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Clinical Utility of PCA3 Assay in Patients with Suspicious Prostate Cancer

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ABSTRACT

Background: this study evaluated the clinical utility of the PCA3 assay in guiding initial biopsy decisions in prostate cancer. **Subjects and Methods:** this study was conducted on fifty patients selected from the Urology Department at Ain Shams University Hospitals and scheduled for prostate biopsy after digital rectal examination first catch urine was collected. PCA3 scores were determined using RT-PCR and compared to biopsy outcome. The diagnostic accuracy of PCA3 was compared to total prostate specific antigen and %free prostate specific antigen.**Results:** the best cutoff for PCA3 was 4.6 folds (RQ). This cutoff had a diagnostic sensitivity of 94.7%, specificity 95% and area under the curve (AUC) was 0.978. Total PSA at the cutoff 10 ng/mL had a diagnostic sensitivity 68%, specificity 70% and AUC was 0.766. At cut off 19%, f/t PSA ratio had a diagnostic sensitivity 38%, diagnostic specificity 90 %, and AUC was 0.529.

Conclusions: the PCA3 assay can aid in guiding biopsy decisions. It is superior to total prostate specific antigen and %free prostate specific antigen in predicting initial biopsy outcome, and may be indicative of prostate cancer aggressiveness.

Keywords: Prostate cancer, PCA3, PSA, BPH.

INTRODUCTION

Prostate cancer is the second leading cause of cancer-related deaths exceeded only by lung cancer among men world-wide [(1)]. In Egypt, the estimated incidence was 2358 cases and the yearly estimated deaths were 1513[(2)].

Current screening techniques are based on measurement of serum prostate specific antigen (PSA) levels and digital rectal examination (DRE). A decisive diagnosis of prostate cancer (PCa) is based on trans-rectal ultrasound (TRUS) guided prostate biopsies [(3)]. Serum PSA has several controversies have arisen about its use, mainly related to its low specificity.This low diagnostic specificity translates to numerous false positive results and many unnecessary biopsies in patients who are suspected to have prostate cancer and this invasive procedure carries a risk of infection and hemorrhage[(4)].

PCA3 is a non-coding messenger RNA, formerly known as Differential Display clone 3 (DD3), is expressed 66–100 times more in prostate cancer cells than in normal prostate tissue. It is also highly expressed in prostate cancer tissue compared to benign tissue. Several studies have shown a 140 times greater expression of PCA3 in cancer cells than in Benign Prostatic Hypertrophy (BPH), which is not a characteristic of PSA[(5)].

AIM OF THIS STUDY

Our aim was to evaluate the clinical utility of PCA3 assay in diagnosis of prostate cancer and to investigate its role in guiding initial biopsy decisions.

SUBJECTS AND METHODS

This study was conducted on fifty patients selected from the Urology Department at Ain Shams University Hospitals and scheduled for prostate biopsy because of an elevated total PSA level and/or a suspicious DRE. According to the results of the TRUS guided biopsy, patients were subdivided into the following subgroups:

A. Subgroup I: Men with Positive Biopsy for Prostate Cancer (n =26):

This group included twenty six patients with a median age of 67 years who were diagnosed with prostate cancer (PCa) as confirmed by TRUS guided biopsy. Tumor stage and Gleason scores were assessed.

B. Subgroup II: Men with Negative Biopsy for Prostate Cancer (n = 24):

This group included twenty four patients with a median age of 66 years who were negative for PCa as confirmed by TRUS guided biopsy.They were diagnosed as BPH, prostatitis or BPH with Prostatis, and pre-neoplastic lesions as atypical acinar proliferation.

Samples:

Urine and blood samples were collected prior to the initial biopsy.The first 20–30 mL of voided urine was collected from each patient, after an extended DRE. Whole urine specimens were labelled and immediately cooled on ice followed by centrifugation 700Xg for 10 minutes, urine sediments were obtained and stored at -70°C to be used for further PCA3 RNA extraction. 3 mL of venous blood were withdrawn from each participant in the study under complete aseptic conditions in serum separator clot activator

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vaccutainers which were left for complete clotting and then serum was separated by centrifugation at 3000 rpm for 10 minutes and was used for the assay of total and free PSA. Hemolysed and/or lipemic samples were discarded.

After an informed written consent, all individuals in this study were subjected to a detailed history taking; an attentive DRE was performed to all participants to detect any palpable tumor. TRUS guided biopsy was performed on any suspected lesion and samples were subjected to histo-pathological examination.

Total and free PSA were assayed via electro-chemiluminescence immunoassay technique applied on [1]Elecsys 2010 immunoassay analyzers. Urinary PCA3 mRNA assaywas performed through several steps including RNA extraction, real-time RT and cDNA synthesis and finally DNA amplification and detection by real-time RT-PCR. All kits used were provided by Qiagen. The study was approved by the Ethics Board of Ain Shams University.

Statistical analysis was performed on IBM computer using statistical program for social science version 23 (SPSS) (V. 23.0, IBM Corp., USA, 2015).

RESULTS

Statistical comparison between the various studied parameters in both of the studied groups using Wilcoxon's rank sum test in table (1). A highly significant difference was found between both groups as regards median urinary PCA3, being higher in patients with positive biopsy ($Z=-5.826$, $p<0.001$). A significant difference was found between both groups as regards both total & f/t PSA ratio ($Z= -2.681, 3.111$ respectively and $p<0.05$).

The diagnostic performance of PCA3, PSA and f/t PSA in discriminating both groups are summarized in table (2). The best cutoff for PCA3 was 4.6 folds (RQ). This cutoff had a diagnostic sensitivity of 94.7%, specificity 95%, positive predictive value (PPV) 94.7%, negative predictive value (NPV) 95%, efficiency 95% and area under the curve (AUC) was 0.978. Total PSA at the cutoff 10 ng/mL had a diagnostic sensitivity 68%, specificity 70%, positive predictive value 68%, negative predictive value 70% and diagnostic efficacy 69% and AUC was 0.766 as shown in figure (1). At cut off 19%, f/t PSA ratio had a diagnostic sensitivity 38%, diagnostic specificity 90 %, positive predictive value 78 %, negative predictive value 60 % and diagnostic efficacy 64 % and AUC was 0.529.

DISCUSSION

Prostate cancer is the second leading cause of cancer-related deaths exceeded only by lung cancer among men world-wide[(1)]**.** Current screening techniques are based on measurement of serum prostate specific antigen (PSA) levels and digital rectal examination (DRE). A decisive diagnosis of PCa is based on trans-rectal ultrasound (TRUS) guided prostate biopsies[(3)]**.** Serum PSA has several controversies have arisen about its use. In This study the diagnostic performance of PCA3 assay was compared to the traditional biomarkers, such as tPSA and % f/t PSA. In this study, the best performance of PCA3 was reached considering a cut-off of 4.6 (RQ) showing a sensitivity and specificity of 94.7 and 95% respectively. We noticed that PCA3 sensitivity and specificity were superior to those of tPSA and %f/t PSA. The diagnostic performance of tPSA at cut-off 10 ng/mL showed a sensitivity of 68% and specificity of 70%, whereas the sensitivity and specificity of %f/t PSA at cut-off 19% were 38% and 90% respectively. Similar results were reported by[(6)]**.** Our ROC curve analysis showed that PCA3 had the highest AUC compared to tPSA and %f/tPSA. AUC for PCA3 was 0.978 whereas it was 0.766 and 0.529 for tPSA and %f/tPSA respectively. The same results were reported[(6)]**.** Unfortunately, it was found that AUC for tPSA outperformed PCA3 on ROC analysis[(7)].

Finally, the present study indicates clearly that PCA3 is a promising marker of PCa, as it introduces PCA3 as a sensitive and a specific biomarker for PCa. Hence, this study highlights the utility of PCA3 as a reliable marker for guiding initial biopsy decisions.

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Table (1): Statistical comparison between Prostate cancer and non-prostate cancer groups regarding the measured parameters using Wilcoxon rank's sum test.

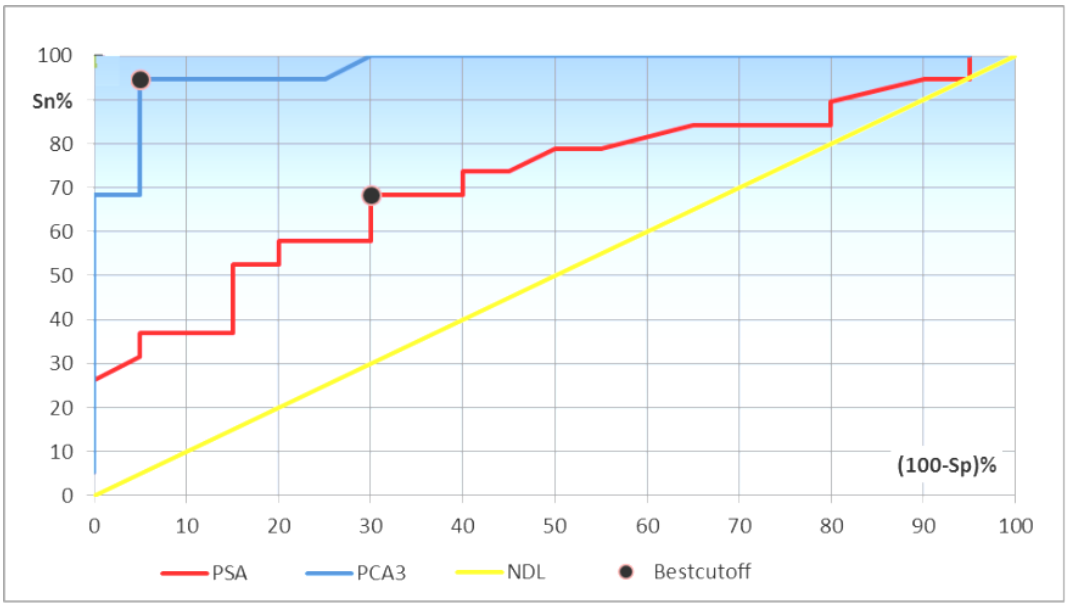
Group / Parameter	Positive Biopsy (n =26) Median (IQR)	Negative Biopsy (n=24) Median (IQR)	Z	P
Total PSA (ng/mL)	19(11-42)	10.4 (7.2-16.9)	-2.681	<0.05(S)
f/t PSA (%)	18.5(15-21)	22.5 (20-29.5)	3.111	<0.05(S)
Urinary PCA3 (RQ)	16.7(9.9-104.7)	2.2 (1.1-3.4)	-5.826	<0.001(HS)

IQR: Interquartile range, f/t: free/total, RQ: Relative quantitation, S: Significant, HS: Highly significant.

Table (2): Diagnostic performance of total PSA, f/t PSA and urinary PCA3 in discriminating patients from positive and negative biopsy groups.

Parameter	Cutoff Value	Diagnostic Sensitivity (%)	Diagnostic Specificity(%)	PPV (%)	NPV (%)	Diagnostic Efficacy(%)
Total PSA (ng/mL)	10	68%	70%	68%	70%	69%
f/t PSA (%)	19%	38%	90%	78%	60%	64%
UrinaryPCA3 (RQ)	4.6	94.7%	95%	94.7%	95%	95%

PPV: Positive predictive value, NPV: Negative predictive value, RQ: Relative quantitation



AUC	
Total PSA	0.766
PCA3	0.978

Figure (1): A ROC curve analysis showing the diagnostic performance of both PCA3 and tPSA in discriminating patients positive and negative prostate biopsy results.