Prostate Cancer: Screening and Selected Treatment Dilemmas

Marc B. Garnick MD

Update in Internal Medicine

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Financial Disclosures

Marc B. Garnick MD, FACP
Gorman Brothers Clinical Professor of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School

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HARVARD MEDICAL SCHOOL
Editor in Chief, HMS Annual Report on Prostate Diseases/HHP
www.harvardprostateknowledge.org; ACP
HMS Risk Management Foundation/CRICO

Member ODAC/FDA that reviewed chemoprevention trials for prostate cancer and both HIFU applications that targeted prostate cancer
For the same patient with prostate cancer, the options range from Radical Treatment to No Treatment. So how can we decide?

Now—Should testing that led to the prostate cancer Dx even be offered?
Case for discussion

53 yo African American male
- Initial annual visit
- Father died of prostate cancer (states that “they got it late”); paternal uncle has prostate cancer
- Married, sexually active; no significant co-morbidities
- No urinary or urological symptoms
- PE: mild hypertension; negative DRE

WHAT ARE YOUR RECOMMENDATIONS REGARDING PSA BASED TESTING?
Your Recommendations

1. Order a PSA test as part of the routine annual bloods, along with lipid panel, glucose, and CBC (patient not informed)

2. Given the lack of symptoms and PE, do not bring PSA issue up, but document your decision in the medical record

3. Briefly discuss controversies about PSA testing and have patient make decision (and document)

4. Briefly discuss controversies about PSA testing and recommend the test (and document)

5. Briefly discuss controversies about PSA testing and do NOT recommend the test (and document)
Framing the Problem

• We screen **older men** who are unlikely to die from a screen detected cancer
• We practice **widespread overtreatment** of low risk disease
• **Surgical complications** are proportional to skill and volume of surgeon, yet most surgeons perform three or fewer prostatectomies per year. *(Vickers cancer letter interview 10/10/14)*
• **Cost to prevent one death** from prostate cancer with PSA screening=$5.2MM
Liability Issues - CRICO

- PSA issues are the leading cause of cancer malpractice claims ... and getting worse
- PSA velocity becoming a common malpractice issue
- Physicians, NPs and Institutions all named as defendants
The Gleason Score

- Two Numbers, each 1 to 5 (most and second most common)
- Based upon Biopsy
  - Gleason 1 = looks like normal prostate tissue
  - Gleason 5 = aggressive looking cancer
- Most cancers are 3+3 or 3+4; (6 or 7)
- More aggressive cancers are 4+3; 4+4; 4+5 or 5+5 (so called 7-10 cancers)
Prostate Cancer in the Contemporary Era: Does it make sense to continue to use a 2-10 scaled grading system?

- Gleason score 6 has favorable outcomes
- Gleason score 6 (low grade) is halfway between Gleason score 2 and 10
  - Contributes to reluctance to choose active surveillance
- Gleason scores 2-5 rarely used and not prognostically different from GS6
- Amount of pattern 4/5 most important for prognosis

The overall Gleason score is based on the core with the highest Gleason score. Gleason scores can be grouped and range from Prognostic Grade Group I (most favorable) to Prognostic Grade Group V (least favorable).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Prognostic Grade Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6</td>
<td>I</td>
</tr>
<tr>
<td>3 + 4 = 7</td>
<td>II</td>
</tr>
<tr>
<td>4 + 3 = 7</td>
<td>III</td>
</tr>
<tr>
<td>8</td>
<td>IV</td>
</tr>
<tr>
<td>9-10</td>
<td>V</td>
</tr>
</tbody>
</table>
The cT Stage (clinical)

- **T1** cancers – non palpable – elevated PSA – most common T1c
- **T2a** – nodule in $\frac{1}{2}$ of one lobe
- **T2b** – nodule in $>\frac{1}{2}$ of one lobe
- **T2c** – abnormality in both R and L lobes
- **T3** – disease clinically o/s capsule or in Seminal Vesicle
Prostate Anatomy - Understanding Complications
Prostate Cancer with “Normal” PSA

- There is no PSA value that segregates those with and without prostate cancer.
- Any PSA value can be associated with prostate cancer.
- PCPT trial showed that 15% of patients with PSA <4 and normal DRE had prostate cancer.
The Screening Controversies

What is your role in primary care? (especially now with new guidelines)
Know four key studies

- **ERSPC**: no survival benefit (OS); small ca specific survival advantage (CSS)
- **PLCO**: no OS or CSS benefit
  - 25% of screened patients had LUTS/BPH
- **PIVOT**: overall, no survival benefit but possible advantage for higher risk subset; low grade did worse
- **ProtecT**: screen, randomize: RP, RT, AM
  - no differences in OS CSS; mets differed
ProtecT and CAP

Figure 1: ProtecT and CAP trial recruitment phases and endpoint assessment
CAP=Cluster randomised trial of PSA testing for Prostate cancer. ProtecT=Prostate testing for cancer and Treatment. NHS=National Health Service.
Know harms associated with PSA screening and Rx

• Bleeding
• Infection
• Incontinence
• Erectile dysfunction
• False positive rates
• Overdiagnosis
• Death
Interactive case

but first, a primer on AUA IPSS Symptom Scores
AUA/IPSS SS
Over the past week/month, how often

- **Not emptying** bladder?
- Urinate after **two** hours?
- **Stops and starts** when urinating?
- Can’t postpone urinating?
- **Weak** stream?
- Push or strain to urinate?
- **Up from sleep** to urinate (0-5x)?

- Not at all ►►0
- Less than 1 time in 5 ►►1
- Less than half the time ►►2
- About half the time ►►3
- More than half the time ►►4
- Almost always ►►5

0-8 mild;9-18mod;>18-35 severe
- QoL Delighted to Terrible
Case:  58 YO Male

- Recent diagnosis of prostate cancer; long standing history of BPH; on alpha blocker; PCP was considering 5 alpha reductase inhibitor because of large size gland;  AUA/IPSS SS = 24

- cT1c; PSA 7.8; Gleason 3+3 in 2/6 cores on R; 2/6 cores on L

- Patient wants to be treated
Which treatment is likely to cause the most significant urinary side effects?

1. External Beam Radiation alone
2. Robotic Laparoscopic Radical Prostatectomy
3. Brachytherapy alone or with EBRT
4. Open Radical Prostatectomy
5. Neoadjuvant hormonal therapy with EBRT
Know four key guidelines

• USPSTF: “Recommends against PSA-based screening for prostate cancer”
  – American Urological Association
  – American College of Physicians
  – Canadian Task Force on Preventive Health Care
Recent Guidelines - ACP

• I: 50-69: inform of potential benefits and significant harms of PSA testing. No testing for those who do not express a clear preference for screening

• II: NO PSA testing for those <50; >69; or LE of <10-15 years

• Talking points provided
► Recent Guidelines - AUA

• I: NO PSA testing under age 40
• II: PSA not recommended 40-54
• III: 55-69: prevent mortality in 1/1000 men over 10 years; PSA testing undergo shared decision making, based upon values and preferences
• IV: for those screened, every two years
• V: NO PSA testing for men >70 with less than 10-15 years of life expectancy
CTF PHC

- Men <55 and ≥70
- Strong recommendation against screening
- “Clinicians should not routinely discuss screening ... unless the topic is raised by the patient”
• Men 55-69

• Weak recommendation against screening

• Risks and benefits discussed

• “Those who place a high value on a small potential reduction in mortality and are less concerned with undesirable consequences may choose to be screened”
After weighing ALL the evidence...
What to do in practice

• **Document** your discussion points

• Shared Decision with patient choice

• Shared Decision with your recommendation

• Your Decision not to discuss
CRICO Decision Support Pearls

• Prostate on PE
  – Normal
  – Symmetrically enlarged
  – Abnormal (asymmetry) > REFER

• Know about changes in PSA on 5ARIs
• Do not recommend empiric ABx
• Establish plan of follow up, including those with negative biopsies
• Be cognizant about recommendations for Testosterone Replacement Rx
Other Important Considerations

- High concern for having prostate cancer if PSA does not decrease by 50% on 5 ARIs
  - (any ▲ on F: 3x risk; 6x HG PrCa)
- Sexual Dysfunction on 5 ARIs
- How to advise patients on 5 ARIs for BPH?
- ►►► Need to weigh benefits of 5 ARIs on AUR and surgical interventions to risk of pr ca
The Prostate Cancer Prevention Trial found that men who had developed high-grade prostate cancer (Gleason scores of 8 to 10) while taking finasteride had lower survival rates at both five and ten years than those taking the placebo.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Deaths</th>
<th>5-year survival</th>
<th>10-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finasteride</td>
<td>101</td>
<td>86%</td>
<td>66%</td>
</tr>
<tr>
<td>Placebo</td>
<td>64</td>
<td>89%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Concept of Active Surveillance—Important for Clinicians

- Diagnosis of prostate cancer made
- Risk stratification for TREATMENT DECISION
- Periodic biopsies
- Treat if certain characteristics evolve
- Change in Gleason, extent of cancer, PSA doubling time, physical exam or symptoms, others
NEW PROSTATE CANCER TESTS

increase the odds of selecting men who may be harboring cancer and...
determine likelihood of cancer growing and spreading
New Pr Ca Tests and What They Do

Purpose: To determine if patient’s prostate cancer is at high risk of growing and spreading

• PROLARIS
  • GENE ACTIVITY

• GENOMIC PROSTATE SCORE (ONCOTYPE Dx)
  • GENE ACTIVITY

• ProstaVysion
  • GENE ACTIVITY
Dr. Garnick, what should I do?

(the 30 sec blurb)
• Mr XX: There is a **blood test** that can help detect unsuspected prostate cancer.

• If results are **abnormal**, refer to urology who would do a prostate **biopsy** to determine if cancer was present.

• If we do a **biopsy** and it shows **cancer**, we would probably recommend **treatment**, either surgery or radiation therapy.

• Treatment can be associated with incontinence, impotence, rectal bleeding and even death.

• Even if we treat, there is **no good evidence** that you will **live any longer** or that treatment will even **decrease the likelihood of your dying of prostate cancer**. If it does decrease the likelihood of dying of prostate cancer, the effect is small.

• What are your values?

• How would you like to proceed?
Final Research Plan

Final Research Plan for Prostate Cancer: Screening

Recommendations made by the USPSTF are independent of the U.S. government. They should not be construed as an official position of the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services.

Preface

The final Research Plan is used to guide a systematic review of the evidence by researchers at an Evidence-based Practice Center. The resulting Evidence Review will form the basis of the USPSTF Recommendation Statement on this topic.

Final USPSTF Guidelines: No to Routine PSA Testing

Nick Mulcahy
USPSTF NEW ANALYTIC FW FOR UPDATE
Two Common Treatment Dilemmas

► Metastatic Castrate Sensitive Prostate Cancer
► Biochemical Relapse
What is the optimal therapy for newly diagnosed castrate sensitive metastatic prostate cancer?

What used to be simple, now quite complex
Many options

• Antiandrogen monotherapy
• LHRH agonist
• GnRH antagonist
• Combination LHRH + antiandrogen
• Combination LHRH + antiandrogen + chemotherapy
• Radiation of N+ disease?
• Even Radical Prostatectomy with the above
• Should second line HT be moved up front?
TOP LINE RESULTS: HT VS HT + DOCETAXEL

- **CHAARTED** (N=790) OS 44 VS 57 MONTHS; EXT DZ: 40% REDUCTION IN DEATH
- **STAMPEDE** (n=2962) HT± D±Z OS 67 v 77 mos
- **GETUG-AFU15** (N=385) OS 81 v 83 M low volume; 35 v 39 hi volume

- One LOCALLY ADVANCED Study
- **RTOG 0521** (n=562) OS from 89% to 93% at 4 years
  - 5 yr DFI: 66% v 73%
  - Deaths in chemo arm
What is the best approach for Biochemical Relapse?

These patients have been treated with curative intent (RT or RP) and now have an elevated PSA value?
Natural History After RRP

Surgery

Biochemical recurrence

Time (years)

Metastases

Death

N=304

Pound et al. JAMA 1999
Key Factors

- PSA doubling time
- Gleason Score
- Time to relapse
- T stage

• WRONG: SIMPLY INSTITUTING ADT!!
# Predictors of PCSM

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR for PCSM</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years from RP to biochemical recurrence</td>
<td>HR (≤3 yrs vs &gt;3 yrs)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>3.53</td>
<td></td>
</tr>
<tr>
<td>PSA-DT</td>
<td>HR relative to ≥15 mo</td>
<td></td>
</tr>
<tr>
<td>&lt;3.0 mo</td>
<td>27.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3.0-8.9 mo</td>
<td>8.76</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>9.0-14.9 mo</td>
<td>2.44</td>
<td>.09</td>
</tr>
<tr>
<td>Pathological Gleason score</td>
<td>HR (≥8 vs &lt;8)</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td>2.26</td>
<td></td>
</tr>
</tbody>
</table>

HR=hazard ratio.
IMPORTANT NEW PROSTATE DRUGS - 2016

- Zytiga – abiraterone – second line HT
- Xtandi – enzalutamide – second line HT
- Xgeva – denosumab – bone health
- Prolia – denosumab – bone health
- Jevtana – cabazitaxel – second line chemo
- Xofigo – Radium 223- bone mets
Your Recommendations

1. Order a PSA test as part of the routine annual bloods, along with lipid panel, glucose, and CBC (patient not informed)

2. Given the lack of symptoms and PE, do not bring PSA issue up, but document your decision in the medical record

3. Briefly discuss controversies about PSA testing and have patient make decision (and document)

4. Briefly discuss controversies about PSA testing and recommend the test (and document)

5. Briefly discuss controversies about PSA testing and do NOT recommend the test (and document)
Hopefully, you are not confused, but....
if you are, blame it on me - the expert...

“An expert is a person who tells you a simple thing in a confused way, in such a fashion as to make you think the confusion is your own fault.”

WB Castle, Harvard Medical Bulletin, 1955
Contact Information

mgarnick@bidmc.harvard.edu

Supplemental Materials
The figure shows the analytic framework, which depicts the 5 key questions for the systematic review for screening for prostate cancer. Key question 1 addresses the effectiveness of PSA-based screening in reducing mortality and morbidity from prostate cancer. Key question 2 addresses the harms of PSA-based screening and diagnostic workup (i.e., biopsy). Key question 3 addresses the effectiveness of treatment of early-stage or screen-detected prostate cancer in reducing morbidity and mortality. Key question 4 addresses the harms of treatment of early-stage or screen-detected prostate cancer. Finally, key question 5 addresses the effectiveness of prostate cancer risk calculators combined with PSA-based screening to increase the detection of clinically significant prostate cancer (i.e., cancer that is more likely to cause symptoms or lead to advanced disease).
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Normal big and two cell layers
Gleason 3-
small and
back to back
Gleason 4

Fused

Fusion of glands
Gleason 5 sheets and singles

Single cell or sheet-like