

# PENINSULA UROLOGY CENTER, INC NEWSLETTER

VOL: 2 ISSUE 2 NOVEMBER 2007

## PROSTATE CANCER UPDATE PART 2

With an annual incidence of 218,890 cases and 27,050 deaths, prostate cancer is an extremely common entity with broad reaching health implications<sup>1</sup>. Complicating the issue of prostate cancer management is that there is no ideal way of screening for its existence or to follow patient response to treatment. Currently we use a combination of digital rectal examination (DRE) and laboratory analysis consisting of the serum prostate specific antigen (PSA) test.

Unfortunately, because the PSA value can fluctuate in an individual, the interpretation of PSA values has become an increasingly complex phenomenon with a constantly evolving body of literature and loosely accepted standards. This issue focuses on the dilemma of PSA and addresses an interesting marker being studied called early prostate cancer antigen-2 (EPCA-2).

Historically many different variations in the serum PSA have been used to help increase the specificity of PSA, however none have yielded any significant promise and still an extraordinary number of "negative" prostate biopsies are performed annually. Preliminary data from Johns Hopkins researchers has suggested that EPCA-2 may supplant PSA in routine prostate cancer diagnosis if further studies prove to be consistent with seminal research. Please join us for an interesting review of both the current literature and prevailing urologic opinion regarding the intricacies of PSA. As always, our physicians, Dr. Bruno and Dr. Threatt are gladly available for routine questions regarding urologic issues as well as more in depth queries regarding interesting cases or diagnostic dilemmas.

## TOPIC OF THE MONTH:

### Early Prostate Cancer Antigen-2(EPCA)

Historically prostate cancer has been the most common male solid organ malignancy and the second most common cause of cancer related death in men. With a 1 in 6 lifetime risk of developing prostate cancer, this malignancy continues to be a significant health issue for American men. Although we have been unable to eradicate prostate cancer, there have been a number of advances in the early diagnosis of this disorder.

One of the most promising contemporary advances in the diagnosis of prostate cancer was the incorporation of PSA testing in 1987. PSA is a 33 Kd glycoprotein with serine protease and arginine esterase activity found almost exclusively in the epithelial cells of the prostate<sup>2</sup>. The use of PSA without DRE is discouraged because it lacks in sensitivity and specificity. It is known that 25% of individuals with prostate cancer have a PSA less than 4.0 ng/ml. As a result we still combine both tests to maximize diagnostic efficacy. It has been demonstrated in different studies that the addition of PSA to prostate cancer screening has allowed the identification of prostate cancer on average 4.0-5.5 years earlier than with DRE alone<sup>3</sup>. The current debate has been on how to better determine which individuals with a "normal" PSA have cancer, as well as which patients with an elevated PSA do not.

It is known that approximately 1.6 million men undergo prostate biopsy annually secondary to an elevated PSA, with 80% of those biopsies being negative. As this is a significant cause of patient discomfort and healthcare system expense, the desire to better stratify individuals

with cancer versus those without has existed for some time. This has led to PSA adjuncts such as percent free PSA, age adjusted PSA, PSA velocity and PSA density,

### Percent Free PSA

Percent free PSA is the first of the PSA adjuncts. Serum PSA comes in free form and in a form bound to plasma proteins such as alpha1-anti chymotrypsin and alpha 2-macroglobulin. In the mid 1990s researchers noted that in patients with prostate cancer a higher percentage of the PSA produced is bound to the aforementioned plasma proteins whereas in patients with benign disease a greater percentage is free. As with many of the other PSA adjuncts, this data is most useful in the PSA range of 4.0-10.0 ng/ml. In a multi-institutional study with men ages 50-75 years with PSA ranges of 4.0-10.0 ng/ml a % free PSA cutoff of 25% detected 95% of cancers and eliminated 20% of unnecessary biopsies<sup>7</sup>. As a result, often times percent free PSA testing is currently ordered in patients with a PSA between 4.0-10.0 ng/ml where a decision is being made as whether to offer a biopsy of the prostate or not. Caution must be exercised when this test is ordered in patients with PSA values outside of the recommended range because the cutoff of 25% was never validated outside of this range.

### Age Adjusted PSA

Age adjusted PSA underscores the discovery that PSA values are a dynamic process with respect to patient age and denotes that younger individuals should have lower PSA standards for detecting clinically significant prostate cancer.

Age	[95% specificity]		[95% sensitivity]	
	white <sup>4</sup>	black <sup>5</sup>	white <sup>5</sup>	black <sup>5</sup>
40	0-2.5	0-2.4	0-2.5	0-2.0
50	0-3.5	0-6.5	0-3.5	0-4.0
60	0-4.5	0-11.3	0-3.5	0-4.5
70	0-6.5	0-12.5	0-3.5	0-5.5

Table 1. Age adjusted PSA guidelines.

### PSA Velocity

PSA velocity on the other hand is a very commonly used PSA adjunct. Currently the accepted standard is that a PSA change of > 0.75ng/ml/year should raise concern for possible prostate cancer. In fact, in a study by Carter et al, 72% of men with prostate cancer had a PSA velocity >0.75ng/ml whereas

only 5% of men without prostate cancer had a PSA velocity >0.75ng/ml<sup>6</sup>. These figures were originally studied in populations with a PSA range of 4.0-10.0 ng/ml and are only valid in this range. The recommended period over which to follow PSA velocity has been 18 months or 3 consecutive values. Most urologist liberalize this and offer biopsy if there is a significant rise in PSA over a one year period.

### PSA Density

PSA density was popularized in the 1990s. This was in response to the fact that 80% of abnormally elevated PSA values are in the range of 4.0-10.0 ng/ml and are the result of benign prostatic hyperplasia and not prostate cancer. It is known that prostate cancer seems to produce more PSA than benign disease per an equivalent volume of tissue. Using the formula: serum PSA /prostate volume (calculated by trans-rectal ultrasound), one can calculate PSA density. A cutoff of 0.15 or greater has been used as the threshold for biopsy as values above this have a greater chance of being associated with cancer. Unfortunately PSA density has not been validated in all studies and is the least commonly used of the PSA adjuncts.

Although the PSA adjuncts are currently the best commercially available aides to PSA testing, they are not ideal. In response to this a team of Hopkins researchers began to search for new biomarkers for prostate cancer using proteomic biology. They subsequently identified a nuclear protein prostate cancer biomarker called EPCA-2. This study involved six groups of men, one control group, and was arranged as follows<sup>8</sup>:

1. 33 men with a PSA of less than 2.5 ng/ml with a normal DRE
2. 30 men with a PSA of 2.5 ng/ml, normal DRE and a negative biopsy
3. 40 men with organ confined prostate cancer
4. 40 men with non organ confined prostate cancer
5. 18 men with a PSA of less than 2.5 ng/ml and prostate cancer
6. 35 men with a normal PSA and symptomatic BPH
7. 134 patients including healthy women, and men and women with benign conditions

Data analysis ultimately determined that EPCA-2 was highly specific in discriminating between men with and without prostate cancer. In the normal patient groups, using a PSA cutoff of 2.5 ng/ml yielded a specificity of 65% whereas using a PSA cutoff of 4.0 ng/ml yielded a specificity of 70%<sup>8</sup>.

In the same group EPCA-2 yielded a specificity of 92%<sup>8</sup>. In the prostate cancer groups (organ confined and non organ confined) a PSA cutoff of 2.5 ng/ml yielded a sensitivity of 90% whereas using a PSA cutoff of 4.0ng/ml yielded a sensitivity of 69%. In the same group EPCA-2 yielded a sensitivity of 94%<sup>8</sup>. Additionally EPCA-2 was highly accurate in separating men with organ confined prostate cancer from men with non organ confined disease. Ultimately this was a pilot study with small numbers that was not representative of a true screening population. This study did however demonstrate some interesting trends which remain to be confirmed in a well designed study to address the screening potential of EPCA-2 as well as its ability to differentiate between organ confined and non organ confined prostate cancer.

#### References

1. 2007 American Cancer Society, surveillance data.
2. Alan Partin and Ronald Rodriguez. The molecular biology, endocrinology, and physiology of the prostate and seminal vesicles. Campbell's Urology (8); 2002. Chapter 37: pg. 1237-1296.
3. H. Ballentine Carter and Alan W. Partin. Diagnosis and treatment of prostate cancer. Campbell's Urology (8); 2002. Chapter 88: pg. 3055-3079.
4. Oesterling JE et al. JAMA 1993; 270: page 860.
5. Morgan TO et al. Age-specific reference ranges for serum prostate specific antigen in black men. NEJM 1996; 335: pg 304-310.
6. Carter HB, Pearson JD, Metter JE, et al. Longitudinal evaluation of prostate specific antigen levels in men with and without prostate disease. JAMA 1992b; 267:2215.
7. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: A prospective multi-center clinical trial. JAMA 1998; 279:1542.
8. Eddy LS et al. EPCA-2: A highly specific serum marker for prostate cancer. Urology 69 (4), 2007.

## CENTER FOR CONTINENCE

Our Center for Continence in conjunction with Dr. Bruno is now offering treatment for men with incontinence after prostatectomy, as well as Interstim treatment for overactive bladder and non-obstructive urinary retention.

If you have any patients interested in Interstim we are conducting monthly educational seminars at our office on the first Tuesday of every month. You can contact Jenny at 650-306-1016 for more information.

## EMERGING TREATMENTS

Our office is currently enrolling patients in two clinical trials. One trial involves a new oral medication for the treatment of OAB with LUTS associated with BOO in males 45 years of age and older. The other trial is for a new oral medication for the treatment of OAB in both males and females between the ages of 20 and 80. If you have any patients you think would be good candidates have them call Linda at 650-306-0750.

## UPCOMING TOPICS

1. Advances in Female Incontinence/ Pelvic Prolapse
2. Erectile Dysfunction
3. Kidney Stones
4. Incontinence
5. Hematuria
6. Renal, Bladder, Prostate, Testicular Cancer
7. Male Menopause
8. Interstitial Cystitis
9. Treatment Advances for UPJ Obstruction
10. Recurrent UTI's
11. Infertility

**Chris B. Threatt, M.D.**  
**Dieter Bruno, M.D., F.A.C.S.**

Diplomates, American Board of Urology

**Peninsula Urology Center, Inc.**  
3351 El Camino Real, Suite 101  
Atherton, California 94027  
Phone: (650) 306-1016  
Fax: (650) 369-3627