Prostate Cancer Screening & Treatment Updates

Daniel Gilbert, D.O.

4/2017
Prostate Cancer Screening
Disclosures, Sponsors & Locations

Nothing to disclose, No sponsors

Hospital Affiliations:
Honor Health
Deer Valley & Thompson Peak
Abrazo Arrowhead Campus
Outline

• Example Cases
• Prostate Cancer & PSA
• Current Controversy & Recommendations
• ERSPC, PLCO trials
• Personalized prostate cancer screening
  • PSA screening derivatives, dynamics and personalized PCM’s
• Treatment updates
Case 1

- 73 year old seen by outside urologist
- h/o BPH and elevated PSA [between 12-18 ng/ml]
- Transrectal biopsy x 3 total of 40 cores [2009-13], benign
- TURP for urinary symptoms in 2015-benign
- PSA 3/2016-24.2 ng/ml
- next step?
- cancer?
• 47 year old male cyclist, fitness enthusiast
• presents with urinary retention and a PSA, 3.7 ng/ml
• normal?
• next step?
Prostate Anatomy & Function

• The Prostate gland
  • organ responsible for ejaculate in male, grows with age
  • surrounded by delicate nerves & closely approximated to rectum & urinary sphincters

• Produces Prostate Specific Antigen [PSA]

• Increases for BPH, inflammation, cancer etc
Gleason-Prostate Cancer Grading System

- Prostate cancer detected on transrectal/transperineal biopsy
- Major and minor component of cancer present is assessed
- Old system [Left], New System [Right] [more intuitive to patient]

<table>
<thead>
<tr>
<th>Table 1: Risk of PSA Relapse 5 Years Following Radical Prostatectomy, Based on Various Biopsy Gleason Scores.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Group 3</td>
</tr>
<tr>
<td>Group 4</td>
</tr>
<tr>
<td>Group 5</td>
</tr>
</tbody>
</table>

Prostate Cancer Screening
Prostate Cancer Overview & Stats

- ~27,000 deaths from prostate cancer in the U.S. in 2016
- 2nd highest cause of cancer deaths in men behind lung cancer
- 2.7 million US men living with prostate cancer
- Would you be surprised that ... ?
  - More men die of prostate cancer annually than colon cancer
  - Prostate cancer deaths decreased ~30% since PSA introduced
  - Although PSA is considered indolent; similar death rate to breast cancer
Controversy: USPSTF Screening Recommendations

- Prostate [2012]: Grade D
  - USPSTF recommended against PSA screening in any men; citing over-diagnosis and treatment
- Cervical Cancer: Grade A
- Colorectal: Grade A
- Breast: Grade B
- Testicular: Grade D

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.</td>
<td>Offer or provide this service.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.</td>
<td>Offer or provide this service for selected patients depending on individual circumstances.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.</td>
<td>Discourage the use of this service.</td>
</tr>
</tbody>
</table>
USPSTF Recommendations

• **ERSPC & PLCO [prostate arm]**, (screening RCT; with several shortcomings)
• Urologists & medical oncologists not involved in recommendation; non-transparent
• AUA among others [ACS] issued statements against wholesale rejection of PSA screening
• The decision was re-evaluated in 2017
PSA screening reduction

- 2012
- PCP’s screening prior to 2012
  - 81%
- PCP’s screening after 2012
  - 50%

MGH Internal Med Review 2012
Possible benefit of screening

The reduction in prostate cancer deaths from prostate-specific antigen (PSA) screening is at most very small. A large U.S. study showed no benefit from screening. A large European study that found the highest reported benefit suggests:

- 1 man in 1,000 – at most – avoids death from prostate cancer because of screening

Expected harms of screening

Most prostate cancers found by PSA screening are slow growing, not life threatening, and will not cause a man any harm during his lifetime. However, there is currently no way to determine which cancers are likely to threaten a man’s health and which will not. As a result, almost all men with PSA-detected prostate cancer opt to receive treatment. In addition to the frequent complications of biopsy that lead to a cancer diagnosis, there can be serious harms from treatment of screen-detected prostate cancer.

For every 1,000 men who are screened with the PSA test:

- 30 to 40 men will develop erectile dysfunction or urinary incontinence due to treatment
- 2 men will experience a serious cardiovascular event, such as a heart attack, due to treatment
- 1 man will develop a serious blood clot in his leg or lungs due to treatment

For every 3,000 men who are screened with the PSA test:

- 1 man will die due to complications from surgical treatment
Treatment Side Effects

- Surgery [immediate with slow recovery]
  - Urinary incontinence, Erectile dysfunction, Pain

- Radiation [typically onset >24 months]
  - Urinary incontinence [urgency], Erectile dysfunction, Bowel Irritation, hormone deprivation-related side effects

- Active surveillance
  - Anxiety, repeat biopsy discomfort/infection, rigorous follow up
Prostate Cancer Screening Controversy

• Biopsies uncomfortable, anxiety, infections [1-2%]
• Treatments are costly
  • Example: Proton beam therapy, centers can exceed $140 Million [versus $2-4 million for IMRT]
  • Medicare reimburse $32K for proton, $19K for IMRT
• Finding the cancer may not improve patient’s health, nor survival
Is Prostate Cancer Unique?

- Most prostate cancers are not lethal
- Is this unique to prostate cancer?

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2017</th>
<th>Estimated Deaths 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>252,710</td>
<td>40,610</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>222,500</td>
<td>155,870</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>161,360</td>
<td>26,730</td>
</tr>
<tr>
<td>4. Colon and Rectum Cancer (135,430)</td>
<td></td>
<td>50,260</td>
</tr>
<tr>
<td>5. Melanoma of the Skin</td>
<td>87,110</td>
<td>9,730</td>
</tr>
<tr>
<td>6. Bladder Cancer</td>
<td>79,030</td>
<td>16,870</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>72,240</td>
<td>20,140</td>
</tr>
<tr>
<td>8. Kidney and Renal Pelvis Cancer</td>
<td>63,990</td>
<td>14,400</td>
</tr>
<tr>
<td>9. Leukemia</td>
<td>62,130</td>
<td>24,500</td>
</tr>
<tr>
<td>10. Endometrial Cancer</td>
<td>61,380</td>
<td>10,920</td>
</tr>
</tbody>
</table>

Prostate Cancer Screening
Is Prostate Cancer Unique?

- Lung Cancer
- Breast Cancer
- Prostate Cancer

Prostate Cancer Screening
Is Prostate Cancer Unique?

Prostate Cancer Kills

Pathological Gleason Score ≤7 [AKA Group 1 & 2]

Pathological Gleason Score 8-10 [AKA Group 4 & 5]

Prostate Cancer-Specific Survival

Time After Biochemical Recurrence, y

P < .001, Log Rank
Prostate Cancer Variability

• Low Risk Disease [Group 1-2]
  • 97% cancer-specific survival at 10 years with active surveillance

• High Risk Disease [Group 4-5]
  • 20% risk of death even after treatment [Hu JC et al]
PSA Screening Controversy

- Detect CA earlier
- Reduce mortality
- Reduce incurability

- False positives
- False negative
- Biopsy risks
- Side effects of Tx

Prostate Cancer Screening
Prostate Cancer Screening

• What does the ideal screening test look like?
PSA Benefits

• How many cancers have a simple blood test with this kind of association

![PSA Benefits Graph](image-url)

- PSA: Prostate Specific Antigen
- Cancer Risk
- Test Value

Prostate Cancer Screening
PSA Benefits

• 30-40% decrease in age-adjusted mortality since early 1990’s
PSA Benefits

- Estimated 66% decrease of late stage (metastatic) diagnoses with PSA
  - 2011 to 2013 - metastatic PCa risen
    - 7.8 to 12% [Hu JC, JAMA oncology]
  - Local pca $9-30K [QALY]
  - Advanced PCa $80-100K [QALY]

- QALY [quality adjusted life year]
USPSTF logic & Harms of PSA Screening

- Prostate, Lung, Colorectal and Ovarian (PLCO) trial
- 77,000 men in U.S. randomized to annual PSA screening for 6yrs vs “usual care”
- No difference seen in mortality
PLCO: What was missed?

• So what did the USPSTF miss?
  • > 40% of controls had PSA within 3 yrs of enrollment
  • 50%+ of controls had PSA during trial (contaminated study)
  • Only 30-40% in study group with abnormal PSA underwent biopsy
  • Follow-up too short
  • 4% black
    • Black Americans: twice the incidence and twice the mortality
Post-Hoc Analysis of PLCO
Crawford et al, JCO Nov 2010

Group A: No Co-morbidities
p = .03
NNT = 5

Group B: ≥1 Comorbidity
p = NS

44% relative risk reduction in mortality in group A
• ERSPC
  • European Randomized Study of Screening for Prostate Cancer (ERSPC) 182,000 men in 7 countries
  • PSA screening every 2-4yrs yielded a 21-29% reduction in prostate cancer specific mortality
• Burden of screening:
  • Need to screen 1410 and treat 48 to avoid one death (at 9 years...

  • .....what about at 13 or 14 years?)
• For men aged 55-69, screening at 14 years:
  • Reduced the death rate by 29%
  • Reduced the need for palliative therapy by 35%

Men aged 55 - 69
Relative risk reduction = 29%
NNS = 98
NNT = 5
ERSPC

• 9, 12 and 14 yr followup, NNS & NND decrease rapidly

• 9 yr (NNS-1410; NND = 48)
• 12 yr (NNS-781; NND = 27)
• 14 yrs
  • NNS-293, NND]-12 [Hu JC et al]

• NNI-# needed to Invite to screen, NND-# needed to diagnosed, NNS-# needed to screen, NNT-# needed to treat
• Swedish Study
• Subset of ERSPC but stand-alone RCT with only $\frac{1}{2}$ represented in ERSPC
• 20K pts randomized to q2yr PSA
• Unique in that median age of men was 56 yo
• 44% reduction in prostate cancer mortality at 14yrs
• NNS = 293 men screened; NNT = 12 diagnosed; to prevent one death
USPSTF Errors

• What else did they miss?
  • Only examined mortality, underestimated morbidity; obstruction, bony metastases
  • Biased demographics; few higher risk patients
  • Heavily weighted flawed PLCO, not enough emphasis on Swedish study [Goteberg]
• PLCO-flawed, but subset analysis shows 44% reduction in prostate cancer death
• ERSPC-burden of screening becomes more desirable as time curve lengthens [12-14 years]
• Swedish study-44% reduction in prostate cancer death
• Is it reasonable to screen average 50 year old man?
  • Ave life expectancy in US: ~79 years;
Prostate Cancer Controversy

• Need to screen smarter, with Individual screening
Current PSA Screening Guidelines

• **USPSTF: Grade D [2012]**
  - No screening in any age

• **AAFP:**
  - Against screening post-USPSTF
  - Do not routinely screen for prostate cancer using a PSA test or DRE

• **NCCN (2.2016):**
  - Discuss benefits and risks starting age 40
  - Age 45-75
    - If PSA <1.0, repeat q2-4 years
    - PSA 1-3, repeat q1-2 years
    - If PSA >3 or abnormal DRE consider bx or personalized screening
Current PSA Screening Guidelines

- ACS [2016]-Informed decision to screen for ave man at age 50
  - with or without DRE, higher risk men at age 45
- AUA (2013 update):
  - No screening <40, >70, <10-15 lifespan
  - Average risk men 40-54; no routine screen
  - Shared decision-making aged 55-69
Screening Concerns for the PCP

• Time-time to discuss risks/benefits of screening with every man over 40 or 55?
• Expectations-Does every elevated PSA need Urologist referral? Will every referral get biopsied? Will every prostate cancer be treated (surgery or radiation)?
• Legal-Lawsuit if I don’t screen or discuss with my patients
Evidence for Personalized PSA Screening

- Harvard; observational study; available biomaterial
- Baseline, Mid-life PSA predicts PC death
- More intensive screening for those above median \[\text{Preston MA et al}\]

| Table 3. Proportion of Lethal Prostate Cancers Captured by Percentiles of Measured PSA Levels at Age 40 to 49, 50 to 54, and 55 to 59 Years |
|---|---|---|
| Stratification | PSA Concentration (ng/mL) | Proportion of Lethal Prostate Cancers in PSA Category (%) |
| Age 40 to 49 years at blood draw (n = 11 lethal events) | | |
| Top 10th percentile | ≥ 1.68 | 55 |
| Quartile 4 | ≥ 1.04 | 82 |
| Above median | = 0.88 | 82 |
| Below median | < 0.68 | 18 |
| Age 50 to 54 years at blood draw (n = 17 lethal events) | | |
| Top 10th percentile | ≥ 1.96 | 65 |
| Quartile 4 | ≥ 1.40 | 65 |
| Above median | = 0.88 | 71 |
| Below median | < 0.88 | 29 |
| Age 55 to 59 years at blood draw (n = 43 lethal events) | | |
| Top 10th percentile | ≥ 2.88 | 51 |
| Quartile 4 | ≥ 1.64 | 70 |
| Above median | ≥ 0.96 | 86 |
| Below median | < 0.96 | 14 |

Abbreviation: PSA, prostate-specific antigen.
• Population based, annual screening and biopsy over 4.0ng/ml is dead.
• Need more judicious & individualize PSA screening, but what else can we do?
• “Currently no way to determine which cancers will threaten a man’s health and which will not.” USPSTF
Individualized Screening Tests

- PSA Derivatives/Dynamics
  - Age-Adjusted
  - PSA Density
  - Free PSA
  - PSA Velocity
- “Prostate Cancer Markers”- [Prostate Health Index®, 4K test®], Select MDx®, PCA-3®
- Nomograms
Individualized Tests

- Prolaris, Oncotype Dx (evaluate bx specimen, [determine risk of aggression]
  - Genetics, Proteionomic tests (cell cycle gene, PTEN etc)

- Imaging & Fusion biopsy
  - Multiparametric MRI
  - Who to biopsy, Who to treat, How to treat

Prostate Cancer Screening
# Age-Adjusted PSA

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Asian</th>
<th>Caucasian</th>
<th>African-American</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>0-2.0 ng/mL</td>
<td>0-2.5 ng/mL</td>
<td>0-2.0 ng/mL</td>
</tr>
<tr>
<td>50-59</td>
<td>0-3.0 ng/mL</td>
<td>0-3.5 ng/mL</td>
<td>0-4.0 ng/mL</td>
</tr>
<tr>
<td>60-69</td>
<td>0-4.0 ng/mL</td>
<td>0-4.5 ng/mL</td>
<td>0-4.5 ng/mL</td>
</tr>
<tr>
<td>70-79</td>
<td>0-5.0 ng/mL</td>
<td>0-6.5 ng/mL</td>
<td>0-5.5 ng/mL</td>
</tr>
</tbody>
</table>
Free PSA

• Unbound PSA in Blood; Decreased in the setting of PCa

<table>
<thead>
<tr>
<th>Total PSA</th>
<th>% + Biopsies</th>
<th>% Free PSA</th>
<th>% + Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 2 ng/ml</td>
<td>1%</td>
<td>0 – 10%</td>
<td>56%</td>
</tr>
<tr>
<td>2 – 4 ng/ml</td>
<td>15%</td>
<td>10.1 – 15%</td>
<td>28%</td>
</tr>
<tr>
<td>4 – 10 ng/ml</td>
<td>25%</td>
<td>15.1 – 20%</td>
<td>20%</td>
</tr>
<tr>
<td>&gt; 10 ng/ml</td>
<td>&gt; 50%</td>
<td>20 – 25%</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 25%</td>
<td>8%</td>
</tr>
</tbody>
</table>
PSA Density

• PSA divided by prostate volume
• < 0.15 - ideal cutoff
• Very large prostate from BPH “allowed” to have a higher PSA
• Example: 150g prostate, PSA = 9
  • PSAd = 0.06
• Example: 20g prostate, PSA = 3.5
  • PSAd = 0.175
PSA Velocity

• Change in PSA over time
• Finds cancers early even before PSA hits a specific “cutoff”
• What is a normal rise in PSA from year to year?
  • Depends on PSA value and gland size
  • 0.35/yr per NCCN
• 0.75 can be “okay” for large gland
# Nomograms (UTSAHCS)

## Characteristics

<table>
<thead>
<tr>
<th>Race</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56</td>
</tr>
<tr>
<td>PSA [ng/mL]</td>
<td>4.1</td>
</tr>
<tr>
<td>Family History of Prostate Cancer</td>
<td>No</td>
</tr>
<tr>
<td>Digital rectal examination</td>
<td>Normal</td>
</tr>
<tr>
<td>Prior biopsy</td>
<td>Never had a prior biopsy</td>
</tr>
<tr>
<td>Percent free PSA</td>
<td>15</td>
</tr>
</tbody>
</table>

## Risk of prostate cancer if biopsy were to be performed

Based on the provided risk factors a prostate biopsy performed would have:

- **14% chance of high-grade prostate cancer.**
- **23% chance of low-grade cancer.**
- **83% chance that the biopsy is negative for cancer.**

About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results.

Click here to watch a video overview of these results.
Kattan Nomogram

Primary Treatment Outcomes

- Probability of Cancer-Specific Survival after Radical Prostatectomy
  - 10 YR: 99%
  - 15 YR: 99%

- Progression-Free Probability after Radical Prostatectomy
  - 5 YR: 87%
  - 10 YR: 63%

Extent of Disease Probability

- Each extent of disease probability percentage is an independent prediction. We therefore would not expect these percentages to equal 100

- Organ Confined Disease: 34%
- Extracapsular Extension: 65%
- Lymph Node Involvement: 9%
- Seminal Vesicle Invasion: 9%
My Recommendations/Practice

- Baseline PSA and DRE at ~40
  - If <1.0, repeat at 50, then at 50, then q 2 years if no symptoms
- Refer at any age if PSA questions, velocity and/or PSA >2.0 ng/ml
- Annual PSA at 40-45 for high risk: FH or African-American
- PSA dynamics, derivatives, PCM’s, MRI
- Repeat PSA’s when possible & get a trend
- No PSA-Life-expectancy <10 years
My Treatment Options: AS & Robotics

- **Active Surveillance (AS)**
  - Rigorous follow up - Repeat biopsy, mp-MRI, PCMs, PSA & derivatives to determine who can avoid active treatment
  - Option is increasing dramatically

- **Robotic Assisted Prostatectomy**
  - Advanced laparoscopic instrumentation,
  - Offers greater oncologic & anatomic precision,
  - Fewer complications, shorter hospital stay [1 day]
Active Surveillance

- No active treatment for men unlikely to progress or die of pca
- Requires close follow up
- Prevent complications and side effects and reserve treatment for those who are more likely to need it
- Typically group 1 and some low volume group 2 prostate cancers
- 97% 10-year CSS rates
Robotic surgery: Prostate Anatomy & Function

• The Prostate gland
  • Surrounded by delicate nerves controlling urine and erection control
• Miniaturized laparoscopic instrumentation, dexterity, magnification
Robotic Prostatectomy Nerve Preservation

Prostate Cancer Screening
Robotic Prostatectomy AmnioFix®
• 73 year old seen by outside urologist
• History of BPH and elevated PSA [b/w 12-18]
• Biopsy x 3 total of 40 cores [2010-14]
• TURP for urinary symptoms in 2015-benign
• PSA 3/2016-24.2 ng/ml
• Next step? cancer?
Case 1

- Prostate MRI - no PIRADS lesions, 180g; PSA density at 0.13
- CT abdomen and pelvis - normal
- 4K test - 10% [ie 90% chance of “no high risk” prostate cancer on repeat bx]
Case 2

- 47 year old healthy cyclist, fitness enthusiast
- Presented with urinary retention and an abnormal PSA, 3.7 ng/ml
- Normal?
- Next step?
• Retention resolved, 3 month recheck PSA free and total 4.0, 15%
• PCA 3-177 [high likelihood of PCa]
• 10/2015-bx demonstrated, group 1 [gleason 3+3 [2/12 cores, 10%]
• Recommended robotic prostatectomy; patient chose active surveillance against advice
• Subsequent PSA-3.6, 3.8, 3.4 [2016-2017], free PSA [16%-18%]
Case 2

- Initial prostate MP-MRI-31g prostate, no PIRADS
- 6/2015-Oncotype Dx-16- [“very low risk disease”]
- Second MP-MRI-33g prostate, PIRADS 3 lesion, 1.2cm
- 12/2016- Oncotype Dx--22- [“Intermediate risk disease”]
- MRI Fusion biopsy in office, 3/3 cores, group 2]
Case 2

• Banked sperm
• Bilateral nerve sparing Robotic prostatectomy
• pT3aN0Mx, Group 2, 25% cancer, focal positive margin
• continent and potent, PSA <0.01
Conclusion

• No more annual, population PSA screening, but still use PSA
  • Screen smarter not harder
• Familiarize yourself with newer screening tests and/or refer when PSA over 2.0ng/ml [or increased PSA velocity]
• Consider the concept of baseline PSA stratifying future risk
• Active surveillance is a viable treatment; robotics improves patient care
## Draft: Recommendation Summary

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men ages 55 to 69 years</td>
<td>The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms of prostate-specific antigen (PSA)-based screening for prostate cancer. The decision about whether to be screened for prostate cancer should be an individual one. Screening offers a small potential benefit of reducing the chance of dying of prostate cancer. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy, overdiagnosis and overtreatment, and treatment complications, such as incontinence and impotence. The USPSTF recommends individualized decisionmaking about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision. Please refer to the Clinical Considerations sections on screening in African American men and men with a family history of prostate cancer for more information on these higher-risk populations.</td>
<td>C</td>
</tr>
<tr>
<td>Men age 70 years and older</td>
<td>The USPSTF recommends against PSA-based screening for prostate cancer in men age 70 years and older.</td>
<td>D</td>
</tr>
</tbody>
</table>
• Questions?
References


What Is the True Number Needed to Screen and Treat to Save a Life With Prostate-Specific Antigen Testing?
Stacy Loeb, Edward F. Vonesh, E. Jeffrey Metter, H. Ballentine Carter, Peter H. Gann, and William J. Catalona


13. Schröder FH, Hugosson J, Roobol MJ et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow up.

14. ACPM 2009: USPSTF Updates Recommendations for colorectal screening


