

Long-Term Erectile Dysfunction and Urinary Morbidity Following Brachytherapy

Nelson N. Stone, MD

Professor Urology and Radiation Oncology

The Icahn School of Medicine at Mount Sinai

New York, New York



Disclosures

- 3DBiopsy, Inc.
 - President, CEO, Owner

Prevention

- Recognize high risk situations
 - Urinary
 - Prior prostate surgery
 - Large gland
 - Outlet obstruction
 - Patient age
 - Comorbidity

Factors Influencing Urinary Symptoms 10 Years After Permanent Prostate Seed Implantation

Nelson N. Stone,^{*},[†] Naamit Kurshan Gerber,[‡] Seth Blacksbury,[‡] Jonathan Stone[‡] and Richard G. Stock[‡]

- **11,491 IPSS SHEETS**
- **1932 PATIENTS (6/patient)**
- **IMPLANT ALONE: 749 PTS**
- **IMPLANT + HORMONAL THERAPY: 486 PTS**
- **IMPLANT AND EBRT: 697 PTS**
- **FOLLOW –UP: 1 MONTH – 18 YEARS (MEDIAN – 6.5 YEARS)**

The good news!

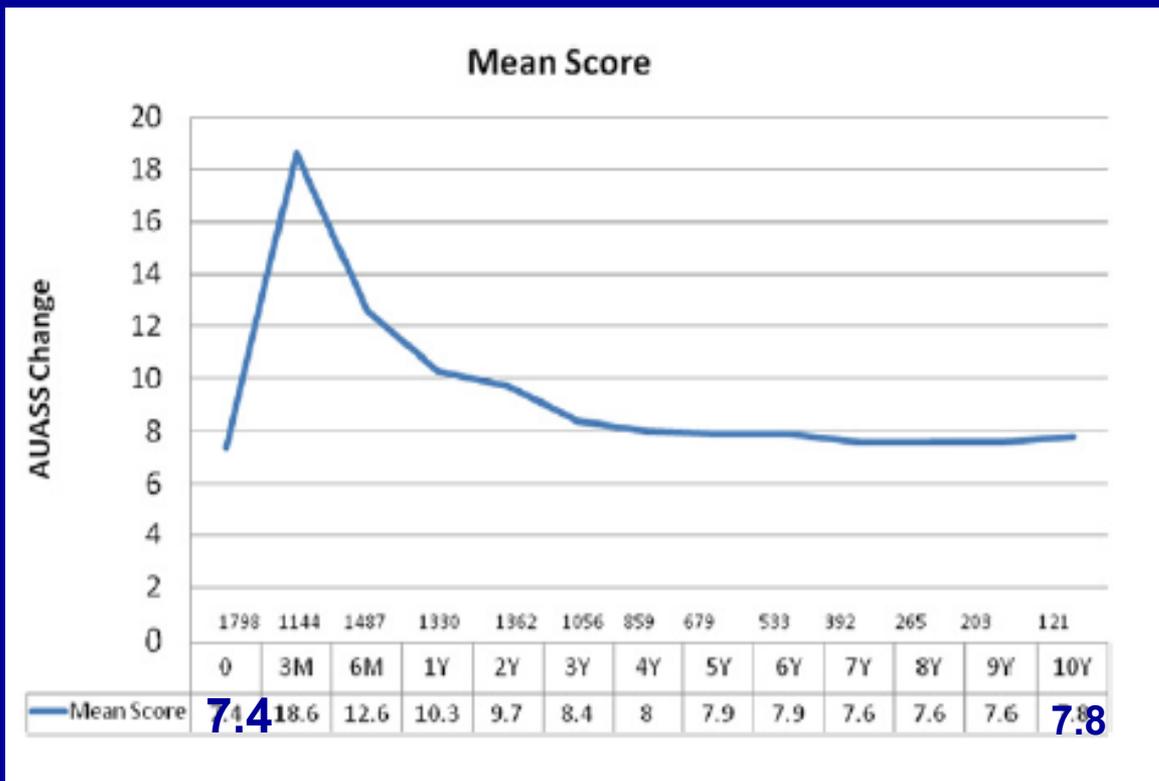




Figure 3. Change in AUASS over time by pre-implant severity category ($p < 0.001$ for all points).

Table 3. Resolution (within 1 point of baseline) of urinary symptoms by pre-implant severity category

Pre-Implant AUASS	Mean Score at Baseline	% Resolved at 2 Yrs	Time When Greater than 50% Resolved
0-7	3.4	39.4	5 Yrs
8-19	11.9	59.5	1 Yr
20 or Greater	24.2	83.3	6 Mos

Differences in mean score at baseline were significant ($p < 0.001$). By year 10 no patients with severe urinary symptoms before implantation remained in the severe (20 or greater) symptom category.

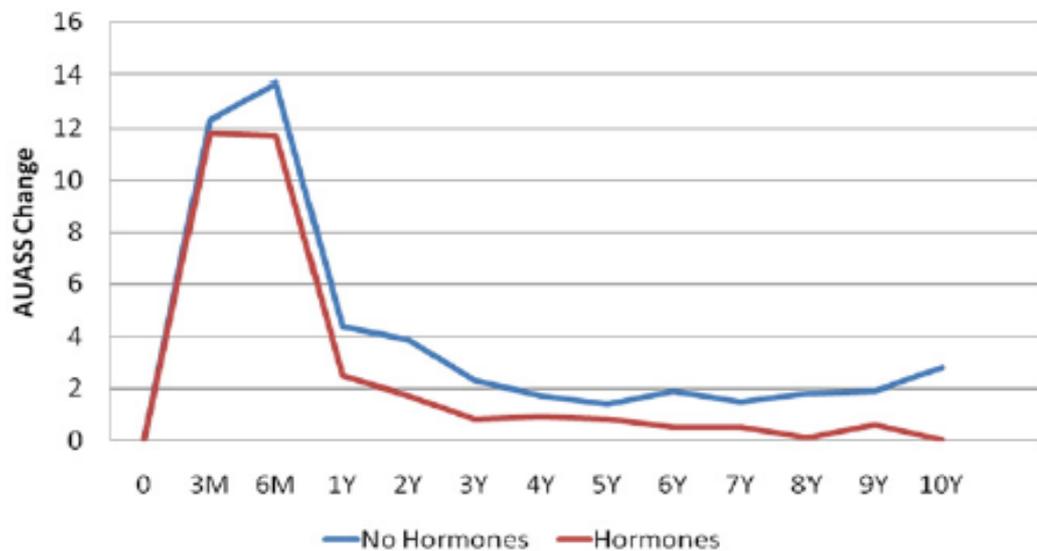
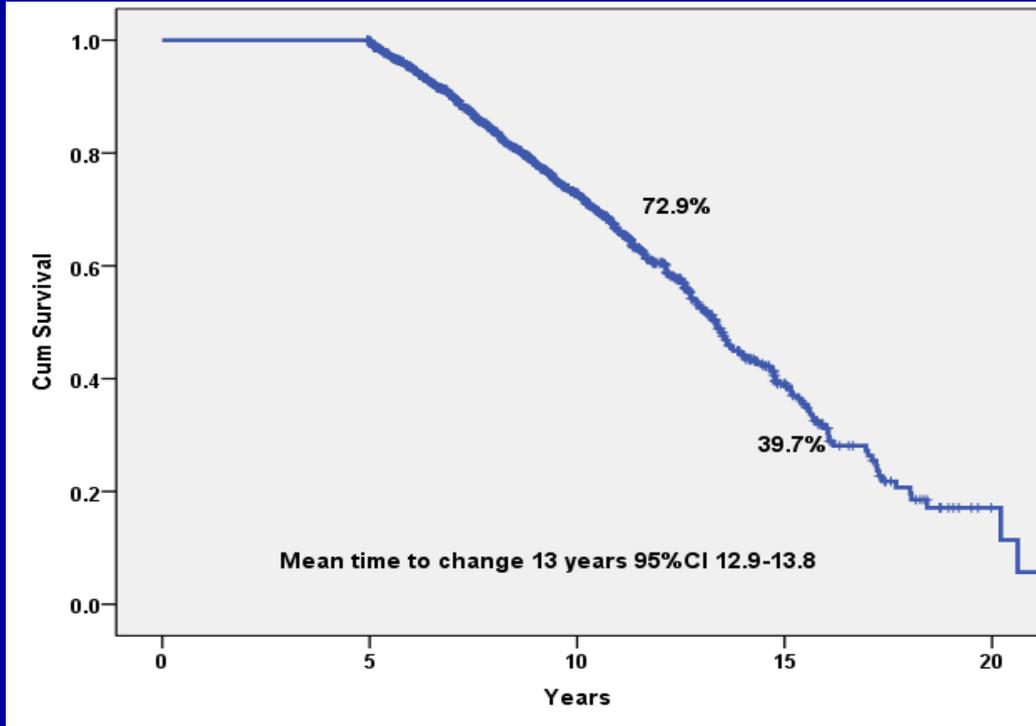


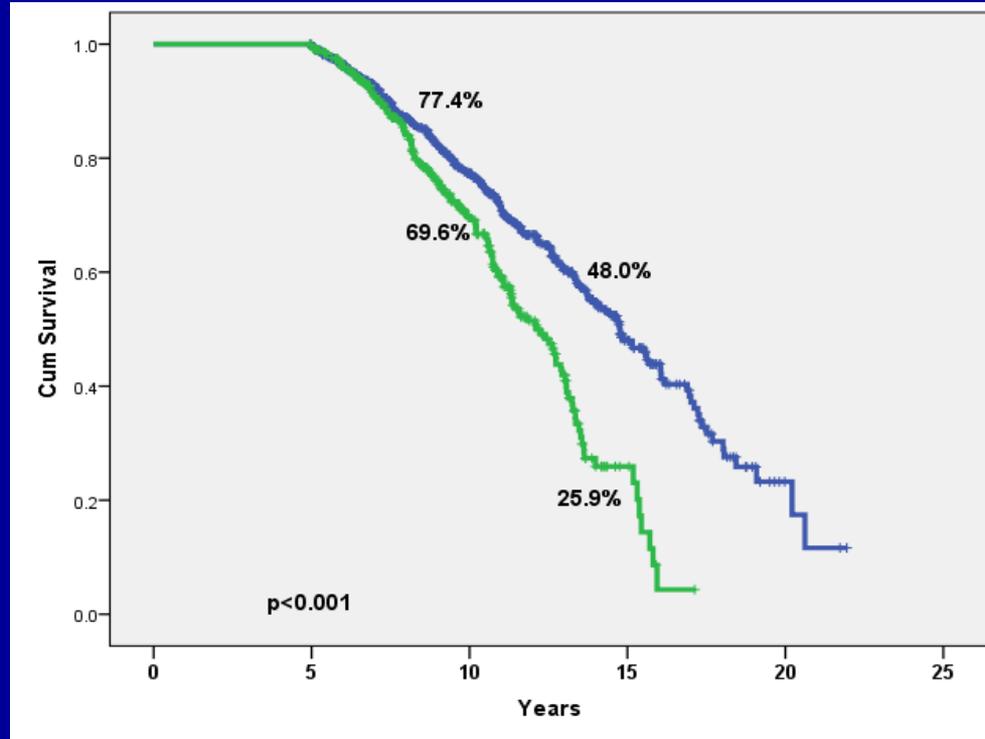
Figure 5. Mean change in AUASS from baseline by hormone vs no hormones. Differences were significant at 3 months ($p = 0.003$), 6 months ($p < 0.001$), 1 year ($p < 0.001$), 2 years ($p < 0.001$), 3 years ($p < 0.001$), 4 years ($p = 0.021$), 6 years ($p = 0.014$), 8 years ($p = 0.048$) and 9 to 10 years ($p = 0.017$).

Factors influencing long-term urinary symptoms following prostate brachytherapy

Variable	Mild symptoms (n=1110)	Moderate (n=641)	Severe (n=91)	P value
Age (years)	65.0 (41-84)	66.5 (39-85)	66.3 (49-84)	<0.001
Prostate Volume (cc)	38.2 (2.4-188)	43.0 (10.8-145)	39.3 (15-98.3)	<0.001
Use of NHT (%)	401/1110 (48.9)	233/641 (59.3)	60/91 (65.9)	<0.001
External Beam Boost (%)	410/1110 (36.1)	233/641 (36.3)	32/91 (35.2)	0.976
BED (Gy2)	196.1 ± 30	195.7 ± 30.6	194.2 ± 30.2	0.834



Likelihood of remaining with mild symptoms



Likelihood of remaining with mild symptoms with and without supplemental EBRT

	Sig.	Hazard Rates	95.0% CI for HR	
			Lower	Upper
Age (years)	0.173	1.010	.996	1.024
EBRT boost	0.004	1.45	1.13	1.81
Smoker	0.622	1.06	0.84	1.33
Alcohol	0.001	1.46	1.17	1.83
Hypertension	0.006	1.37	1.10	1.72
NHT	0.817	.972	.768	1.232
BED \geq 200Gy	0.024	1.273	1.032	1.571

Cox hazard rates for freedom from worsening urinary symptoms

Prior Prostate Surgery



Prior Prostate Surgery



Management of Large Prostate

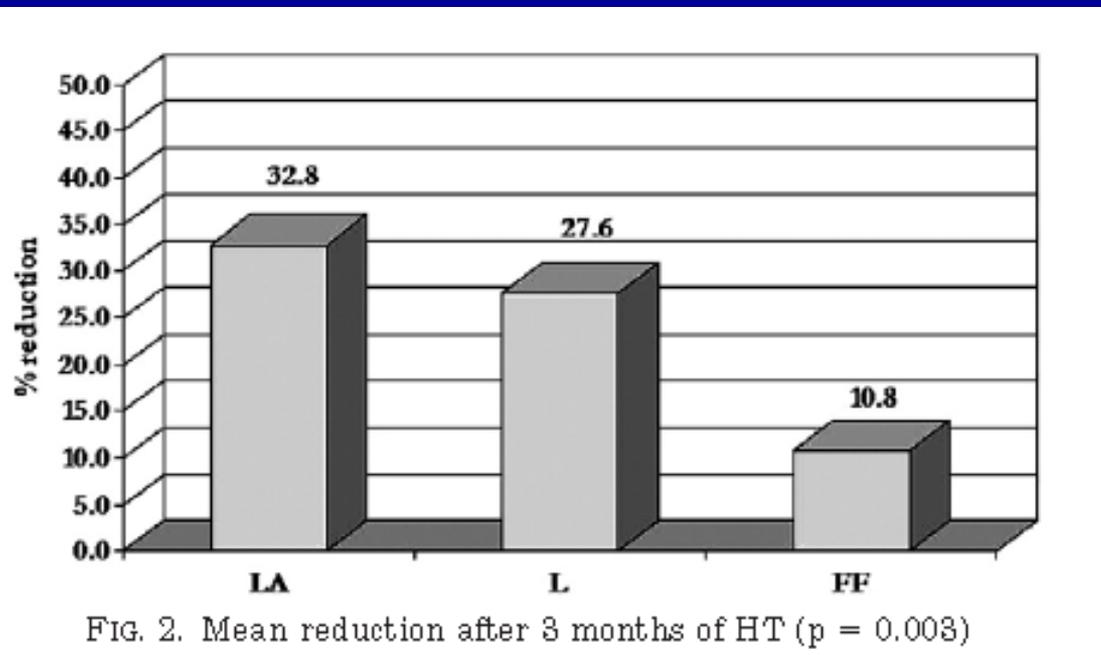
Large gland

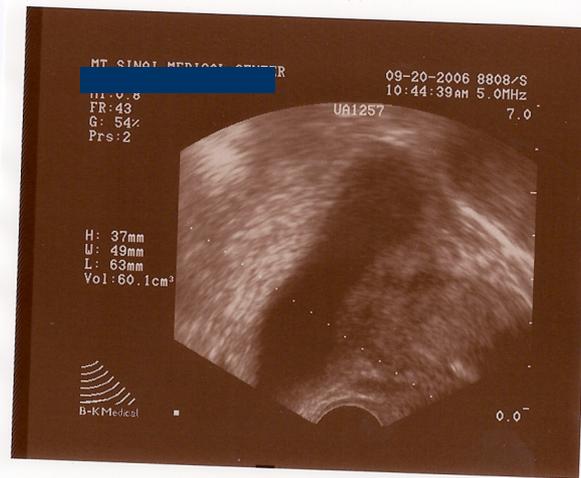
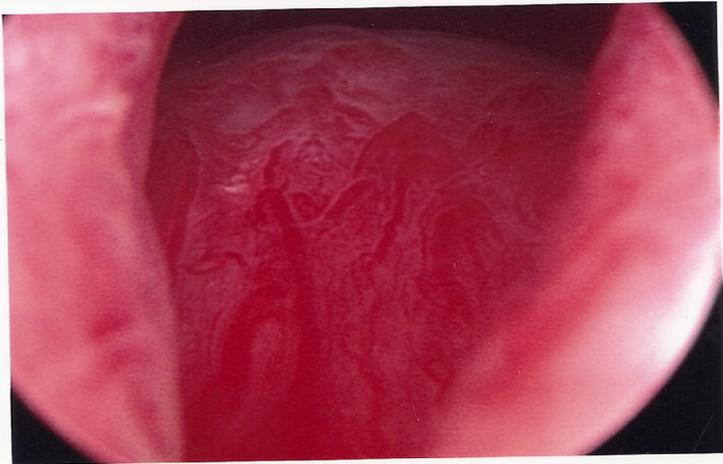
- Size limitation?
 - 50, 75, 100, 100+
- Adequacy of implant
- Intravesical lobe

The Effect of Brachytherapy, External Beam Irradiation and Hormonal Therapy on Prostate Volume

Nelson N. Stone* and Richard G. Stock

From the Departments of Urology and Radiation Oncology (RGS), Mount Sinai School of Medicine, New York, New York





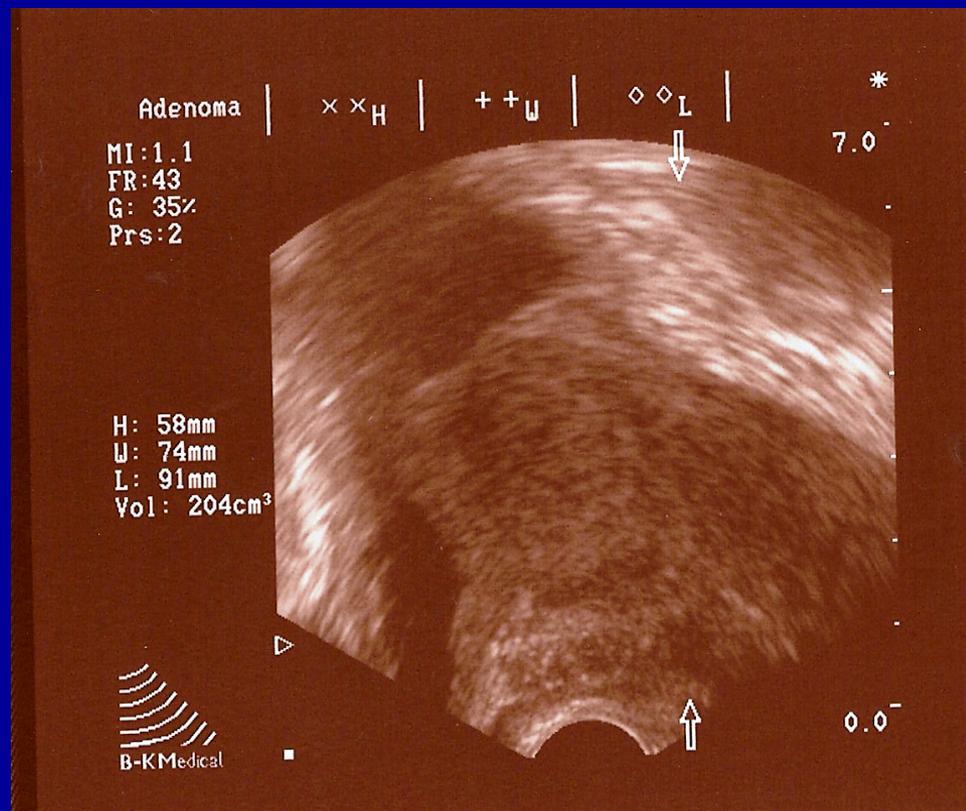
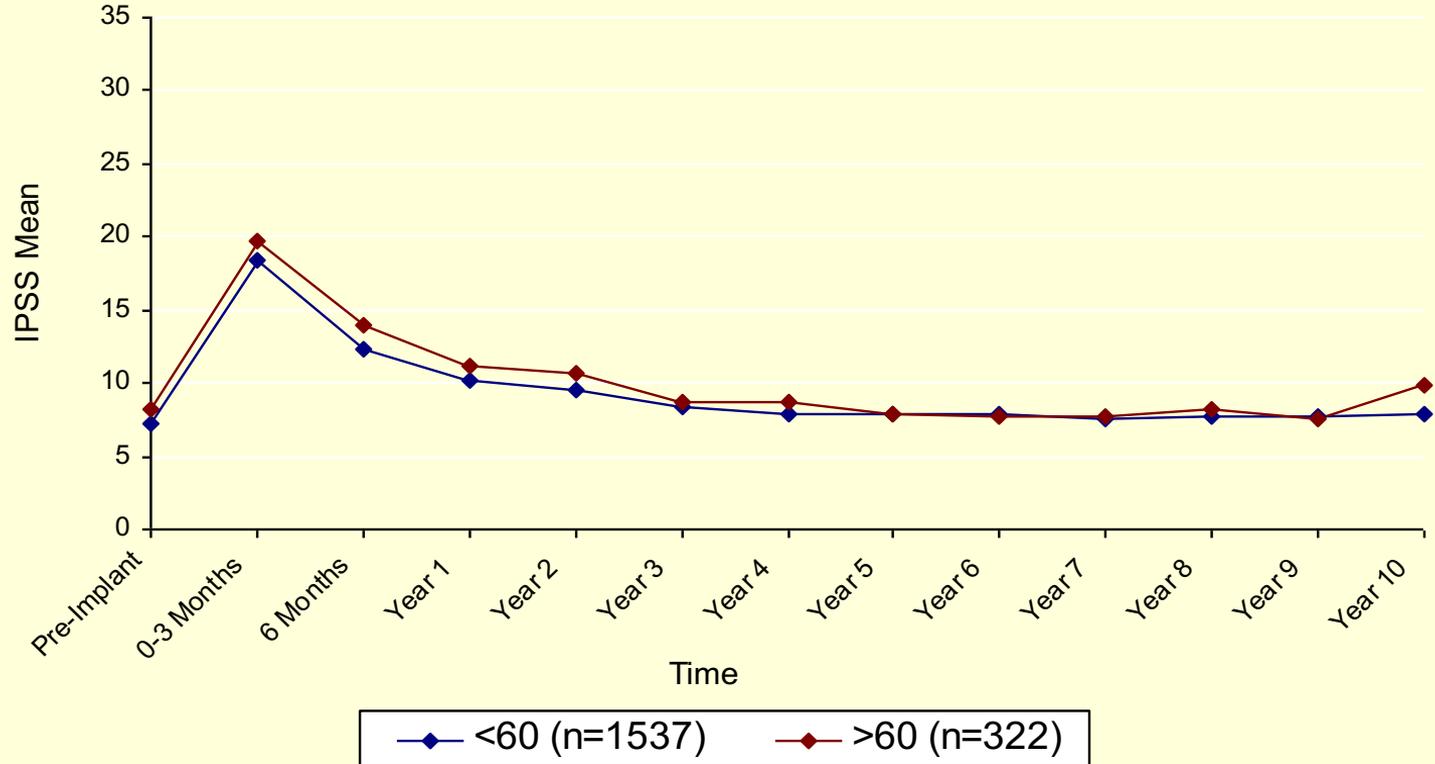


Figure 6: Prostate Volume



PROSTATE BRACHYTHErapy IN PATIENTS WITH PROSTATE VOLUMES $\geq 50 \text{ cm}^3$: DOSIMETIC ANALYSIS OF IMPLANT QUALITY

NELSON N. STONE, M.D. AND RICHARD G. STOCK, M.D.

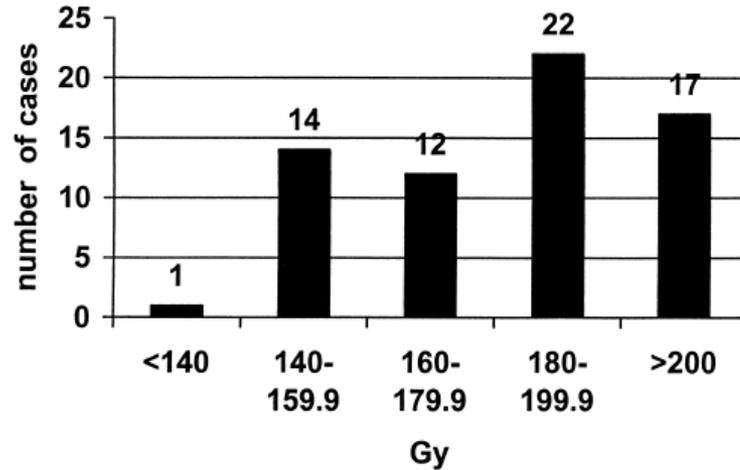


Fig. 3. Distribution of D90s in 66 patients implanted with ^{125}I with prostate volumes $\geq 50 \text{ cm}^3$. Median implant D90 was 18,750 cGy.

Does Neoadjuvant Hormonal Therapy Improve Urinary Function When Given to Men With Large Prostates Undergoing Prostate Brachytherapy?

Nelson N. Stone,^{*,†} David T. Marshall,[‡] Jonathan J. Stone, Jamie A. Cesaretti[§] and Richard G. Stock

Table 3. Comparison of values with vs without urinary retention

Variable	Mean \pm SD No Retention	Mean \pm SD Retention	p Value (ANOVA)
Age	66.5 \pm 6.9	66.9 \pm 7.0	0.564
PSA (ng/ml)	7.9 \pm 4.8	8.1 \pm 7.1	0.814
Baseline I-PSS	7.9 \pm 5.9	8.9 \pm 5.3	0.318
Biologically effective dose (Gy)	194 \pm 35	190 \pm 37	0.494
UD30	140 \pm 31	147 \pm 29	0.245
PV (cc)	57.4 \pm 14.3	56.8 \pm 17.3	0.815

Urinary retention 41/395(10.4%)

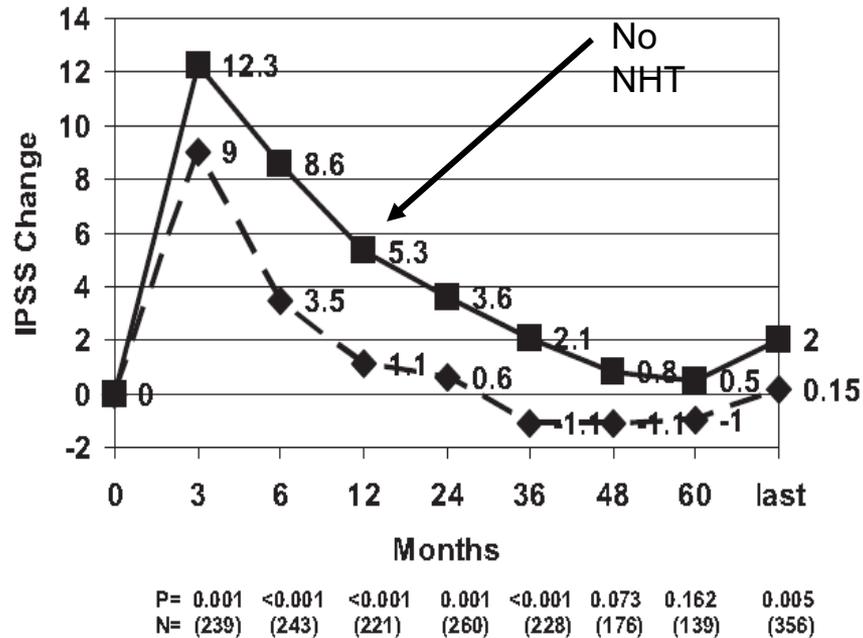


Figure 1. After implantation from baseline (*time 0*) patients without HT (squares) had greater increase in I-PPS and needed longer to return to baseline than those with NHT (diamonds).

Retention and high IPSS

- IPSS ≥ 15 , n=52
 - No NHT: 2/15 (25%)
 - NHT: 2/40 (5)%
 - OR 6.3, 95% 1-43, p=0.04

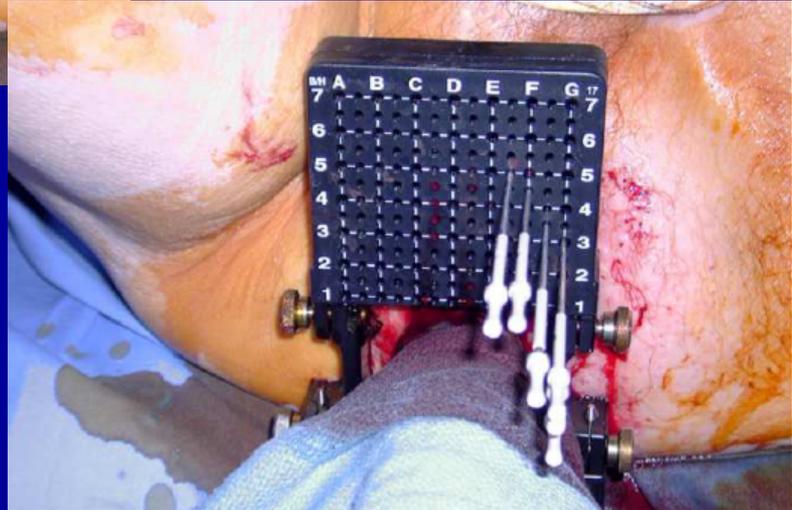
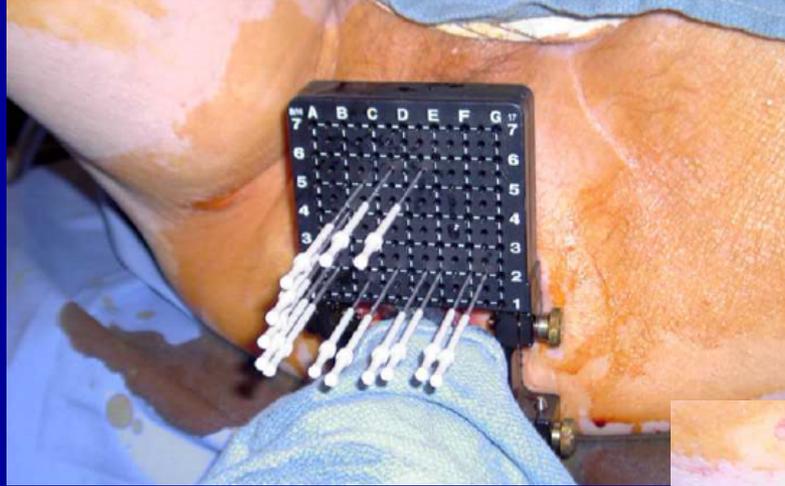
Prostate brachytherapy in men with gland volume of 100 cc or greater: Technique, cancer control, and morbidity

Nelson N. Stone^{1,*}, Richard G. Stock²

Table 1
Characteristics of the 2051 men treated by prostate brachytherapy

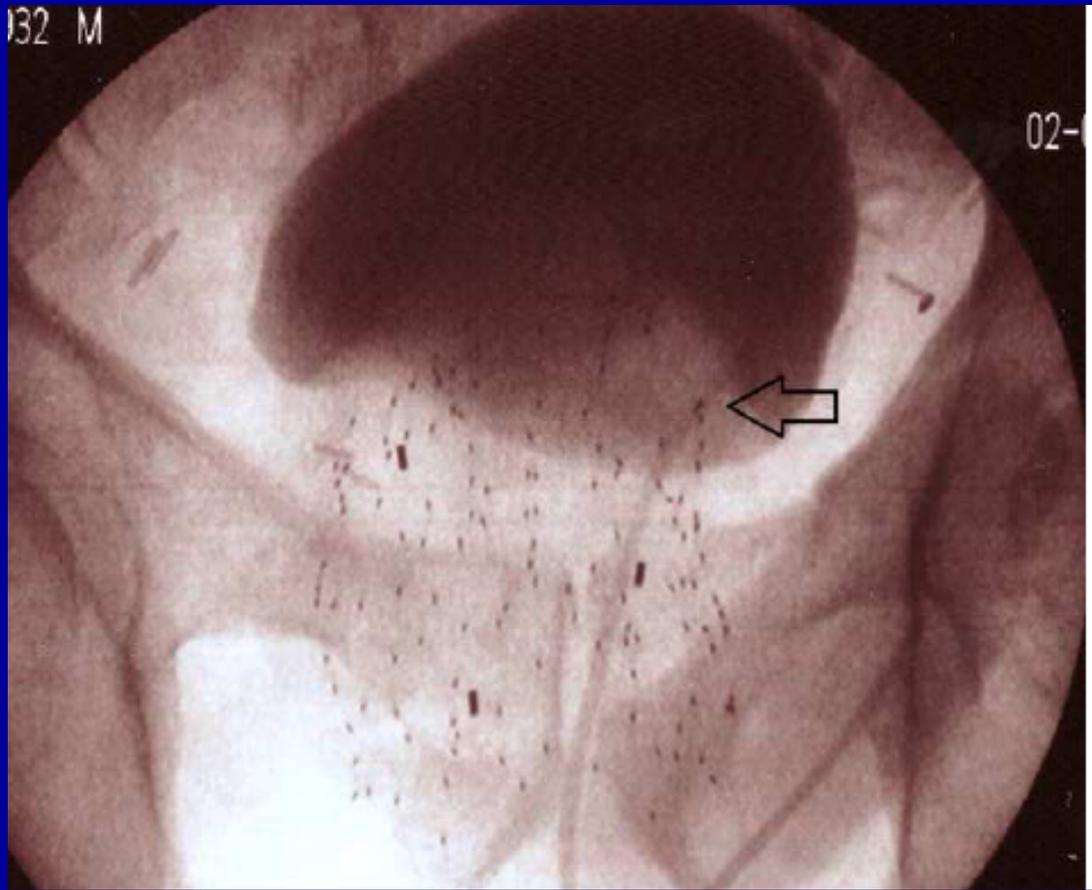
Variable	PV < 100 (%)	PV ≥ 100 (%)	<i>p</i> -Value
PSA (ng/mL)			
<10	1509 (74.8)	14 (41.2)	<0.001
10.1–19.9	363 (18)	14 (41.2)	
≥20	145 (7.2)	6 (17.6)	
Gleason score			
≤6	1365 (66.7)	22 (64.7)	0.819
7	472 (22.4)	9 (26.5)	
8–10	220 (10.9)	3 (8.8)	
Stage			
T1c–T2a	1378 (68.4)	22 (64.7)	0.362
T2b–T2c	581 (28.8)	10 (29.4)	
T3	58 (2.8)	2 (5.9)	
Initial IPSS	7.4	8.5	0.283
Preimplant TURP			
Yes	106 (5.3)	0 (0)	0.170
Hormonal therapy			
Yes	1110 (54.5)	30 (88.2)	<0.001
BED (Gy ₂)			
≤150	163 (9.3)	4 (11.8)	
>150–200	851 (43.5)	17 (50)	
>200	943 (48.2)	13 (38.2)	0.476
Followup time (y)	6.5	7.0	0.372

Two-Phase Technique



032 M

02-



Biochemical Control

Table 3
Regression analysis of PSA failure (bFFF)

Parameters	Significance	HR	95% CI for HR	
			Lower	Upper
Age	0.303	0.989	0.969	1.010
Stage	0.000	1.341	1.178	1.526
PSA	0.000	1.009	1.005	1.013
Gleason score	0.000	1.385	1.204	1.592
Hormone therapy	0.025	1.489	1.051	2.110
BED	0.000	0.989	0.985	0.992
Prostate volume	0.646	1.309	0.414	4.137

Management of Retention

Complications Following Permanent Prostate Brachytherapy

N.N. Stone*, R.G. Stock

Departments of Urology and Radiation Oncology, Mount Sinai School of Medicine, 1 Gustav Levy Place, New York, NY 10028, USA

Urinary retention rates following prostate seed implantation ($^{125}\text{I}/^{103}\text{Pd}$, both isotopes used alone, EBRT/ ^{125}I either isotope alone or in combination with EBRT, EBRT + ^{103}Pd , isotope combined with EBRT, EBR-T/ $^{125}\text{I}/^{103}\text{Pd}$, isotopes alone or in combination with EBRT)

Study	Number	Treatment	Retention rate (%)
Blasko	196	^{125}I	7
Vijverberg	46	^{125}I	22
Wallner	92	^{125}I	14
Storey	206	^{125}I	11
Terk	251	$^{125}\text{I}/^{103}\text{Pd}$	5
Kaye	76	EBRT/ ^{125}I	5
Dattoli	73	EBRT + ^{103}Pd	7
Ragde	152	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	10
Merrik	170	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	6
Benoit	1409	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	14.5
Zeitlin	212	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	1.5

Management of Significant or Persistent Obstructive Symptoms

- Full dose alpha blockers
 - Push dose
 - 2 tamsulosin HCl in am then increasing doses of terazosin at hs
 - Add anti-inflammatory medications
 - Consider PDE-5s

What about patients with obstructive and irritative voiding symptoms?

- Maximize alpha blockers
- Add anticholinergic at hs
 - Start with 25-50 mg of diphenhydramine (especially if nocturia)
 - Then low dose anticholinergic
 - Check for glaucoma

Prolonged retention

CIC or TURP?

TURP rates following prostate brachytherapy

Study	Number	Treatment	TURP rate (%)
Wallner	92	^{125}I	8.7
Storey	206	^{125}I	0
Nag	32	^{103}Pd	6.2
Terk	251	$^{125}\text{I}/^{103}\text{Pd}$	2.4
Dattoli	73	EBRT + ^{103}Pd	2.8 ^a
Merrik	170	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	1.2
Benoit	1409	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	8.3
Gelblum	693	EBRT/ $^{125}\text{I}/^{103}\text{Pd}$	4.0

^a An additional six patients (8.2%) had a TURP at time of implant.

Risk of Urinary Incontinence Following Post-Brachytherapy Transurethral Resection of the Prostate and Correlation with Clinical and Treatment Parameters

Stephen Mock,^{*,†} Michael Leapman,[†] Richard G. Stock,[†] Simon J. Hall[‡] and Nelson Neal Stone[§]

From the Mount Sinai School of Medicine, New York, New York

- 2,495 seed implantation
 - pre-implant TURP were excluded
 - 79 (3.3%) underwent channel TURP due to urinary retention or refractory obstructive urinary symptoms
- Median follow up after implantation was 7.2 yrs (range 2.2 to 18.5 yrs)
- Median time to first post-implantation TURP was 14.8 months (range 0.5 to 188 months)
- Twenty of the 79 patients (25.3%) had urinary incontinence compared with 3.1% for implantation only patients (odds ratio 10.4; 95% CI, 6-18; p<0.001).

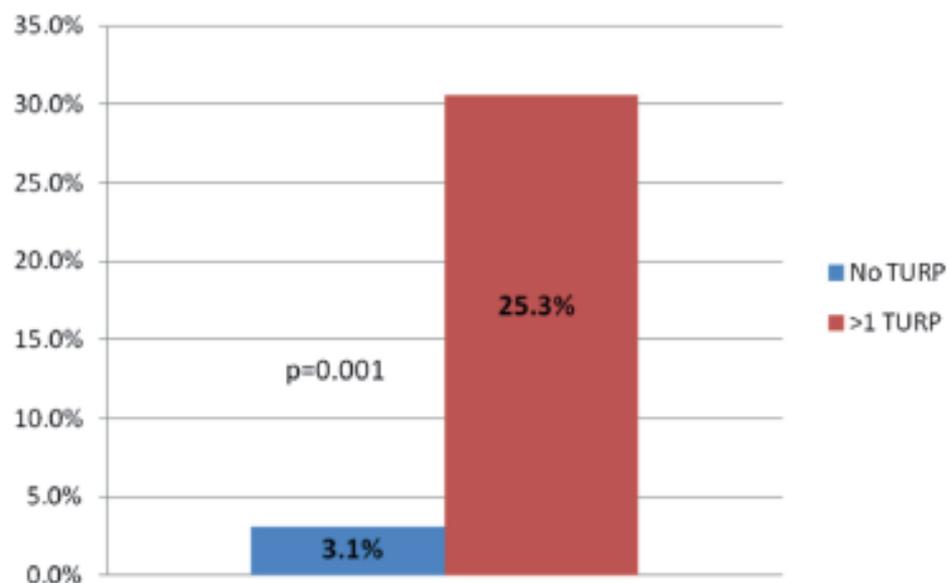
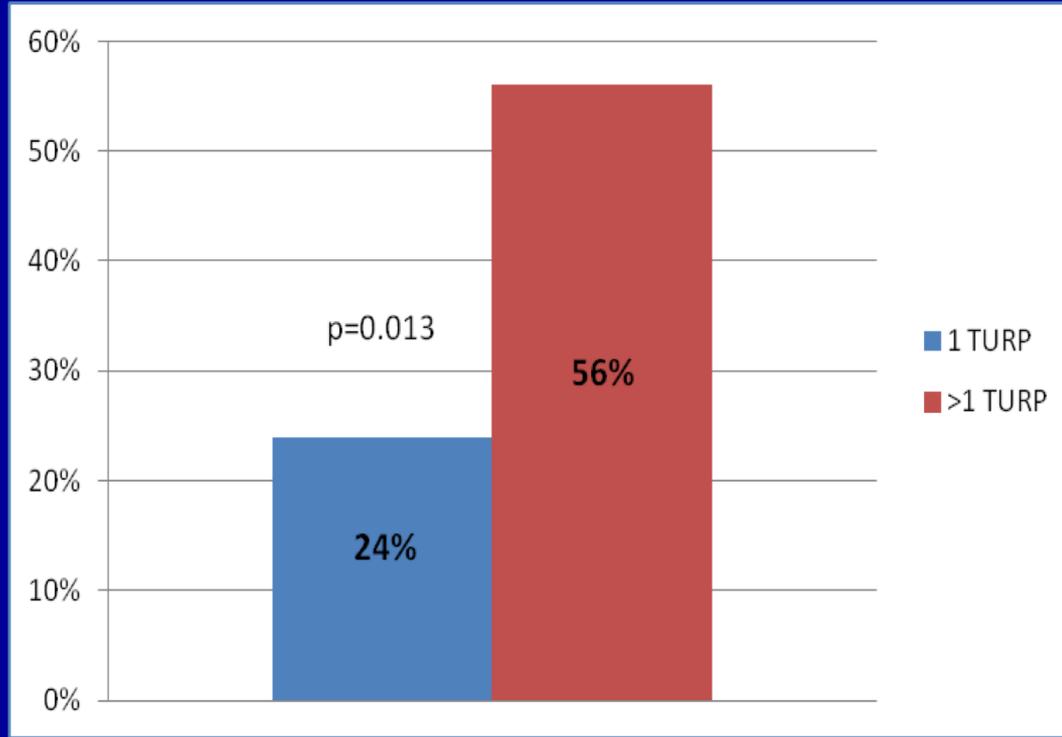


Figure 1. Incontinence rates for implantation only vs post-implantation TURP.

Effect of Multiple TURPs on Incontinence



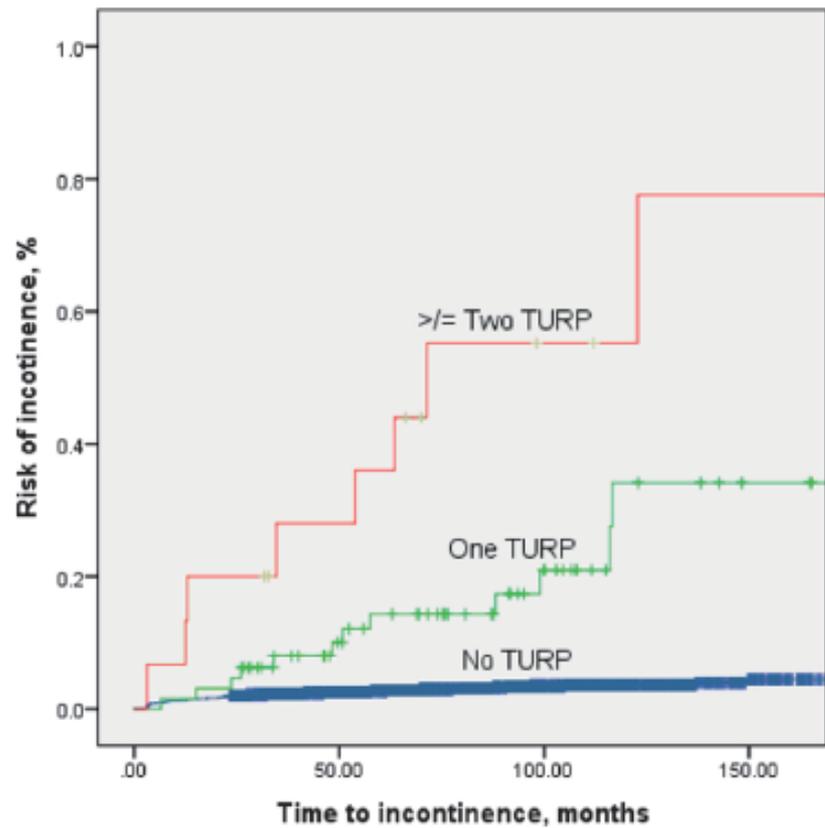


Figure 3. Kaplan-Meier curve for risk of incontinence stratified by number of transurethral prostate resections.

Table 2. Risk table from Kaplan-Meier curve

No. TURP	No. 1 Yr (%)	No. 5 Yrs (%)	No. 10 Yrs (%)
0	32 (1.4)	63 (3)	69 (3.6)
1	2 (3.1)	8 (14.3)	12 (34.1)
2+	2 (13.3)	6 (44)	8 (77)

Table 4. Multivariate linear regression analysis with incontinence vs other significant clinical and treatment variables as predictors

	Hazard Rate	p Value
Stage	0.57	0.57
Hormone use	2.28	0.02
TRUS vol	0.02	0.99
CT vol	1.28	0.2
Total BED	1.45	0.15
No. post-implantation TURP	11.1	0.00

Bottom Line:

- CIC for at least 1 year
- Minimum channel TURP
 - Preserve blood vessels at 5 and 7 o' clock positions
 - Utilize minimum fine cautery
 - Avoid laser and widespread tissue destruction

URINARY SYMPTOM FLARE FOLLOWING I-125 PROSTATE BRACHYTHERAPY

JAMIE A. CESARETTI, M.D.,* NELSON N. STONE, M.D.,[†] AND RICHARD G. STOCK, M.D.*

Departments of *Radiation Oncology and [†]Urology, Mount Sinai School of Medicine, New York, NY

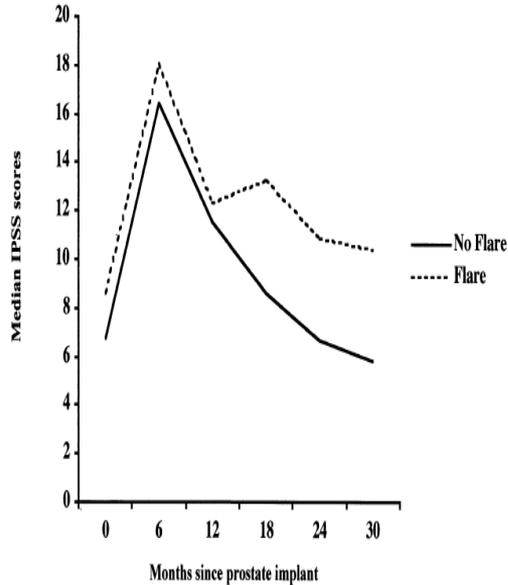


Fig. 2. International Prostate Symptom Score (IPSS) at 6-month intervals for the flare and nonflare groups.

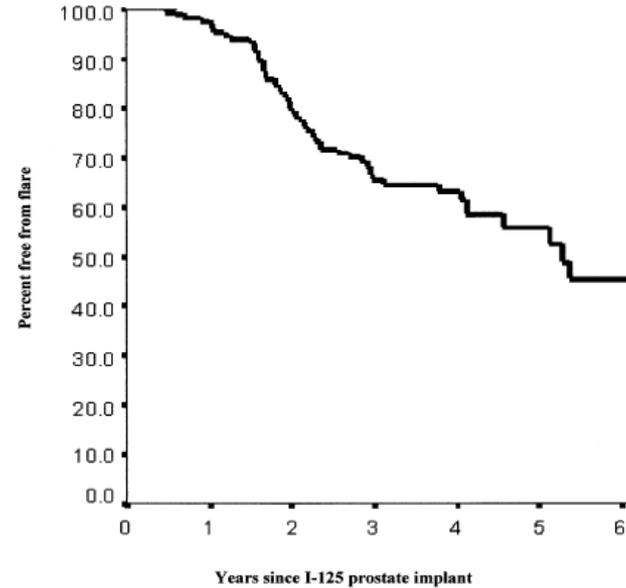


Fig. 3. Actuarial incidence of flare over time for 172 patients after I-125 prostate therapy.

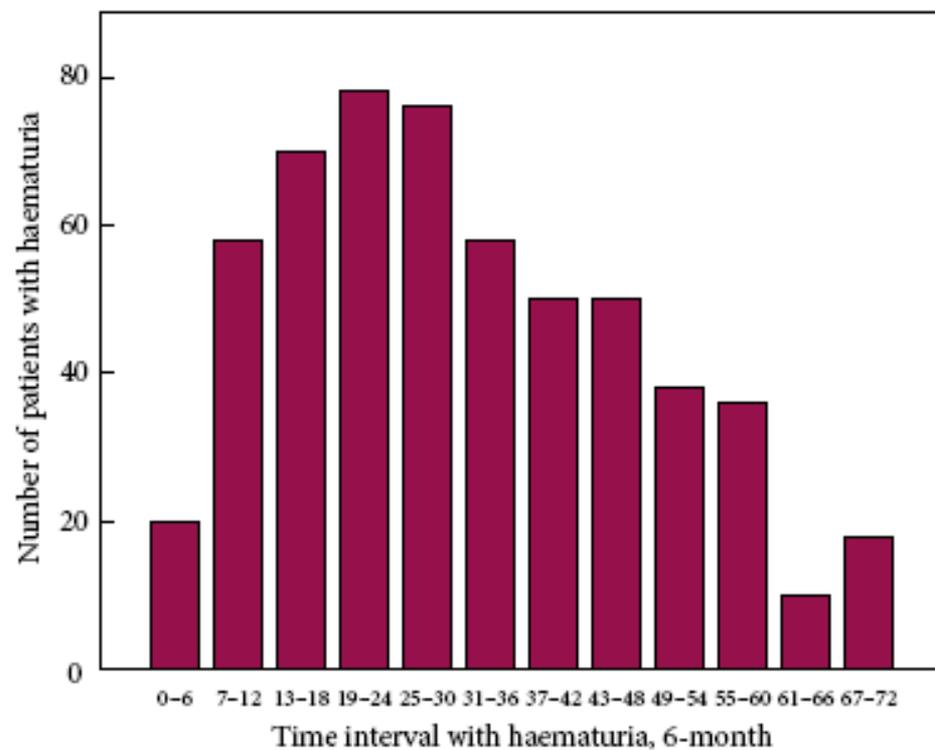
Haematuria after prostate brachytherapy

Michael S. Leapman*, Simon J. Hall*, Nelson N. Stone*† and Richard G. Stock†

*Departments of *Urology and †Radiation Oncology, Mount Sinai School of Medicine, New York, NY, USA*

- 2454 patients treated with transperineal
- prostate brachytherapy over a 20-year period at a single
- Patients were followed for a median of 5.9 years.
- 218 men (8.9%) reported gross haematuria at a median time of 772.2 days after implantation.

Fig. 2 Number of patients with haematuria in each 6-month time interval post-implantation.



Time to haematuria in 218 patients following prostate brachytherapy

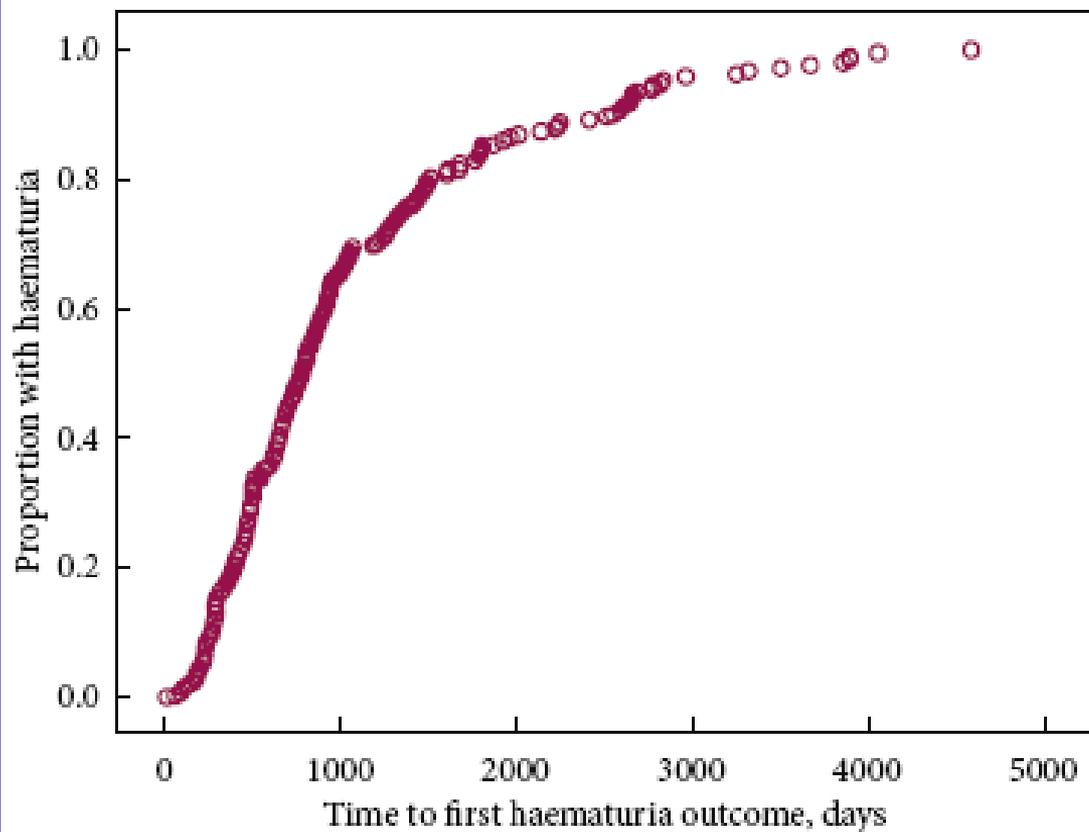


Table 3 Binary logistic regression model for covariants associated with haematuria.

Variable	SE	Significance	95% CI	
			Lower	Upper
Race	0.085	0.854	0.859	1.201
Prostate cancer stage	0.073	0.052	0.753	1.002
Biochemical failure	0.355	0.035	1.052	4.222
ADT	0.173	0.478	0.631	1.241
Urinary retention	0.254	0.404	0.751	2.034
PSA >10 ng/mL	0.201	0.151	0.505	1.111
Gleason score >7	0.232	0.720	0.690	1.712
BED >200 Gy	0.157	0.268	0.875	1.621
Prostate volume >40 cm ³	0.152	0.002	1.193	2.166
External beam radiation	0.240	0.001	0.289	0.738

Findings at Cystoscopy Performed for Cause After Prostate Brachytherapy

Michael S. Leapman, Richard G. Stock, Nelson N. Stone, and Simon J. Hall

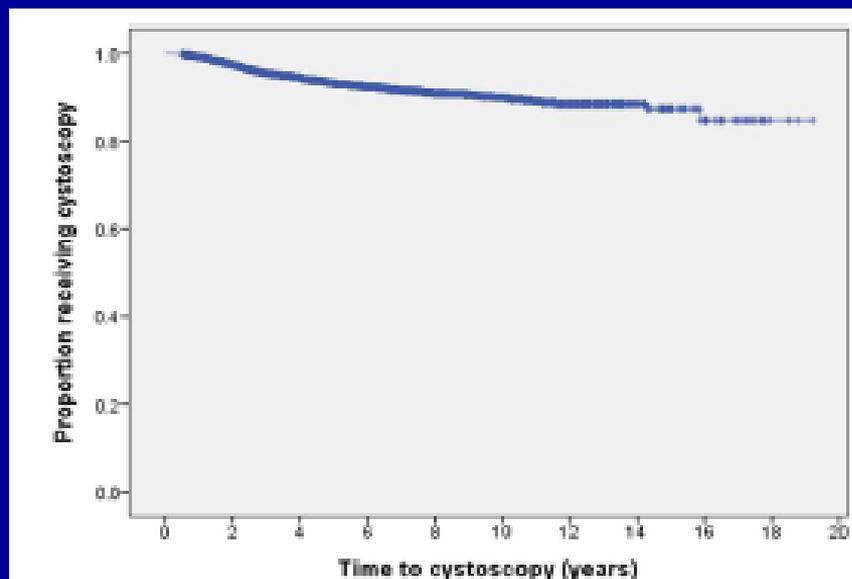
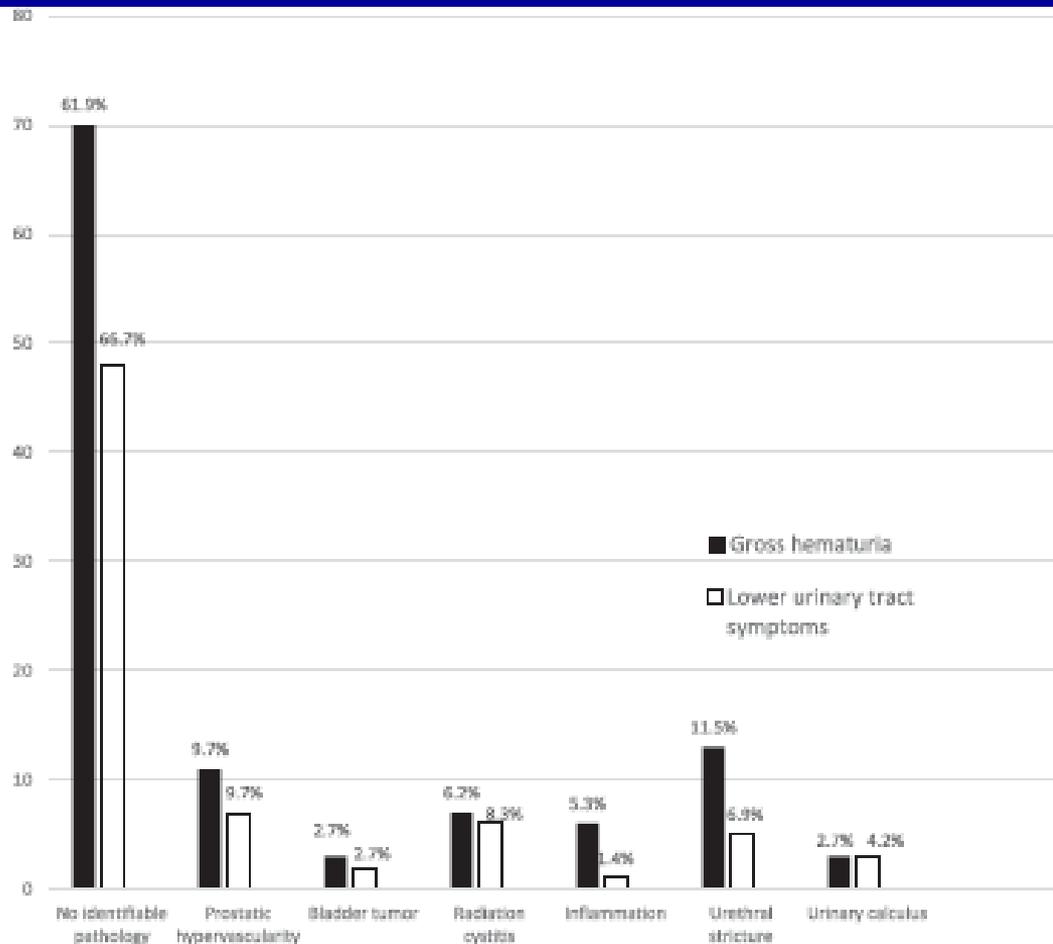


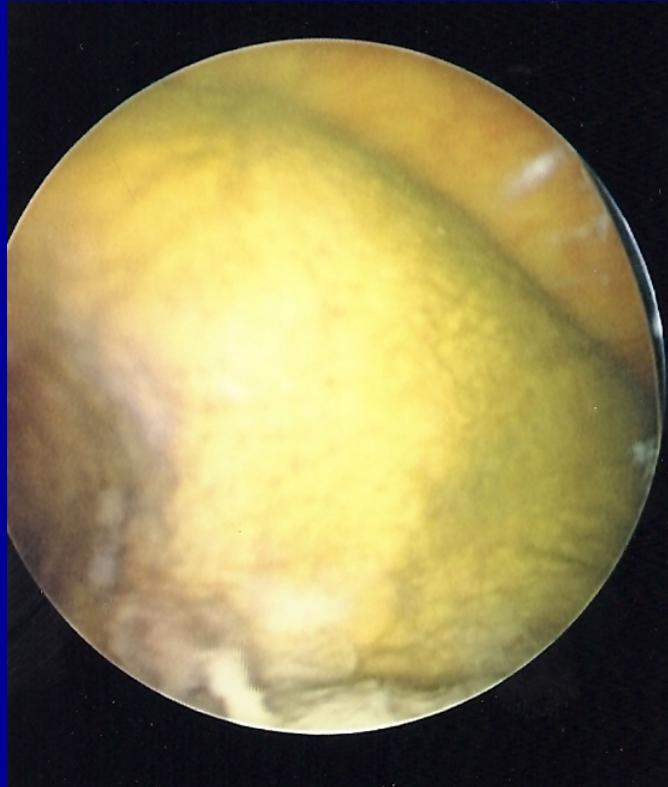
Figure 1. A total of 185 men underwent cystoscopy for hematuria or refractory urinary symptoms after prostate brachytherapy. The median time to cystoscopy in 181 men was 2.7 y. The 10-y freedom from cystoscopy was 89%. (Color version available online.)



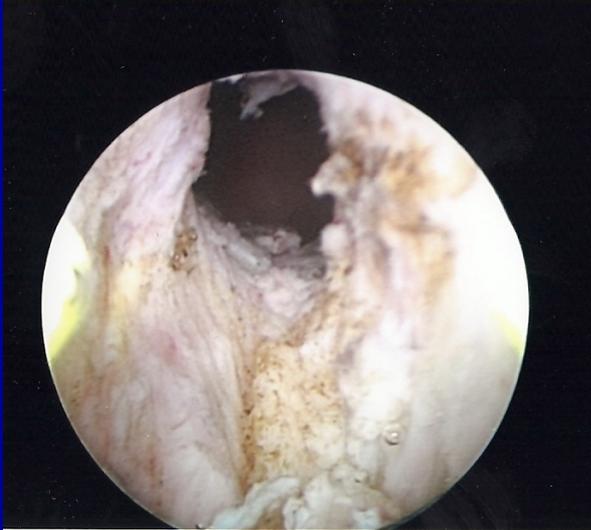
Bladder Tumor

- 18 bladder tumors (18/2532, 0.7%)
- median time to detection of bladder cancer was 3.1 years (8.4 months-14.3 years)
 - one-third (6 patients) diagnosed within 2 years of radiation therapy.
- 13 (72.2%) were identified as low-grade, noninvasive urothelial carcinoma.
- 3 individuals (16.7%) had high-grade noninvasive (Ta) with concomitant carcinoma in situ.
- 2 individuals (11.1%) invasive (T2) disease

Do not leave seeds in bladder!

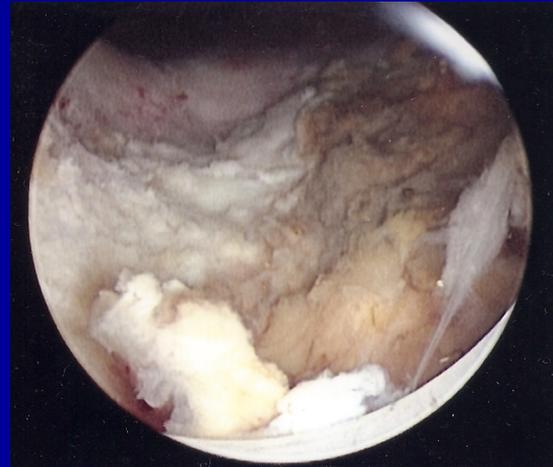


Limit size of resection!

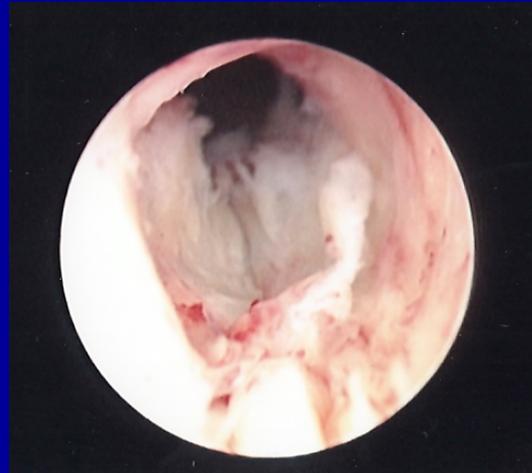
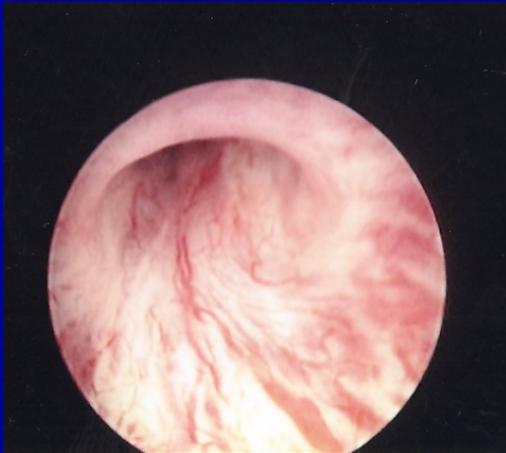


Small TURP

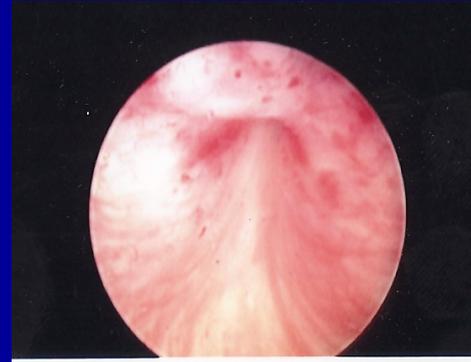
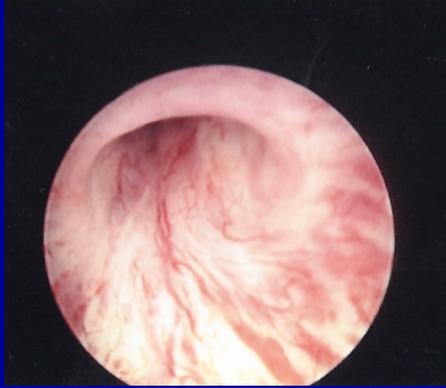
Big TURP: this patient is incontinent!

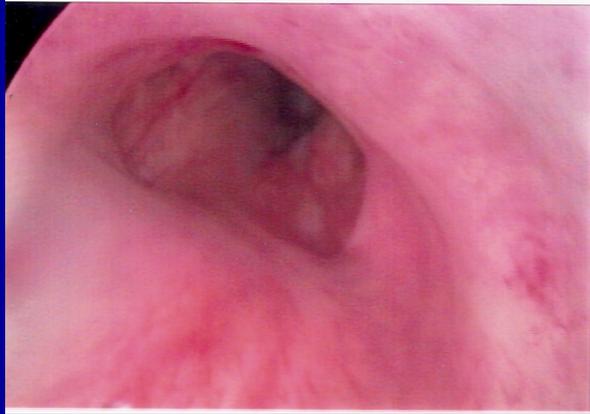
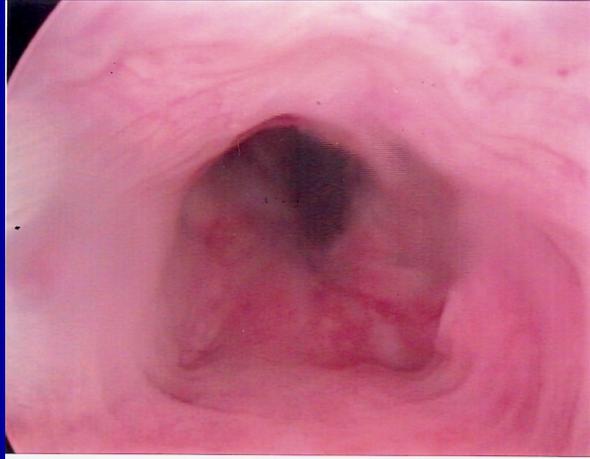


Management of incontinence



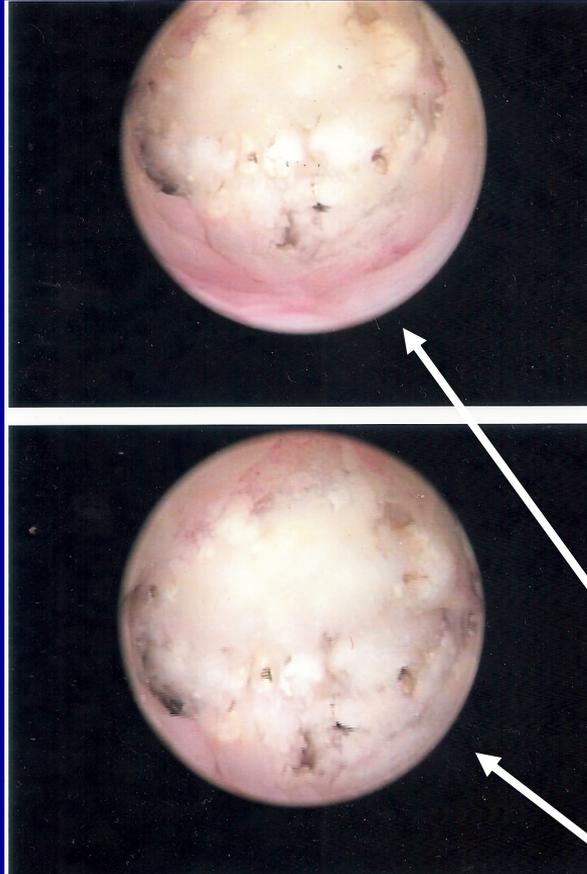
Try Collagen Injections





Worst Situation

- Patient who has multiple resections and ends up with stricture posterior urethra and incontinence
- Avoid sending him to a cowboy urologist
- First treat the stricture by either urethrotomy or dilation followed by patient self catheterization with progressive increase in intervals. It may take a year to rehabilitate urethra.
- Then deal with incontinence



64 y/o low risk, PV 65cc, no NHT

I-125 D90 194 Gy

Obstructive symptoms

Local urologist did extensive TURP
at 9 months

Developed retention 4 months later

Another TURP

Developed retention 3 months later

Has SP tube placed

Presents now 2 years post-implant

Has TURP scraping of calculi and
started on CIC

Not able to pass cath, cysto 4 weeks
later



Long-term Erectile Function Following Prostate Brachytherapy: Effect of Race and Vascular Comorbidities

	TOTAL (997)	CAUCASIAN (782)	AFRICAN AMERICAN (112)	HISPANIC (58)	ASIAN (19)	OTHERS (26)	P VALUE
BRACHYTHERAPY TYPE							0.006
IMPLANT	380 (38.1%)	322 (41.2%)	28 (25.0%)	16 (27.6%)	8 (42.1%)	6 (23.1%)	
IMPLANT+HT	204 (20.5%)	161 (20.6%)	26 (23.2%)	8 (13.8%)	2 (10.5%)	7 (26.9%)	
IMPLANT+EBRT	97 (9.7%)	76 (9.7%)	9 (8.0%)	6 (10.3%)	2 (10.5%)	4 (15.4%)	
IMPLANT+HT+EBRT	316 (31.7%)	223 (28.5%)	49 (43.8%)	28 (48.3%)	7 (36.8%)	9 (34.6%)	
BED Gy2							0.282
≤ 150	11 (1.1%)	8 (1.0%)	2 (1.8%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	
150 - 200	398 (39.9%)	299 (38.8%)	51 (45.5%)	28 (48.3%)	5 (26.3%)	15 (57.7%)	
> 200	576 (57.8%)	463 (60.1%)	59 (52.7%)	29 (50.0%)	14 (73.7%)	11 (42.3%)	
RECEIVED NHT	520 (52.2%)	384 (49.1%)	75 (67.0%)	36 (62.1%)	9 (47.4%)	16 (61.5%)	0.003

	Pre-Implant (%)	Last follow up (%) min. 5 years	% preserved
	n	n	
White	539 (68.9)	349 (64.7)	64.7%
AA	74 (66.8)	55 (74.3)	74.3%
Hispanic	38 (65.5)	26 (68.4)	68.7%
Asian	15 (78.9)	9 (60.0)	60.0%
Other	14 (53.8)	11 (78.6)	78.6%
TOTAL	680	450	66.17%

SHIM \geq 12 remaining \geq 12

Variable		10 years potency % (n)	12 years potency % (n)	Mean time years (CI)	p value
Age	≤ 65	71.2 (131)	52.6 (53)	11.7 (11.3-12.1)	<0
	> 65	55.4 (78)	32.1 (31)	10.1 (9.7-10.6)	
BED	≤ 150	30 (11)	(1)	8.1 (6.1-10.1)	0.017
	150 - 200	61.7 (79)	37.8 (22)	10.7 (10.2-11.2)	
	> 200	67.2 (129)	47.5 (61)	11.2 (10.8-11.3)	
NHT	Yes	58.0(97)	37.2(39)	10.4(10.0-10.8)	<0
	No	70.7 (112)	49.6 (44)	11.7 (11.2-12.11)	
T300	yes	64 (74)	37.6 (22)	?	0.160
	No	67.2 (103)	46.4 (45)	?	
Smoker	Yes	58.9 (78)	41.9 (30)	10.6 (10.1-11.0)	0.200
	No	68.3 (130)	44.8 (53)	11.3 (10.9-11.7)	
Diabetes	Yes	60.9 (17)	42.2 (8)	10.6 (9.5-11.1)	0.515
	No	64.5 (191)	43.5 (76)	11.0 (10.7-11.3)	
CAD	Yes	69.1 (13)	23.0 (2)	9.9 (8.8-11.0)	0.169
	No	64.4 (200)	44.3 (81)	11.1 (10.7-11.4)	
EtOH	Yes	61.8 (100)	43.1 (43)	10.8 (10.3-11.2)	0.072
	No	68.3 (111)	44.4 (40)	11.3 (10.9-11.8)	
Afib	Yes	16.2 (1)	16.2 (1)	8.5 (6.6-10.5)	0.011
	No	65.4 (209)	43.8 (83)	11.1 (10.7-11.4)	
Heart Disease	Yes	57.8 (7)	43.4 (6)	10.0 (8.8-11.3)	0.081
	No	64.9 (200)	43.4 (78)	11.1 (10.8-11.4)	
HTN	Yes	60.5 (66)	39.1 (23)	10.6 (10.1-11.1)	0.095
	No	66.1 (45)	45.5 (60)	11.2 (10.8-11.6)	

	Sig.	Hazard Ratio	95.0% CI for Hazard Ratio	
			Lower	Upper
Age at Initial Rx	.000	1.043	1.023	1.064
Total BED	.661	.999	.992	1.005
Last Testosterone	.659	1.000	.999	1.001
Smoker	.327	.870	.659	1.149
CAD	.101	.608	.336	1.101
Alcohol	.085	.779	.586	1.035
Atrial Fibrillation	.520	.740	.296	1.850
Heart Disease	.596	.859	.489	1.508
Hypertension	.284	.859	.649	1.135
TotalHRMs	.000	1.057	1.026	1.089

