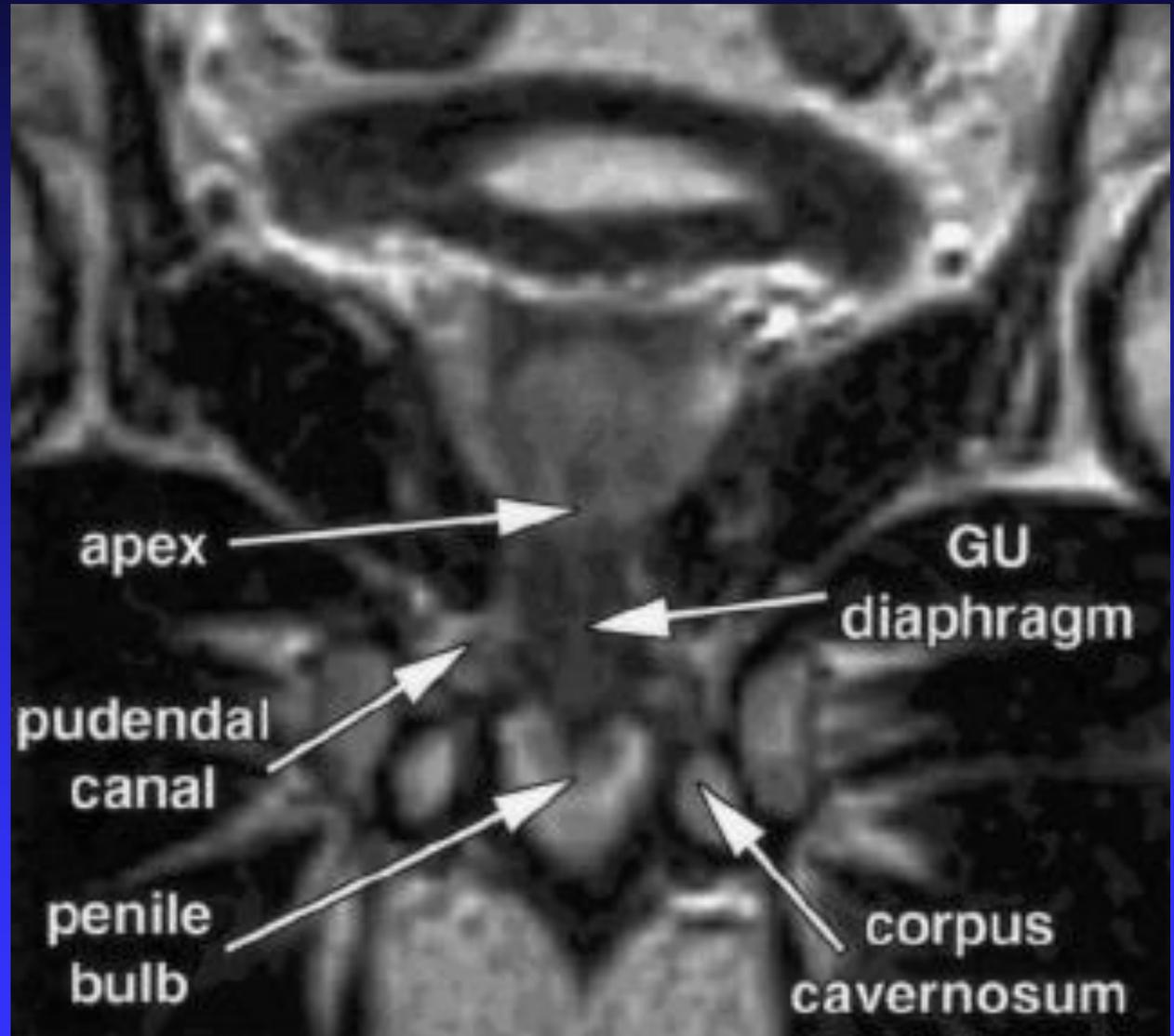


□ Allan Pollack, M.D.

Role of Magnetic Resonance Imaging In Reducing Late Toxicity

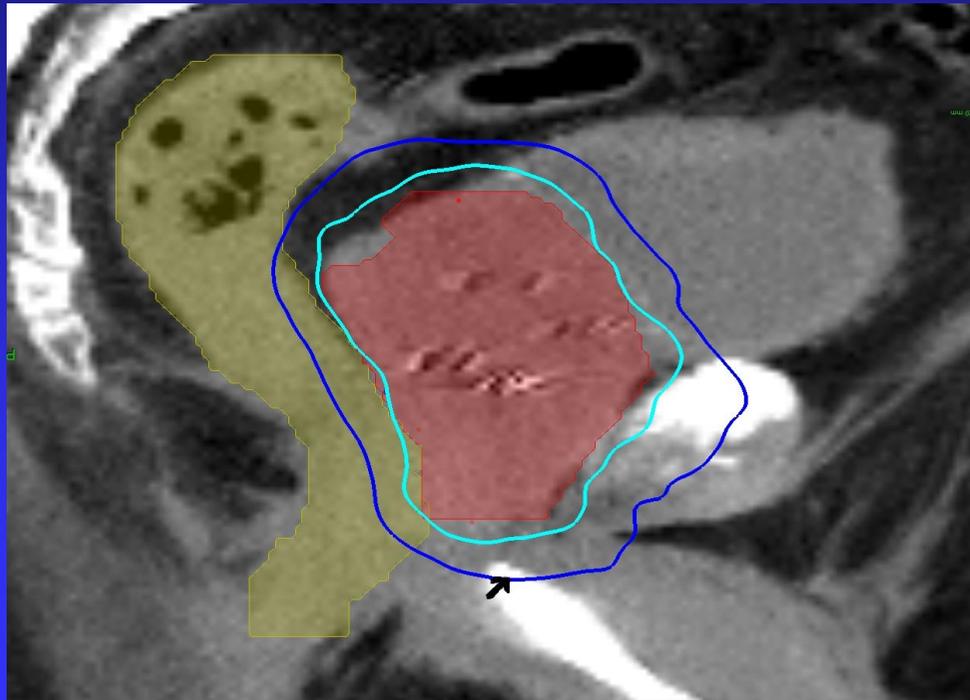
□ MRI scan better defines:

- Bladder neck
- Prostate apex
- Penile bulb
- Membranous urethra
- Prostate rectal interface

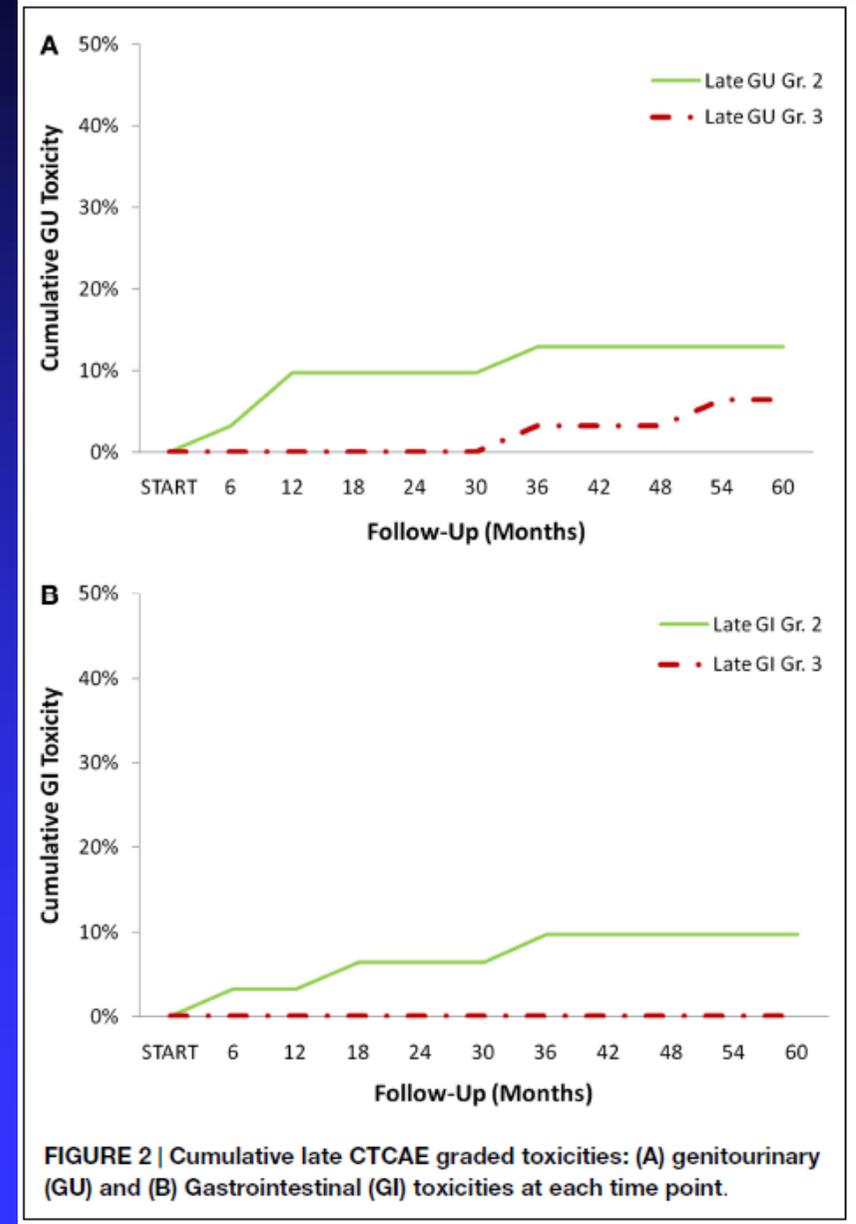


Urethrogram-directed SBRT for Prostate Cancer in Patients with Contraindications to MRI

□ Increased rates of urethral stricture requiring dilation and rectal bleeding requiring cauterization



□ Paydar, *Frontiers in Radiation Oncology*, 2015

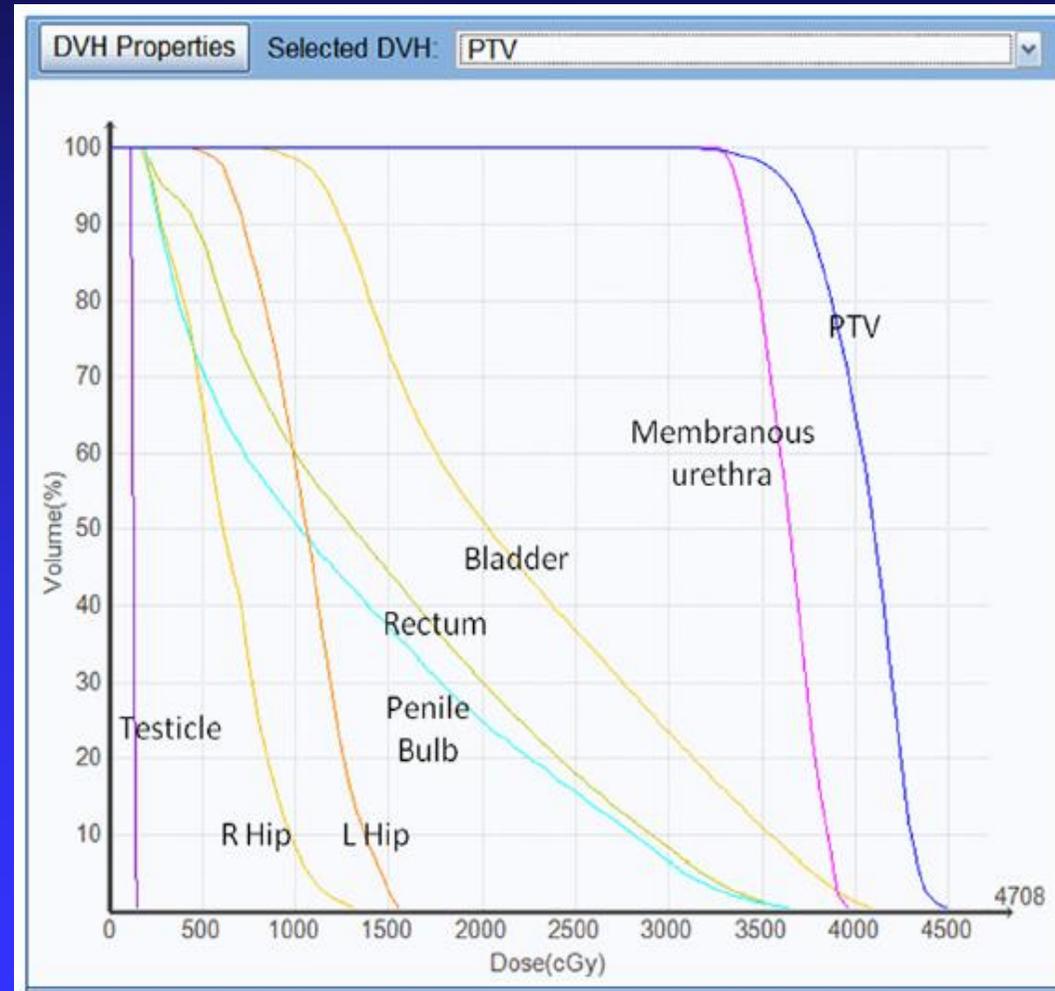


SBRT Dose Constraints and Targets

□ The prescription isodose line was limited to > 75 % to limit the maximum prostatic urethra dose to 133% of the prescription dose

36.25 Gy plan constraints

Global Max Dose	48.33 Gy
PTV	V (36.25 Gy) ≥ 95%
Rectum	V (36 Gy) < 1 cc V (100%) < 5% V (90%) < 10% V (80%) < 20% V (75%) < 25% V (50%) < 50%
Bladder	V (37 Gy) < 5 cc V (100%) < 10% V (50%) < 40%
Penile Bulb	V (29.5 Gy) < 50%
Membranous urethra	V (37 Gy) < 50%
Sigmoid colon	V (30 Gy) < 1 cc
Testicles	D (20%) < 2 Gy



Commonly Utilized Dose Constraints

Table 4 Examples of dose constraints used in the authors' institutions and on clinical trials

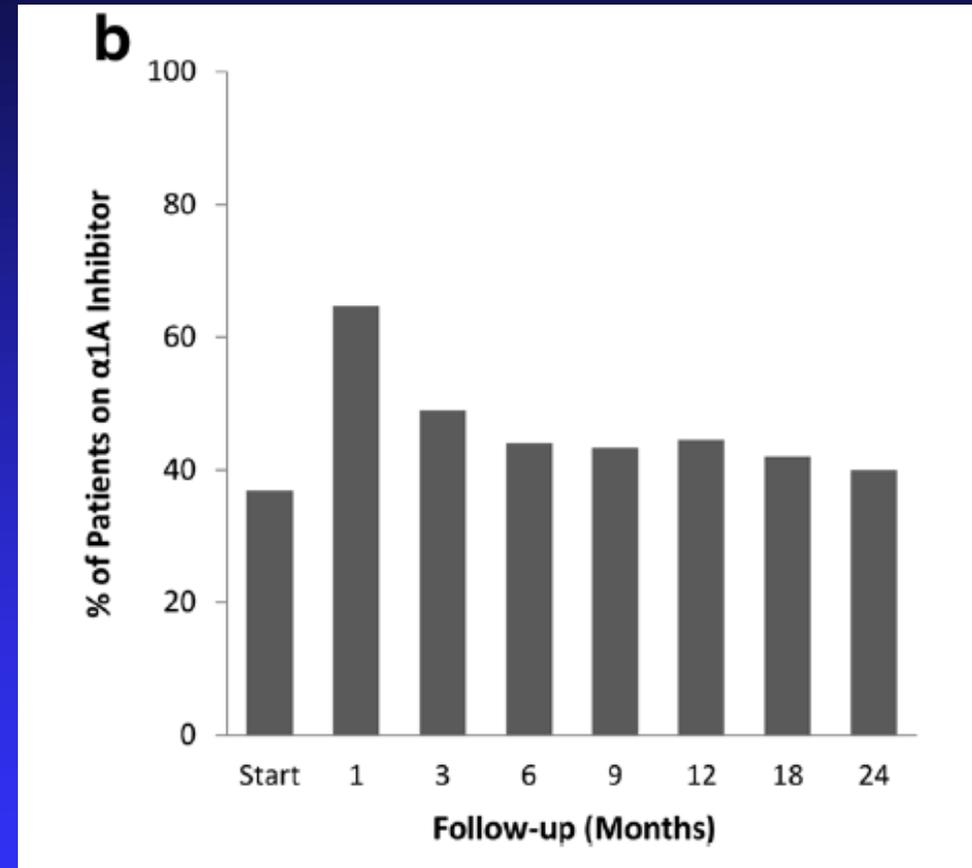
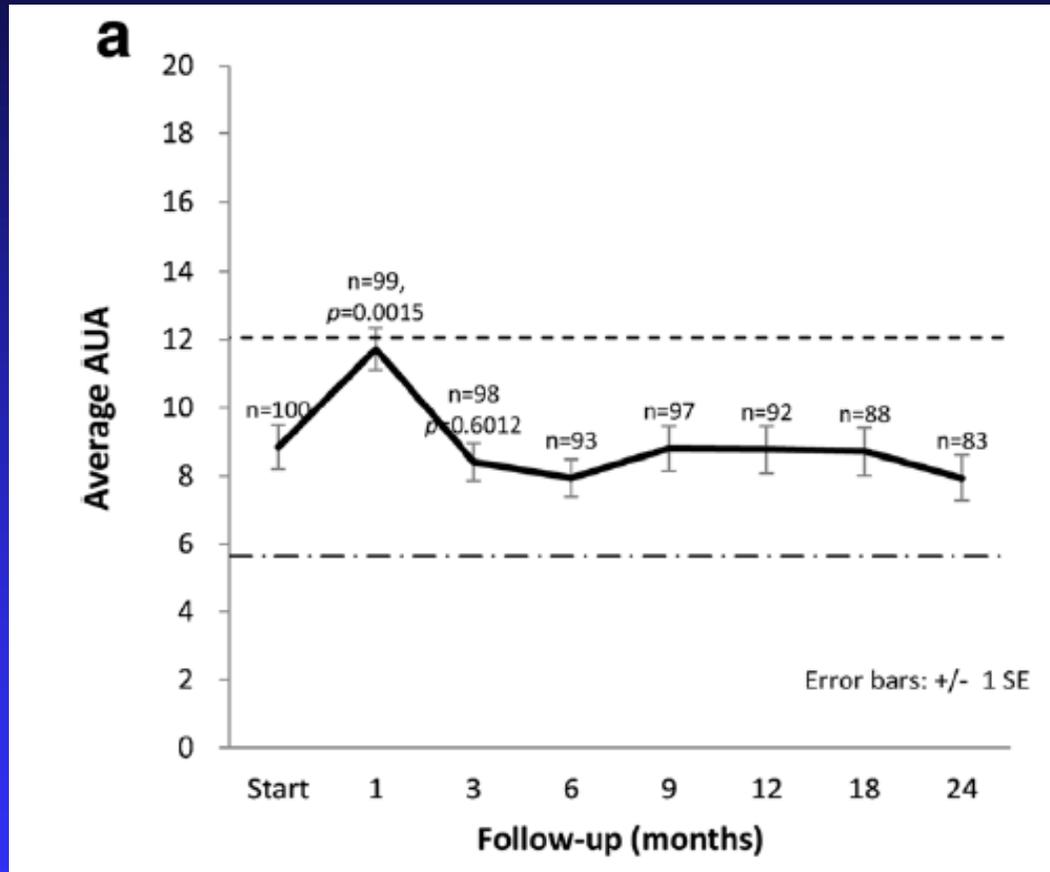
	Georgetown* (35-36.25/5 fx, for 2 wk)	UNC (NCT 00643617)* (38 Gy/4 fx for 4 d)	RTOG 0938 ⁵⁵ (36.25 Gy/5 fx for 2.5 wk)	NRG GU-005 ⁵⁶ (36.25 Gy/5 fx for 2.5 wk)
PTV	≤125% prescription dose		D0.03cc ≤8.78 Gy (Linac) D0.03cc ≤43.5 Gy (CyberKnife)	Dmax ≤38.78 Gy
Prostatic urethra	V42 Gy ≤0.03 cc	Dmax <40 Gy	D0.03cc ≤38.78 Gy	D0.03cc ≤38.78 Gy
Bladder	V37Gy ≤5 cc	Dmax <45.6 Gy D10cc <41.8 Gy	D1cc ≤38.06 Gy D10% ≤32.63 Gy D50% ≤18.13 Gy	D0.03cc ≤38.06 Gy D10% ≤18.12 Gy
Rectum	V36 Gy ≤1 cc	Dmax <38 Gy	D1cc ≤38.06 Gy D3cc ≤34.4 Gy D10% ≤32.63 Gy D20% ≤29 Gy D50% ≤18.13 Gy	D0.03cc ≤38.06 Gy D3cc ≤34.4 Gy D10% ≤32.63 Gy D20% ≤29 Gy D50% ≤18.13 Gy
Penile bulb	V29.5 Gy ≤3 cc		Dmax ≤36.25 Gy D3cc ≤20 Gy	D0.03cc ≤36.25 Gy D3cc ≤19.9 Gy

Abbreviations: fx = fractions; OAR = organ at risk; PTV = planning target volume; RTOG = Radiation Therapy Oncology Group; UNC = University of North Carolina.

Bladder and rectum volumes are defined as solid organs. For RTOG 0938 and NRG GU-005, the rectum is defined as extending 15 cm from the anus or to the rectosigmoid flexure.

* Dosimetric parameters currently used at authors' institutions.

Obstructive Voiding Symptoms Following Robotic SBRT



□ Chen *et al*, *Rad. Onc.*, 2013

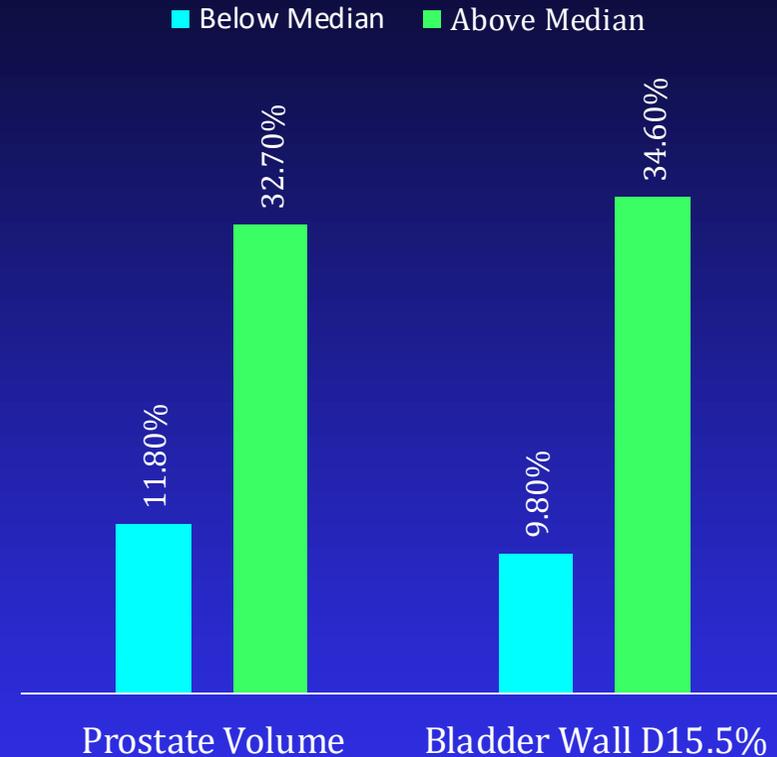
Predictors of Acute Urinary Symptom Flare

□ Definition

- AUASI > 15
- > 5 points above baseline

□ Predictors

- Prostate Volume > 36 cc
- Bladder wall D15.5%



Parameter	OR	95% CI	p-value	Median	Toxicity (<median)	Toxicity (>median)
Prostate Volume (per 10 cc)	1.02	1 - 1.04	0.019	36 cc	11.80%	32.70%
Bladder Wall D15.5% (per Gy)	1.62	1.02 - 2.59	0.043	32.6 Gy	9.80%	34.60%

Urinary Symptoms During Every-Other-Day SBRT Treatment May Require Medical Management

- Approximately 50% develop moderate to big problems with urinary function

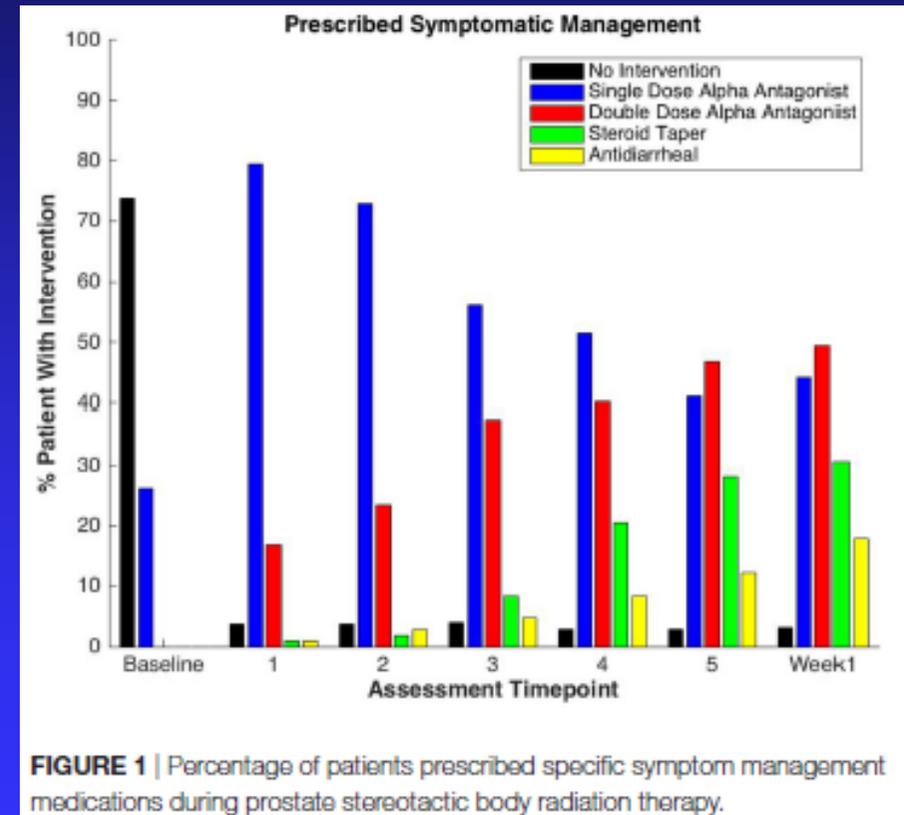
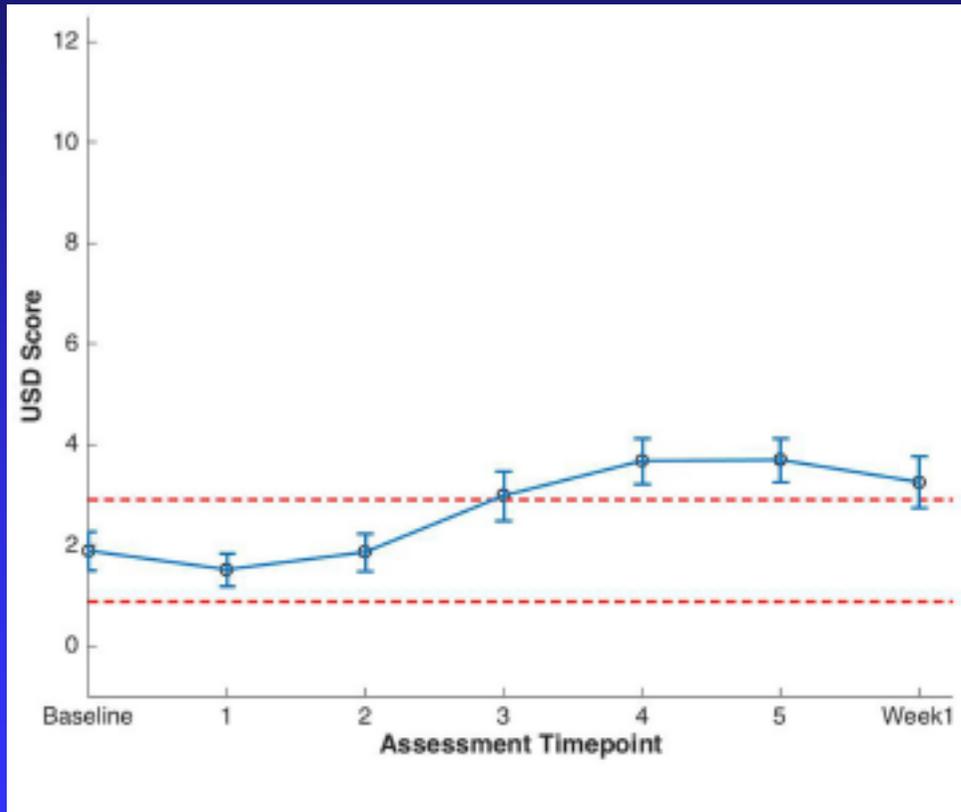
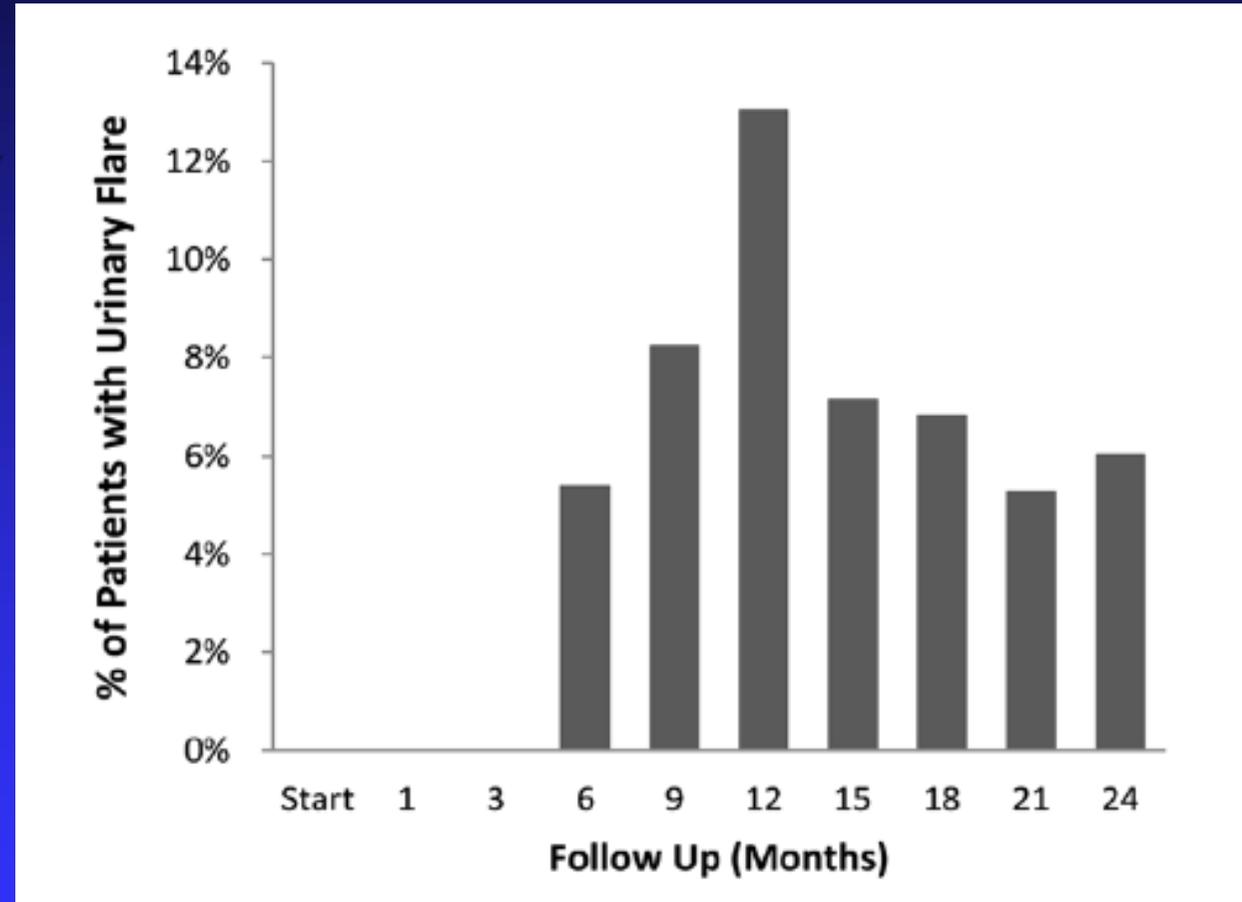


FIGURE 1 | Percentage of patients prescribed specific symptom management medications during prostate stereotactic body radiation therapy.

Late Urinary Symptom Flare Following SBRT

- Characterization
 - Similar to brachytherapy
 - Incidence 21%
 - Median magnitude
 - 9 points
 - Median time to flare
 - 9 months
 - Median duration
 - 3 months



□ Chen *et al*, *Rad. Onc.*, 2013

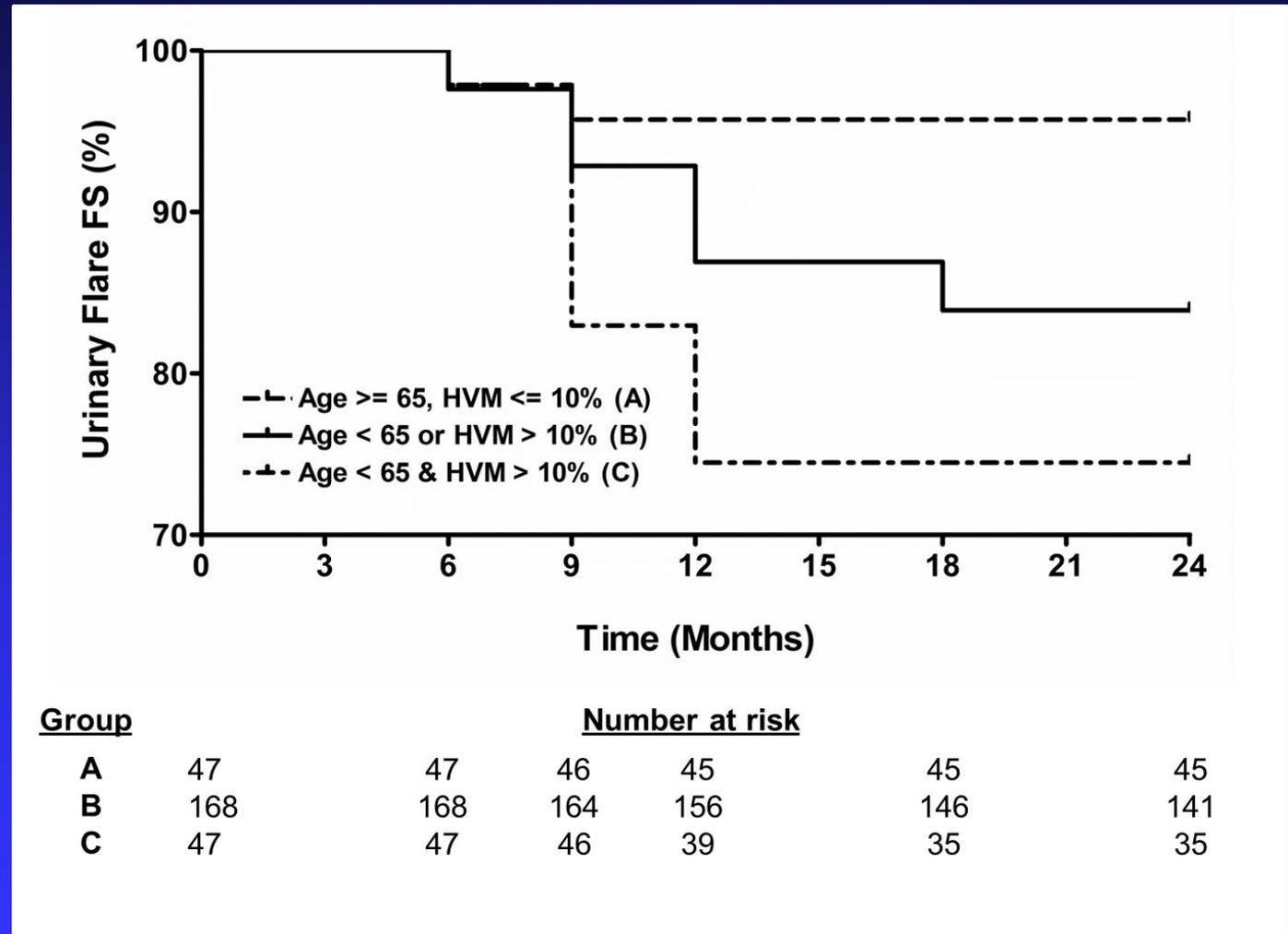
Predictors of Late Urinary Symptom Flare

□ Predictors

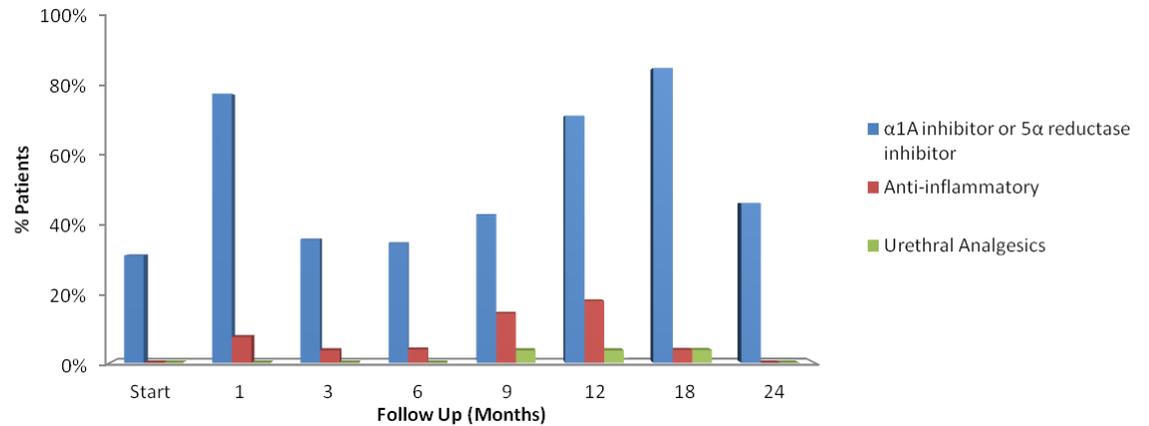
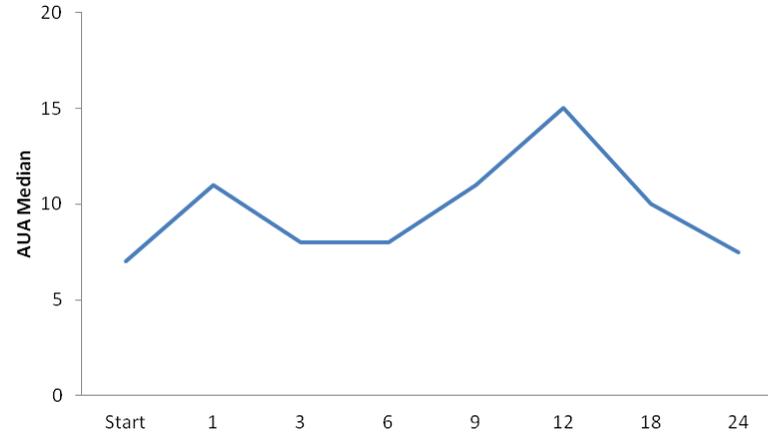
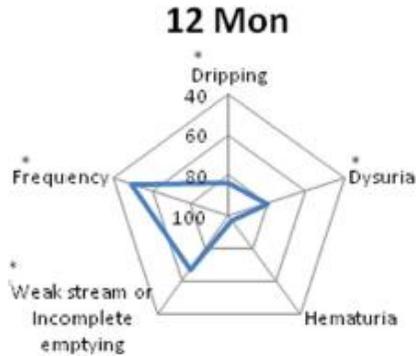
□ Age < 65 yo

□ Bladder D12.7%

□ > 33.5 Gy



Late Urinary Symptom Flare Responds to Conservative Management



□ Avoid Surgical Interventions:

□ Cystoscopy

□ TURP

□ King, IJROBP, 2012

□ Woo et al, Front. Oncol., 2015

Summary:

Factors Associated with Late Urinary Side Effects

Table 1 Selected studies analyzing factors associated with late urinary side effects

Study	n	Treatment details	Med. f/u (y)	Urinary endpoint	Dosimetric factors associated* with worse urinary outcomes	Nondosimetric factors associated* with worse urinary outcomes
King et al. ²⁰ 2012 (Stanford)	67	36.25 Gy (5 fx), QD/QOD	2.7	RTOG G2: 5.0% G3: 3.5%		QD (vs QOD) treatment schedule (for RTOG ≤G2 toxicity) Urologic instrumentation Prior procedure for BPH
Bolzicco et al. ²¹ 2013 (Vicenza)	100	35 Gy (5 fx), QD	3.0	RTOG G2: 3.0% G3: 1.0%		
Elias et al. ²² 2014 (Sunnybrook)	84	35 Gy (5 fx), QW	4.2	EPIC QOL MID: 17.9%	Bladder D5cc >34 Gy	Bladder volume
Katz et al. ²³ 2014 (Flushing)	515	35-36.25 Gy (5 fx), QD	6.0	RTOG G2: 9.1% G3: 1.7%	Prescription dose 36.25 Gy (vs 35 Gy)	Prostate volume >60 cc
Bernetich et al. ²⁴ 2014 (Drexel)	142	79%: 35-36.25 Gy (5 fx), QOD 21%: 37.5 Gy (5 fx), QOD	3.0	CTCAE v3 G2: 14% G3: 2%	Prescription dose 37.5 Gy (vs 35-36.25 Gy)	
Gurka et al. ²⁵ 2015 (Georgetown)	208	35-36.25 Gy (5 fx), QOD	4.0	CTCAE v4 ≥G2 bleed: 2.4%		Prostate volume Prior procedure for BPH Alpha antagonist use
Gomez et al. ²⁶ 2015 (UCLA)	75	40 Gy (5 fx), QOD	1.0	EPIC QOL (avg of obs/irrit and incont)	Bladder V40 Gy >5.5 cc	Larger prostate volume
Seymour et al. ²⁷ 2015 (UCSF)	56	38 Gy (4 fx), QD/QOD	3.0	CTCAE v4 G2: 19.6% G3: 3.6%	Urethra Dmax >47 Gy Bladder V19 Gy More heterogeneous plan	Prostate volume ≥50 cc
Qi et al. ²⁸ 2016 (UCLA)	86	40 Gy (5 fx), QOD	1.0	EPIC QOL Obs/irrit MID: 46% Incont MID: 28%	Bladder mean (obs/irrit, incont) Bladder V34-40 Gy (obs/irrit) Bladder D2-10cc (obs/irrit)	Larger prostate volume (incont)
Kole et al. ²⁹ 2016 (Georgetown)	216	35-36.25 Gy (5 fx), QOD	4.0	IPSS Late urinary flare: 13%	Bladder D12.7% >33.5 Gy	Age <65
Helou et al. ³⁰ 2017 (Sunnybrook)	259	32%: 35 Gy (5 fx), QW 39%: 40 Gy (5 fx), QW 29%: 40 Gy (5 fx), QOD	3.2	RTOG G2: 32.6% G3: 1.9%	Prescription dose 40 Gy (vs 35 Gy)	Higher age Shorter treatment duration
Zhang et al. ³¹ 2017 (UCSF)	78	38 Gy (4 fx), QD/QOD	3.0	CTCAE v4 G2: 19.2% G3: 2.6%	Urethra V42 Gy	Shorter treatment duration More heterogeneous plan
Jackson et al. ³² 2018 (Multicenter)	66	37 Gy (5 fx), QOD	3.1	EPIC QOL Obs/irrit MID: 25% Incont MID: 24%	Bladder Dmax (obs/irrit) Bladder V3.7-37 Gy (incont)	

Tips for Minimizing Urinary Symptoms

- Every other day treatment
 - Increase overall treatment time to 11 days
 - King CR *et al. Int J Radiat Oncol Biol Phys.* 2012
- Prophylactic Alpha Antagonists
 - Continue until resolution of symptoms
- Bladder neck dose reduction
 - V37 Gy < 5 cc
- Prostatic urethra dose reduction
 - Limit central hot spot
 - Prescription isodose line $\geq 80\%$
 - Maximum point dose to the prostatic urethra limited to 42 Gy

Predictors of Acute Bowel Symptoms

Intermediate dose levels

Grade 2 toxicity - V20 Gy

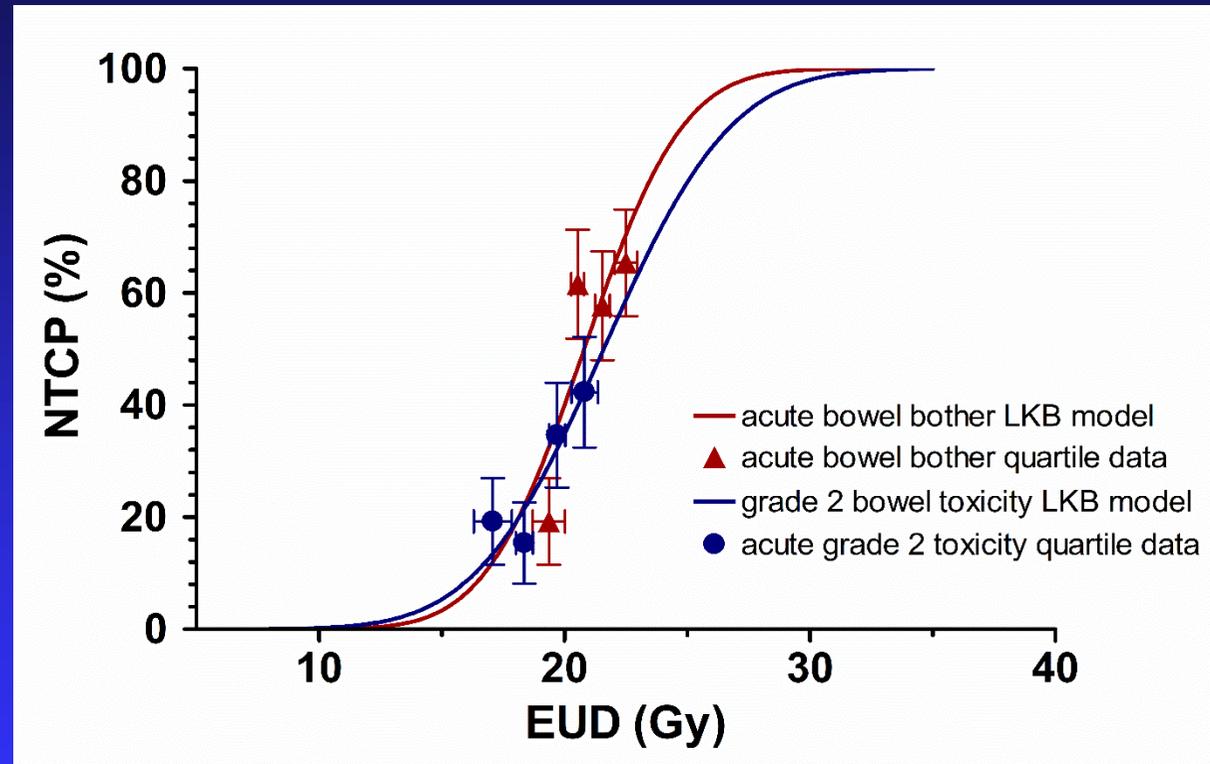
< 30.2% 15%

> 30.2% 39%

Bowel bother- D19%

< 24.8 Gy 39%

> 24.8 Gy 65%



Kole *et al*, ISRS, 2015

PATRIOT Trial: Once-Weekly SBRT Decreases Acute Symptoms

□ Minimum clinically important change (MCIC)

□ Urinary

□ Every other day 94%

□ Once per week 78%

□ Moderate to Severe Problems

□ Bowel

□ Every other day 57%

□ Once per week 20%

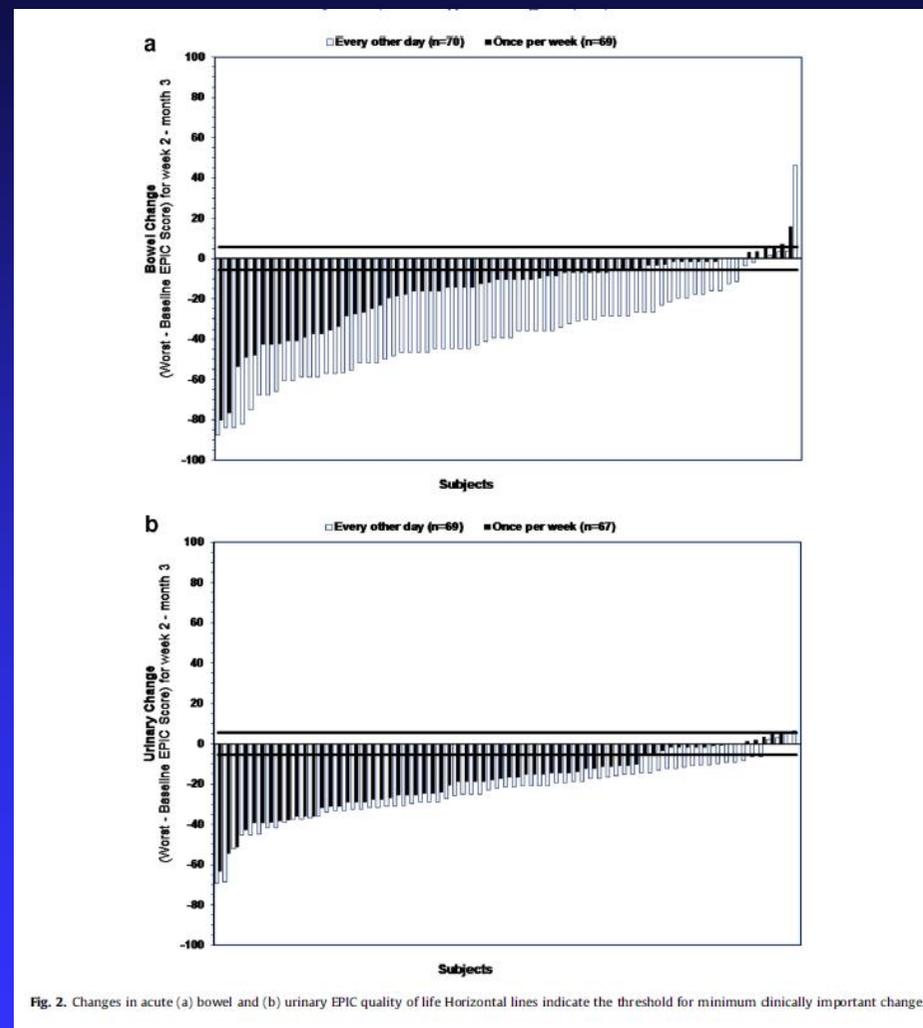


Fig. 2. Changes in acute (a) bowel and (b) urinary EPIC quality of life. Horizontal lines indicate the threshold for minimum clinically important change.

□ Quon, *Radioth. Oncol.*, 2018

Hematuria Following SBRT is Multifactorial

□ Multi-factorial

- Bladder tumor
- Kidney stone

□ Radiation-induced

- Pretreatment TURP may increase risk
- **Resolves with time!**

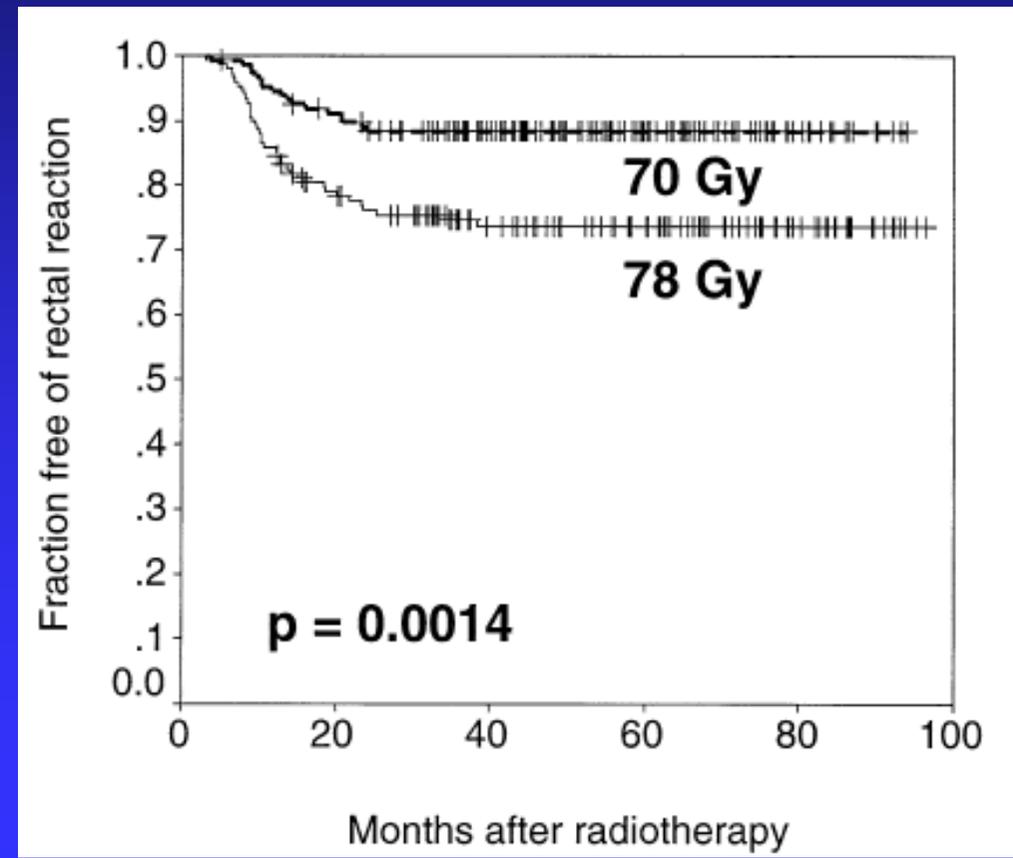
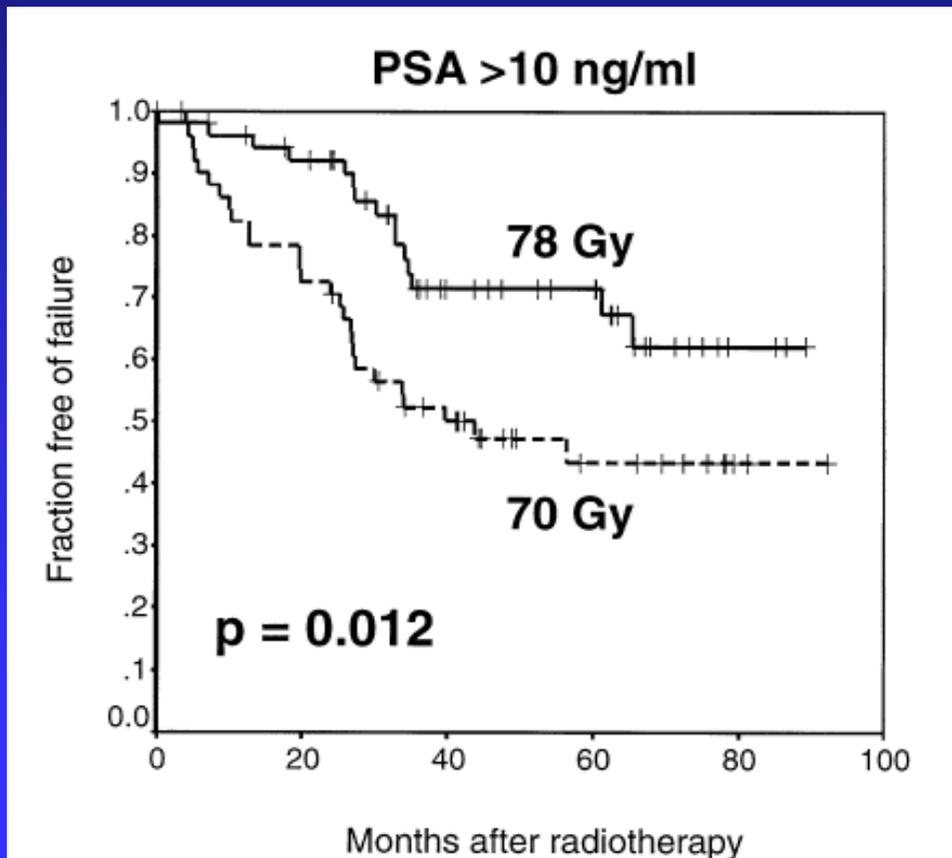
Factors	p-Values
Age	0.419
Race	0.917
D'Amico's Risk Groups	0.122
Prostate Volume	0.022†
Initial PSA	0.804
Androgen Deprivation Therapy	0.507
RT Dose	0.012*
TURP prior to RT	0.002*†
Initial AUA	0.897
α_{1A} Antagonist usage	0.008*
Charlson Comorbidity Index	0.101
Anticoagulant usage	0.435

*significant in multivariate analysis; †significant in univariate analysis

□ Gurka et al, Rad. Onc., 2013

Radiation Dose Escalation

- Increases biochemical control
- Increases rectal toxicity when conventional treatment employed

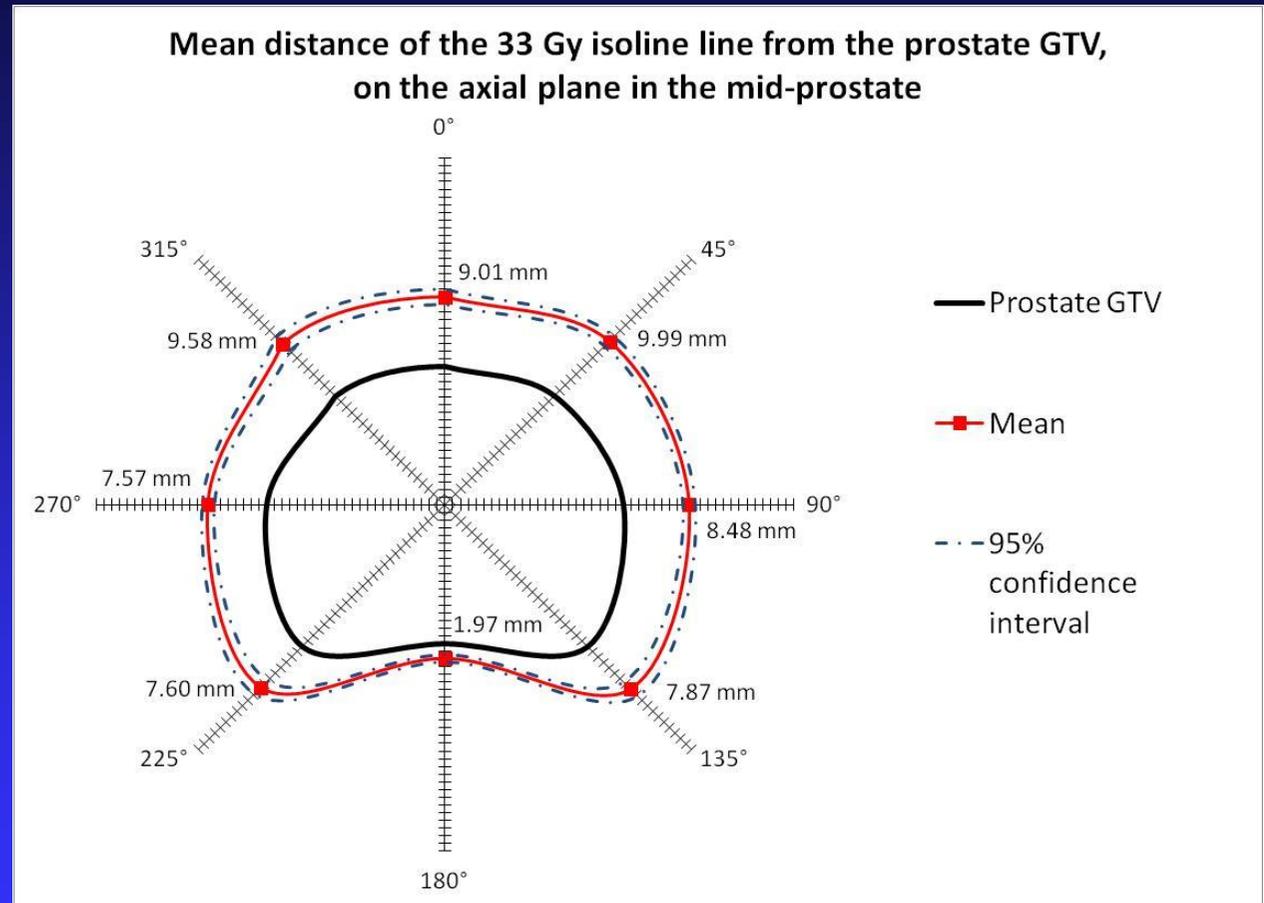


SBRT Dose Distribution

- Rectal Goals

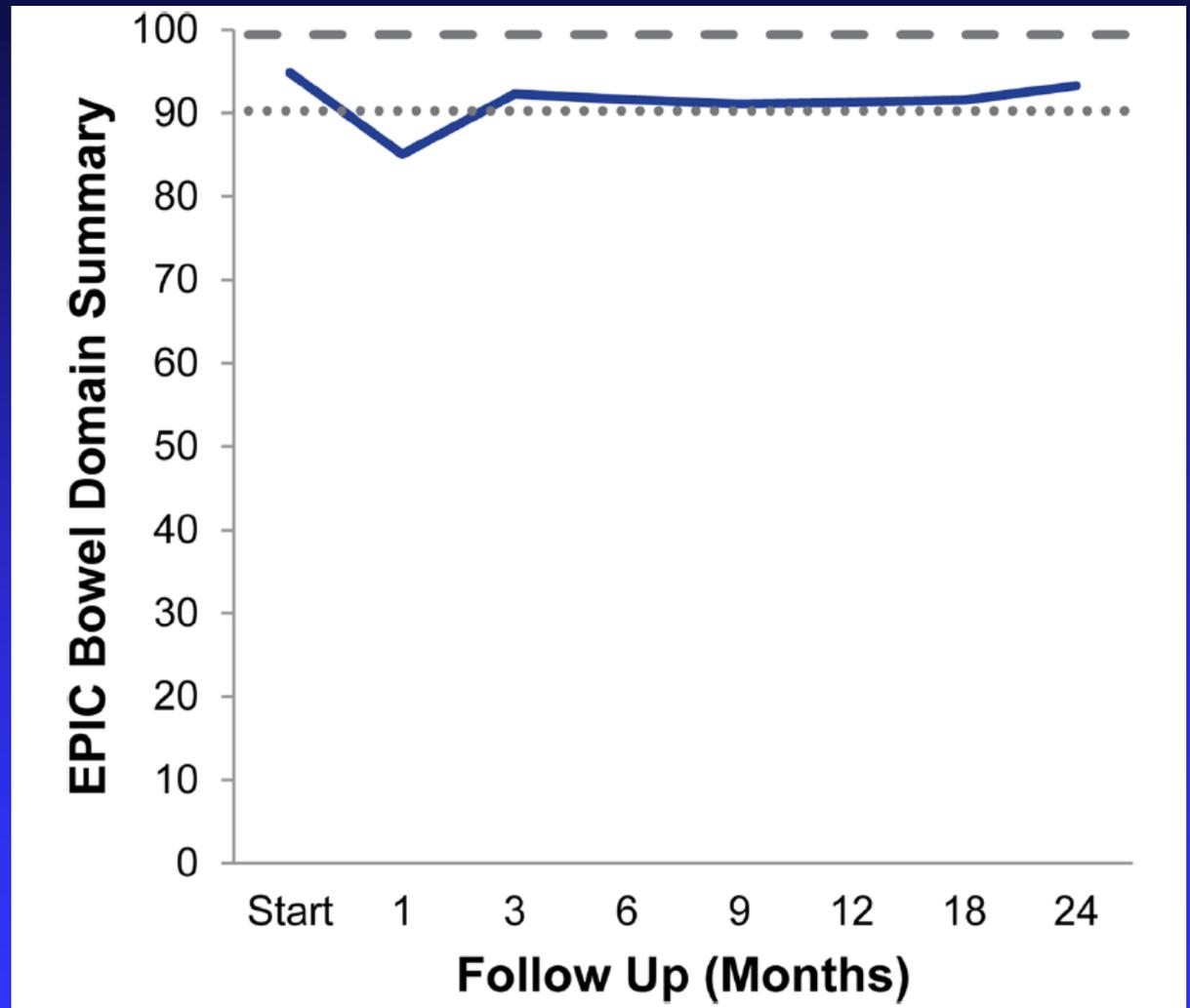
- < 1cc receiving 36 Gy
- < 20% receiving 80% of proscribed dose
- < 50% receiving 50% of proscribed dose

- **Tight posterior margin!**



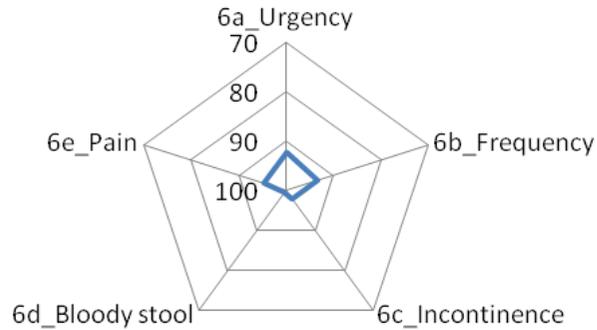
Bowel Quality of Life

- Minimal Bowel Toxicity
- Grade 2 rectal bleeding
 - 1.5%
- EPIC Bowel Score
 - Dip at one month
 - Recovery at 3 months

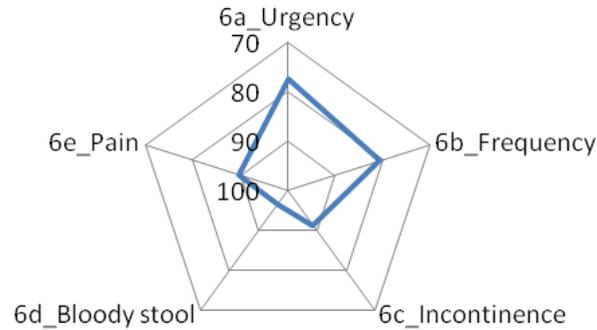


Proctitis Following Robotic SBRT

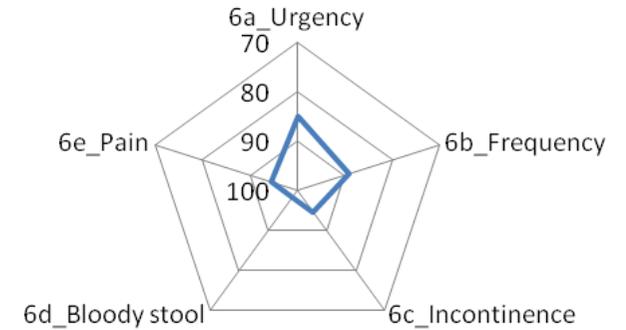
Start



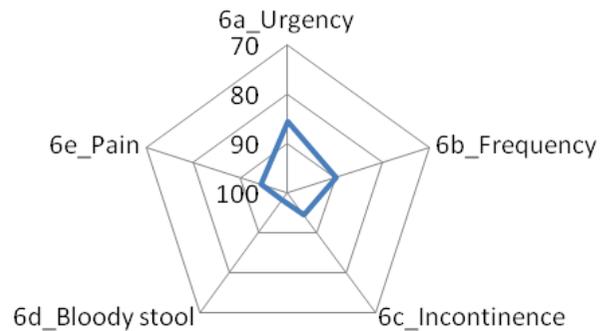
1 Month



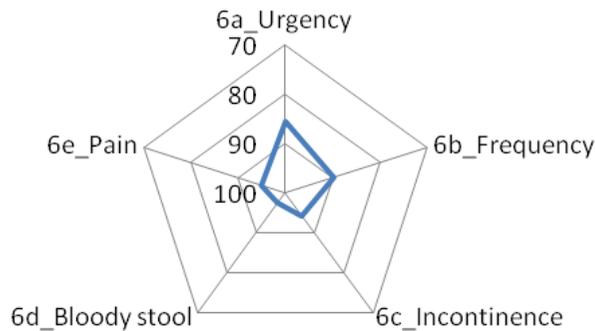
6 Month



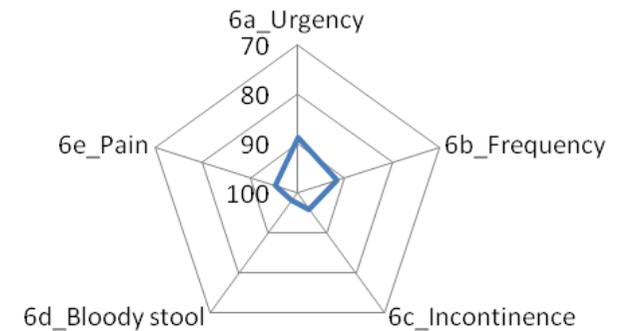
12 Month



18 Month



24 Month



Dosimetric Predictor of Bowel Quality of Life Following SBRT

- Dose to 1 cc of rectal wall > 35 Gy was associated with a minimally important clinical change in bowel QOL.

Table 5

Mean DVH parameters obtained and univariate and multivariate logistic regression analysis of QOL in urinary, bowel and sexual domains on the DVH scores.

	Parameter		Univariate		Multivariate		
	Mean	SD	OR (95% CI)	p-Value	OR (95% CI)	p-Value	
Urinary	Bladder						
	Volume (cc)	261	169	3.36 (1.08, 11.19)	0.040	3.36 (1.08, 11.19)	0.040
	V20 (%)	22	13	0.56 (0.16–1.76)	0.337		
	V28.5 (%)	11	7	0.56 (0.16–1.76)	0.337		
	V31.8 (%)	7	5	0.60 (0.17–1.87)	0.389		
	V35 (%)	2	2	0.40 (0.09–1.42)	0.190		
	D5cc (Gy)	34	3	3.54 (0.88–23.88)	0.114		
Bowel	Rectum						
	V20 (%)	37.5	10	1.32 (0.50–3.58)	0.574		
	V28.5 (%)	17	5	2.53 (0.93–7.43)	0.078		
	V31.8 (%)	10	4	3.59 (1.29–11.18)	0.019		
	V35 (%)	3	3	2.16 (0.78–5.96)	0.135		
	D1cc (Gy)	35	1	3.09 (1.13–9.12)	0.032	3.53 (1.19, 11.63)	0.028
	D5cc (Gy)	33	2	2.07 (0.76–6.09)	0.164		
Sexual	PB						
	V35	4	6.5	3.14 (1.18, 8.67)	0.024	3.14 (1.18, 8.67)	0.024
	V20	40	24	2.73 (1.07, 7.24)	0.039		

Abbreviations: SD = standard deviation; OR = odds ratio; CI = confidence intervals, PB = Penile Bulb.

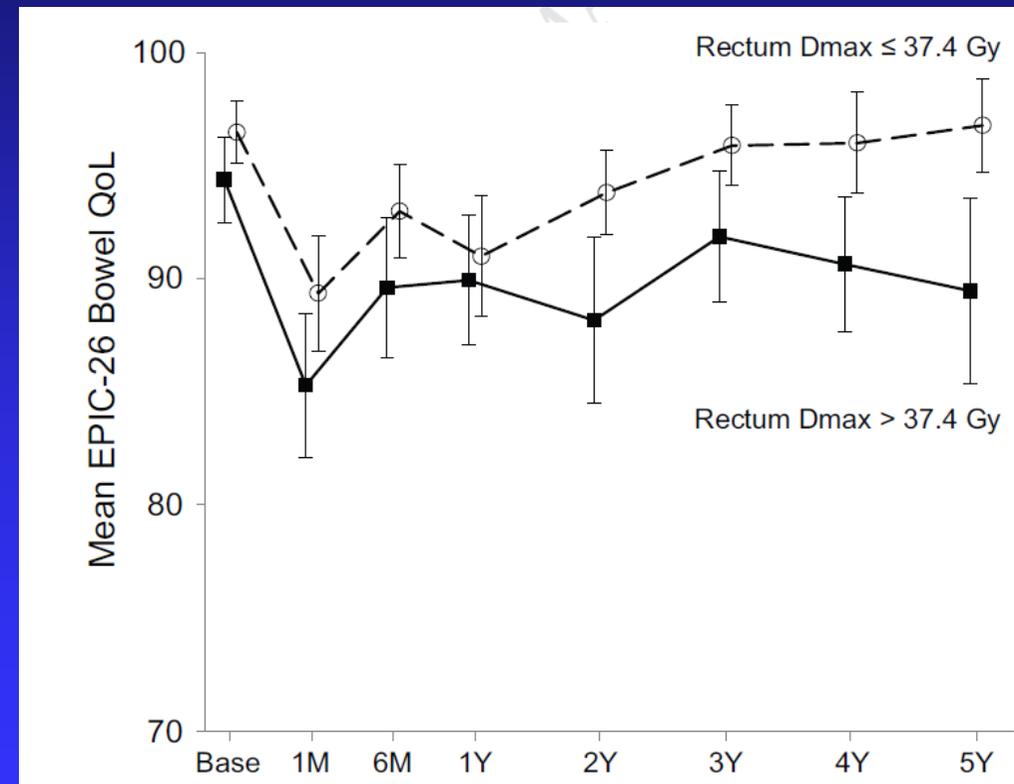
Dosimetric Predictor of Bowel Quality of Life Following SBRT

□ Moderate to Big Problems (2 years)

□ Max Point Dose to Rectum

□ < 37.4 Gy 2%

□ > 37.4 Gy 11%



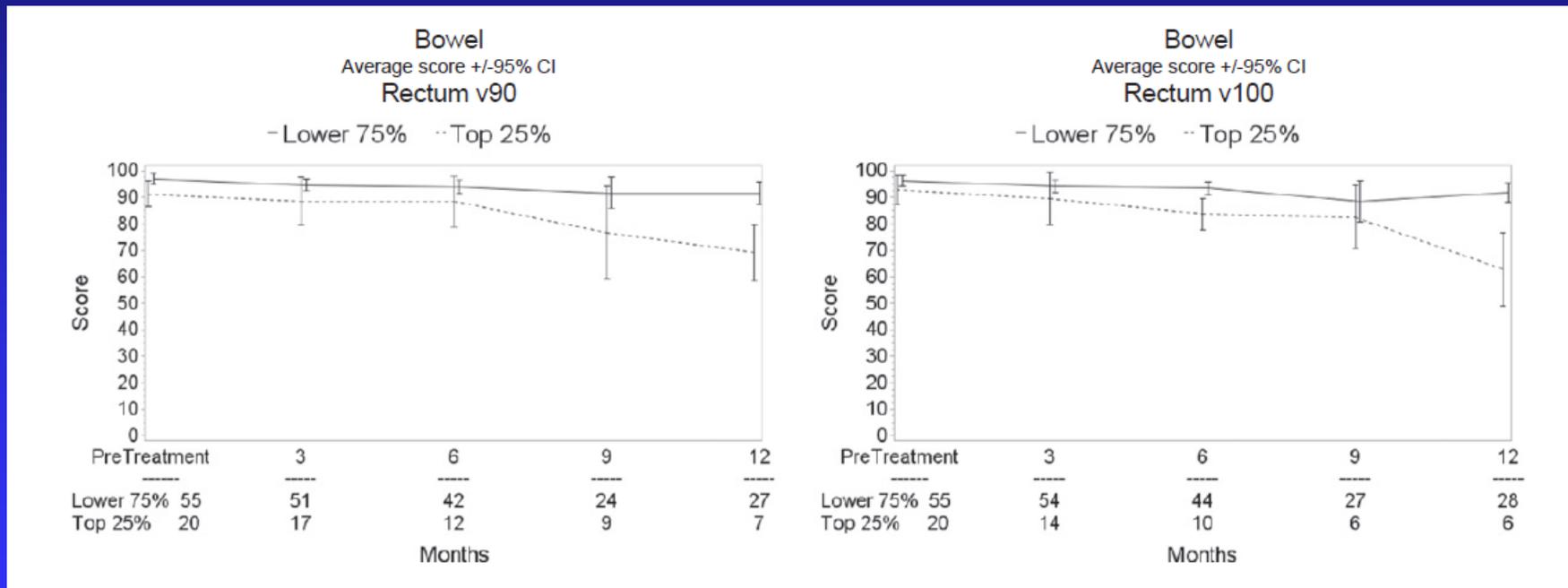
□ Wang, IJROBP, 2018

Dosimetric Predictor of Bowel Quality of Life Following SBRT

□ Bowel QOL is decreased if:

□ Rectal V36 Gy > 4.2 cc

□ Rectal V40 Gy > 1.5 cc



□ Gomez, PRO, 2015

Summary: Factors Associated with Late Bowel Side Effects

Table 2 Selected studies analyzing factors associated with late bowel side effects

Study	n	Treatment details	Med.	Bowel endpoint	Dosimetric factors associated* with worse bowel outcomes	Nondosimetric factors associated* with worse bowel outcomes
			f/u (y)			
King et al, ²⁰ 2012 (Stanford)	67	36.25 Gy (5 fx), QD/QOD	2.7	RTOG		QD (vs QOD) treatment schedule
		16%: 45 Gy (5 fx), QOD	2.0	CTCAE v3	Rectum V50 Gy >3 cc Rectum Circumference V39 Gy >35%	
Kim et al, ³³ 2014 (multicenter)	91	16%: 47.5 Gy (5 fx), QOD		G2: 23.1%		
		67%: 50 Gy (5 fx), QOD		G3: 3.3% G4: 2.2%		
Elias et al, ²² 2014 (Sunnybrook)	84	35 Gy (5 fx), QW	4.2	EPIC QOL MID: 26.2%	Rectum V31.8 Gy >10% Rectum D1cc >35 Gy	
Gomez et al, ²⁶ 2015 (UCLA)	75	40 Gy (5 fx), QOD	1.0	EPIC QOL	Rectum V40 Gy >1.5 cc Rectum V36 Gy >4.2 cc	
Musunuru et al, ³⁴ 2016 (Sunnybrook)	258	33%: 35 Gy (5 fx), QW	2.5	CTCAE v3	Rectum V38 Gy >2 cc Prescription dose 40 Gy (v 35 Gy)	SV treatment (vs prostate only) PTV margin 5 mm (vs 4 mm) Hemorrhoids Anticoagulant use
		67%: 40 Gy (5 fx), QW or QOD		G2 bleed: 16.2% G3 bleed: 1.6% G4 bleed: 1.6%		
Miszczyk et al, ³⁵ 2017 (Poland)	400	36.25 Gy (5 fx), QOD	1.3	RTOG G1: 4.7% G2: 0.6% G3: 0.3%		Diabetes

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; EPIC = Expanded Prostate Cancer Index Composite; Med f/u = median follow-up; MID = minimally important difference; PTV = planning target volume; QD = every day; QOD = every other day; QOL = quality of life; QW = every week; RTOG = Radiation Therapy Oncology Group; SV = seminal vesicle; UCLA = University of California, Los Angeles.

* Included if reported as trend or statistically significant on univariate or multivariable analysis.

Tips for Minimizing Bowel Symptoms

- Low Residue Diet
 - Start five days prior to treatment
 - Maximize distance between the prostate and the rectal wall
 - Minimize intrafraction prostate motion
- Pretreatment Fleets Enema
 - Prior to simulation and each treatment
- Rectal dose reduction
 - $V_{36} \text{ Gy} < 1 \text{ cc}$
 - Posterior PTV expansion 3 mm
- Rectal Spacer
 - For high risk patients if considering dose escalation

Potency Preservation Following Robotic SBRT

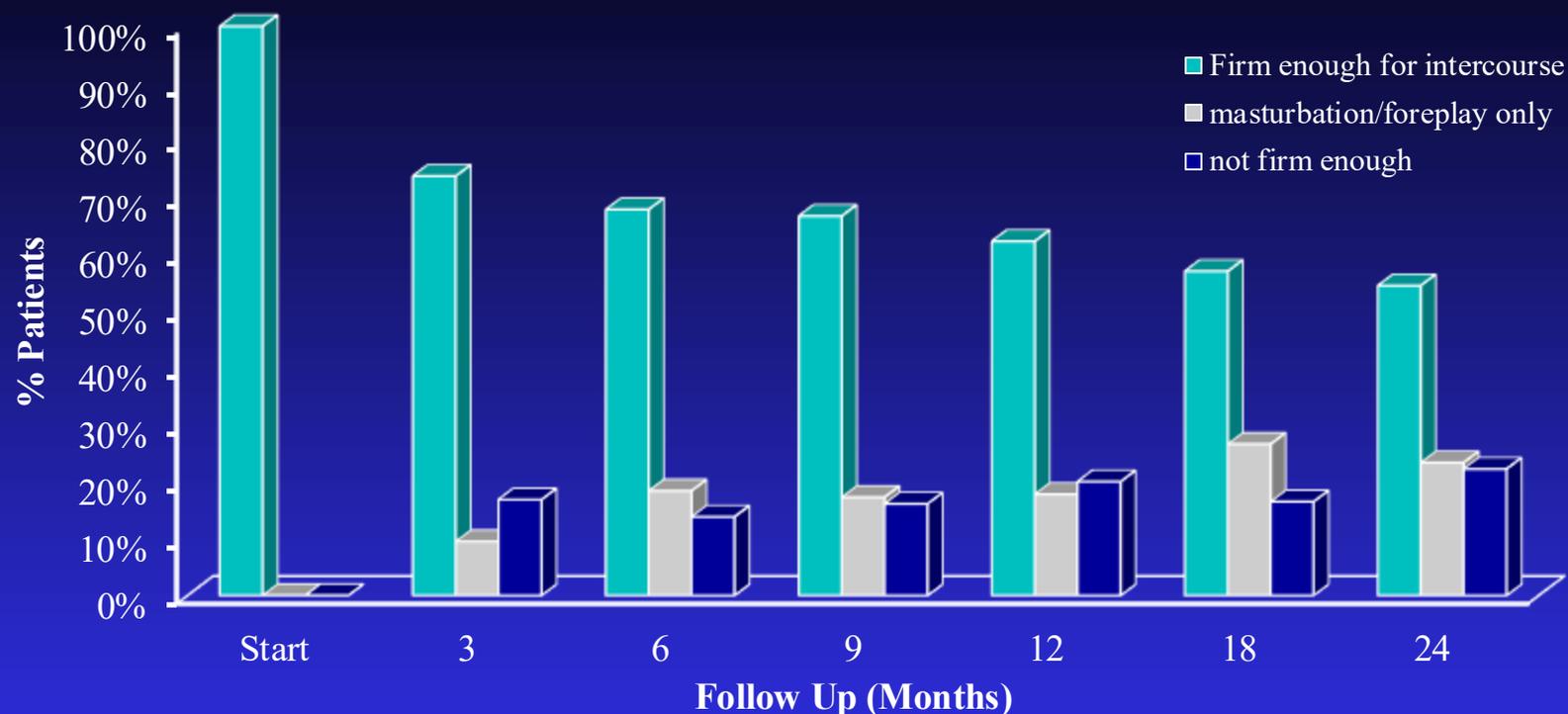
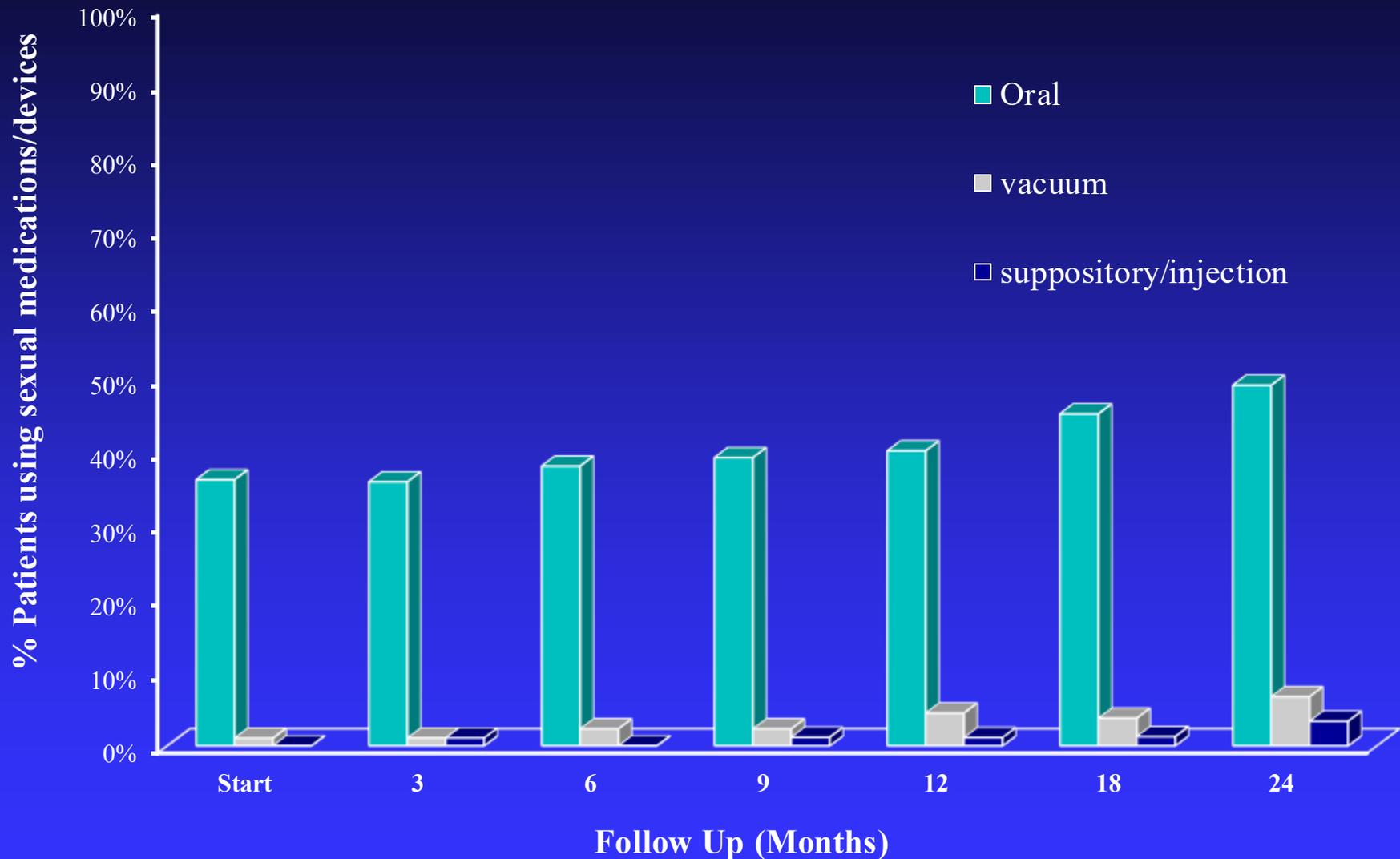


Table 2 Quality of erection following SBRT for prostate cancer (patient-reported responses to question 9 of the EPIC-26)

Follow up (months)	Start	3	6	9	12	18	24
Firm enough for intercourse	100.0%	73.7%	67.8%	66.7%	62.2%	57.0%	54.4%
Firm enough for masturbation and foreplay only	0.0%	9.5%	18.4%	17.2%	17.8%	26.6%	23.3%
Not firm for any sexual activity	0.0%	16.8%	13.8%	16.1%	20.0%	16.5%	22.2%
<i>p</i>		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Total patient	97	95	87	87	90	79	90

Potency Preservation Following Robotic SBRT



Patient-Reported Sexual Aid Efficacy After Robotic SBRT

- Most Men With Baseline Function Reported Sexual Aids Were Helpful!
- “Helpful” at First Use Declined with Time
- Sexual Aids Durably Helpful in Approximately 80%

Answered choices included

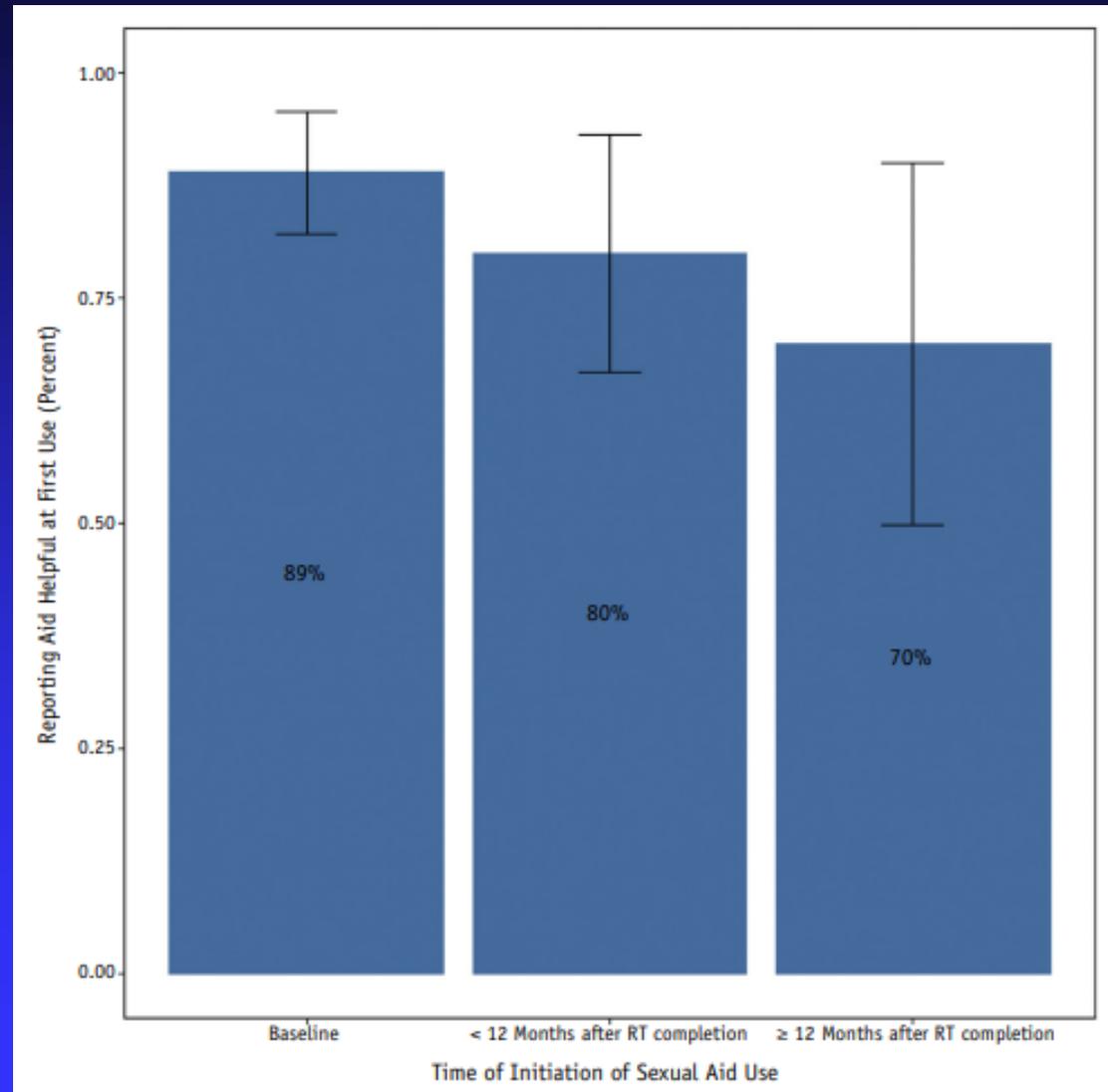
Have NOT tried it

Tried it, but was **NOT HELPEFUL**

It HELPED, but I am NOT using it NOW

It HELPED, and I used it SOMETIMES

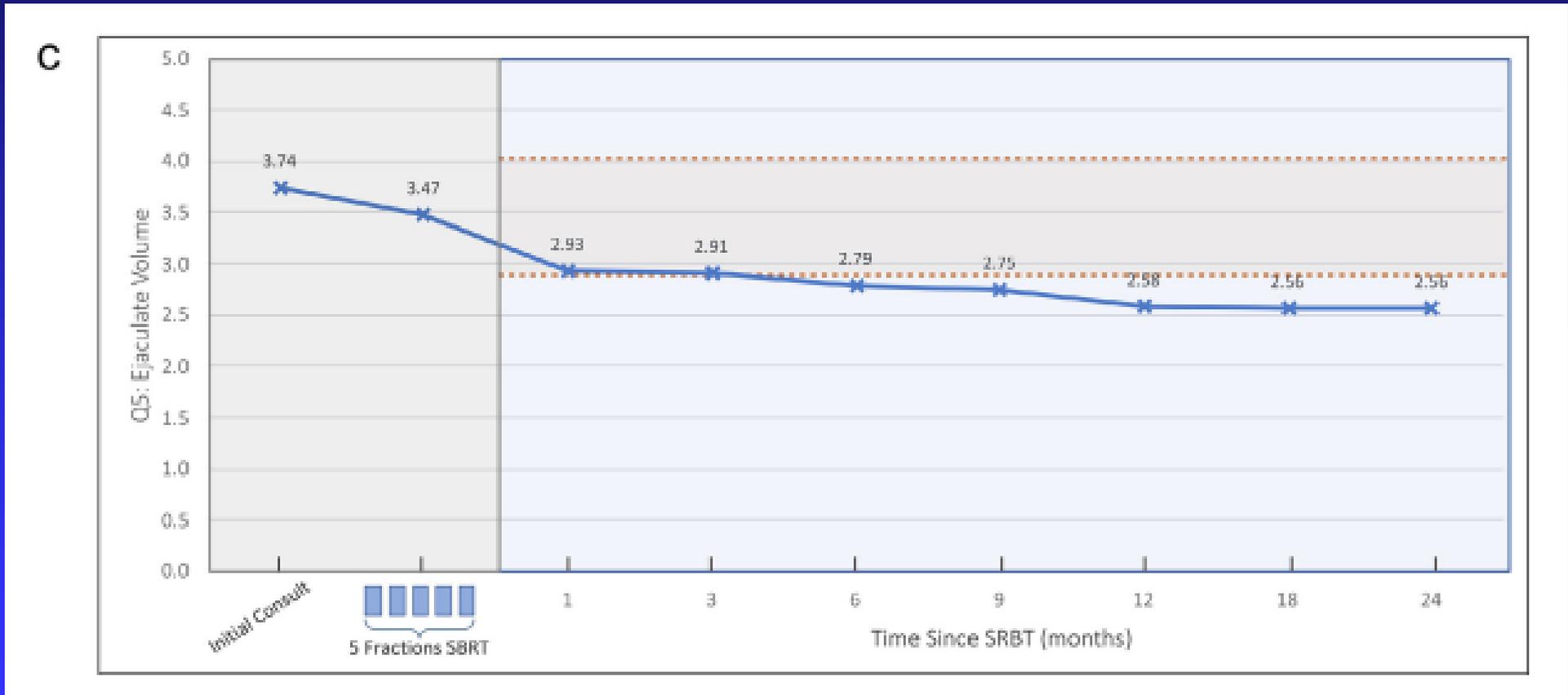
It HELPED, and I use it ALWAY



□ Dess *et al*, *IJROBP*, 2018

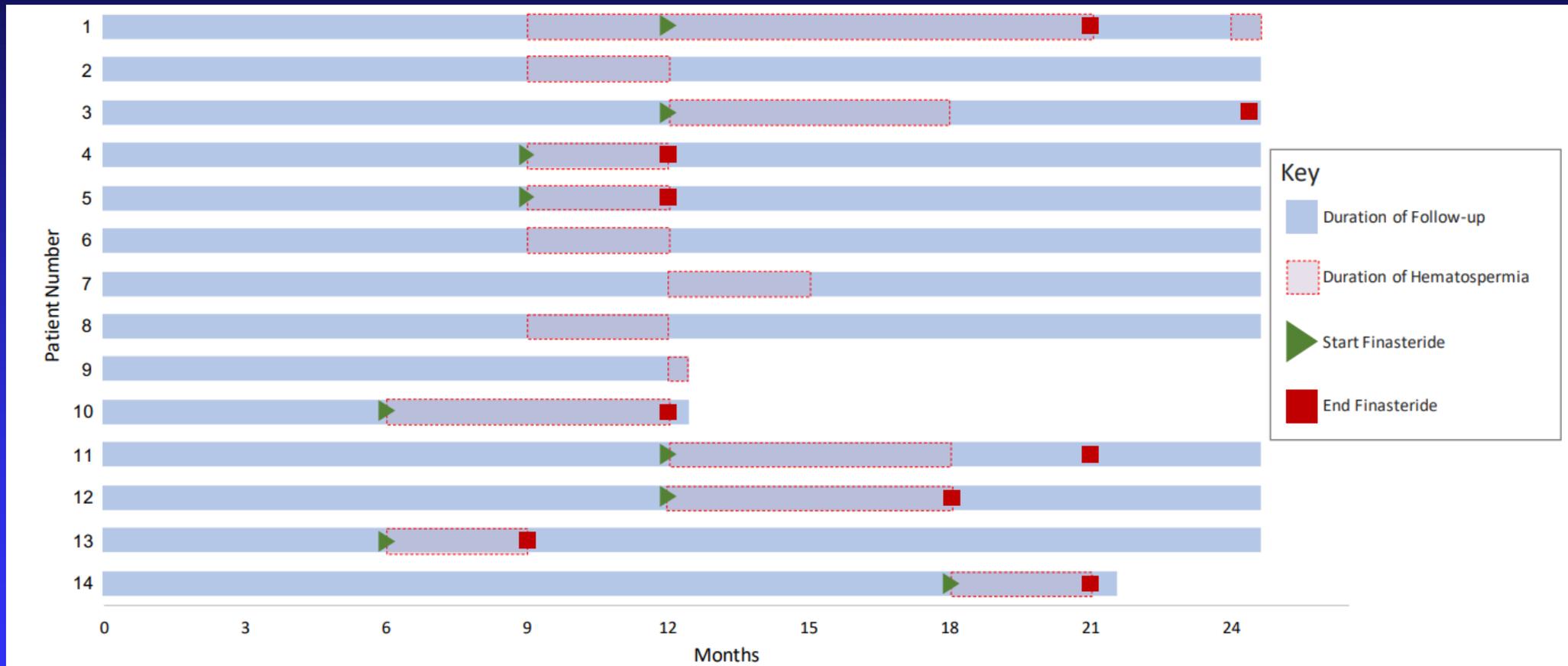
Ejaculatory Function Following Robotic SBRT

- The 2-Year Anejaculation Rate was 15%



Bothersome Hematospermia Following Robotic SBRT

- The 2-Year Cumulative Incidence of Transient Hematospermia was 5.6%



- Responds to 5-Alpha Reductase Inhibitors!

Summary: Factors Associated with Late Sexual Side Effects

Table 3 Selected studies analyzing factors associated with late sexual side effects

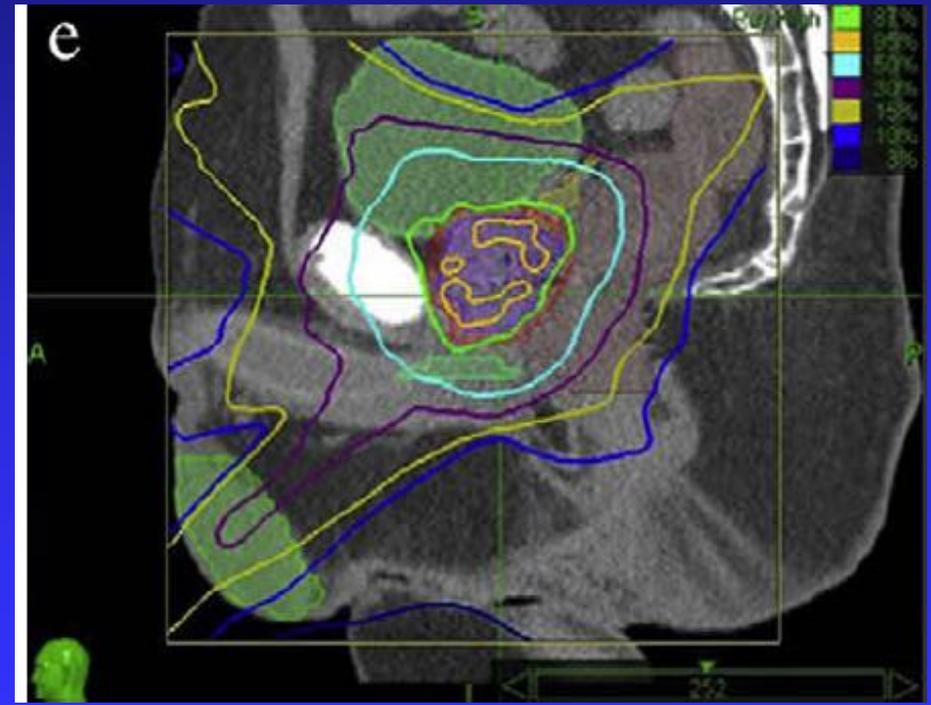
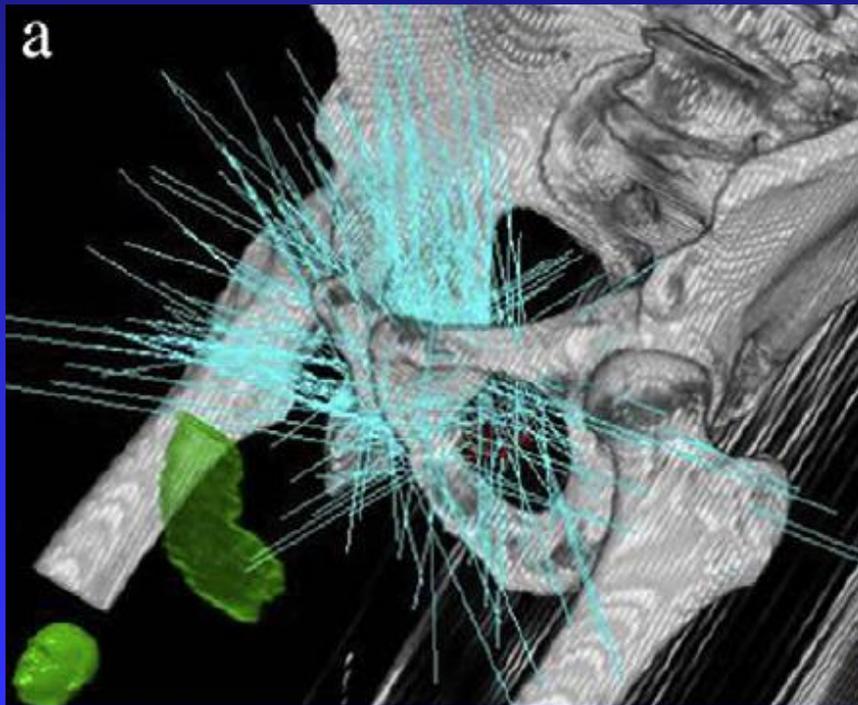
Study	n	Treatment details	Med. f/u (y)	Sexual endpoint	Dosimetric factors associated* with worse sexual outcomes	Nondosimetric factors associated* with worse sexual outcomes
Wiegner et al, ³⁶ 2010 (Stanford)	32 (no ADT)	36.25 Gy (5 fx), QD/QOD	3.0	EPIC QOL 20M impotency: 61% (23% if potent at baseline)	(PB not associated)	Older age
Obayomi-Davies et al, ³⁷ 2013 (Georgetown)	97 (potent at baseline, no ADT)	35-36.25 Gy (5 fx), QOD	2.7	EPIC QOL 2Y impotency: 45.6%	(PB not associated)	Charlson Comorbidity Index ≥ 1
Elias et al, ²² 2014 (Sunnybrook)	84 (4% ADT)	35 Gy (5 fx), QW	4.2	EPIC QOL MID: 37.5%	PB V20 Gy >40% PB V35 Gy >4%	
Dess et al, ³⁸ 2018 (Georgetown)	373 (no ADT)	35-36.25 Gy (5 fx), QOD	4.7	EPIC QOL 2Y impotency: 66% (43% if potent at baseline)	(PB not analyzed)	Older age Higher body mass index Diabetes Hypertension Coronary artery disease

Abbreviations: ADT = androgen deprivation therapy; CTCAE = Common Terminology Criteria for Adverse Events; EPIC = Expanded Prostate Cancer Index Composite; Med f/u = median follow-up; MID = minimally important difference; PB = penile bulb; QD = every day; QOD = every other day; QOL = quality of life; QW = every week.

* Included if reported as trend or statistically significant on univariate or multivariable analysis.

Testicular Dose from Prostate Cyberknife: a Cautionary Note.

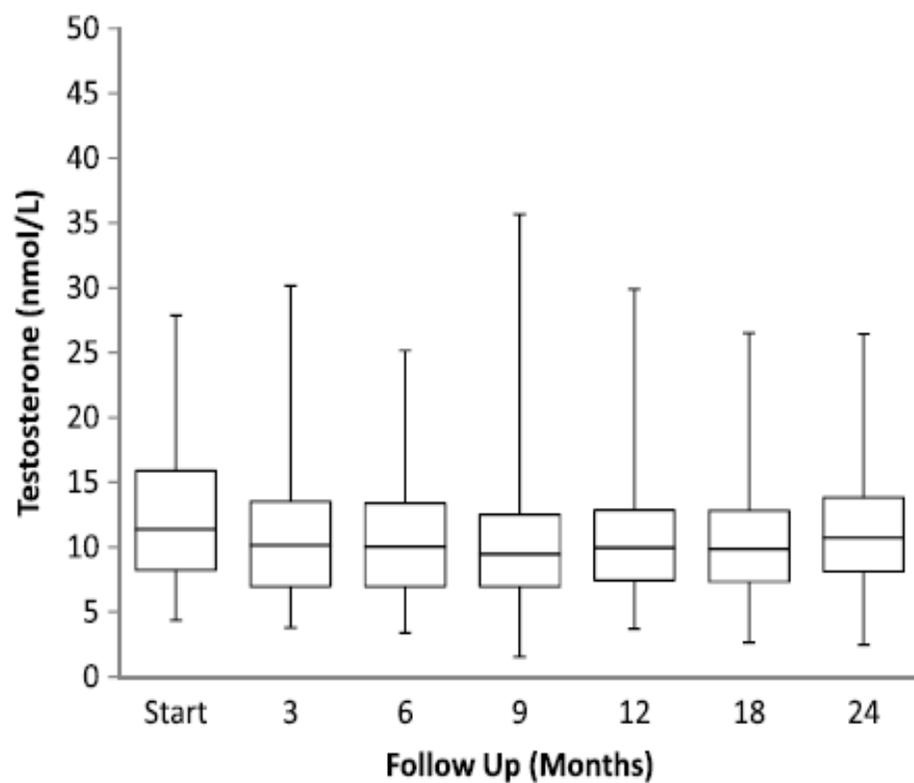
- Non-coplanar beams
- Hypogonadism can be apparent at doses in the range of 2 to 4 Gy



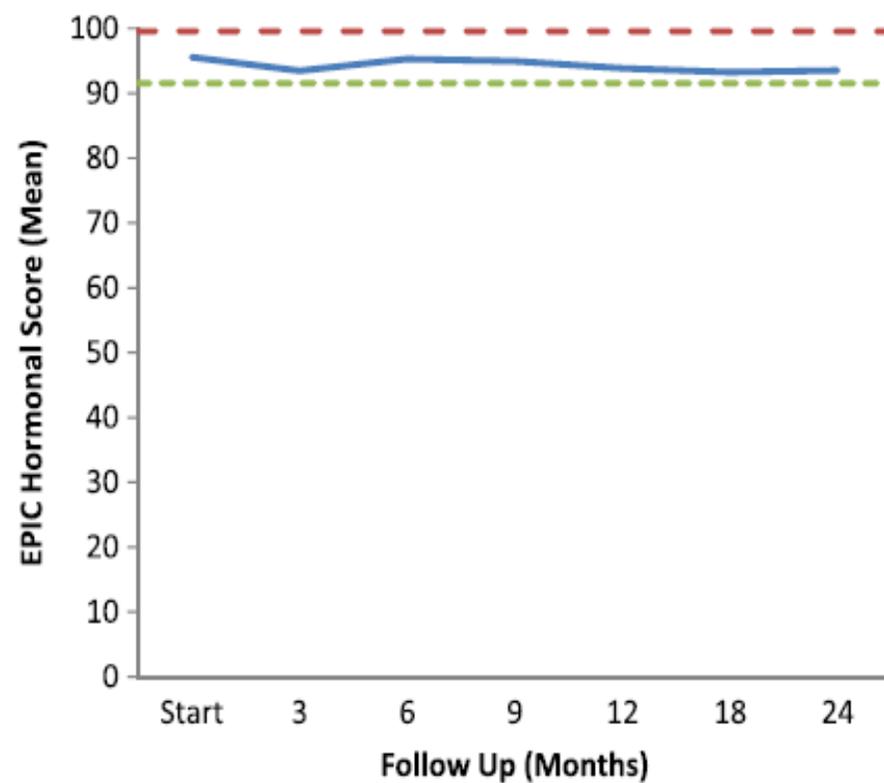
Hypogonadism Following SBRT

- Minimal if you block beams that transverse testis

(a)

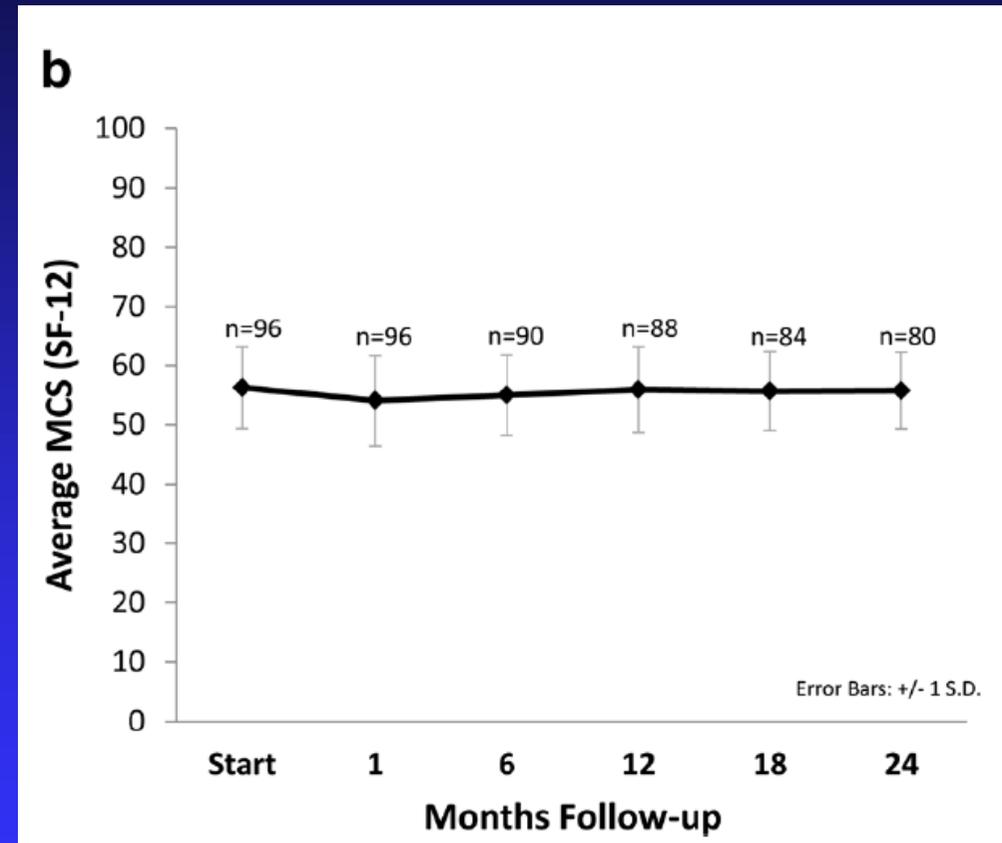
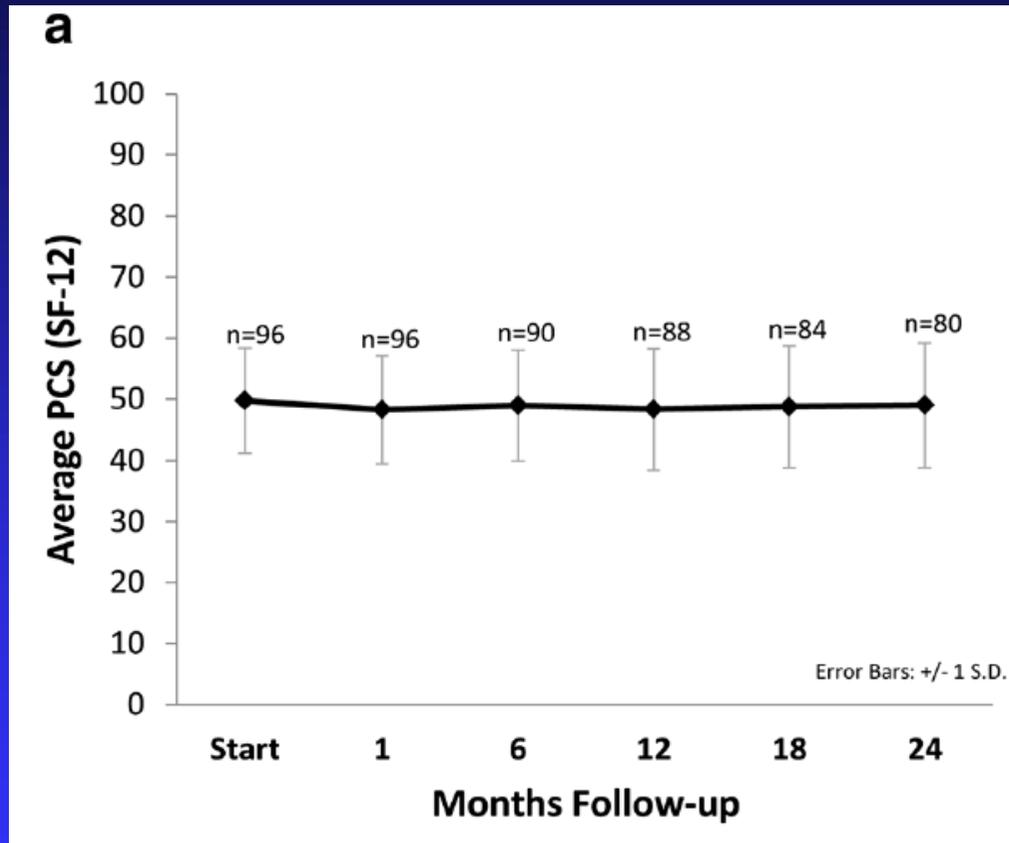


(b)



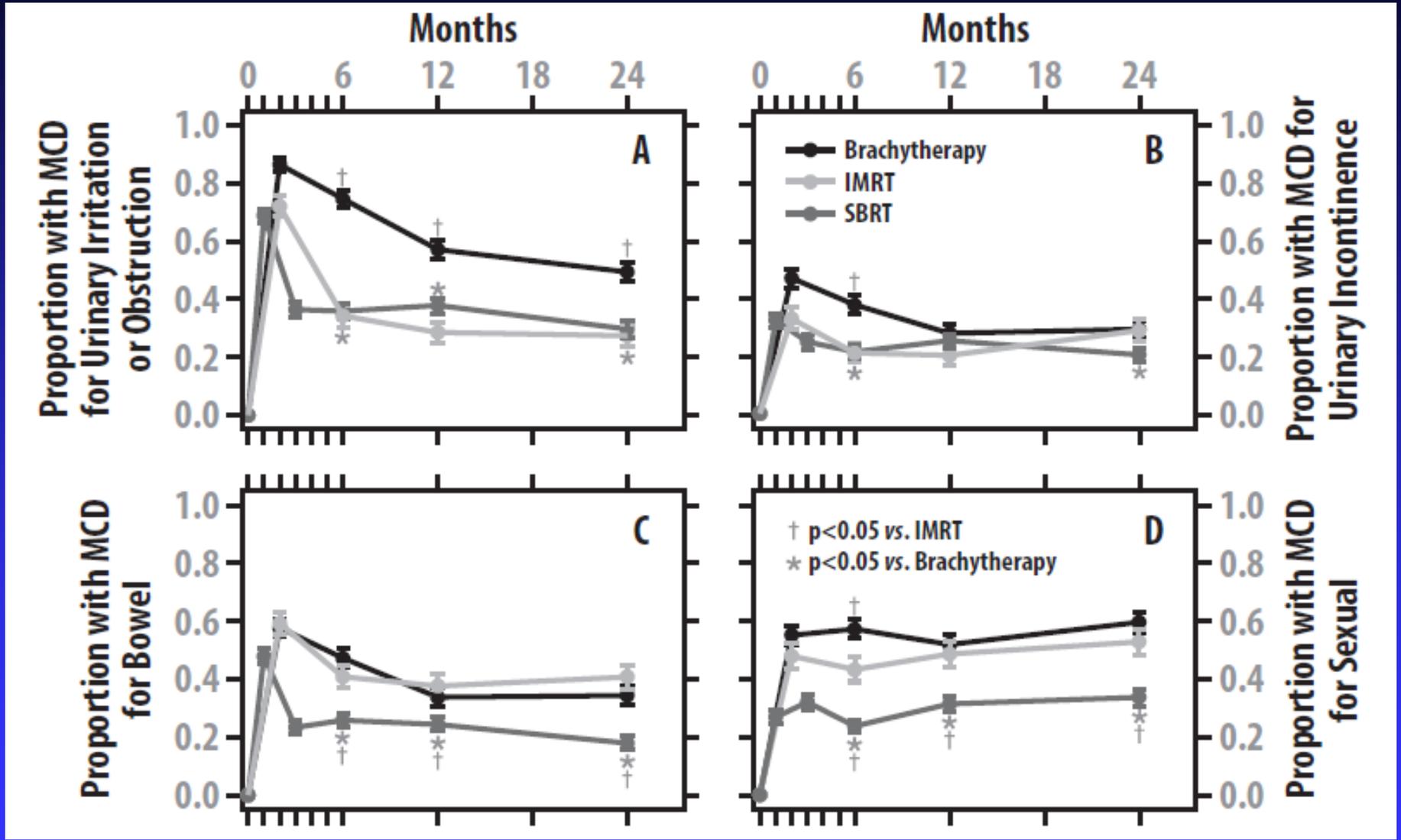
Quality of Life Following Robotic SBRT

□ Minimal Impact



□ *Chen et al, Rad. Onc., 2013*

Proportion of Patients with Minimally Important Differences



Proportion of Patients Responding Moderate-Severe to Individual EPIC items

□ Overall Urinary Problems (2 years)

- IMRT 12%
- Brachy 14%
- SBRT 5%

□ Overall Bowel Function (2 years)

- IMRT 10%
- Brachy 7%
- SBRT 2%

Thank You for Your Attention!

