Prostate Cancer - Screening and beyond: genetics, prevention and therapy

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Patient Perspectives on PROSTATE DISEASES

Patients speak out on the therapies they chose, why they chose them—and how it worked out

Bayer Pharmaceuticals consultant Data safety monitoring board member
Prostate Cancer Factoids
(by the numbers)

• **13%** – lifetime risk of being diagnosed

• **2.5%** - lifetime risk of prostate cancer death

• **80** – median age of death from prostate cancer
For the same patient with prostate cancer, the options range from Radical Treatment ________ No Treatment so how can we decide?

Now– Should testing that led to the prostate cancer Dx even be offered?
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 a 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)
• Prognostic risk groups now being used
To DRE or not to DRE?

• ► Most controversial topic I face in this lecture with primary clinicians
• Other reasons for prostate cancer screening
• Can’t assess cT stage without it
• Only study that showed survival advantage for RP used DRE for clinical diagnosis
• There is no “textbook” unambiguous answer
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 five key studies

- **ERSPC**: no survival benefit (OS); small ca specific survival advantage (CSS)
- **PLCO**: no OS or CSS benefit
- **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
- **UK CAP**: one time PSA screen: negative
...The USPSTF recommends that clinicians inform men ages 55 to 69 years about the potential benefits and harms.

The USPSTF recommends individualized decision making 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.

►►”C” recommendation 55-69
►►”D” recommendation ≥ 70
What are the benefits?

In men aged 55 to 69 years, may prevent approximately 1.3 deaths from prostate cancer over approximately 13 years per 1000 men screened.

Screening may prevent approximately 3 cases of metastatic prostate cancer per 1000 men screened.
What are the harms?

- Harms include erectile dysfunction, urinary incontinence, and bowel symptoms.
- About 1 in 5 men who undergo radical prostatectomy develop long-term urinary incontinence.
- 2 in 3 men will experience long-term erectile dysfunction.
- Harms of screening in men > 70 are at least moderate and greater than in younger men.
Know other guidelines

• Canadian Task Force on Preventive Health Care, AAFP – NO

• ACP, AUA shared with patient preference; 10-15 yr life expectancy

• ACS - shared decision, discussion at age 50 years and earlier for AA men and men with a father or brother with a history of prostate cancer before age 65 years.

• Every two or more years
What to do in practice 2018

• **Document** your discussion points (harms and benefits)

• **Shared Decision with patient choice**

• **Shared Decision with your recommendation**

• Clinicians should not screen men who do not express a preference for screening.
CRICO
PSA Testing Decision Support Tool – minimizing risks in primary practice
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
Concept of Active Surveillance—Important for Clinicians

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

- A main reason for a change in USPSTF recommendation
PREVENTION??
Do these drugs (finasteride and dutasteride; Proscar and Avodart) reduce the risk of developing prostate cancer?

Answer: YES!! (the good news)

Relative reduction in both studies of about 25% (absolute reduction of 6%)
Reduction in Risk Limited to GS ≤ 6

Vertical lines represent 95% confidence intervals
Positive (benefit) and Negative Risk Assessments

- Low risk cancers -
  - “treatment to prevention” ratio: 60:1

- Gleason 8-10 cancers –
  - “treatment to increased risk” ratio: 200:1
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
Other Factors in Prostate Health

- **Age** – older age, more cancer
- **Race** – African Americans highest
- **Family History** – strong association
- **Nationality** – NZ, AUS, WeEU, CN, US, CRB >> TH, IN, NoAF, JP, SoKO
- **Vasectomy** – probably no association
What about diet and supplements?
The SELECT Study

• SELECT (selenium and Vit E Cancer Prevention Study to decrease incident prostate cancer)

• N = 35,500

• Vit E // selenium // both // placebo //
  - NO BENEFIT
  - Significant INCREASE IN PR CA IN VIT E
Others

• Vitamin D – good for a number of reasons
• Calcium -- modify intake amount
• Statins – emerging data on potential benefits
• Metformin – data still inconclusive
Diet and Exercise

- Fruits and Veggies – antioxidant balance; lycopenes
- Mediterranean diet: generally good,
- Fish – generally good, but some conflicting data
- Exercise -- generally good,
- Weight -- maintain healthy weight
My advice to patients

• Avoid red meats
• Maintain ideal body weight
• If taking prostate cancer meds – avoid or moderate alcohol intake
• Exercise and stretch regularly
• Avoid nutritional supplements, especially Vit E and selenium
• For others, and you are interested, consider entry to clinical trials
NEW PROSTATE CANCER TESTS

increase the odds of selecting men who may be harboring cancer and...
determine likelihood of cancer growing and spreading
BioMarker Landscape

Prostate Cancer 2017: Decisions, decisions

- Draw PSA?
  - SNPs?
  - PCA3
  - phi
  - 4K
  - SelectMDx
  - ExoDx

- 1st biopsy?
  - ConfirmMDx
  - PCA3
  - phi
  - 4K

- 2nd biopsy?
  - Pre-treatment
    - OncoType
    - Prolaris
    - Decipher
    - ProMark

- Post-op treatment?
  - Decipher
  - Prolaris
  - OncoType

mpMRI
PSMA-PET/CT

- Advanced
disease
  - ARv7?
Tests of interest

• PCA -3/SelectMDx
  – Concerned about a PNB - may help sway

• Oncotype Dx – Been diagnosed with Pr Ca and deciding on Rx or AS
  – Likelihood of finding HG disease
  – Likelihood of have non OC dz
  – Can re-categorize Very Low, Low and Intermediate risk categories to other categories

• “Know Error”- Specimen Provenance
Is there a prostate cancer gene?
Is there a prostate cancer gene?

Risk estimates for prostate cancer by genes associated with hereditary cancer syndromes

Giri et al, Sem Oncol; 2016

<table>
<thead>
<tr>
<th>Gene</th>
<th>Risk of PCa</th>
<th>Risk of aggressive PCa</th>
<th>Risk of early-onset PCa</th>
<th>Specific outcomes</th>
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A  Radiologic Progression–free Survival

- Biomarker-positive, median: 9.8 mo
- Biomarker-negative, median: 2.7 mo

P<0.001 by log-rank test

B  Overall Survival

- Biomarker-positive, median: 13.8 mo
- Biomarker-negative, median: 7.5 mo

P=0.05 by log-rank test
CP 81 YO M

• 1997- prostate cancer Rx with Surgery
• 2000 – Relapse (PSA high) - RT
• 2002- present:
• Multiple therapies (hormones, Radiation, chemo, others)
• 2017: Cancer getting worse in the pelvis and around the rectum - Bx
• Genomic Testing on rectal mass bx:
Genomic Testing

- Identified an abnormality called MSI High
- Commonly seen in colon cancer, very rarely in prostate cancer
- Suggested treatment based on MSI High
PSA declined from 43 to 0.3 after MSI treatment!!

Complete resolution of soft tissue nodal disease and symptoms
PSA declined from 43 to 0.3 after MSI treatment!!

Complete resolution of soft tissue nodal disease and symptoms

Rx: Checkpoint inhibitor
Checkpoint Inhibitors
Anti-PD-1: Blocking T cell Suppression

Daily Clinical Dilemmas and Practice Changing Developments

► Multiparametric MRI
► BCR- rising PSA
► AR-V7
► Abiraterone + Prednisone
MRI to determine need for PNB


• More high grade cancers with MRI guidance
  ► 38% v 26%

• 13% fewer low grade cancers

• 28% avoided biopsy
Timing of Androgen Deprivation Therapy

Prostate Cancer progression in the setting of approved use of androgen deprivation therapy

Primary Curative Therapy

Local Prostate Cancer → PSA-Only Recurrent Disease → Metastatic Disease → Metastatic Castration Resistant

Delayed ADT

Metastasis

Detectable PSA

Undetectable PSA

Food & Drug Administration 2011
Timing of Androgen Deprivation Therapy

The non-metastatic castrate resistant prostate cancer population is a result of early off-label use of androgen deprivation therapy.
Predictors of Prostate Cancer Specific Mortality

- Gleason 8-10
- PSA doubling time of ≤ 3 months
- Time to biochemical relapse within 3 years of primary therapy.
- In those who recur, survival rates range from 50% at 5 years to 80% at 15 years, depending upon risk factors.
- ★ APALUTAMIDE: improved MFS in nmCRPC
- ★ Axumin™ Scan- biochemical recurrence
Androgen Receptor Biology
AR-V7 Splice Variants

AR-V7 is a truncated form of the AR that lacks the ligand-binding domain (LBD), the target of enzalutamide and abiraterone, but remains constitutively active as a transcription factor.
Results

- PSA response to Abiraterone or Enzalutamide
  - AR-V7 mutation positive pts: 0%
  - AR-V7 negative pts: 53-68 %
- All secondary EP favored AR-V7 neg patients

- Will influence practice choices
Pharmacology of Novel Agents of Importance for Primary Clinicians
Adrenal Steroid Synthesis Pathways

Abi inhibits 17αOH and 17,20 lyase

Figure A: The Three Major Pathways of Adrenal Steroid Production
Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer

Karim Fizazi, M.D., Ph.D., NamPhuong Tran, M.D., Luis Fein, M.D.,

- N= 1199
- Randomize:
  - ADT + Plcbo
  - ADT + Abi (1000) + Prednisone (5)
- OS and Radiographic PFS
Overall Survival

Hazard ratio, 0.62 (95% CI, 0.51–0.76)
P<0.001

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In summary...

• Provide updated USPSTF recommendations regarding PSA based screening

• Explored the expanding landscape of genes involved in prostate cancer

• Reviewed some exciting treatment options that previously did not exist
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.”

mgarnick@bidmc.harvard.edu
So, why do the data not show survival improvements to a meaningful extent?
Possible Explanations

Screened population

• The cancers that are found are unlikely to ever cause mortality; hence finding them does nothing to alter that (and may even increase mortality due to treatment)

• The “bad actors” will behave badly regardless of when they are found

Unscreened population

• The indolent non-aggressive cancers did not need to be diagnosed

• The “bad actors” will behave badly regardless of when they are found

• So no difference in OS or CSS
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
MP-MRI

- PROMIS STUDY PMID: 28110982

- mp-MRI performed (n=576)
- Two types of biopsies:
  - Sample every 5 mm
  - Standard 12 core TRUS
- MRI identified 89% of men with PrCa
- No Intermediate or High Grade Misses
- Would have spared 27% need for PNBx