



Predicting (and avoiding) Morbidity in LDR Prostate Brachytherapy



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Categories of Morbidity

- *Urinary*
 - IPSS
 - retention
 - stricture
- *Rectal*
 - bleeding
 - fistula
- *Sexual*
 - erectile function

Functional/technical considerations

- Prostate volume
 - Total volume
 - Volume with respect to body habitus
 - Transition zone volume/ TZ index
- Voiding function
 - IPS score
 - Voiding study/ flow rate & post void residual
- TURP before or after
- Hormonal therapy to downsize
- Planning aspects
 - seed activity (# seeds/needles)

Prostate volume predicts retention

Author	Year	n	Factors	p-value
Lee	2000	91	vol >35 cc # needles	p<0.05 p<0.04
Locke	2002	62	volume	p=0.02
Crook	2002	150	volume/ hormones	p=0.003 p=0.007
Hineman- Mulroy	2004	116	preH vol hormones	
Henderson	2004	255	volume urodynamics IPSS	p<0.05
Kelly	2006	111	volume/ IPSS	
Martens	2006	207	volume/ PFR<10ml/s	p=0.009 p=0.004

Predictors of Retention

author	year	n	factors	P-value
Keyes	2009	712	Volume # needles IPSS HT	MVA
Mabjesh	2007	655	Volume IPSS	OR: 6.8 OR: 3.1

Prostate size

- no absolute limit
 - can you get under the pubic arch?
 - how well do they pee?

Prostates > 60 cc

- require larger number of seeds & needles
(↑ risk urinary morbidity)
- technically difficult b/o PAI
- no absolute cut-off for size/ depends on relationship to pubic arch
 - with small frame, may get PAI @ 40-45 cc, while in large frame 65 cc OK
- Hip-position and TRUS probe-angle important

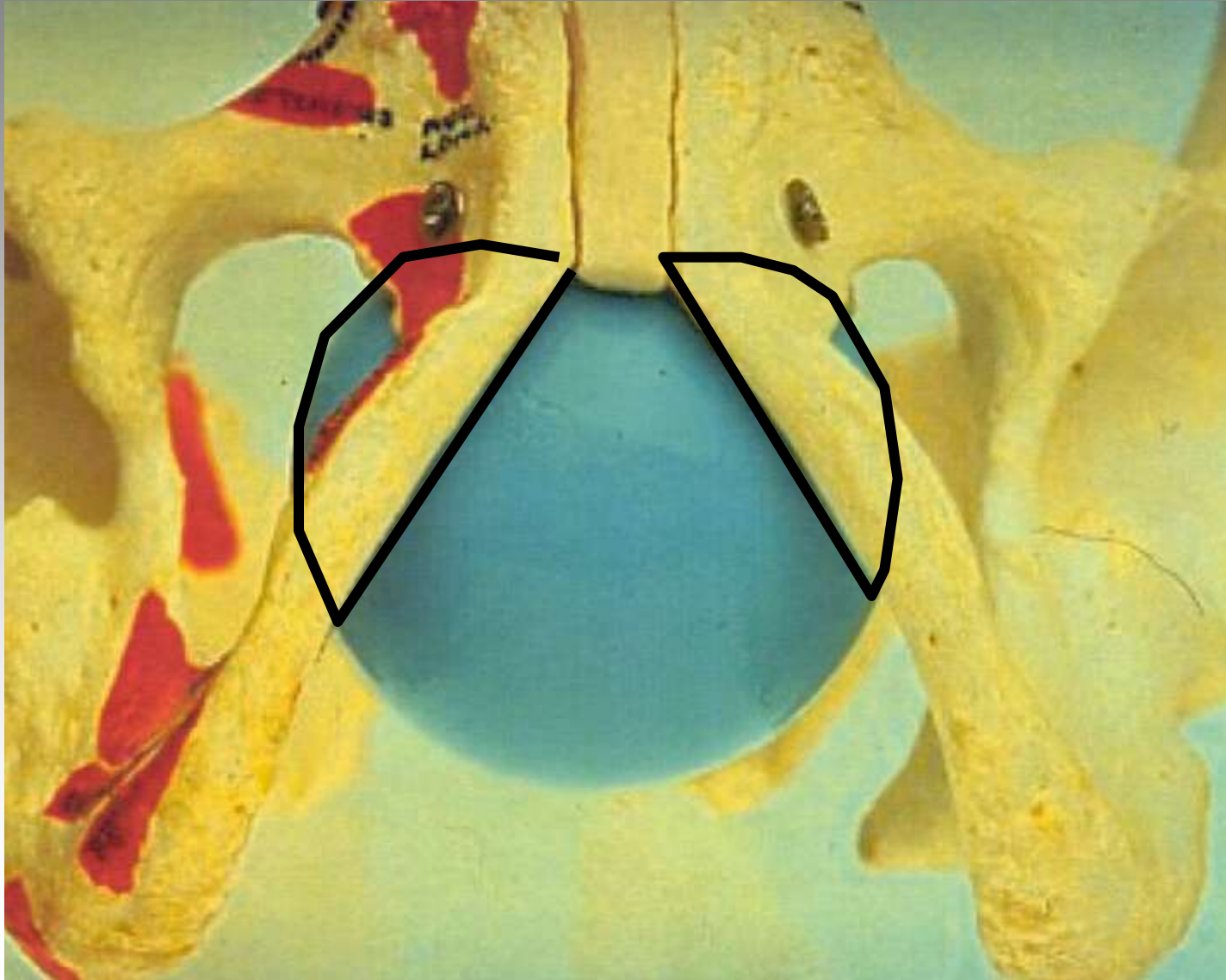
The big prostate

- a. check for PAI
- b. flatten the probe
- c. hyperflex the hips

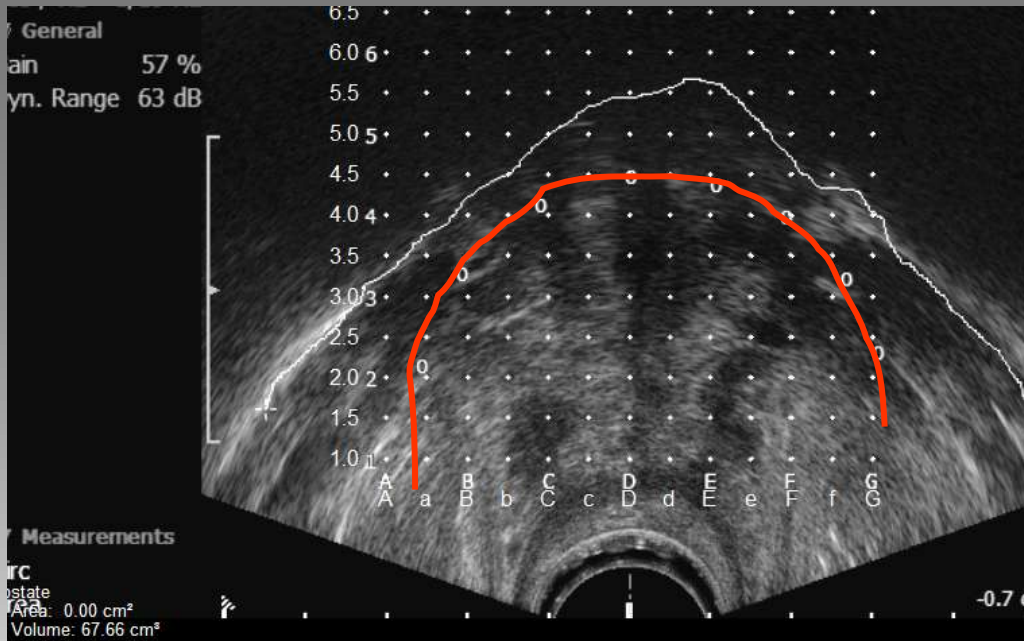
To improve access under pubic arch:
Hip angle more acute and flatten probe



Pubic arch interference

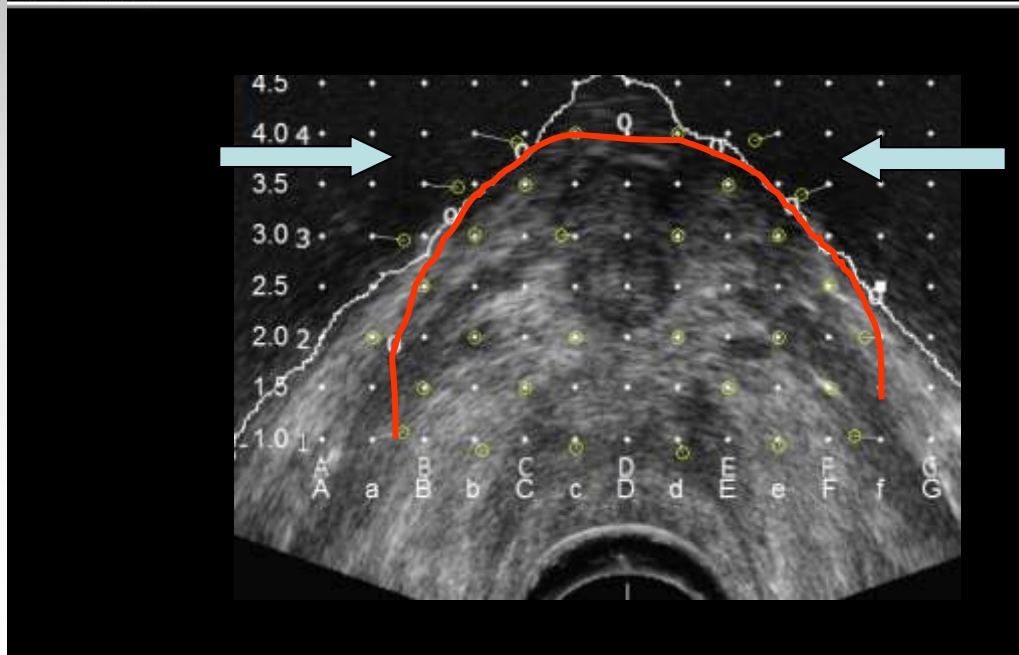


Pubic arch interference



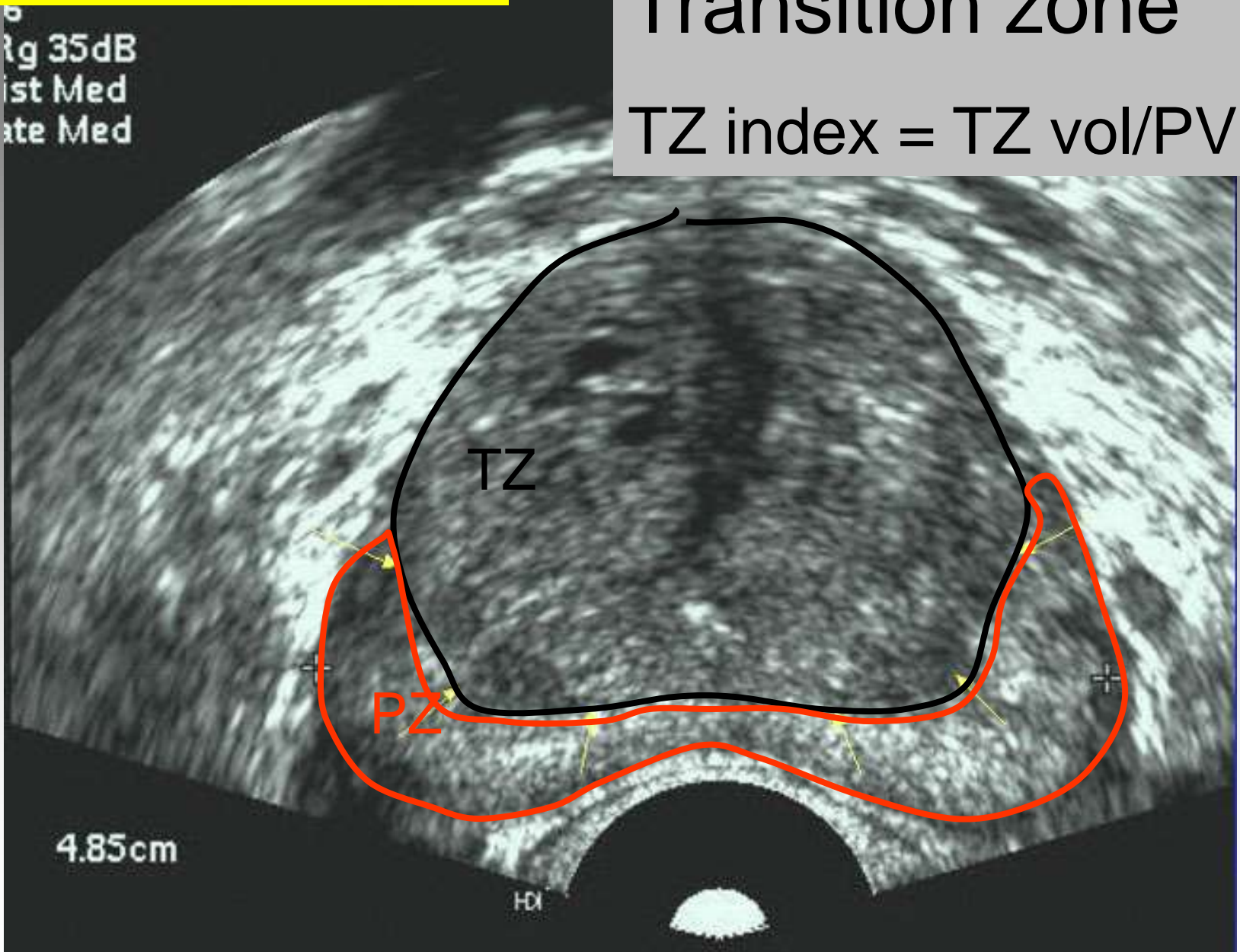
Relates to body habitus, race and frame size

- Blacks and Asians: narrow pubic arch
- broad shoulders more important than height



Transition zone

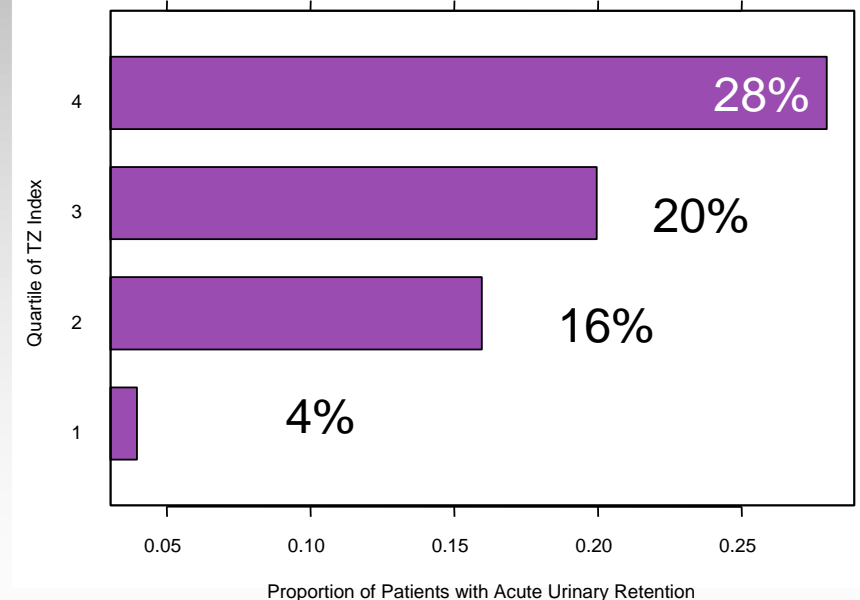
$$\text{TZ index} = \text{TZ vol}/\text{PV}$$



Transition zone data

- Predicts retention
(multivariate) *Thomas 2000:*
- Predicts IPSS peak & normalization *Merrick 2001*
- Post H TZ predicts catheter dependence *Hinerman-Mulroy 2004*
- TZI < 35% AUR 4%,
> 55% AUR 28% *Crook 2002*

Figure 1



IPSS: x/35

- Subjective feeling of being “empty”
- Frequency of < 2 hour intervals
- Interrupted stream
- Having to push or strain to start
- Weak stream
- Difficulty postponing urination
- # of times up at night



Very subjective!

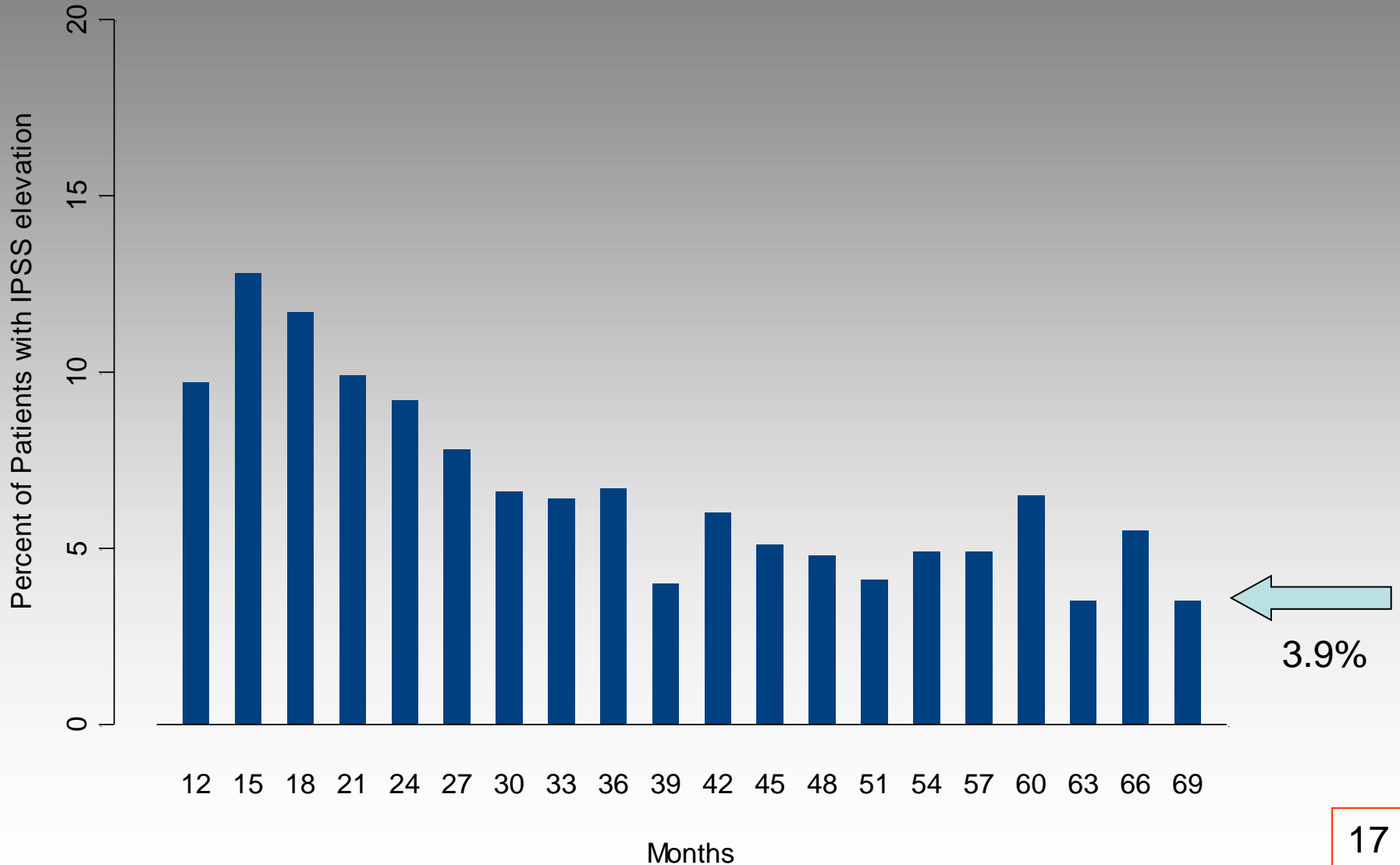
IPSS: experience at PMH n=1100

- Median IPSS at baseline: 5
- at 5 years : 6
- at 10 years: 3
- Median time for return to normal: 12 mo
- By 2 years: 71% returned to normal
- By 3 years: 83%
- FLARE: IPSS > 15 and \uparrow > 5 over nadir
35%; peak time 16-24 mo
- *Keyes et al IJROBP 2009*: n=712; 30% nadir +8
52% nadir +5

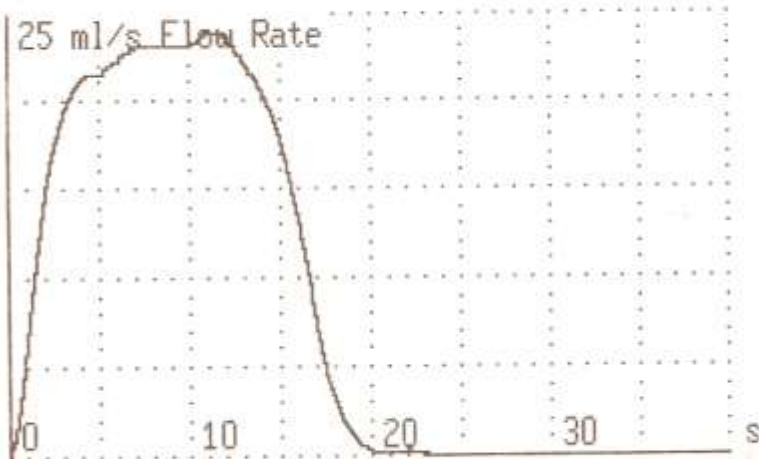
Experience based on urethral dose constraints

- catheter for post plan CT
- identify on each slice from base to apex
- DVH for UD5 (dose to 5% in cGy)
 - mean 210 Gy (SD 30) (goal < 150%)
- UD30 (dose to 30% in cGy)
 - mean 188 Gy (SD 22) (goal < 125%)
- UV150 (vol. cc receiving 150% of prescribed dose) less helpful (should be 0)

% of men with elevated IPSS



Voiding study



Results of UROFLOWMETRY

Voiding Time	T100	20	s
Flow Time	TQ	20	s
Time to max Flow	TQmax	11	s
Max Flow Rate	Qmax	23.8	ml/s
Average Flow Rate	Qave	16.8	ml/s
Voided Volume	Vcomp	330	ml

Shape of the curve
Peak flow: 23.8 ml/sec
Voided volume: 330 ml

Relationship of the International Prostate Symptom score with urinary flow studies, and catheterization rates following iodine 125 prostate brachytherapy

Chandra Martens¹, Greg Pond², Dennis Webster³,
Michael McLean¹, Caitlin Gillan³, Juanita Crook^{1,*}

- Age $p=0.38$
- *Voided volume* $p=0.64$
- IPSS $p=0.85$
- *PVR* $p=0.37$
- Prostate size $p<0.001$
- Hormones $p<0.001$
- *PFR* $p=0.011$

• *Multivariate analysis*

–PFR $p=0.003$

–Prostate volume $p=0.005$

Voiding studies

volume: 148 ml
max flow 8.2 ml/sec

#1

Results

2-1-2007 2:57PM
Voiding Time: 50 s
Flow Time: 41 s
Time to Max Flow: 28 s
Max Flow Rate: 8.2 ml/s
Average Flow Rate: 3.6 ml/s
Voided Volume: 148 ml
Filter: PVR
Sensor: Standard Spinning Dis

PVR: 320 ml

volume: 316 ml
max flow 13.2 ml/sec

#2

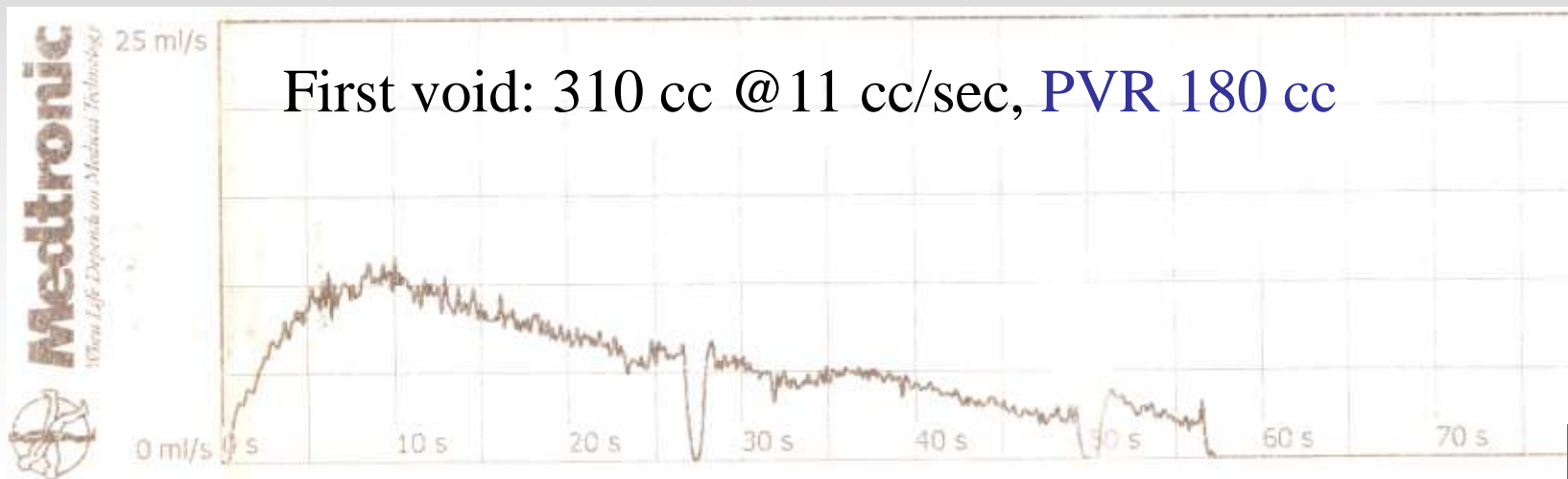
Results

2-1-2007 2:08PM
Voiding Time: 50 s
Flow Time: 47 s
Time to Max Flow: 22 s
Max Flow Rate: 13.2 ml/s
Average Flow Rate: 6.6 ml/s
Voided Volume: 316 ml

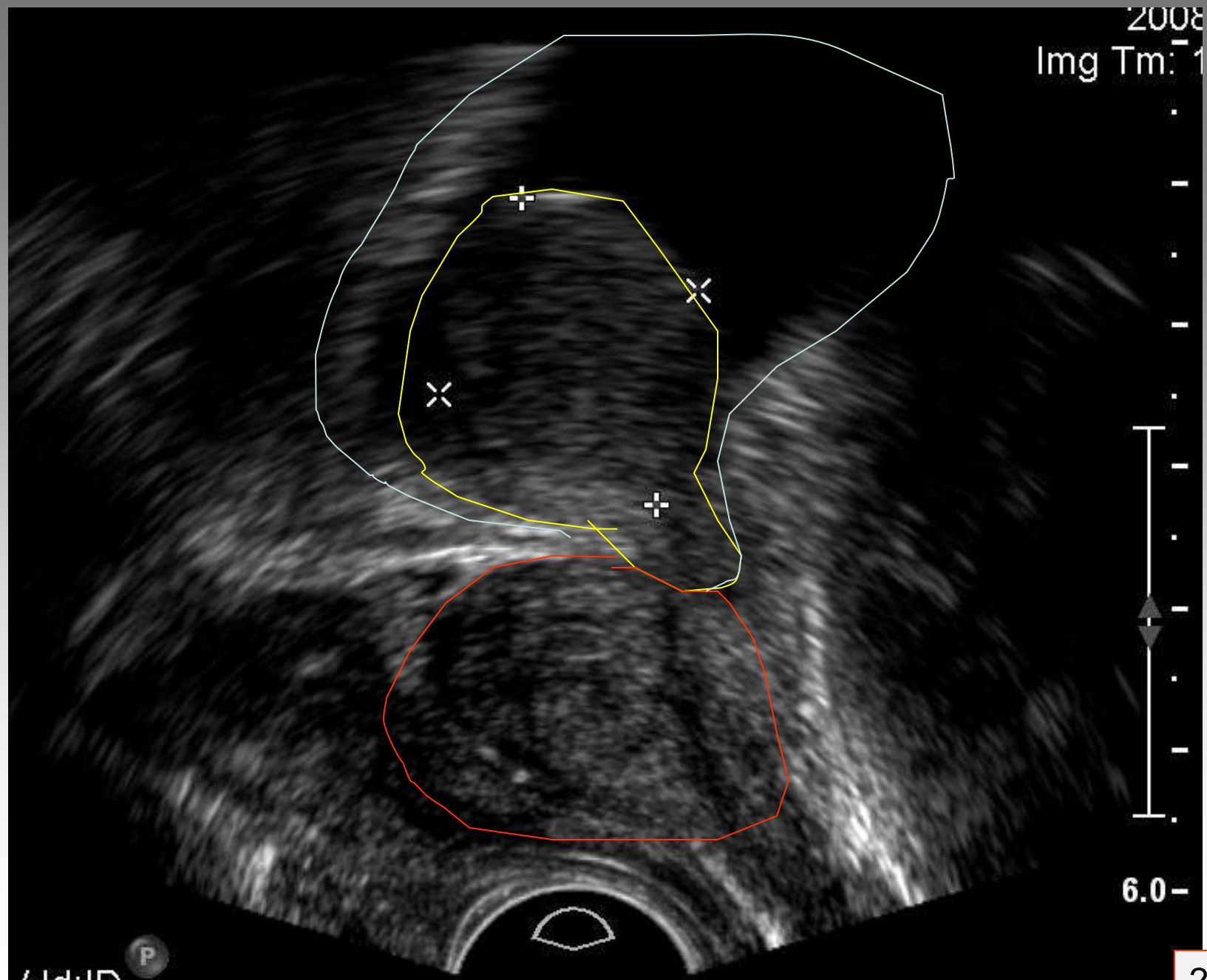
PVR: 204 ml

Case: Mr. RC

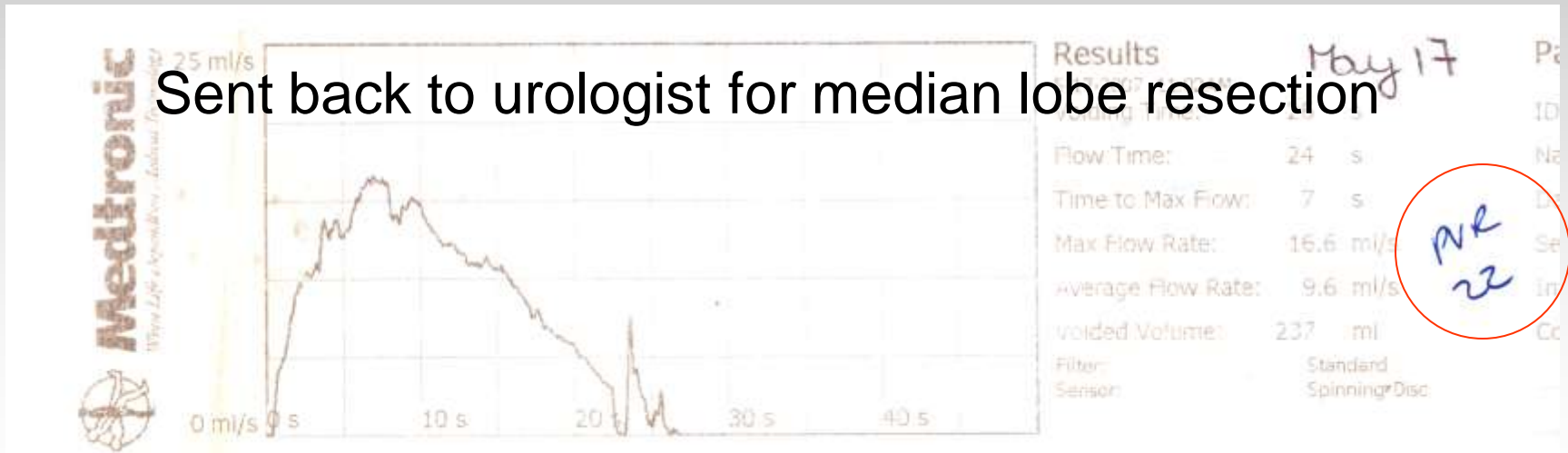
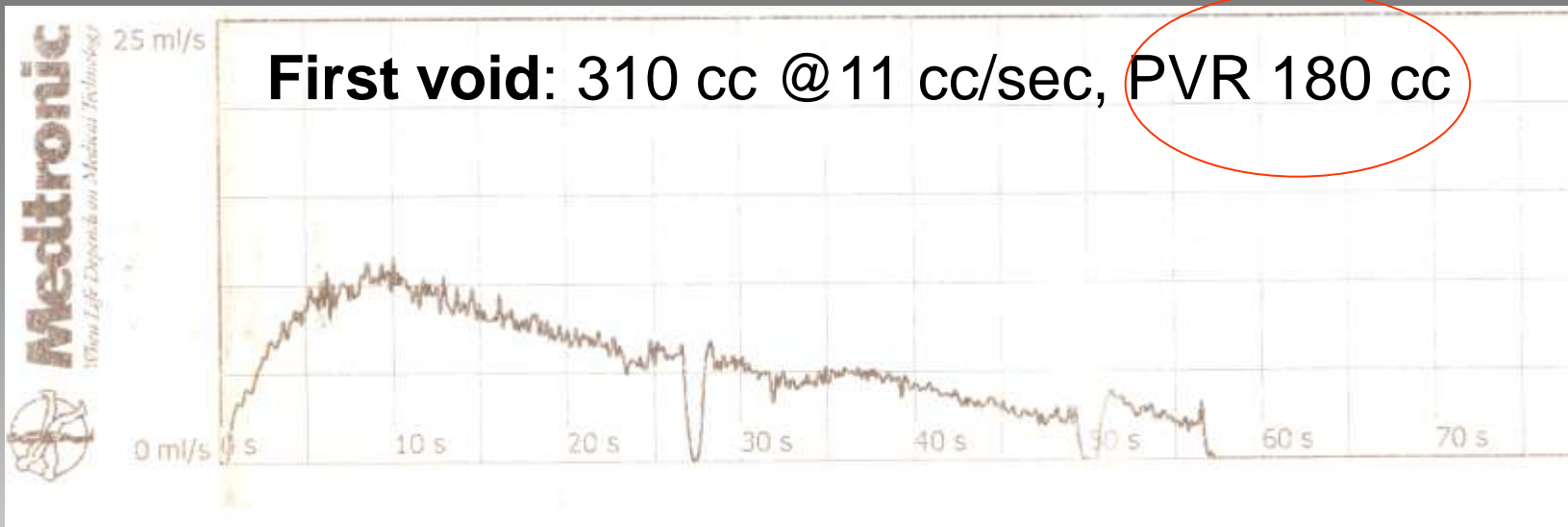
- Age 55
- PSA 5.5
- TRUS 29 cc
- Bx: 3/15 cores positive GS 6/10 (all $\approx 5\%$)
- IPSS 9/35, IIEF 19/25



2008
Img Tm: 1

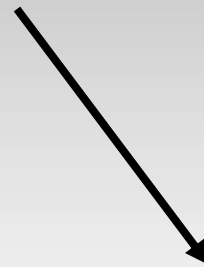
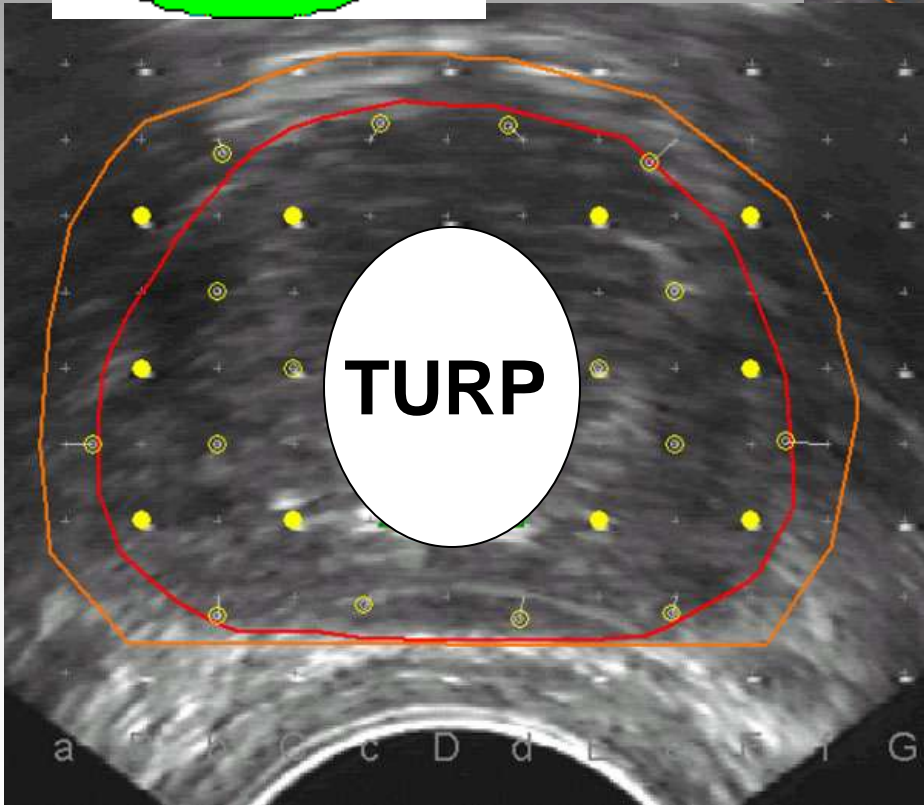
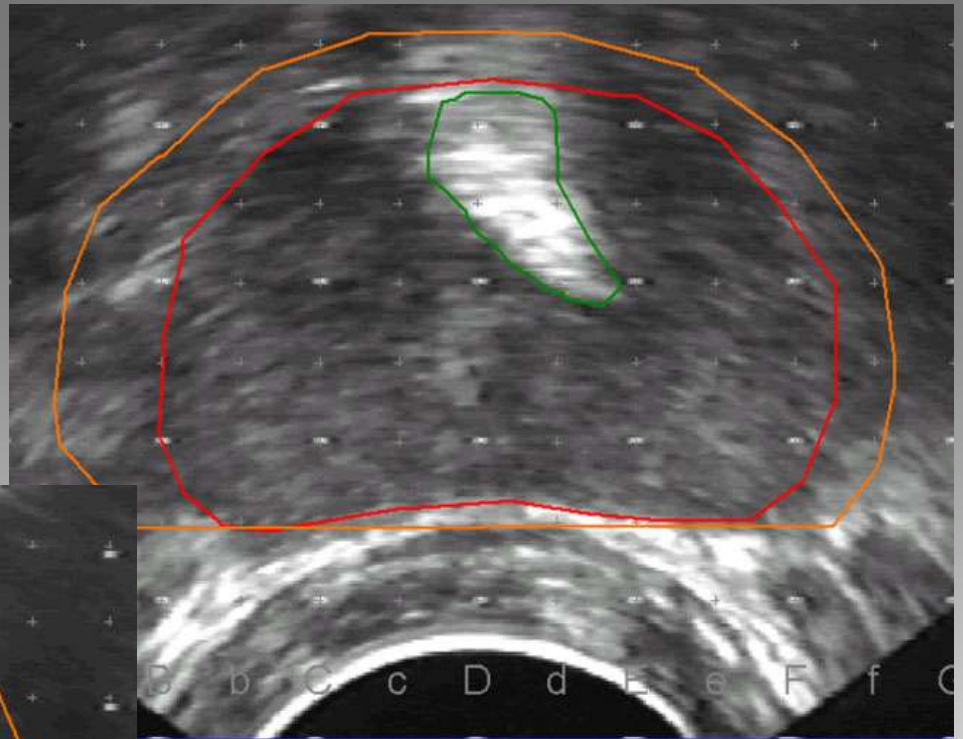


P



6 mo post brachy: no retention/ no problems

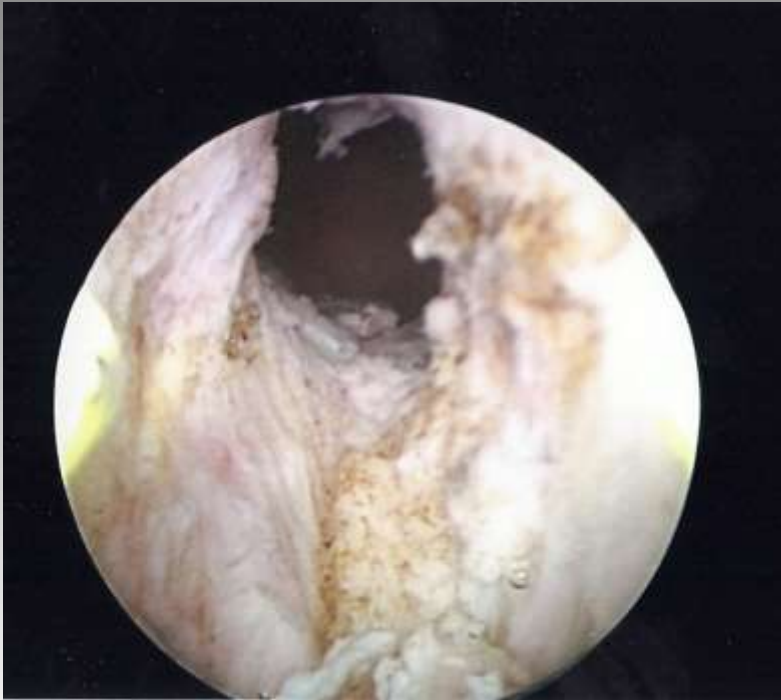
Functional/technical considerations



To TURP or not to TURP

- **Merrick** *IJROBP 2004*: n =27 pre and/or post implant TURP
 - Pre implant TURP better with similar urinary QOL to non TURP patients
 - Post implant TURP: 50% had significant urinary dysfunction
- **Wallner** *IJROBP 1997*: 19 men with prior TURP med 3 yrs prev (2 mo – 15 yrs), only 1 mild stress incontinence post brachy
- **Mabjeesh** *Urology 2007* 13 post implant channeling TURP after 6 mo; no incontinence (n=655)

Limit size of resection!



Small TURP

Big TURP: this patient is incontinent!

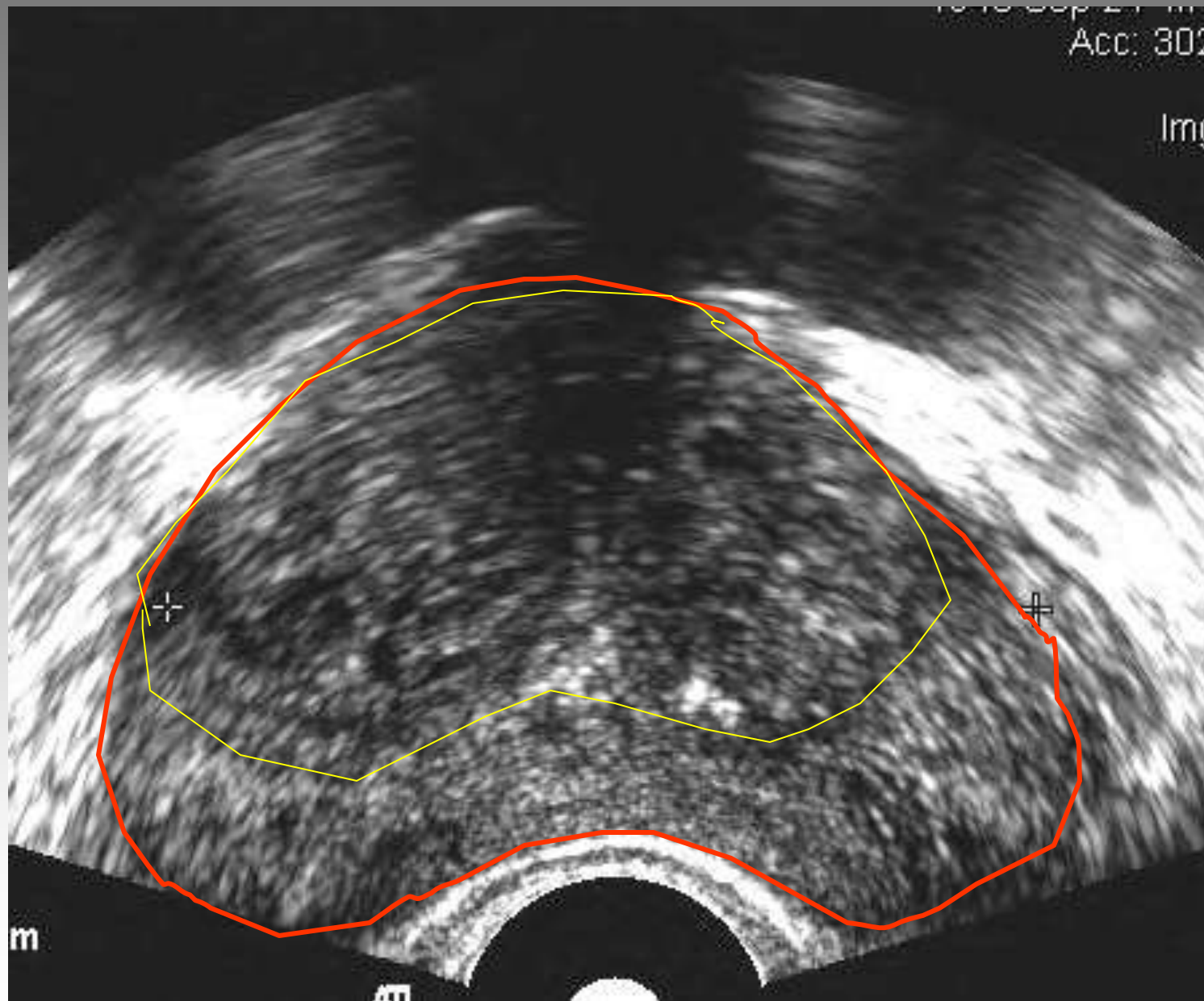


Prior TURP

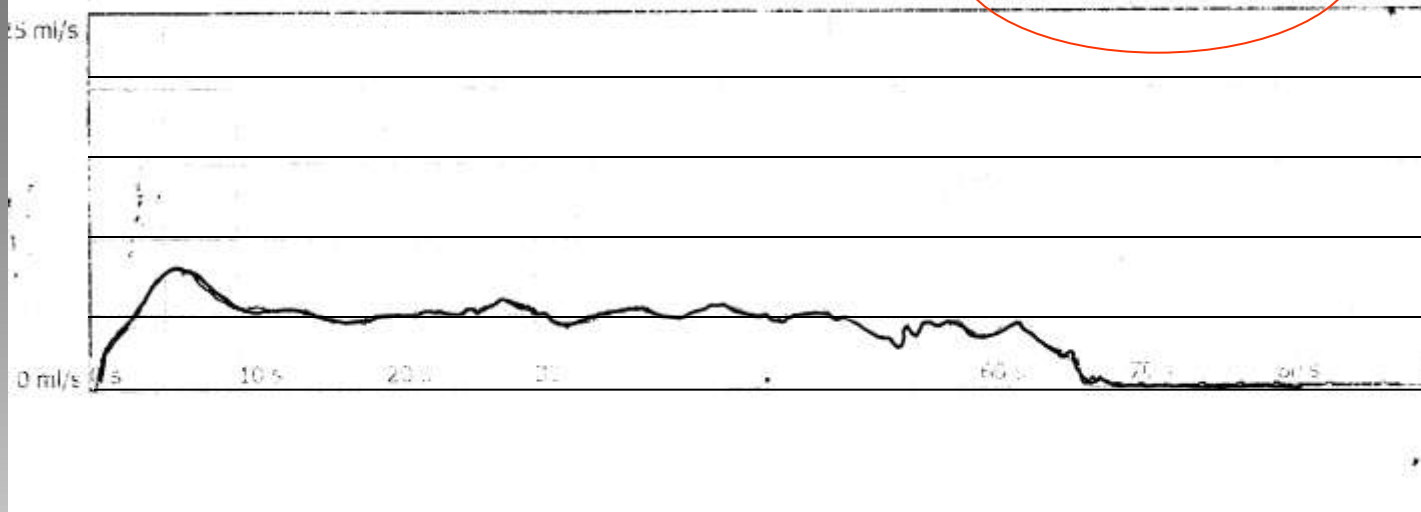
- large TURP defect → seed loss and poor dosimetry
- possible ↑ risk of urethral necrosis, stricture, urinary incontinence
- exclude those with large or poorly healed TURP defect
- small TURP OK with peripheral loading
- allow minimum 3 months for healing

Case: Mr. PS

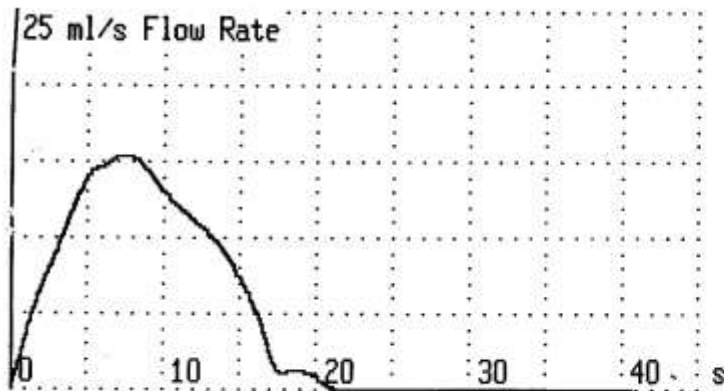
- Age 62
- PSA \uparrow 5.9 \rightarrow 7.3
- TRUS 58 cc
- Bx: 3/12 cores positive GS 6/10 10-15%
- Wife is a GP
- IPSS 19/35
- IIEF 19/25 (priority)



First void: PFR 7.8 ml/sec, PVR 270 cc



Sent back to urologist for limited TURP...



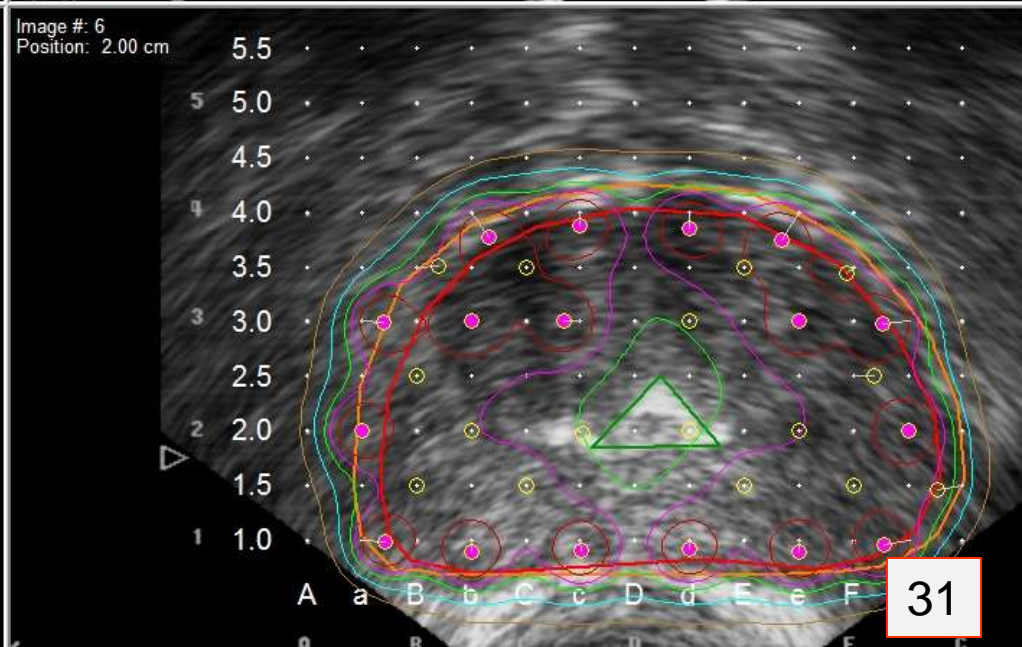
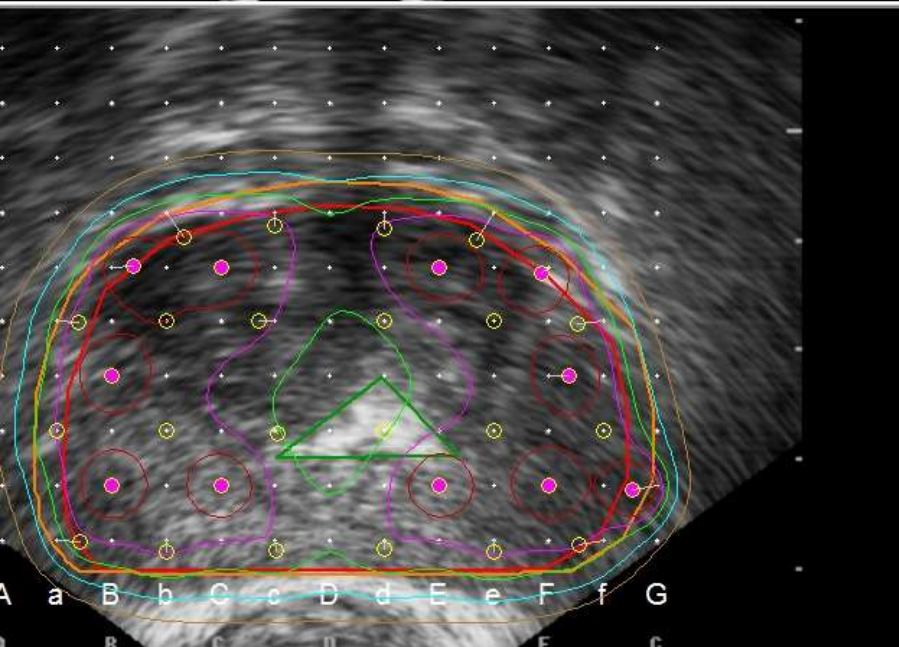
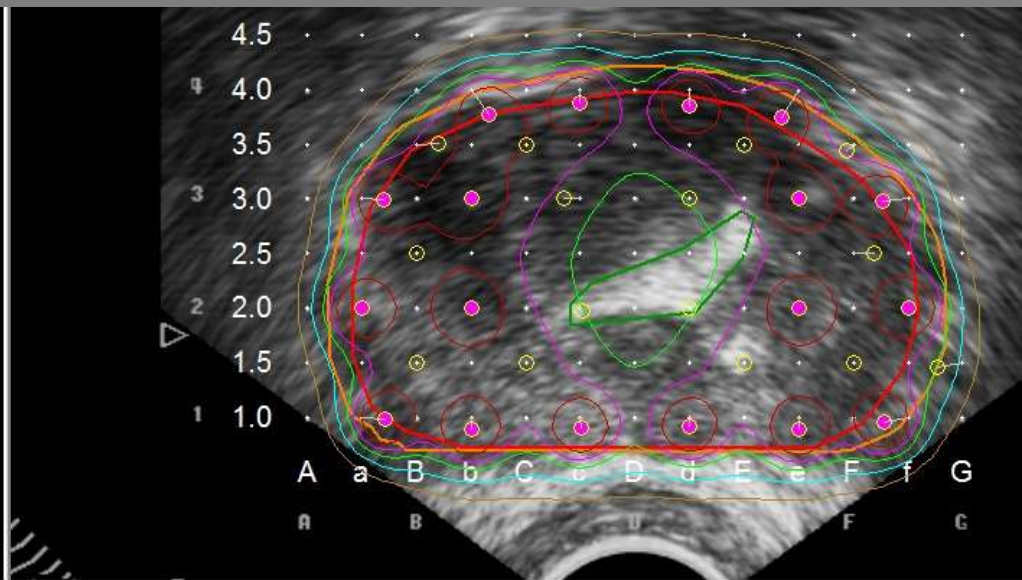
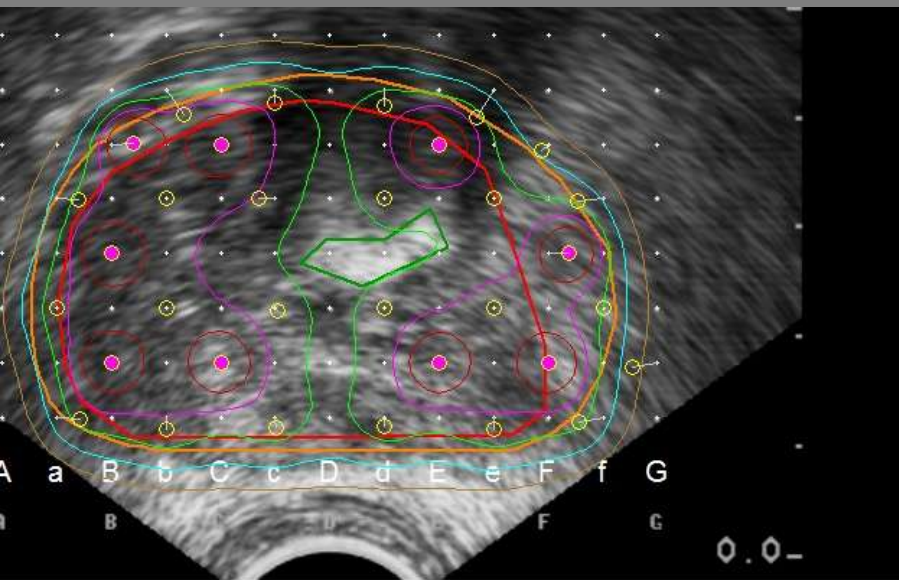
● Results of UROFLOWMETRY

PVR 0

Voiding Time	T100	20	s
Flow Time	TQ	20	s
Time to max Flow	TQmax	7	s
Max Flow Rate	Qmax	15.4	ml/s
Average Flow Rate	Qave	8.8	ml/s
Voided Volume	Vcomp	179	ml

BT 18 mo ago, IPSS now 9/35, IIEF 17, PSA 0.2

Planning around a TURP



urethral identification

- opacify with aerated gel
- allows you to plan around it and keep dose to $< 125\%$ of prescription dose
- catheter distorts prostate and doesn't show you extent of the defect



ELSEVIER

Hormonal down-sizing

IJROBP 2002

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CLINICAL INVESTIGATION

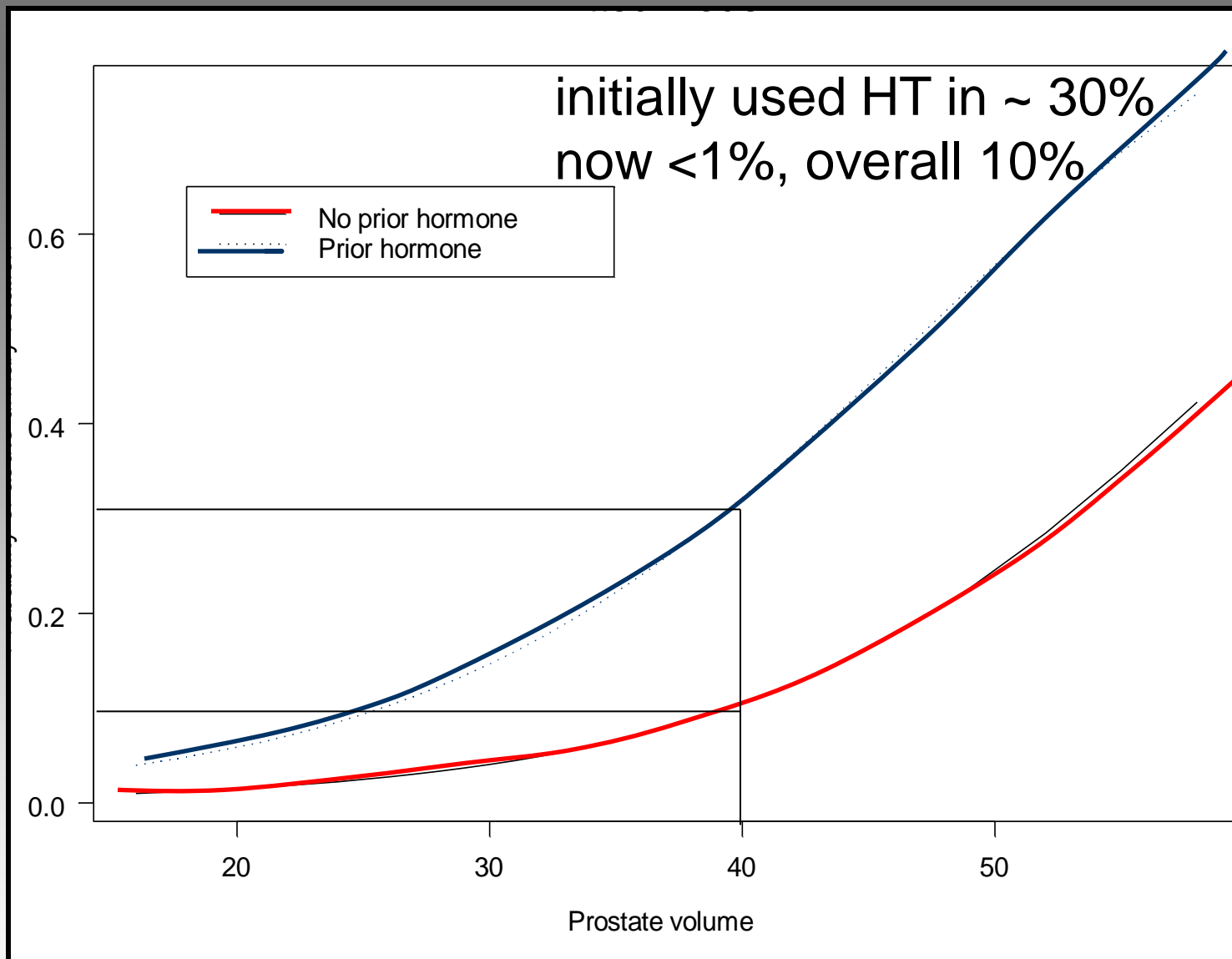
Prostate

FACTORS INFLUENCING RISK OF ACUTE URINARY RETENTION AFTER TRUS-GUIDED PERMANENT PROSTATE SEED IMPLANTATION

JUANITA CROOK, M.D.,* MICHAEL McLEAN, M.D.,* CHARLES CATTON, M.D.,* IVAN YEUNG, PH.D.,[†]
JOHN TSIHLIAS, M.D.,[‡] AND MELANIA PINTILIE, M.Sc.[§]

BCCA: 65% had 6 mo of HT
n=1006, 1998-2003
Morris et al, Urology 2009

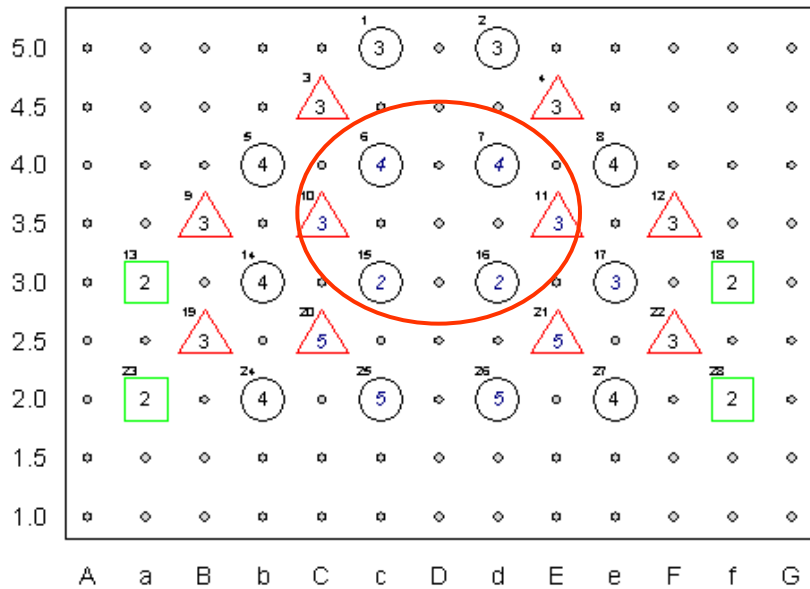
n=150; 31% had HT
retention: 13%
24% if HT vs. 8.7%



Risk of retention according to HT & prostate volume

Planning aspects

- 0.32 mCi per seed (0.4 U)
- use higher activity in larger prostates to keep # of seeds and needles reasonable

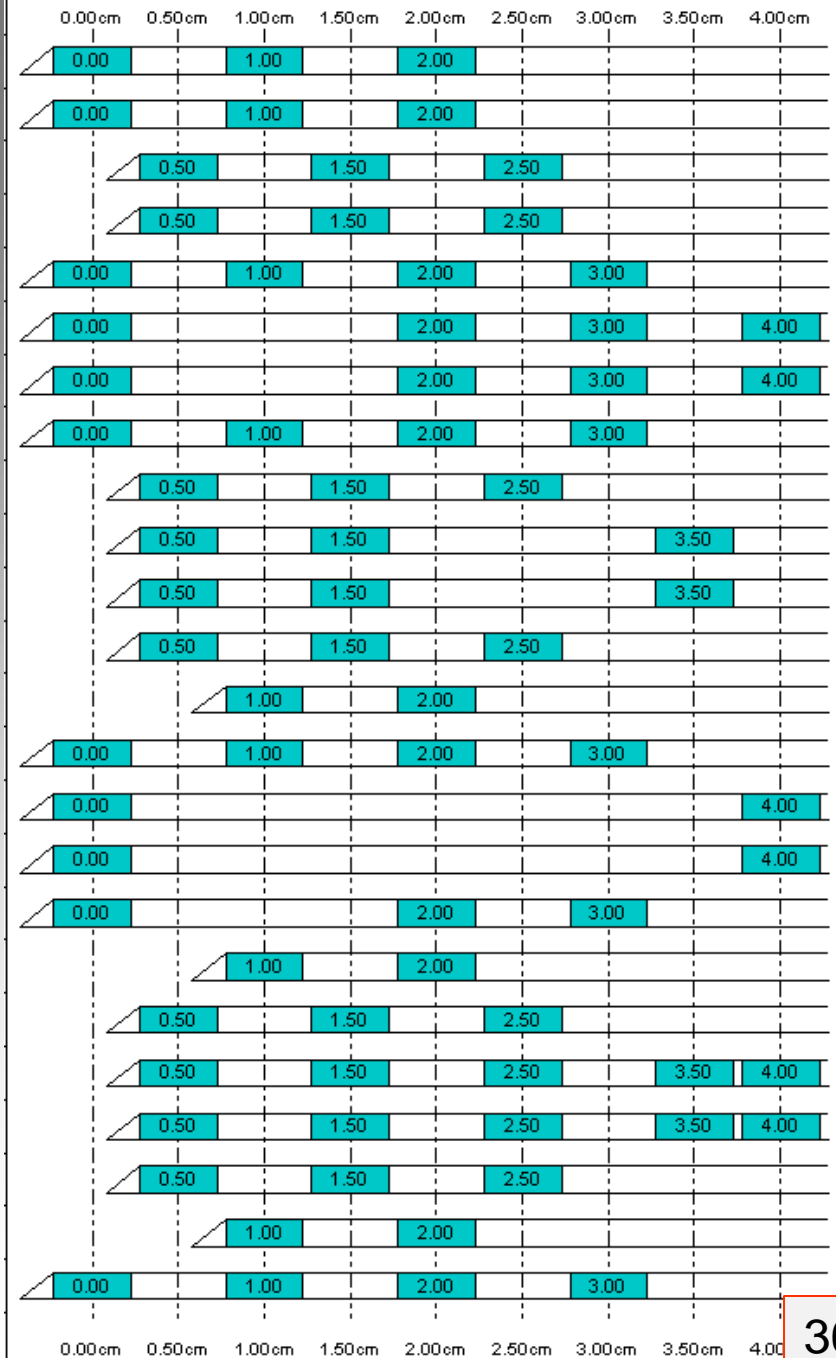


Retraction Legend					
Plane 0	Plane 1	Plane 2	Plane 3	Plane 4	Special
0.00 cm	0.50 cm	1.00 cm	1.50 cm	2.00 cm	Other

Classic Seattle plan

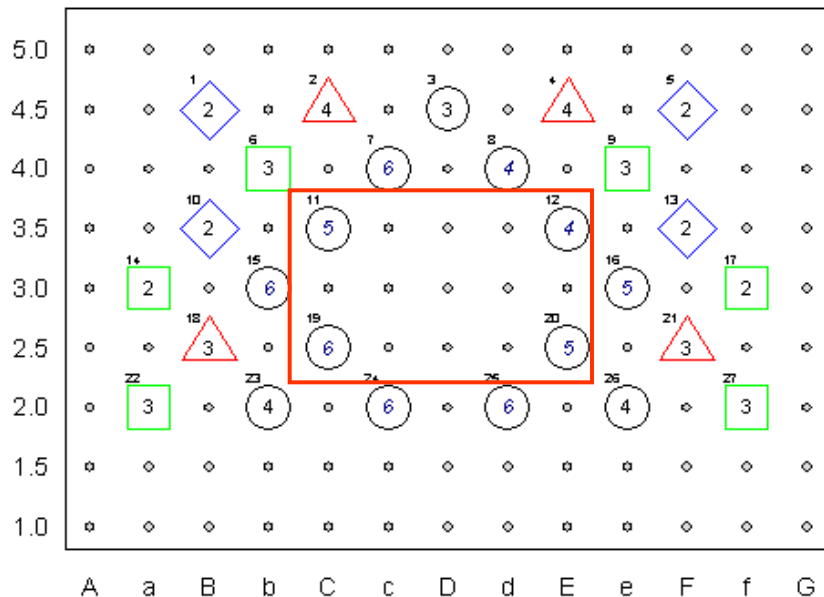
Number of Needles	Seeds per needle
6	2
11	3
7	4
4	5

Plan Summary	
Total Activity [U]	39.25
Total Activity [mCi]	30.90
Total Needles	28
Total Seeds	93
Extra Seeds	
Total Seeds to Order	



Preplan parameters

- margin 5mm cephalad and caudad and anteriorly, 3 mm laterally and same as prostate capsule posteriorly
- 25-30% of seeds are extracapsular
- D90 ~ 120-125%
- V100 > 99%, V150: 55-60%,
V200: 15-18%

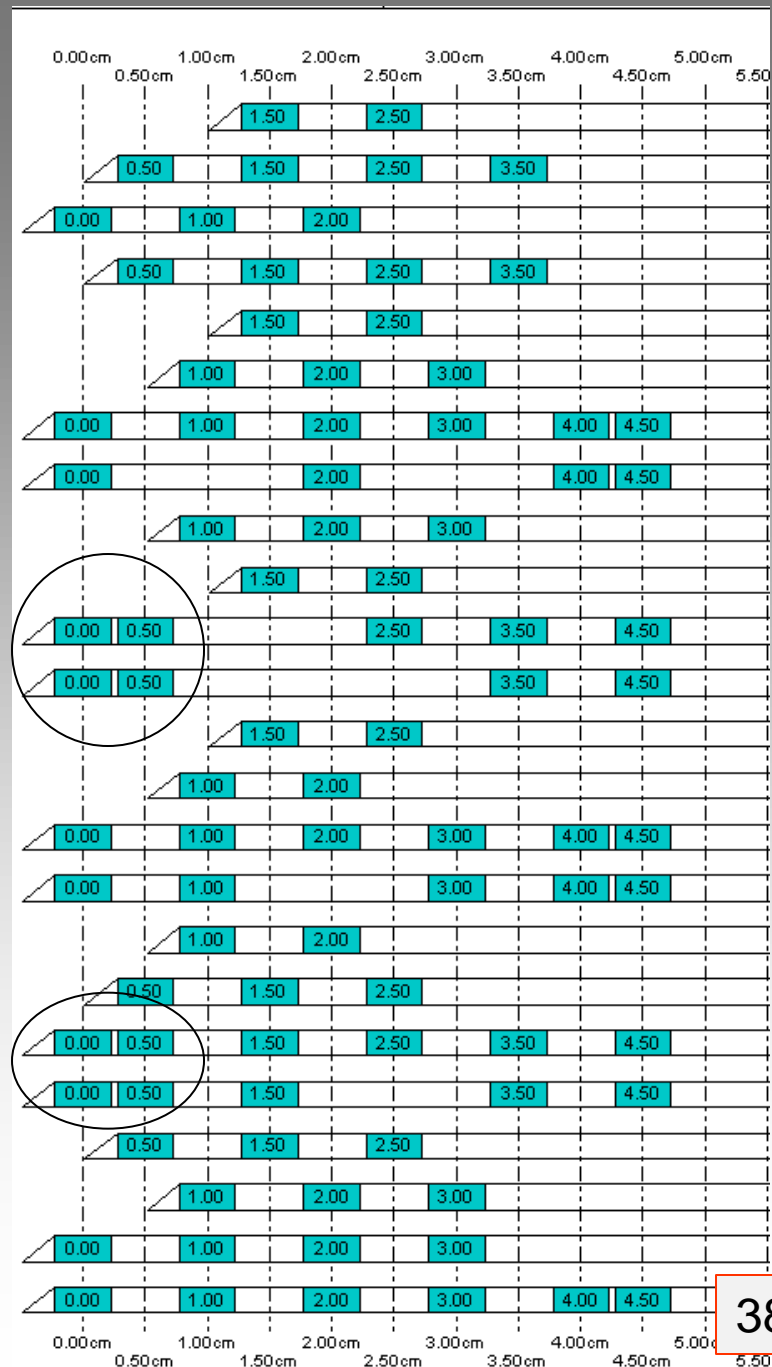


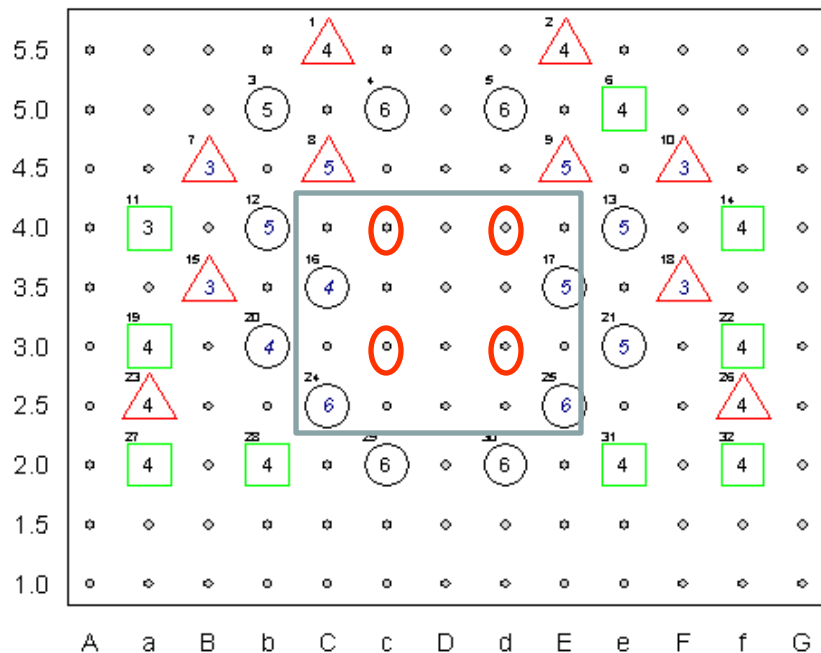
Retraction Legend					
Plane 0	Plane 1	Plane 2	Plane 3	Plane 4	Special
0.00 cm	0.50 cm	1.00 cm	1.50 cm	2.00 cm	Other

Modified to reduce central trauma

Number of Needles	Seeds per needle
6	2
7	3
6	4
3	5
5	6

Plan Summary	
Total Activity [U]	43.04
Total Activity [mCi]	33.89
Total Needles	27
Total Seeds	102
Extra Seeds	
Total Seeds to Order	

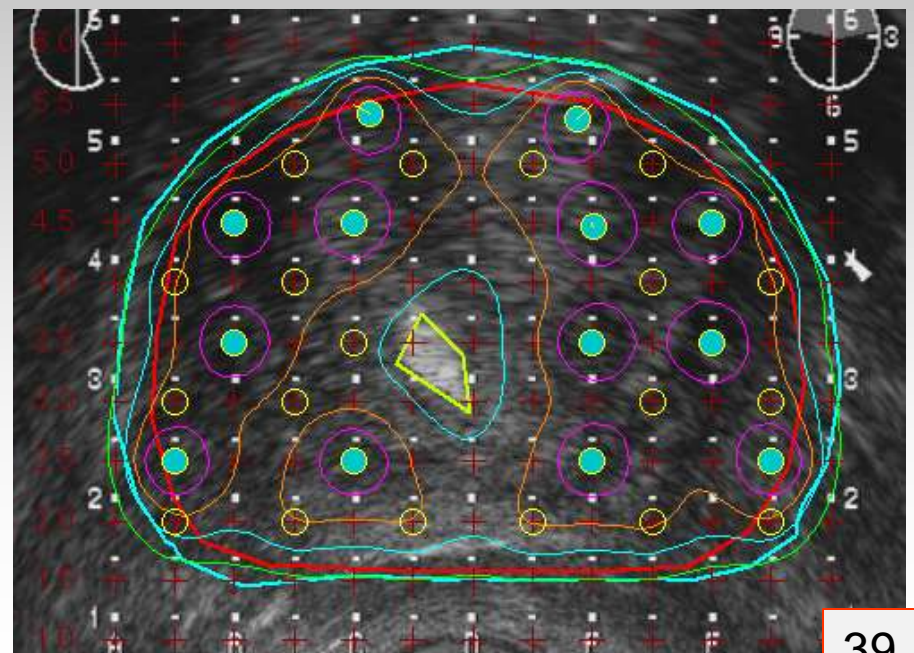
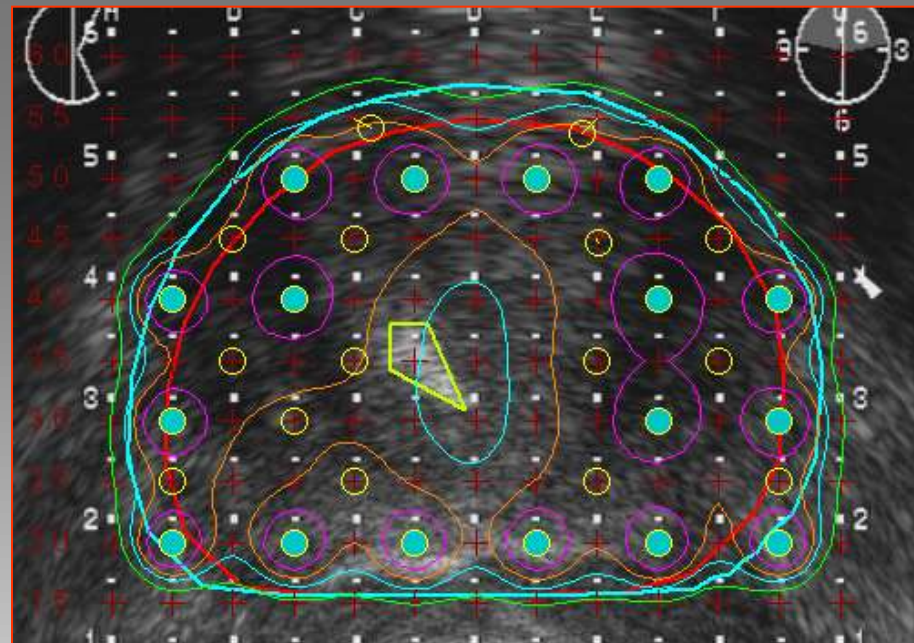


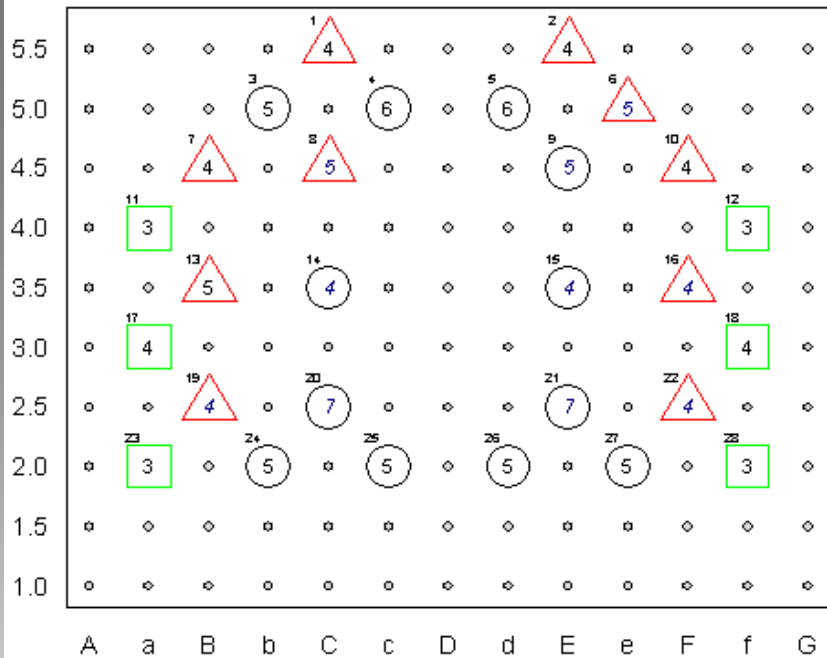


Retraction Legend					
Plane 0	Plane 1	Plane 2	Plane 3	Plane 4	Special
0.00 cm	0.50 cm	1.00 cm	1.50 cm	2.00 cm	Other

“normal” activity: 0.32 mCi/0.422 U
32 needles/142 seeds

Number of Needles	Seeds per needle	Plan Summary	
5	3	Total Activity [U]	59.92
14	4	Total Activity [mCi]	47.18
7	5	Total Needles	32
6	6	Total Seeds	142
		Extra Seeds	
		Total Seeds to Order	



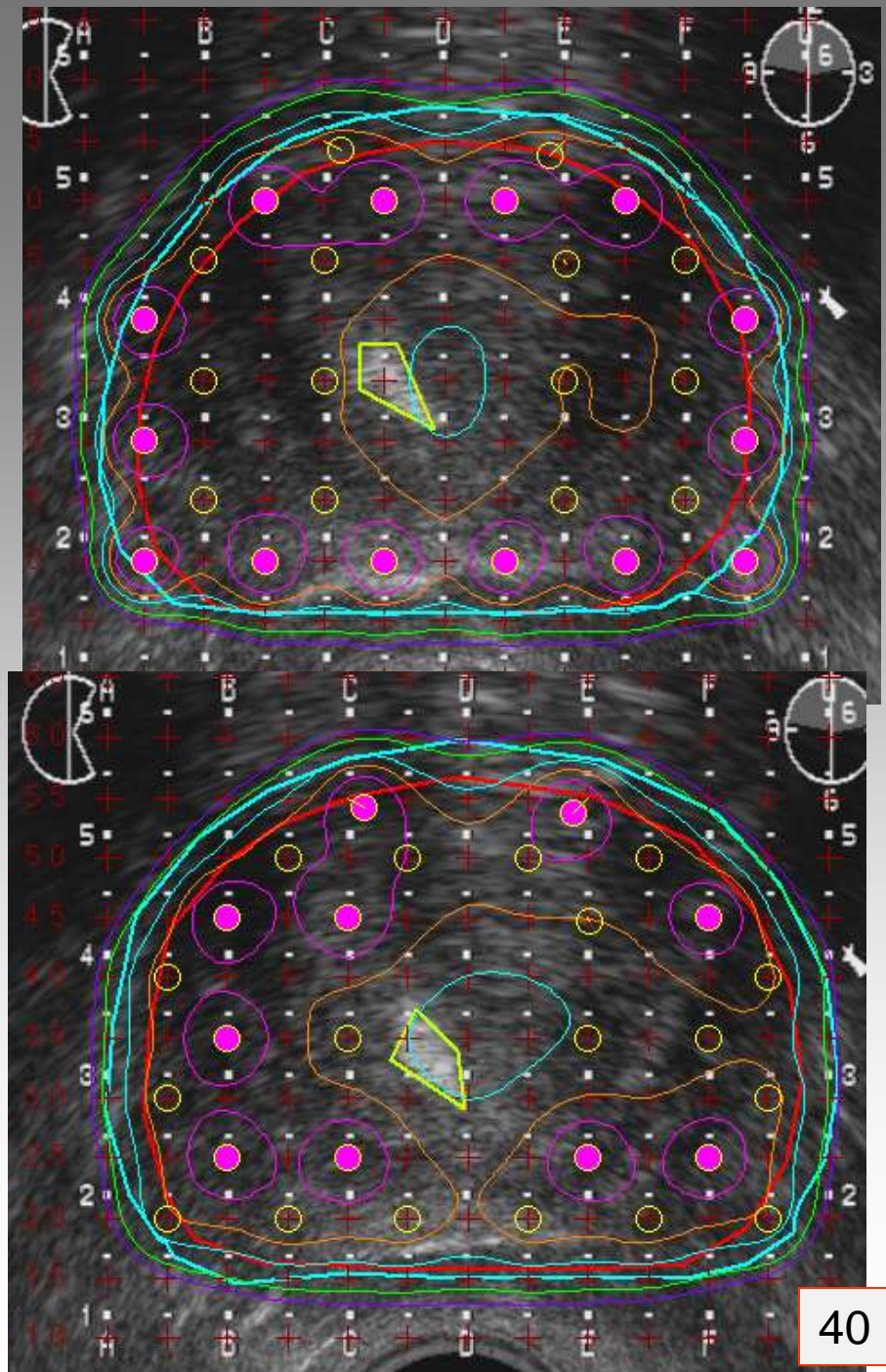


Retraction Legend					
Plane 0	Plane 1	Plane 2	Plane 3	Plane 4	Special
0.00 cm	0.50 cm	1.00 cm	1.50 cm	2.00 cm	Other

“High” activity seeds: 0.39 mCi/0.51U
28 needles/127 seeds

Number of Needles	Seeds per needle
4	3
11	4
9	5
2	6
2	7

Plan Summary	
Total Activity [U]	63.12
Total Activity [mCi]	49.70
Total Needles	28
Total Seeds	127
Extra Seeds	
Total Seeds to Order	



Rectal toxicity

Plan in such a way as to minimize risk

Be honest in post plan evaluation

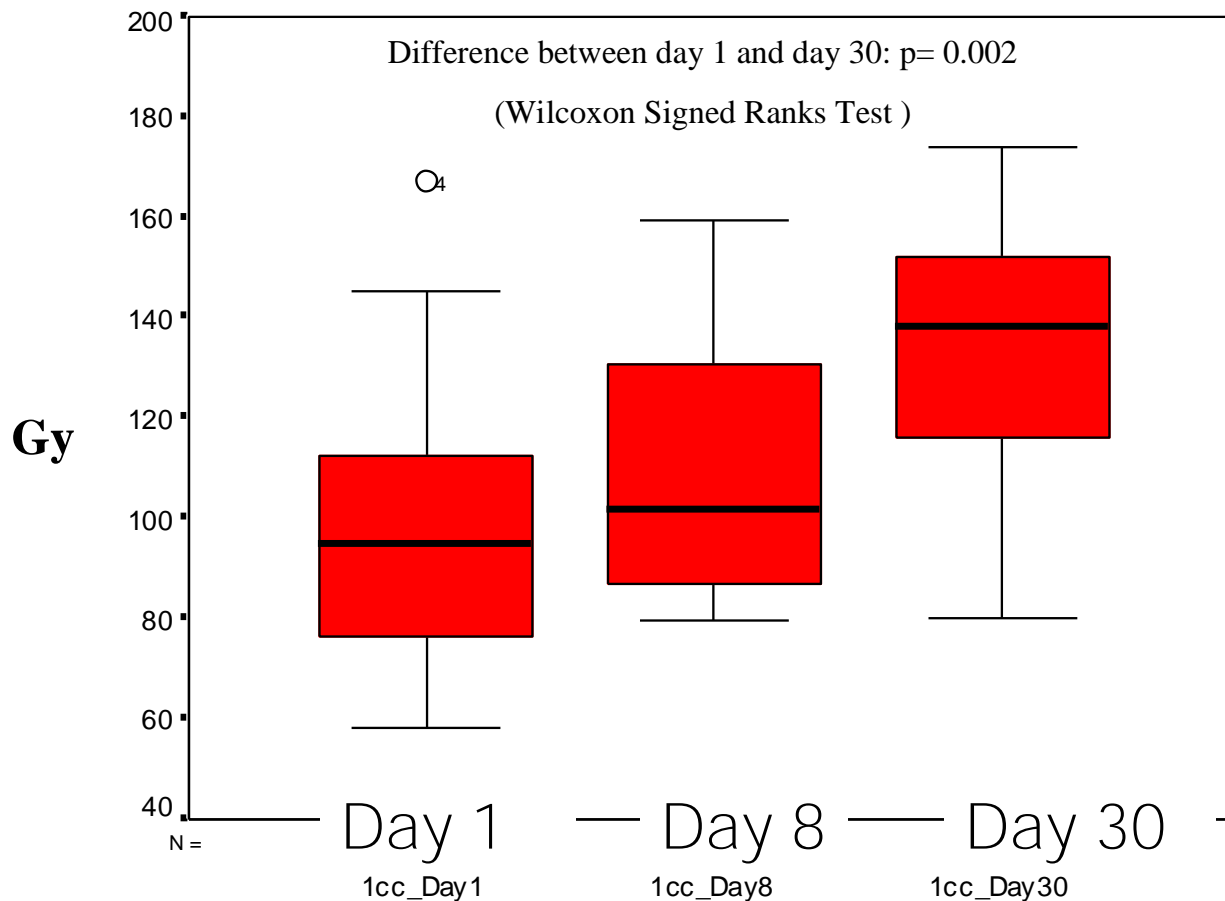
KNOW your rectal doses!

Factors influencing rectal dose

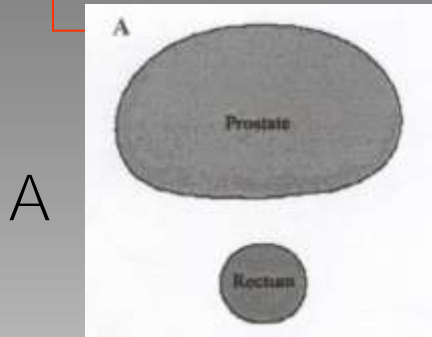
Factor	Effect	What to do
timing	↓RV100 if day 0 or day 1	be consistent
BMI	↓ RV100 if high BMI	wary of low BMI
rectal content	↑ RV100 if full rectum	scan empty avoid constipat ⁿ
length of source	↑ RV100 if long source train	be accurate in length
activity	↑ RV100 if ↑ activity	insert deeper
probe <	↑ RV100 if probe not	follow post caps ^L

Timing: When do we contour?

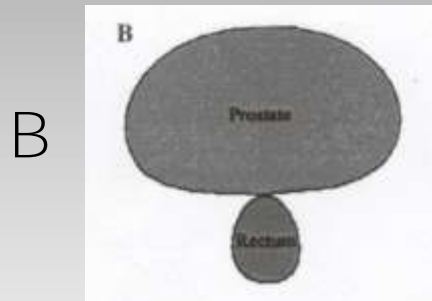
Dose in Gray to 1 cc of anterior rectal wall



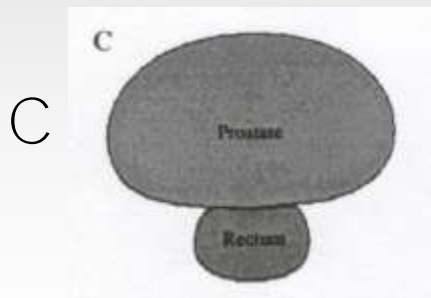
Anatomic variation in degree of rectal contact



No contact



Limited contact

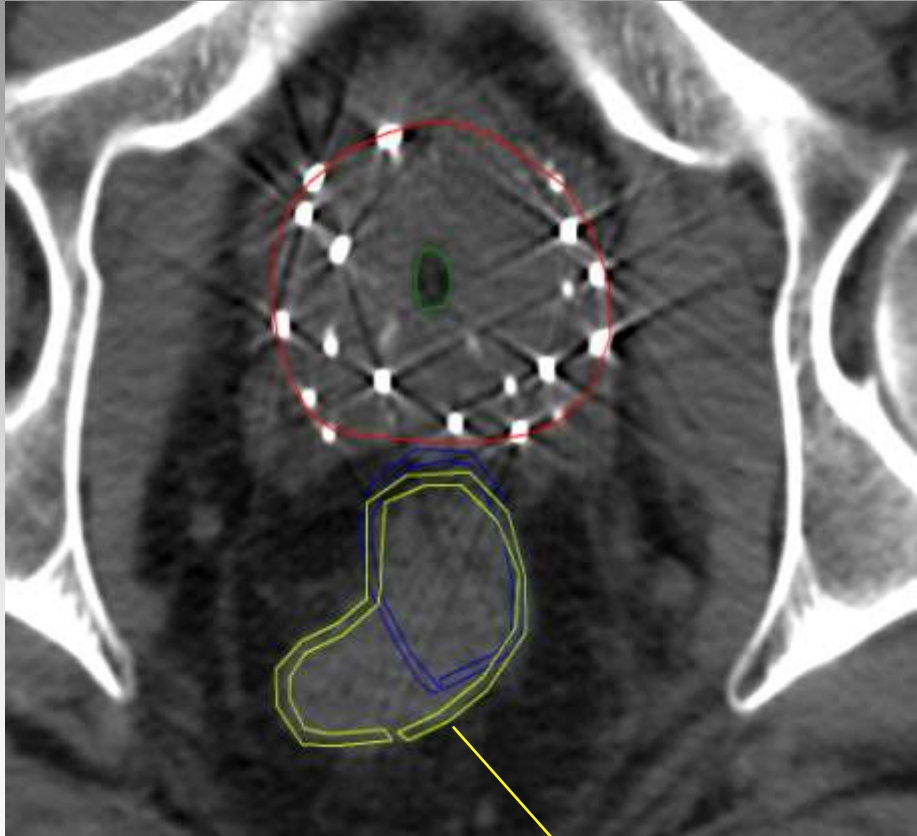


Full contact

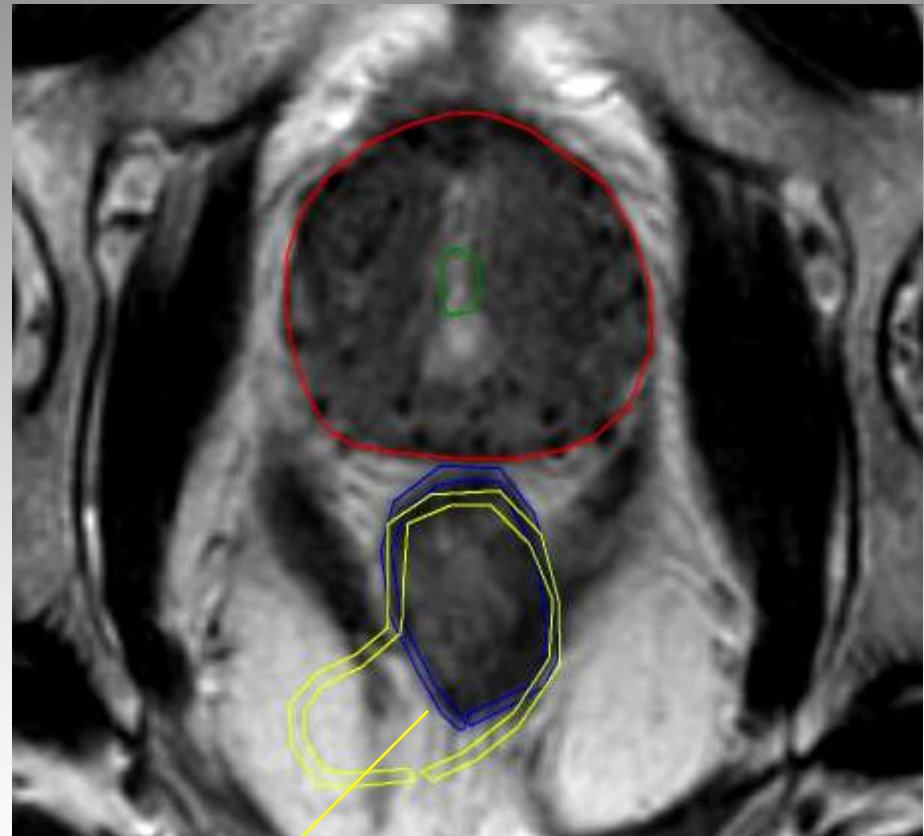
- Han and Wallner 2001
- Pre-implant CT scans define 3 groups
- 100% (9/9) of proctitis pts in group C vs 39% (7/18) of controls

Influenced by BMI and constipation

Scan with empty rectum for consistency

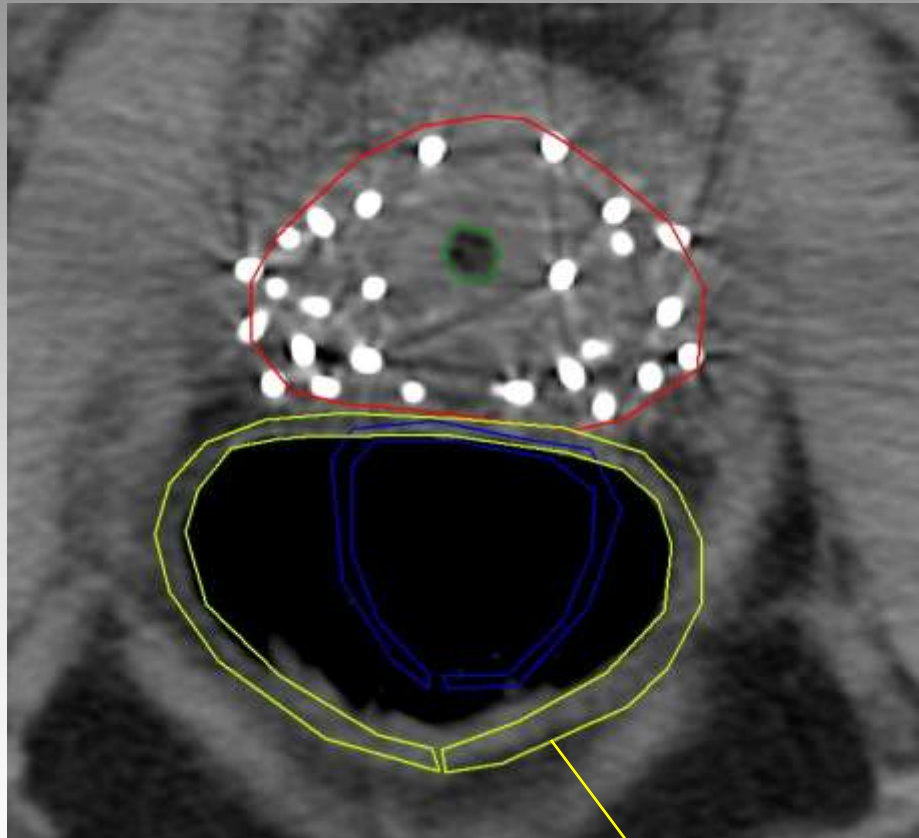


Rectal wall CT

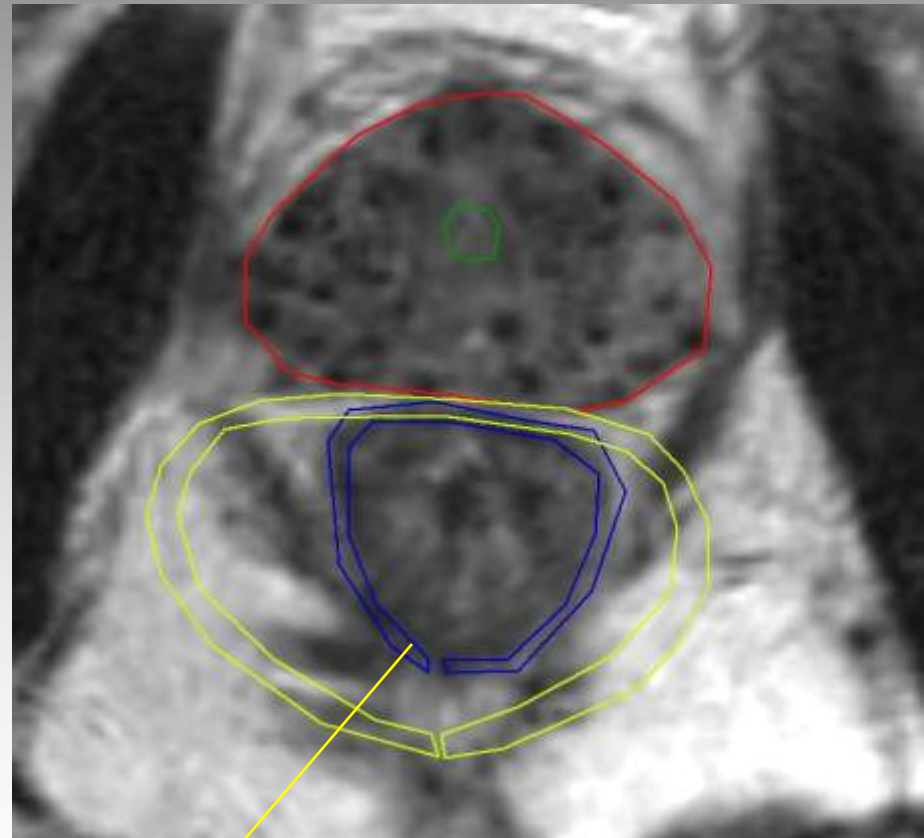


Rectal wall MRI

Snapshot of a Dynamic process

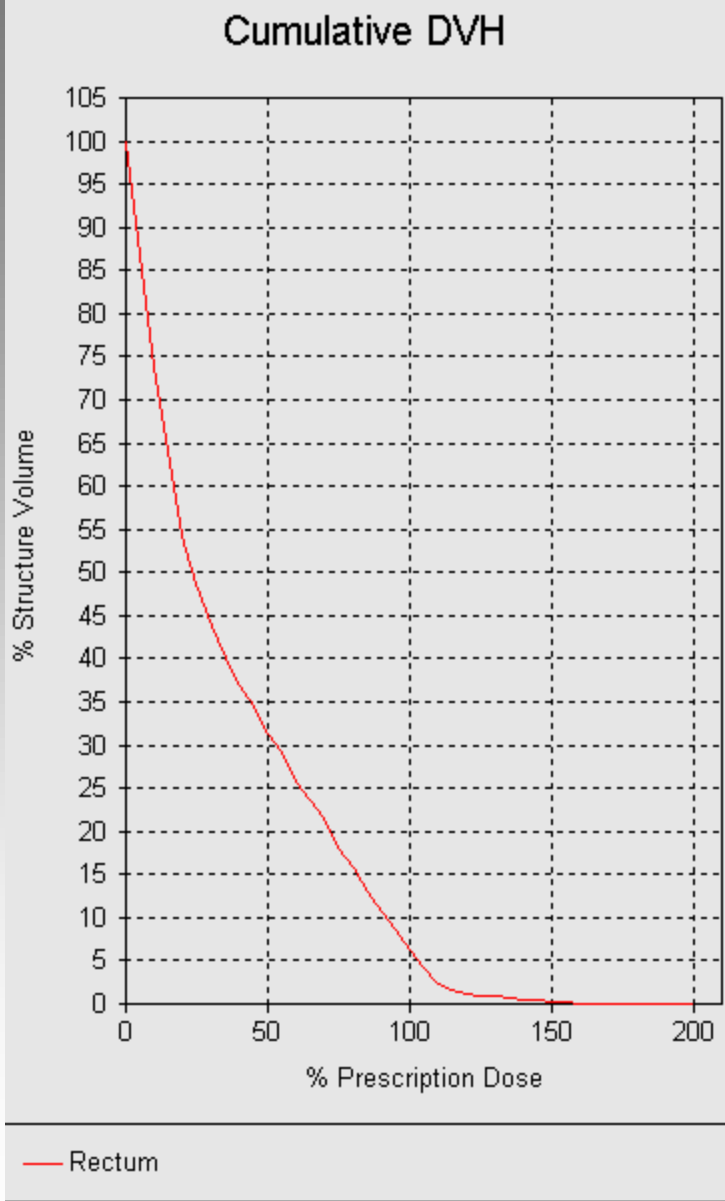


Rectal wall CT



Rectal wall MRI

Rectal DVH



Dose		Cum. DVH	
Gy	%	cc	%
0.00	0.00	7.80	100.00
7.25	5.00	6.77	86.81
14.50	10.00	5.74	73.66
21.75	15.00	5.00	64.17
29.00	20.00	4.24	54.35
36.25	25.00	3.79	48.62
43.50	30.00	3.42	43.81
50.75	35.00	3.13	40.18
58.00	40.00	2.88	36.94
65.25	45.00	2.70	34.63
72.50	50.00	2.44	31.24
79.75	55.00	2.28	29.23
87.00	60.00	2.00	25.63
94.25	65.00	1.85	23.71
101.50	70.00	1.68	21.55
108.75	75.00	1.41	18.10
116.00	80.00	1.24	15.85
123.25	85.00	1.01	13.00
130.50	90.00	0.83	10.64
137.75	95.00	0.67	8.53
145.00	100.00	0.49	6.34
152.25	105.00	0.32	4.16
159.50	110.00	0.18	2.29
166.75	115.00	0.13	1.69
174.00	120.00	0.09	1.11
181.25	125.00	0.07	0.94
188.50	130.00	0.06	0.81
195.75	135.00	0.06	0.78

- 1cc: 123 Gy
- 2cc: 87 Gy
- 145 Gy (prescribed dose) to 0.49 cc
- Do not use D10 or D30 since dose to % of the organ depends on contouring limits

Fitting the literature results to your own experience...Han and Wallner IJROBP 2001

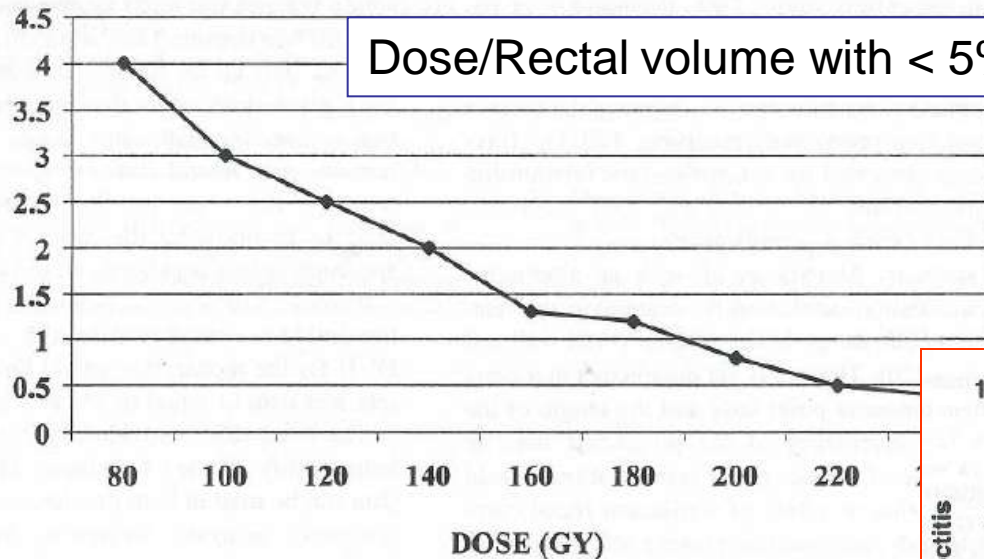
- 9 proctitis of 160 cases (6/9 comb EBRT)
- each matched to 2 controls by prostate size, isotope, prostate dose
- all 9 had “full contact” anatomy
- controls: 39% full, 33% partial, 28% none
- RV100: 0.6 cc non-bleeders vs. 2.5 cc proctitis $p=0.00008$ (Day 0 scan)

Fitting the literature results to your own experience... Snyder, Stock, Stone 2001

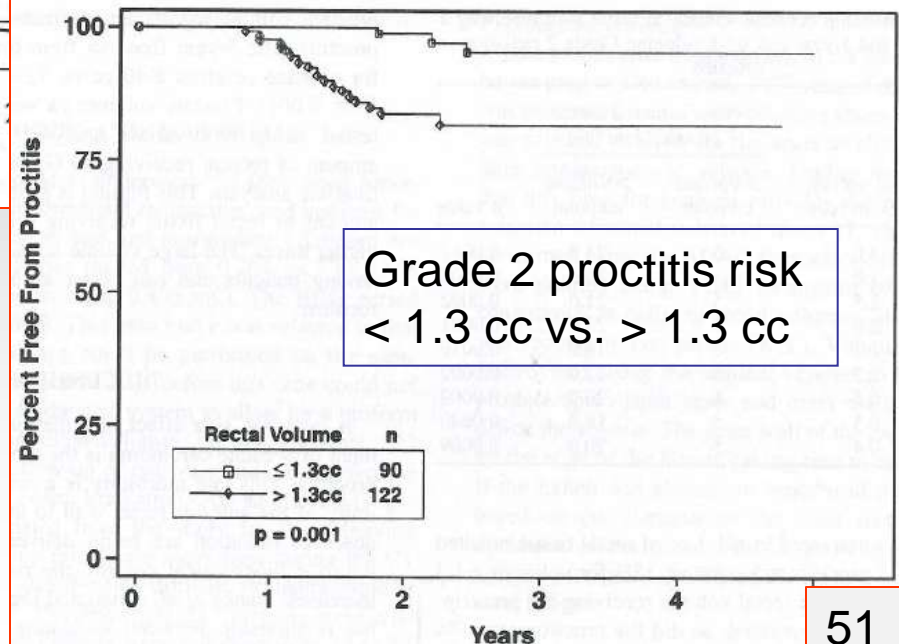
- n= 212, Iodine 125 only
- 22 cases grade 2 proctitis
 - 14% in year 1, 72% year 2, 14% year 3
- RV100 \leq 1.3 cc: 5% proctitis vs. 18% p=0.001
 - 8% > 1.3 – 1.8 cc
 - 25% > 2.3 cc p=0.002

Fitting the literature results to your own experience... Snyder, Stock, Stone 2001

CC OF RECTAL VOLUME



Dose/Rectal volume with < 5% risk

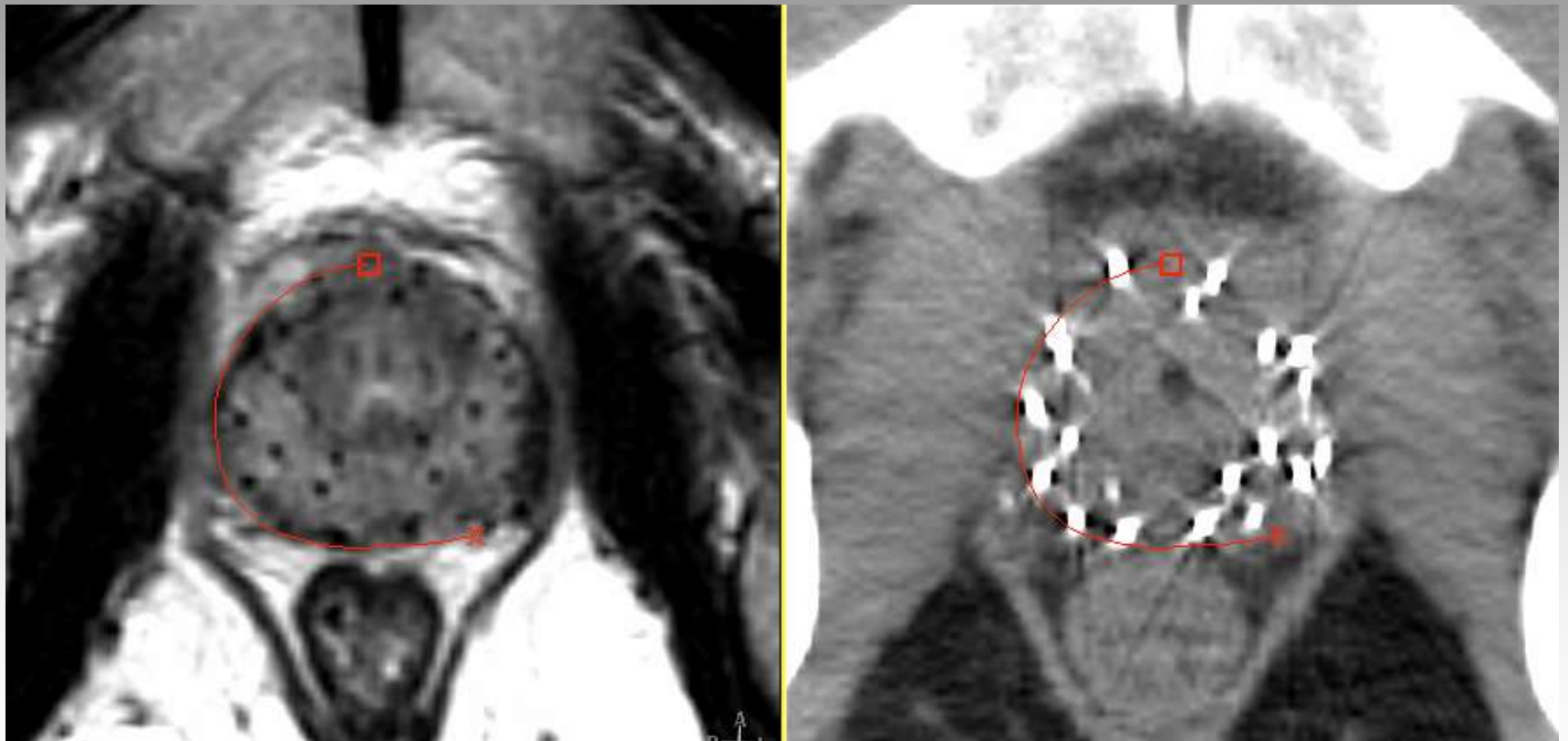


Grade 2 proctitis risk < 1.3 cc vs. > 1.3 cc

Rectal toxicity

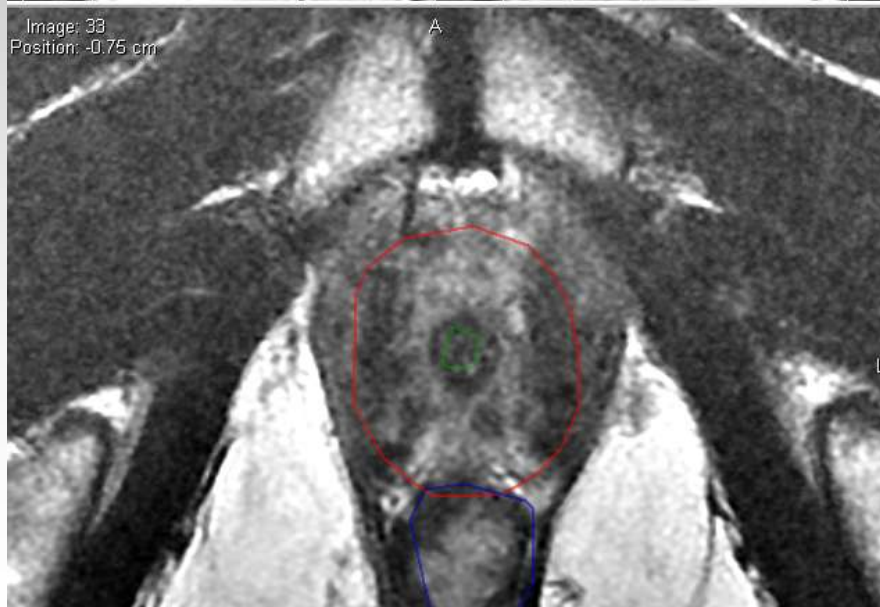
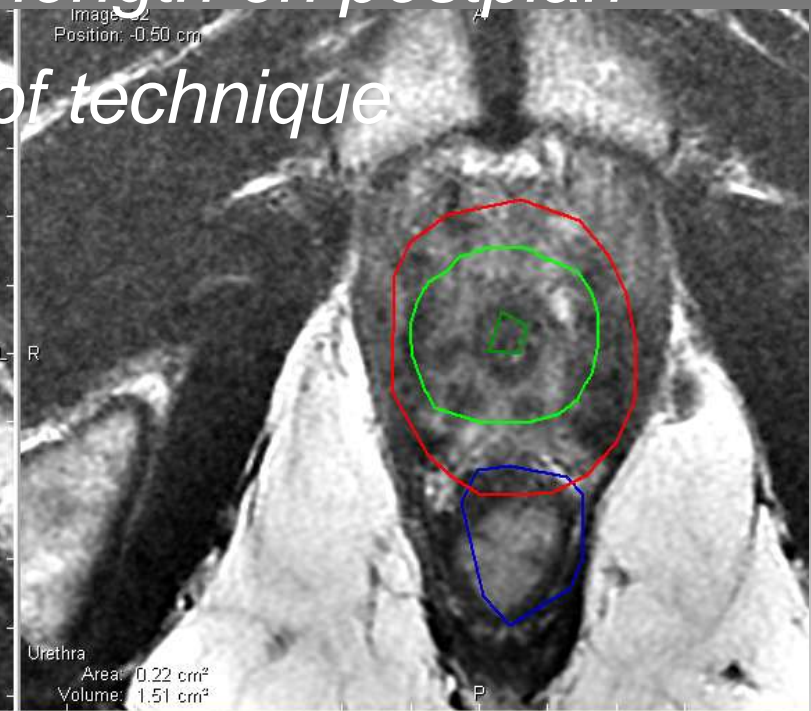
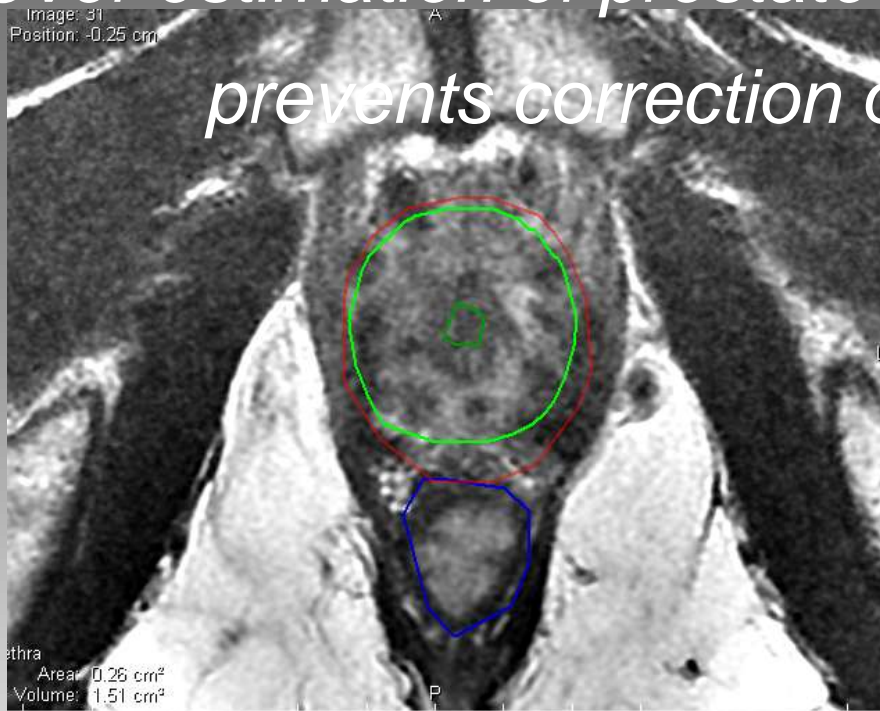
- document RV100 on post plans
- strive to keep < 1 cc
- probably doesn't matter if rectal wall or just outer contour
- MR-CT fusion a very useful tool to accurately evaluate seed placement relative to prostate contours

MRI-CT fusion

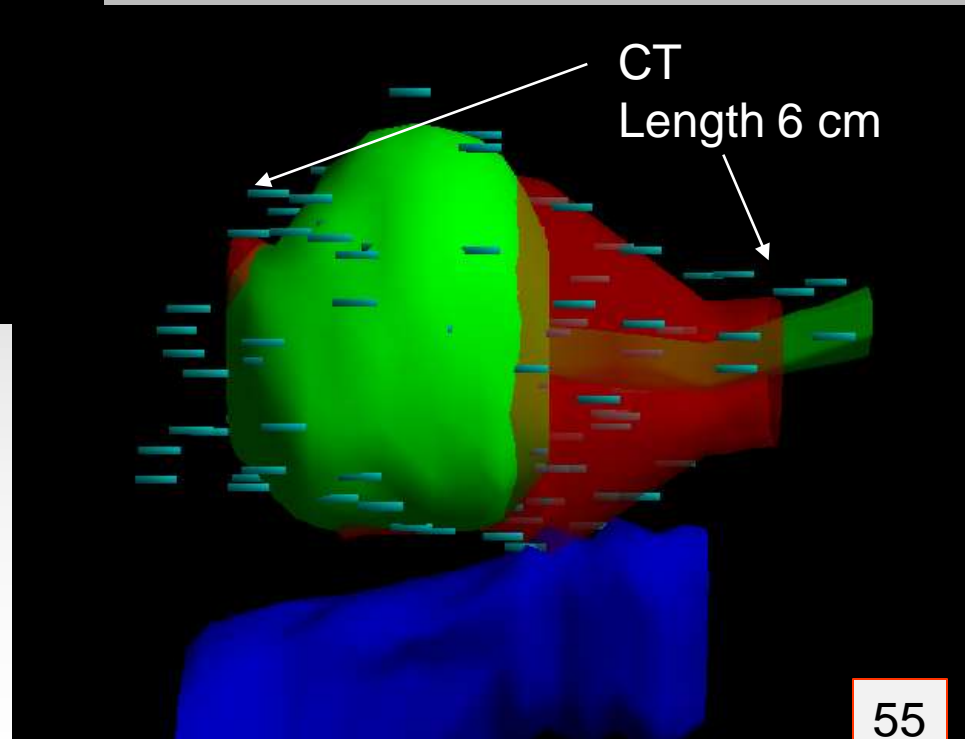
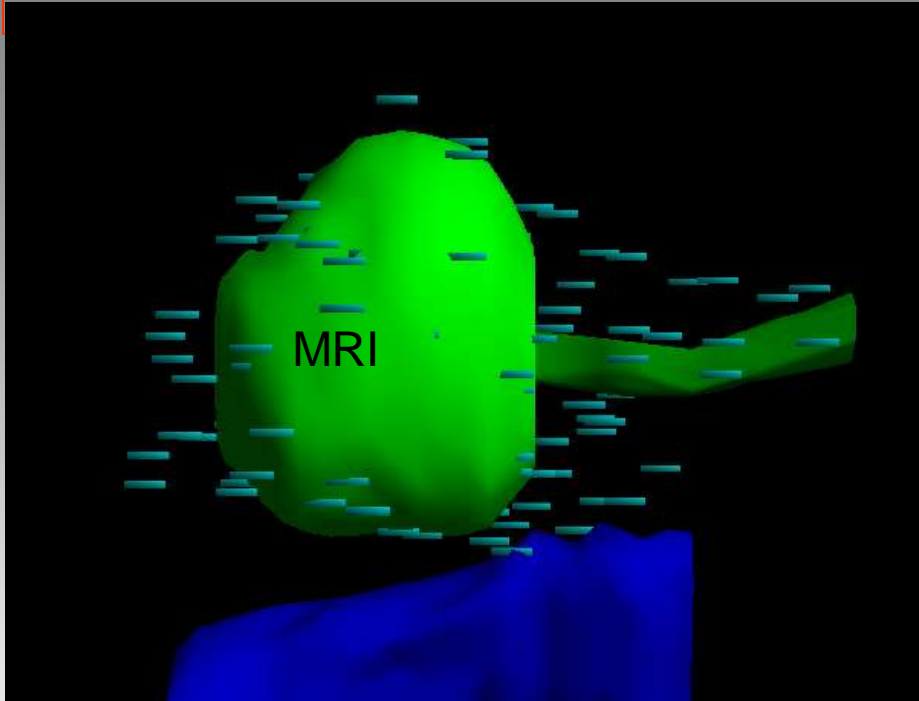


Over estimation of prostate length on postplan

prevents correction of technique



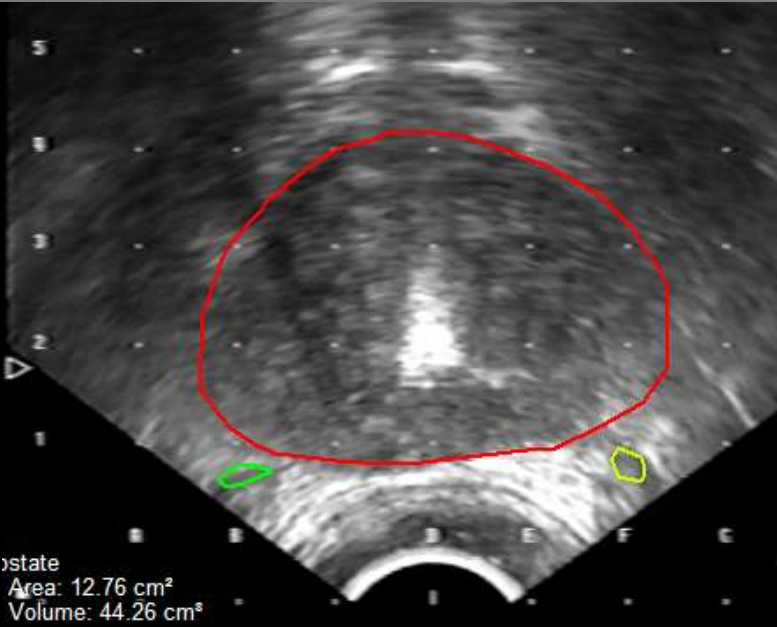
MRI-determined prostate vs. CT-determined



Sexual function

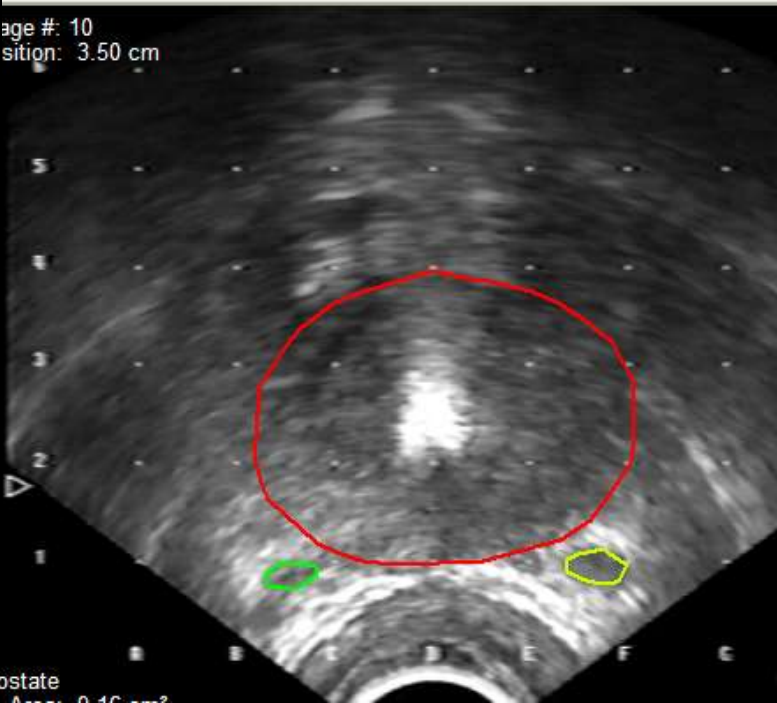
- recorded as 1/0 +/- PDE5's for all patients at each visit
 - 84% potent pre BT
 - 82.5% potent at last follow-up (82.8% with follow-up > 5 yrs)
- since 2005, baseline IIEF and annually
 - 83.4% > 15 @ baseline
 - 84.4% @ 2 yrs and 3 yrs
- *PDE-5's discussed with every patient, samples offered and use encouraged*

Neurovascular bundles on TRUS



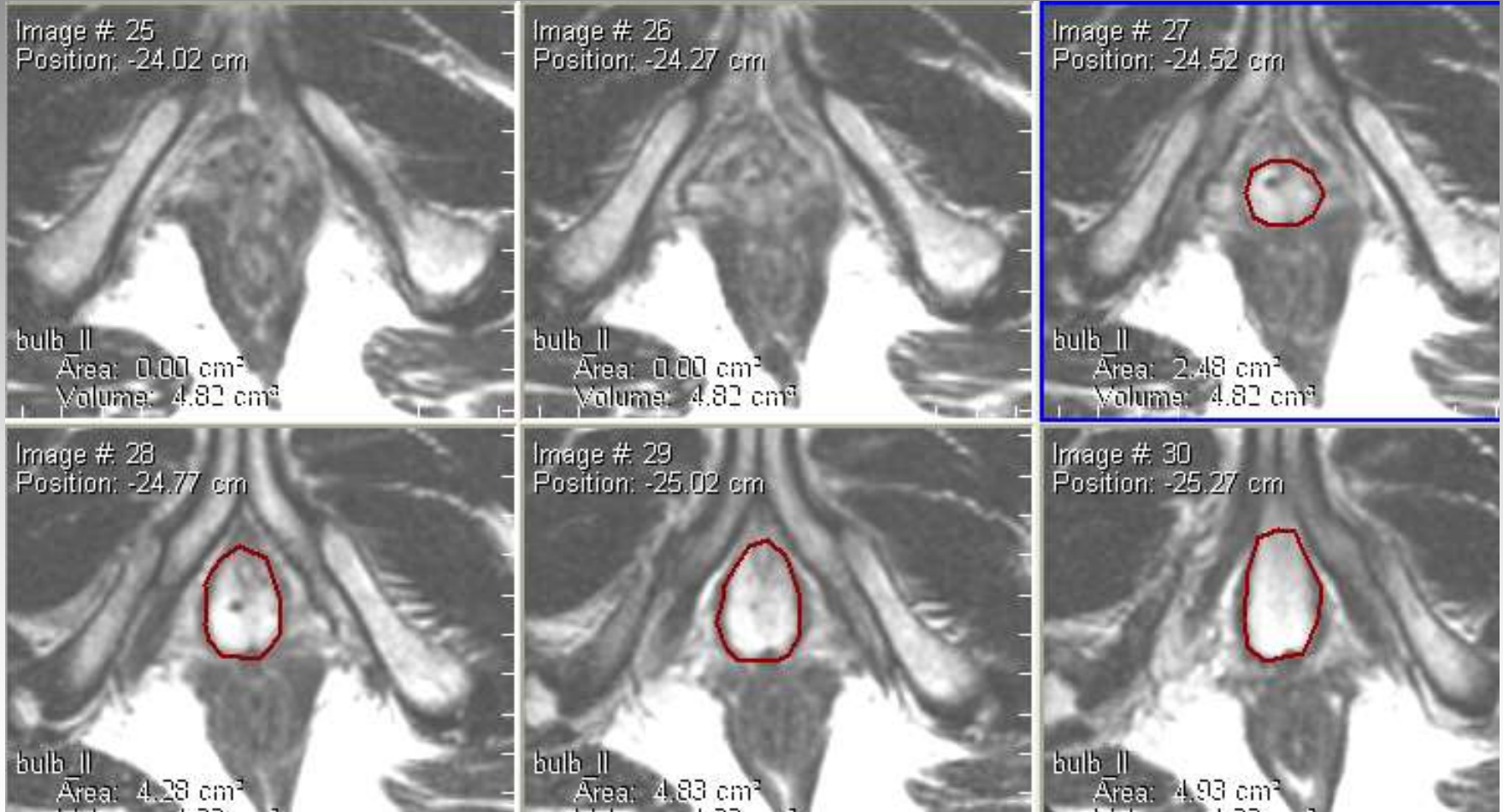
Prostate
Area: 12.76 cm²
Volume: 44.26 cm³

Age #: 10
Position: 3.50 cm

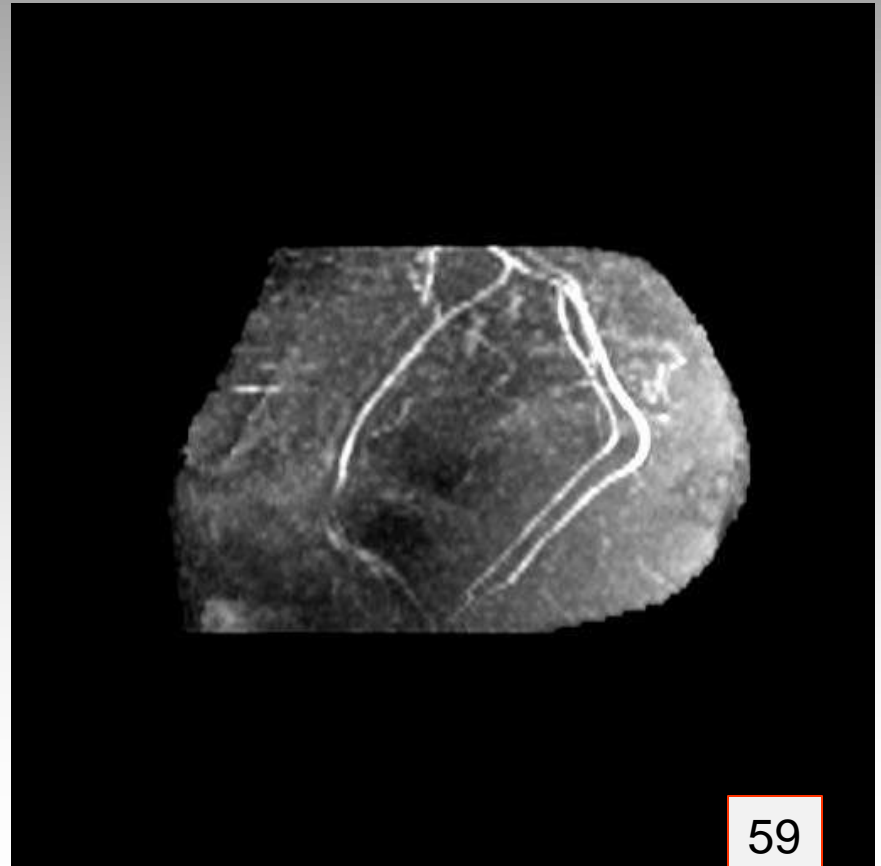
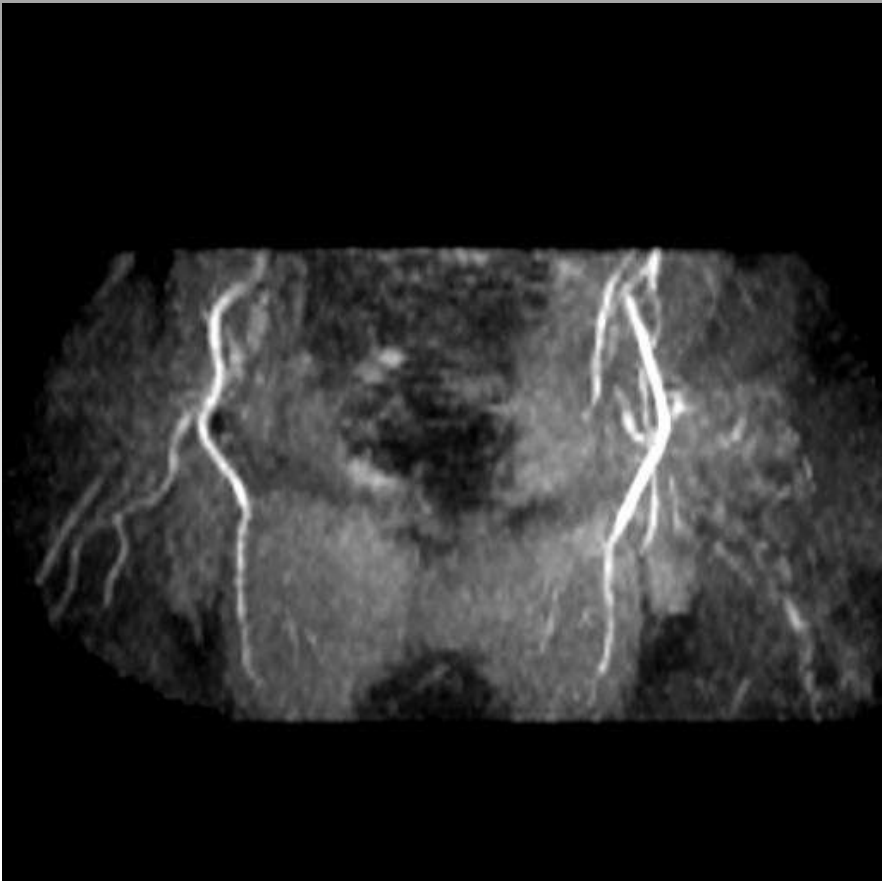


Prostate
Area: 0.16 cm²

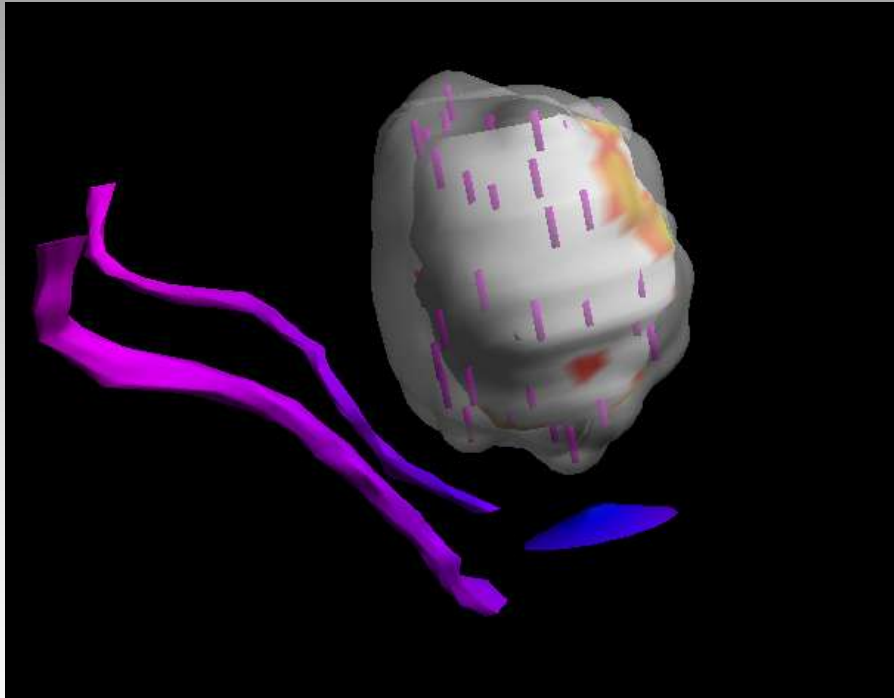
Penile bulb on MRI



Time-of-flight non contrast MR angiograms of Internal Pudendal Arteries

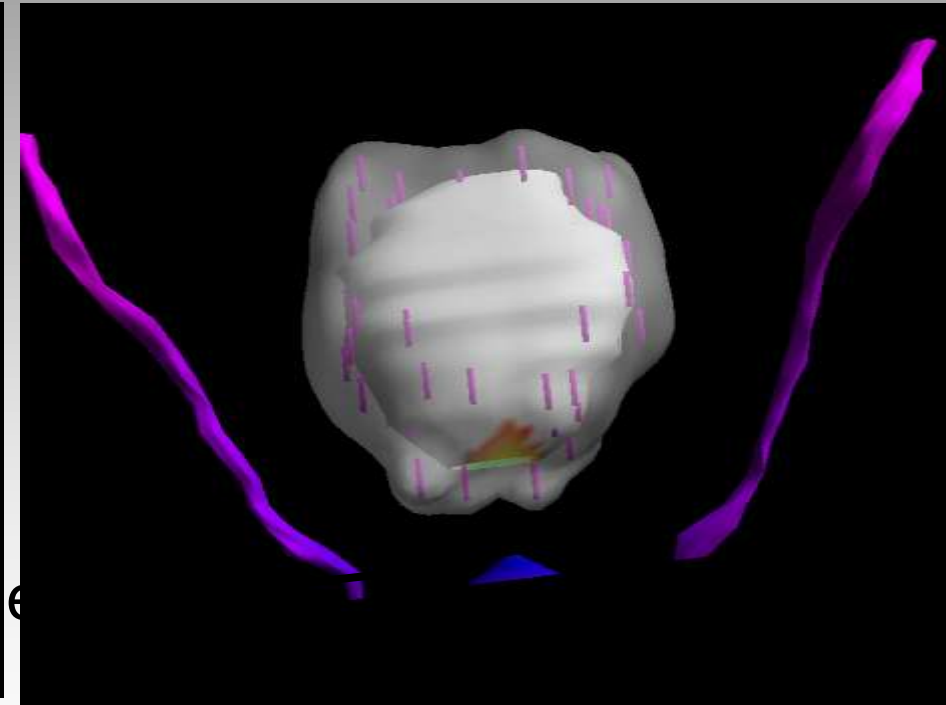


Relation of IPA and penile bulb to brachytherapy dose



Lateral view

Mean peak dose 17 Gy

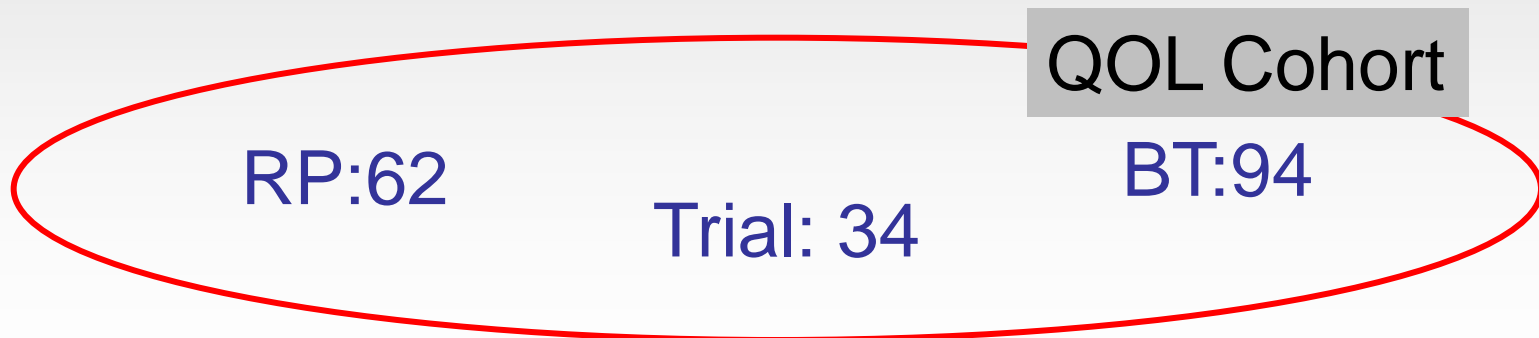


Posterior view

Gillan, Crook et al, IJROBP 2006

SPIRIT: *Surgical Prostatectomy* *vs. Interstitial Radiation Intervention Trial*

- Phase III randomized trial comparing RP and BT for favourable risk prostate cancer
- 2002: opened in 31 centers across N America: sponsored by ACOSOG: Target accrual: 1980
- Closed May 2004 due to poor accrual
- Trial-specific educational session attended by 263 eligible men of whom 190 underwent RP or BT by choice or on trial



QOL cohort study

- Median follow-up 5.2 years (3.2-6.5)
- Cancer-specific 50 item EPIC (Expanded Prostate cancer Index Composite
- SF-12 PCS/MCS (Physical/Mental Component Score)
- Response rate 88.4%
 - 6 lost/16 declined

Results: assessment of QOL @ 5 years

	BT	RP	p-value
N (chose/randomized)	86/15	52/15	
age	61.5	59.5	0.06
Bowel domain	93.0	94.3	0.43
Hormonal domain	93.5	90.0	0.09
SF-12 PCS	55.8	55.5	0.37
SF-12 MCS	45.4	44.2	0.046
Urinary Domain	91.8	88.1	0.02
Sexual domain	52.3	39.7	0.002
Satisfaction	93.6	77.2	<0.0001

Specific questions with significant differences

- Urinary

- Frequency of leakage
- Urinary control
- Problem with leakage

} $p < 0.0001$

- **Sexual**

- **Ability to have an erection $p=0.0007$**
- **Reach orgasm $p=0.048$**
- **Quality of erection $p=0.0002$**
- **Frequency of erection $p=0.003$**

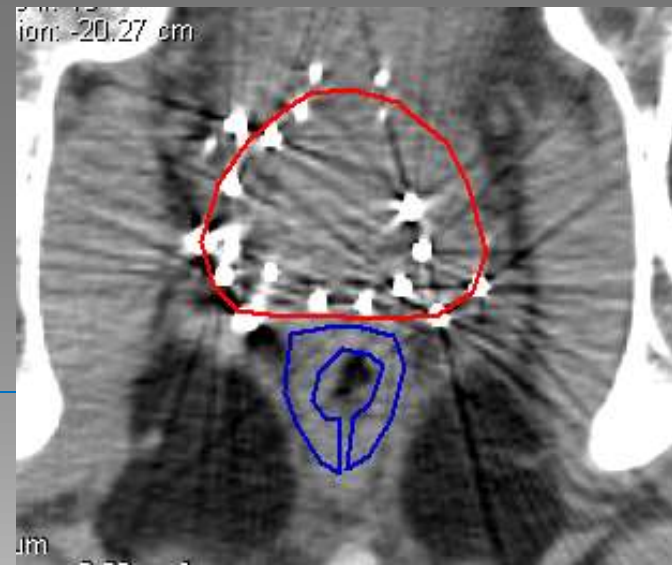
Anonymous patient-reported data consistent with entire BT experience @ PMH

- Erections firm enough for sexual activity were reported by **79%** of men treated with BT compared to 48% of those treated by RP ($p=0.0002$)
- **66%** had erections at least half the time when they wanted as compared to 40% of men after surgery ($p=0.003$).

Summary: urinary morbidity

- Prostate and transition zone volume voiding function, and HT are inter-related
- Large prostates can be safely implanted
 - excellent voiding function
 - minimize operative trauma by using higher activity seeds and fewer central needles
- Strictures usually @ membranous urethra
 - don't over estimate length @ planning
 - don't over-implant apex

Summary: rectum



Rectum:

- contour inner and outer wall
- contour all slices with seeds
- report as dose to fixed volume (1cc, 2cc) OR *volume (cc) receiving certain dose levels (100% = RV100, 150% = RV150, 200% = RV200)*

Summary: sexual

Penile bulb

- hard to identify on CT
- easily contoured on MR
- need more data
- encourage those centers using MR to routinely contour and report

Conclusions

- Your way of planning and executing an implant is probably unique
- Technique can only be disseminated through fellowship training (6-12 months)
- The toxicity of others may not be relevant to what you do (but may provide clues)
- Study your own results. Know your toxicity and what it relates to. Tweak your technique and see what happens!

Conclusion

THE DEVIL IS IN
THE DETAILS

