PROSTATE SPECIFIC ANTIGEN: PERSISTENT SOURCE OF ANXIETY

Altaf Qadir Khattak, Marc Lucky

Department of Urology,
Royal Liverpool University Hospital, Liverpool - United Kingdom

Prostate specific antigen (PSA) is a serine protease enzyme which is produced by the columnar acinar and ductal prostatic epithelial cells. Its function is to liquefy the semen in seminal coagulum in order to allow the sperm to swim freely[1]. It is also thought to be important in dissolving the cervical mucous cap, allowing the entry of sperm into the uterus. The half-life of PSA is approximately 2.2 days. The normal range of serum PSA in men varies with age. Serum PSA concentrations also vary physiologically, according to race and prostate volume.

PSA is present in small quantities in the serum of men with healthy prostates. However, any condition breaching the basement membrane of the columner epithelium of prostate will result in elevated serum PSA levels by allowing the PSA to escape into the circulation in larger quantities than normal from the confines of the epithelium of prostate. Prostate cancer will disrupt the integrity of the basement membrane of prostatic adenoma causing raised PSA levels, hence, its use in detection, treatment and follow up of prostate cancer patients. However, PSA is not prostate cancer specific. PSA sensitivity and specificity for prostate cancer vary by age, especially for PSA values less than 4.0ng/mL. PSA levels can also be elevated in men with urinary tract infection, prostatitis, after catheterisation and instrumentation of bladder, benign prostatic hyperplasia and even after recent ejaculation (up to 72 hours). Digital rectal examination has been shown in several studies to produce an increase in PSA, however, the effect is clinically insignificant[2]. Serum PSA can be checked after performing digital rectal examination. Serum PSA levels are halved after six months of treatment with 5 alpha reductase inhibitors (Finesteride, Dutesteride) for benign prostatic hyperplasia. As a result, reference ranges and calculations of the rate of change in PSA levels must be adjusted accordingly in men taking such drugs.

PSA was first discovered in 1970 and measured quantitatively in the blood in the 1980s. Stamey et al carried out the initial work on the clinical use of PSA as a marker of prostate cancer. The first commercial test of PSA for prostate cancer became available in 1986. Since, PSA has established itself as a very useful marker in the detection, treatment and follow up of prostate cancer patients. The use of PSA in screening/detection for prostate cancer is a widely debated and controversial topic. This is because in the majority of men who develop the disease, it is unlikely to be the cause of mortality. Screening is expensive and time consuming, and it is argued that the lives saved do not justify the added morbidity caused by over treatment of individuals who would have otherwise remained undiagnosed. Recently, two large trials have reported on PSA use in screening for prostate cancer. The European Randomised Study of Screening for Prostate Cancer looked at 182,000 men between the ages of 50 and 74 years in seven European countries. Subjects were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such

Table 1: Age-adjusted normal range for PSA

Age Range	Normal PSA range (ng/ml)
All ages	<4.0
40-49	<2.5
50-59	<3.5
60-69	<4.5
>70	<6.5

screening. During a median follow-up of almost 9 years, the cumulative detected incidence of prostate cancer was 820 per 10,000 in the screening group and 480 per 10,000 in the control group. There were 214 prostate cancer deaths in the screening group and 326 in the control group. It was concluded that PSA-based screening did reduce the rate of death from prostate cancer by 20%, but that this was associated with a high risk of overdiagnosis. This meant that to prevent one death from prostate cancer at 9 years follow up 1410 men had to be screened and 48 men had to be treated to save one life though 48 to 1 ratio may go down with longer follow up[3].

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, looked at the general effectiveness of a screening program involving both PSA and DRE methods. 76,693 men at 10 U.S. study centres were enrolled and 38,343 subjects received screening (an annual PSA testing for 6 years and DRE for 4 years), while a control group of 38,350 subjects received standard care. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2,820 cancers) in the screening group and 95 (2,322 cancers) in the control group. The incidence of death attributed to prostate cancer per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group. It was concluded that, after 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups[4]. Currently PSA remains the best test available for early detection of prostate cancer, but it still remains controversial, due to its lack of sensitivity and specificity. At the present moment in time, it is recommended that PSA levels should be checked in individuals presenting with lower urinary tract symptoms, abnormal digital rectal examination, high risk patients (having first degree relatives as prostate cancer patients and Afro-Carribean), and for monitoring of prostate cancer patients. It can also be checked in patients with unexplained anaemia or weight loss where a diagnosis cannot be made. PSA levels may be checked upon patient request but only after careful counselling regarding the pros and cons of this test. Current UK guidelines do not recommend the use of PSA as a screening tool for prostate cancer. As a medical practitioner, one should consider the pros and cons of PSA testing and tailor it to each individual case, taking into account risk factors and life expectancy. PSA is also helpful in deciding about the treatment options after the diagnosis of prostate cancer. Currently the cut off level for offering radical prostatectomy to the patients with clinically organ confined cancer is 20ng/mL though age of the patient at diagnosis is also a major factor, surgical option being not offered commonly after the age of 70 years. Staging MRI and Bone Scan are not performed in the majority of the centres in patients with prostate cancers considered for radical treatment with PSA of less than 10 ng/mL and Gleason Score of 7 and less on biopsy of protate. Prostate cancer patients with PSA greater than 40ng/mL are unlikely to benefit from radical treatment be it radical prostatectomy or radical radiotherapy as the potential for micrometastases is very high though the bone scan may be negative in these patients. Patients who are managed with watchful waiting by monitoring their PSA velocity should be considered for hormone manipulation once their PSA goes higher than 40ng/mL as there is evidence that early hormone manipulation in metastatic prostate cancer patients results in overall survival advantage[5].

PSA levels are monitored periodically (usually every 6-12 months) after treatment for prostate cancer. If surgical therapy (i.e. radical prostatectomy) is successful at removing all prostate tissue (and prostate cancer), PSA becomes undetectable within 6-8 weeks. A subsequent rise in PSA level above 0.2 ng/mL is generally regarded as evidence of recurrent prostate cancer after a radical prostatectomy; less commonly, it may simply indicate residual benign prostate tissue.

Following radiation therapy of any type for prostate cancer, some PSA levels might be detected, even when the treatment ultimately proves to be successful. This makes it more difficult to interpret the relationship between PSA levels and recurrence/persistence of prostate cancer after radiation therapy. PSA levels may continue to decrease for several years after radiation therapy. The lowest level is referred to as the PSA nadir. A subsequent increase in PSA levels by 2.0 ng/mL above the nadir is the currently accepted definition of prostate cancer recurrence after radiation therapy.

If recurrent prostate cancer is detected by a rise in PSA levels after curative treatment, it is referred to as a "biochemical recurrence." The likelihood of developing recurrent prostate cancer after curative treatment is correlated to various risk factors, such as the grade of prostate cancer (Gleason score), PSA level prior to treatment, and the stage of disease prior to treatment. Patients with low-grade cancer (Gleason score ≤ 6), PSA < 10, and tumors that are not palpable by digital rectal examination are at the lowest risk of recurrence.

Hormone relapsed prostate cancer can be detected at an earlier stage when PSA starts rising again after reaching a nadir in patients with advanced cancer of prostate who initially had anti-androgens or LH

RH analogues or castration as the treatment for their advanced disease being not candidates for radical treatment modalities.

In conclusion, PSA is a very useful tumor marker in prostate cancer and has an important role in the detection, treatment and follow up of prostate cancer patients but its value should be interpreted in the light of other factors influencing its serum levels rendering its sensitivity and specificity less than ideal. Having said this, PSA remains a "Persistent Source of Anxiety" for the urologists and their patients.

REFERENCES

1. Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. J Clin Oncol 2003;21:383–91.
2. Crawford ED, Schutz MJ, Clejan S, Drago J, Resnick MI, Chodak GW, et al. The effect of digital rectal examination on prostate-specific antigen levels. JAMA 1992;267:2227–8.
3. Schroder FH, Hugosson U, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate cancer mortality in a randomized European study. N Engl J Med 2009;360:1320-8.
4 Andriole GL, Crawford ED, Grubb RL, Uys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate cancer screening trial. N Engl J Med 2009;360:1310-9.
5. Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, et al. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst 2003;95:1300-11.

Address for Correspondence:
Dr. Altaf Qadir Khattak
Consultant Urological Surgeon,
Department of Urology,
Royal Liverpool University Hospital, Liverpool - United Kingdom