Re-examining Prostate Cancer in Light of the PSA Controversy

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I am a speaker for Pfizer. All honoraria go to the OHSU urology resident education fund.

Prostate Physiology
- Hormone-responsive exocrine gland
- Requires 5α-DHT (5α-di-hydrotestosterone) to develop
- Salvia reductase in the prostate converts testosterone to 5α-DHT
- Produces Prostate Specific Antigen (PSA)
  - PSA is a serine protease that liquefies the semen
  - Kallikrein family of genes
- Has the highest levels of zinc of any organ in the body
  - Function of zinc unknown
  - ?antibacterial
  - ?cofactor that complexes as a metalloprotein

Prostate Anatomy
- Normal volume 20-25 cc (walnut)
- Increase in size with age > 40
- Rough correlation exists between size and PSA
- NO correlation between prostate size and
  - degree of obstruction
  - severity of symptoms

Introduction to the Prostate

PSA
- Distribution
  - High concentrations in seminal plasma
  - Present in plasma in bound and free states
  - Levels vary with age, race, prostate volume
  - AA men have higher PSA levels than caucasian men
  - PSA increases 4%/mL of gland volume
- PSA production is highly sensitive to androgen
  - Increased levels with testosterone and DHEA
  - PSA levels halved with Salvia reductase inhibitors
  - Finasteride/Dutasteride/Propecia®
Factors Affecting PSA Levels

- Most important determinant of a man’s PSA level is the presence of prostatic disease
  - BPH
  - Prostatitis/UTI
  - Prostate cancer
- Disruption of the prostatic architecture produces elevations in PSA
- PSA “leaks” into the general circulation
  - Prostatic massage
  - Instrumentation (Foley placement, cystoscopy, biopsy, surgery)
- NO significant rise with DRE
- Rise with ejaculation controversial: wait 48 hours

Prostate Cancer (CaP)

- Most common noncutaneous cancer in men
- Second most common cause of cancer death in men
- Approximately 241,740 new cases in 2012
- Approximately 28,170 men will die in 2012
- Overall risk of having CaP, 16% in lifetime or 1:6
- Average age at diagnosis is 67

“More men will die WITH prostate cancer than OF prostate cancer.”

*Statistics courtesy of the American Cancer Society

Diagnosis of Prostate Cancer

- Early prostate cancer is rarely associated with symptoms
  - Abnormal DRE
  - Induration or nodule (asymmetry)
  - Elevated PSA
  - DRE < PSA < DRE + PSA
    - Both PSA + DRE provide greatest detection rate
  - Confirmation by transrectal U/S + biopsy

PSA Quandary

- Not all men with prostate cancer have elevated PSA levels and not all men with elevated PSA levels have prostate cancer
  - PSA is a poor tumor marker if expressed as an absolute value
    - Question of “normal” levels
      - 3.4 ng/mL
      - 3.2.5 ng/mL (AA males or high-risk males)
  - Significance of a given PSA value should be taken in the context of family history, race, and DRE findings

Transrectal U/S + Biopsy

When is Biopsy Warranted?

- A PSA level that is considered suspicious for prostate cancer should be re-measured before performing a prostate biopsy, because of fluctuations in PSA that could create false-positive elevations (Eastham et al, 2003)
- It is the trend or change in PSA over time that best signals when a biopsy should be done
  - Linear elevation is a danger sign
  - Wide fluctuations in PSA may actually signal a benign state (Garzotto, personal communication)
  - Transient inflammation
What About Free PSA?
- Unbound fraction of PSA, “% free PSA”, can help establish the significance of an elevated PSA value
- Risk stratification and reduction of unnecessary biopsies
- Generally used for PSA values between 4 and 10 ng/mL
- “Diagnostic gray zone”
- 5-35% of PSA is unbound to serum proteins
- Men with CaP have a greater bound fraction of PSA
- > 18% free:total PSA corresponds to low risk of CaP
- Size matters: for larger glands, cut point declines to 14%

What are “Good” Cancers?
- Gleason score 6 (3+3) or less
- Small-volume tumors
- Low-risk patients
- Indolent PSA rise
- PSA as a measure of biologic activity of the cancer

How Bad is the Prostate Cancer?

<table>
<thead>
<tr>
<th>Gleason's Pattern Scale</th>
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</thead>
<tbody>
<tr>
<td>1. Small, uniform glands.</td>
</tr>
<tr>
<td>2. More spaces (absent) between glands.</td>
</tr>
<tr>
<td>3. Uniformity indicates ratio of grade 1 and grade 4.</td>
</tr>
<tr>
<td>4. Uniform spaces of nonuniform cells with low grade.</td>
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<tr>
<td>5. Lack of or nonuniform glands, nodules of units.</td>
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Treatment of Localized CaP
- Active surveillance (watchful waiting)
- Radical prostatectomy
- Radiation therapy
  - Brachytherapy
  - External beam radiation therapy (IMRT)
- Cryotherapy
- “HIFU” (High-frequency focused ultrasound)
Morbidities of Therapy

- Active surveillance
  - Advancement of tumor

- Radical prostatectomy
  - Surgery, pain, incapacitation, incontinence, erectile dysfunction

- Radiation therapy
  - Need for adjuvant androgen deprivation, fatigue, cystitis, proctitis, hematuria, rectal bleeding, erectile dysfunction

The Data is Muddy

- Are we finding more cancers – Yes.
- Are we finding more early-stage cancers - Yes.
- Are we overtreating some cancers and causing unnecessary morbidity – Yes.
- Are we saving lives by screening – Maybe.

Guidelines for Screening

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>American Urological Association</th>
<th>American Cancer Society</th>
<th>U.S. Preventive Services Task Force</th>
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</thead>
<tbody>
<tr>
<td>Age at which screening begins for patients at average risk</td>
<td>Yes</td>
<td>Yes (consider use only)</td>
<td>Yes (consider use only)</td>
</tr>
<tr>
<td>Age at which screening begins for high-risk patients</td>
<td>45</td>
<td>45</td>
<td>Not applicable</td>
</tr>
<tr>
<td>PSA threshold at which prostate biopsy should be performed</td>
<td>40</td>
<td>40</td>
<td>Not applicable</td>
</tr>
<tr>
<td>PSA threshold at which prostate biopsy should be performed with genotyping</td>
<td>40</td>
<td>40</td>
<td>Not applicable</td>
</tr>
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The PSA Controversy

Dr. Willet Whitmore, the father of urologic oncology, is perhaps best remembered for his question: “For a patient with prostate cancer, if treatment for cure is necessary, is it possible? If possible, is it necessary?” This question crystallized the dilemma of decision making for patients and physicians and, in the third decade of prostate-specific antigen (PSA) screening, is now even more pertinent and pressing than ever.

AUA Position

- The decision to use PSA for the early detection of prostate cancer should be individualized. Patients should be informed of the known risks and the potential benefits. (AUA 2009)

- Considerations:
  - Patient comorbidities
  - Life expectancy (>10 years)
  - Family history
    - Longevity
  - First-degree relatives with prostate cancer
Case in Point

- 57 yo male presented for treatment of nephrolithiasis
- DRE revealed a nodule
- PSA 1.7 at diagnosis
- Biopsy performed: Gleason 4+5 prostate cancer
- Tx: Androgen deprivation therapy and radical prostatectomy
- Current status: Patient now has metastatic disease and is back on androgen deprivation therapy

Questions?