

# Prostate Brachytherapy: A Physician's Perspective

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Webpage: <http://go.g/BIIR6B>



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## Disclosures

- I have served on the following scientific advisory boards within the past 3 years
  - Myriad Genetics
  - GenomeDX
  - Astellas/Medivation
- Principal Investigator for a Myriad Genetics study
- I am a radiation oncologist



## A little bit about me...



Athlan Tward MD, PhD

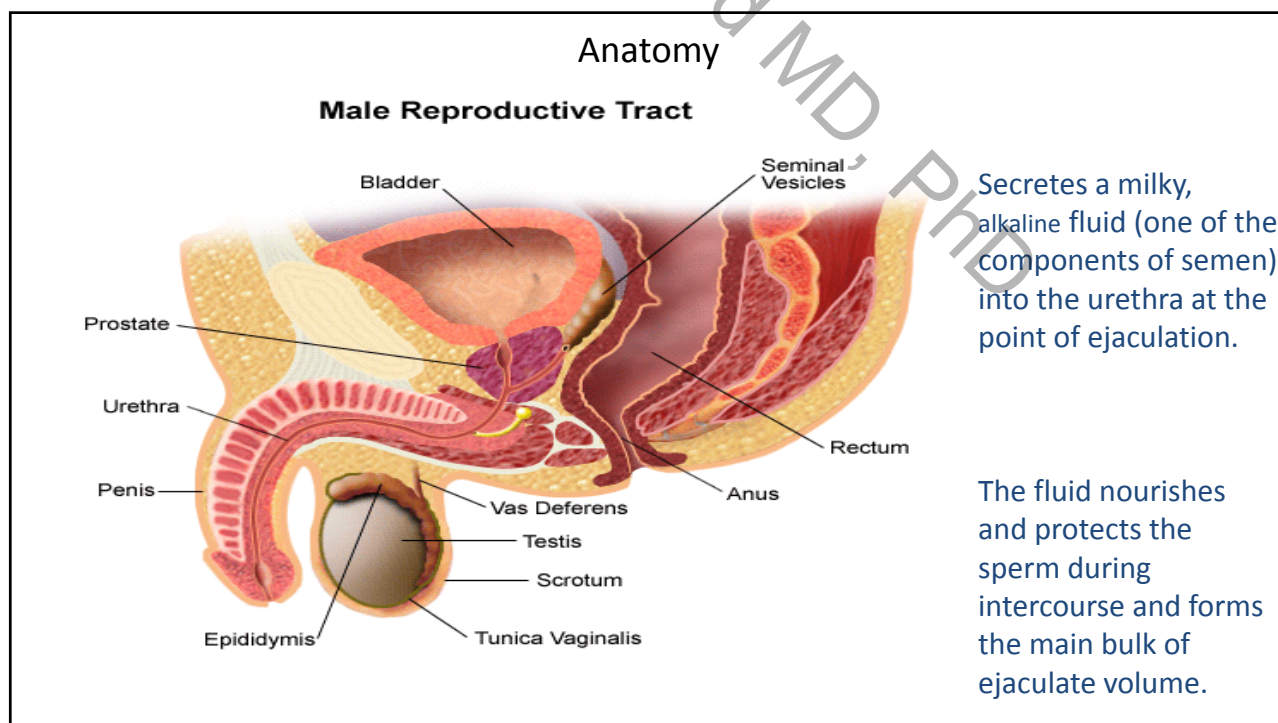
## In Memorium

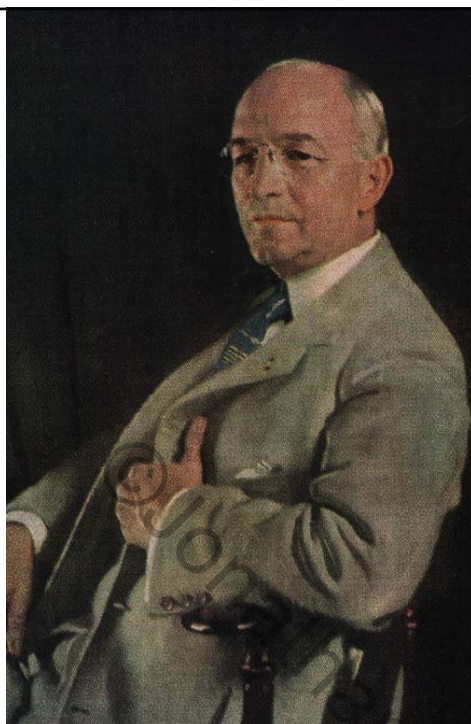


Peter D. Grimm, D.O.  
July 17, 1952 – February 20, 2016

# What we will cover:

- Function of the prostate
- History of Prostate Brachytherapy
- Risk Stratification
- Outcomes definitions
- Physician Bias
- Comparative Effectiveness
- Toxicity
- Decline of brachy
- Technical Details
- Wrapup





## A little History

Hugh  
Hampton  
Young

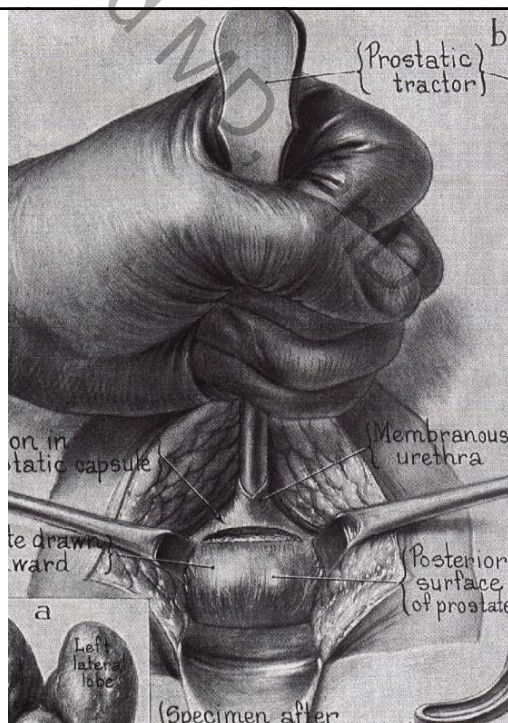
Johns Hopkins

Slide courtesy of Jesse Aronowitz, MD  
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## Young's Transperineal Prostatectomy

1904

Slide courtesy of Jesse Aronowitz, MD



Jonathan Tward MD, PhD

Between 1904 and 1926,  
Young performed  
only 26 radical prostatectomies

*© How did he treat his other  
prostate cancer patients?*

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Young's radium prostate implants:

- 66 in the first 2 years
- 500 between 1915 and 1927,  
(fractionated radiation therapy)

Slide courtesy of Jesse Aronowitz, MD  
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# SOME NEW METHODS IN THE TREATMENT OF CARCINOMA OF THE LOWER GENITO-URINARY TRACT WITH RADIUM\*

HUGH H. YOUNG and WILLIAM A. FRONTZ

*From The James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland*

During the past two years, we have treated with radium sixty-six cases of cancer of the prostate. In forty-two of these, the tumor was extensive, not only the prostate but the seminal vesicles being involved. In nineteen the process was confined apparently to one half of the prostate and the corresponding vesicle, while in four the vesicles were apparently free from invasion.

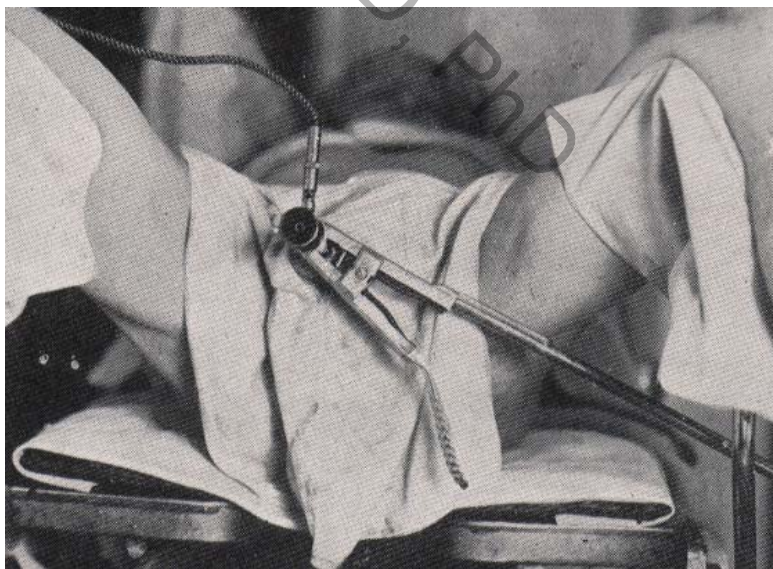
## 1917 Young's First *J Urology* Article

Slide courtesy of Jesse Aronowitz, MD  
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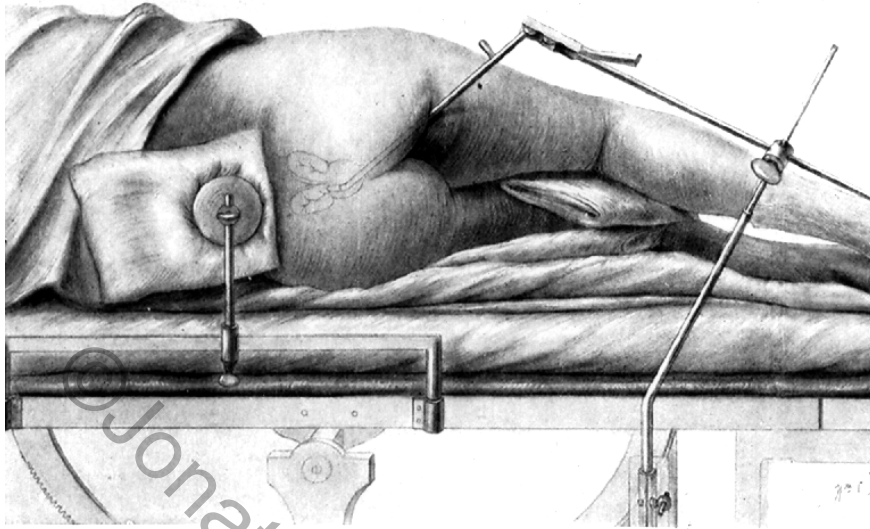
## Intraurethral Radium Application



Young's  
Radium Applicator

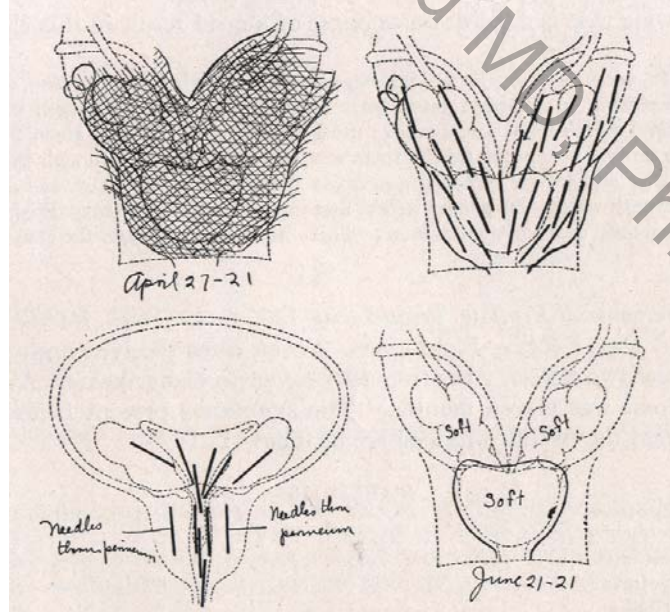


Slide courtesy of Jesse Aronowitz, MD  
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Slide courtesy of Jesse Aronowitz, MD

## Intrarectal Radium Application



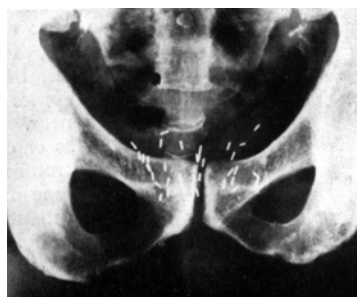
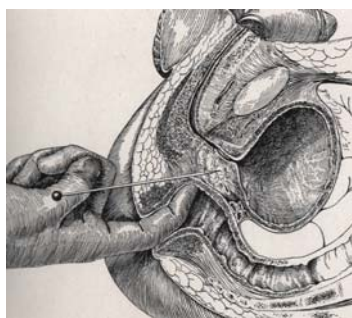
## Young's Radium Map

Slide courtesy of Jesse Aronowitz, MD and Jonathan Tward MD, PhD



Slide adapted and courtesy of Jesse Aronowitz, MD

**Benjamin Barringer**  
1877 - 1953



Memorial Hospital

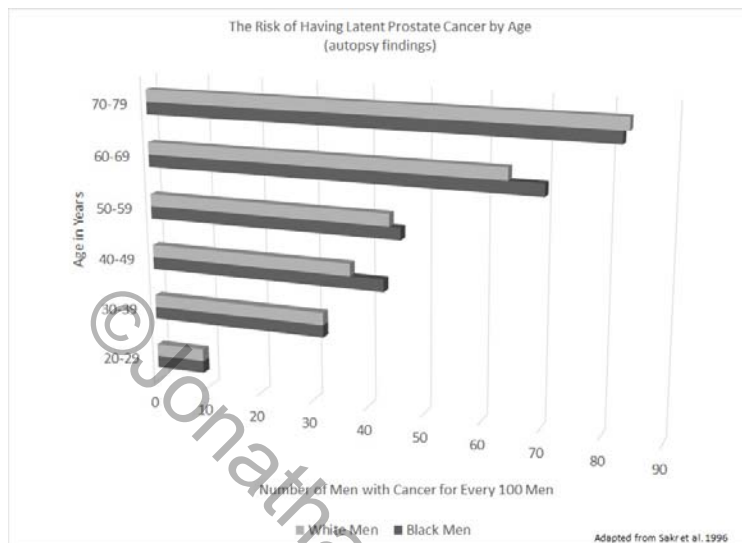
## Barringer Innovations

- Transperineal & Suprapubic implantation
- Transperineal biopsy
- Combined implant & ebrt
- Combined implant & castration
- Screening for prostate cancer

Slide courtesy of Jesse Aronowitz, MD  
Copyright Jonathan Tward MD, PhD



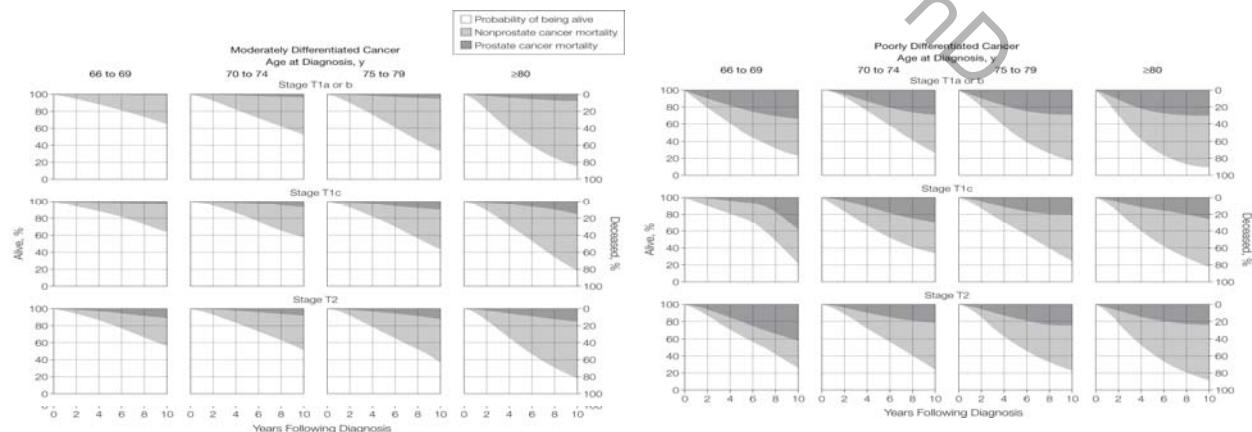
# Is Prostate Cancer “Normal”?



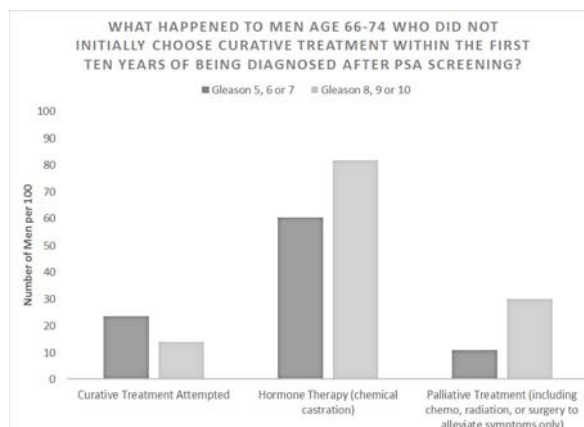
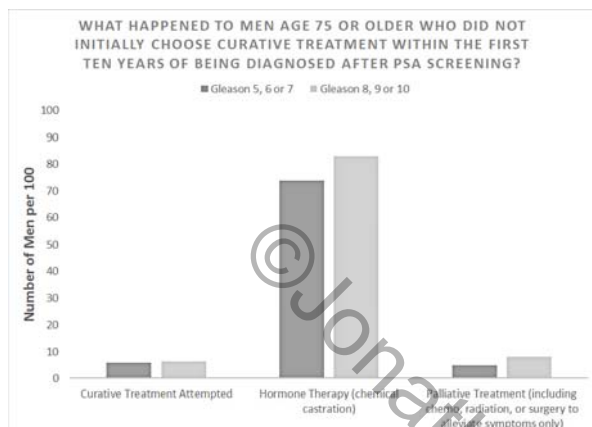
The JAMA Network

## From: Outcomes of Localized Prostate Cancer Following Conservative Management

JAMA. 2009;302(11):1202-1209. doi:10.1001/jama.2009.1348



## Fates other than death, should we screen?

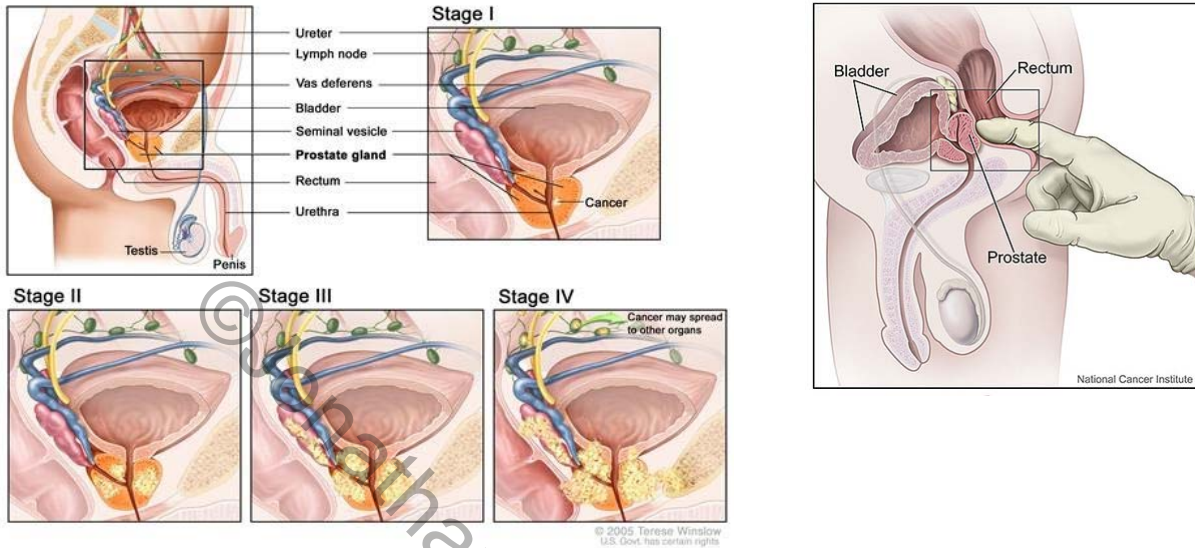


## PSA – Prostate Specific Antigen

Prostate-specific antigen, or **PSA**, is a protein produced by cells of the prostate gland. The **PSA** test measures the level of **PSA** in a man's blood. For this test, a blood sample is sent to a laboratory for analysis. The results are usually reported as nanograms of **PSA** per milliliter (ng/mL) of blood.

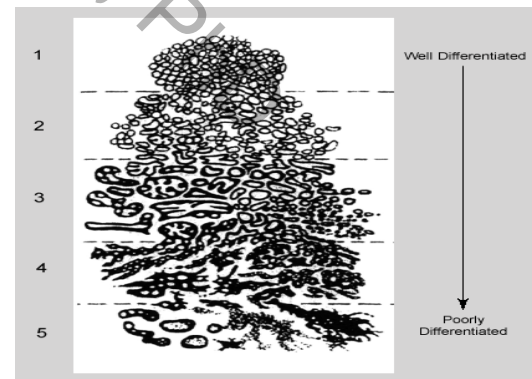


# T-Staging



## Gleason Grading System

- Describes the appearance of the cancerous prostate tissue
- Gleason Sum
  - sum of the 2 Gleason grades (range 1-5) assigned to the 2 most prevalent glandular patterns of the tumor cells
  - ranges from 2-10
  - modified: includes most malignant grade
- Upgrading may occur depending on specimen
- Intraobserver variability in assigning Gleason sum occurs



Gleason DF. In: Tannenbaum M, ed. *Urologic Pathology: The Prostate*. Philadelphia, Pa: Lea & Febiger; 1977:171-197.

Glodé LM. In: *Advances in Internal Medicine*. Vol 45. St. Louis, Mo: Mosby Inc.; 2000.

## RISK STRATIFICATION

### Very Low:

- T1c
- Gleason score  $\leq 6$
- PSA  $<10$  ng/mL
- Fewer than 3 prostate biopsy cores positive,  $\leq 50\%$  cancer in any core
- PSA density  $<0.15$  ng/mL/g



ACTIVE SURVEILLANCE  
or  
Watchful Waiting

### Low:

- T1-T2a
- Gleason score  $\leq 6$
- PSA  $<10$  ng/mL



ACTIVE SURVEILLANCE  
or  
Any type of monotherapy:

- Surgery
- EBRT
- Brachy

### Intermediate:<sup>e,n</sup>

- T2b-T2c or
- Gleason score 7 or
- PSA 10–20 ng/mL



- Active Surveillance (select pts)
- Any type of monotherapy:
  - Surgery
  - EBRT
  - Brachy
- Combined Modality
  - EBRT + ADT
  - EBRT + Brachy
  - Surgery + EBRT
  - Surgery + EBRT + ADT

### High:<sup>e</sup>

- T3a or
- Gleason score 8–10 or
- PSA  $>20$  ng/mL



- Combined Modality
  - EBRT + ADT
  - EBRT + Brachy
  - Surgery + EBRT
  - Surgery + EBRT + ADT

### Very High:

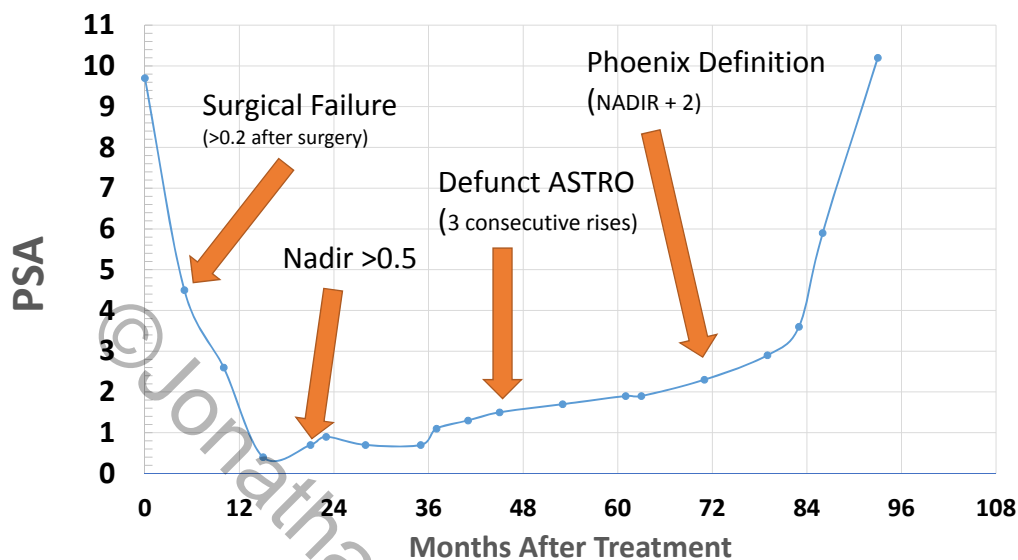
- T3b-T4
- Primary Gleason pattern 5 or
- $>4$  cores with Gleason score 8–10



## Outcomes Definitions

- Biochemical Failure
  - After surgery, PSA  $\geq 0.2$
  - After EBRT, the nadir PSA + 2
  - After EBRT, 3 consecutive rises (defunct ASTRO definition)
  - After Brachy...no agreed upon definition (some like  $>0.5$ )
- Freedom from progression = not finding any type of evidence of cancer recurrence i.e. biochemical, clinical or imaging
- Cause-specific-survival=death from prostate cancer
- Overall survival = Death from any cause

## Biochemical Failure – Apples and Oranges?



## The Menu... a few years ago





## The Menu... Now

Diagnostics		Treatments	
RECTAL EXAM	\$10 <i>Do I have to?</i>	EXPECTANT MANAGEMENT	\$0.00 <i>just let nature take its course</i>
PSA BLOOD TEST	\$80 <i>Find your cancer 12 years before you need to</i>	ACTIVE SURVEILLANCE	\$35,000 <i>getting biopsied every year or two won't hurt...</i>
BONE SCAN	\$1,500 <i>Great for high risk cancers, one of our most unnecessarily ordered dishes!</i>	GRANDPAS OLD-FASHIONED PROSTATECTOMY	\$12,000 <i>Grandmas can finally sleep at night</i>
TRUS BIOPSY	\$800 <i>Hope the nerve block worked...otherwise bite down on this wooden spoon</i>	ROBOTIC PROSTATECTOMY	\$25,000 <i>No better outcome than laparoscopic, but it sure brings in the customers</i>
CT SCAN	\$400 <i>Great scan to give a negative result so one can book the OR with a clear conscience</i>	INTENSITY MODULATED RADIATION	\$45,000 <i>Great value for those who own the machine. Add Image Guidance for \$8,000 more</i>
MRI PROSTATE/PELVIS	\$1200 <i>Excellent Detail...Does it change outcome?</i>	STEREOTACTIC BODY RADIATION	\$35,000 <i>Possibly better than IMRT, prepare to battle and lose to insure</i>
4K SCORE	\$Market Price <i>Make an elevated PSA screen even more expensive</i>	PROTON RADIATION	\$90,000 <i>Great for those people who fail to sales pitches</i>
MYRIAD PROLARIS	\$Market Price <i>Prognostic information from bx and surg path with no proof of change in outcome yet</i>	SEED BRACHYTHERAPY	\$12,000 <i>Convenient, effective, requires skill</i>
GENOME-DX DECIPHER	\$Market Price <i>Helps you decide on Adjuvant RT. Too bad only 3% of urologists consider adjuvant now</i>	HDR BRACHYTHERAPY	\$30,000 <i>2 sessions used to be effective, until reimbursement went down and we learned 3 is better</i>
GENOMICHEALTH ONCOTYPE DX	\$Market Price <i>Can predict surgical path from biopsy path, but does Gleason still matter after surgery?</i>	Hormone Therapy	\$50,000 <i>Who needs a cure when we can ruin quality of life and let people live on?</i>
PET SCANS	\$Market Price <i>Your choice of FDG, CHOLINE-11, PROSTASCINT, or 18F-SODIUM FLUORIDE The ultimate for fans of the Will-Rogers Phenomenon!</i>	The Kitchen Sink Combo	\$130,000 <i>Combine any 2 or 3 above!</i>
		Cryotherapy or HIFU	\$30,000 <i>Burn it or freeze it, just keep em away from Rad Onc</i>

## Biases

Kim et al

Medical Care • Volume 52, Number 7, July 2014

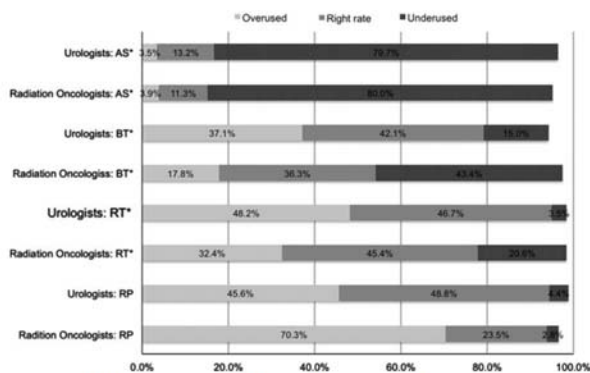
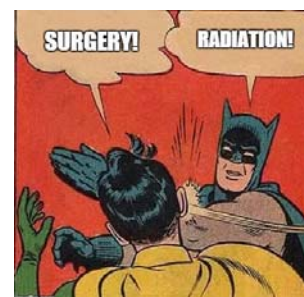


FIGURE 2. Perceptions about current rates of different types of primary therapy for localized prostate cancer by physician specialty. \* $P < 0.05$ . AS indicates active surveillance; BT, brachytherapy; RT, radiation therapy; RP, radical prostatectomy.



# How does specialist multidisciplinary consultation alter the pattern?

## ORIGINAL INVESTIGATION

### Physician Visits Prior to Treatment for Clinically Localized Prostate Cancer

Thomas L. Jang, MD, MPH, Justin E. Bekelman, MD, Yihai Liu, MS, Peter B. Bach, MD, MAPP, Ethan M. Balk, MD, MS, Elena B. Elkin, PhD, Michael J. Zelefsky, MD, Peter T. Saunders, MD, Colin B. Begg, PhD, Deborah Schrag, MD, MPH

Arch Intern Med. 2010;170(5):440-450.  
doi:10.1001/archinternmed.2010.1

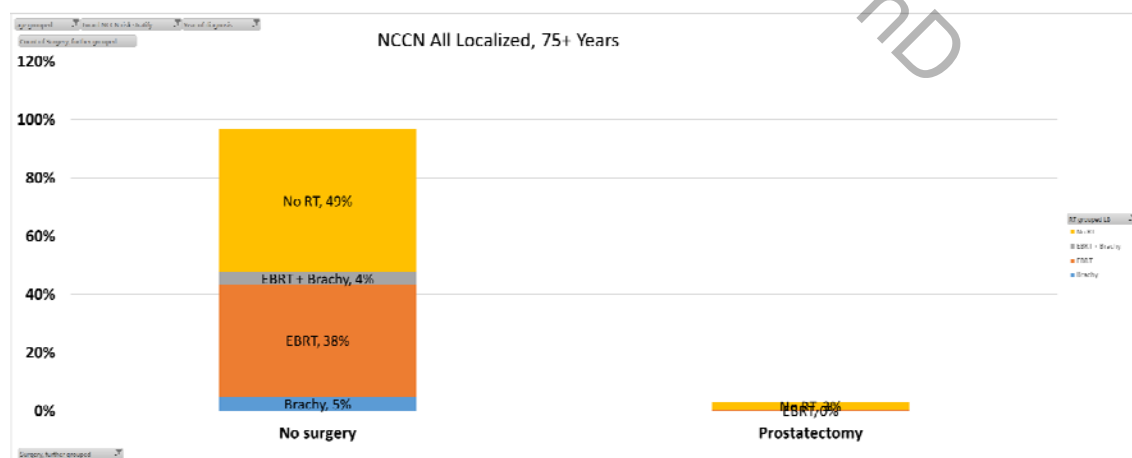
**Conclusions:** Specialist visits relate strongly to prostate cancer treatment choices. In light of these findings, prior evidence that specialists prefer the modality they themselves deliver and the lack of conclusive comparative studies demonstrating superiority of one modality over another, it is essential to ensure that men have access to balanced information before choosing a particular therapy for prostate cancer.

Table 3. Primary Treatment for Medicare Beneficiaries Diagnosed as Having Clinically Localized Prostate Cancer, According to Specialist Consulted and Patient Age

Specialist	Primary Treatment, % of Patients			
	Radical Prostatectomy	Radiation Therapy	Primary Androgen Deprivation Therapy	Expectant Management
Consultation with urologist only (n=42 309), patient age, y				
65-69 (n=12 248)	70.1	4.3	7.2	18.4
70-74 (n=10 751)	44.6	7.8	15.8	30.8
75-79 (n=8927)	10.0	7.1	35.3	46.6
80-84 (n=8607)	1.0	2.2	50.4	46.3
≥85 (n=3776)	0.5	0.5	55.3	43.6
All ages (n=42 309)	33.9	6.1	20.8	39.1
Consultation with urologist and XRT oncologist (n=37 540), patient age, y				
65-69 (n=10 604)	15.2	78.0	3.1	3.8
70-74 (n=14 050)	7.3	84.8	3.8	4.1
75-79 (n=9965)	2.7	86.7	5.5	5.2
80-84 (n=2464)	1.3	81.2	9.9	7.7
≥85 (n=428)	1.2	84.8	23.1	11.2
All ages (n=37 540)	7.8	82.3	4.6	4.6
Consultation with urologist and medical oncologist (n=2329), patient age, y				
65-69 (n=601)	53.1	17.1	14.0	15.8
70-74 (n=857)	37.6	21.3	17.4	23.1
75-79 (n=545)	9.4	24.2	35.4	31.0
80-84 (n=334)	1.2	7.5	54.5	36.8
≥85 (n=192)	1.0	0.5	59.9	38.5
All ages (n=2329)	26.8	17.4	29.5	26.3
Consultation with urologist, XRT and medical oncologist (n=2910), patient age, y				
65-69 (n=990)	19.8	70.2	5.2	4.0
70-74 (n=1047)	8.4	79.5	7.2	4.9
75-79 (n=705)	3.1	81.5	8.7	6.7
80-84 (n=205)	0.4	76.2	17.0	6.4
≥85 (n=43)	0.0	55.8	32.6	11.6
All ages (n=2910)	9.5	76.5	8.4	5.5

## The Effect of Age

NCCN Low, Int, High and Very High (2010-2011)



Enough about bias....  
What do the data show?

**Low:**

- T1-T2a
- Gleason score  $\leq 6$
- PSA  $<10$  ng/mL

↓

**ACTIVE SURVEILLANCE**  
or  
**Any type of monotherapy:**

- Surgery
- EBRT
- Brachy



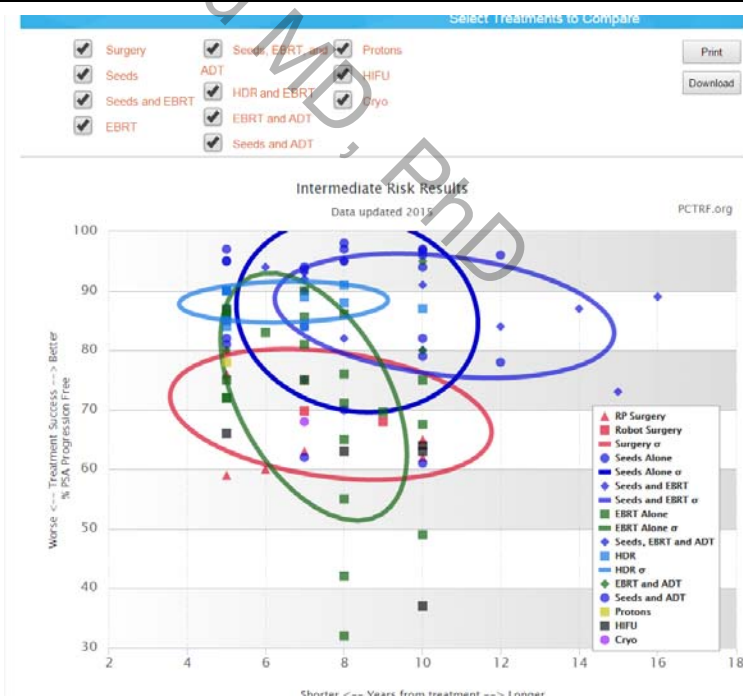
Enough about bias....  
What do the data show?

**Intermediate:<sup>e,n</sup>**

- T2b-T2c or
- Gleason score 7 or
- PSA 10–20 ng/mL

↓

- Active Surveillance (select pts)
- Any type of monotherapy:
  - Surgery
  - EBRT
  - Brachy
- Combined Modality
  - EBRT + ADT
  - EBRT + Brachy
  - Surgery + EBRT
  - Surgery + EBRT + ADT



Enough about bias....

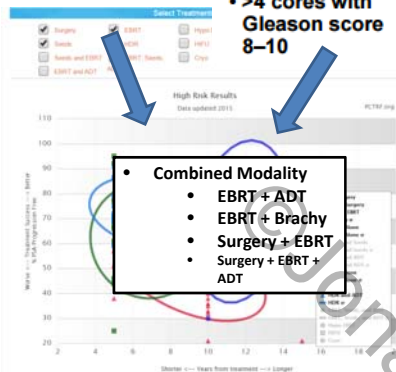
What do the data show?

High:®

- T3a or
- Gleason score 8–10 or
- PSA >20 ng/mL

Very High:

- T3b-T4
- Primary Gleason pattern 5 or
- >4 cores with Gleason score 8–10



## Schema (primary intervention period)

How about a prospective randomized trial?

DE-EBRT  
boost ARM

LDR-PB  
boost ARM

8m of neo-adjuvant ADT  
LHRH agonist +4 weeks\* of NSAA

q2-m CBC, PSA and TTT  
Clinic visits at T+4m and T+8m  
toxicity, IPSS and QOL

EPNI 46 Gy 23# at T-8m  
prostate, SV and regional nodes

DE-EBRT 32 Gy boost  
(78 Gy/39 total)

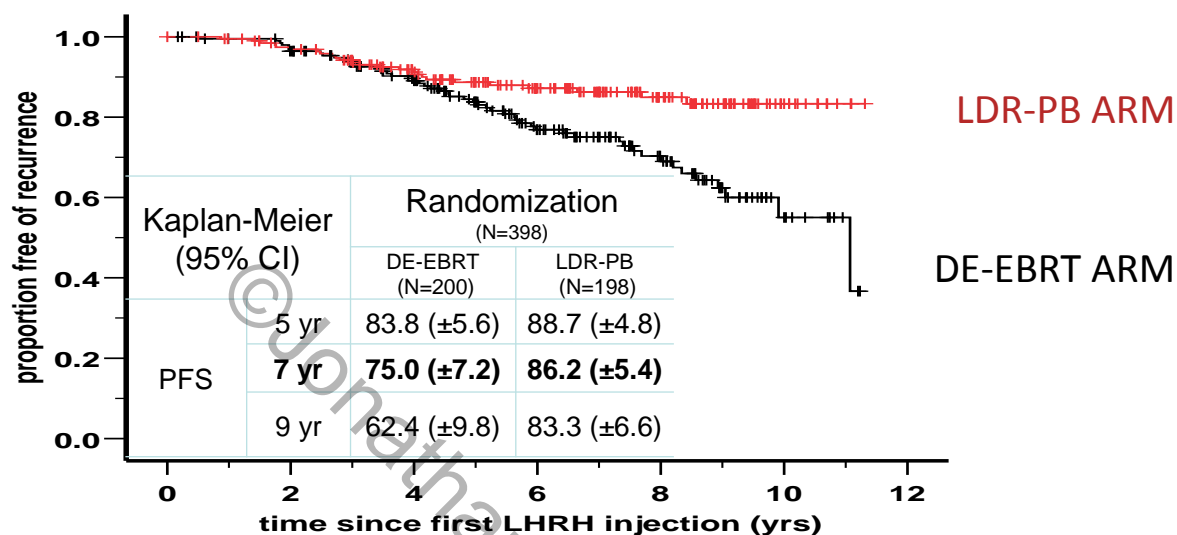
LDR-PB boost  
115 Gy BT

Clinic visits at T+12m T+18m

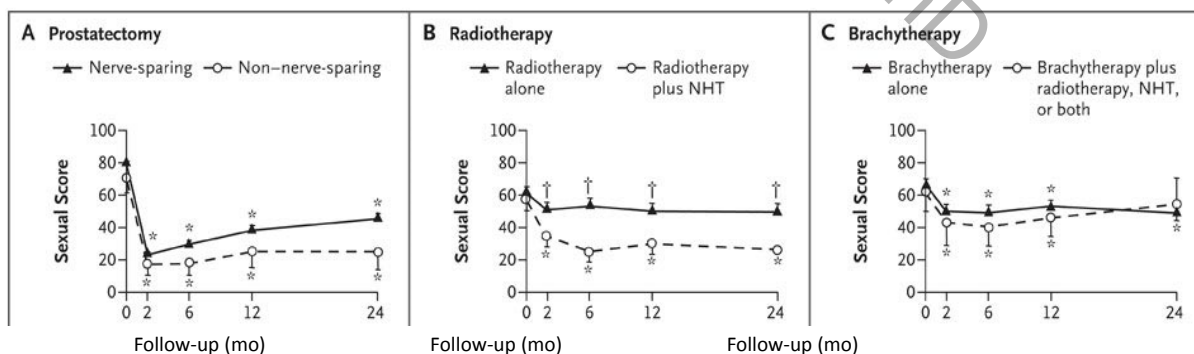
Assessment of acute toxicity  
IPSS, QoL  
CBC, PSA and TTT at T+12m  
T+15m and T+18m

## Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint



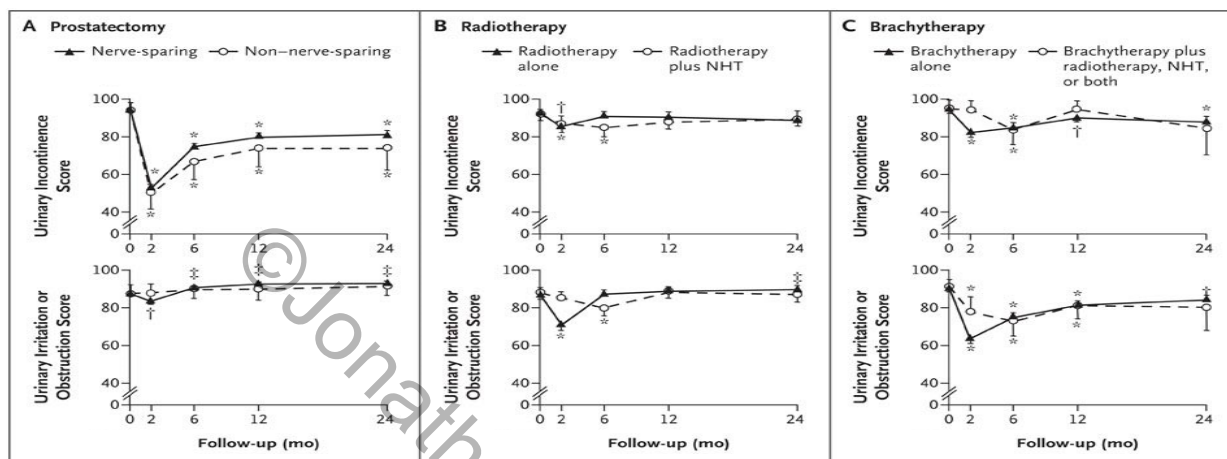
## Effects on Sexual Function...acute phase



NHT = neoadjuvant hormone therapy  
Sanda MG, et al. *N Engl J Med*. 2008;358:1250.

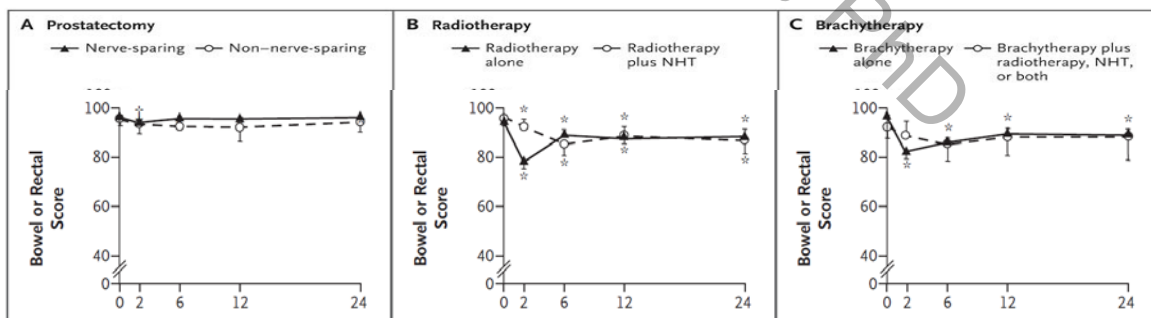


## Effects on Urinary Function...acute phase



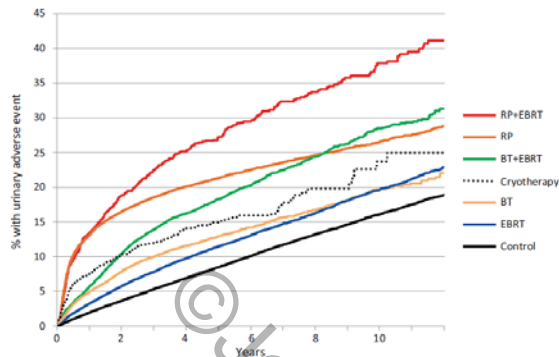
Sanda MG, et al. *N Engl J Med*. 2008;358:1250.

## Effects on Bowel Function



Sanda MG, et al. *N Engl J Med*. 2008;358:1250.

## What about long term effects (urinary)?



	Number of individuals at risk					
	0 yr	2 yr	4 yr	6 yr	8 yr	10 yr
RP+EBRT	1557	897	607	399	251	163
RP	26 790	16 922	12 571	9040	6084	4030
BT+EBRT	11 835	7710	5134	3651	1275	456
Cryotherapy	2115	1096	537	213	72	— <sup>a</sup>
BT	44 318	27 438	18 049	11 006	5761	2974
EBRT	14 259	9529	6236	3380	1280	452
Control	144 816	77 348	48 457	31 287	20 729	13 262

<sup>a</sup>Cell masked for n < 11, in accordance with National Cancer Institute guidelines.

### Propensity-weighted Long-term Risk of Urinary Adverse Events After Prostate Cancer Surgery, Radiation, or Both

Stephanie L. Jarosek<sup>a,\*</sup>, Beth A. Virnig<sup>b</sup>, Haitao Chu<sup>c</sup>, Sean P. Elliott<sup>b</sup>

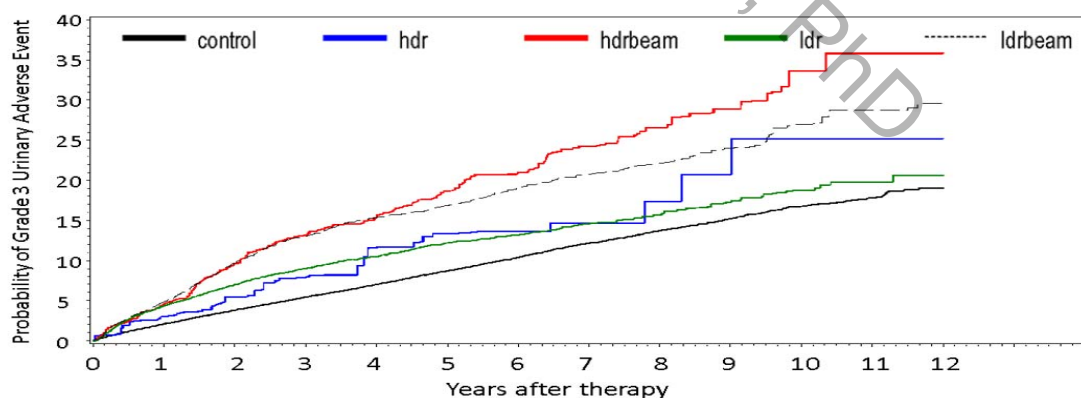
<sup>a</sup>Department of Urology, Medical School, University of Minnesota, Minneapolis, USA; <sup>b</sup>Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, USA; <sup>c</sup>Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, USA

EUROPEAN UROLOGY 67 (2015) 273–280

### Events of interest

were procedures for bladder spasm, cystitis, hematuria, incontinence, urinary fistula, ureteral obstruction, benign prostatic hypertrophy (BPH), and urethral stricture/BNC

## Tward et al. submitted



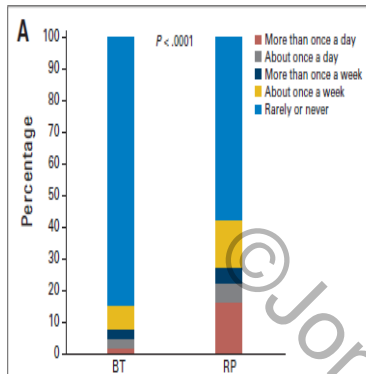
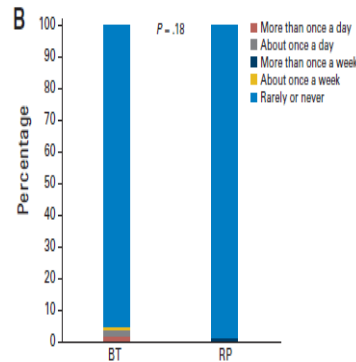
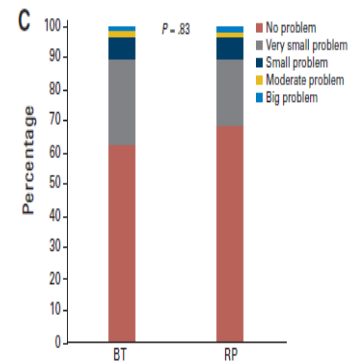
	Number at Risk Years After Therapy										
	0	1	2	3	4	5	6	7	8	9	10
control	93748	66008	48863	36338	26615	19075	13121	8662	5695	3275	1522
hdr	493	381	298	235	193	164	132	84	51	24	13
hdr + beam	1842	1434	1091	829	645	477	339	240	162	93	46
ldr	11765	9239	7123	5576	4263	3211	2303	1597	1017	574	273
ldr + beam	6971	5413	4275	3378	2644	2040	1456	991	628	363	173

## 1 randomized trial on side effects...

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

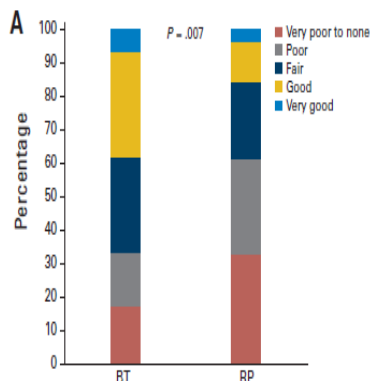
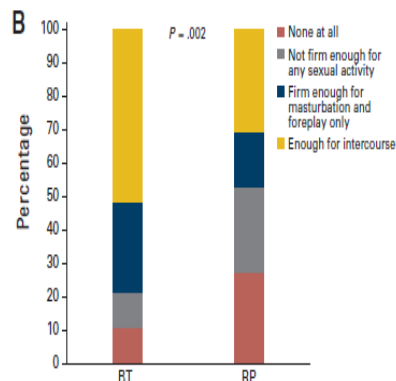
Comparison of Health-Related Quality of Life 5 Years After  
SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation  
Intervention TrialJames M. Cook, Alison Cohen-Soraggi, Kiro Wadwa, Clarence Ma, Sharon Fung, Shabbir Abbasi,  
Michael Jewen, and Neil FinkelsteinHow often do you  
have urinary Leakage?How often do you  
have pain and burning with  
Urination?How often do you  
have weak stream or  
Emptying?

## 1 randomized trial on side effects...

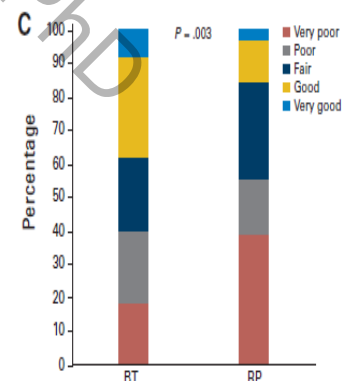
VOLUME 29 • NUMBER 2 • FEBRUARY 1, 2011

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ORIGINAL REPORT

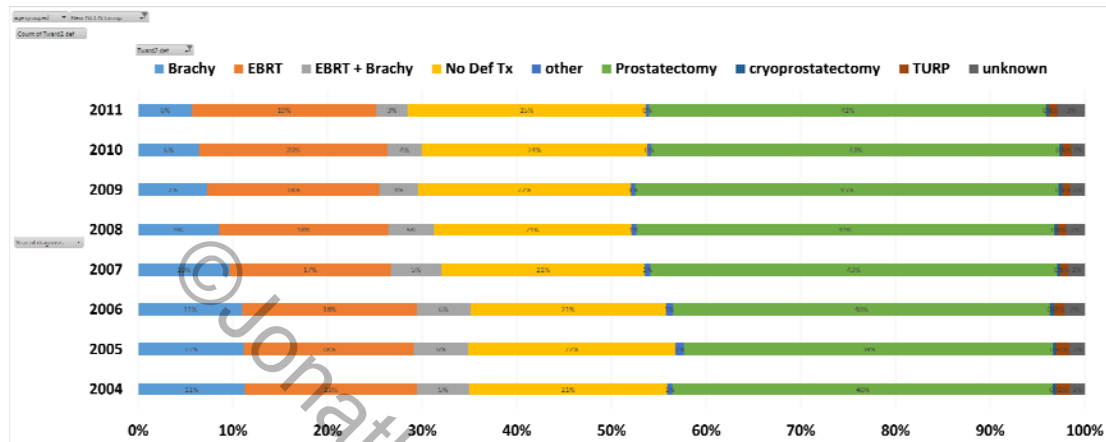
Comparison of Health-Related Quality of Life 5 Years After  
SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation  
Intervention TrialJames M. Cook, Alison Cohen-Soraggi, Kiro Wadwa, Clarence Ma, Sharon Fung, Shabbir Abbasi,  
Michael Jewen, and Neil FinkelsteinThe ability to have an  
erection?

The quality of erections?

The ability to function  
sexually?

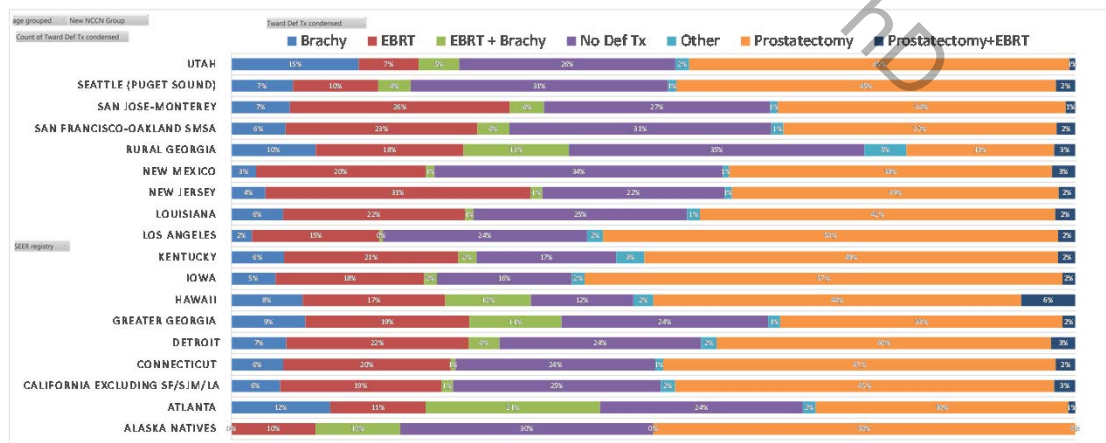
# Time Trends

NCCN Low, Int, High, Very High



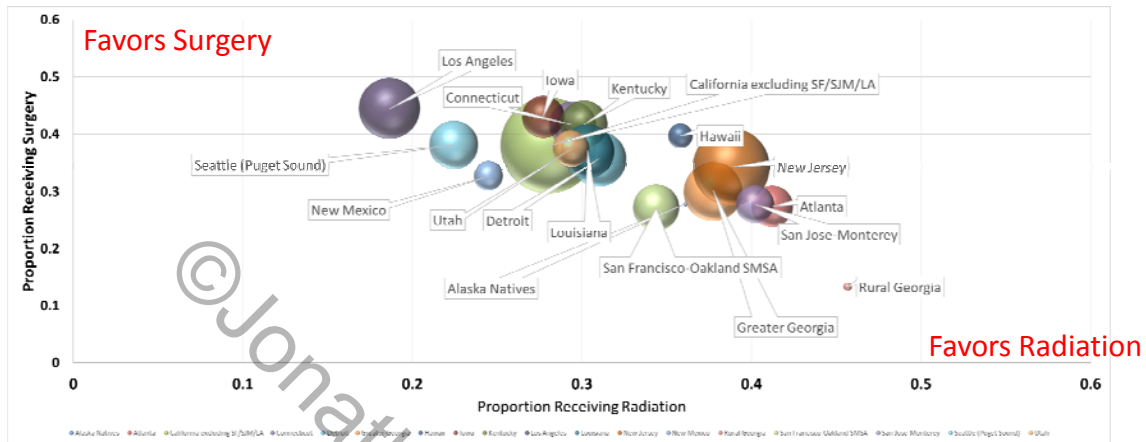
# Regional Variation

NCCN Low, Intermediate, High Risk 2010-2011



# All Risk Groups

2010-2011

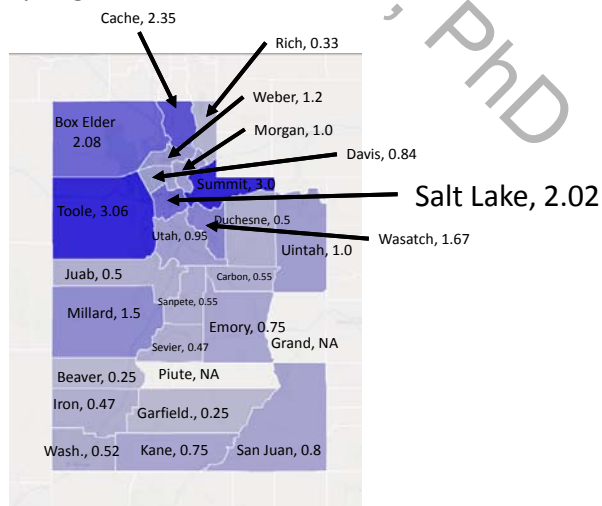


## Ratio of Surgery to Radiation

Very Regional Differences



Value 0.250 1.63 3.00







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## Questions?

