Relation of Prostate Specific Antigen and Histopathology of Prostate Biopsy.

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ABSTRACT

Background and Objectives: Prostate cancer is now the commonest cancer in men and the second commonest cause of cancer death after lung cancer. The introduction of prostate specific antigen (PSA) testing has revolutionized the early detection, management and follow-up of patients with prostate cancer and it is considered to be one of the best biochemical markers currently available in the field of oncology. This prospective study was aimed to Evaluate the diagnostic performance characteristics of prostate specific antigen (PSA) by comparing serum PSA value with histopathological finding of prostate biopsy , Determine the relation between PSA and various prostatic diseases, and To explain the effect of age on PSA testing.

Methods: To fulfill these objectives, 92 specimens of prostate biopsy from patients with history of prostatism who underwent prostate surgery (prostatectomy, TURP and true cut biopsy of prostate) with samples of serum for tPSA analysis taken preoperatively during a period of 10 months. In addition to 33 samples of serum taken from apparently healthy individuals for tPSA analysis.

Results: From 92 cases 12 of them were malignant, 49 cases were BPH and 31 cases were BPH with prostatitis. Statistically there was significant relation between PSA values and histopathological findings of prostate biopsy and significant relation between age and PSA value of apparently healthy individuals. PSA sensitivity was (100%), specificity (46.25%), PPV (21.8%), and NPV (100 Sensitivity of PSA testing was better than specificity.**Conclusions:** It is concluded that PSA evaluation is a sensitive marker for prostate cancer but because of various other conditions that affect serum PSA concentration. Other methods of investigations such as DRE, TRUS and histological examination should be combined to confirm diagnosis.

Key words: Prostate cancer, Prostate specific antigen

INTRODUCTION:

Prostate specific antigen (PSA) is an androgen-regulated serine protease and member of the tissue kallikrein family of proteases[1]. It is produced primarily by prostate ductal and acinar epithelium and is secreted into the lumen, where its function is to cleave semenogelin I and II in the seminal coagulum. It is normally found in low concentration in sera. PSA within sera circulates in both bound and unbound forms. Most PSA in sera is bound or complexed to the antiproteases ACT (antichymotrypsin) and MG (macroglobulin)[2]. Elevated serum PSA levels have become an important marker of prostate pathologies which include benign prostatic hyperplasia, prostatitis, and especially prostate cancer. Prostatic intraepithelial neoplasia (PIN) does not appear to raise serum PSA levels[3]. Prostate specific antigen is a tumor marker currently used for early detection of prostate cancer. Measurement of serum PSA levels has significant clinical application in other areas of prostate disease

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management[4]. Prostate cancer is the most common form of non cutaneous cancer in men in the United State, and the second leading cause of male cancer mortality. In 1997 approximately 209,000 men diagnosed with prostate cancer and approximately 42,000 men died from the disease[5],while in 1999 prostate cancer was the first commonest ten cancers by gender constituted 29% of total male cancers[6] . In Iraq prostate cancer was the tenth commonest ten cancers during 1995-1997 in which 437 cases were recorded constituted 3.3% of total male cancers[7]. According to the National Saudi Tumor Registry, prostate cancer ranked 9th and 10th, and constituted 2.9% among male cancers in the 1994-1996 and 1997-1998 reports[8]. The lowest incidence of prostate cancer was seen among Chinese and Indonesian men, and the highest in black Americans[9]. Some studies have found that a large proportion of patients diagnosed with clinically localized prostate cancer who did not receive early aggressive treatment still had favorable clinical outcomes and normal life expectancies[10]. PSA testing is one of several measures that can be used to identify high risk tumors. Other such measures include; Gleason score, clinical stage, and the patient's estimated life expectancy[4]. The value and appropriate use of PSA screening remain controversial, but the success of primary therapy is certainly dependent on identifying tumors before they have spread outside the prostate[11].

MATERIALS AND METHODS:

This prospective study consisted of (92) prostate gland specimens of patients admitted to the urosurgical ward in Rizgary Teaching Hospital in Erbil from August,1st 2006 to June,1st 2007 who presented with lower urinary tract symptoms and underwent surgical operation for prostate (prostatectomy, TURP, and true cut needle biopsy of prostate). Full history and physical examination were done(except DR examination) then blood samples were collected preoperatively and sent for estimation of serum tPSA by using VIDAS TPSA which is an automated quantitative test for use on the VIDAS instrument, for the quantitative measurement of PSA level in human serum or plasma using the ELFA technique (Enzyme Linked Fluorescent Assay). Values up to 4.0 ng/ml regarded normal. In addition to 33 samples of serum taken from apparently healthy individuals for analysis of PSA value in control. Sections from the specimens was prepared by the routine paraffin wax method.

STATISTICAL ANALYSIS: For statistical analysis Chi square test was used in this study and for determination of cancer detection rate the following formula was used:
DR= no. of cancer cases / total no. X 100.
Calculation of sensitivity, specificity, PPV, and NPV done as the following:
Sensitivity = TP / TP + FN X100.
Specificity = TN / TN + FP X100.
PPV = TP / TP + FP X 100.
NPV = TN / TN + FN X100.

RESULT:

The age of patients ranged from (48-89) years with a mean age of (66.4) years. The most involved age group was (60-69) by 37 cases. The distribution of cases with result of biopsies is shown in (Table 1). tPSA levels in 37 cases were within range (0-4 ng/ml) in which all of them were benign, while 55 cases with tPSA level above (4ng/ml) in which 12 cases were malignant and the other 43 cases were benign as shown in (Table 2). Statistically by chi square test, there was a significant relation between PSA value and histopathological results of prostate biopsy (P value =0.00231). PSA sensitivity was (100%), specificity (46.25%), PPV (21.8%), and NPV (100%).
Statistically by chi square test there was no significant relation between PSA levels and age group of patients (P value = 0.5545). While comparing with 33 cases of apparently healthy individuals in the same age groups, statistically there was significant relation between PSA level and age groups (P value = 0.0071) as shown in (Figure 1). As shown in (Table 3) there were

statistically significant relations between PSA values in different prostatic disease conditions and in apparently healthy individuals.

Table 1: Age Distribution of Patients with Results of Biopsy.

Age groups	No. of cases	No. of Malignant cases	No. of Benign cases
40 - 49	1	0	1
50 - 59	16	1	15
60 - 69	37	5	32
70 - 79	27	6	21
80 - 89	11	0	11
Total	92	12	80

Table 2: Relation of PSA with Biopsy Results.

tPSA Value	No. of Cases	%	Biopsy Finding	
			Benign	Malignant
0 – 4 ng/ml	37	40.2	37	0
Above 4 ng/ml	55	59.8	43	12
Total	92	100	80	12

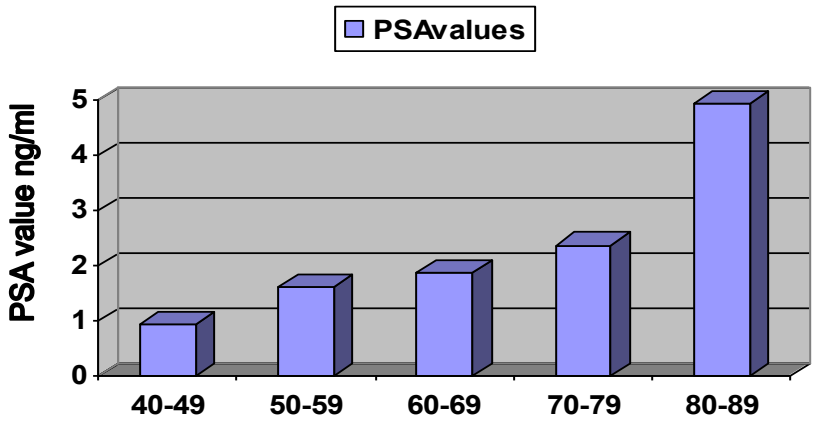

Figure 1: PSA Values in Apparently Healthy Individuals of Different Age Groups.

Table 3: Serum PSA Values in Different Prostatic Disease Conditions and in Apparently Healthy Individuals.

Disease conditions	No. of cases	Age range (in years)	tPSA (ng/ml) mean ± SD	P value
Apparently healthy cases	33	41-87	2.209 ± 1.726	0.0071
Benign prostatic hyperplasia	49	48-82	11.030 ± 6.591	0.0041
BPH + prostatitis	31	52-89	13.840 ± 9.156	0.0026
Adenocarcinoma	12	57-78	62.281 ± 29.441	0.0029
Total	125			

DISCUSSION:

Prostate cancer is now the commonest cancer in men and the second commonest cause of cancer death after lung cancer[12]. Prior to the recent addition of serum PSA testing to the traditional DRE, most prostate cancer were diagnosed only after they had become locally advanced or metastatic. Prostate cancer is a real risk for the aging male, with almost 10% of men over 50 years likely to develop clinically significant disease [13]. The measurement of PSA in serum is the most clinically useful tumor marker for the diagnosis of early curable adenocarcinoma of the prostate, although specific for prostate tissue, it is not prostate cancer specific [14].In this study the most affected age group by malignancy were (70-79) which constitute about (50%) of total cancer cases which is near to (54.1%) of the same age group reported by Flamerz[15] from Sulaimany and (56%) by Mansoor[16] in Saudi Arabia. This similarity may be due to the same life style and diet. The number of cases with prostate cancer was 12 cases (13.04%) which is near to the result of (14.6%) reported by Gohji et al[17], but lower than the result of (27.9%) reported by Flamerz[(15)], and higher than (10.9%) by George & Thomas[18] and (11.2%) by Kehinde[19]. The reason for these differences may be due to limited sample size of present study in comparison with large sample size of most other studies. The sensitivity of PSA was (100%), while specificity (46.25%), this low specificity may be due to appreciable number of false positive cases which affect both specificity and PPV; manipulation of the prostate gland, benign conditions as BPH and prostatitis which contribute to elevated PSA level.It is well known that PSA values for prostate cancer and BPH overlaps considerably, between 21% and 47% of men with histologically proven BPH have PSA levels more than 4ng/ml, and up to 43% of men with prostate cancer will have a PSA level of less than 4ng/ml. This overlap makes it harder to differentiate BPH from prostate carcinoma in the absence of a biopsy [20]. In this study all cancer cases were associated with high PSA (more than 4ng/ml). It has been reported by Oesterling et al[14] that serum PSA concentration directly correlated with patient's age and prostatic volume. Prostatic volume in turn is directly correlated with patient's age, since each 1 gm of benign hyperplastic tissue (BPH) gives rise to 0.2 ng/ml of PSA in the serum. In other words, as men grow older their prostate glands enlarge and PSA concentrations increase. Figure (1) shows that serum PSA values increase with increasing of age in a group of apparently healthy individuals. Our result is near to the results reported by Emokpae et al[21] and Hosseini et al[22]. These results indicate that as men grow older; their prostate gland may become more leaky. The normal physiological barrier that keep PSA in the prostate duct system (the basal cells lining the acini, the basement membrane of the acini, the basement membrane of the capillaries, and

the endothelial cells lining the capillaries) may become more permeable as a result PSA escapes from the acini, diffuses into the stroma of the gland itself, and enters the capillaries and lymphatic ducts coursing through the organ, and an additional slight increase in serum PSA concentration results [23]. Thus, rather than rely on a single reference range for men of all age groups, it is more appropriate to have age-specific reference ranges. These age-specific reference ranges have the potential to make serum PSA a more discriminating tumor marker for detecting clinically significant cancers in older men (increasing specificity)[14]. As shown in (Table 3) other factors contributing to increase in PSA as men age include episode of subclinical or clinical prostatitis, intermittent bouts of prostatic ischemia, infarction (see Figure 2) and the presence of prostate cancer (see Figure 3).

A PSA value above 4 ng/ml signals the need for further investigations, although Some patient's prostate tissue does not secrete much PSA even in the presence of prostate cancer [24, 25]. The results of this study indicate that the serum PSA is effective in the diagnosis of prostate cancer. BPH can lead to considerable rise in serum PSA levels. Nevertheless a mild to moderate rise in serum PSA level alone (without having any other concurrent diagnostic procedure) may prove inadequate in the diagnosis and confirmation of prostate cancer and this may even lead to a false and misleading conclusion by a clinician. The percent of free PSA will be helpful for men with PSA values less than 10 ng/ml to enable definitive diagnosis to be made. To obtain good performance from PSA evaluation, blood samples for PSA should be taken first before any physical manipulation of the prostate gland. When PSA is combined with other methods of diagnosis, early diagnosis will be made possible and prognosis of patients will be better.

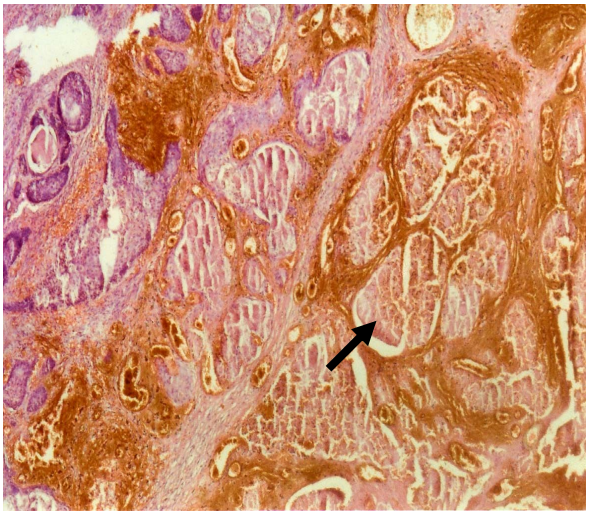

Figure 2: Prostatic infarction show area of coagulative necrosis (arrow). H & E stain X100.

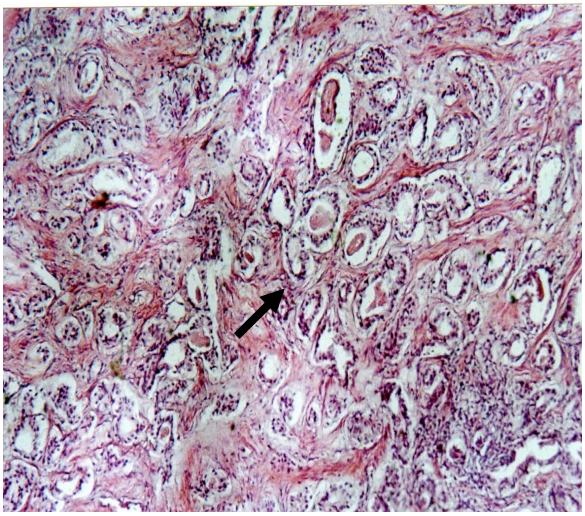

Figure 3: Prostatic adenocarcinoma, well differentiated (arrow), Gleason Score (2+2=4). H & E stain X40.

CONCLUSION:

It is concluded that PSA evaluations is a sensitive marker for prostate cancer but because of various other conditions that affect serum PSA concentration, other methods of investigations such as DRE, TRUS and histological examination should be combined to confirm diagnosis.

REFERENCES:

1. Yousef GM, Diamandis EP. The new human tissue kallikrein gene family: structure, function, and association to disease. Endocr Rev 2001; 22: 184 - 204.
2. Lilja H, Christensson A, Dahlen U, et al. Prostate-specific antigen in serum occurs predominantly in complex with alpha 1-antichymotrypsin. Clin Chem 1991; 37:1618-1625.
3. Alexander EE, Qian J, Wollan PC, et al. Prostatic intraepithelial neoplasia does not appear to raise serum prostate-specific antigen concentration. Urology 1996; 47(5):693-698.
4. Thompson I, Carroll P, Coley C, et al. Prostate-Specific Antigen (PSA) Best Practice Policy. American Urological Association. Oncology 2000; 14:267-270.
5. Nash AF, Melezink I. The role of prostate specific antigen measurement in the detection and management of prostate cancer. Endocrine-Related Cancer 2000; 7: 37-51.
6. Albertsen PC: Clinical Epidemiology: Incidence Rates, Databases, Age, and Co-Morbidity. In: Kantoff PW, Carroll PR, D'Amico AV, et al. Prostate Cancer: Principles & Practice, Philadelphia, Lippincot Williams&Wilkins, 2002:180-181.
7. Iraqi Cancer Board. Results of Iraqi Cancer Registry 1995-1997. Iraqi Cancer Registry Center, Ministry of Health, 1999: 22-31.
8. Taha SA, Kamal BA. Screening program for prostate cancer at a university hospital in eastern Saudi Arabia. Saudi Med J 2005; 26(7): 1104-1106.
9. Mosli H.A.M. Prostate Cancer in Saudi Arabia: A review of the literature (1975-1996). Ann Saudi Med 1997; 17(5): 510-514.
10. Coley CM, Barry MJ, Fleming C, et al. Early detection of prostate cancer: I. Prior probability and effectiveness of tests. Ann Intern Med 1997; 126:394-406.
11. Balk SP, Ko YJ, Bubley GJ. Biology of Prostate–Specific Antigen. J clin Oncol 2003; 21 (2):383-391.
12. Presti JC: Neoplasms of the Prostate Gland. In: Tanagho EA, McAninch JW. Smith's General Urology. 15th ed, USA, Lange Medical Books McGraw-Hill, 2000: 399-416.
13. Brett TD. An analysis of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer in general practice. Family Practice Oxford University Press 1998; 15 (6): 529-533.
14. Oesterling JE, Jacobsen SJ, Chute CG, *et al*. Serum prostate specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993; 270(7): 860-4.
15. Flamerz L.A.H. The role of TRU-CUT needle biopsy in detection of prostate cancer in comparison to PSA, DRE & TRUS examinations. A thesis for the degree of Master of Science in Pathology, University of Sulaimany, 2006.
16. Mansoor IA. Pattern of Prostatic Diseases in Saudi Arabia. The Internet Journal of Pathology 2003; 2 -9).
17. Gohji K, Okamoto M, Morisue K, *et al*. Usefulness of digital rectal examination, serum prostate specific antigen, transrectal ultrasonography and systematic prostate biopsy for the detection of organ-confined prostate cancer. Int J Urol 1995; 2(2):116-20.
18. George E, Thomas S: A Histopathologic Survey Of Prostate Diseases In The Sultanate Oman. The Internet Journal of Pathology 2005; 3(2): 1528-537.
19. Kehinde EO, Sheikh M, Mojimoniyi OA, *et al.* High serum prostate-specific antigen levels in the absence of prostate cancer in Middle-Eastern men: the clinician's dilemma. BJU International 2003; 91:618-622.
20. Mistry K, Cable G. Meta- analysis of prostate specific antigen and digital rectal examination as screening tests for prostate carcinoma. J Am Board Fam Pract 2003; 16(2):95-101.
21. Emokpae MA, Das SC, Orok T, *et al*. Early Detection of Prostate Cancer: Evaluating the Diagnostic Performance of Prostate Specific Antigen by Comparing with Histological Technique Among Africans. Indian Journal of Clinical Biochemistry 2004; 19(1): 62-66.
22. Hosseini SY, Moharramzadeh M, Ghadian AR, *et al.* Population-based screening for prostate cancer by measuring total serum prostate-specific antigen in Iran. International Journal of Urology 2007; 14(5): 406-411.
23. Oesterling JE. Age- Specific Reference Ranges for Serum PSA. N Engl J Med 1996; 335(5): 345-346.
24. Babaian RJ, Johnston DA, Naccarato W, *et al*. The Incidence of Prostate Cancer in a Screening Population with a Serum Prostate Specific Antigen Between 2.5 and 4.0 ng /ml. Relation to Biopsy Strategy. Journal of Urology 2001; 165: 757 -760.
25. Beardo P, Fernan Dez P, Corral J, *et al*. Undetectable Prostate Specific Antigen in Disseminated Prostate Cancer. Journal of Urology 2001; 166: 993.