PSA: Prostate Cancer Screening

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OBJECTIVES

• To discuss PSA characteristics and its true normal values

• To discuss factors and conditions that may affect PSA elevation

• To discuss risk factors that elevates PSA level which warrant evaluation and referral to subspecialist for further management

• To discuss strategies to improve diagnostic yield of PSA value
Prostate Gland

- In Greek, it literally means "one who stands before", "protector", "guardian"
- a compound tubuloalveolar exocrine gland of the male reproductive system in most mammals

Prostate Cancer

• Prostate cancer is second only to nonmelanoma skin cancer and lung cancer as the leading cause of cancer and cancer death, respectively.

• Worldwide, in 2008 there were estimated to be 903,000 new cases of prostate cancer and 258,000 prostate cancer deaths.

• It is the second most commonly diagnosed cancer in men.

• It is the sixth leading cause of male cancer death.

Risk factor and Epidemiology of Prostate Cancer

• **Age** —
  - All men are at risk for prostate cancer, and greatly increases with older age
  - Prostate cancer is rarely found in men younger than 50 y/o

• **Ethnic background** —
  - African-American men develop prostate cancer more often than white, Hispanic and Asian men
Risk factor and Epidemiology of Prostate Cancer

• **Family medical history** —
  – Men who have a first-degree relative (a father or brother) with prostate cancer are more likely to develop the disease

• **Diet** —
  – A diet high in animal fat or low in vegetables may increase a man's risk of prostate cancer.
Presentation of Prostate Cancer

• Currently, 47% of prostate cancers are identified in patients who are asymptomatic.

• Diagnosis in such cases is based on abnormal screening prostate-specific antigen (PSA) level or findings on digital rectal examination (DRE).

• It can be an incidental pathologic finding when tissue is removed during transurethral resection to manage obstructive symptoms from benign prostatic hyperplasia.

National Comprehensive Cancer Network: Prostate Cancer Early Detection 2011
Prostate cancer work-up

- **Screening** for prostate cancer involves:
  - serum prostate-specific antigen (PSA) testing
  - digital rectal examination (DRE)

- Further **workup** depends on the clinical staging and the need to refer to specialist

National Comprehensive Cancer Network: Prostate Cancer Early Detection 2011
Rationale of Prostate Cancer Screening

• It is inherent that as we maximize the detection of early prostate cancer we will increase the detection of both non-aggressive (slow growing) and aggressive (faster growing) prostate cancers.

• The challenge is to identify the biology of the cancer that is detected and thus identify cancers that, if treated effectively, will result in a significant decrease in morbidity and mortality.
Screening for Prostate Cancer

- Prostate cancer screening has been a controversial issue.

- European Randomized Study of Screening for Prostate Cancer (ERSPC) reported a small absolute survival benefit with PSA screening after 9 years of follow-up (Number needed to screen: 1410 to prevent 1 death).

- Considerable data show the potential harms from aggressive treatments, including:
  - Erectile dysfunction
  - Urinary incontinence
  - Bowel problems

Screening for Prostate Cancer

- Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, published concurrently with the European trial, found no benefit for annual PSA and digital rectal examination (DRE) screening after seven to ten years of annual follow-up

PROSTATE SPECIFIC ANTIGEN (PSA)

• A **glycoprotein** produced by prostate epithelial cells

• PSA levels may be **elevated** in men with prostate cancer because PSA **production** is increased

• Tissue **barriers** between the prostate gland lumen and the **capillary** are **disrupted**, releasing more PSA into the serum.

PROSTATE SPECIFIC ANTIGEN (PSA)

• Studies have estimated that PSA elevations can precede clinical disease by 5 to 10 years

• May be elevated in a number of benign conditions, particularly benign prostatic hyperplasia (BPH) and prostatitis

Measuring PSA

- PSA values are described in ng/mL and is equivalent to the SI units of mcg/L
- Normal value ranges 0-4ng/ml
- PSA has a half-life of 2.2 days and levels elevated by different benign conditions will have variable recovery times

Conditions affecting PSA Elevation

- Digital rectal examination (DRE) has minimal effect on PSA levels, leading to transient elevations of only 0.26 to 0.4 ng/mL.

- Ejaculation can increase PSA levels by up to 0.8 ng/mL, though levels return to normal within 48 hours.
Conditions affecting PSA Elevation

- **Bacterial prostatitis** may cause elevation, but return to baseline **six to eight weeks** after symptoms resolve.

- **Acute urinary retention** may elevate PSA levels, but the levels can be expected to decrease by **50 percent** within **one to two days** following resolution.
Conditions affecting PSA Elevation

- **Prostate biopsy** may elevate PSA levels by a median of 7.9 ng/mL within four to 24 hours following the procedure, levels will remain elevated for two to four weeks.

- Transurethral resection of the prostate (TURP) can elevate PSA levels by a median of 5.9 ng/mL, levels will remain elevated for a median time of approximately **three weeks**.
Effect of Medications on PSA

• 5 Alpha reductase such as Finasteride and Dutasteride can lower PSA by a median 50 percent within six months of use

National Comprehensive Cancer Network: Prostate Cancer Early Detection 2011
Accuracy of PSA Screening

• A PSA test can also be normal even when a man does have prostate cancer—“False Negative”

• About 1 out of 7 men with PSA level less than 4ng/ml have prostate cancer, which means 6 out of 7 do not.

• The higher a man’s PSA level is across all PSA ranges from zero on up, the more likely a man is to have prostate cancer, this is true even with in the so-called “normal” range below
Accuracy of PSA Screening

• According to American Cancer Society
  – Estimated sensitivity of a PSA
    • cutoff of 4.0 ng/mL = 21% for detecting any prostate cancer and 51% for detecting high-grade cancers (Gleason ≥8)
    • cutoff of 3.0 ng/mL = 32 and 68% sensitivity
  – Estimated specificity
    • cutoff of 4.0 ng/mL = 91%
    • cutoff of 3.0 ng/mL = 85%

Accuracy of PSA Screening

According to American Cancer Society

– Positive Predictive Value (PPV)
  • PSA level $>4.0 \text{ ng/mL} = 30\% \text{ PPV}$
  • Less than one in three men with an elevated PSA will have prostate cancer detected on biopsy
  • PSA levels between $4.0 \text{ to } 10.0 \text{ ng/mL}, = 25\% \text{ PPV}$
  • PSA levels $>10 \text{ ng/mL} = 42 \text{ to } 64\% \text{ PPV}$

Improving PSA accuracy

• PSA velocity is the change in PSA level over time.
• A sharp rise in the PSA level raises the suspicion of cancer and may indicate a fast-growing cancer.
• A 2006 study found that men who had a PSA velocity above 0.35 ng/mL per year had a higher relative risk of dying from prostate cancer than men who had a PSA velocity less than 0.35 ng/mL per year.

Improving PSA accuracy

- **PSA density** considers the relationship between the level of PSA and the size of the prostate
- PSA density $> 0.15 \text{ ng/mL/cm}^3$
- The use of PSA density to interpret PSA results is controversial because cancer might be overlooked in a man with an enlarged prostate.

PSA circulates in the blood in two forms: Free or attached to a protein molecule.

The free PSA test is more often used for men who have higher PSA.

With benign prostate conditions (such as BPH), there is more free PSA, while cancer produces more of the attached form.

Free PSA >25% of Total PSA level.

Majority of immunoreactive PSA in cancer patients is complexed with alpha-1-antichymotrypsin

Complex PSA (cPSA) >2.2ng/ml higher chance of cancer

cPSA assay provided a 10-22% improvement in specificity over total PSA (tPSA), resulting in fewer false positives

Improving PSA accuracy

• **Age-specific** reference ranges
  - 40 to 49 years — 0 to 2.5 ng/mL
  - 50 to 59 years — 0 to 3.5 ng/mL
  - 60 to 69 years — 0 to 4.5 ng/mL
  - 70 to 79 years — 0 to 6.5 ng/mL

• Prostate cancer antigen 3 gene (PCA3)- ratio of PCA3 mRNA over PSA mRNA
  - -- determined from urine specimen collected after a vigorous digital rectal examination

National Comprehensive Cancer Network: Prostate Cancer Early Detection 2011
American Urological Association (AUA) Recommends Informed Decisions

- Patient should be involved in making the decision whether or not to be screened
- Prostate cancer screening may reduce the chance of dying from prostate cancer. However, the evidence is mixed and the absolute benefit is small
AUA Recommends Informed Decision

- Prostate cancer screening is associated with a substantial risk of being diagnosed with prostate cancer.
- Many cancers detected by screening are considered "overdiagnosed", meaning that they never would have caused problems during a man's lifetime.
AUA Recommends Informed Decisions

• In order to determine whether a cancer is causing an abnormal test, men need to undergo a prostate biopsy.
• The PSA test and digital rectal exam (DRE) can both have false positive and false negative results.
• Prostate biopsies may also miss finding cancers.
The PSA blood test with or without the DRE can detect cancer at an earlier stage than when cancers are found because they are causing problems.

Aggressive therapy is necessary to realize any benefit from finding an early-stage prostate cancer.
AUA Recommends Informed Decisions

- Surgery and radiation therapies are the treatments most commonly offered in an attempt to cure prostate cancer; however, they can lead to problems with:
  - Urinary (Urethral stricture, Radiation Cystitis)
  - Bowel (Radiation colitis)
  - Sexual function (Erectile Dysfunction)

- No current tests can accurately determine which men with a cancer found by screening are most likely to benefit from aggressive treatment
AUA Recommends Informed Decisions

• Most men with prostate cancer will die from other causes, many will never experience health problems from their cancer

• A strategy of active surveillance may be appropriate for men who are at low risk for complications from prostate cancer
NCCN Guidelines™ Version 1.2011
Prostate Cancer Early Detection

**BASELINE EVALUATION**
- H&P\(^a\) including:
  - Family history\(^b\)
  - Medications
  - History of prostate disease and screening, including prior PSA and/or isoforms, exams and biopsies
  - PSA velocity, if available\(^c\)

**RISK ASSESSMENT**
- Start risk and benefit discussion
- Offer baseline DRE and PSA at age 40 (category 2B)

**SCREENING EVALUATION**
- PSA ≥ 1.0 ng/mL\(^e\)
or African American or Family history or Men taking 5-alpha-reductase inhibitors (5ARI)

**FOLLOW-UP**
- PSA ≤ 1.0 ng/mL → Repeat at age 45
- PSA > 1.0 ng/mL → Annual follow-up (category 2B):
  - DRE
  - PSA

- PSA ≤ 1.0 ng/mL → Repeat at age 45

- PSA > 1.0 ng/mL → Annual follow-up (category 2B):
  - DRE
  - PSA

If PSA ≤ 1.0 ng/mL, offer screening at age 50\(^g\)

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\(^a\) Screening in men over 75 y should be considered individually.

\(^b\) History of prostate disease and screening, including prior PSA and/or isoforms, exams and biopsies

\(^c\) PSA velocity, if available

\(^d\) Risk assessment

\(^e\) PSA threshold

\(^f\) Annual follow-up (category 2B): DRE, PSA

\(^g\) Screening at age 50 y
Management of Prostate Ca

- American Urological Association (AUA) Prostate Cancer Clinical Guideline Update recommended that the initial evaluation and treatment discussion with the patient focus on 3 factors:

Three Factors to Consider in Prostate Cancer Management

– The patient’s overall life expectancy, as determined by age and comorbidities
– The biological characteristics of the tumor, together with its predicted aggressiveness and behavior
Three Factors to Consider in Prostate Cancer Management

– The preferences of the patient for the various treatment options, with consideration of the ff:
  • Complications
  • Adverse effects
  • Relative efficacy
  • Quality-of-life issues
Important Factors When Beginning Early Detection Program

1. Patient’s Age
2. Life Expectancy
3. Family History
4. Race
5. Previous Early Detection Test
General Principles for Early Detection

- Accurate **history** and complete **physical examination**
- General health, medical **comorbidities** and **life expectancy**
- Prostate cancer **risk factors** (family history and **race**)
- There is evidence that associates the use of **5-alpha reductase inhibitors** to increase capacity of PSA to detect **high grade prostate tumors**

National Comprehensive Cancer Network: Prostate Cancer Early Detection 2011
Prostate cancer in its early stages has no identifiable symptoms.

In advanced disease, symptoms may include:

- Urinary obstruction
- Prostate bleeding
- Hematospermia
- Bone pain
General Principles for Early Detection

• To educate patients about the distinction between benign prostatic enlargement and advance prostate cancer

• Patient’s history of prior testing, including DRE, PSA, PSA derivatives and prostate biopsy should be considered in designing an early detection program
General Principles for Early Detection

- There is synergy of DRE and PSA testing in increasing the sensitivity of the prostate cancer detection
PSA Determination
“When PSA values have been recognized to be critical and warrant opinion, in-depth decision and intervention, then a referral to your Friendly Urologist for further work-up and management is appreciated.”
THANK YOU !!!