Men’s Health: Benign Prostatic Enlargement and Prostate Cancer

Mikel Gray, PhD, PNP, FNCP, CUNP, FAANP, FAAN
University of Virginia
Department of Urology & School of Nursing
Charlottesville, VA

Objectives

• Define and discuss most prevalent urologic issues encountered in older men:
  – Lower Urinary Tract Symptoms (LUTS); their clinical relevance in older men and its relationship to prostatic disorders (benign prostatic enlargement and prostate cancer)
  – Erectile Dysfunction in men, including its epidemiology, pathophysiology, evaluation and treatment
• Outline latest advances in assessment and management of prostate cancer

Learning Outcome

• At the end of this lecture the learner will:
  – Evaluate, manage and refer men with prostate enlargement or prostatic cancer.
Anatomy and Physiology of the Prostate and Lower Urinary Tract

LUT in the Male: Anatomy

- Lower urinary tract in men consists of bladder, urethra, and pelvic floor muscles
  - Urinary bladder: base at superior border of symphysis pubis
  - Urethra: longer and more tortuous than female; proximal male urethra functionally comparable to female urethra
  - Pelvic floor muscles: denser and stronger than female; descent of bladder base not clinical predictor of LUTS as with female
Prostatic Anatomy and its Relation to Lower Urinary Tract

- 70 glands with 30-50 lobules leading to 15-30 secretory ducts
- Weight: 20 ± 6 grams
- Seminal vesicles adjacent to prostate, secrete but do not store semen
  - Acini is a secretory duct lined by smooth muscle

The Prostate: Relationship of Size & Age

20 grams   50-60 grams   140-150 grams

LUTS, Prostate Enlargement (BPH) and Erectile Dysfunction
Pathophysiology of BPH

Definitions

- Prostatic enlargement is the most common cause of **lower urinary tract symptoms** (LUTS) in aging men.
- 3 terms are frequently used to describe the clinical phenomenon we are discussing: enlargement (BPE), hyperplasia (BPH), and bladder outlet obstruction (BOO).

Etiology of BPH: Traditional Understanding

**BPH: Current Understanding**

- Androgens do **not** cause BPH per se; they are necessary for prostatic growth and maintenance.
- Hyperplasia is imbalance between cell proliferation and programmed cell death (apoptosis).
- **Growth factors** are more likely etiologic factors.


**Pathophysiology of BPH: Bladder Outlet Obstruction**

- Prostatic growth creates BOO when it constricts the urethral lumen; hypertrophy of smooth muscle in the prostate is a secondary cause.
- Analogy of the doughnut with its hole applies: size is only **weakly** correlated with magnitude of obstruction.

**Assessment**
3 Main Components

- **History**
  - Evaluate LUTS
  - LUTS Symptom Score
  - Focused review of systems
- **Physical Examination**
  - Abdominal examination
  - Digital rectal examination (DRE)
- **Laboratory Testing**
  - Urinalysis
  - ± Serum Creatinine*
  - ± PSA*

* Highly selected cases only

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History: Assessing LUTS

[Images and diagrams related to storage and voiding symptoms]

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Pathophysiology of Male LUTS: Myths & Realities

- Prostatic enlargement is **not** the single cause of LUTS in men
- LUTS is caused by obstruction (BOO), overactive bladder (OAB), detrusor changes associated with BOO and **and** aging, polyuria, and multiple other factors

[Diagram showing connections between Prostate Enlargement, BOO, Urodynamic Response, OAB, LUTS, and Comorbidities]
History: Storage LUTS

- **Daytime Voiding Frequency**: report of voiding too frequently
  - Normal range: ≤ 8 voids / 24 hours or ≤ 2 hours while awake
- **Nocturia**: interruption of sleep owing to desire to urinate
  - Normal range: absence of enuresis by end of 5th year of life; 0-2 episodes considered normal; ≥3 considered clinically relevant
- **Classic Urgency**: sudden and compelling desire to urinate that is not easily postponed or deferred
- **Nociceptive Urgency/LUT Pain**: burning or pressure felt in suprapubic or retropubic areas; in this case, urgency is provoked by pain
- **UI**: involuntary urine loss
  - Urgo urine loss with urgency and detrusor overactivity

2.  

History: Other LUTS

- **Voiding LUTS**
  - Slow stream (weak or poor force of stream)
  - Intermittent stream (stars & stops >1 time)
  - Hesitancy (difficulty initiating stream)
  - Terminal dribble (prolonged end to micturition, when the flow has slowed to a trickle/dribble)
- **Post-void LUTS**
  - Post-void dribbling (involuntary loss of urine immediately person has finished passing urine, for men when leaving the toilet)
  - Incomplete emptying


LUTS Tool: IPSS/AUA-7

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain in lower back</td>
<td>0</td>
</tr>
<tr>
<td>Pain in lower abdomen</td>
<td>0</td>
</tr>
<tr>
<td>Pain in penis</td>
<td>0</td>
</tr>
<tr>
<td>Pain in scrotum</td>
<td>0</td>
</tr>
<tr>
<td>Pain in perineum</td>
<td>0</td>
</tr>
<tr>
<td>Pain on coughing or sneezing</td>
<td>0</td>
</tr>
<tr>
<td>Pain on straining</td>
<td>0</td>
</tr>
<tr>
<td>Pain on change of position</td>
<td>0</td>
</tr>
<tr>
<td>Pain on sitting</td>
<td>0</td>
</tr>
<tr>
<td>Pain on lying supine</td>
<td>0</td>
</tr>
<tr>
<td>Pain on ambulation</td>
<td>0</td>
</tr>
<tr>
<td>Pain on sexual activity</td>
<td>0</td>
</tr>
<tr>
<td>Pain on defecation</td>
<td>0</td>
</tr>
</tbody>
</table>

Do you have pain in:
- Lower back? [ ]
- Lower abdomen? [ ]
- Penis? [ ]
- Scrotum? [ ]
- Perineum? [ ]
- When you cough or sneeze? [ ]
- When you strain to void? [ ]
- When you change position? [ ]
- When you are lying down? [ ]
- While you are moving? [ ]
- While you are having sexual activity? [ ]
- While you are having a bowel movement? [ ]

Scoring: 0-8 = Mild LUTS, 9-19 = Moderate LUTS, 20-35 = Severe LUTS
History: ROS

• Focused Review of Systems
  – Urologic: UTI, stones, tumors, etc.
  – Male Reproductive: prostate problems, stricture, erectile dysfunction
  – GI: bowel elimination patterns, fecal continence
  – Neurological: CNS disorders, disc disease, neurogenic bladder triad (bowel, bladder, sexual dysfunction)

History: Current Medications

– Sedatives/ hypnotics/ narcotics/ anxiolytics: ↓ awareness of bladder fullness
– Antidepressants/ antipsychotics/ drugs for parkinsonism anticholinergic effects
– Calcium channel blocker ↓ detrusor contraction strength (especially when administered with anticholinergic drugs)
– Diuretics: polyuria may exacerbate urgency
– Alpha Adrenergic agonists (decongestants)/ centrally acting antihistamines: ↑ risk of urinary retention

Physical Examination
Physical Examination

- **General Approach**
  - Height and weight (cachexia/constitutional signs with malignancy, obesity with endocrine disorders)
  - **Cognitive & functional status**
  - **Locus of control**

Male GU Assessment

- **Percussion of Bladder and Evaluation of Acute or Chronic Urinary Retention**
  - Inspect for midline mass in lower abdomen (LLQ and RLQ)
  - Percuss midline; starting well above midline, fluid in bladder percusses as “dull”, gas in bowel resonant
  - Bladder must contain 150 ml to be detectable via percussion

Physical Examination: Abdominal Examination

- Inspect Abdomen for midline mass with severely distended bladder
- Percuss from midline to detect residual urine
  - Dull to percussion above symphysis pubis ≥ 150 ml
  - Dull to percussion around umbilicus ≥ 500 ml
Assessment: Digital Rectal Examination (DRE)

- Multiple Purposes: assess prostatic size, consistency, symmetry between lobes, stool or mass in rectal vault

Palpating the Prostate

- We describe prostate as having lobes in context of physical assessment
  - Do not exist as distinct anatomic entities
  - You are looking for 2 lateral bulges (lobes) with central valley or depression (sulcus)
  - BPH: symmetric enlargement of prostate with loss or "flattening" of central sulcus
  - Cancer: asymmetric enlargement of lateral lobes or nodules

DRE: Estimate Prostate Size

20 grams  50-60 grams  140-150 grams

IN A HEALTHY  IN SOME SEVERE CASES OF  IN A HEALTHY PROSTATE: A BASEBALL
ADULT MAN... PROSTATE... A BEDBALL
Assessment: Routine Study

• Urinalysis
  • Dipstick:
    – UTI (nitrites & leukocytes)
    – Diabetes mellitus (glucose)
    – Diabetes insipidus/ water intoxication (specific gravity)
    – LUT tumor (blood, RBC)
  • Microscopic examination
    – UTI (WBC & bacteria)
    – LUT (red blood cells)

Assessment: Studies in Selected Men

• Catheterization
  – Gold standard for accuracy
  – 1%-2% risk of UTI, small risk of urethral trauma/ bleeding

• Ultrasonic PVR:
  – More expensive but noninvasive with no risk of UTI
  – Reasonable accuracy as compared to catheterization
  – Equipment easy to learn and use

Assessment: Studies in Selected Men

• PSA: when indicated, will discuss in part 2 of this presentation
• Serum creatinine: routine testing not supported in AUA clinical practice guideline for BPH BPE/BPH and acute urinary retention, febrile or recurring UTI

Assessment:
Studies in Selected Men

• **Urodynamic Testing**
  — *Highly selected patients*
  — Defines pathophysiology of LUTS
  — Determine cause of urinary retention
  — Typically completed in context of referral to specialist or prior to surgical intervention

AUA/SUFU. Clinical Practice Guideline: Adult Urodynamics 2012; http://www.auanet.org/content/media/adult_urodynamics_guideline.pdf

Management

Management Options

• **Watchful waiting vs Active Surveillance**
  — Behavioral interventions
  — Prevention/management of AUR

• **Pharmacologic**
  — 5-α reductase inhibitors
  — α-adrenergic antagonists

• **Surgical**
  — Open, transurethral or minimally invasive procedures
Watchful Waiting (WW) vs Active Surveillance

- **Watchful waiting**: taking no immediate action; requires careful follow-up to monitor progression and contingency plan for intervention if serious complications or progression-related sequela occur.
- **Active surveillance** combines watchful waiting with behavioral or other interventions designed to prevent complications and sequela.

URL: http://medical-dictionary.thefreedictionary.com/active+surveillance

Active Surveillance (WW)

- **Rationale**
  - Slow progression in most; remission in many; maximum uroflow rate ↓ about 2% per year and prostate size ↑ about 1.9%.
  - Best prospective cohort study is Olmsted County cohort; about 15%–17% (about 1 in 6) will have significant progression within 5 years, 3% will experience episode of AUR, <1% will develop renal insufficiency.
  - Need greater research in non-white males.

Self-Management for LUTS associated with BPH

- Concept of self-management offshoot of behavioral interventions for UI; useful for raising WW to active surveillance and as adjunctive with pharmacotherapy.
- Sparse research demonstrates self-management strategies as feasible and providing health related quality of life (HRQOL) and magnitude of bother associated with LUTS when compared to WW alone².

Self-Management for LUTS associated with BPH

• **Education & Reassurance**
  - Discuss prostate enlargement and its relationship to LUTS; explain its natural history
  - Differentiate BPH from prostate cancer

• **Fluid management**
  - Fluid intake as described earlier (1500ml-2000ml), fluid restriction when toilet access limited
  - Restrict fluids 2 hours before HS when nocturia is a problem

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Self-Management for LUTS associated with BPH

• **Caffeine & Alcohol**
  - They advise elimination of caffeine; alternative is restriction based on access to toilet and personal preference
  - Substitute high volume with lower volume alcohol; consume in moderation and avoided 2 hours before HS

• **Concurrent medications**
  - Consider dosage and timing of diuretic based antihypertensives

• **Miscellaneous**
  - Avoid constipation

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Self-Management for LUTS associated with BPH

• **Toileting behaviors**
  - Teach men to double void, especially when incomplete emptying (urinary residuals) have been documented
  - Counsel about urethral milking for post-void dribbling
  - Consider habit training/ retraining and urge suppression for BPH with urgency

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Behavioral Interventions: In my clinical experience...

• Teach men to prevent or manage Acute Urinary Retention (difficulty voiding)
  – Void on regular basis; every 3 hours or so
  – Warm up when shivering and attempting to void
  – Modify alcohol intake as noted previously, avoid binge drinking (≥ 5 units per day)
  – When experiencing difficulty voiding
    • Drink caffeinated beverage to bolster desire to urinate
    • Take warm shower or sit in tube with warm water to boost voiding
    • Seek immediate assistance if unable to void for more than 6 hours despite desire to urinate
  – Avoid OTC decongestants or antihistamines

Pharmacotherapy for LUTS with BPH

• α-adrenergic receptor blockers
  – Doxazosin (Cardura): 1, 2, 4, 8 mg daily (should be titrated)
  – Terazosin (Hytrin): 1, 2, 5, 10 mg daily (should be titrated)
  – Tamsulosin (Flomax): 0.4 mg daily ½ hour after meal
  – Alfuzosin (Uroxatral): 10 mg daily after meal
  – Silodosin (Rapaflo): 8 mg daily after meal

• 5α-reductase inhibitors
  – Finasteride: 5 mg daily
  – Dutasteride: 0.5 mg daily

• Combination therapy
  – Tamsulosin + dutasteride (Jalyn)

• Phosphodiesterase inhibitors
  – Tadalafil
**Adrenergic Receptors in the LUT**

- $\alpha$-adrenergic receptors predominate in urethral smooth muscle, subtypes ($\alpha_{1L}$ and others)
- $\alpha$-adrenergic receptor blockers relax smooth muscle of prostate and proximal urethra
- Also thought to act on bladder and spinal cord; precise nature of these actions are not clear


**Pharmacotherapy: $\alpha$-adrenergic blockers**

- **Historical Perspective**
  - Prazosin & dibenzyline oldest; not recommended in current CPG (no evidence)
  - Doxazosin (Cardura) & Terazosin (Hytrin) more uro-selective and longer acting
  - Tamsulosin (Flomax), alfuzosin (Uroxatral), silodosin (Rapaflo) do not require titration as do others listed above; they are even more receptor specific, AKA “uroselective”


**$\alpha$-adrenergic blockers**

- Doxazosin, start 1 mg at HS, titrate to 4-8 mg and Terazosin start at 1 mg HS then titrate to 5-10 mg; effect within days to several weeks, does not effect prostate size
  - Higher risk of postural dizziness as SE than newer agents, requires titration; assess blood pressure
  - Uncommon to rare SE include profound fatigue, rhinitis, lower prevalence of retrograde ejaculation than tamsulosin or silodosin
  - No evidence they are less effective than more selective drugs in this class
  - Inexpensive, generic forms available

α-adrenergic blockers

- Tamsulosin, Alfuzosin, Silodosin do not require titration
  - Equal efficacy to long-acting agents but specificity to α-adrenergic receptors in proximal urethra and prostate up to 162 fold higher
  - Postural dizziness less likely than doxazosin or terazosin; sexual dysfunction (retrograde ejaculation more prevalent; it is least prevalent in alfuzosin)

Pharmacotherapy

- Potential adverse side effects of α-adrenergic blockers
  - Floppy iris syndrome: progressive pupillary constriction occurs in 2% of patients undergoing cataract surgery, causes iris to prolapse toward area of cataract extraction with impairment or loss of vision, discontinue these drugs (especially tamsulosin, but all in class have been linked) 2 weeks prior to surgery

5α reductase inhibitors

Act by blocking enzyme in the metabolic pathway that converts T to DHT; 2 receptors involved here, Type 1 and Type 2
Pharmacotherapy: 5 alpha-reductase inhibitors

• Finasteride* and Dutasteride
  – Slower effect in both drugs as compared to the alpha-adrenergic blockers, dutasteride is more 45 x more potent inhibitor of type 1 5AR (5 alpha-reductase) receptors than finasteride and slightly more potent type 2 5AR receptor inhibitor (2.5 x)
  – Head to head trial (EPICS) showed no significant difference in reductions in prostate size, maximum flow rate, symptom scores at 12 weeks; both require 24 weeks (6 months) for maximum effect
  – No differences in efficacy or side effect frequency when measured at 12 months


Pharmacotherapy: 5 alpha-reductase inhibitors

• Finasteride and Dutasteride
  – Reduce serum about 50%; this must be accounted for if PSA levels are being used for early detection of prostate cancer or when monitoring PSA as part of active surveillance of prostate cancer
  – Was not approved for prevention of prostate cancer by US FDA after extensive trials of both drugs
  – Should not be used for men with LUTS and BPH without evidence of prostate enlargement on DRE, use alpha-adrenergic blockers in these men when beginning pharmacotherapy
  – Can be used for men with refractory hematuria associated with BPH; research is limited to finasteride but similarity in agents renders it likely both may perform similarly


Pharmacotherapy: 5 alpha-reductase inhibitors

• Adverse Side Effects of 5 alpha-reductase inhibitors
  – Erectile dysfunction
  – Impaired libido (permanent in very rare cases)
  – Diminished ejaculatory volume (not retrograde)
  – Gynecomastia
  – Hypertension
  – Acute urinary retention

Selecting a Drug

• Both drug classes are appropriate for first line therapy for BPH with moderate to severe LUTS (AUASS ≥8)
• 5-α-reductase inhibitors appropriate in men with estimated prostatic size > 30 grams; they are not recommended in men with smaller prostate glands
• Select α-adrenergic blocker if prostate volume small
• 5-α-reductase inhibitors appropriate when BPH accompanied by BPH-related hematuria


Consider Combination Therapy

• Combination therapy
  — More effective than monotherapy in 2 large studies, MTOPS and COMBAT
  — Single agent combines 2 classes in single capsule (Jalyn: tamsulosin + dutasteride)
  — Best for larger glands with moderately severe to severe LUTS or following episode of AUR


BPH: Phytotherapeutic Agents

• Saw palmetto (Serenoa repens) most commonly used in US
  — Active ingredients uncertain, contains more than 100 fatty acids
  — Many OTC formulations available; the amount of Saw Palmetto in each varies widely; some are undetectable
  — Price may be a good indicator of likelihood of amount of detectable Saw Palmetto

Pharmacotherapy for Men with BPH and OAB (urgency ± Urge UI)

- Tradition states that BPH with BOO is a contraindication for use of antimuscarinic drugs owing to risk of Acute Urinary Retention
- Significant body of research supports combination therapy as feasible, safe, and more effective than monotherapy


What about the patient with BPH and OAB?

- Start with drugs indicated for BPH
  - 5α-reductase inhibitor ± α-adrenergic blocker
  - Add antimuscarinic drug of choice if urgency persists after reasonable trial with BPH agent (about 6-12 weeks)
  - Proceed with considerable caution if elevated urinary residual volume found (>250-300 ml); poor detrusor contractility associated with elevated residuals and ↑ risk for acute urinary retention


BPH: Surgical Management

- Open prostatectomy
- TURP* (gold standard)
- TUIP (transurethral incision)
- VaporTrode
- Laser techniques
- Microwave therapy (TUMT)
- TUNA (transurethral needle ablation)
Surgical Treatment: Latest Trend

• Prostatic urethral lift
  – Surgeon uses non-absorbable tensioned sutures to retract obstructive encroaching lateral lobes
  – Designed to avoid morbidity associated with traditional TUR type therapies, especially retrograde ejaculation.

Prostate Cancer

Epidemiology

• Facts & Figures
  – 220,800 new cases in 2015 (20.7% of total in Caucasian, 49.8% in AA/ blacks; most common new diagnosis)
  – Second leading cause of cancer related deaths (behind lung) 27,540 in 2015 (∼ 10% of total)
  – Prostate CA deaths ↓ between 2006 and 2011
  – >90% of all cancers affecting prostate are adenocarcinomas

Cancer Facts & Figures 2015:
Epidemiology

• 2 forms of prostate cancer: some die with disease and some die because of this disease.¹,²
  – Latent (incidental): most prevalent; 65% of all prostate cancers diagnosed in men > 65 years of age; majority will die with disease owing to non-related causes
  – Clinically aggressive (biologically aggressive): especially prevalent in younger men (< 50 years of age)


Epidemiology: Risk Factors

• Race: African Americans (almost 2x) > European American > Japanese (living in Japan)
• Family history: 2 first degree relatives with prostate cancer increase 3.5 fold; 3 first degree relatives have an 11 fold risk
• 15% of cases are familial/ genetic; 85% classified as “sporadic”


Epidemiology: Dietary Risk Factors¹,²

• Grilled or processed meats: ↑ risk when 5 or more servings consumed per week
• Animal or saturated fats: high intake (not quantified)

Epidemiology: Dietary Protective

- Lycopene and tomato: 2 servings/week; 5mg lycopene/day; cooked better than raw (alternative flavonoid sources: apples, onion, tea, red wine, parsley, thyme)
- Selenium: ↑ levels reduce risk and likelihood of invasion (Brazil nuts, tomato sauce, cod, turkey)


Epidemiology: Protective Dietary Substances

- Several popular dietary sources lack sufficient evidence to label protective or refute as having no protective effect
  - Green tea: contain flavonoids1-3; weak evidence suggests 3-5 cups/day needed
  - Red wine: has polyphenol antioxidants that ↓ PC cells in in vivo (animal model) studies; California men’s health study found no protective effect in humans4
  - Others include phytoestrogens, weak supportive evidence (soya, tofu, miso, etc.)1


Epidemiology: Chemoprevention

- Selenium: no protective effects (± vitamin E) in 2 large RCT (SELECT, Physician’s Health Study III)1,2
- Vitamins E or C: no protective effects (± selenium) in 2 large RCT (SELECT, Physician’s Health Study III)1,2
- Aspirin/NSAID: may ↓ risk of multiple cancers through variety of essentially antiinflammatory actions; requires daily administration over 10 year period; must weigh against SE (ACS advises against)2
- Statins: growing evidence suggests regular use of statins may ↓ risk of prostate CA

Screening and Early Detection

Prostate Specific Antigen

- Excreted exclusively from prostatic duct cells
- Elevated whenever prostate is metabolically active; due to sexual activity, benign growth, inflammation, trauma (no significant ↑ with DRE), malignancy
- Normal range <4ng/ml; if PSA is 4-10 ng/ml 31% will have prostate CA, if PSA is >10ng/ml 50%-65% will have prostate CA
- Bound PSA more closely associated with prostate cancer (>25% of PSA unbound indicates ↑ likelihood of no cancer)


Routine PSA Testing: Indicated? Justified?

- Screening undoubtedly effective at increasing detection rate of prostate CA but does not differentiate latent vs aggressive forms
- ↑ risk of overtreatment...
- Results of 2 large trials have shifted nature of ongoing debate dramatically

**Does DRE + PSA reduce prostate cancer mortality?**

- **US Study**
  - 76,693 men; 38,343 allocated to annual screening vs 38,350 men allocated to "usual care"
  - After 7 years: incidence of death per 10,000 person-years was 2.0 in screening group vs 1.7 in control group; data at 10 years were 67% complete and consistent with these overall findings

- **European Study**
  - 162,243 men allocated to screening vs usual care
  - Ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80 (95% CI: 0.65 - 0.98)
  - 1410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer


**Current Recommendations Concerning PSA Screening for Prostate Cancer**

- The American Cancer Society recommends that men make an informed decision with their doctor about whether to be tested for prostate cancer...Starting at age 50, talk to your doctor about the pros and cons of testing so you can decide if testing is the right choice for you. If you are African American or have a father or brother who had prostate cancer before age 65, you should have this talk with your doctor starting at age 45. If you decide to be tested, you should have the PSA blood test with or without a rectal exam.¹

- United States Preventive Services Task Force Recommendation: Level D²

¹. ACS Guidelines: [http://www.cancer.org/docroot/cid/content/cid_2_3x_acs_cancer_detection_guidelines_36.asp](http://www.cancer.org/docroot/cid/content/cid_2_3x_acs_cancer_detection_guidelines_36.asp)

**PSA Measurement in 2015**

- Discussion with 3 expert urologic oncologists... “more art than science at this point”
  - Discuss whether to follow PSA, bearing in mind known risk factors, African American heritage, family history involving brothers/father
  - Measure PSA no more than annually
  - If PSA is detected, refer to urologist for additional evaluation, value of PSA velocity not well established
  - Measurement of free vs bound PSA useful (higher proportion of bound indicates higher likelihood of prostate cancer)
Prostate Health Index

- New test that combines total, free and [-2]proPSA into cumulative score
  - Total PSA rises with any metabolic activity of prostate, higher proportion of bound PSA associated with greater likelihood of cancer
  - Free PSA has several isoforms including [-2]proPSA; measuring its presence is even more revealing of the likelihood of prostate cancer that the portion of bound vs free PSA
  - The real question is...does PHI help us differentiate clinically aggressive tumors from latent ones


Prostate Health Index

- Multicenter trial
  - 658 men, ≥ 50 years of age
  - Compared PSA, free and bound %, [-2]proPSA isoform and PHI to predict pathology obtained form biopsy cores
  - Results: Cumulative PHI score was better predictor for Gleason 7 or higher (3+4 or 4+3) than total, free, or [-2]proPSA isoform alone, at 90% sensitivity cut point PHI spared 30.1% from having unnecessary biopsy vs 21.7% using free PSA score


Prostate Health Index

- Described by some as revolutionary, evidence is insufficient for firm conclusions
- More likely an evolutionary step, but initial findings are encouraging and it is approved for early detection and screening by US FDA
- More research is needed...

Definitive Diagnosis of Prostate Cancer

- Transrectal Ultrasound with biopsies
- Additional tests include CT scan with contrast, MRI, bone scan,

Grading

- Pathologic grade evaluates biologic aggressiveness of this tumor; calculated by adding most common grade with second most common grade so 4+3 ≠ 3+4
  - Gleason 6-7: moderately aggressive
  - Gleason 8-10: highly aggressive

Prostate Cancer: TNM Staging

URL: [http://www.cancer.gov/cancertopics/pdq/treatment/prostate/Patient/page2](http://www.cancer.gov/cancertopics/pdq/treatment/prostate/Patient/page2)
Treating Localized Prostate Cancer

- Watchful waiting
- Hormone therapy
- External beam radiotherapy
- Interstitial radiotherapy (brachytherapy)
- Surgery (radical prostatectomy)
- Cryotherapy

Treating Localized Prostate Cancer

- **External Beam Radiation Therapy**
  - High dose radiation (≥ 70 Gy or >) over 5-6 week period in divided doses
  - Megavoltage equipment (parallel AP or lateral portals): sometimes called ‘box’ therapy
  - 3-dimensional techniques use CT reconstruction: conformal techniques (↓ proctitis & radiation cystitis by half)
  - Heavy particle therapy: conformal proton beam or neutron therapy
  - Intensity modulated radiation therapy (hypofractionated stereotactic body RT): fewer but higher doses delivered (80 Gy), ↓ toxicity compared to box therapy; treat QD to QOD


Treating Localized Prostate Cancer

- **Intensity modulated radiation therapy (IMRT)**
  - Uses conformal techniques but also provides multiple intensity levels when delivering single radiation beam to prostate; efficacy comparable to conformal technique
  - Can be used to deliver higher doses (up to 78 Gy)
  - Adverse side effects 10%-30% range comparable to older techniques

Brachytherapy

- Brachytherapy: radioactive seeds implanted into prostate under ultrasonic guidance in most cases (I\textsuperscript{131} or palladium)


Treating Localized Prostate Cancer

- Adverse side effects of External Beam Radiotherapy
  - Radiation cystitis: 25%-37% during & immediately following treatment; chronic; prolonged and severe radiation cystitis < 10\%
  - Radiation proctitis: 74%-93% during and immediately following procedure; chronic rectal urgency in about 20%; avoid rectal instrumentation to reduce risk of trauma to rectal wall
  - Rectal bleeding: 9%
  - Erectile Dysfunction: 50%-63%
  - Skin injury (radiation dermatitis): 11% in group of 283 patients undergoing EBRT


Treating Localized Prostate Cancer

- Radical Prostatectomy
  - Radical retropubic prostatectomy most common
  - Open technique
  - Best approach to preserve erectile function in younger male
Treating Localized Prostate Cancer

- **Laparoscopic RP**
  - Offers typical advantages on laparoscopic approach
  - Must weigh against cost, learning curve needed to master, anesthesia time
  - Complications
    - Positive margins: 10-22% for T2 tumors
    - Major rectal injury: 7%
  

- **Robotic prostatectomy**
  - Enhances laparoscopic techniques using robotic arms; provides magnified 3-D view
  - Increasing popularity and expertise by multiple surgeons
  - Positive margins: 15%
  - Rectal injury: 0%-5%


Radical Prostatectomy: Adverse Side Effects

- Urinary incontinence
- Erectile and ejaculatory dysfunction
- Urethral stricture (anastomotic site)
- Bleeding and infection
- Short-term risk for DVT

Treating Advanced Stage Prostate CA (T3 & T4 tumors)

- Androgen ablation therapy
- Chemotherapy
- Radiotherapy
- Combination radiation therapy & androgen ablation
- Palliative treatments: radiotherapy for “hot spots”, salvage hormone protocols, glucocorticoids

Conclusions

- Prostatic disorders produce a variety of seemingly unrelated symptoms including LUTS and poorly localized pelvic pain and discomfort
- Traditional evaluation and treatment has focused on the prostate exclusively
- Management of benign prostatic enlargement or prostate cancer focuses on the entire man and incorporates his partner/spouse to the greatest extent possible