The Prostate and its Challenges in the Aging Male

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Goals

- Review the basics of prostate anatomy and function
- Discuss BPH and etiology and management of lower urinary tract symptoms (LUTS)
- Discuss prostate cancer screening and management
- Answer your questions!

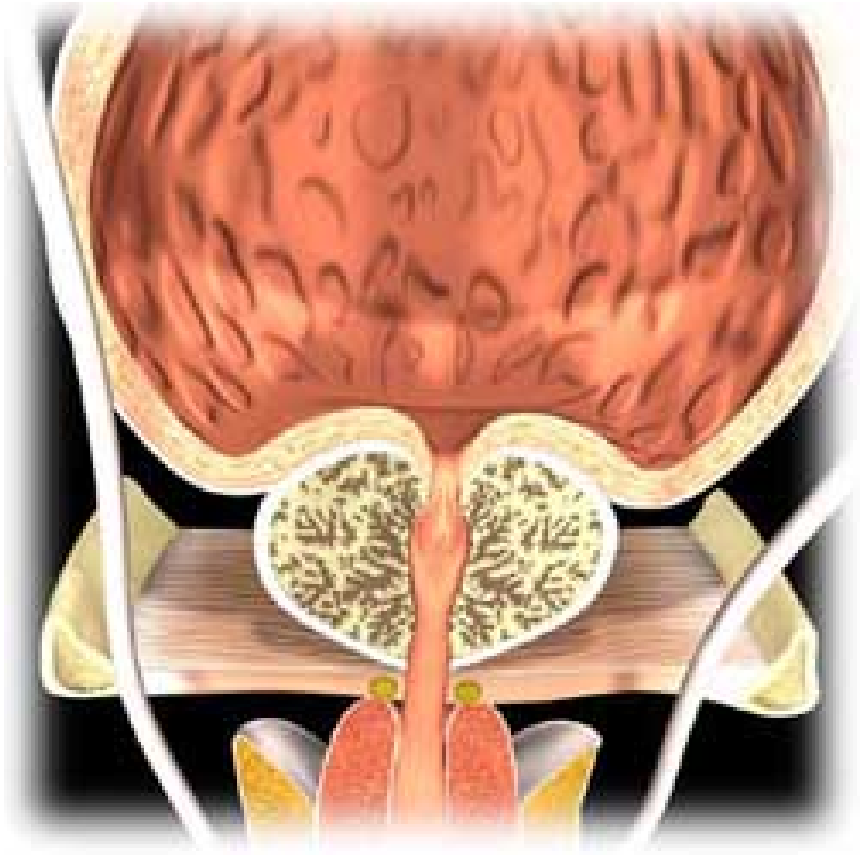
Case 1

- 68 year old retired teacher with urinary frequency, urgency and nocturia x 4.
- He has had these symptoms for more than 3 years, but he thought it is normal, since his friends also complain of the same symptoms.
- Presently, symptoms worsened to the point that it affected his activities of daily living

Case 1
(continued)

- He has no significant past medical history
- He has no history of trauma or sexually transmitted diseases
- Social History:
  - Married
  - Two children
  - Drinks 2 glasses of wine/day
  - Quit smoking 15 years ago after 30 pack year smoking
- Family History:
  - No family history of prostate cancer

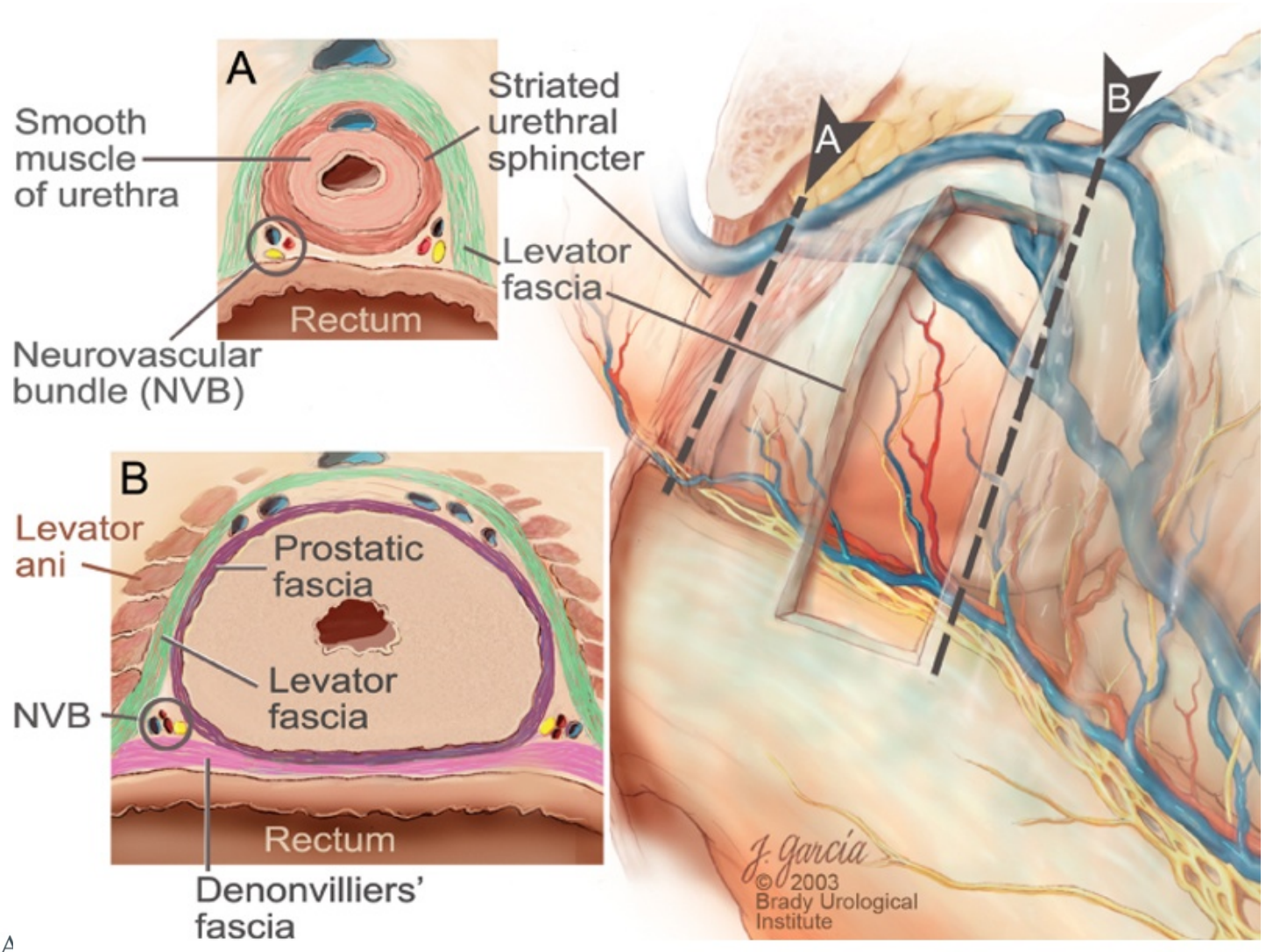
Anatomy



- Prostate is a chestnut shape/size structure, located in front of the rectum, just below the bladder. It surrounds the last segment of male urethra:

  the prostatic urethra.

Anatomy



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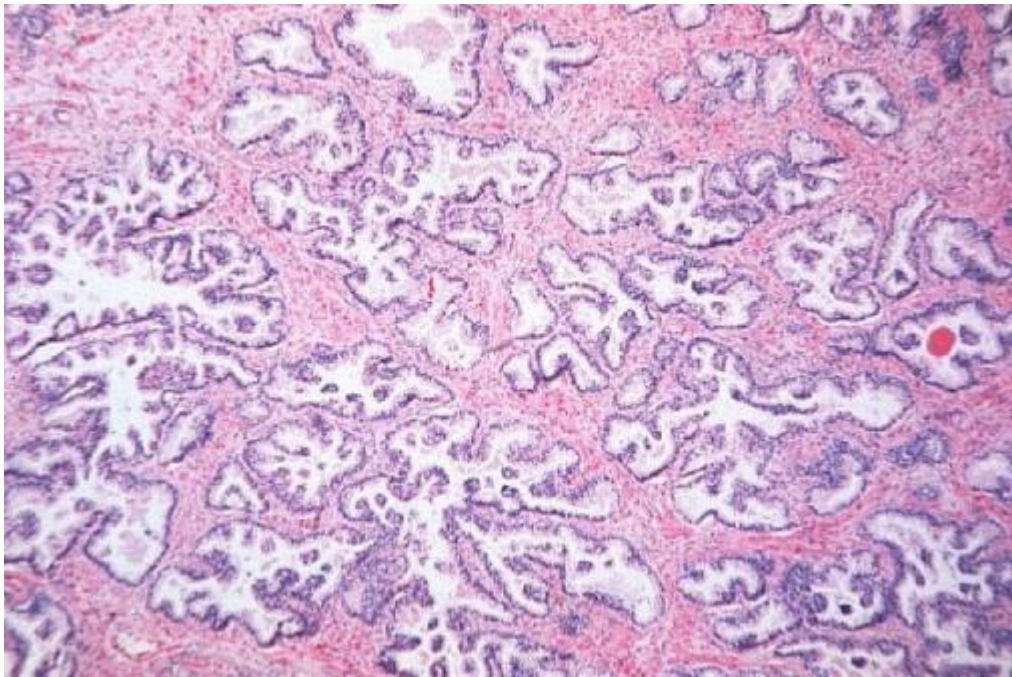
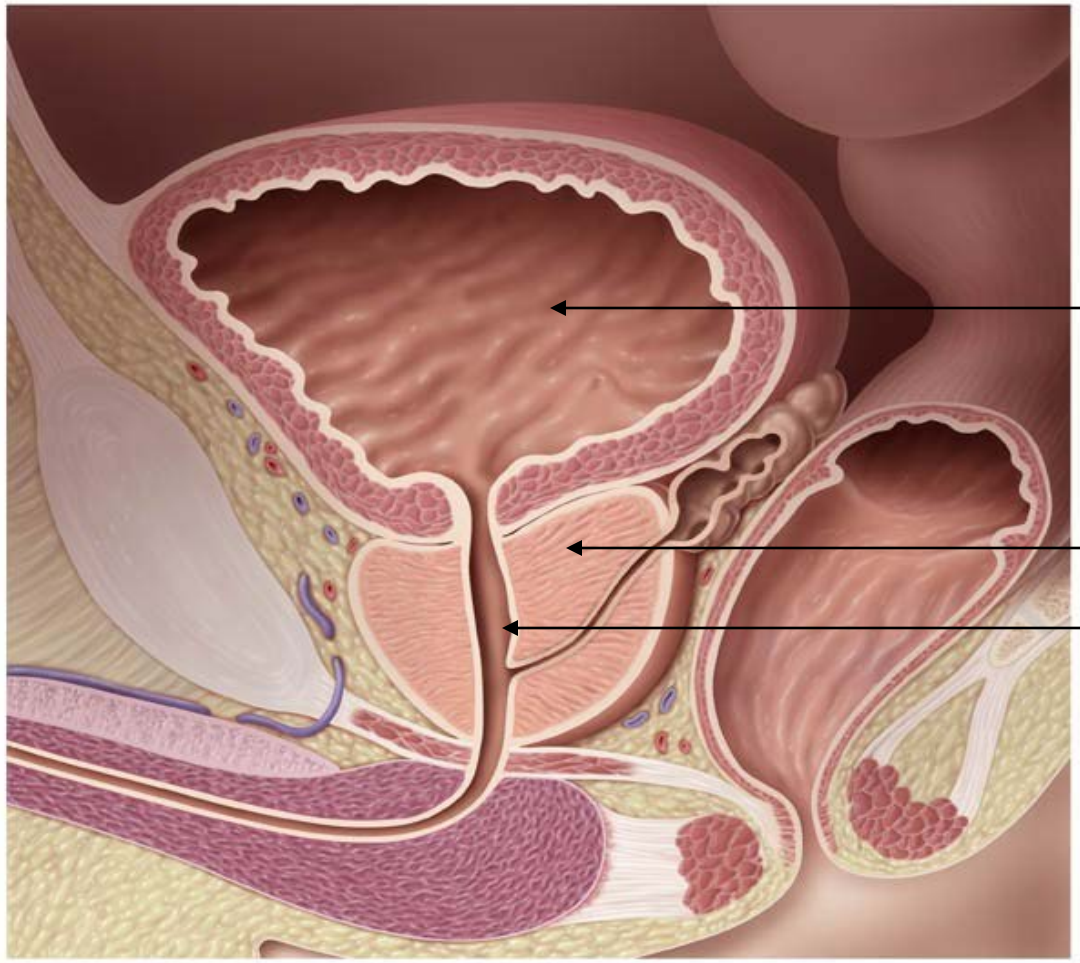
Campbell-Walsh Urology, 2007

Prostate Structure

- **Epithelial Cells**
  - Glandular epithelial cells
  - Basal Cells
  - Neuroendocrine cells
- **Stromal Cells (30%)**
  - Fibroblasts
  - Smooth muscle cells
- Stroma and tissue matrix.
  - A biologic scaffolding or residual skeletal structure that organizes and locates cells

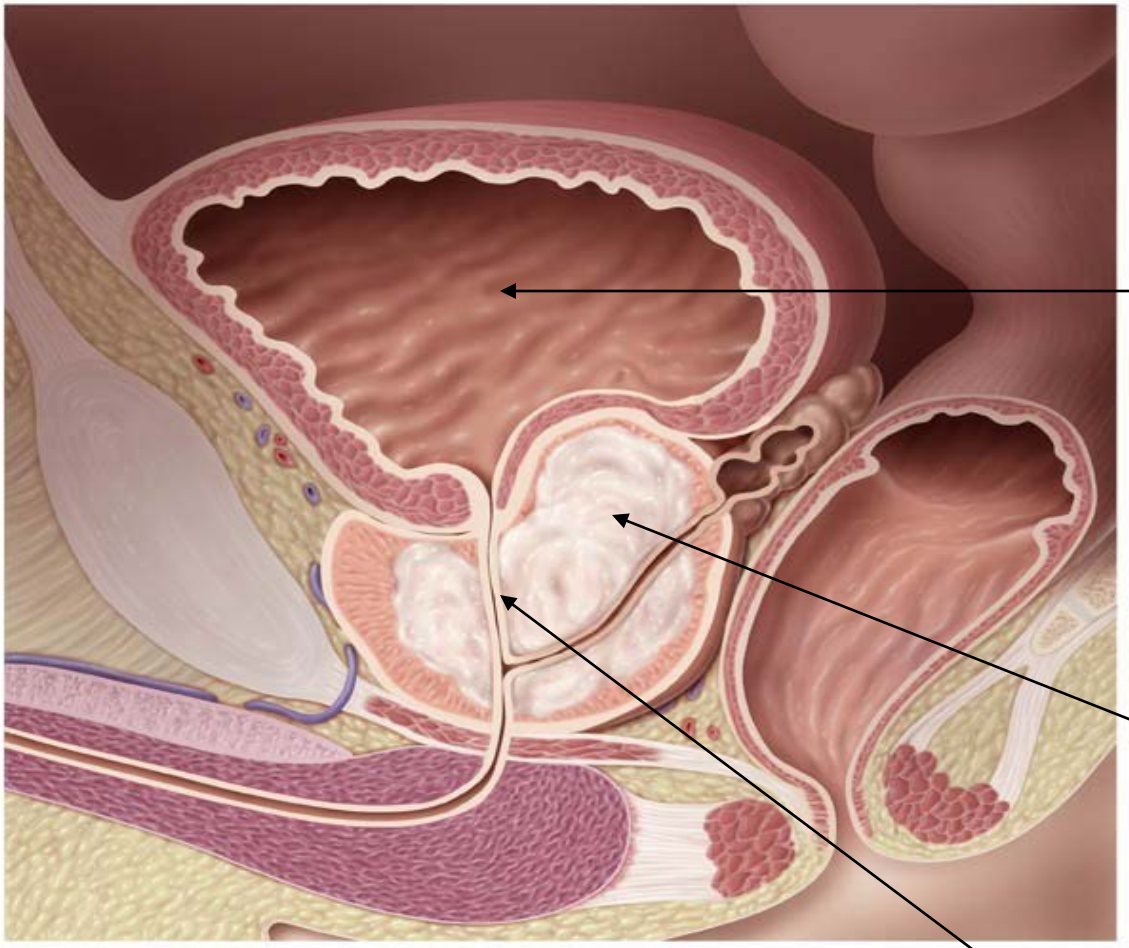


Normal Prostate Anatomy



Prostate Exam

- Prostate is non nodular, non tender
- Prostate is measured to be 3.5 x 4 cm



Epidemiology

- Urologic Diseases in America BPH* project suggests: Progressive increase in prevalence of moderate-to-severe lower urinary tract symptoms, rising to nearly 50% by the eight decade

- 90% of men have some type of lower urinary tract symptoms between 45-80 years of age

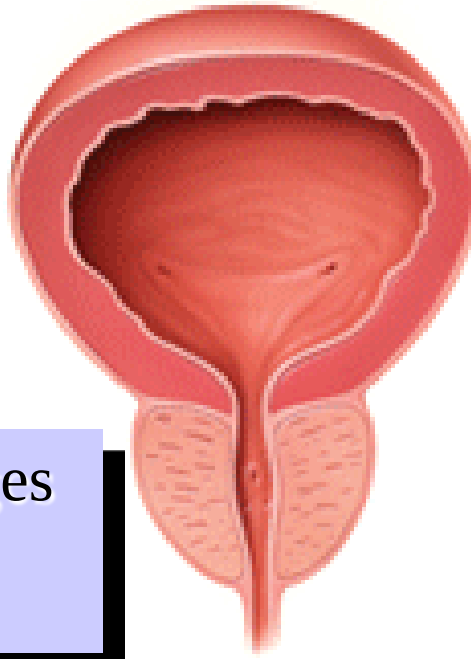
*BPH=Benign prostatic hyperplasia

Lower urinary tract symptoms – A constellation of voiding and storage symptoms

Storage symptoms	Voiding symptoms	Post-micturition
Urgency	Hesitancy	Post-void dribble
Frequency	Poor flow	Sensation of incomplete emptying
Nocturia	Intermittency	
Incontinence	Straining	
Other incontinence	Terminal dribble	

Benign Prostatic Hyperplasia Pathophysiology

Increased Urethral resistance (voiding symptoms)



- **Slow stream**
- **Dribbling**
- **Hesitancy**

Obstruction-induced detrusor changes (Storage symptoms)

- **Frequency**
- **Urgency**
- **Nocturia**

- **Not all urinary symptoms are related to BPH**

- History:
  - Nature and duration of LUTS
    - Frequency
    - Urgency
    - Hesitancy
    - Intermittency
    - Weak stream
    - Straining
    - Incomplete emptying
    - Incontinence
    - Nocturia
  - Timing of symptoms
  - Dietary – caffiene, EtOH, fluid intake

International Prostate Symptom Score (I-PSS)

Patient Name: _____ **Date of birth:** _____ **Date completed** _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	**1 Time**	**2 Times**	**3 Times**	**4 Times**	**5 Times**	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

AUA-7 Symptom Index for Benign Prostatic Hyperplasia

	Not at All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?			2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0			3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0				4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1				5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2			5
6. Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3		
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 time	2 times	3 times	4 times	5 or more times

Bladder Emptying

Frequency

Intermittency

Urgency

Decreased flow

Straining

Nocturia

AUA Symptom Score = sum of questions A1–A7 = _____

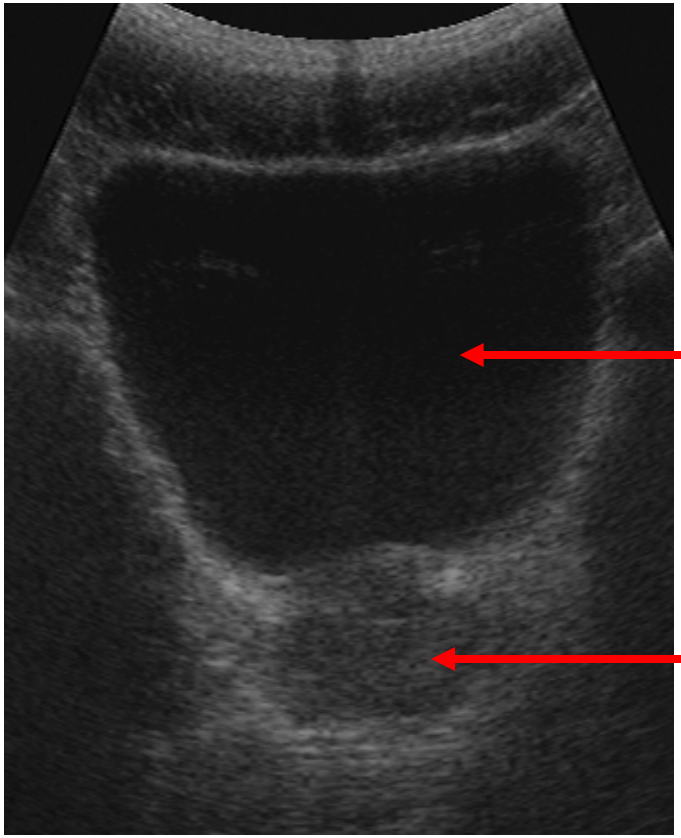
Quality of life due to urinary symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Lower urinary tract symptom evaluation

- H & P
  - Body mass index, Obesity?
  - Supra-pubic distension, dullness in percussion
  - External Genitalia
  - Rectal exam
- Symptom questionnaire
- U/A
- Serum
  - Creatinine?
  - PSA
- Optional:
  - Ultrasound estimate of post void residual volume (PVR)
  - Flow Rate Recording

- Physical Exam:
  - Suprapubic region for bladder distension
  - Motor and sensory function of perineum and lower extremities
  - DRE –
    - Anal sphincter tone
    - Prostate –
      - Size/volume
      - Consistency
      - Suspicion for prostate cancer
- Urinalysis: Hematuria or evidence of infection
- Serum PSA
- Frequency/Volume charts (voiding diary) when nocturia is predominant symptom

Bladder Ultrasound
Post Void Residual Assessment



Transabdominal ultrasound imaging of bladder

AUA-7 Symptom Index (Case 1)

	Not at All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	**1**	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	**4**	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	**0**	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	**4**	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	**2**	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	**0**	1	2	3	4	5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 time	2 times	**3** times	4 times	5 or more times

AUA Symptom Score = sum of questions A1–A7 = 14/35

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Case 1 (continued)

- AUA symptom index: 14/35
  quality of life score: 3/35
- Physical exam: unremarkable
- Post void residual: 10 cc
- Urinalysis: Unremarkable
- PSA: 2.8 ng/ml
- Creatinine 1.0 mg/dl

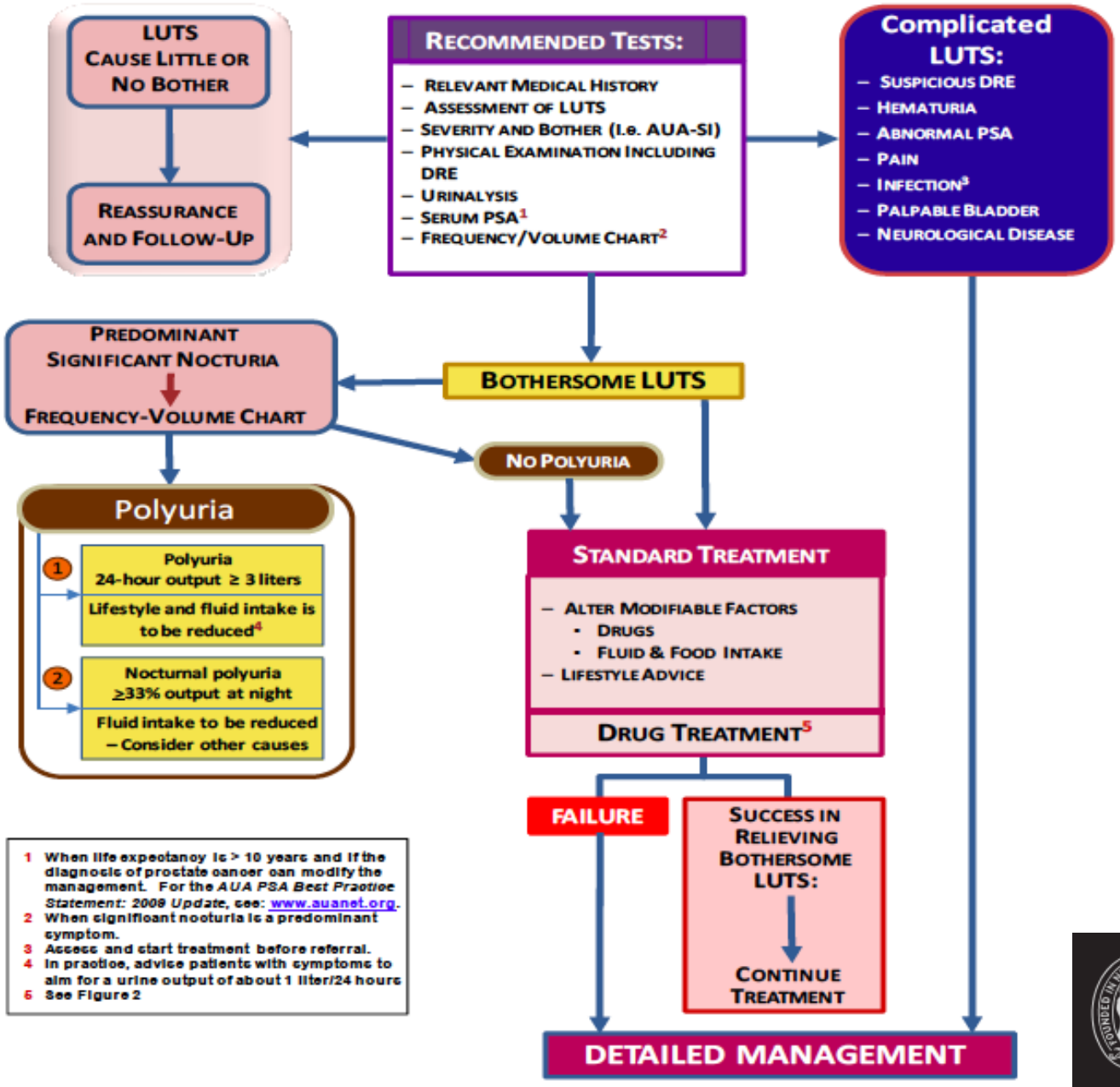
Treatment Options for BPH

- Watchful Waiting
- Medical Therapy
- Minimally Invasive Therapies
- Surgery (TURP / Laser)

Goals of Therapy
BPH/ lower urinary tract symptoms

- Relieve "bothersome" symptoms to improve quality of life
- Prevent acute urinary retention
- Preserve bladder and renal function

Basic Management of LUTS in Men



1 When life expectancy is > 10 years and if the diagnosis of prostate cancer can modify the management. For the *AUA PSA Best Practice Statement: 2009 Update*, see: www.auanet.org.
2 When significant nocturia is a predominant symptom.
3 Assess and start treatment before referral.
4 In practice, advise patients with symptoms to aim for a urine output of about 1 liter/24 hours
5 See Figure 2

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Frequency Volume Chart for men with *bothersome* LUTS

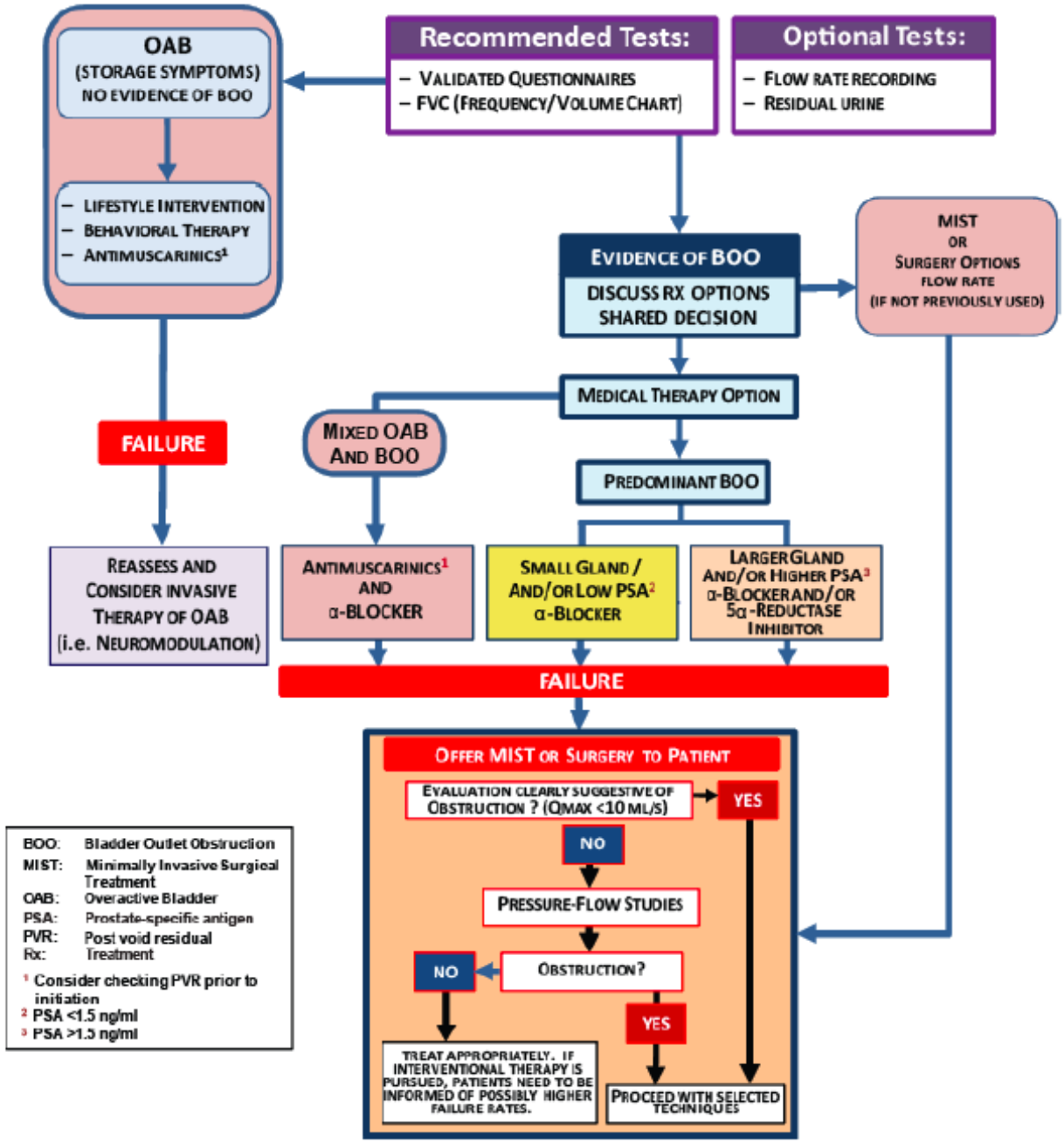
Voiding Diary						
	Intake					
Time	Type	Amount	Urge	Voided	Leak	Activity
8am	coffee	1 cup				
9[10]			X	X		
10[15]	water	1 cup				
10[30]					X	standing

Your doctor may ask you to keep a voiding diary to record the time and amount of urine leakage.

>30% of total urine output at night indicates nocturnal polyuria

Identifies excess alcohol or caffeinated drinks

Detailed Management for Persistent Bothersome LUTS after Basic Management



BOO:	Bladder Outlet Obstruction
MIST:	Minimally Invasive Surgical Treatment
OAB:	Overactive Bladder
PSA:	Prostate-specific antigen
PVR:	Post void residual
Rx:	Treatment

[1] Consider checking PVR prior to initiation
[2] PSA <1.5 ng/ml
[3] PSA >1.5 ng/ml

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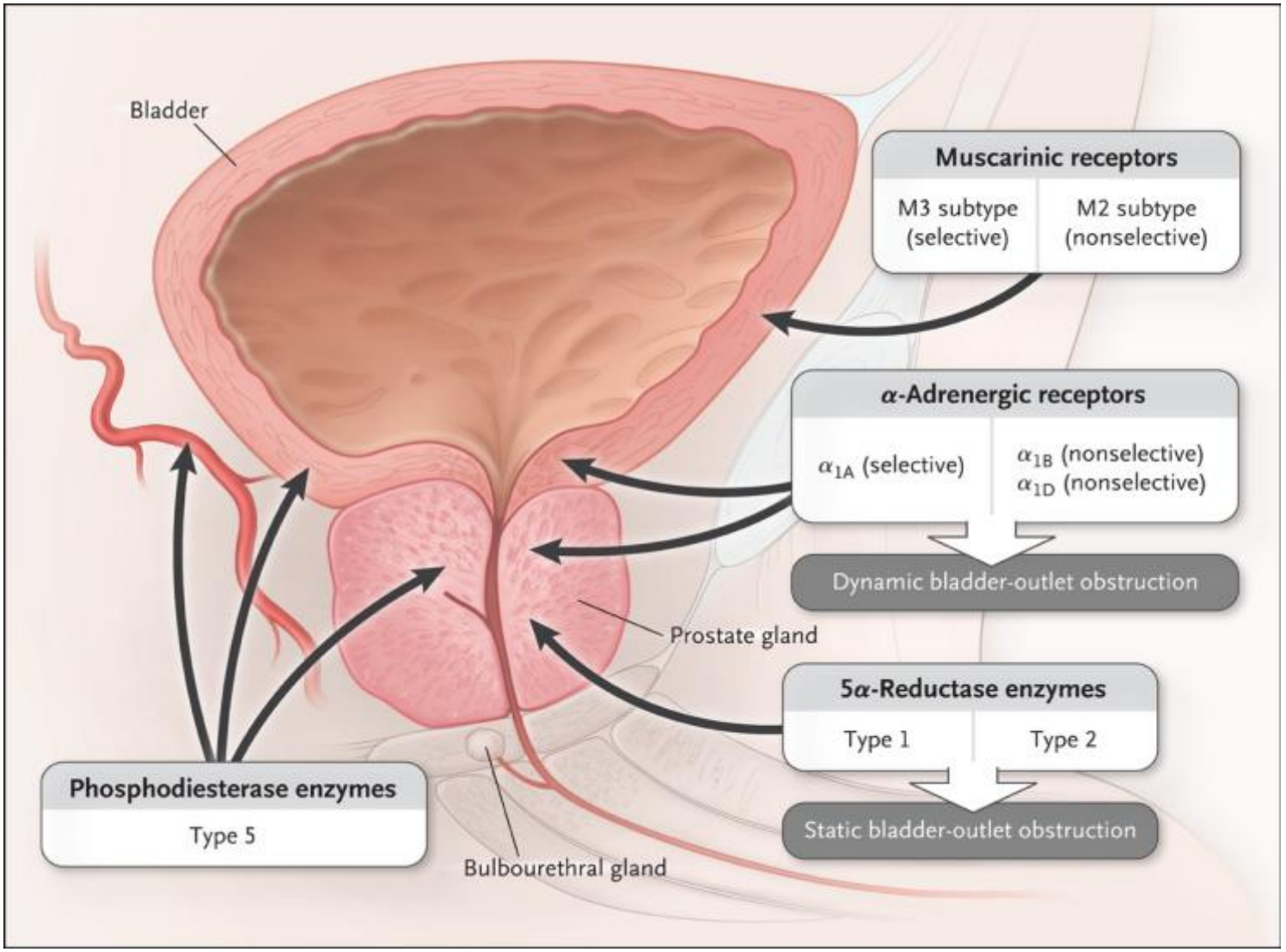
Table 1.1. Treatment alternatives for patients with moderate to severe symptoms of BPH

Watchful Waiting
Medical Therapies *Alpha-Blockers* - Alfuzosin - Doxazosin - Tamsulosin - Terazosin - Silodosin* *5- Alpha-reductase inhibitors (5-ARIs)* - Dutasteride - Finasteride *Combination Therapy* - Alpha blocker and 5-alpha-reductase inhibitor - Alpha blocker and anticholinergics *Anticholinergic Agents*
Complementary and Alternative Medicines (CAM)
Minimally Invasive Therapies - Transurethral needle ablation (TUNA) - Transurethral microwave thermotherapy (TUMT)
Surgical Therapies - Open prostatectomy - Transurethral holmium laser ablation of the prostate (HoLAP) - Transurethral holmium laser enucleation of the prostate (HoLEP) - Holmium laser resection of the prostate (HoLRP) - Photoselective vaporization of the prostate (PVP) - Transurethral incision of the prostate (TUIP) - Transurethral vaporization of the prostate (TUVP) - Transurethral resection of the prostate (TURP)

Mechanisms of Action and Targets for Intervention in Benign Prostatic Hyperplasia and Lower Urinary Tract Symptoms.



Sarma AV, Wei JT. N Engl J Med 2012;367:248-257.

The NEW ENGLAND JOURNAL of MEDICINE

Alpha Blockers

Tamsulosin, Terazosin, Doxazosin, Alfuzosin, Silodosin

Mechanism: block adrenoceptors on the bladder neck and the prostate and lead to relaxation of the muscle tone

Adverse effects:

Central actions→ orthostatic hypotension

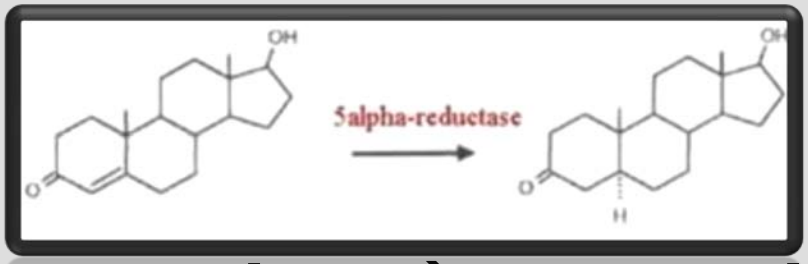
Caution:

- α-Blockers do not inhibit the growth or progression of BPH /lower urinary tract symptoms
- improvement of symptoms does not to reduce the risk of complications such as acute urinary retention or the need BPH-related surgery.

5α-Reductase Inhibitors

finasteride (Proscar, Propecia), dutasteride (Avodart)

Mechanism: Inhibition of 5α-reductase results in decreased conversion of testosterone to DHT



- Reduce prostate volume → response depends on: prostate size (PSA)

↓ risk of acute urinary retention or need for surgery

- Combination therapy with an alpha blocker leads to greater improvement (8%) in symptoms

Adverse effects: ↑ erectile dysfunction, ↓libido, breast tenderness/enlargement

Case 1

Tamsulosin and finasteride were started and at follow-up, 2 months later

- Significant improvement in his lower urinary tract symptoms
- AUA symptom index: 6/35 with QOL score of 2/6
- Post void residual: 5 cc

→ The patient was told to return in one year for follow up, but he failed to keep his appointment because of relocation

Case 1

- Two years later, he presented to the ER with nausea, lack of energy and worsening lower urinary tract symptoms.

- He reports worsening of his symptoms, including more frequency and urgency, some urge incontinency and slow urinary flow. He has problem with post void dribbling and significant hesitancy.

AUA-7 Symptom Index (Case 1)

	Not at All	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	**5**
2. Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	**4**	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	**4**	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	**4**	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	**5**
6. Over the past month, how often have you had to push or strain to begin urination?	0	**1**	2	3	4	5
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	None	1 time	2 times	3 times	**4 times**	5 or more times

AUA Symptom Score = sum of questions A1–A7 = 27/35

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Case 1 (continued)

- PMHx: No change
- Meds: Tamsulosin and finasteride
- Exam:
  BP: 170/90; PR: 90; RR: 22; T: 98.9
- Pertinent findings in exam:

  Abdomen: palpable, mildly tender midline mass at the level of umbilicus that is dull on percussion, mild bilateral flank tenderness.

  GU: Normal Phallus, scrotal exam.

  Rectal exam: Normal tone anal sphincter. 4.5 x 5 cm prostate without nodularity or tenderness

Case 1 (continued)

- Exam:
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  GU: Normal Phallus, scrotal exam.

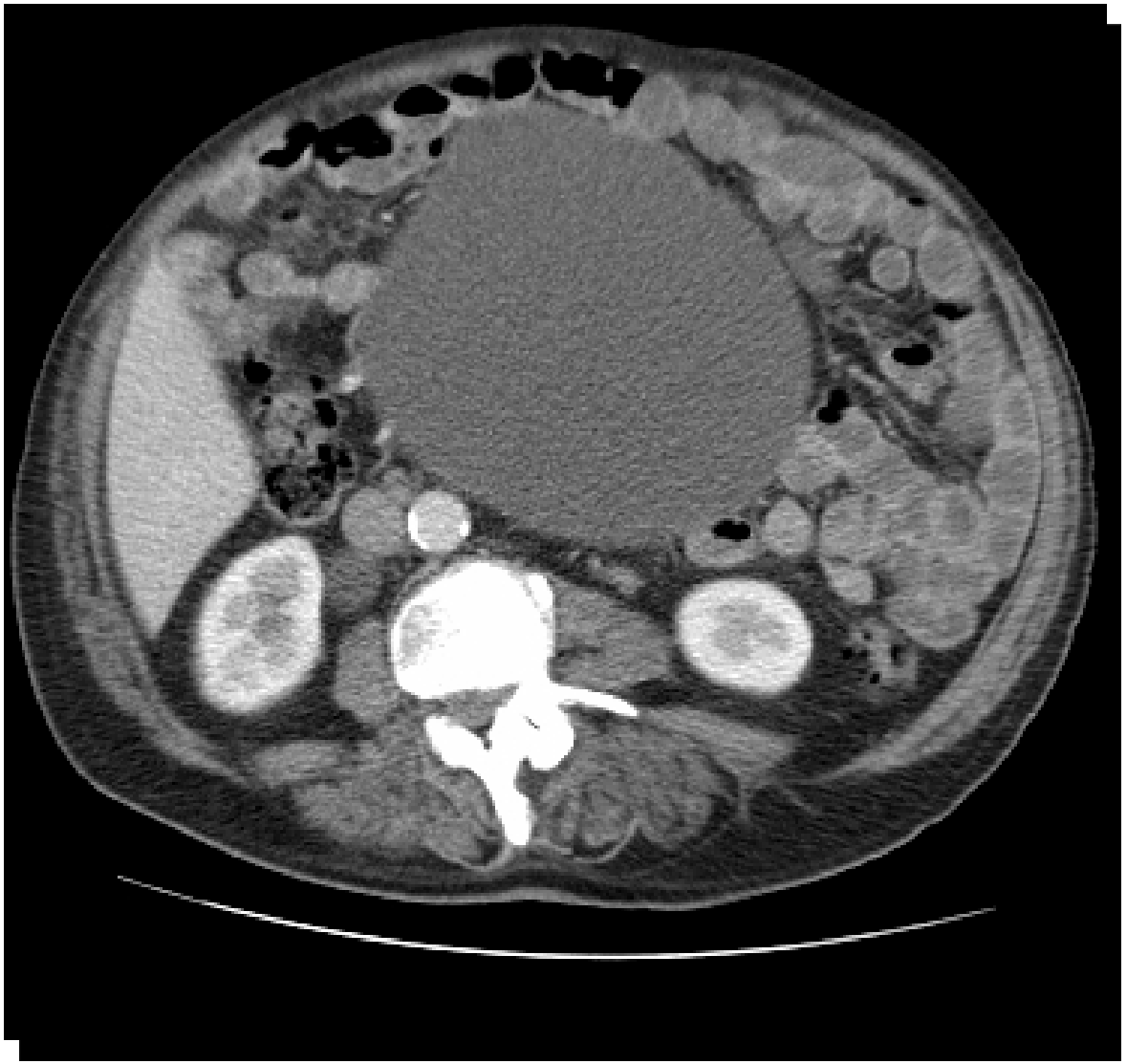
  Rectal exam: Normal tone anal sphincter.

  4.5 x 5 cm prostate without nodularity or tenderness

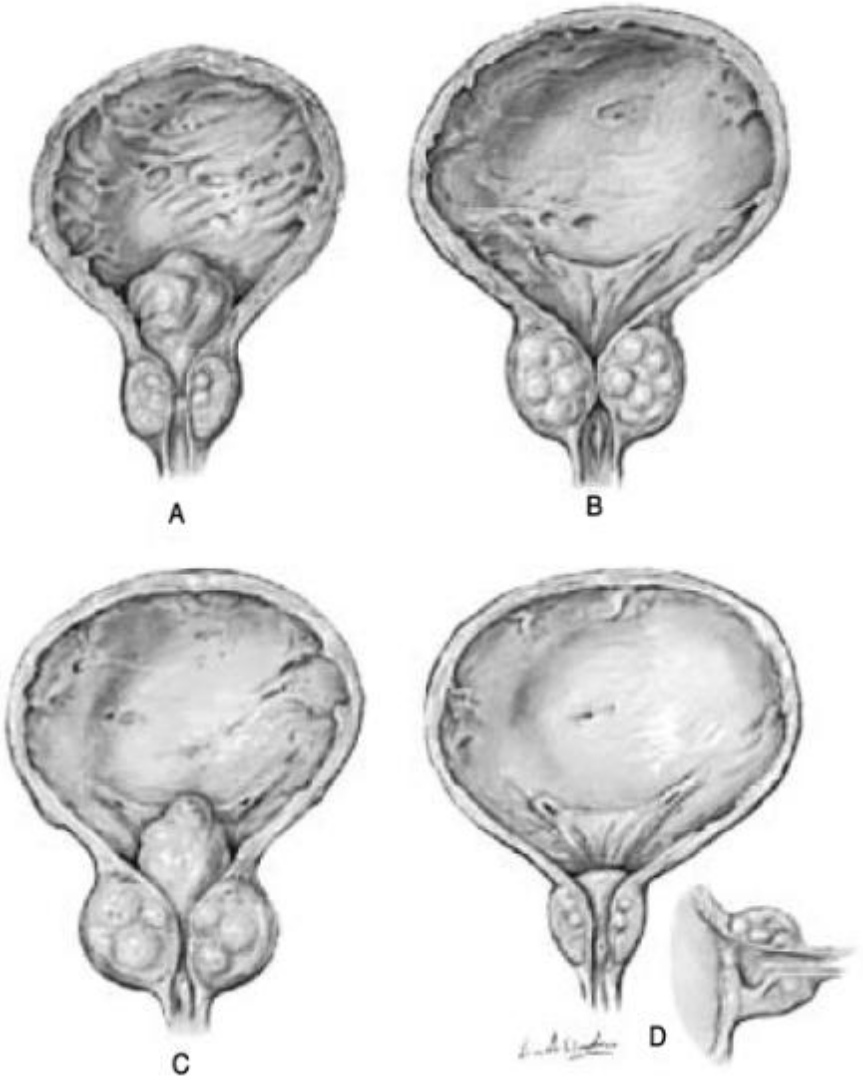
Case 1 (continued)

- Post void residual: 1250 cc
- Urinalysis: Unremarkable
- PSA: 1.4 ng/ml
- BUN 75 mg/dl
- Creatinine 6.2 mg/dl
- Sodium and potassium are in normal range

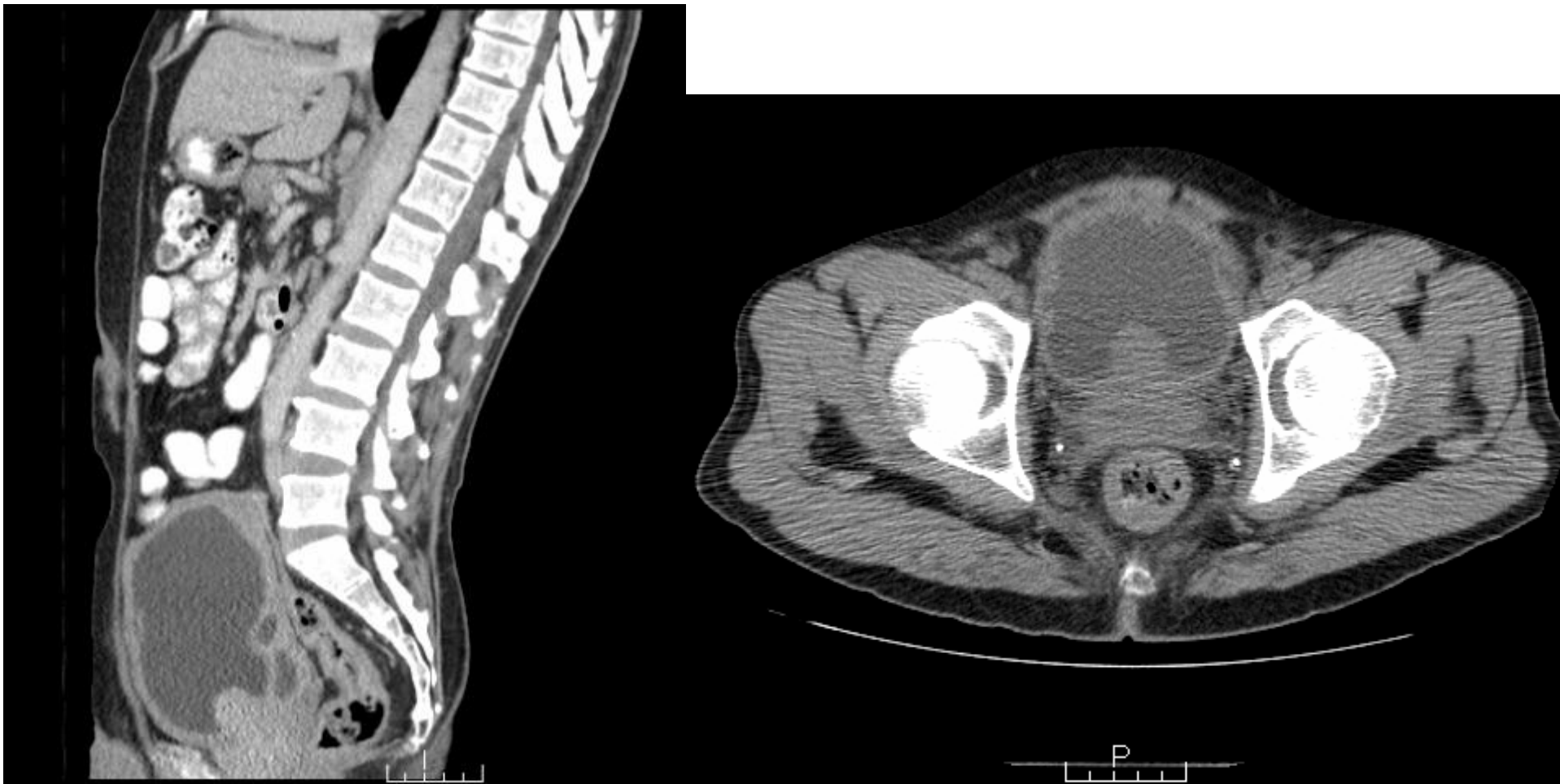
Urinary retention



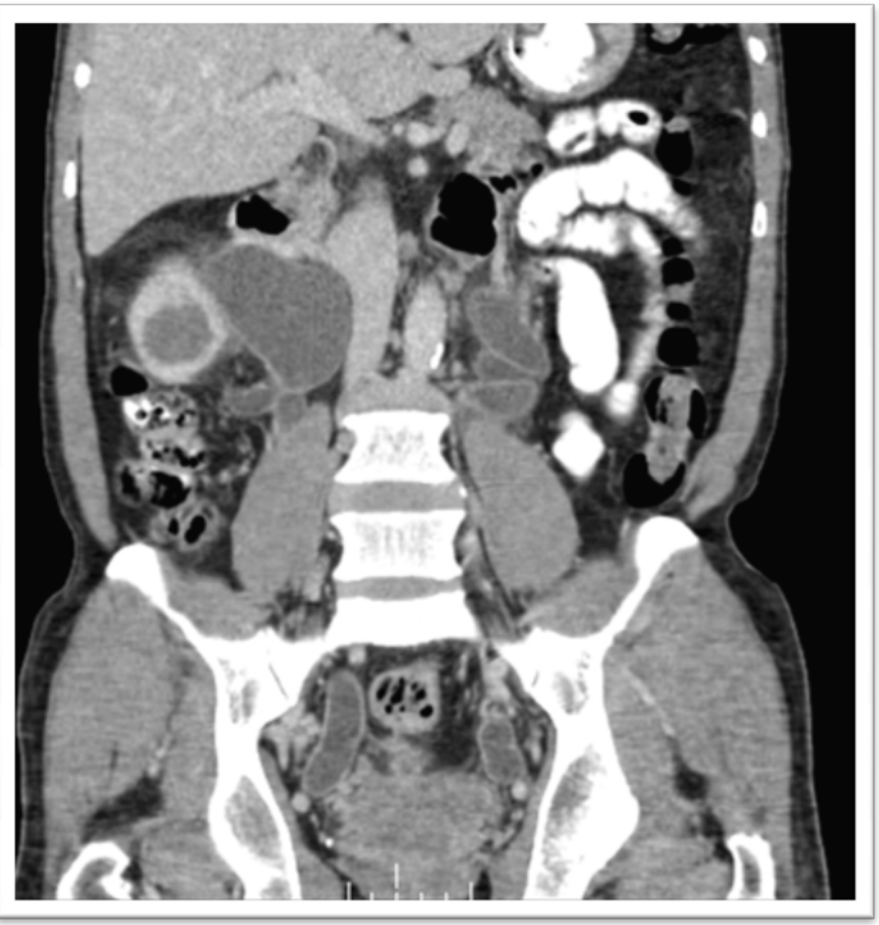
BPH Pathophysiology

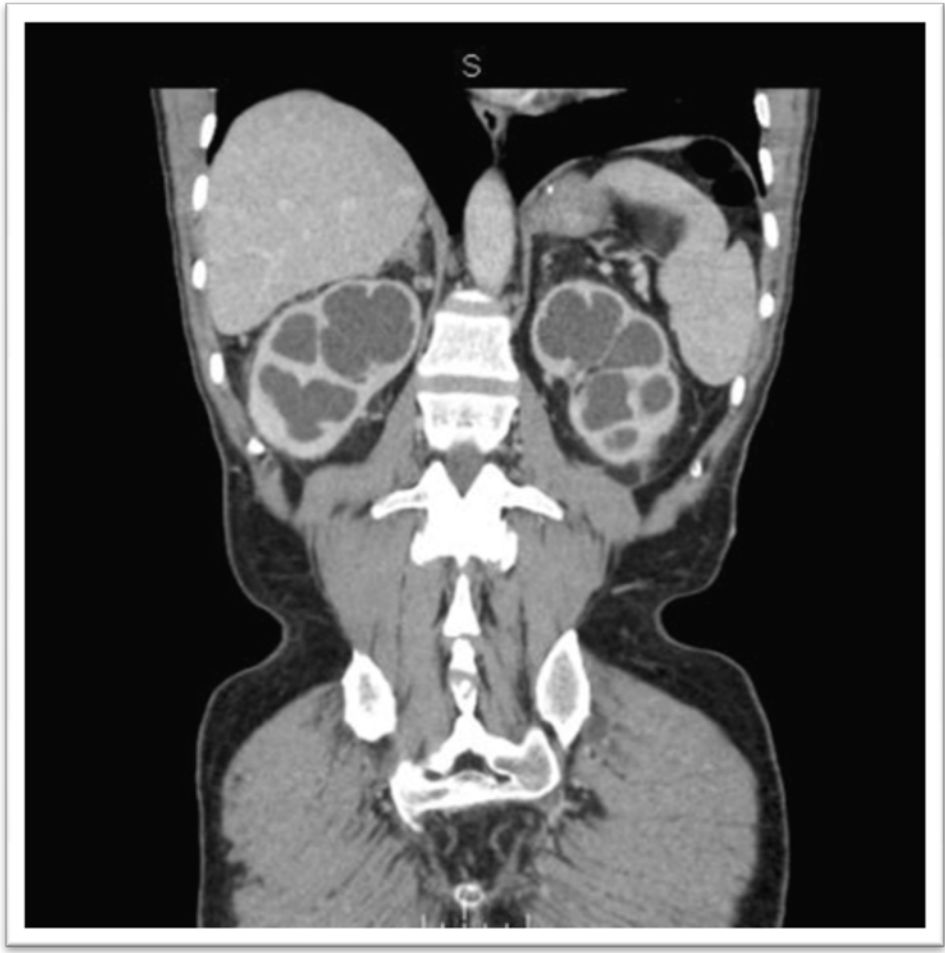


Median lobe causing upper tract deterioration



Bilateral Hydronephrosis due to bladder outlet obstruction

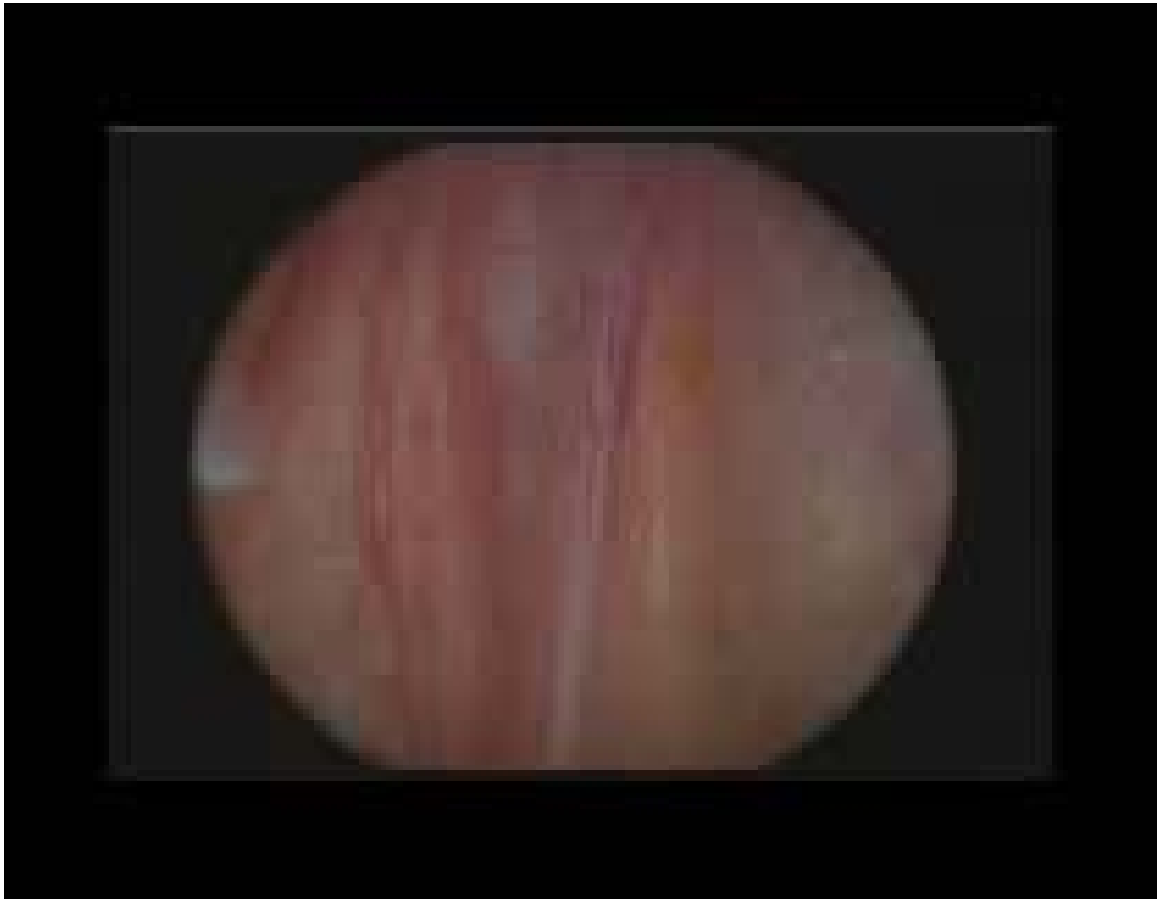




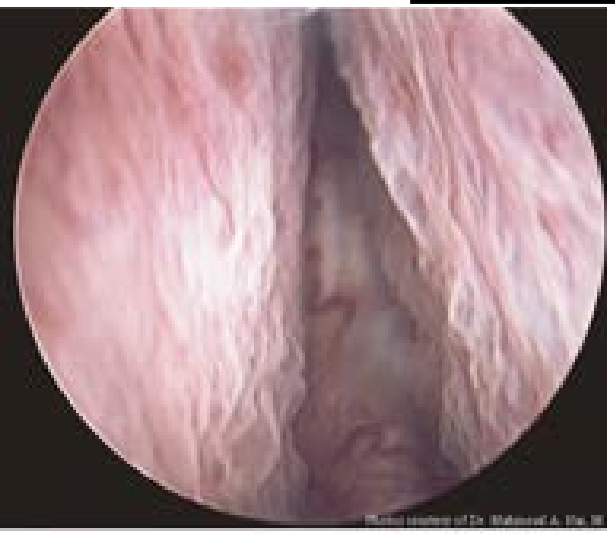
Treatment Options for BPH

- Watchful Waiting
- Medical Therapy
- Minimally Invasive Therapies
- Surgery (TURP-transurethral resection of the prostate / Laser)

Prostate Reduction Therapy (Laser TURP)

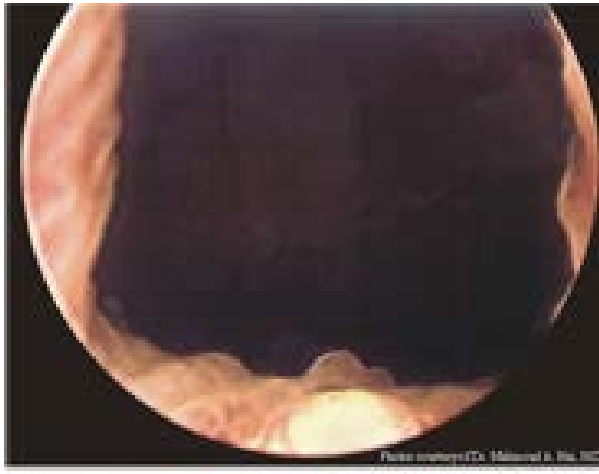


Photoselective vaporization of the prostate (PVP)



Pre-PVP Procedure

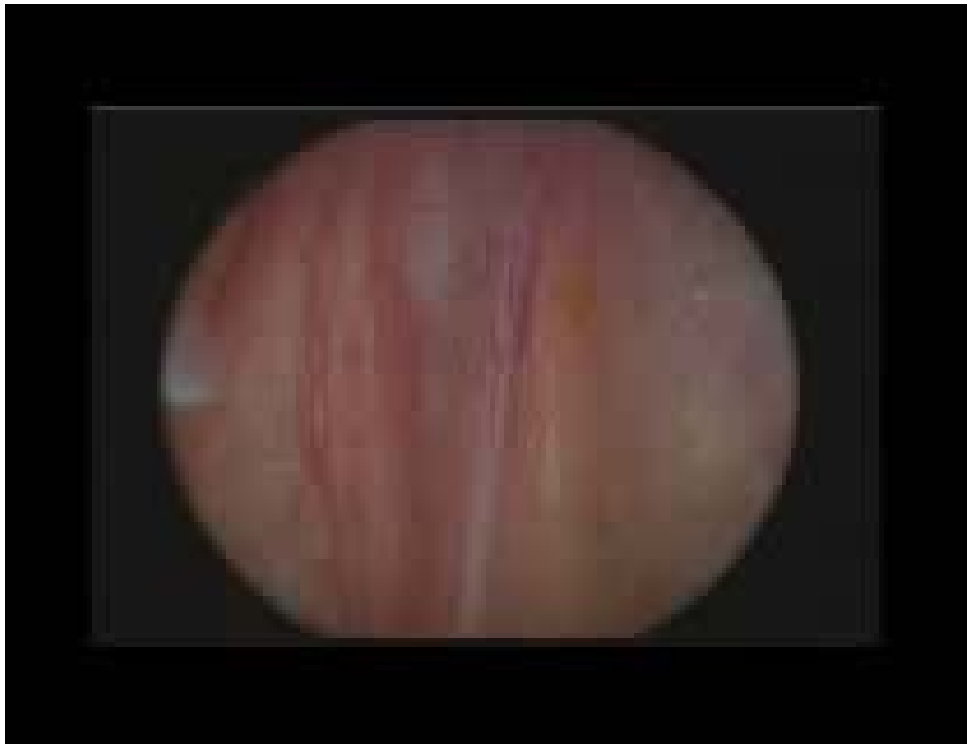
Immediate Post PVP



Three Months Post-PVP

Transurethral Resection of Prostate Complications

- Bleeding (5-10%)
- Dysuria (15%)
- Extravasation (2-3%)
- Incontinence (1-2%)
- Impotency: (5-15%)
- Retrograde ejaculation (60-80%)
- TUR syndrome (1-5%)



Summary – Case #1

- Lower urinary tract symptoms
  - Obstructive & Urgency Symptoms
  - Besides BPH, variety of other entities can present with similar symptoms: infections, tumors, ureteral stones, neurologic conditions, diabetes
- Bladder Outlet Obstruction from BPH
  - Medical therapies – alpha adrenergic blockers and/or 5-alpha reductase inhibitors
  - Surgical therapies – prostate reduction therapy

Case 2 – Mr. S

- 62 yo M with a history of DM, HTN, OSA, and hyperlipidemia who has been complaining of fatigue and generalized weakness
- Feels very tired with lack of energy, exhausted all the time, daytime somnolence x 2 yrs.
- Libido intact but has poor erections – these symptoms have been worse over the past 6 months – Viagra does not work like it used to
- Wife (2nd) is 22 years younger. Has 3 toddlers and two older children in college. 1st wife died of cancer.
- Only uses his CPAP some of the time

Case 2 – Mr. S

- PMH
  - DM – HgbA1c recently 10.3 despite his reported FSBS being in low 100s.
  - Hypophosphatemia
  - HTN
  - Dyslipidemia
  - Fatty liver
  - GERD
  - Obesity
  - Asthma
  - Depression
  - OSA
- Medications
  - Albuterol
  - Aspirin
  - Glyburide
  - HCTZ
  - K-Phos
  - Metformin
  - Prilosec
  - Zestril
- SH
  - Rare EtOH, No tobacco
- FH
  - DM in brother
- PE - Unremarkable

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Case 2 – Mr. S

- Testosterone – 194
  - However, this was drawn at 4pm
- Early AM testosterone - 255 (270-1070)
- Free testosterone 10 (9-30)
- SHBG 21 (13-71), LH 4.5 (2-12), FSH 2.1 (1-12), TSH normal, prolactin normal, Cr 1
- PSA 5.62, free PSA 11%

Urologic evaluation

- Evaluated by endocrine (already following for hypophosphatemia) for hypogonadism
- Referred to Urology for elevated PSA
- PSA history:

1999 – 1.9	2005 – 3.0
2000 – 2.5	2009 – 5.7
2001 – 3.1	2010 – 4.86
2002 – 3.2	2012 – 5.62

Urologic evaluation

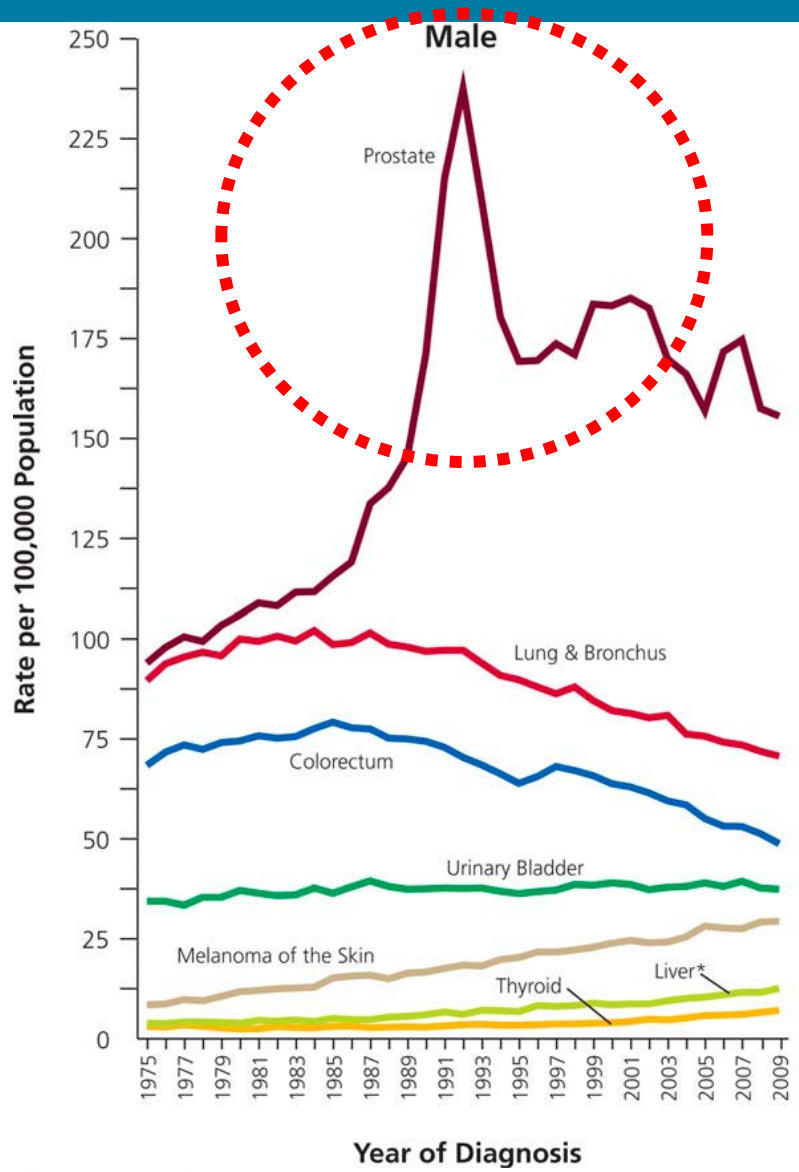
- Voiding history:
  - Hesitancy, weak stream, some urgency and frequency, nocturia x 2-3
- IPSS 15/35 QOL 3/6
- Sexual function: libido intact, limited erections even with viagra
- PE:
  - Testes normal size, no masses
  - DRE – prostate 40-50g, no nodules, no rectal masses

Next steps?

- Options:
  - Continued observation
  - Prostate biopsy
  - Imaging:
    - Endorectal coil prostate MRI
    - Transrectal ultrasound
- What about testosterone replacement?

- Let’s discuss his PSA first

Annual Age-Adjusted Cancer Incidence Rates



Peak in 1992 – ~5 years after initiation of PSA

Fall in incidence – "cull effect"

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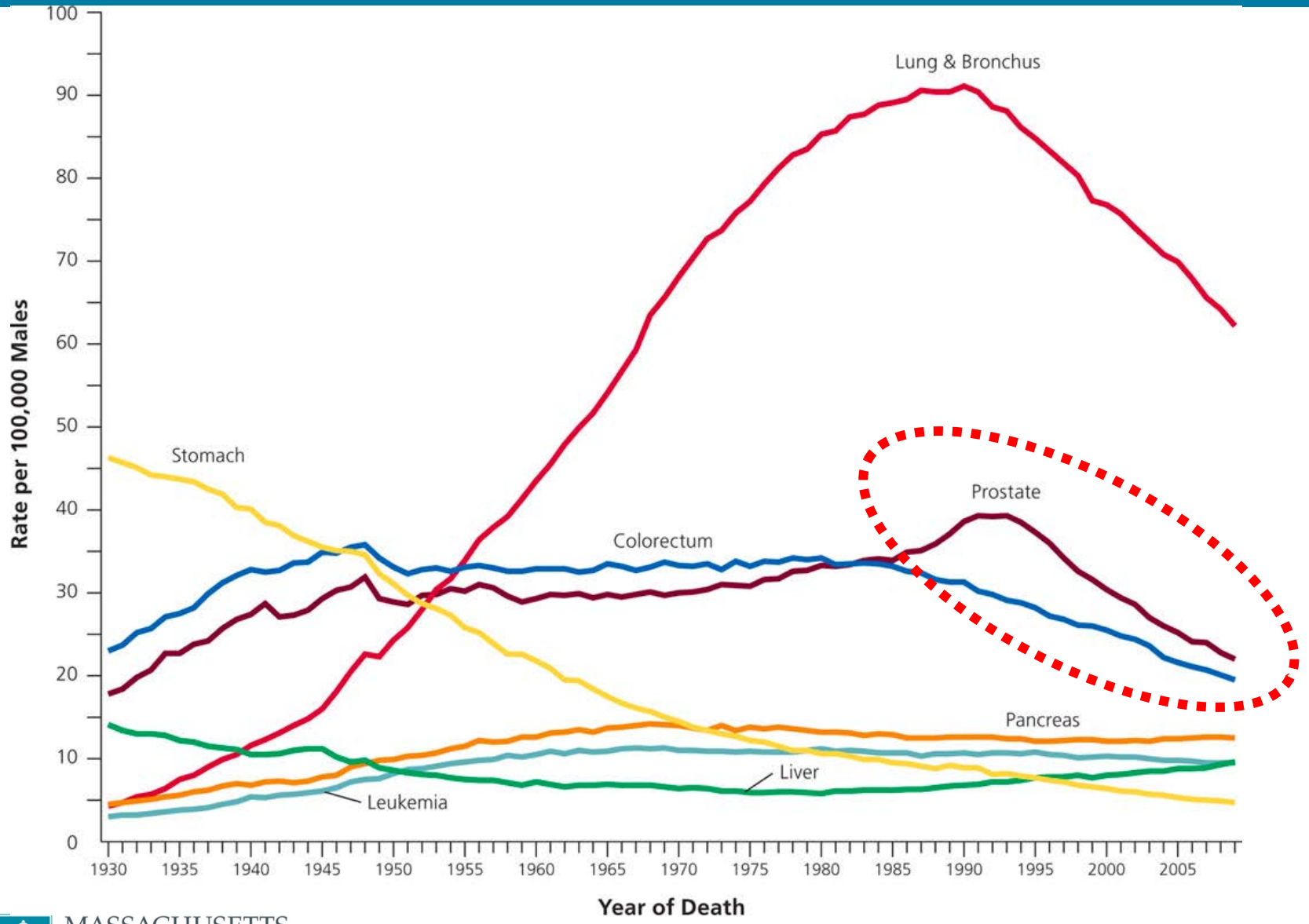
Siegel R, et al. Cancer Statistics. CA CANCER J CLIN 2013;63:11–30

Annual Age-Adjusted Cancer Death Rates



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Siegel R, et al. Cancer Statistics. CA CANCER J CLIN 2013;63:11–30

PSA Screening

- May 21, 2012 – USPSTF finalizes a Grade D recommendation for PSA based screening
- AUA and ASCO respond:
  - Men with a 10-15 life expectancy should discuss risks and benefits of prostate cancer screening with PCP
  - Screening for prostate cancer must include a DRE
- April 2013 – AUA updates its guidelines on early detection of prostate cancer

2013 AUA Guidelines on Early Detection of Prostate Cancer

1. The Panel recommends against PSA screening in men under age 40 years
2. The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk
   - *Higher risk: Family history, African American race*
3. The Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences
   - *The greatest benefit of screening appears to be in men ages 55 to 69 years.*
4. To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening
5. The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy
   - *Some men age 70+ years who are in excellent health may benefit from prostate cancer screening*

Considerations in Approach

- Non-cancer causes of an elevated PSA
  - BPH
  - Inflammation –
    - Urinary tract infection
    - Prostatitis
  - Acute urinary retention
  - Iatrogenic prostate manipulation
    - DRE
    - Prostatic Biopsy
    - Cystoscopy
  - Ejaculation

Shortfalls of the historical "normal" PSA cutoff

- Prostate Cancer Prevention Trial (*Thompson, et al NEJM 2003 and 2005)*

Prevalence of prostate cancer in 2950 men with "normal PSA"

PSA	Incidence	High grade
≤0.5	7%	13%
0.6 - 1.0	10%	10%
1.1 - 2.0	17%	12%
2.1 - 3.0	24%	19%
3.1 - 4.0	26%	25%

Historically, when PSA 4 – 10: 22-26% CA

What are the data? PLCO Cancer Screening Trial

(Prostate, Lung, Colorectal, and Ovarian)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

CONCLUSIONS

After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. (ClinicalTrials.gov number, NCT00002540.)

previously.[13] In the control group, the rate of PSA testing was 40% in the first year and increased to 52% in the sixth year; for subjects who reported having undergone no more than one PSA test at baseline (89% of subjects), the rate of PSA testing was 33% in the first year and 46% in the sixth year. The rate of screening by digital rectal examination in the control group ranged from 41 to 46%.

Andriole, et al. NEJM. 2009;360:1310-9.

- Findings at 7 yrs:
  - PCa incidence 116/10,000 person-years in Screened Grp vs. 95/10,000 in Control Arm
  - Deaths: 2/10,000 in Screened vs. 1.7/10,000 in Control
- Findings at 13 yrs:
  - Deaths: 3.7/10,000 in Screened vs. 3.4/10,000 in Control

[Andriole, et al. JNCI. 2012;104:125–132]

- Concerns:
  - Contamination of Control Arm
    - 40% had PSA in 1st year
    - 52% had PSA by 6th year
  - Compliance with Biopsy only 40-52%

What can we take from the PLCO trial?

Cancer Causes Control (2012) 23:827–835
DOI 10.1007/s10552-012-9951-8

ORIGINAL PAPER

The impact of PLCO control arm contamination on perceived PSA screening efficacy

Roman Gulati · Alex Tsodikov · Elisabeth M. Wever · Angela B. Mariotto · Eveline A. M. Heijnsdijk · Jeffrey Katcher · Harry J. de Koning · Ruth Etzioni

- Investigated if a clinically significant mortality reduction from screening could have been masked by control arm contamination
- Utilized multiple computer simulation models of the PLCO trial with the baseline assumption that there was a significant difference in mortality
- All iterations of the models demonstrated that control arm contamination masked the assumed baseline difference in mortality

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What are the data? ERSPC – European Randomized Study of Screening for Prostate Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

CONCLUSIONS

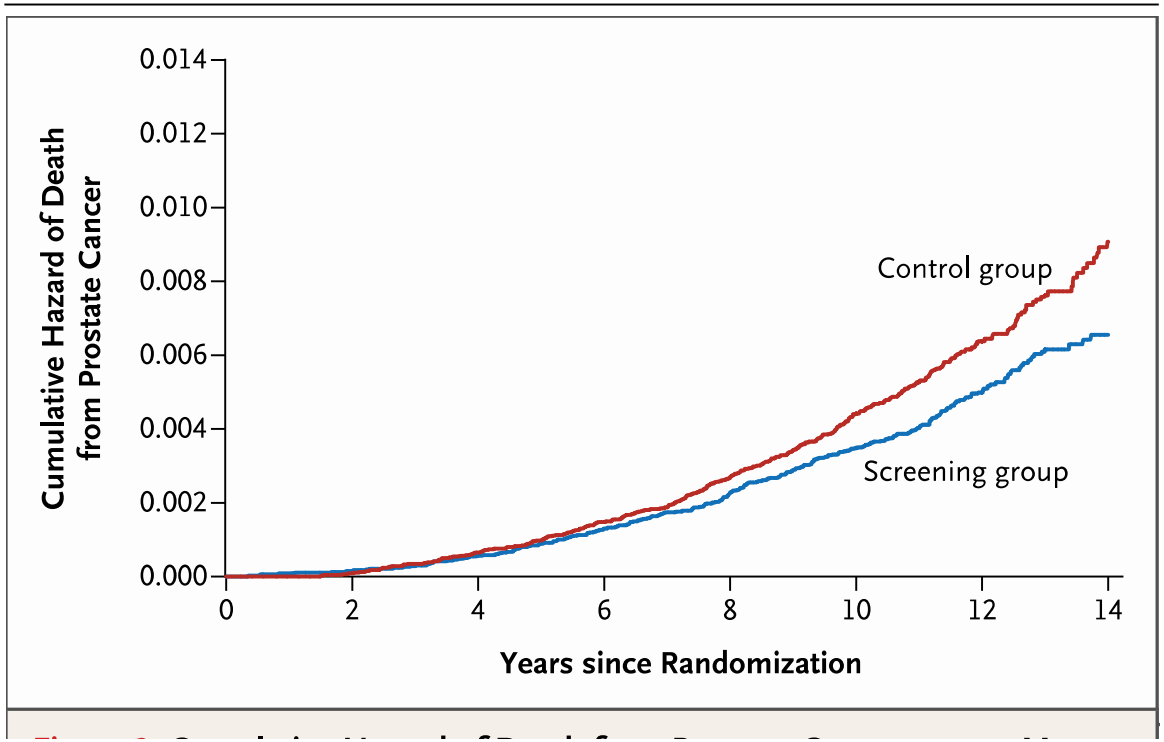
PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis. (Current Controlled Trials number,

- Findings at 9 yrs:
  - Ratio of PCa death was 0.8 in screened group compared to control (20% reduction)
  - To prevent 1 PCa death: 1410 men need to be screened and 48 cases of PCa need to be treated
- Findings at 11 yrs:
  - Relative risk reduction in prostate cancer death was 21%
  - To prevent 1 PCa death: 1055 men screened; 37 need to be detected

Schroeder, et al. NEJM. 2009;360:1320-8.

Schroeder, et al. NEJM. 2012;366:981-90.

What are the data? ERSPC – European Randomized Study of Screening for Prostate Cancer



- Significant difference in Pca mortality in core age group (55-69)
- There was no mortality reduction seen in men ≥70 yo
- No reduction in all cause mortality was seen

- High NNT highlights the risk of overdiagnosis and the need to utilize active surveillance when appropriate

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The less well known prostate cancer screening trial

Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

Lancet Oncol 2010; 11: 725–32

- 20,000 Swedish men aged 50-64 in 1994 randomized to screening or no screening

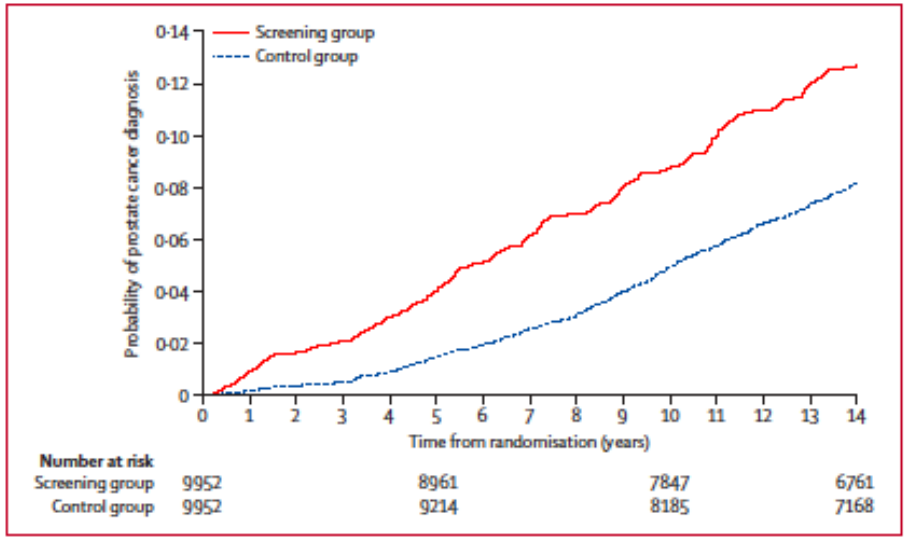

Figure 2: Cumulative incidence of prostate cancer in the screening group and in the control group

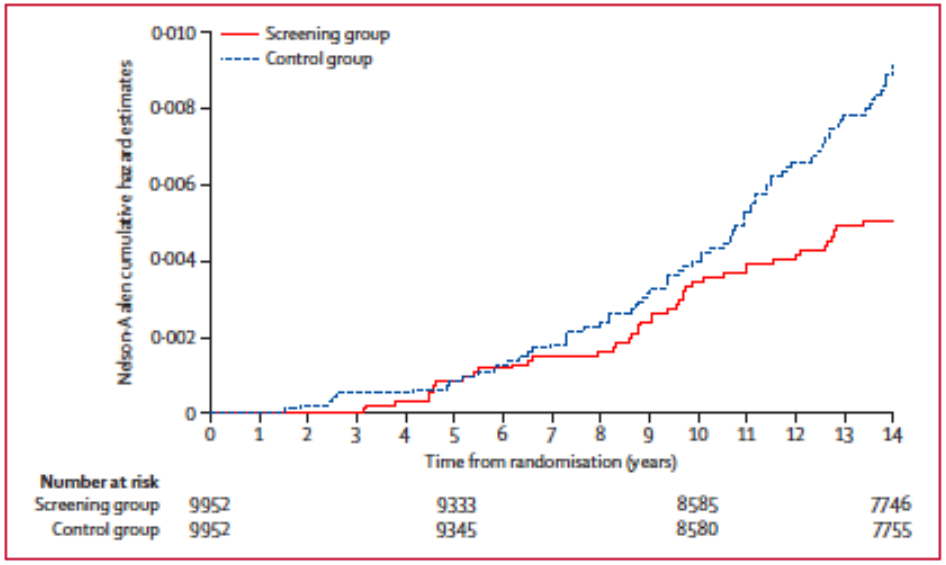

Figure 3: Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates

What is the long term risk of an elevated PSA?

- Malmo Preventive Project:
  - 1167 Swedish men aged 60 in 1981
  - Highly accurate outcome data through 2006
  - Frozen serum samples from 1981 measured for PSA
  - PSA at age 60 predicts long term risk of prostate cancer metastases and death

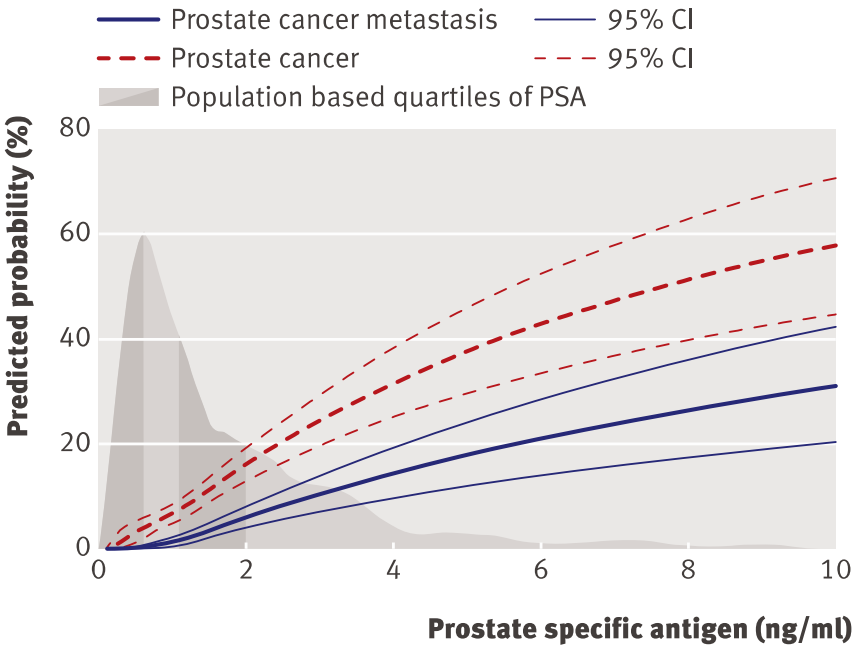

Fig 1 | Lifetime risk of clinically diagnosed prostate cancer or prostate cancer metastasis. Shaded region represents population based distribution of prostate specific antigen. Curves for risk of death from prostate cancer nearly overlap with curves for prostate cancer metastasis and are not shown

Vickers, et al. BMJ 2010;341:c4521

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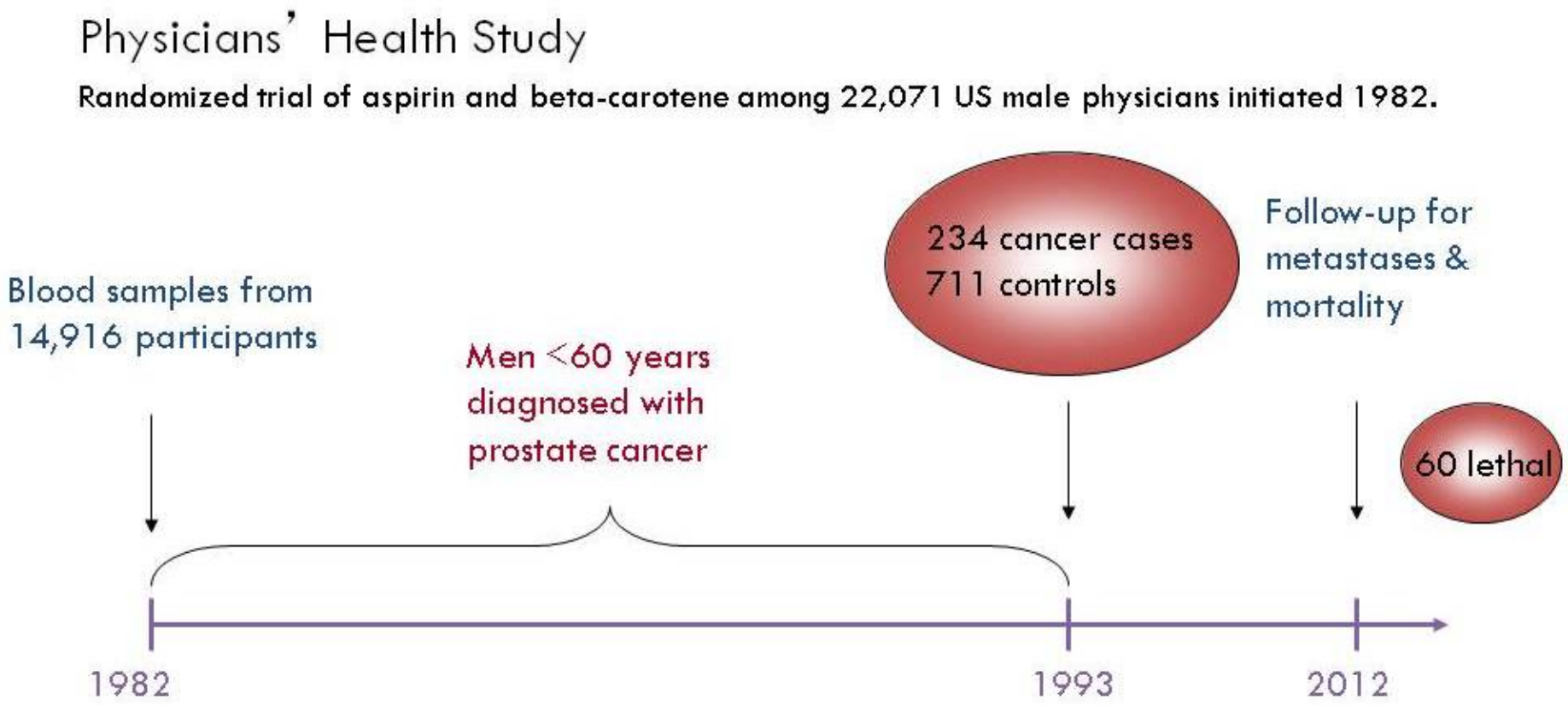
Can baseline PSA levels in men <60 years of age predict lethal prostate cancer?



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Does baseline PSA predict lethal prostate cancer?

Age		<50th Percentile	>75th Percentile	>90th Percentile
	PSA Value	**<0.95**	**>1.60**	**>2.88**
55-59.9	OR (95% CI)	1.00 (ref)	**10.7 (3.2-35.8)**	**17.1 (4.6-64.0)**
	PSA value	**<0.90**	**>1.40**	**>1.93**
50-54.9	OR (95% CI)	1.00 (ref)	4.0 (0.9-18.0)	**7.0 (1.3-38.5)**
	PSA Value	**<0.68**	**>1.07**	**>1.68**
40-49.9	OR (95% CI)	1.00 (ref)	**6.4 (1.3-32.0)**	**11.5 (1.5-89.3)**

Can we stop PSA screening at 60?

Age		>50th Percentile	0-25th Percentile	25-50th Percentile
	PSA Value	**>0.95**	**0.06-0.60**	**0.60-0.95**
55-59.9	OR(95% CI)	1.00 (ref)	**0.16 (0.04-0.77)**	**0.22 (0.06-0.76)**

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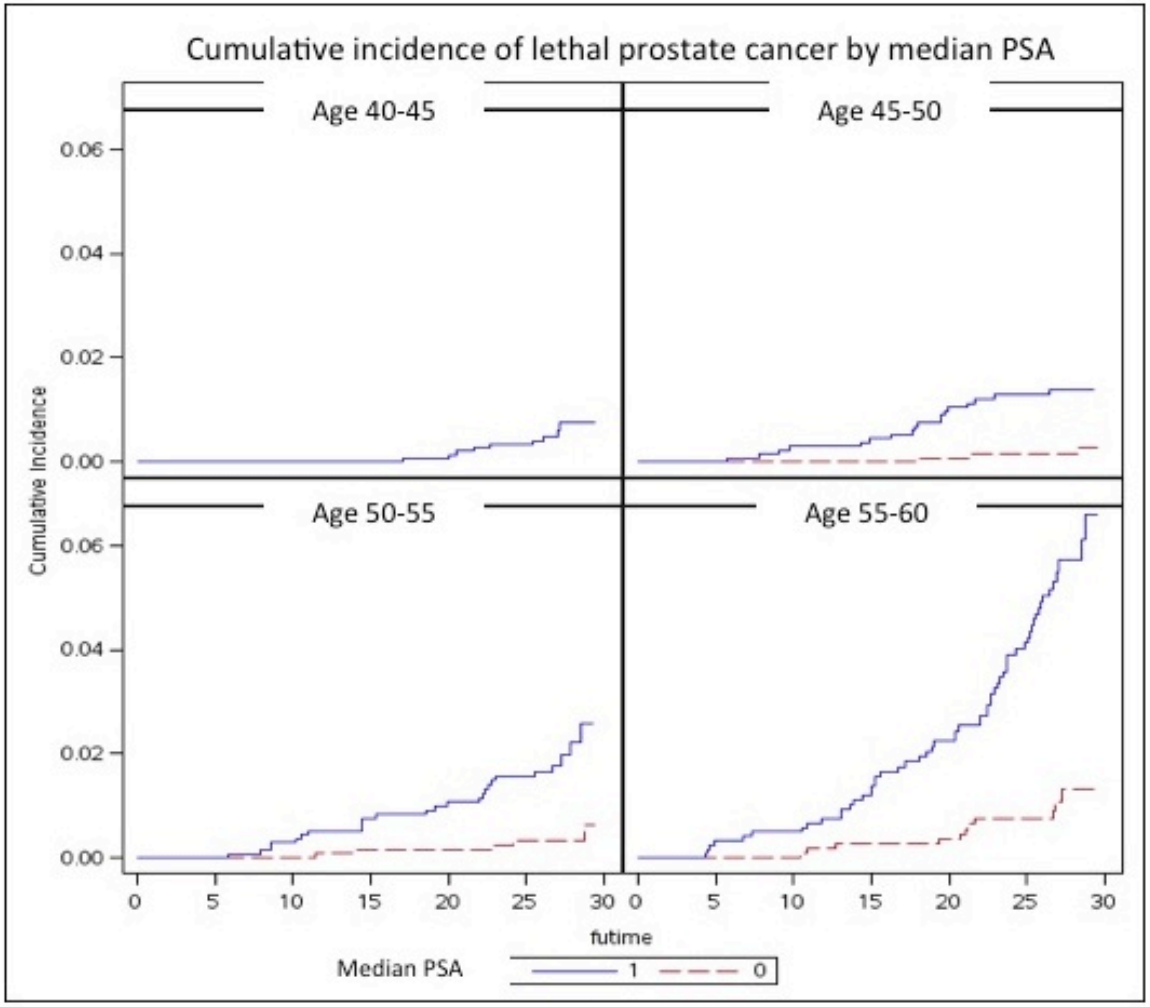
US data similar to Swedish baseline cohort



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Are there better biomarkers than PSA?

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Are there better biomarkers than PSA?

- Urine based:
  - PCA3
    - FDA approved for elevated PSA and prior negative biopsy
    - PCA3 is a noncoding mRNA 1st identified in 1999
    - Expression is restricted to the prostate.
      - Expressed in 95% of prostate tumors
    - PCA3 score is independent of prostate volume, age, BPH and prostatitis.
    - Correlates with risk of cancer

PCA3 Molecular Urine Test as a Predictor of Repeat Prostate Biopsy Outcome in Men with Previous Negative Biopsies: A Prospective Multicenter Clinical Study

Marc C. Gittelman,*,† Bernard Hertzman, James Bailen, Thomas Williams, Isaac Koziol, Ralph Jonathan Henderson,‡ Mitchell Efros, Mohamed Bidair and John F. Ward§

THE JOURNAL OF UROLOGY® Vol. 190, 64-69, July 2013

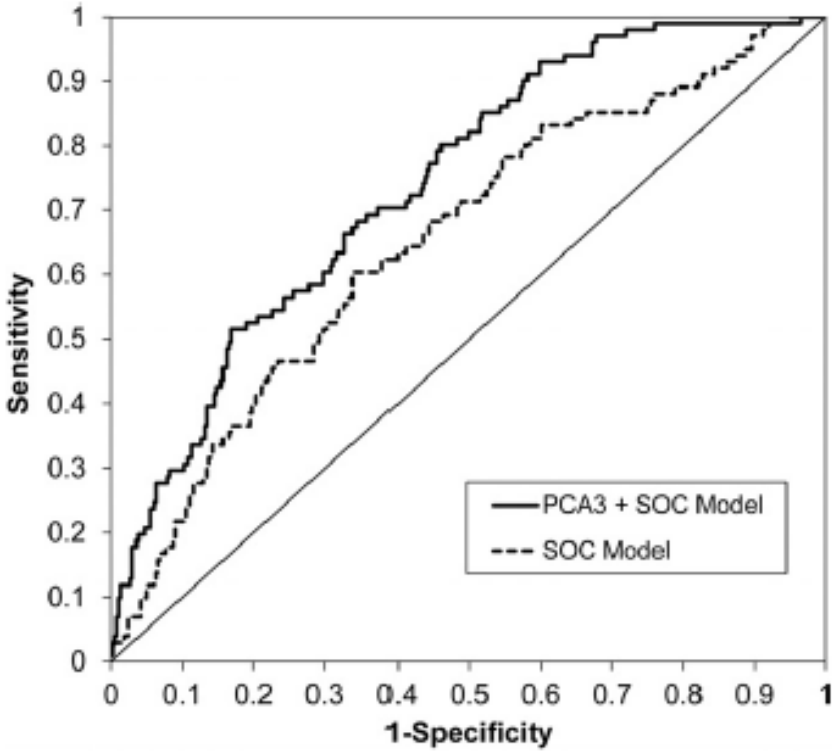

Figure 1. Multivariable ROC curves of model containing PCA3 and SOC factors, including age, DRE result, PCa family history, race, sPSA as continuous factor and number of previous negative biopsy sessions, vs model containing only SOC factors.

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Are there better biomarkers than PSA?

- Urine based:
  - PCA3 + TMPRSS2:ERG – Michigan Prostate Score or MiPS test
    - Transmembrane Protease, Serine 2 (TMPRSS2) gene
    - TMPRSS2–ERG gene fusion is highly PCa specific and found in ~50% of PSA-screened PCa

Urine *TMPRSS2:ERG* Fusion Transcript Stratifies Prostate Cancer Risk in Men with Elevated Serum PSA

Scott A. Tomlins,[1] Sheila M. J. Aubin,[2] Javed Siddiqui,[1] Robert J. Lonigro,[1,3] Laurie Sefton-Miller,[1] Siobhan Miick,[2] Sarah Williamsen,[2] Petrea Hodge,[2] Jessica Meinke,[2] Amy Blase,[2] Yvonne Penabella,[2] John R. Day,[2] Radhika Varambally,[1] Bo Han,[1] David Wood,[4] Lei Wang,[1] Martin G. Sanda,[5] Mark A. Rubin,[6] Daniel R. Rhodes,[1] Brent Hollenbeck,[4] Kyoko Sakamoto,[7] Jonathan L. Silberstein,[7] Yves Fradet,[8] James B. Amberson,[9] Stephanie Meyers,[4] Nallasivam Palanisamy,[1] Harry Rittenhouse,[2] John T. Wei,[4] Jack Groskopf,[2] Arul M. Chinnaiyan[1,3,4,10]*

www.ScienceTranslationalMedicine.org 3 August 2011 Vol 3 Issue 94 94ra72

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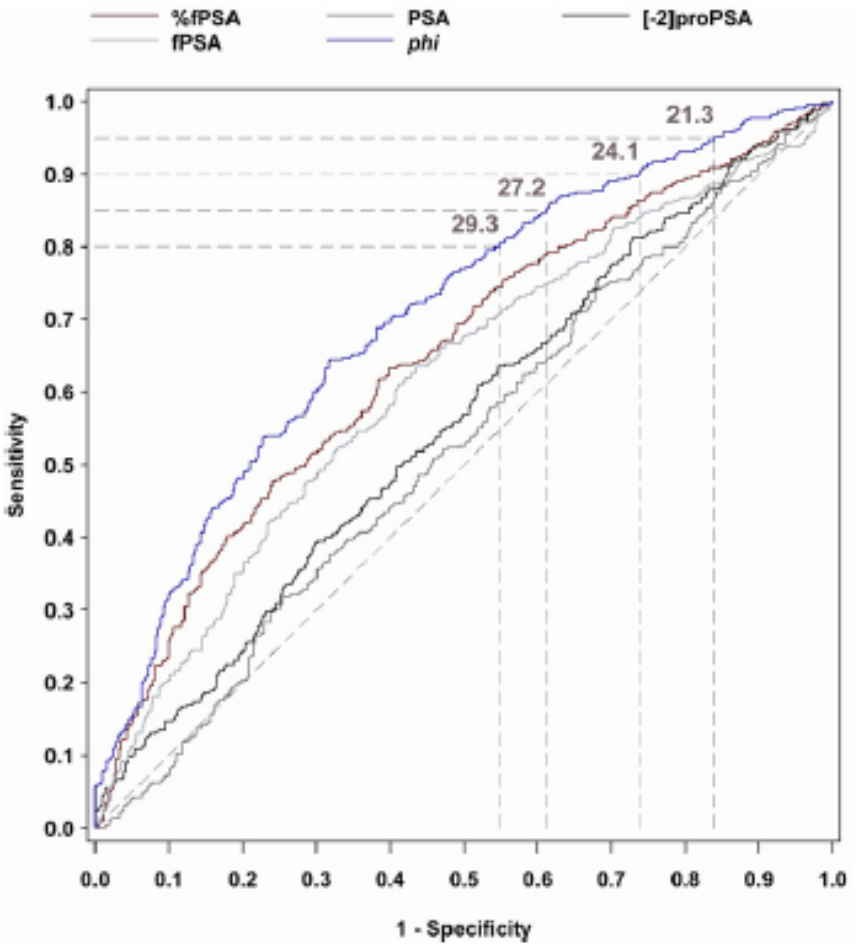
Are there better biomarkers than PSA?

- PHI – Prostate Health Index
  - Combines [-2]Pro-PSA with free PSA and total PSA
  - [-2]Pro-PSA FDA approved in 2012 for PSA 4-10 with negative DRE
  - “ratio of PSA precursor protein to free PSA multiplied by the square root of the PSA score at diagnosis”

A Multicenter Study of [-2]Pro-Prostate Specific Antigen Combined With Prostate Specific Antigen and Free Prostate Specific Antigen for Prostate Cancer Detection in the 2.0 to 10.0 ng/ml Prostate Specific Antigen Range

William J. Catalona,*,† Alan W. Partin,‡ Martin G. Sanda,‡ John T. Wei,§ George G. Klee,‡ Chris H. Bangma, Kevin M. Slawin,‖ Leonard S. Marks, Stacy Loeb, Dennis L. Broyles,‡ Sanghyuk S. Shin,‡ Amabelle B. Cruz,‡ Daniel W. Chan, Lori J. Sokoll, William L. Roberts,¶ Ron H. N. van Schaik and Isaac A. Mizrahi‡

THE JOURNAL OF UROLOGY® Vol. 185, 1650-1655, May 2011



PSA, fPSA, [-2]proPSA, free-to-total PSA and PHI (*phi*) ROC curves in 2 to 10 ng/ml PSA range show sensitivity × 1 − specificity at sequential cutoffs.

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How do we select men for a biopsy?

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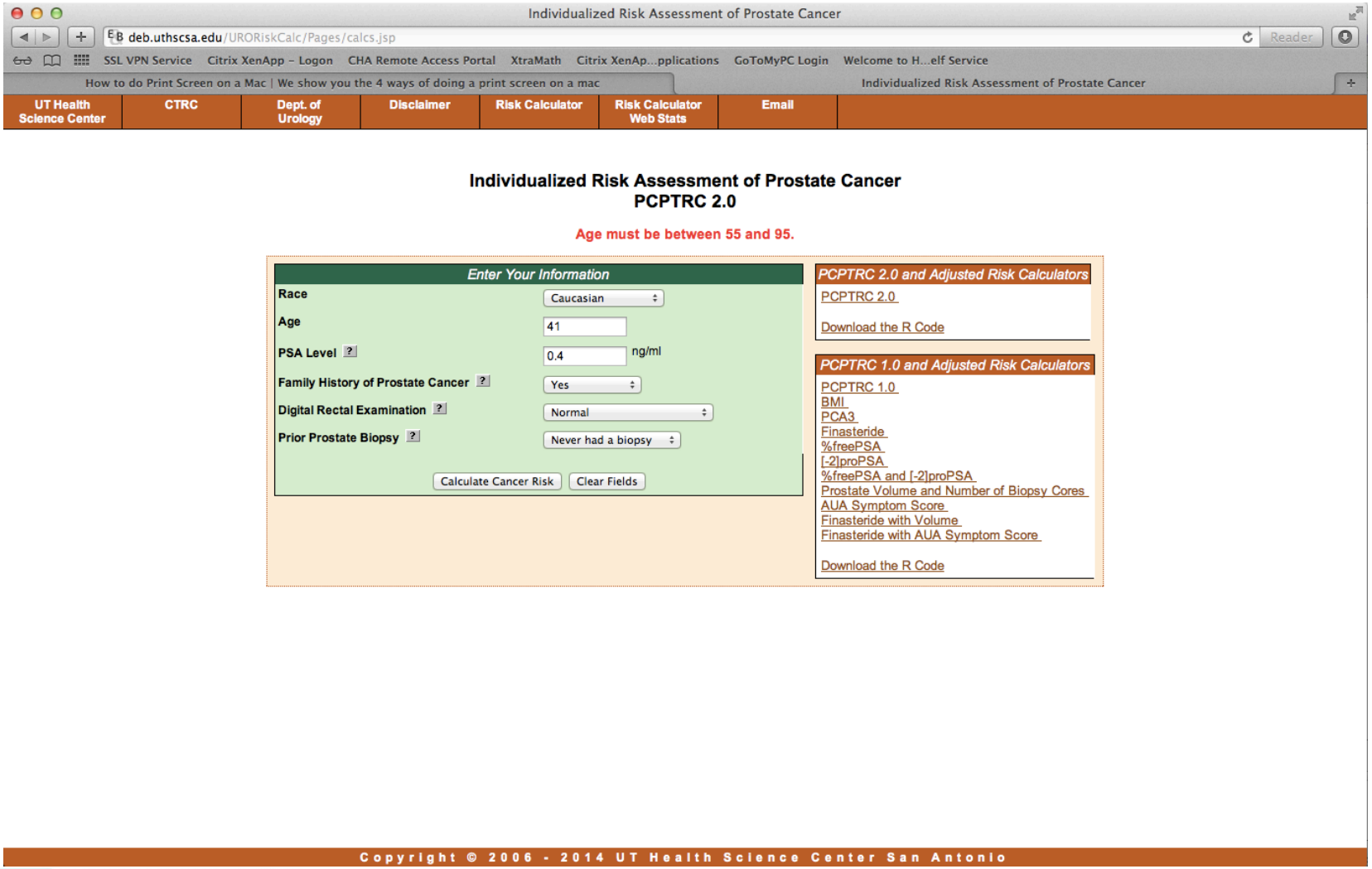
How do we select men for a biopsy?

- PCPT nomogram



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QPID PrOE

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56/M Visit Date: 2014-03-24 Selected Intervention: Prostate Biopsy Assessment completed.

Intervention | Clinical Summary | **Guidelines** | Risks | Assessment | Consent | Schedule

Presentation

*Prostate cancer in first degree relative **Modified**
(•) Yes ( ) No

*Prostate cancer leading to death in first degree relative
( ) Yes ( ) No

*Taking Finasteride/Dutasteride **Modified**
( ) Yes (•) No

*Life expectancy > 10 years
(•) Yes ( ) No

Prior Prostate Biopsy

Date (YYYY-MM-DD)

[ ] Benign **Modified**
[ ] HGPIN **Modified**
[ ] ASAP

Prior PSA (ng/mL)

*Confirm significant PSA rise **Modified**
(•) Yes ( ) No ( ) Unknown

#	DATE	PSA Total	Edit/Delete
1	2014-02-28	6.76	Edit Delete
2	2013-12-26	8.08	Edit Delete
3	2012-09-20	6.28	Edit Delete
4	2010-11-12	4.44	Edit Delete
5	2008-01-15	3.14	Edit Delete

Suspicious Prostate Characteristics on DRE

Prostate size (cc)

*Characteristics **Modified**
(•) Normal ( ) Suspicious ( ) Indeterminate ( ) Unknown

Suspicious Prostate Characteristics on Imaging

*Type of imaging
(•) Ultrasound ( ) MRI ( ) CT ( ) None

Prostate size (cc)

[ ] Prior abnormal MRI
[x] Suspicious findings

PSA (Most Recent)

PSA Free

Most recent PSA Total (ng/mL)	6.76
PSA velocity (ng/mL/yr)	0.66
PSA density (%)	N/A
Free/Total PSA Ratio	0.00

< Back - Summary Save References Explanations Next - Risks >

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56/M Visit Date: 2014-03-24 Selected Intervention: Prostate Biopsy Assessment completed.

Intervention | Clinical Summary | Guidelines | **Risks** | Assessment | Consent | Schedule

Risk Calculator Variables

DRE Findings **Modified**

- (•) Normal
- ( ) Suspicious
- ( ) Indeterminate
- ( ) Unknown

Most recent PSA Total (ng/mL) 6.76

I-PSS Variables

Urinary symptoms score (0-35) 5

Quality of Life Due to Urinary Symptoms

- ( ) Delighted - 0
- (•) Pleased - 1
- ( ) Mostly satisfied - 2
- ( ) Mixed - 3
- ( ) Mostly dissatisfied - 4
- ( ) Unhappy - 5
- ( ) Terrible - 6
- ( ) Unknown

Risks of Bleeding

- [ ] Taking coumadin
- [ ] Taking aspirin
- [ ] Other anticoagulants
- [ ] Large prostate volume

Risks of Infection

- [x] Antimicrobials 6 months prior to biopsy
- [ ] Hospital employee
- [ ] Recent international travel
- [x] Prior prostate biopsy

< Back - Guidelines Save References Explanations Next - Assessment >

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56/M Visit Date: 2014-03-24 Selected Intervention: Prostate Biopsy Assessment completed.

Intervention | Clinical Summary | Guidelines | Risks | **Assessment** | Consent | Schedule

Appropriateness Scores

Prostate Biopsy — **Appropriate** — Confirm Prostate Biopsy

Alternatives:

Follow up 4-6 months — Confirm Follow up 4-6 months

Annual Screening — Confirm Annual Screening

Rarely Appropriate | May Be Appropriate | Appropriate

Risk Scores

(PCPTRC) UT Health Science Center - High Grade	6.7%
(PCPTRC) UT Health Science Center - Low Grade	18.5%

Risks of bleeding

none

Risks of infection

- Antimicrobials 6 months prior to biopsy
- Prior prostate biopsy

I-PSS Urinary Symptom Score	5
Quality of Life Due to Urinary Symptoms	1

< Back - Risks | Print | EHR Note | References | Explanations | Next

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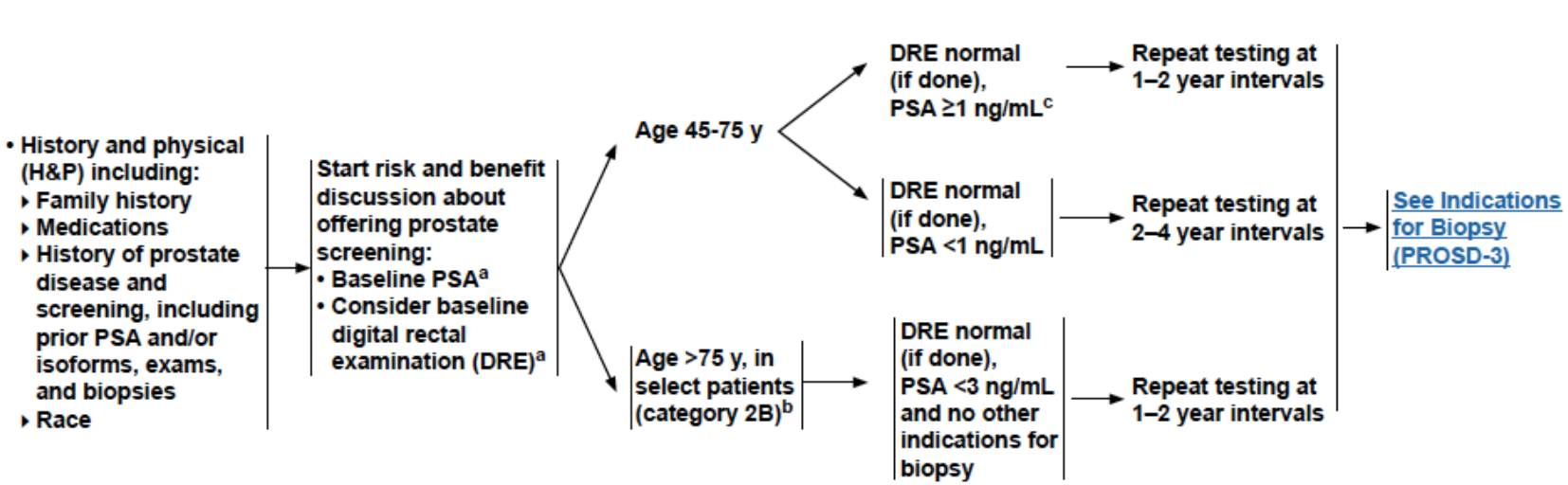

[a]The best evidence supports the use of serum PSA for the early detection of prostate cancer. DRE should not be used as a stand-alone test, but should be performed in those with an elevated serum PSA. DRE may be considered as a baseline test in all patients as it may identify high-risk cancers associated with "normal" serum PSA values. Medications such as 5α-reductase inhibitors (finasteride and dutasteride) are known to decrease PSA by approximately 50%, and PSA values in these men should be corrected accordingly.

[b]Testing above the age of 75 years of age should be done with caution and only in very healthy men with little or no comorbidity as a large proportion may harbor cancer that would be unlikely to affect their life expectancy, and screening in this population would substantially increase rates of over-detection. However, a clinically significant number of men in this age group may present with high-risk cancers that pose a significant risk if left undetected until signs or symptoms develop. One could consider increasing the PSA threshold for biopsy in this group (ie, >4 ng/mL). Very few men above the age of 75 years benefit from PSA testing.

[c]The reported median PSA values for men aged 40–49 y range from 0.5–0.7 ng/mL, and the 75th percentile values range from 0.7–0.9 ng/mL. Therefore, the PSA value of 1.0 ng/mL selects for the upper range of PSA values. Men who have a PSA above the median for their age group are at a higher risk for prostate cancer and for the aggressive form of the disease. The higher above the median, the greater the risk. Finally, men at age 60 years with a serum PSA <1.0 ng/mL have a very low risk of metastases or death due to prostate cancer. Similarly, a cut point of 3.0 ng/mL at age 75 years also has a low risk of such outcomes.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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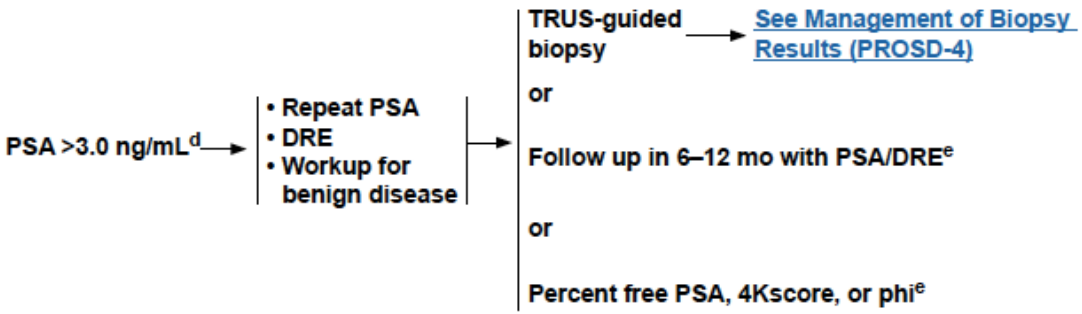
INDICATIONS FOR BIOPSY



TRUS-GUIDED BIOPSY
Initial and Repeat
Extended-pattern biopsy (12 cores)

- Number of cores:
  - Sextant (6),
  - Lateral peripheral zone (6), and
  - Lesion-directed at palpable nodule or suspicious image
- Anteriorly directed biopsy is not supported in routine biopsy. However, the addition of a transition zone biopsy to an extended biopsy protocol may be considered in a repeat biopsy if PSA is persistently elevated.
- Multiparametric MRI may help identify regions of cancer missed on prior biopsies and should be considered in selected cases after at least 1 negative biopsy.
- For high-risk men with negative biopsies, consideration can be given to a saturation biopsy strategy (including transperineal techniques) and/or the use of multiparametric MRI followed by an appropriate biopsy technique based on the results.
- Local anesthesia can decrease pain/discomfort associated with prostate biopsy and should be offered to all patients.

[d]The level of PSA correlates with the risk of prostate cancer. The Prostate Cancer Prevention Trial (PCPT) demonstrated that 15% of men with a PSA level of ≤4.0 ng/mL and a normal DRE had prostate cancer diagnosed on end-of-study biopsies. Approximately 30% to 35% of men with serum PSA between 4 to 10 ng/mL will be found to have cancer. Total PSA levels >10 ng/mL confer a greater than 67% likelihood of prostate cancer.

[e]Biomarkers that improve the specificity of detection are not recommended as firstline screening tests. However, there may be some patients who meet either PSA or DRE standards for consideration of biopsy, but for whom the patient and/or the physician wish to further define the probability of high-grade cancer. A percent free PSA <10%, phi >35 or 4Kscore (which provides an estimate of the probability of high-grade prostate cancer) are potentially informative in patients who have never undergone biopsy or after a negative biopsy; a PCA3 score >35 is potentially informative after a negative biopsy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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MANAGEMENT OF BIOPSY RESULTS

Cancer → See NCCN Guidelines for Prostate Cancer

Atypia, suspicious for cancer → Extended pattern rebiopsy (within 6 mo) with increased sampling of the affected site and adjacent areas. If no cancer is found, close follow-up with PSA and DRE is recommended at 1 year interval initially

High-grade prostatic intraepithelial neoplasia (PIN)

- Multifocal (>2 sites) → Extended pattern rebiopsy (within 6 mo) with increased sampling of the affected site and adjacent areas. If no cancer is found, close follow-up with PSA and DRE is recommended at 1 year interval initially
- Focal → Follow with PSA and DRE at 1 year interval initially (See PROSD-2)
  Repeat biopsy based on risk[f]

Benign[f] → Repeat biopsy based on follow-up in 6-12 mo with PSA/DRE
or
Percent free PSA, 4Kscore, phi, or PCA3

[f]It is well known that a negative biopsy does not preclude a diagnosis of prostate cancer on subsequent biopsy. Those patients with negative biopsies should be followed with DRE and PSA. Tests which improve specificity in the post-biopsy state—including 4Kscore, phi, percent free PSA and PCA3—should be considered in patients thought to be at a higher risk despite a negative biopsy (See PROSD-3). Emerging evidence suggests that the use of multiparametric MRI and/or the use of refined biopsy techniques (transperineal or saturation biopsies) may be of value as well. Also, as noted in the discussion section, PSA testing may be discontinued at certain ages and PSA cutpoints.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Mr. S

- Elects for TRUS guided prostate biopsy
- Prostate volume by ultrasound 96cc

FINAL PATHOLOGIC DIAGNOSIS:

A. PROSTATE BIOPSY, RIGHT APEX:

Benign prostatic tissue with atrophic changes and focal chronic inflammation.

B. PROSTATE BIOPSY, RIGHT MID:

Benign prostatic tissue with atrophy.

C. PROSTATE BIOPSY, RIGHT BASE:

Benign prostatic tissue.

D. PROSTATE BIOPSY, LEFT APEX:

Benign prostatic tissue with atrophic changes and chronic inflammation.

E. PROSTATE BIOPSY, LEFT MID:

Prostatic adenocarcinoma, Gleason score 3 + 3 = 6/10, involving 40% and 20% each of two (2) of two (2) cores and 30% of examined tissue.

Perineural invasion is identified.

F. PROSTATE BIOPSY, LEFT MID:

Benign prostatic tissue.

- Mr. S comes to the multidisciplinary GU oncology clinic to discuss management options
  - Radical prostatectomy
  - External beam radiation
  - Prostate brachytherapy
  - Active surveillance

Active surveillance for low risk prostate cancer

- Accepted management strategy for very low risk localized disease
- Actively monitors the course of disease with the expectation to intervene with curative intent if cancer progresses
- Goals to reduce “overtreatment” and avoid potential complications of treatment

Active surveillance: Published series

Johns Hopkins [7,8]	≤T2a	–	≤3 + 3	≤2	≤50%	PSA DT ≤0.15
University of Toronto [9]	NS	≤10	≤3 + 3[*]	NR	NR	–
UCSF [10]	≤T2a	≤10	≤3 + 3	≤33%	≤50%	–
ERSPC (PRIAS criteria) [11]	≤T2a	≤10	≤3 + 3	≤2	NR	PSA DT ≤0.2
Royal Marsden Hospital [12]	≤T2a	≤15	≤3 + 4	≤50%	NR	–
MSKCC [13]	≤T2a	≤10	≤3 + 3	≤3	≤50%	–
University of Miami [14,15]	≤T2a	≤10	≤3 + 3	≤2	≤20%	–

a PSA ≤15 and Gleason score ≤3 + 4 were included.

Johns Hopkins [8]	2011	66	769	2.7	255 (33)	2.2	Histology	19	0	2
University of Toronto[*] [9]	2010	70.3	450	6.8	135 (30)	NR	PSA	16	1	21.4
UCSF[*] [24]	2011	61.9	649	3.9	113 (30)[**]	3.5	Histology	–	0	3
ERSPC[*] [25]	2009	66	988	3.9	197 (32)	2.6	NR	22	0.2	11.2
Royal Marsden Hospital[*] [12]	2008	67	326	1.8	65 (20)	1.3	PSA	NR	0	2
MSKCC [13,26]	2011	62	238	1.8[***]	25 (11)	NR	Histology	NR	NR	NR
University of Miami [15,27]	2011	64	272	2.9	67 (25)	2.6	Histology	NR	0	2

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Dall'Era, et al. Eur Urol 62 (2012) 976–983

Active Surveillance: MGH Cohort

- Single institution active surveillance cohort of 469 men diagnosed with prostate cancer between 1997 and 2009
- Active Surveillance Criteria (Formalized in 2008; > 90% of cohort meet these criteria)
  - Candidate for curative treatment
  - Clinical stage T1c, T2a
  - Gleason ≤ 6 (Gleason 3+4 in select patients with low volume)
  - No more than 3 cores positive with ≤20% in each core
  - PSA <10 (<20 allowed for select subjects)
- Follow-up Protocol (Formalized in 2008)
  - PSA and DRE every 4 mo x 1 yr, every 6 mo X 2 yrs, then annually
  - Repeat 12 core biopsy at 12-18 mo
  - Additional biopsies at discretion of treating physician

MGH Study Cohort Characteristics

- Vast Majority:
  - < 75 years old
  - PSA ≤ 10
  - Gleason Sum ≤ 6
  - Clinical Stage T1c
  - Low volume disease with < 33% of cores positive

Variable	Median (range) or n (%)	Mean
N	469	
Follow-up (years)	4.8 (2-14.5)	5.6
Age (years)	68.1 (38.8-82.7)	67.4
Age <65	168 (36%)	
Age 65-75	215 (46%)	
Age >75	86 (18%)	
PSA at diagnosis	5.1 (0.4-19.2)	5.6
≤ 10	439 (94%)	
> 10	30 (6%)	
Gleason Sum at diagnosis		
≤6	461 (98%)	
7	8 (2%)	
T stage at diagnosis		
1c	441 (94%)	
2a	28 (6%)	
# biopsy cores taken	12 (5-22)	10.9
# positive cores	1 (1-3)	1.38
Diagnostic biopsies ≥ 33% of cores positive	21 (4.5%)	

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MGH Active Surveillance Results

- 65.7% of cohort had at least one repeat prostate biopsy
- Gleason Score progression defined as:
  - Any increase in Gleason Score
  - Score progression - 17.9%
- Cancer volume progression defined as:
  - Increase from <33% of cores positive to ≥33% of cores positive
  - Volume progression – 16.8%

	Median (range), N (%)	Mean
# Biopsy cores taken	12 (5-22)	10.9
# Positive cores	1 (1-3)	1.38
Post diagnosis biopsy	1 (1-5)	1.5
Number of prostate rebiopsies		
1	308 (65.7%)	
> 1	107 (22.8%)	
> 2	25 (5.3%)	
Pathologic finding on 1st rebiopsy (n=308)		
Atypia	3 (1.0%)	
Benign	67 (21.8%)	
Prostate Cancer	209 (67.9%)	
PIN	29 (9.4%)	
Gleason score progression (from Gleason 6)	55 (17.9%)	
Gleason 3 + 4 = 7	33/55 (60.0%)	
Gleason 4 + 3 = 7	13/55 (23.6%)	
Gleason 8 - 10	9/55 (16.4%)	
Cancer volume progression (from <33% positive cores to ≥33%)	52 (16.8%)	

Reason for intervention	n=116	%
Pathologic progression	52	44.8
PSA progression	35	30.2
Patient preference	14	12.1
DRE progression	6	5.2
Metastasis	3	2.6
Other	6	5.2

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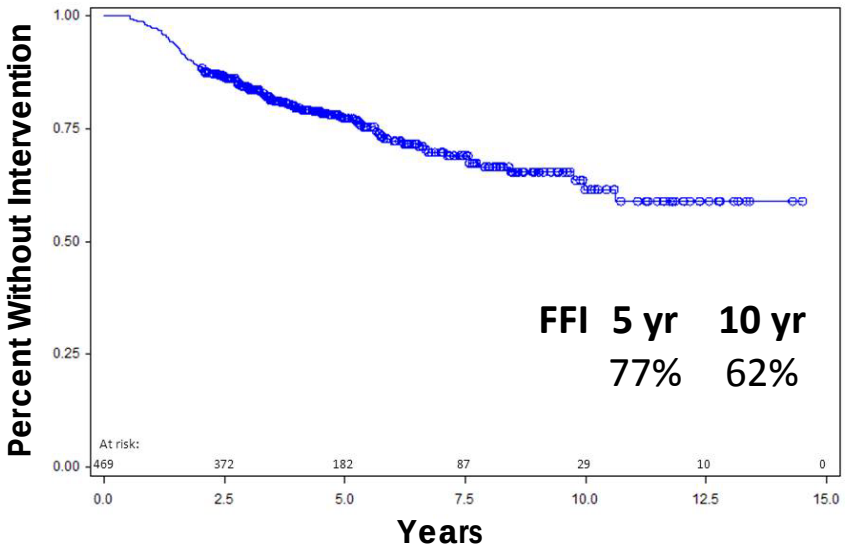
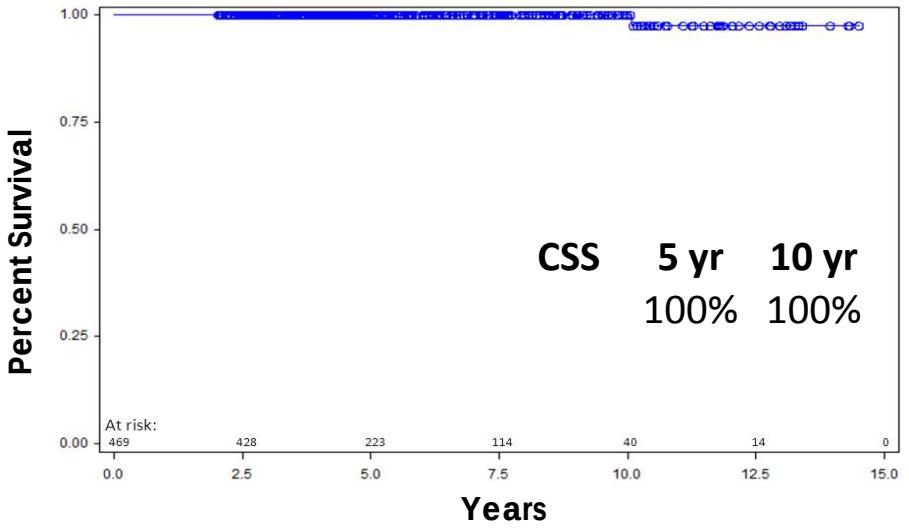
MGH Active Surveillance Results

Freedom From Intervention

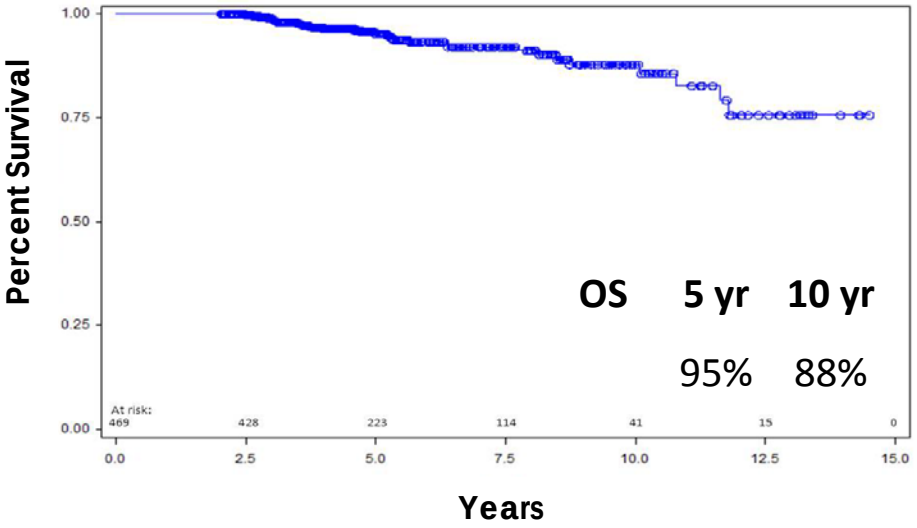


Disease Specific Survival



- 77% of patients remained on AS at 5 years and 62% at 10 years
- AS is a treatment method which spares the majority of properly selected men from intervention, provides adequate time for intervention if required, and has durable CSS and OS

Overall Survival



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- Cancer of the Prostate Risk Assessment (CAPRA) score

Risk Assessment for Prostate Cancer Metastasis and Mortality at the Time of Diagnosis

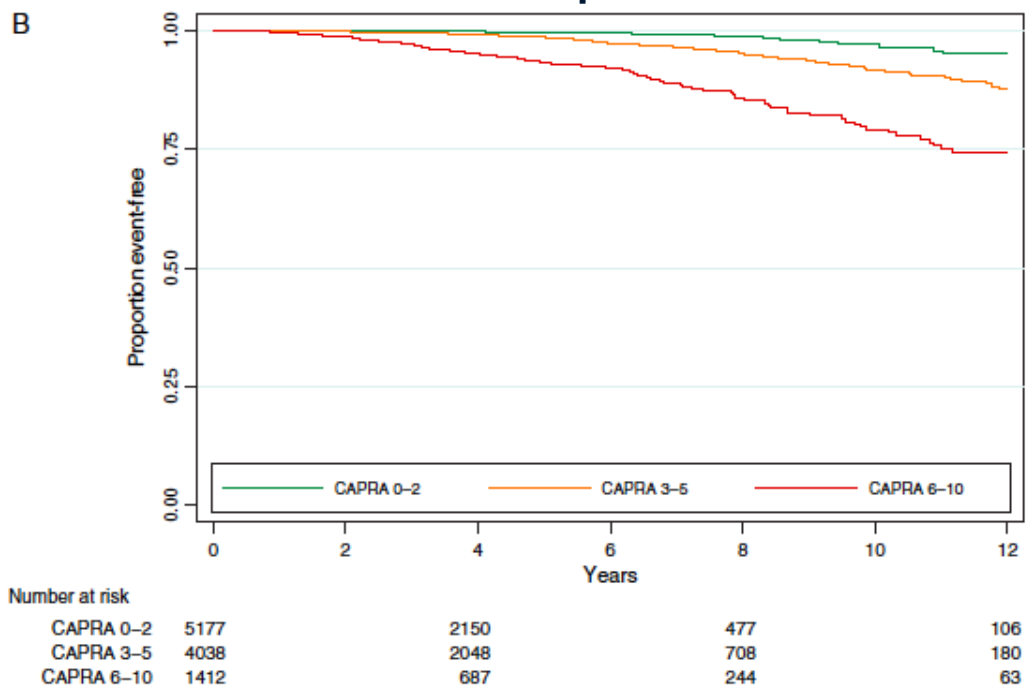
Matthew R. Cooperberg, Jeanette M. Broering, Peter R. Carroll

J Natl Cancer Inst 2009;101:878–887

Table 1. Calculation of the University of California, San Francisco Cancer of the Prostate Risk Assessment (CAPRA) score*

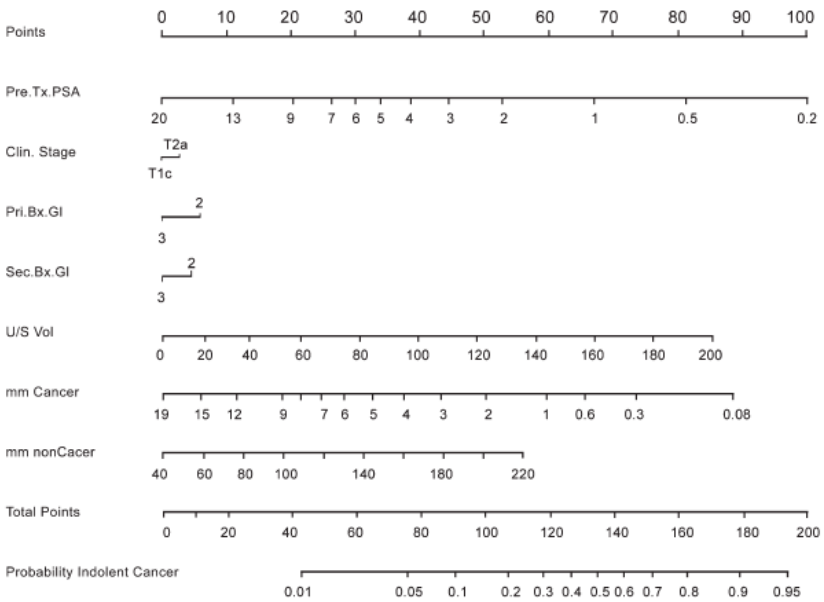
Variable	Corresponding points
PSA at diagnosis, ng/mL	
<6.0	0
6.0–10	1
10.01–20	2
20.01–30	3
>30	4
Gleason score at biopsy examination, primary/secondary pattern	
1–3/1–3	0
1–3/4–5	1
4–5/1–5	3
Age at diagnosis, y	
<50	0
≥50	1
Clinical tumor stage	
T1a–T2c	0
T3a	1
% of biopsy cores positive for cancer	
≤33	0
>33	1

Risk of PCa specific survival



Can we improve our selection of men for active surveillance?

- Nomograms
  - Kattan nomograms



Instructions for Physician: Locate the patient's PSA on the Pre.Tx.PSA axis. Draw a line straight upwards to the Points axis on determine how many points towards having an indolent cancer the patient receives for his PSA. Repeat this process for the remaining axes, each time drawing straight upward to the Points axis. Sum the points achieved for each predictor and locate this sum on the Total Points axis. Draw a line straight down to find the patient's probability of having indolent cancer.
Instruction to Patient: "Mr. X, if we had 100 men exactly like you, we would expect "predicted probability from nonogram × 100" to have indolent cancer."

Figure 1 Nomogram predicting the presence of indolent prostate cancer (pathological Gleason score ⩽3+3, cancer volume <0.5 ml, organ-confined) based on pretreatment PSA level (Pre.Tx.PSA), clinical stage (Clin.Stage), primary (Pri.Bx.Gl) and secondary (Sec.Bx.Gl) biopsy, Gleason grade, prostate volume by ultrasound (U/S Vol), length of cancer (mm) in biopsy specimens (mm Cancer) and length of non-cancer (mm) in biopsy specimens (mm nonCancer). PSA, prostate-specific antigen.

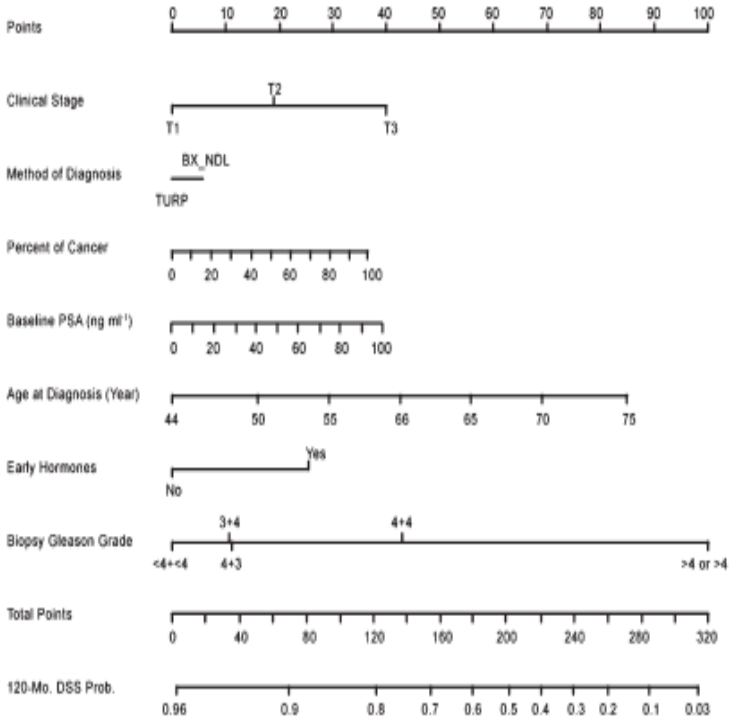


Figure 2 Nomogram for predicting 10-year disease-specific survival for men with localized prostate cancer who are initially managed with a deferred treatment strategy. The parameters included in the nomogram are clinical stage, method of diagnosis (needle biopsy (BX_NDL) vs. transurethral resection of the prostate (TURP)), percentage of cancer in the biopsy specimen, PSA level at diagnosis, age at diagnosis, the use of early androgen deprivation therapy (within 6 months of diagnosis) and biopsy Gleason score. 120-Mo DSS Prob., 120 months disease-specific survival probability. PSA, prostate-specific antigen.

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Can we improve our selection of men for active surveillance?

- Can we do better than standard pathologic parameters?

Prognostic value of a cell cycle progression signature for prostate cancer death in a conservatively managed needle biopsy cohort

J Cuzick*[,1], DM Berney[2], G Fisher[1], D Mesher[1], H Møller[3], JE Reid[4], M Perry[4], J Park[4], A Younus[4], A Gutin[4], CS Foster[5], P Scardino[6], JS Lanchbury[4] and S Stone[4] on behalf of the Transatlantic Prostate Group

[1]Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary, University of London, Charterhouse Square, London EC1 M 6BQ, UK; [2]Department of Molecular Oncology, Barts Cancer Institute, Queen Mary, University of London, London EC1 M 6BQ, UK; [3]King's College London, Thames Cancer Registry, London, SE1 3QD, UK; [4]Myriad Genetics, Inc., 320 Wakara Way, Salt Lake City, UT 84108, USA; [5]Department of Cellular Pathology and Molecular Genetics, Liverpool University, Liverpool, L1 3GA, UK; [6]Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA

Prolaris®

MYRIAD

Genomic Health™ | oncotype DX® Prostate Cancer Assay

- At what cost?
  - Prolaris = $3400 Oncotype Dx = $3800
- Will they improve outcomes for men on active surveillance in a cost-effective manner?
  - To be determined…

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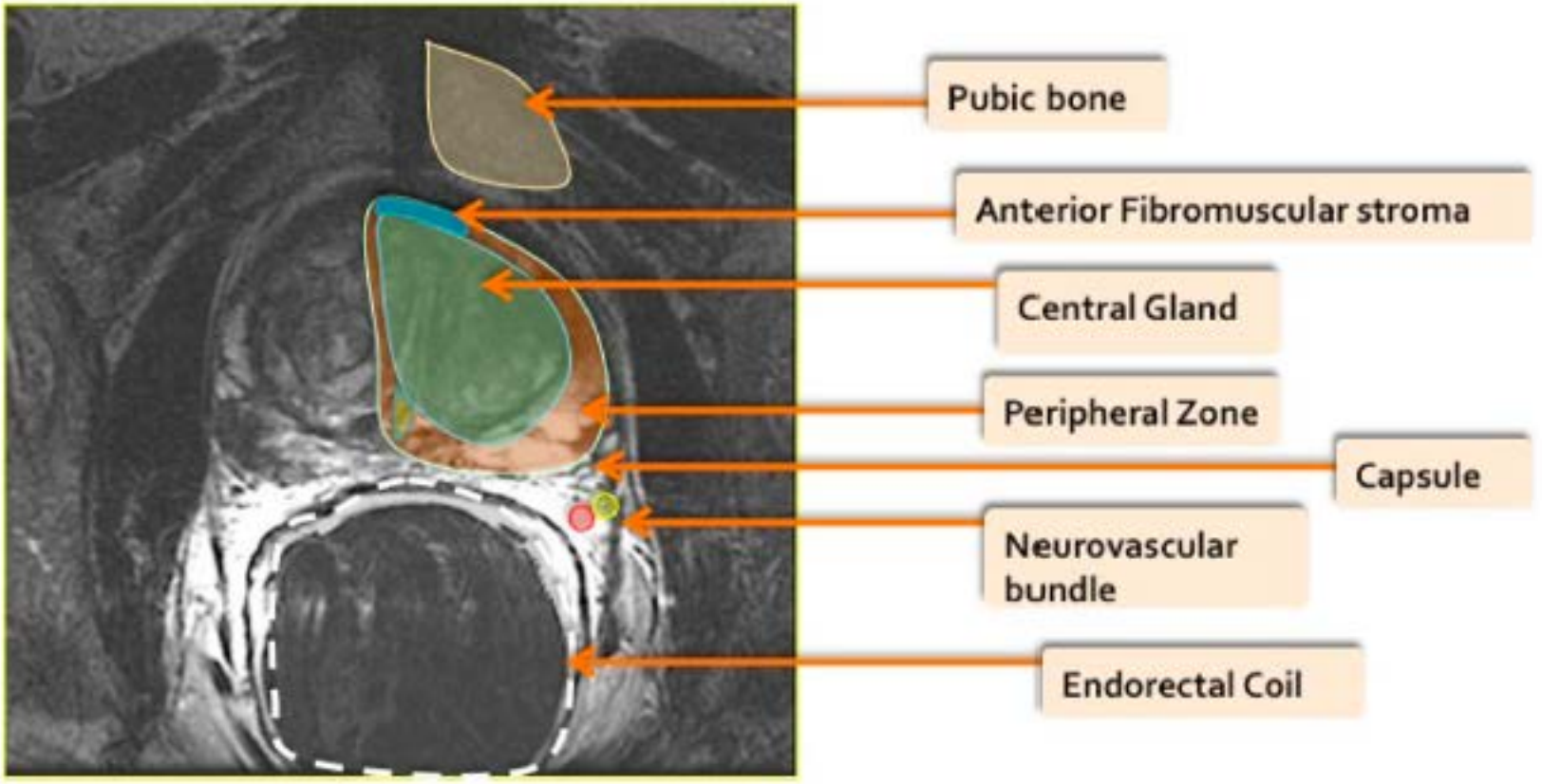
- Multiparametric endorectal coil MRI



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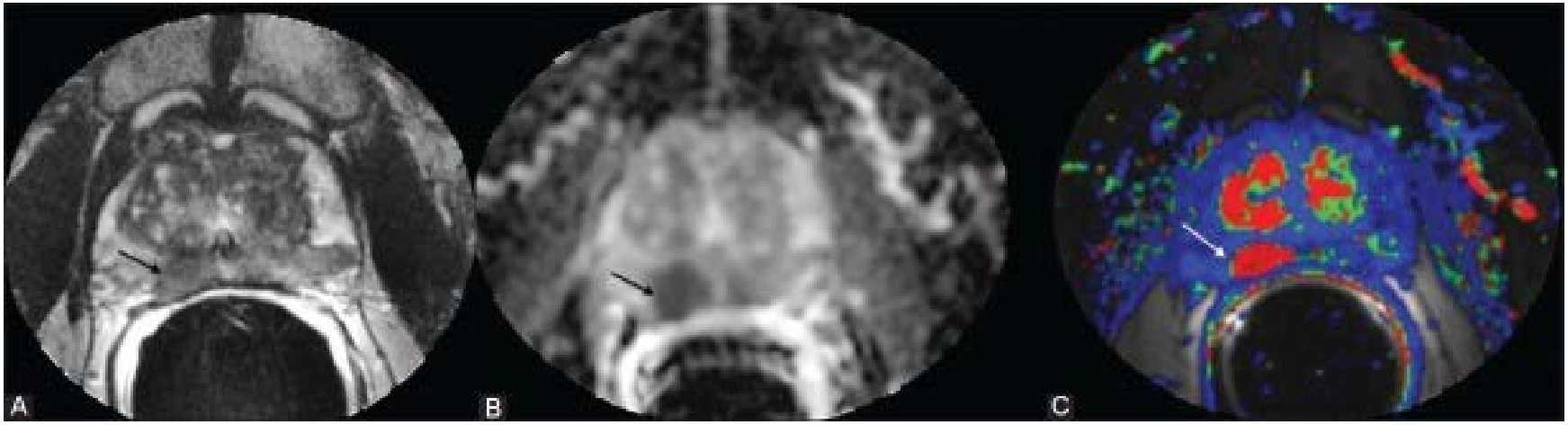
S. S. Hedgire et al.: Interpretation and reporting multiparametric prostate MRI Abdom Imaging (2014)



Multiparametric magnetic resonance imaging of prostate cancer.

Hedgire SS1, Oei TN, McDermott S, Cao K, Patel M Z, Harisinghani MG.

Indian J Radiol Imaging. 2012 Jul-Sep; 22(3): 160–169.

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Can we use imaging to rule out occult aggressive disease

Impact of Multiparametric Endorectal Coil Prostate Magnetic Resonance Imaging on Disease Reclassification Among Active Surveillance Candidates: A Prospective Cohort Study

David Margel,* Stanley A. Yap, Nathan Lawrentschuk, Laurence Klotz, Masoom Haider, Karen Hersey, Antonio Finelli, Alexandre Zlotta, John Trachtenberg and Neil Fleshner†

THE JOURNAL OF UROLOGY® Vol. 187, 1247-1252, April 2012

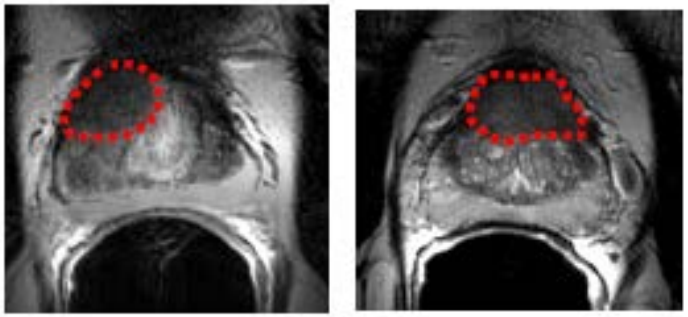
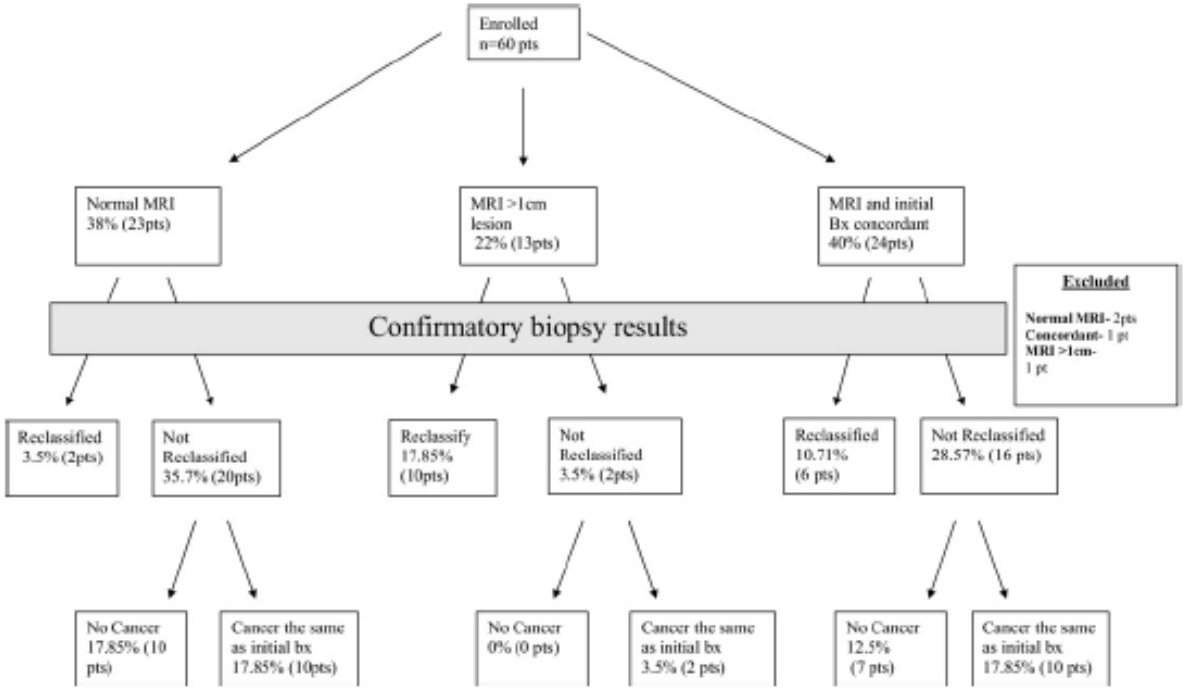


Figure 2. MRI reveals large anterior tumor missed on initial diagnosis. Red dotted outline indicates tumor.



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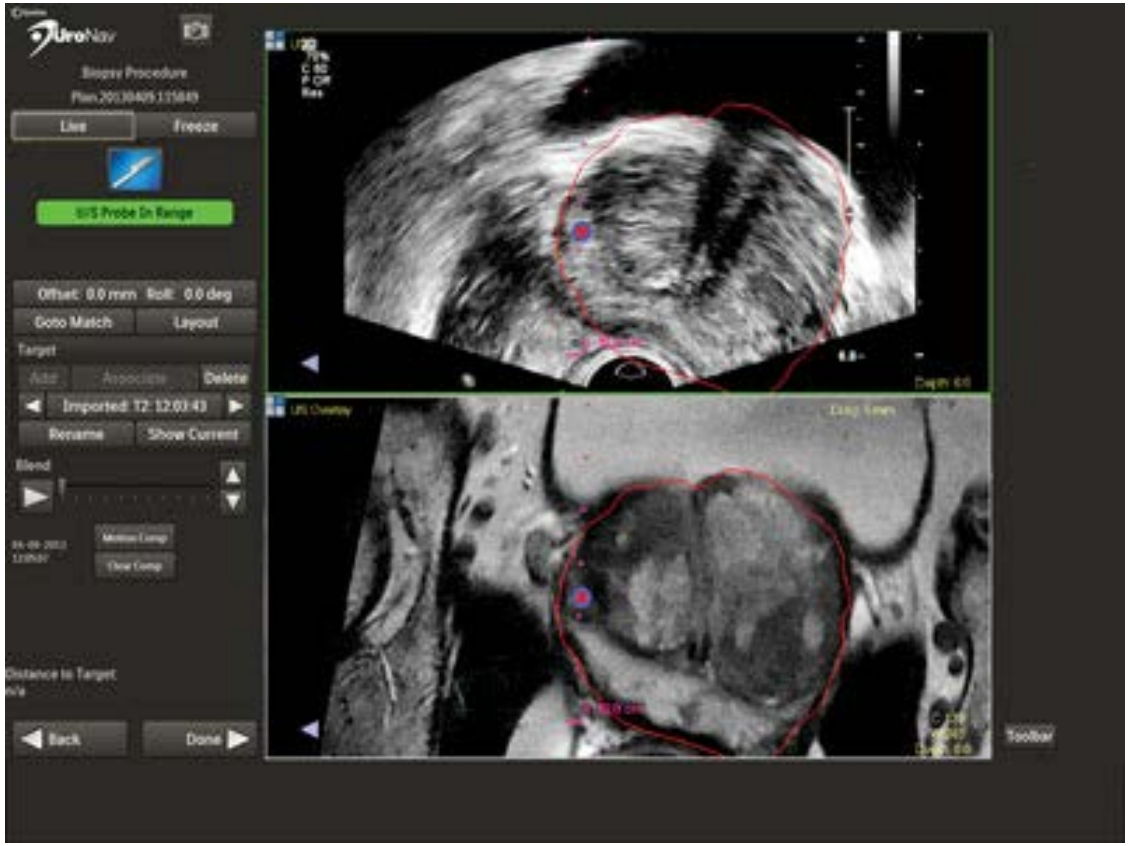
Can we use imaging to rule out occult aggressive disease

- MRI/Ultrasound fusion biopsy
- 2 planned studies at MGH:
  - Active Surveillance
  - Rising PSA + prior negative biopsy



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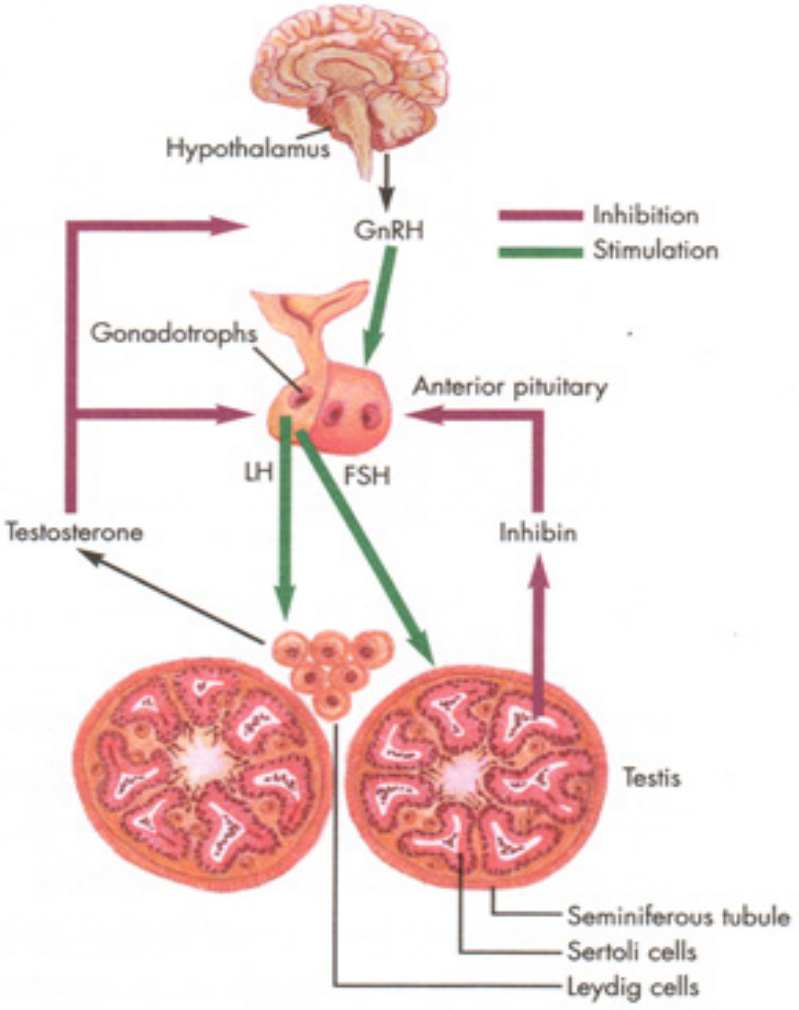
What about his questionable hypogonadism

- Mr. S asks if he can take testosterone supplementation
- Again, symptoms are: feels very tired with lack of energy, exhausted all the time, daytime somnolence x 2 yrs, Libido intact but has poor erections

Clinical features and diagnosis of hypogonadism

- Symptoms:
  - Decreased vigor and libido
  - Depressed mood
  - Decreased muscle mass and body hair – does not occur for at least a year
  - Hot flashes if severe hypogonadism
  - Gynecomastia - more likely to occur in primary hypogonadism
  - Infertility – also more common in primary hypogonadism
- Physical Exam:
  - Testicular length normally 4-7cm
  - Assess body hair and musculature– although there is normal variability
  - Gynecomastia - more likely to occur in primary hypogonadism; elevated LH and FSH stimulate testicular aromatase

HPT axis



GnRH → LH and FSH production

LH – Leydig cells → Testosterone

FSH – Sertoli cells → Spermatogenesis

Negative feedback by:

Testosterone → Estradiol, DHT

Inhibin

Hypogonadism

Endocrine status	T	FSH	LH	PRL
Primary hypogonadism	low	HIGH	HIGH	Normal
Secondary hypogonadism	low	low	low	Normal
Hyperprolactinemia	low	low	low	HIGH
Androgen resistance	HIGH	HIGH	HIGH	Normal

Primary Hypogonadism

- Congenital abnormalities:
  - Klinefelter syndrome or other chromosomal abnormalities
  - Cryptorchidism
  - Varicocele
  - Disorders of androgen synthesis
  - Myotonic dystrophy
- Acquired abnormalities:
  - Mumps orchitis (or other infection)
  - Radiation
  - Glucocorticoids
  - Alkylating agents
  - Trauma; testicular torsion
  - Autoimmune
  - Chronic systemic illness – cirrhosis, chronic renal failure, AIDS
  - Idiopathic

Secondary Hypogonadism

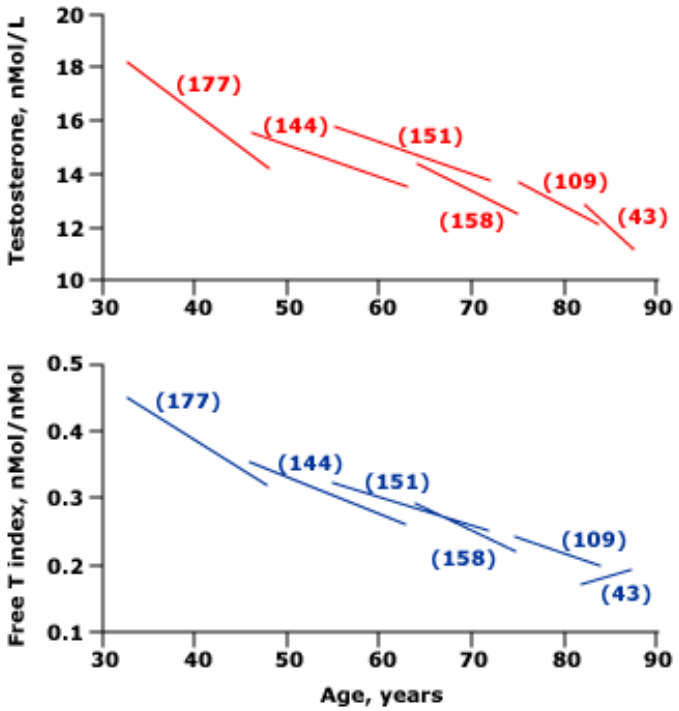
- Congenital abnormalities:
  - Kallmann's syndrome –
  - Mutations in DAX1, GPR54, Leptin or receptor, Gonadotropin subunit
  - Pituicyte differentiation gene mutations
- Acquired abnormalities:
  - Suppression of gonadotropins:
    - Hyperprolactinemia
    - Meds/drugs: Gonadal steroid use, glucocorticoid treatment, opiates
    - Critical illness or chronic systemic illness
    - Diabetes mellitus
    - Idiopathic
  - Damage to gonadotroph cells: tumors, infection, trauma, surgery, radiation

Laboratory evaluation

- Serum total testosterone
  - Maximum testosterone level around 8am
  - If low, should be repeated as there can be fluctuation
- Free testosterone – not bound to sex-hormone binding globulin (SHBH)
  - May be helpful in obesity, which can reduce binding to SHBH and SHBH serum concentration
  - Increased binding in male senescence
- LH and FSH –when T low to determine primary or secondary
- Pituitary function testing in acquired secondary hypogonadism:
  - Prolactin, cortisol (8am), thyroxine, iron saturation
  - Brain MRI if other pituitary hormonal abnormalities, visual field deficit, or other neurologic abnormality

Changes with Age

- Decrease in total testosterone
- Increase in SHBH
- Decrease in free testosterone
- Decline in spermatogenesis
- Increase in gonadotropins
  - FSH > LH



Baltimore Longitudinal Study of Aging:

Harman SM, et al. J Clin Endocrinol Metab 2001; 86:724

Massachusetts Male Aging Study:

Travison TG, et al. J Clin Endocrinol Metab 2007; 92:549

European Male Aging Study:

Wu FC, et al. J Clin Endocrinol Metab 2008; 93:2737

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Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes:

An Endocrine Society Clinical Practice Guideline

We recommend that clinicians assess prostate cancer risk in men being considered for testosterone therapy. We recommend against testosterone therapy without further urological evaluation in patients with palpable prostate nodule or induration or PSA > 4 ng/ml or PSA > 3 ng/ml in men at high risk of prostate cancer, such as African Americans or men with first-degree relatives with prostate cancer. (1 | ⊕◯◯◯)

TABLE 4. Conditions in which testosterone administration is associated with a high risk of adverse outcome and for which we recommend against using testosterone

Very high risk of serious adverse outcomes

- Metastatic prostate cancer
- Breast cancer

Moderate to high risk of adverse outcomes

- Unevaluated prostate nodule or induration
- PSA > 4 ng/ml (>3 ng/ml in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
- Hematocrit >50%
- Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by AUA/IPSS score >19
- Uncontrolled or poorly controlled congestive heart failure

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But there is controversy in men with prostate CA

A summary of the available studies that have used TST in men with previously diagnosed PCa. *J.R. Kovac et al./Steroids 89 (2014) 27–32*

Author	Year	Study design	Patient #	Type of tx	Results
Calof et al.	2005	Meta-Analysis	644	TST in men with no hx of PCa	Rates of PCa, PSA >4 ng/ml, and biopsies were higher in the TST group than in placebo although differences between the groups were not statistically significant. Higher incidence of hematocrit >50% in TST group. The frequency of CV events, sleep apnea or death was not significantly different between the two groups.
Shabsigh et al.	2009	Systematic Review	2292	Various	No studies demonstrated that TST increased PCa risk or increased Gleason grade in treated vs untreated men. TST did not have a consistent effect on PSA.
Morgentaler et al.	2011	Retrospective case series	13	TST in men with untreated Pca	Mean serum total testosterone increased from 238 to 664 with no significant change in PSA or prostate volume. Biopsies in 2 men suggested upgrading. Repeat biopsy in one man and a prostatectomy in another indicated no progression. No local progression or distant disease.
Morales	2011	Retrospective case series	7	TST in men with untreated Pca	Unpredictable, variable increase in PSA with TST. Interruption of TST invariably decreased PSA to pre-therapy levels.
Morgentaler	2009	Case report	1	TST in a man with untreated Pca	Overall decline in PSA after receiving TST for 2 years. No clinical progression of disease noted.
Rhoden & Morgentaler	2003	Retrospective case series	75	TST in men with and without high grade PIN	PSA similar at baseline and 12 mo after TST in men with and without PIN. One man in the PIN+ group was found to have cancer on biopsy after abnormal DRE.
Sarosdy	2007	Retrospective case study	31	TST in men after brachytherapy for early prostate cancer	None showed recu… all patients.
Morales et al.	2009	Prospective case study	5	TST in men after external beam radiotherapy	One of five patients had transitory increase in PSA after a mean follow-up of 14.5 months. None had PSA levels >1.5 ng/ml. Mean serum testosterone and improvement in hypgonadal symptoms increased significantly.
Pastuszak et al.	2013	Retrospective case series	13	TST after radiation therapy for Pca	At median follow-… increase in mean testosterone… bin hematocrit PSA. No significant… any follow-up interval
Pastuszak et al.	2013	Retrospective case series	103	TST in men after radical prostatectomy	At median follow-… one and PSA in both high risk and non-high risk prostate cancer groups. Referrals to radiation oncology or subsequent salvage therapy more frequent in reference control group. Significantly increased number of T3b tumors in reference group vs TST group.
Agarwal & Oefelein	2005	Retrospective case series	10	TST in men after radical prostatectomy	At median followup of 19 months, all patients had PSA <0.1 with statistically significant improvements in serum testosterone and hypogonadal symptoms.
Kaufman & Graydon	2004	Retrospective case series	7	TST in men after radical prostatectomy	No biochemical or clinical evidence of cancer recurrence. PSA remained <0.1 in all patients.
Khera & Lipshultz	2009	Retrospective case series	57	TS\T in men after radical prostatectomy	After a mean follow up of 13 months after initiation of TST after radical prostatectomy, no increases in PSA values were noted.

Small series

Relatively short follow-up

Controversy over cardiovascular risks

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 8, 2010 VOL. 363 NO. 2

Adverse Events

Shehzad Basaria, M.D.,
Wildon R. Farwell, M.
Jagadish Ulloor, Ph
Norman A. Mazer, M.D., Ph.D
Brad Brooks, B.S., E
Leif Hede-Brierley, A

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD;
Thoma
Margar

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JAMA

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle[1]*, Sander Greenland[2], Gregory K. Ridgeway[1], John L. Adams[1], Melissa A. Frasco[1], Michael B. Cook[3], Joseph F. Fraumeni Jr.[3], Robert N. Hoover[3]*

1 Consolidated Research, Inc., Los Angeles, California, United States of America, 2 Department of Epidemiology and Department of Statistics, University of California, Los Angeles, California, United States of America, 3 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

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