

## **Significance of prostate specific antigen in prostate cancer patients and in non cancerous prostatic disease patients**

Muhammad Hanif<sup>1</sup>, Parveen Zaidi<sup>1</sup>, Shahid Kamal<sup>1</sup>, Samreen Idrees<sup>2</sup>, Sheikh Ajaz Rasool<sup>3</sup>

Karachi Institute of Radiotherapy and Nuclear Medicine<sup>1</sup>, Department of Microbiology, Jinnah University for Women<sup>2</sup>, University of Karachi<sup>3</sup>.

### **Abstract**

**Objective:** To evaluate the significance of prostate specific antigen (PSA) and scan in prostate cancer patients and in non cancerous prostatic disease patients.

**Methods:** The study was carried out in Radioimmunoassay (RIA) lab, KIRAN Hospital, Karachi during 2002 to 2006. A total of 149 serum samples were collected in which 93 samples were biopsy positive prostate cancer patients referred to KIRAN hospital for treatment. The other 56 samples were collected from patients having other prostatic diseases and advised PSA tests by physicians and urologists from 'The Lab' Karachi. The PSA (total) was measured by immunoradiometric assay (IRMA) in which two monoclonal antibodies against two different epitopes of PSA molecules were used. The results were correlated with bone scan and age of the patients.

**Results:** A total of 149 patient samples were analyzed in which 93 were from biopsy positive prostate cancer patients and 56 from patients having other prostatic diseases. Out of 93 prostate cancer patients sample, 74 (79.6%) had elevated PSA level (>4 ng/ml) and 19 (20.4%) had PSA within normal range (<4 ng/ml). Among 74 elevated PSA level cases, 48 (64.8%) had a positive bone scan and 26 (35.2%) had negative bone scan. Minimum age recorded was 40 years (Mean age 66.4±9.1 years). In fifty six (56) serum samples which were collected from 'The Lab' and having other prostatic diseases, 49 (87.5%) had PSA within normal range (≤ 4 ng/ml).

**Conclusion:** Prostate specific antigen has a significant role for the diagnosis of prostate cancer (and has a significant correlation with bone scan). Immunoradiometric assay has a sensitivity of 79.5% and specificity of 87.5% for prostate cancer (JPMA 57:248;2007).

## Introduction

Adenocarcinoma of the prostate represents the most common form of cancer in adult males. Increase in incidence is more pronounced in the United States, Canada, Australia, France and the Asian countries while mortality rates are increasing more rapidly in Asian countries than in high-risk countries.<sup>1</sup> It is the most common diagnosed neoplasm and the second most common cause of cancer death after lung cancer in America.<sup>2</sup> Worldwide prostate cancer ranks third in cancer incidence and sixth in cancer mortality. The incidence of prostate cancer is low in Pakistan, with a figure of 3.8% of our male population. The most likely explanation for this is lower life expectancy and no screening for prostate cancer in Pakistan.<sup>3</sup>

Prostate-specific antigen (PSA) is now recognized as the premier tumor marker for prostatic cancer.<sup>4</sup> Wang<sup>5</sup> et al. reported PSA in the prostate in 1977 and characterized the protein definitively in 1979. PSA was purified from both prostatic tissue and seminal plasma.<sup>6</sup> PSA's unique tissue specificity is what makes it significant as a tumor marker. A single polypeptide, PSA occurs both in normal and malignant prostatic tissue and in the glands of men with BPH, but not in any other human tissue.

PSA is very effective as a tumor marker for prostatic cancer. It is useful for monitoring therapeutic efficacy, staging, prognosis, tumour volume evaluation, detection of recurrent disease, differential diagnosis, confirmation of tissue of prostatic origin, and, in some cases, for screening and early diagnosis.<sup>6</sup>

Wang<sup>5</sup> et al., in their early work, identified and measured PSA by using isoelectric focusing, immuno diffusion, immuno electrophoresis, and rocket immunoelectrophoresis.<sup>7</sup> An enzyme-linked immuno sorbent assay, more amenable to clinical analysis, was also developed by this group.<sup>7,8</sup> The lower limit of detection (LLD), commonly referred to as the sensitivity, of this assay is 0.1 ng/dl. Loo<sup>9</sup> et al. explored various modifications of this method, developing two and three-site enzyme immuno metric assays and using polystyrene beads for a solid support.

Both radio immuno assay (RIAs) and immuno radiometric assay (IRMAs) have been developed for PSA.<sup>10,11</sup> Most of the clinical data reported in the literature are derived from an RIA and an IRMA. The Pros-Check assay is a traditional polyclonal RIA that was widely used in the past, but it lacks approval by the Food and Drug Administration (FDA).<sup>12</sup> Inter-assay coefficients of variances (CVs) of 5.5-7.1% have been reported, with an LLD of 0.25 ng/ml and recoveries of 96.1-116.1%. The Tandem-R test for PSA is an IRMA, is approved by the FDA, and, as reflected by the literature, was the most commonly used assay in the US until recently, when it started to be replaced by non radio isotopic tests.<sup>10,12</sup> For the Hybritech assay a monoclonal antibody to PSA is coated on a plastic bead. The linear range of this assay is 2-100 ng/ml with an LLD of 0.1-0.2 ng/ml, recoveries of 97-102%, and inter-assay CVs of 1.3-4.9%. The assay drift after analyses of 100 samples is reportedly ~4%.

The IRMA count PSA assay is another IRMA procedure.<sup>13</sup> In this system, biotin-coated tubes are used so that sandwich formation can occur in the liquid phase and the <sup>125</sup>I-labeled antibody-PSA complex becomes immobilized on the cell wall after complex formation. The LLD is ~0.1ng/ml, run-to-run CVs are <6.7%, and a linear range of 0-200 ng/ml is reported.

Prostate specific antigen (PSA) was found to be high in 40-67% of localized and 76-100% of metastatic prostate cancer cases as reported in a study by Chybowski et al.<sup>14</sup> It is an important tumor marker also in evaluating the response of the treatment. Bone scintigraphy is not only highly sensitive in demonstrating the bone metastasis but also in evaluating the response of treatment. Particularly in cases with no metastatic appearance on direct X-ray, bone scintigraphy can demonstrate the presence of bone metastasis. The probability of positive bone scans increase with the increasing level of PSA. In various studies bone metastasis were rarely seen in scan of patients whose PSA levels were 20 ng/ml or lower.<sup>14</sup>

The FDA has approved serum PSA for use as a prostate cancer screening laboratory test. Like so many serum tumour markers, it is produced by both normal and cancerous glands. In men with prostate cancer, the serum levels can be elevated with both localized and advanced or disseminated disease. PSA levels are generally proportional to the volume of the cancer. Like any laboratory test, there is a significant overlap between PSA levels found in cancer and benign prostatic hyperplasia. Thus, it is important to obtain sequential levels in low or borderline elevated values. A rise in the level as compared to an earlier measurement an ominous sign.

The objective of the study was to evaluate the significance of PSA and bone scan and age for the diagnosis of prostate cancer and to suggest PSA values for prostate cancer and in other prostatic diseases.

## Patients and Methods

The study was carried out in Radioimmunoassay lab, KIRAN Hospital, Karachi during 2002 to 2006. Serum samples were collected from 93 diagnosed prostate cancer patients registered at KIRAN for treatment. The exclusion criteria were prostate surgery, patients already receiving chemotherapy/radiotherapy and patients having cancer other than prostatic origin. Other 56 serum samples were collected from 'The Lab' Karachi from persons having other prostatic diseases and advised PSA tests by physicians and urologists. The PSA (total) was measured by immunoradiometric assay (IRMA) on gamma counter and by using PSA total kit supplied by IMMUNOTECH (Beckman Coulter) in which two monoclonal antibodies against two different epitopes of PSA molecules were used. Bone scans were done in Nuclear Medicine department KIRAN. A dye, methyl diphosphate (MDP) and a radiolabelled tracer, Tcm-99 were injected to the patients. These tracers accumulate in certain organs and tissues, such as bones. Once introduced into the body, tracers emit gamma waves of radiation, which are

detected by a special Gamma camera [E cam and Toshiba]. This camera produces images that are interpreted by nuclear medicine specialists. The results were correlated with bone scan and age of the patients. Data analysis was conducted with Minitab software for the calculation of sensitivity, specificity and accuracy of the tests.

### Results

All 93 prostate cancer patients had highly variable serum PSA values ranging from 2.01ng/ml to >500ng/ml. In this group of patients, 74 (79.6%) had PSA levels >4.0 ng/ml (Mean 122.49ng/ml) and 19 (20.4%) had PSA <4.0 ng/ml (Mean 2.71 ng/ml) (Table 1).

PSA level in 56 serum samples collected from 'The Lab' was also variable and 49 (87.5%) showed PSA within normal range ( $\leq 4$  ng/ml) (Mean 2.72 ng/ml) (Table 1) and among other seven cases in which PSA was above normal range three were diagnosed as prostate cancer later on.

Among 74 samples, with PSA > 4 mg/l, 48 (64.9%) patients had positive bone scan and 26 (35.1%) had a negative bone scan. In the other 19 prostate cancer patients in whom PSA was within normal range, 13 (68.4%) had a negative bone scan and 6 (31.5%) had positive bone scan (Table 2).

Minimum age recorded was 40 years (Range 40 to 90 years) and maximum number of patients was among the age group of 60-69 years.

### Discussion

The main reason of high mortality in prostate cancer is its frequent occurrence in elder population and its late diagnosis in most of the cases.<sup>15</sup> Over a period of four years, February 2002 through February 2006, 174 patients were registered as prostate cancer patients in our Institute.

In the present study we performed PSA testing in

**Table 1. Normal and elevated PSA in two groups of patients.**

	Prostate Ca Patients (n=93)	Other Prostate Disease Patients (n=56)	Total
Elevated PSA	74 (79.6%)	7 (12.5%)	81
Normal PSA	19 (20.4%)	49 (87.5%)	68
	93	56	149

Sensitivity = 79.6%  
Specificity = 87.5%

**Table 2. Bone scans and PSA levels in prostate cancer patients.**

	Positive Bone scan	Negative Bone scan	Total
PSA level >4 ng/ml	48 (64.9%)	26 (35.1%)	74
PSA level $\leq 4$ ng/ml	6 (31.6%)	13 (68.4%)	19
	54	39	93

biopsy positive prostate cancer patients and found that ~80% of these patients have PSA level >4 ng/ml. Other studies have provided similar estimates of sensitivity and specificity for PSA level with a cut-point of 4.0 ng/mL.<sup>16</sup> Specificity for PSA screening is lower among men with

larger prostate glands, including the large number of older men with benign prostatic hyperplasia. One study of four carefully chosen samples found that the likelihood ratios for various PSA levels were much lower among men with benign prostatic hyperplasia than among men without benign prostatic hyperplasia.<sup>17</sup> Thus, the PSA test is not as accurate in detecting cancer in men with benign prostatic hyperplasia as in those without.

Although PSA is tissue specific, it is not cancer specific, because it is found in benign, normal, and malignant prostates.<sup>18</sup> Many men have prostatic cancer, but many more have BPH. Some BPH patients are asymptomatic; others exhibit prostatism. Distinguishing BPH from prostatic cancer is crucial and a major challenge.

Similarly, PSA level was found within normal range (<4 ng/ml) in 87.5% among other prostatic disease patients. Other studies have provided similar results.<sup>19,20</sup> In most patients with BPH the increase is modest, but an estimated 3-21% of patients have PSA values >10 ng/ml.<sup>21,22</sup> In one study, 13% of BPH patients and 87% of cancer patients had a PSA concentration >10 ng/ml; in another study, the numbers were 14.1% of BPH patients and 84.4% of cancer patients with PSA >10 ng/ml.<sup>19-21</sup> Conversely, cancer patients may also show only minimal increases in PSA. One group found that only 3% of 168 BPH patients had PSA >10 ng/ml but only 44% of 231 cancer patients exceeded that value.<sup>19</sup> Palken<sup>22</sup> et al. found that 10% of patients had normal PSA concentrations in spite of the presence of cancer.

We also compared PSA level with increasing age in patients with prostate cancer, the age of these patients ranged between 40-90 years with average age of 66 years and observed that 54.4% of patients were 60-69 years old and result was similar to the report of Dijkman<sup>23</sup> et al in 1996 that carcinoma of prostate is a strongly age dependent tumor as 50% of patients were found between 61-70 years of age.

Overall cancer detection rate (sensitivity 79.6% and specificity 87.5%) was also similar to the other studies.<sup>10</sup> Because of the overlap in PSA concentrations between healthy, or at least non cancerous, individuals in the case of BPH, and diseased populations with regard to prostatic cancer, it is difficult to pick a critical PSA value to separate the two. When 2.5 ng/ml is selected, PSA sensitivity is ~94% and specificity is only ~44%.<sup>24</sup> If the cutoff is raised to 4 ng/ml, the sensitivity decreases to ~68-75%, while specificity increases to ~60-80%.<sup>10</sup>

One of the aims was to find out the relation between bone scintigraphy in detecting bone metastasis and PSA level. We found that bone scan was positive in ~65% of the patients having PSA >4 ng/ml and negative in ~74% of the patients having PSA < 4 ng/ml. Bone scintigraphy is not only highly sensitive in demonstrating the bone metastasis but also in evaluating the response of the treatment. Particularly in cases with no metastatic appearance on direct X-ray, bone scintigraphy can demonstrate the presence of

bone metastasis. The probability of positive bone scans increase with the increasing level of PSA. In various studies bone metastasis were rarely seen in scan of patients whose PSA levels were 20 ng/ml or lower.<sup>14</sup>

### Acknowledgements

We are thankful to Dr. Iqbal, Director "The Lab" Karachi for providing samples for this study. We are also thankful to Miss Dilshad Fatima, Lab technician KIRAN for her help throughout this study and for data compilation.

### References

1. Hsing AW, Tsao L, Devasa SS. International trend and patterns of prostate cancer incidence and mortality. *Int J Cancer* 2000;85:60-7.
2. Boring C, Squires TS, Tong T, Montgomery S. Cancer statistics, CA Cancer J Clin 1994;44:7-26.
3. Aziz Z, Sana S, Saeed S, Akram M. Institution based tumor registry from Punjab: Five year data based analysis. *J Med Pak Assoc* 2003;53:350-3.
4. Gittea RF. Prostate-specific antigen. *N Engl J Med* 1987;317:954-5.
5. Wang MC, Chu TM, Kuciel R, Valenzuela L, Murphy GP. Enzyme markers in human prostatic carcinoma. *Cancer Treat Rep* 1977;61:193-209.
6. Schiffman RB, Ahmann FR, Elvick A, Ahmann M, Coulis K, Brawer MK. Analytical and physiological characteristics of prostate-specific antigen and prostatic acid phosphatase in serum compared. *Clin Chem* 1987;33:2086-8.
7. Kuriyama M, Wang MC, Papiridero LD, Killian CS, Schimono T, Valenzuela L, et al. Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. *Cancer Res* 1980;40:4658-62.
8. Kuriyama M, Wang MC, Papsidero LD, Killian CS, Schimono T, Valenzuela L, et al. Prostate antigen of human cancer patients. *Methods Cancer Res* 1982;19:179-97.
9. Loor R, M'Timkulu T, Dewitt SK. Individual and simultaneous monoclonal antibody-based immunoassays of prostate-specific antigen and prostatic acid phosphatase. *J Clin Immunoassay* 1986;9:159-63.
10. Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. *J Urol* 1991; 145:907-23.
11. Miki M, Machida T, Yanagisawa M, Yoshida M, Yamozaki H, Kondo N, et al. Clinical evaluation of serum prostatic specific antigen measurement by radioimmunoassay. *Jpn J Urol* 1984;75:1982-8.
12. Chan DW, Bruzek DJ, Oesterling JE, Rock RC, Walsh PC. Prostate-specific antigen as a marker for prostatic cancer a monoclonal and a polyclonal immunoassay compared. *Clin Chem* 1987;33:1916-20.
13. Ooi DS, Pronovost C, Escares E. Performance evaluation of DPC's IRMA Count PSA assay [Abstract]. *Clin Chem* 1990;36:1050.
14. Chybowski FM, Larson-Keller JJ, Bergstralh EJ, Oesterling JE. Predicting radionuclide bone scan findings in patients with newly diagnosed, untreated prostate cancer: Prostate-specific antigen is superior to all other clinical parameters. *J Urol* 1991;145:313-8.
15. Giuliani L, Pescatore D, Giberti C, Martorana G, Natt G. Treatment of advanced prostatic carcinoma with cyproterone acetate and orchiectomy: 5-year follow-up. *Eur Urol* 1980;6:145-8.
16. Jacobsen SJ, Bergstralh EJ, Guess HA, Katusic SK, Klee GG, Oesterling JE, et al. Predictive properties of serum-prostate-specific antigen testing in a community-based setting *Arch Intern Med* 1996;156:2462-8.
17. Meigs JB, Barry MJ, Oesterling JE, Jacobsen SJ. Interpreting results of prostate-specific antigen testing for early detection of prostate cancer *J Gen Intern Med* 1996;11:505-12.
18. Brewer MK. Laboratory studies for the detection of carcinoma of the prostate. *Urol Clin North Am* 1990;17:759-68.
19. Bernstein LH, Rudolph RA, Pinto MM, Viner N, Zuckerman H. Medically significant concentrations of prostate-specific antigen in blood assessed. *Clin Chem* 1990;36:515-8.
20. Ercole CJ, Lange PH, Mathisen M, Chiou RK, Reddy PK, Vessella RL. Prostatic specific antigen and prostatic acid phosphatase and staging of patients with prostatic cancer. *J Urol* 1987;138:1181-4.
21. Armitage TG, Cooper EH, Newling DW, Robinson MR, Appleyard I. The value of the measurement of serum prostate-specific antigen in patients with benign prostatic hyperplasia and untreated prostate cancer. *Br J Urol* 1988; 62:584-9.
22. Palken M, Cobb DE, Warren BH, Hoak DC. Prostate cancer correlation of digital rectal examination, trans rectal ultrasound and prostate specific antigen levels with tumor volume in radical prostatectomy specimens. *J Urol* 1990; 143:1155-62.
23. Dijkman GA, Debruyne FM. Epidemiology of prostate cancer. *Eur Urol* 1996; 30:281-95.
24. Leitenberger A, Altwein JE. Efficacy and discriminative ability of prostate-specific antigen as a tumor marker. *Eur Urol* 1990;17:12-16.