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Original Article

Role of Serum PSA in Diagnosis of Prostate Cancer with Histopathological Correlation and Predictive Value of Serum PSA in Early Detection of Prostate Cancer

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Abstract
Prostate cancer is second leading cause of death in cancer related mortality after lung cancer i.e. mortality of prostate cancer is 6.6% and that of lung cancer is 23.6%. But 5 year prevalence of prostate cancer is highest i.e. 25.5. So Prostate cancer (PC) is an important medical and socio-economical problem due to its increasing incidence among the male populationand It is becoming an enormous health care burden and its early diagnosis is crucial for a successful treatment which ultimately will prolong and improve the quality of life. Widespread use of serum prostate specific antigen (PSA) level screening has dramatically increased the diagnosis of even small, early-stage prostate cancer lesions.
Aims: *Role of serum PSA level in diagnosis of prostate cancer with its histopathological correlation.*
Methods and Material: *The study is a diagnostic cross-sectional study and Patients were informed about the nature and objective of the study and written informed consent was taken before recruiting them into the study after approval of the Institutional Ethics Committee.*
Results: *1) Use of serum prostate specific antigen (PSA) level measurement increases the diagnostic accuracy of even small, early-stage prostate cancer lesions.*
2) PSA level is a strong indicator of stage and prognosis.

Conclusions: *The findings of study indicates that serial measurement of serum PSA level help in diagnosis of even small and early-stage prostate cancer. PSA level is indirect indicator of stage and prognosis of prostate cancer. Screening is advised in male population older than 50 years.*
Keywords: *prostate specific antigen, Prostate cancer, early diagnosis, screening*
Key Messages: *Screening male adults over 50 years of age with Prostatic specific antigen (PSA) can help diagnose prostate cancer early so as to prevent complications arising out of late diagnosis. Serum PSA is cost effective, easily available and non-invasive screening test.*

Introduction

Prostate cancer is disease of elderly male population. Its incidence has been increase in last few years. It is second leading cause of death in cancer related mortality after lung cancer Prostate cancer (PC) is an important medical and socio-economical problem due to its increasing incidence among the male population and It is becoming an enormous health care burden and its early diagnosis is crucial for a successful treatment which ultimately will prolong and improve the quality of life.

Prostate cancer is one of the most common cancer in men and is responsible for 19% of all newly diagnosed male cancers. Serum prostate specific antigen (PSA) screening is helpful in early diagnosis and staging of prostate cancer[1]. Prostate cancer (PC) is the most common in men above the age of 50years, more than 60% of cases occurring in men over 70 years of age.

Incidence rates rise steeply with age. Ninety percent of malignant prostate tumours are adenocarcinoma. The aetiology of PC remains controversial, although several risk factors have been identified. The most important risk factors include increasing Age, family History and ethnicity (male from black African, African American or black Caribbean ancestry). Men with prostate cancer may remain asymptomatic or may present with problems with urination, such as frequent urination, hematuria, urgency, burning, micturition, inability to urinate or control urine flow, weight loss, decreased appetite, back pain, etc. although these symptoms are not specific to prostate cancer**.**

PSA is a protein produced by normal prostate cells. This enzyme participates in the dissolution of the seminal fluid coagulum and plays an important role in fertility. The highest concentration of PSA is found in the seminal fluid, where it was first discovered. The half-life of PSA is about 2.2 to 3.2 days. Because of its relatively long half-life, a minimum of 2-3 weeks is required for the serum PSA to reach its nadir following radical prostatectomy, when it should be undetectable.Widespread use of serum prostate specific antigen (PSA) level screening has dramatically increased the diagnosis of even small, early-stage prostate cancer lesions.PSA is the product of prostatic epithelium and is normally secreted in the semen. It is an androgen regulated serine protease whose function is to cleave and liquefy the seminal coagulum formed after ejaculation. In normal male, only minute amount of PSA circulate in serum.

PSA Level test

PSA level is a strong indicator of stage and prognosis and is helpful in monitoring response to therapy for prostatic lesion[2]. PSA levels are elevated in prostate cancer but they may also be elevated in prostatitis and benign prostatic hyperplasia. The normal serum PSA level is under 4 ng/ml. A PSA level of 4to 10 ng/ml is considered borderline for abnormality; 20% of such patients have prostate cancer. Most patients with a PSA greater than10 ng/l have prostate cancer. In addition to diagnosis, PSA level is also correlated with pathologic stage. Several refinements to the standard PSA measurement have been introduced in order to increase the accuracy of prostate-specific cancer identification. These refinements include PSA density (PSA divided by the prostate volume), PSA transition zone density (PSA divided by the volume of the

transition zone), free to total PSA ratio (the fraction of unbound serum PSA), and PSA velocity (the rate of change in PSA over time).in last few decades incidence of prostate cancer has been increased,so it is an important medical and socio-economical problem due to its increasing incidence and It is becoming an enormous health care burden.

Subjects and Methods

After approval of the "Institutional Ethics Committee"cross-sectional study done to evaluate and compare the role of PSA in screening and diagnosis of prostate cancer with MRI prostate. Patients were informed about the nature and objective of the study and written informed consent was taken before recruiting them into the study. The source of data for the study were patients with prostatic pathologies presenting to the Radiology and Surgery OPD at tertiary carehospital/ our institute.

USG machine - Mylab 50 and my lab 40, corevision.

All the laboratory/pathology tests were carried out in a single setting at our institute.

Methodology

Relevant history of illness and significant clinical findings of all patientswere recorded. Previous investigations were reviewed. Serum PSAlevel assessed and post-operative or post-biopsy follow up was taken.

Inclusion Criteria

All patients with suspicion of prostate pathologies (lower urinary tract symptoms like increased frequency of micturition, hesitancy, urgency & hard /enlarged prostate on digital rectal examination), enlarged prostate on ultrasound abdomen and/or PSA levels (>4ng/ml).

Exclusion Criteria

Any previous biopsy done, less than 6 weeks before.

Statistical Analysis

Continuous variables were summarized as mean and standard deviations whereas nominal /categorical variables as proportions (%). A Chi-square test was used for analysis of nominal/ categorical variables. Z test for difference between two proportions was used for comparison of nominal/categorical variables. Unpaired ―t‖ test and ANOVA test were used for continuous variables. Diagnostic accuracy of PSA and MRI was assessed by means of sensitivity, specificity, PPV and NPV.

P value < 0.05 was taken as significant. Medcalc 14.0.0 version wasused for all statistical calculations

Results

Maximum patients were in age group of 61-70 years.

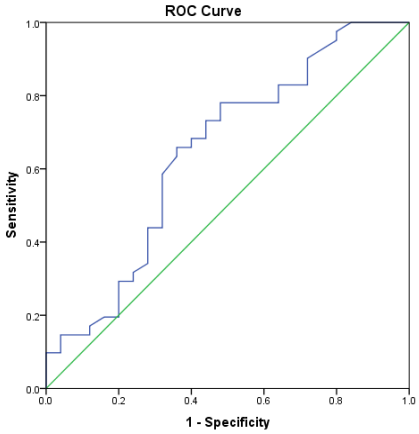
Mean age in the benign category (patients with histopathologically, no cancer) was 60 years, while mean age in the malignant category (patients with histopathologically, cancer) was 69 years.

Table 2- Distribution of patients as per zonal distributions of lesions on USG

Zone	No. of patients (%)
Central	5 (7.57)
Peripheral	28 (42.4)
Transition	31 (46.9)
Peripheral and transition	2 (3.03)
Total	66

Table 3 shows the distribution of patients as per zonal distribution of lesions on USG. Maximum 47 %lesions in were in transition zone, followed by 43% in peripheral zone. There were 5 (7.57%) in the central and 2 (3.03%) in the peripheral and transition zone.

ROC analysis – Prostate Specific Antigen (PSA) with Histopathological finding



ROC curve analysis for PSA in comparison with histopathological finding

Area under curve (95% CI)	0.645 (0.503 - 0.788)
Standard error	0.073
P-value	0.049
PSA cut-off value	11.15
Sensitivity	78%
Specificity	52%
Positive predictive value	72.73%
Negative predictive value	59.09%

Table 2 provides the statistics for receiver operating characteristics (ROC) curve analysis for prostate specific antigen (PSA) when compared with histopathological finding.

The analysis resulted into an AUC of 0.645 with 95% CI of 0.503 – 0.788. The PSA cut-off obtained was 11.15 using Youden index, which resulted into sensitivity of 78%, specificity of 52%, PPVof 72.73% and NPV of 59.09%.

Table 3: Association of PSA with histopathological finding

PSA categories	Histopathological finding		Total
	Benign	Malignant	
<= 4	4	0	4
4.1 – 10	6	9	15
>= 10.1	15	32	47
Total	25	41	66

Chi-square: 7.2991; P-value: 0.026 (Significant)

The association between PSA levels and histopathological findings was statistically significant with P-value of 0.026 (P < 0.05) using Chi-square test.

Those patients who were having higher PSA values but benign disease were either gross prostatomegaly or serum PSA studied after prostate manipulation (per rectal clinical examination or TRUS) or patients having prostatitis.

In the literature it is given that not only malignant lesions but benign prostatic hyperplasia, manipulation, biopsy, per rectal examinations.

Discussion

Prostate is an organ in which various focal or diffuse, benign or malignant primary pathology/ lesion can be found. Use of serial serum prostate specific antigen (PSA) level measurement increases the diagnosis prostate cancer lesions .Serum PSA level is strongly correlated with stage and prognosis of prostate cancer. There is strong controversy in the literature whether serum PSA should be done for screening for prostate cancer early diagnosis so as to prevent complications associated with the late diagnosis. However in our study we found that as serum PSA study is non-invasive, cost effective and easily available test and should be done routinely as a screening test for prostate cancer.

Physiological Considerations

The main role of the prostate is to produce fluid, which accounts for up to 30% of the semen volume. It aids sperm motility and provides nourishment. Prostatic fluid is a thin, milky alkaline liquid containing citric acid, calcium, zinc, acid phosphatase and fibrinolysin as well as PSA. PSA helps to keep the semen in its liquid form. It is an enzyme in the form of a glycoprotein produced primarily by cells lining the acini and ducts of the prostate gland.

PSA is considered as the most useful tumor marker for diagnosis, staging and monitoring of prostate cancer. It correlates well with advanced clinical and pathological stages in most cases, but due to low specificity it cannot accurately stage an individual patient as there is large overlap between different tumor stages. Also, other benign causes such as benign prostatic hyperplasia and prostatitis can cause elevated PSA levels.

PSA [3,4,5,6,] is a protein produced by normal prostate cells. This enzyme participates in the dissolution of the seminal fluid coagulum and plays an important role in fertility. The highest concentration of PSA is found in the seminal fluid, where it was first discovered. The half-life of PSA is about 2.2 to 3.2 days. Some PSA escapes the prostate and can be found in the serum. PSA was first identified and purified in 1970s. However, its widespread use in clinical urology did not occur until 1980s. PSA levels are elevated in prostate cancer but they may also be elevated in prostatitis and benign prostatic hyperplasia. The normal serum PSA level is under 4 ng/ml. A PSA level of 4 to 10 ng/ml is considered borderline for abnormality; 20% of such patients have prostate cancer. Most patients with a PSA greater than10 ng/l have prostate cancer. In addition to diagnosis, PSA level is also correlated with pathologic stage. In a Mayo Clinic study of 945 radical prostatectomies, the percentage of patients with extra prostatic disease was related to PSA level.

PSA (ng/ml)	<2	2-10	10-25	25-50	>50
Extra-prostatic Disease	30%	47%	67%	83%	93%

Recent research studies however has criticised its effectiveness in detecting cancer through PSA. It has been shown that many men may harbour prostate cancer despite low levels of PSA. Several refinements to the standard PSA measurement have been introduced to try and increase the accuracy of prostate-specific cancer identification. These refinements include PSA density (PSA divided by the prostate volume), PSA transition zone density (PSA divided by the volume of the transition zone), free to total PSA ratio (the fraction of unbound serum PSA), and PSA velocity (the rate of change in PSA over time). These new refinements have not yet entered into widespread clinical practice**.**

T. Rieden (2012) et al [7] prospectively evaluated 56 patients (mean age 67±5,4 years) with elevated serum prostate specific antigen (PSA) levels (4,0>ng/mL), who were referred to MRI studies before prostate biopsy. All the patients underwent 12-core prostate biopsy which was he reference standard. Mean value of PSA level in 56 patients was 12,8±7,2 ng/mL. In 50 patients (89,3% of patients) 68 sites of suspected cancer were found. 6 patients (10,7% of patients) were diagnosed with benign prostatic hyperplasia (BPH). 33 sites (48,5%) were localized in transition zone (TZ), 23 (33,9%) in peripheral zone (PZ), 12 (17,6%) in both zones. Histologically prostate cancer was proven in 39 of 50 patients (78%) with suspected cancer, mean PSA level 13,8±8,6 ng/mL. The median Gleason score was 6,6. Cancer cells were found in 54 of 68 sites (79,4%): 23 sites (42,6%) were localized in TZ, 19 (35,2%) - in PZ, 12 (22,2%) - in both zones Among 14 of false-positive sites 10 were localized in transition and 4 in peripheral zone; in all of them histological pattern of BHP was found. Furthermore, in 12 sites of 14 false positives (8 - TZ, 4 - PZ) prostatic intraepithelial neoplasia (PIN) was diagnosed (8 of 11 patients with non-proven cancer, mean PSA level 10,5±4,2 ng/mL). In some of them focal area suspicious for neoplastic lesion on ADC map was very small, so it was difficult to measure ADC value correctly because of insufficient ROI square. ADC values were measured in 60 of 68 sites suspected for prostate cancer (88,2%),its mean value was 0,81x10-3 mm²/s (0,42x10-3 mm²/s - 1,2x10-3 mm²/s). For 14 non cancer sites mean ADC value was 1,18 x 10-3 mm²/s (0,79x10-3 mm²/s - 1,5x10-3 mm²/s). As today PIN is considered a pre-malignant lesion DWI with either separate or fused images showed 100% sensitivity, 75% specificity and 96,4% accuracy. Fusion images didn't significantly improve the performance of standard MRI+DWI, but they were helpful in more precise localization of the cancer sites which were not clearly visible on T2WI alone Pre-biopsy DWI with high b-value improves diagnostic performance of MRI in prostate cancer detection and localization with higher accuracy in peripheral zone; it can show additional sites to be carefully histologically examined. Fusion T2WI+DWI imaging is helpful

for better localization of suspected tumor sites [7]. PSA remains the best and most widely used tumor marker in urology today.

PSA modalities

Modalities to enhance PSA usability are PSA velocity, PSA density, age-specific PSA and free/total PSA ratio.

PSA velocity

Is defined as the change of PSA value over time; it enhanced the specificity for prostate cancer detection from 42% to 96%, compared to a single reading of PSA. In another recent large scale study which involved 4,272 patients [9] and which extended over a 10 year period, men with prostate cancer were found to have significantly greater PSA velocity than those without cancer (0.39versus 0.03). PSA velocity as a predictor of tumour stage and grade remains controversial[10,11]. Another important and established role of PSA velocity is the follow up of patients with prostate cancer who are either on active surveillance strategy, hormone manipulation or post radical treatment [12].

PSA density

This is defined as the serum PSA level divided by the volume of the prostate.

It allows adjustments for the PSA component that arise from benign prostatic hypertrophy which arises mainly in the transitional zone[13]. The clinical use of PSA density has been debated. In a study done by *Freedland et al* [14] the additional time and effort required to calculate PSA density was not justified by the minimal improvement in predicting tumour stage, surgical margin and biochemical recurrence after radical prostatectomy. However, more recent studies have shown that PSA density may add additional prognostic value to predict cancer progression. *Tosoian et al*, from John Hopkins Hospital, considered PSA density as an important criterion for patients who opted for an active surveillance strategy[15].

Role of free/total PSA

This parameter has emerged after the discovery that PSA exists in a bound form with other proteins and free (unbound) form that can be detected with immunoassays. Stenman *et al*[16]were the first to establish that men with prostate cancer had more complexed PSA (cPSA) than free PSA (fPSA), in contrast to men with benign prostatic hypertrophy, suggesting that the assay of the complex and its proportion to total PSA immune reactivity can be used to differentiate between PSA elevations caused by benign and malignant prostatic disease. A clinical study done in Egypt showed that men with prostate cancer and a lower free/total PSA ratio had higher Gleason scores than those with higher free/total PSA [17].

PSA testing is minimally invasive, simple and safe. Serum PSA elevation may indicate the presence of prostatic disease (including prostate cancer, benign prostatic hypertrophy, urinary retention and prostatitis) or result from prostate manipulation such as transrectal biopsy and prostatic massage. Elevation of PSA above 4ng/mL carries a 22% probability of prostate cancer and a further increase above 10ng/mL raises the cancer risk to 63%[18].

Conclusion

Present study indicates that measurement of serum PSA level in patients with strong clinical suspicion of Prostate pathologies increases the diagnostic accuracy of even small, early-stage prostate cancer lesions. PSA level is correlated with stage and prognosis of prostate cancer. Due to increasing incidence of prostate cancer, prostate cancer can be picked and further imaging studies can be done in patients with elevated PSA. Biopsy is advised for suspicious lesion.

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