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PROSTATE SPECIFIC ANTIGEN IN PATIENTS OF BENIGN PROSTATE HYPERTROPHY AND CARCINOMA PROSTATE

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ABSTRACT

Prostate Specific Antigen (PSA) has emerged as the most applicable and important tumor marker for carcinoma prostate. In the present study PSA was determined in serum of healthy subjects, patients of benign prostate hypertrophy (BPH) and Carcinoma Prostate (Ca-P) to evaluate its diagnostic efficiency in day to day management of prostate cancer patients and in differentiating patients of early prostate cancer from those with BPH. Receiver operating characteristic curve (ROC) revealed 2 ng/ml and 10 ng/ml cut off serum PSA level for BPH and untreated carcinoma prostate patients (Ca-P). An extremely significant increase ($P<0.0001$) was observed in mean PSA concentration in BPH patients and adenocarcinoma prostate patients when compared to healthy males. Clinical relevance of PSA was highlighted by a case study of cancer patient prior to any therapy till death.

KEY WORDS

Total PSA, BPH, Carcinoma Prostate, long term case study

INTRODUCTION

Prostate cancer is the most prevalent cancer found in men above the age of fifty years and is frequently diagnosed in men between 45 and 89 years of age with a median age of 72 years. The age of Indian patients of prostate cancer (Ca.P) varies from 32-86 years with an average age of 43.5 years, which is much lower when compared to the average age of patients in western countries. Prostate cancer is the third most common cancer in men and number two cancer killer above the age of seventy years. Individuals with positive family history are likely to develop disease at younger age compared to the people without family history of cancer. Both incidence and mortality of prostate cancer is low in Oriental men and higher in Scandinavian men and in American blacks (1, 2).

Benign prostate hyperplasia (BPH) is a universal phenomenon in aging men. The disease affects men over the age of 45 and increases with advancing age. By the eighth decade, more than 90 per cent of men have prostatic hyperplasia and it remains a leading cause of morbidity in elderly men.

Histology alone could give final diagnosis of Ca-P approximately in 67% of cases whereas 33% are diagnosed with the help of other modalities. At the time of presentation at the hospital, 42.3% of patients already had extensive multiple bone metastases, whereas 31% had loco regional spread and rest 27% had localized tumor. Hence prevention and early detection of prostate cancer is a valuable life saving and cost effective health strategy. For early detection of prostate cancer, the American Urological Association (AUA) and Food and Drug Administration (FDA) have recommended combined use of digital rectal examination and serum PSA estimation annually in all men at the age 50 years without any family history of cancer and at the age of 40 years with family history of prostate cancer (3). Our earlier report has clearly documented that healthy Indian males have lowest concentrations compared to western and oriental populations (4).

PSA, a useful tumor marker is a single chain glycoprotein consisting of 93% amino acids and 7 % carbohydrates. In healthy males, the prostate epithelium synthesizes and secretes PSA and efficiently prevents the escape of the protease into the

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circulation. However, minor amount of PSA does enter into the blood circulation. Hence it is worthwhile to determine serum PSA concentrations in patients of benign and malignant conditions of prostate, which could help in differential diagnosis. The present study was undertaken firstly to determine serum PSA in patents with confirmed diagnosis of BPH and in different subgroups of Ca.P at different stages of disease and to compare their values with serum PSA concentration of healthy males, secondly to evaluate clinical relevance of PSA in diagnosed patients of adenocarcinoma prostate prior to administration of any mode of therapy, at recurrence and during stable course of disease, and thirdly to study applicability of serum PSA in monitoring the efficacy of any mode of therapy for eg., chemotherapy or radiation therapy and in judging the efficacy of surgical resection of tumor by illustrating in detail a case study of a 55 year male cancer prostate patient.

MATERIAL AND METHODS

Serum total PSA was estimated in 583 healthy males, 1090 patients of benign prostate hypertrophy (BPH) and 651 patients of adenocarcinoma prostate. Cancer prostate group further consisted 267 patients at pre therapy stage, 122 patients at recurrence and 262 at stable course of the disease. The diagnosis of BPH and Ca. Prostate was made based on multimodality approach by performing physical examination, digital rectal examination, serum PSA quantitation, trans rectal ultrasound (TRUS), and true cut prostate biopsy. Care was taken to collect serum samples for PSA determination before any kind of prostate manipulation.

Serum was separated and stored frozen at -10^0 C for 3 to7 days before the analysis was made (5). PSA was estimated using Roche diagnostic immunoassay kit based on streptavidin biotin technology. Statistical calculations (confidence interval low - high, mean, standard deviation and significance) were performed by using Graph pad Instat, statistical software from Sigma chemical company (USA). Receiver operative characteristic (ROC) curves were constructed by using MTBW32 software.

RESULTS

The findings on serum PSA in healthy males and in patients of BPH and Ca.P were described in Table 1, Table 2 and in Fig. 1. The mean age of healthy male group was 59 years. The youngest healthy male was 19 years and the oldest was 86 years. In the BPH group, the youngest patient was 40 years and oldest was 90 years old, the mean age being 63 years. The mean age was 65 years in the adenocarcinoma prostate group.

The determination of serum PSA in healthy males revealed a mean value of 1.1 ng/ml. The highest value of PSA was 6.1 ng/ml but the confidence intervals low

Table 1. Total prostate specific antigen (PSA, ng/ml)

	N	Range Min-max	CI (L-H)	Mean ± SD	P
Healthy Males	583	0-6.1	1.3 - 1.6	1.45 ± 1.3	—
Benign Prostate Hyperplasia	1091	0-28	3.2-4.0	3.63 ± 3.4	<0.0001
Ca. Prostate Pretherapy	267	10-9800	283-533	408±10042	<0.0001
Ca. Prostate Recurrence	122	5.5-10500	380-916	648 ±1510	<0.0001
Ca. Prostate Stable dis.	262	0-8.7	1.9-2.4	2.1 ± 2.1	<0.0001

Table 2. Frequency of elevated serum PSA in BPH

PSA, ng/ml	<2 n (%)	2-10 n (%)	>10 n (%)	<4 n (%)	4-10 n (%)	>10 n (%)
BPH n=1090	532 (48.8)	469 (43)	89 (8.2)	774 (71)	227 (20.8)	89 (8.2)
Healthy Males N=583	450 (77.2)	133 (22.8)	Nil	565 (96.9)	18 (3.1)	Nil

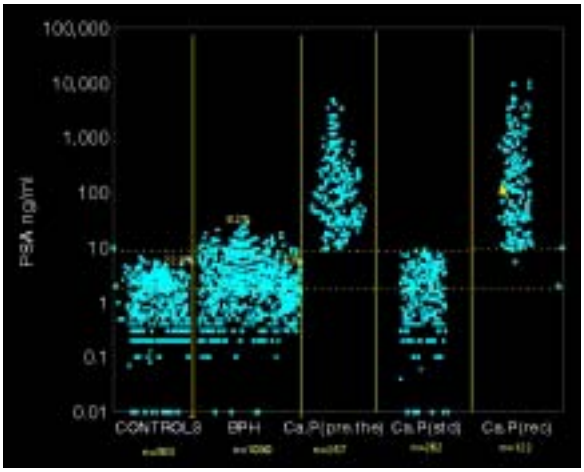


Fig. 1. Scatterogram of PSA in healthy male, BPH and adenocarconoma prostate

and high (95th percentile lower and upper limit) ranged from 1.3 to 1.6 ng/ml. Among BPH group the mean PSA concentration was 3.6 ng/ml. The maximum PSA concentration was 28 ng/ml. For this group confidence intervals ranged from 3.2 to 3.4 ng/ml. Adenocarcinoma prostate patients prior to therapy revealed a mean PSA concentration of 408 ng/ml. The minimum and maximum PSA values in this group were 10 and 9800 ng/ml respectively. The confidence intervals ranged from 283 to 533 ng/ml. The Ca.P group at recurrence had mean concentration of 648 ng/ml with a minimum and maximum values of 5.5 and 10,500 ng/ml. The low and high confidence intervals in this group ranged from 380 to 916 ng/ml. Adenocarcinoma prostate patients during stable course of disease showed near normal values. The mean serum PSA in this group was 2.1 ng/ml and the maximum PSA value was 8.7 ng/ml. The confidence intervals in this group ranged from 1.9 to 2.4 ng/l. Ca.P patients prior to therapy had extremely significant ($p<0.0001$) increase of 291 fold in mean PSA concentration, whereas in BPH patients the significant rise of mean PSA concentration was 113 fold compared to mean concentrations of 1.1 ng/ml in healthy males.

Frequency of elevated PSA beyond selected cut off was described in BPH and healthy males in Table 2. In our earlier report on PSA concentration in healthy Indian males, a PSA concentration of 2 ng/ml was selected as cut off and the gray zone range as 2-10 ng/ml. In healthy male group, 77.2% had PSA less than 2 ng/ml and 22.8% had concentrations ranging from 2-10 ng/ml. None of the healthy males had shown serum PSA concentration of more than 10 ng/ml. In BPH group 48.8% patients had PSA concentrations less than 2 ng/ml, 43% had shown PSA in the range of 2-10 ng/ml and only 8.2% patients had PSA more than 10 ng/ml. None of the Ca-P patients prior to therapy had serum PSA below 10 ng/ml. All the Ca.P patients during stable course of disease had PSA concentration below 10 ng/ml. In summary the 22.8% healthy males and 43% BPH patients had PSA concentration within gray zone. The individual data points on serum PSA pertaining to all 583 healthy men, 1090 patients of BPH and 651 patients of adenocarcinoma prostate (267 pretherapy, 122 at recurrence and 262 at stable course of disease) are depicted in the scatterogram (Fig. 1).

The specificity for serum PSA was 77.2% and the sensitivity for BPH group was 52% by selecting 2 ng/ml as cut off value for Indian healthy males. The PSA exhibited 100% sensitivity in pretherapy adenocarcinoma prostate group (Table 3).

ROC curve revealed cut off value of 2 ng/ml PSA for BPH patients (Fig. 2). At 2 ng/ml PSA concentration the sensitivity was 63% and specificity was 76% in BPH group (Table 4). For pretherapy adenocarcinoma group the ROC curve revealed a cut off concentration of PSA as 10 ng/ml (Fig. 3). At this concentration, the pretherapy cancer prostate group had shown absolute i.e., 100% sensitivity and specificity (Table 5).

Case study

55 years male (Fig. 4) was referred to our department for serum PSA estimation with a complaint of urine infection, increased frequency of urination, urinary obstruction, nocturia, and past history of acute

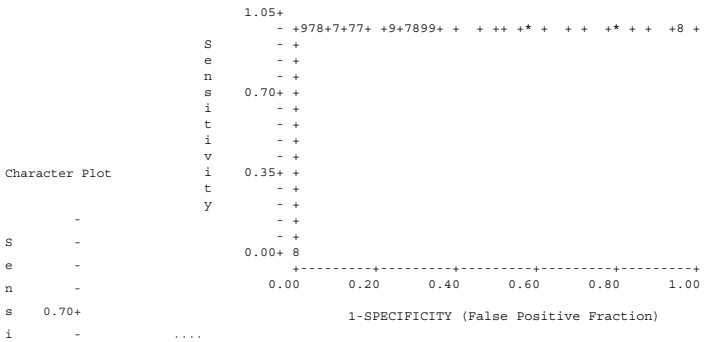
Table 5. PSA in healthy males vs. adenocarcinoma prostate pretherapy patients

PSA (ng/ml)	TPF	Sensitivity %	Specificity %	FPF
1.0	1.00	100	47.4	0.526
2.0	1.00	100	76.2	0.238
3.0	1.00	100	89.8	0.102
4.0	1.00	100	97.2	0.028
5.0	1.00	100	98.5	0.015
6.0	1.00	100	99.6	0.004
10.0	1.00	100	100	0.00
11.0	0.988	98.8	100	0.00
12.0	0.98	98.0	100	0.00
13.0	0.97	97.0	100	0.00
14.0	0.95	95.0	100	0.00
15.0	0.947	94.7	100	0.00

TPF: True positive fraction, FPF: False positive fraction, % Specificity: (100 - FPF)

cutoff	2.04000	arearoc	0.765844
arease	0.0148035	lowci	0.736829
upci	0.794859		

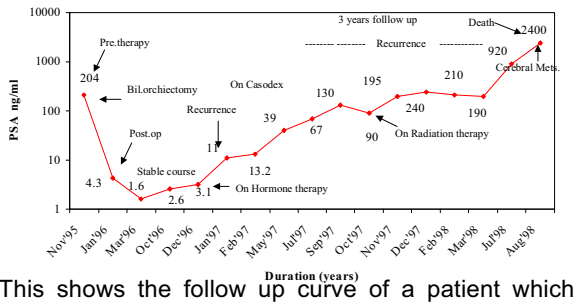
Fig. 2. ROC curve; PSA in healthy males vs. BPH



Data display
Cutoff 10.0000
area roc 1.00000

Healthy males n = 583,
Pretherapy adenocarcinoma prostate n = 267

Fig. 3. ROC curve for PSa in healthy males vs. pretherapy adenocarcinoma prostate



This shows the follow up curve of a patient which correlated at every stage of the disease with PSA concentration

Fig. 4. PSA in poorly differentiated adeno-carcinoma of prostate (55 yrs, M, SLS)

Table 4. PSA in healthy males vs. BPH

PSA (ng/ml)	TPF	Sensitivity %	Specificity %	FPF
1.0	0.839	83.9	47.4	0.526
2.0	0.628	62.8	76.3	0.237
3.0	0.448	44.8	89.8	0.102
4.0	0.35	35.0	97.2	0.028
5.0	0.26	26.0	98.5	0.015
6.1	0.208	20.8	99.8	0.002
7.0	0.17	17.0	100	0.00
8.0	0.15	15.0	100	0.00
9.0	0.12	12.0	100	0.00
10.2	0.099	9.9	100	0.00
11.0	0.080	8.0	100	0.00
12.0	0.069	6.9	100	0.00
13.0	0.055	5.5	100	0.00
14.0	0.05	5.0	100	0.00
15.0	0.036	3.6	100	0.00

TPF: True positive fraction, FPF: False positive fraction, % Specificity: (100 - FPF)

Table 3. Efficacy variable for total PSa in healthy males, BPH and prostate cancer patients prior to therapy

Total PSA Cut off concentration	Sensitivity	Specificity
HEALTHY MALES		
2 ng/ml cutoff (ClHighIndian cut off value)	—	77.2
4 ng/ml cut off (western cut off value)		96.9
BPH		
2 ng/ml cut off	52	—-
4 ng/ml cut off	31	—-
ADENO CA. PROSTATE (pretherapy)		
2 ng/ml cut off	100	——
4 ng/ml cut off	100	——

myocardial infarction and coronary angio bypass graft. Prior to administration of any therapy the serum PSA concentration was 204 ng/ml. The bonescan at this stage indicated multiple hot spots at rt. scapula, ribs, D12/L1 vertebra. rt. SI joints, rt.acetabulum, lt. ischium. Subsequently the patient underwent transurethral resection of the prostate (TURP) and bilateral orchidectomy. The histopathological examination (HPE) confirmed poorly differentiated adenocarcinoma of prostate at Gleason's Class III. Following administration of hormone therapy consisting of 250 mg Flutamide, the serum PSA declined to 4.3 ng/ml within three months, later patient was very stable clinically and had complete remission. PSA further declined to 1.6 ng/ml within five months. PSA remained normal for further nine months. The patient remained in remission for almost one year and was asymptomatic, clinically all PSA values at multiple measurements remained normal (less than 2 ng/ml) which clearly indicated excellent responsiveness of malignant cells to Flutamide. After one month the PSA rose to 11 ng/ml. After another month the PSA was elevated to 13.2 ng/ml but patient remained clinically asymptomatic. The PSA was further elevated to 39 ng/ml after three months. At this stage patient had pain in the ribs. After five months the bonescan revealed multiple skeletal metastases with progression of disease in right 7th rib and in 1st lumbar spine and PSA sharply rose to 67 ng/ml. Patient was administered second course of hormone therapy consisting of casodex (bicalutamide) which caused only slight decline of PSA to 30 ng/ml. Trans rectal ultrasound showed right mid zone coin lesion in lung with right basal pleural effusion and cardiomegaly. Further the patient was given 10 exposures of palliative radiation therapy to ribs. However, due to unresponsiveness of tumor to both radiation and hormone therapy there was steady and progressive increase in serum PSA from 195 ng/ml to 240 ng/ml within additional five to six months. Though the biochemical evidence of recurrence was noticed in January'97 with rise of PSA from 3.1 to 11 ng/ml, the clinical recurrence was noticed after 6 months in July 97. At this stage the patient complained of haematuria and retention of urine. The digital rectal examination showed enlarged prostate and repeat TURP was performed. Bonescan showed multiple metastases with progression of disease as number and intensity of bone scan lesions increased. PSA further rose to 200 ng/ml. A sharp rise in PSA levels 920 ng/ml to 2400 ng/ml was noticed during monthly determinations. At this stage patient developed cerebral metastasis and expired. The very high PSA levels with multiple bone metastases clearly indicated the bad prognosis.

DISCUSSION

The early diagnosis and management of BPH and adenocarcinoma prostate could be achieved in the first phase by the combined use of serum PSA determination, digital rectal examination and in the second phase prostate imaging by transrectal ultrasound of prostate gland and ultrasound guided biopsy of prostate in select cases. Of these, serum PSA played a dominant role because of its highest sensitivity for Ca.P compared to other modalities (6). The diagnostic efficiency of any tumor marker is judged by its specificity and sensitivity. The mild rise of PSA in BPH and grossly elevated serum PSA levels was observed in untreated adenocarcinoma prostate patients in our study. However, the overlapping values of serum PSA falling especially in gray zone i.e., between 2-10 ng/ml offer great difficulty in differentiating early adenocarcinoma from BPH. It is well documented in literature that PSA concentration in healthy males varies from one population to other throughout globe. We had reported lowest values of serum PSA in healthy males compared to many other populations in Western as well as Asian Pacific countries (4). In our study the 95th percentile value of PSA in healthy Indian males was only1.6 ng/ml, which is quite low compared to the universally accepted cut off PSA value of 4 ng/ml (5). PSA specificity decreased from 96.9% to 77.2% by selecting 2 ng/ml as cut off value for healthy Indian males instead of 4 ng/ml as upper limit of confidence intervals. However, the sensitivity for BPH increased from 31% to 52% by selecting 2 ng/ml as cutoff value for healthy Indian males. For adenocarcinoma prostate pretherapy group the PSA sensitivity was 100% by selecting both 2 ng/ml as well as 4 ng/ml as cut off concentration. The absolute sensitivity was probably due to advanced stage of untreated adenocarcinoma prostate at the time of referral to our hospital. For BPH patients at 2 ng/ml serum PSA optimum specificity was 76.2% and sensitivity was 63%. At cut off of 10 ng/ml for Ca.P patients the PSA had 100% specificity and sensitivity. Kuriyama et al., (1982) reported a sensitivity of 79% but a specificity of 59% (7). Barak et al (8) reported a sensitivity of 93.3% and a specificity of 97.4% with 4 ng/ml cut off of PSA. By raising cut off from 4 to 10 ng/ml their specificity increased to 100% and sensitivity decreased to 84.4% for patients of adenocarcinoma prostate group. In BPH patients from different countries the mean values reported for PSA were 2.1, 3.1, 4, 5, 9.8 and 7.9 ng/ml (9, 10, 11, 12 and 13). Our study indicated a mean PSA of 3.6 ng/ml for BPH patients.

Several studies from different populations have documented varied percentage of patients having serum PSA concentration in gray zone area i.e. 4 to 10 ng/ml, for eg., 18%, 19%, 31%, 32.6% and 46% (14, 15, 16, 7 and 12). However, in our study 43% of BPH patients had PSA concentrations in gray zone (2-10 ng/ml) area selected for Indian patients and

20.8% patients falling between 4-10 ng/ml as per universally accepted gray zone concentration of PSA.

The PSA values beyond upper limit of gray zone i.e., 10 ng/ml were reported as 7% and 14% by Partin *et al* and Barak *et al*. However, several studies reported only 2-3% of BPH patients to have PSA greater than 10 ng/ml (14, 15, 17, 18 and 19). Our study revealed 8.2% BPH patients to have PSA greater than 10 ng/ml. The maximum PSA concentration in patients of BPH was 37 ng/ml in a report by Stamey *et al*. (1987). However, in our group of BPH patients the maximum concentration of PSA was observed to be 28 ng/ml. It is a matter of debate whether such high concentrations are due to advanced course of benign prostate hypertrophy or due to very early malignancy of prostate at multiple occasions. It is valuable to determine PSA concentration in such patients to observe any exponential rise in PSA concentration due to early malignant prostate. However, transient rise and fluctuating concentration of PSA is suggestive of benign disease of prostate. A report by Myrtle *et al*., (18) described PSA levels greater than 10 ng/ml in 30% of stage A and 50% of stage B Ca-P patients. In a study by Hudson et al., (15) 35% of clinically localized prostate cancer patients had PSA greater than 10 ng/ml. Cooner *et al*. (20) reported very high proportion of Ca-P patients (55%) with more than 10 ng/ml. The diagnosis of adenocarcinoma prostate was established by biopsy in all these patients. Hence, it is appropriate to state that patients with more than 10 ng/ml should undergo biopsy to confirm adenocarcinoma prostate and serial measurements of PSA is advocated for early diagnosis of localized Ca-P. Additionally the trimonthly serial determination of serum PSA in patients of clinically diagnosed BPH with gray zone values will be of some help in segregating individuals of BPH from individuals harboring early focus of malignancy or localized malignant disease. Individuals with fluctuations of PSA on three occasions are less likely to have prostate malignancy whereas individuals with early or localized Ca-P will show exponentially steady rise of serum PSA. Stamey et al., (13) demonstrated that mean serum PSA concentrations were proportionate to clinical stage (A1 to D2). They concluded that higher preoperative serum PSA levels (>40 ng/ml) were useful to predict advanced disease while lower serum levels (<15 ng/ml) were useful to predict organ confined disease. The study by Ercol *et al*. (19) in 209 men with various stages of prostate cancer suggested that preoperative serum PSA levels may be useful in staging carcinoma of the prostate. The results clearly indicated that serum PSA levels greater than 10 ng/ml were more common among patients with extra capsular disease. However, reports by Partin *et al*. and Oesterling *et al*. (12, 21) concluded that the role of preoperative PSA in the detection of organ confined prostate cancer remained ill defined. In the present study, mean serum PSA concentration was very high (408 ng/ml) due to advanced malignancy in majority of untreated 267 patients diagnosed as adenocarcinoma patients. Similarly, Stamey *et al*. (22) reported a mean serum PSA of 563 ng/ml in 35 untreated prostate cancer patients.

This study clearly indicated rise of serum PSA with increasing burden of malignancy as almost all untreated patients and those with recurrence had very high PSA concentration. The efficacy of treatment could be indicated by near normal mean PSA values (2.1 ng/ml) in Ca-P patients with stable course of disease without any clinical symptoms of carcinoma prostate. However, 39% of the patients had PSA in the range of 2-10 ng/ml and none had more than 10 ng/ml. The small rise of PSA in appreciable proportion of patients may be due to micrometastases present in these clinically asymptomatic patients. This group of patients need frequent follow up and serial monthly determination of serum PSA to predict early recurrent disease for better management.

REFERENCES

1. Pienta and Esper (1993). Risk factors for prostate cancer. Ann Inter Med.118, 793-803.

2. Morgan, T.O., Steven, J., Jacobsen, W.F., McCarthy, D.J., Jacobson, D.G., McLeod and Moul, J.W. (1996). Age Specific reference ranges for serum prostate specific Antigen in Black Men. New. Engl. J. Med. 335 (5), 304-310.

3. Kramer, B.S., Brown, M.L., Prorok, P.C., Potosky, A. and Gohagan, J.K. (1993). Prostate caner screening: what we know and what we need to know. Ann. Intern. Med. 119, 914-923.

4. Malati, T. and Rajani Kumari, G. (2004). Racial and Ethnic variation of Prostate Specific Antigen in global population: Age specific reference intervals for serum Prostate Specific Antigen in healthy South Indian males. Ind. J. Clin. Biochem. 19(1), 32-137.

5. Rajani Kumari, G. and Malati, T. (2004). Stability of total and free prostate specific antigen in serum samples at different storage conditions. Ind. J. Clin. Biochem. 19 (2), 10-13.

6. Malati, T., Rajani Kumari, G., Murthy, P.V.L.N., Rammurthy, S., Aruna Prayag, Rami Reddy, Surya Prakash and Nanda Kumar (2003). The role of Free and Molecular Complexes of PSA, TRUS and DRE in Diagnosis and management of BPH and Prostate Carcinoma. International Proceedings of 22nd World Congress of Pathol. & Lab Medicine, Busan, Korea, Aug 30-Sept 3, 79-88.

7. Kuriyama, M., Wanf, M.C., Lee, C.L. *et al*. (1982) Multiple marker evaluation in prostate cancer with the use of tissue-specific antigen. JNCI. 69, 99-105.

8. Barak, M., Yoel, M., Aharon, L.JR and Nachran, G. (1989). Evaluation of prostate specific antigen as marker for adenocarcinoma of the prostate. J. Lab Clin. Med. 113 (5), 598-603.

9. Brawer, M.K. and Lange, P.H. (1989). Prostate-specific antigen: its role in early detection, staging and monitoring of prostatic carcinoma. J. Endo Urol. 3, 227.

10. Okihara, K., Cheli, C.D., Partin, A.W., Fritche, H.A., Chan, D.W., Sokoll, L.J., Brawer, M.K., Schwartz, M.K., Vessella, R.L., Loughlin, K.R., Johnston, D.A. and Babaian, R.J. (2002). Comparative analysis of complexed prostate specific antigen, free prostate specific antigen and their ratio in detecting prostate cancer. J. Urol.167 (5), 2017-2023.

11. Lee, F., Trop Pedersen, S.T., Carroll, J.T., Siders, D.B., Christensson, D.C. and Mitchell, A.E. (1989). Use of transrectal ultrasound and prostate-specific antigen in diagnosis of prostatic intraepithelial neoplasm. Urology. 34, 4.

12. Partin, A.W., Carter, B.H., Chan, D.W., Jonathan, Estein, J.I., Oesterling, J.E., Rock, R.C., Weber, J.P. and Walch, P.C. (1990). Prostate specific antigen in the staging of localized prostate cancer: Influence of tumor differentiation, tumor volume and benign hyperplasia. J. Urol. 143, 747-752.

13. Stamey, T.A., Yang, N., Hay, AR., McNeal, J.E., Freiha, F.S. and Redwine, E. (1987). Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. New. Engl. J. Med. 317, 909-916.

14. Lange, P.H., Ercole, C.J., Lightner, D.J., Fraley, E.E. and Vessella, R. (1989). The value of serum prostate specific antigen determinations before and after radical prostatectomy. J. Urol. 141, 873-879.

15. Hudson, M.A., Bahnsen, R.R. and Catalona, W.J. (1989). Clinical use of prostate specific antigen in patients with prostate cancer. J. Urol. 151, 1291.

16. Monda, J.M., Barry, M.J. and Oesterling, J.E. (1994). Prostate-specific antigen can not distinguish stage T 1a (A1) from benign prostatic hyperplasia. J. Urol.142, 1011.

17. Wodrum, D.L., Brawer, M.K., Partin, A.W., Catalona, W.J. and Southwick, P.C. (1998). Interpretation of free prostate specific antigen clinical research studies for the detection of prostate cancer. J. Urol. 159, 5-12.

18. Myrtle, F. (1989). Normal levels of prostate-specific antigen (PSA). In: Clinical aspects of prostate cancer. (Eds) Catalona, W.J, Coffey, D.S. and Kaor, J.P. Elsevier Science Publishing Co., New York, p. 183-189.

19. Ercole, C.J., Lange, P.H., Mathsen, M., Chiou, R.K., Reddy, P.K. and Vessella, R.L. (1987). Prostate specific antigen and prostatic acid phosphatase in the monitoring and staging of patients with prostate cancer. J. Urol. 138, 1181.

20. Cooner, W.H., Mosley, B.R., Rutherford, C.L., Jr., Beard, J.H., Pond, H.S., Terry, W.J., Igel, T.C. and Kidd, D.D. (1990). Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. J. Urol.143, 1146.

21. Oesterling, J.E., Chan, D.W., Epstein, J.I., Kimball, A.W., Jr.,Brujek, D.J., Rock, R.C., Brendler, C.B. and Walch, P.C. (1988). Prostate-specific antigen in the preoperative and postoperative evaluation of localized prostate cancer treated with radical prostatectomy. J. Urol.139, 766.

22. Stamey, T.A., Kabalin, J.N. and Ferrori, M. (1989). Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. 1. Untreated patients. J. Urol. 141, 1070.