PSA: Problems, Possibilities and Best Practice

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Disclosures

- No disclosures to report
- “I like what works for me, don’t like what doesn’t and acknowledge equivalence when it occurs”…….
Prostate Specific Antigen

- Introduction
- PSA for early detection of prostate cancer
  - Epidemiology
  - Who and how to screen
  - Potential ways to improve PSA testing
  - When is Prostate biopsy indicated
  - Brief look at treatment options for prostate cancer

Prostate Specific Antigen

- PSA and Prostate Cancer
  - Pretreatment staging
  - Guide to predict local therapy results
  - Post treatment management of prostate cancer
What is PSA?

- Prostate Specific Antigen
- Glycoprotein produced primarily by the epithelial cells within the prostate glands
- Purpose is to lyse the seminal coagulum
- PSA normally concentrated in the prostate with generally low serum levels
- Disruption of the normal prostate architecture (prostate disease or trauma) can lead to greater amounts of PSA in the general circulation

Alteration of PSA Levels in the Blood

What will significantly increase PSA?
- Trauma
- Manipulation
  - Cystoscopy
  - Biopsy
  - Foley catheter
- Prostatitis
- Benign prostatic hypertrophy (BPH)
- Prostate Cancer

What will not significantly raise PSA?
- Ejaculation
- Digital exam
- Medications
  - Testosterone supplementation
Alteration of PSA Level in the Blood

What will lower the PSA level in the blood

- Medication
  - 5 Alpha recuctase inhibitor (Finesteride, Dutesteride)
  - LHRH agonists or antagonists
  - Oral antiandrogens
- Surgery
  - Radical or simple prostatectomy, TURP
- Ablative therapy
  - Radiation
  - Heat (microwave, RF, HIFU)
  - Cold (Cryoablation)
- Supplements?
  - Saw Palmetto perhaps

PSA: Early Detection of Prostate Cancer

Prostate Cancer

- Most common malignancy in men in the US
- Second leading cause of male cancer mortality
  - Estimated 28,660 deaths in 2008
- 1/3 men over 50 years of age probably have histologic prostate cancer (autopsy studies)
- BUT
- 80% of these limited or clinically insignificant
- Life time risk of prostate cancer death is approximately 3%
Early Detection of Prostate Cancer

- Goal: Reduce the overall morbidity and mortality of Prostate cancer

Evidence that Screening is Associated with a Fall in Mortality

- Fall in mortality now seen
  - SEER
  - Olmsted County
  - Canada/Quebec
  - Department of Defense (US)
  - Tyrol, Austria

- Mortality fall *not seen* (where PSA screening not performed)
  - Mexico
Prostate Cancer Mortality

% Decline in Mortality


Decline from peak year (1991)

PSA Screening Impact

Stage Migration

- Prior to PSA Screening
  - 35% had positive lymph nodes
  - 2/3 of patients had pathologically advanced disease

- Now
  - Approximately 50% are non-palpable (PSA driven dx)
  - 85% clinically localized at time of diagnosis
PSA Screening: Problems

- Over detection
  - Estimated to be as high as 27% at age 55
  - Estimated to be as high as 56% at age 75
- Abnormal test often leads to biopsy
- Despite lower risk disease, 90% will ultimately chose some sort of therapy
- Cost?

Results of Cost Analysis of Screening

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Cost per QALY Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Transplantation</td>
<td>$237,000</td>
</tr>
<tr>
<td>Screening mammography (&lt;50)</td>
<td>$232,000</td>
</tr>
<tr>
<td>Worst case – CAP Screening</td>
<td>$145,600</td>
</tr>
<tr>
<td>CABG – 2 vessel/angina</td>
<td>$106,000</td>
</tr>
<tr>
<td>Captopril for hypertension</td>
<td>$82,600</td>
</tr>
<tr>
<td>HCTZ for hypertension</td>
<td>$23,500</td>
</tr>
<tr>
<td>Best case – CAP Screening</td>
<td>$8,700</td>
</tr>
<tr>
<td>Stop smoking MD message</td>
<td>$1,300</td>
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</table>
Prostate Cancer Screening: Will We Ever Get an Answer?

- ERSPC trial
  - Large European randomized study of screening vs. control
  - Address issues such as overdiagnosis, cost, risk/benefit analysis
- Maturation of the PLCO screening trial
- Results expected 2006-2010
How to Screen

- Screening should be for asymptomatic men with a 10-year life expectancy
- Screening should include both PSA and DRE
  - DRE abnormal in 6%–15% of men
  - About 25% of cancers found with DRE alone
Improving the Performance of PSA

- Repeat test if abnormal
  - Lab error, false elevation, etc.
- Age adjustment
- Free/total ratio of PSA
- PSA Density/Transition zone Density
  - Require Ultrasound thus not routinely used
### Age-Adjusting the PSA

- Based upon fact that PSA rises with age
- In young men, adjusting *down* finds more tumors
  - Increased sensitivity
- In older men, adjusting *up* results in fewer biopsies
  - Increased specificity
- Can't have it both ways!

### Age Adjusted PSA

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Recommended Reference Range for Serum PSA (ng/mL)</th>
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<tbody>
<tr>
<td></td>
<td>White</td>
</tr>
<tr>
<td>40-49</td>
<td>0.0-2.5</td>
</tr>
<tr>
<td>50-59</td>
<td>0.0-3.5</td>
</tr>
<tr>
<td>60-69</td>
<td>0.0-4.5</td>
</tr>
<tr>
<td>70-79</td>
<td>0.0-6.5</td>
</tr>
</tbody>
</table>

Advantages/Disadvantages of Percent Free PSA

**Advantage**
- Eliminates about 13% of unnecessary prostate biopsies in men with PSA of 4.0-10.0 ng/mL

**Disadvantage**
- Misses about 5% of cancers that would be detected with PSA alone

Which is better? Fewer biopsies? Fewer tumors?
AUA 2002: PLCO Trial

- 154,000 men and women
- 55-74 age range
- Screening vs. usual care
- Prostate Screening
  - PSA (Hybritech, Central lab) yearly X 6
  - DRE yearly X 4
- Exclusion
  - Ca P, finasteride, >1 PSA test in last 3 years (1995)

Conversion to PSA ≥ 4

Cumulative Percent Converting to PSA ≥ 4 ng/ml

By Study Year and Baseline PSA level

Percent Converting

Study Year

< 1 1-2 2-3 3-4 Baseline PSA (ng/ml)
PLCO Conclusions

- PSA <1 ng/ml check every 5 years
- PSA 1-1.9 ng/ml check every 2 years
- 99% of above would have negative yearly screenings
- 55% decrease in number of PSA tests
- Annual cost savings of $500M-$1B

AUA 2002 Courtesy Dr. David Crawford

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PLCO Conclusions

- Conversion to PSA > 4.0
  - 34% PSA of 2-2.9 ng/ml
  - 83% conversion rate with PSA of 3-4 ng/ml
- Suggests candidates for further studies
  - Chemoprevention, alternative screening strategies

AUA 2002 Courtesy Dr. David Crawford
Recent* Prostate-Specific Antigen (PSA) Test Prevalence (%), by Educational Attainment and Health Insurance Status, Men 50 Years and Older, US, 2001-2002

*A prostate-specific antigen (PSA) test within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.

Recent* Digital Rectal Examination (DRE) Prevalence (%), by Educational Attainment and Health Insurance Status, Men 50 Years and Older, US, 2001-2002

*A digital rectal examination (DRE) within the past year. Note: Data from participating states and the District of Columbia were aggregated to represent the United States.
TRUS and Biopsy of the Prostate
- Abnormal DRE
- Abnormal PSA
- Office-based
- Local anesthesia

Laterally-Directed Peripheral Zone Biopsy Samples Anterior Horn of PZ

Standard Biopsy is 10 – 12 cores with Ultrasound Guidance

Continuous vs. Intermittent Imaging With Contrast

Gleason 9 lesion left base

If Cancer is Present, Will TRUS/BX Find It?

- Cancer detection rate approximately 96% using 10 – 12 core biopsy scheme
- Ultrasound alone inadequate to detect cancer
Risk Stratification in Localized Prostate Cancer

Treatment Options

- Observation
- Radical Prostatectomy
- Ablative
  - Cryotherapy and HIFU
- Radiation Therapy
  - External, seeds, combo
- Hormonal Therapy
- Chemotherapy
- Multimodality therapy
  - NHT, AHT, chemo-hormonal

Getting the Correct Match

- Stage
- Gleason grade
- PSA level
- Health status/age
- Patient preference/QOL
- Surgery
- Radiation
- Brachytherapy
- Cryotherapy
- Hormonal Therapy
- Watchful waiting
- Investigational Rx
Prostate Cancer Therapy: Active Observation

Candidates
- Low volume CA
- Gleason 6 or less
- PSA stable, <10

Repeat biopsy (6-12 month intervals)
PSA followup
Primary treatment if PSA progression, increase volume/grade of CA
Surgical Treatment of Prostate Cancer

- Open radical prostatectomy (RP)
- Laparoscopic RP
- Robotic assisted RP
- Perineal prostatectomy
External Beam Radiation Therapy

- IMRT (intensity modulated RT)
- Gamma Knife
- Neutron Therapy
- Proton Therapy

Prostate Brachytherapy
(Radioactive seed implant)
Identification of Urethra on TRUS with Foley catheter

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Prostate Cancer Staging

- T1 = localized to prostate, non palpable
- T2 = nodule, confined to prostate
- T3 = nodule, extending beyond prostate capsule
- T4 = locally invasive into other structures
- N+ = nodal disease (pelvic)
- M+ = distant metastasis (retroperitoneal nodes, bone)
**PSA Use for Staging**

- PSA < 25 – CT/MRI generally not necessary
- PSA < 20 – Bone Scan unnecessary
- PSA < 10 – Pelvic lymph node dissection not required during surgery
- PSA < 20 with Gleason<8, < T2

**PSA and Treatment Response**

- Patients with PSA < 10ng/ml are most likely to respond to local therapy
- PSA volume (PSAV) is an independent predictor of PCA specific and overall survival after therapy
  - PSAV greater than 2.0ng/ml have higher risk of failure after XRT
PSA in Post-treatment Management of Prostate Cancer

Post Surgery
- Best use of PSA testing
- PSA should be “undetectable”
- Timing of PSA recurrence is important
  - < 1 year = probably distant disease
- PSA doubling time helpful in determining timing/need of adjuvant therapy
- PSA checked about every 6 months for 5 years, yearly after that

PSA in Post-treatment Management of Prostate Cancer

PSA following Radiation/Ablative therapy
- Nadir value important (< 0.5 is generally good)
- Rising PSA usually means recurrence
  - Exception after Brachytherapy
- Failure = any rise of 2.0 ng/ml over nadir
PSA in Post-treatment Management of Prostate Cancer

- PSA Nadir after Initiation of Androgen Deprivation therapy
  - PSA nadir > 0.2 ng/ml associated with 20 fold higher risk of PCA specific mortality
- PSA Doubling time of >15 months associated with low risk of PCA specific Mortality

PSA: Summary

- Should I screen for Prostate Cancer with PSA testing?
  - Yes, include a yearly DRE
  - Repeat any abnormal values
  - Consider using age adjusted PSA levels
Screening Guidelines for the Early Detection of Prostate Cancer
American Cancer Society 2003

- The prostate-specific antigen (PSA) test and the digital rectal examination (DRE) should be offered annually
  - Beginning at age 50
  - To men who have a life expectancy of at least 10 years
- Men at high risk (African-American men and men with a strong family history of one or more first-degree relatives diagnosed with prostate cancer at an early age) should begin testing at age 45
- For men at average risk and high risk, information should be provided about what is known and what is uncertain about the benefits and limitations of early detection and treatment of prostate cancer so that they can make an informed decision about testing

PSA Summary

- If my patient has prostate cancer, should I order other studies?
  - PSA < 20ng/ml
    - Probably not unless there is another indication
  - PSA > 20ng/ml and/or Gleason grade of 8 or higher
    - CT and Bone Scan reasonable
PSA: Summary

My patient was treated a few years ago, should I continue to check a PSA?

- Yes
  - Every 6 months up to 5 years, then yearly
- Add data points
  - Check every three months if PSA rising post therapy
PSA: Problems, Possibilities and Best Practice

Questions?

Thank You