ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 2 Issue 2 February 2019

Research Article

Significance of Free to Total Prostate Specific (fPSA:tPSA) Antigen in Prostate Cancer

Kankonkar SR[1]*, Joshi SV[2] and Thatte SW[3]

[1]*Ex-HOD Tissue Typing Laboratory, Medical Research Centre, Bombay Hospital, India*

[2]*Ex-Research Officer, Medical Research Centre, Bombay Hospital, India*

[3]*Hon. Urologist, Medical Research Centre, Bombay Hospital, India*

***Corresponding Author:** Kankonkar SR, Ex-HOD Tissue Typing Laboratory, Medical Research Centre, Bombay Hospital, India.

Received: January 28, 2019; **Published:** February 23, 2019

Abstract

Prostate Specific Antigen (PSA) is essential for diagnosis and monitoring of the patients with prostate cancer. The developments in the field of PSA screening are important to understand the inherent variability of PSA. The low specificity of tPSA in the diagnostic "Grey-Zone" level between 4 - 10 ng/ml causes dilemma which in turn results in unnecessary biopsies.

Screening only tPSA does not add to diagnostic value. However, fPSA (free PSA) molecules in free forms hold the promise for detection, staging, prognosis and monitoring of PCa.

Total 183 patients with clinical BPH were examined between October 2012 and November 2014 for estimation of Total and Free PSA. Elecsys 2010 analyzer of Roche was used in confirming the application of free-total PSA ratio. This was to counsel patients with Grey-Zone level PSA with regards to their risk of prostate cancer and need for further follow up to rule out malignancy.

Keywords: PSA- Prostate Specific Antigen; tPSA Total Prostate Specific Antigen; fPSA Prostate Specific Antigen; PCa Prostate Cancer; BHP Benign Prostate Hyperplasia

Introduction

The Prostate specific antigen (PSA) was described as a single test with highest positive predictive value for diagnosing carcinoma of prostate [1]. In addition, PSA test has been used as an indicator for progression of disease and/or clinical response after treatment for prostate cancer, but the prognostic value of this marker was found limited. Some studies have evaluated a number of alternative markers, such as PSA-related parameters, human kallikrein 2, Osteoprotegerin and the gene DD3(PCA3), that may improve the specificity of current PSA-based diagnostics and the prognostic value of PSA [2]. However, the wide availability of total prostate-specific antigen (tPSA) has revolutionized PCa screening and ushered in the tPSA era which has resulted in earlier PCa detection [3].

The serine protease, PSA, circulates in the serum in multiple molecular forms consisting of both free (unbound to other proteins) and complexed PSA (i.e. mainly bound to the protease inhibitor alpha-1-antichymotrypsin, ACT). The FDA approved the use of percent free PSA testing [i.e., (free PSA/tPSA) × 100] as an adjunct to tPSA in men with a serum tPSA concentration between 4 and 10 ng/mL. Several studies have shown that percent free PSA helps discriminate men with BPH from those with PCa, the magnitude of this effect varies across populations [4,5].

Since then the free-to-total PSA ratio has been recommended as an effective strategy to improve the specificity of total PSA for "Grey-Zone" values between 2.0 and 10.0 ng/ml. Meta-analysis showed that using the investigator-selected free-to-total PSA cut point yielded modest revisions of probability estimates for cancer [6].

Aim: The aim of this study was:

1. Use the ratio of free-to-total PSA to differentiate between benign and malignant prostate cancer and grading the severity
2. To determine range of ratios as related to age
3. Post-operative status of prostate cancer (progressing/regressing.)
4. To determine the feasibility of staging
5. Choose the relevant therapeutic tool for each.

Methods and Materials

One hundred and eighty three patients with clinical BPH were examined between October 2012 and November 2014 referred to

Tissue Typing Laboratory. Prostate specific antigen (total PSA: n = 186, Free PSA: n = 146) was estimated by Chemo-luminescent assay on Elecsys 2010 Analyzer using specific kits. Fourteen cases were for follow up of tPSA and 27 subjects for free PSA. Ratio of free PSA/ total PSA (fPSA/tPAS) was used for the diagnosis and prognosis of prostate cancer.

Initial assessment including the "International Prostate Symptoms Score", and the quality of life index, digital rectal examination, uro-analysis, uro-flow and residual urine estimation were carried out by urologists.

Limitations of the study

In the present study, clinicians did not refer all their cases for total PSA and free PSA hence, there were discrepancies in number of subjects studied. Our findings are based on the limited cases studied which were at our disposal.

Results

In the present Study, total 183 patients with BPH were examined between October 2012 and November 2014 for estimation of Total and Free PSA. Out of these, 146 subjects referred for free PSA evaluation, 17 were already diagnosed for prostate cancer. Further evaluation showed that 14 cases had persistent high values indicating presence of active disease; however, it was confirmed in only 4 cases with the help of fPSA/ tPSA ratio. And remaining patients were referred only for PSA testing due to positive (+ve) symptoms of prostate dysfunction. Exact values of PSA and ratio are mentioned in table 1.

	Cancer (n = 4)	Gray (n = 72)	Benign (n= 70)
PSA ng/ml	1150.96 ± 1824.94	9.477 ± 10.56	5.63 ± 13.54
fPSA/tPSA	0.68 ± 0.026	0.143 ± 0.029	0.315 ± 0.100

Table 1:

Total No.of cases 146.

On the basis of ratio, 49.32% cases were in gray zone whereas 47.94% benign and 2.74% had prostate cancer (Figure 1).

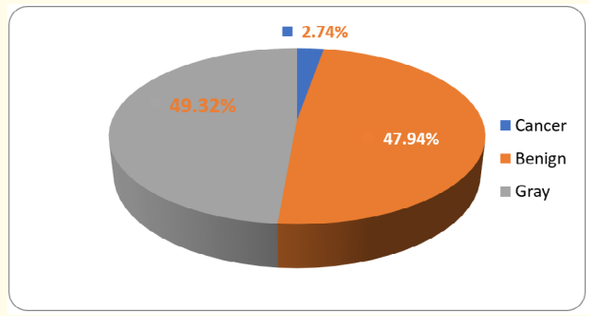


Figure 1: Correlation tPSA Between fPSA/.

When compared with the reference values for tPSA age-wise, analysis showed that upper limit of tPSA was highest (50.88%) in 60-69 age-group as compared to other age groups. Whereas, Free: Total PSA ratio, was highest in 50-59 and 70-79 age groups. The percentage of benign cases was more (Table 2).

Age group	Total (n)	Qualifying PSA	Ratio <0.10	Ratio 0.11-0.18	Ratio 0.19-0.25	Ratio >0.25	Total	Insufficient Data
40 TO 49	10	3	1	2	2	4	9	1
%		30	11.11	22.22	22.22	44.44	100	
50 TO 59	38	4	0	16	7	7	30	7
%		10.53	0	53.33	23.33	23.33	100	
60 TO 69	57	29	1	14	15	17	47	11
%		50.88	2.13	29.79	31.91	36.17	100	
70 TO 79	51	17	1	23	7	8	39	12
%		33.33	2.56	58.97	17.95	20.51	100	
ABOVE 80	19	12		5	1	7	13	6
%		63	0	38.46	7.69	53.85	100	
TOTAL	175	76	3	60	32	43	138	
%		43.43	2.17	43.48	23.19	31.16	100	

Table 2: Correlation between Age and free PSA/tPSA ratio.

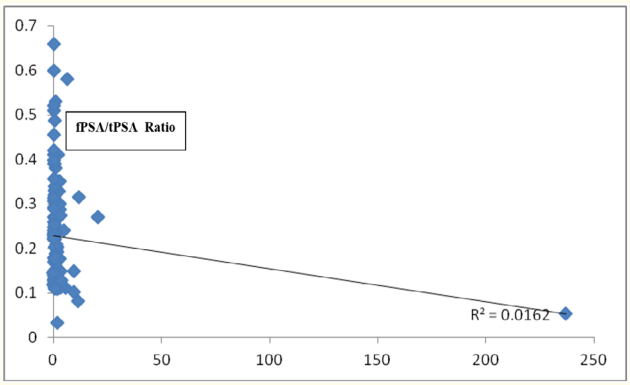
Grey-zone value of tPSA 4 -10ng/ml.

The values were 34.93% on the basis of Grey- zone of PSA (i.e. 4-10ng/ml) and 50.65% on the basis of ratio of fPSA/ tPSA of grey-zone (0.11-0.22).

Although the tPSA values in the group < 4ng/ml were (23. 18%), however, these patients were falling in grey-zone on the basis of fPSA/tPSA ratio. Subsequently, there was rise in the values of percentage (%) of the grey-zone viz. (76.47%) in 4.1 -10ng/ml, (76.92%) in 11-20 ng/ml, and (80.0%) in 21-30 ng/ml in these groups. Further, when tPSA was in 31-40 ng/ml category, we found (33.33%) of patients were in grey-zone ratio (refer above Table 3 and Graph below).

PSA (ng/ml)	Benign (n = 70), (%)	Gray (n = 72) (%)	Malignant (n = 5), (%)
< 4.0	53 (76.81)	16 (23.81)	--
4-10	10 (19.61)	39 (76,47)	2 (3.92)
11- 20	3 (23.08)	10 (76.92)	--
21- 30	1 (20.0)	4 (80.0)	--
31- 40	2 (66.67)	1(33.33)	--
41- 50	--	1 (100)	--
51- 60	--	1 (100)	--
61- 100	--		1 (100)
>4000	--	--	1 (100)

Table 3: Diagnosis on the Basis of fPSA/tPSA Ratio and Correlation with Total PSA.



Graph: Correlation between fPSA/tPSA.

These findings indicate that ratio of fPSA/tPSA is significant in predicting the state of the disease progression.

Follow up in 14 cases: It was found during the latest follow up patients that, 2 out of the 14 patients with prostate cancer had PSA serum levels which were significantly higher than those without prostate cancer.

Discussion

As there is no PSA value at which the prostate cancer can be definitely ruled out, and no specific cut-off value to determine a positive screening test has been accepted [7,8] as one of the tools for discriminating between prostate cancer and benign prostatic diseases in patients showing Gray- Zone PSA levels, the detection of free PSA and estimation of free to total PSA ratio have been widely used for improving diagnostic accuracy especially that of specificity.

Present study showed that nearly 50 per cent subjects with normal PSA values on the basis of detection of free PSA values, were found in grey-zone (0.11-0.22) while maintaining sensitivity. Hence, estimation of Free PSA could help in avoiding the process of biopsy.

Literature has quoted that the total PSA range of 4.0 to 10.0 ng/ml. has been described as a diagnostic "Gray- Zone," in which the free: total PSA ratio helps to determine the relative risk of prostate cancer (see table 4 below). Therefore, some urologists recommend using the free: total ratio to select which men should undergo biopsy. However, even in some cases, a negative result of prostate biopsy does not rule-out prostate cancer. Up to 20% of men with negative biopsy results have subsequently been found to have cancer [9-11].

In some findings it has been mentioned that ratio of grey zone increases with age [9-11]. However, in the present study, the age between 50 to 59 yrs, there were 16 cases (53.33%), from 60 to 69 yrs, 14cases (29.79%) and above 70 to 79 yrs, 23 cases (58.97) respectively. The percentage was comparable and above the age of 70 yrs showed rise in grey-zone.

Explanations for these inconsistencies may lie in the limited stability of free PSA in blood, particularly in stored sera [12,13]. In addition, PCa patients with larger prostate volumes have higher percentage of free PSA thereby resulting in lower specificity due to the dilution effect [14]. Finally, the most appropriate percent free PSA cut-off value for clinical decision-making remains controversial and percent free PSA may be more valuable as a continuous risk variable. Despite all these limitations, in a recent meta-analysis of 66 studies, percent free PSA has been shown to outperform tPSA and complexes PSA as a predictor for biopsy outcome [15].

The values were 34.93% on the basis of Grey-Zone of PSA ie 4-10 ng/ml which increased to 50.65% on the basis of ratio of fPSA of Grey-Zone *(0.11-0.22).

In literature, large multicentre, prospective trials evaluated that age between 50-75 year with PSA levels between 4.0 to 10.0 ng/ml. including 379 with PCa and 394 with benign prostate disease6 in screening populations is about 25%. However, the detection rate increased to 56% in men with free-to total ratio less than 10% [16]. Another meta-analysis came to conclusion that free to total PSA ratio is generally, only clinically helpful at extreme values of the ratio.

Conclusion

Results show that there is a significant correlation between total PSA and fPSA/tPSA ratio, hence, fPSA holds the promise for detection, staging, prognosis and monitoring of prostate.

Acknowledgement

Thanks are due to Medical Research Cenre, Bombay Hospital Trust, clinicians and the technical staff of Tissue typing Lab.

Bibliography

1. Carter HB and Partin A. "Diagnosis and Staging of prostate cancer". In :Walsh, Retik, Vaughan, Editor. Cambell's Urology. 8th Ed. Saunders Publication (2002): 3057-3058

2. Schenk-Braat EA., *et al*. "The search for better markers for prostate cancer than prostate-specific Antigen". *Nederlands Tijdschrift voor Geneeskunde* 150.23 (2006): 1286-1290.

3. Shahrokh F., *et al*. "Screening for Prostate Cancer: An Update". *The Canadian Journal of Urology* 15.6 (2008): 4363-4374.

4. Catalona WJ., *et al*. "Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial". *JAMA* 279 (1998): 1542-1547.

5. Woodrum DL., *et al*. "Interpretation of free prostate specific antigen clinical research studies for the detection of prostate cancer". *Journal of Urology* 159 (1998): 5-12.

6. Jaeschke R., *et al*. "Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients?" *JAMA* 271 (1994): 703-707.

7. Gjertson CK., *et al*. "Use and assessment of PSA in P rostate Cancer". *Medical Clinics North America* 95 (2011): 191-200.

8. Djavan B., *et al*. "Prostate -Specific antigen testing and prostate cancer screening". *Primary Care Clinics in Office Practice* 37 (2010): 441-459.

9. Catalona WJ., *et al*. "Evaluation of percentage of free serum prostate-specific antigen to improve specificity of prostate cancer screening". *JAMA* 274.15 (1995): 214-1220.

10. Oesterling JE., *et al*. "Free, complexed and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios". *Journal of Urology* 154 (1995): 1090-1109.

11. Dworschack RT., *et al*. "Clinical evaluation of the free/total PSA ratio generated with the Elecsys total and free PSA assays on the Elecsys 1010 and 2010 systems". *Clinical Chemistry* 47 (2001).

12. Ulmert D., *et al*. "Reproducibility and accuracy of measurements of free andtotal prostate-specific antigen in serum vs plasma after long-term storage at -20 degrees C". *Clinical Chemistry* 52 (2006): 235-239.

13. Vickers AJ., *et al*. "A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening in Goteborg, Sweden". *BMC Medicine* 6 (2008): 19.

14. Stephan C., *et al*. "The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia". *Cancer* 79 (1997): 104-109.

15. Roddam AW., *et al*. "Use of prostate-specific antigen (PSA) isoforms for the detection of prostate cancer in men with a PSA level of 2-10 ng/ml: systematic review and meta-analysis". *European Urology* 48 (2005): 386-399.

16. Thompson IM., *et al*. "Prevalence of prostate cancer among men with a prostate specific antigen level < 4.0 ng/ml". *The New England Journal of Medicine* 350 (2004): 2239

Volume 2 Issue 2 February 2019