PSA Interpretation

The Art, Science and Controversy

Mark McClure, MD
Cheryl Elliott, ANP

1st take away message

Nurse practitioners have the opportunity to make a difference in prostate cancer outcomes with screening and early detection and treatment.

Case presentation

HPI: from PCP- Healthy 50 year old white male with routine screening PSA in 1993 of 3.4 Not repeated for 3 years. In 1996 his PSA was 10.7, a repeat PSA 3 weeks later was 12.

Urology referral: Biopsy revealed a *poorly* differentiated carcinoma with a Gleason grade of 9 in one core, and 7 (3+4) in others.

His DRE was normal in exams 1993-1996

Case presentation

- Tumor was aneuploid(abnormal DNA)
- Bone scan with an abnormality that was not felt to be malignant.
- 9/10/96 underwent RRP (prostate54g)
- Gleason Grade 7 (path report)
- No evidence of disease in lymph nodes
- Positive left seminal vesicle
- Positive right apical margin

Case presentation

- His post-operative PSA was 6.7 (should be non-detectable)
- A rib lesion was biopsied and found to be metastatic

53 year with metastatic prostate cancer

Risk Factors

- Family: Grandfather died of prostate cancer at age 76
- Nationality: Prostate cancer is *most* common in North America and northwestern Europe. It is less common in Asia, Africa, Central America, and South America.
- Diet: He has a meat-based diet, high in calories and saturated fat.

What is Prostate Specific Antigen?

- 1st introduced in 1988
- Protein manufactured by prostate ductal cells
- Function is to dissolve seminal coagulum
- Made by benign and prostate cancer cells
- Cancer cells liberate 10 times as much PSA as benign cells due to lack of basement membrane

Polascik, T.J.et al. (1999) Prostate Specific Antigen: A Decade of Discovery: What we have learned and where we are going
Journal of Urology 162, 293-306

Causes of an abnormal PSA

- Benign Prostatic Hypertrophy
- Prostate Cancer
- Prostatitis: 4-6 weeks to normalize PSA
- Instrumentation: catheters, cystoscopy, biopsy
- Ejaculation: rarely significant
- Rectal examination: OK to check PSA after DRE

Yuan, I.J. et al. (1992) Effects of Rectal examination, prostate massage, ultrasonography and needle biopsy on serum PSA levels.*Journal of Urology 147:* 810-814

PSA Screening-not just a blood test

- Digital Rectal Exam (DRE)
- Validated questionnaire AUA Symptom Score Index also called IPSS
- PSA recommendations
  - Annually for white men age 50 and older with a life expectancy of 10 years
  - Annually age 40-45 for African American men and men with 1st degree relatives with prostate cancer

Richie, J.P. (1994) Effect of patient age on early detection of prostate cancer with serum PSA.
Urology 42: 365-374

Prostate Cancer

- Leading cause of cancer in men
- 2nd leading cause of cancer-related death
- 16% of men will develop clinical prostate cancer in their lifetime.
- 3 % of men die from prostate cancer

Carroll, P et al (2001) Prostate specific antigen best practice policy part 1: early detection and diagnosis of prostate cancer *Urology 54*: 217-224

PSA sensitivity and specificity

- 67.6-80% sensitivity if PSA < 4ng/ml (normal range) [avoid false positive]
- 60-70% specificity if PSA > 4ng/ml (elevated) [avoid false negative]

Brawer, M.K. (1999) Prostate Specific Antigen: current status
Cancer Journal for Clinicians 49: 264-281

Ways to increase sensitivity

- Age adjusted PSA
- PSA velocity (>0.75 ng/dl per year)
- Lower the threshold for normal PSA to (0-2.5 = normal) will detect 20% more CaP, but increase the false positive rate.

Age-adjusted PSA

Age range	Asians	African Americans	Whites
40-49	0-2	0-2	0-2.5
50-59	0-3	0-4	0-3.5
60-69	0-4	0-4.5	0-4.5
70-79	0-5	0-5.5	0-6.5

Ways to increase specificity

- Age-adjusted PSA
- Free-to-total PSA most of PSA is bound to protein in blood "free" PSA is higher in prostate cancer for reasons we do not know.
- PSA Density ratio of PSA to prostate volume (if TRUS prostate vol ÷PSA >.15 ↑ CaP)

Catalona, et al (1998) Use of percentage of free PSA to enhance differentiation of prostate cancer form benign prostate diseases.

JAMA 279: 1542-1547

Total/Percentage free PSA

Catalona et al: (1998) JAMA 279:1542-1547

PSA NG/ML	% Free PSA	Probability Ca
0-2	N/A	1%
2-4	N/A	15%
4.1-10	0-10%	56%
	11-15%	28%
	16-20%	20%
	21-25%	16%
	> 26%	8%
> 10	N/A	> 50%

When to refer to a Urology Nurse Practitioner/Urologist

- Abnormal PSA reading –follow age adjusted chart and consider repeating the lab test
- Abnormal DRE
- Significant PSA rise (>0.75 ng./ml from one test to the next)

Prostate Biopsy

- PSA > 4 and < 10, risk of CaP is 20-30% when 12 biopsies are taken via rectal ultrasound.
- PSA 2.5-4.0, risk of CaP is 27%
- PSA > 10, risk of CaP is 42-64%
- Comparing PSA < 4 to PSA > 4, odds of finding clinically significant CaP within the prostate increases by 1.5-3 fold., and odds of extracapsular PSA increases by 3-5 fold.

Coley, CM et al (1997) Early detection of prostate cancer-Part 1 prior probability and effectiveness of tests. *Annuals of Internal Medicine 126*: 394-406

Gleason Grading Scores

The pathologist assigns a primary grade from 1 to 5, with 5 being the most aggressive, to the pattern occupying the greatest area of the specimen. A secondary grade is then assigned to the pattern occupying the second largest area. These two grades are added to determine the Gleason score, which ranges from 2 to 10. It is generally agreed that tumors with a Gleason score of 2 to 4 have lower biological aggressiveness, scores of 5 to 6 have an intermediate aggressiveness, and those with a Gleason score of 7-10 are biologically aggressive tumors.

Bone Scan Indications

According to a Mayo Clinic study of 852 patients with newly diagnosed prostate cancer, 66% had a PSA concentration of 10.0 ng/mL and only 3 (0.8%) had a positive bone scan. Only 0.6% of men with a PSA between 10.1 and 15.0 ng/mL and 2.6% of men with a PSA between 15.1 and 20.0 ng/mL had a positive scan consistent with metastasis Therefore, routine use of a bone scan is not required for staging asymptomatic men with clinically localized prostate cancer when their PSA is equal to or less than 20.0 ng/mL

Oesterling, Martin, & Bergstralh, (1993).
The use of prostate-specific antigen in staging patients with newly diagnosed prostate cancer.
JAMA , 269, 57-60.

Controversy regarding PSA: The benefits

- AUA and ACS support
- Earlier detection of prostate cancer
- 4% decrease in death rate since 1994
- Earlier detection and diagnosis find fewer high grade extracapsular tumors

Controversy regarding PSA:The risks

- Detection of insignificant CaP

(most are clinically significant)

- Unnecessary treatment

(50% of cancers with normal DRE and PSA between 4-10 are extended outside the prostate)

- Cost to Health Care System

(Between $2300-$4600 per year of life saved by screening and treatment)

Carroll, P. et al *(2001)*

Prostate Specific Antigen: best practice policy part 1: early detection and diagnosis of prostate cancer

Urology 54:217-224

What to tell men about prostate cancer screening

Controversial

2 prospective randomized trials are underway to provide additional guidance.

The European randomized study of screening for prostate cancer-190,000 men age 55-70 completion in 2008

In the US: Prostate, Lung, Colorectal, and Ovarian Cancer screening trial with 74,000 men: results expected in 2006

The US preventative services task force do not recommend routine screening:

Rationale: The USPSTF found good evidence that PSA screening can detect early-stage prostate cancer but mixed and inconclusive evidence that early detection improves health outcomes. Screening is associated with important harms, including frequent false-positive results and unnecessary anxiety, biopsies, and potential complications of treatment of some cancers that may never have affected a patient's health. The USPSTF concludes that evidence is insufficient to determine whether the benefits outweigh the harms for a screened population.

http://www.ahcpr.gov/clinic/uspstf/uspsprca.htm

Risk groups for prostate cancer

- African American: 2 times the incidence of CaP then Caucasians.
- Family history- one 1° relative →2-fold risk; two 1° relatives → 6-fold risk; three 1° relatives → 11–fold risk (if under age 55 → 15-fold risk).

Carter, B.S.et al (1992)
Mendalian inheritance of familial prostate cancer
Proc National Academy of Science 89: 3367-3371

PSA after treatment for Prostate Cancer

- After radical prostatectomy it should be non detectable.
- After XRT, brachytherapy(radioactive seeds) it should drop to a nadir within 17 months and remain stable-ideally this number should be < 0.5ng/ml.
- PSA doubling time can vary between every 2 weeks to every 10 years.

Take away message

- Rule #1 Consider repeating the PSA when a value is higher than expected.
- Age-adjusted PSA is a necessary consideration for your patients: 0-4 is not for everyone
- The Art: Establishing a baseline and following trends over time helps you gain confidence in reassuring your patient a high PSA value is normal for him.