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Research Article

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Abstract

Objective: The primary objective of this study is to determine the performance characteristics and clinical utility of the PCA3 assay in detecting pCA at repeat biopsy.

Patients and methods: 78 patients with history of one or more negative TRUS prostatic biopsy result were enrolled in the study. All scheduled for repeat biopsy. The data of the patients with positive biopsy results were compared with negative ones. Evaluation of the diagnostic accuracy and efficiency of two different cut-off of PCA3 score (20 and 35) as an indication for repeat biopsy was carried out.

Results: The mean age was 66.1 ± 3.9 years, the mean prostate volume was 66.5 ± 19.4 gram, 51.3% had one negative previous biopsy, and 48.7% had two previous biopsies, their mean PSA was 18.2 ± 8.1 ng/ml, and mean PCA3 scores was 36.3 ± 21.5.The mean PCA3 score was statistically significant higher in the patients with positive results than those with negative results (54.2 ± 26.8 vs. 54.2 ± 26.8, P=.0.001).As regard score of 35 as PCA3 cut-off, the was statistically significant higher percent of patients with PCA3 scores more than 35 in the patients with positive result than with negative results (68.2% vs.31.8%, respectively, P=0.02).Sensitivity, specificity, PPV and NPV of PCA3 score cut-off of 20 vs 35 were 90.9 vs 63.4%, 27.8 vs 83.9%, 43.5 vs 60.9% and 83.4 vs 85.5%, respectively.

Conclusions: PCA3 remained a good predictor of prostate cancerin patients scheduled for repeat biopsy, and could prevent unnecessary prostate biopsies if the value is low.

Keywords: PCA3; Prostate Cancer; Repeat Biopsy

Introduction

Prostate cancer (pCA) is one of the most common male cancers in the Western world [1]. Currently, early detection of pCA relies primarily on an abnormal Digital Rectal Examination (DRE) and an elevated Prostate-Specific Antigen (PSA) level leading to a prostate biopsy. However, because of low positive predictive values, up to 75% of men with PSA values in the 2.5-10-ng/ml range and/or suspicious DRE have a negative first biopsy. Further,10-35% of these patients have pCA detected on repeat prostatic biopsy [2,3]. In patients with a negative first biopsy but still having persistent suspicion of pCA, the European Association of Urology (EAU) guidelines recommend a repeat biopsy [1]. However, about 80%of patients whose did repeat prostatic biopsies are negative. Not only economic aspects but also anxiety, discomfort, and sometimes severe complications are associated with prostate biopsies [2,3]. So, there is a bad need for additional tests and biomarkers to increase the probability of detecting pCA specially these patients needed a repeat biopsy to reduce the number of unnecessary biopsies.

In this point of view, the Prostate Cancer gene 3 (PCA3) assay, a new pCA gene-based marker, has shown promising results. The PCA3 gene is highly over expressed (median: 66-fold) in >95% of malignant (ie, tumor or metastatic) prostate tissue compared to benign and normal prostate tissue [4-7]. The PROGENSA PCA3 assay measures PCA3 and PSA mRNA concentrations in post-DRE urine [1]. The PCA3 assay has been reported to be Sensitive, quantitative, and relatively an easy test [5-7]. We explored the potential utility of the PCA3 assay in an especially challenging group of patients, with elevated serum PSA levels and persistent suspicion of prostate cancer but negative previous prostate biopsy.

Objective

The primary objective of this study is to determine the performance characteristics and clinical utility of the PCA3 assay in detecting pCA at repeat biopsy.

Patients and Methods

Between November 2012 and December 2014, 78 patients with history of one or more negative TRUS prostatic biopsy result were enrolled in the study. All of them still had suspicion of prostate cancer and scheduled for repeat biopsy. The indications for repeat biopsy in those patients were persistent elevation of PSA, rising of PSA, abnormal or suspicious DRE and presence of atypical small acinar proliferation or extensive intra-epithelial neoplasia in the histopathogy of the biopsy.

Exclusion criteria included men receiving medical therapy known to affect serum PSA, urinary tract infection (UTI) and a history of pCA or invasive treatment for benign prostatic hyperplasia (BPH).All patients were evaluated by DRE, urine culture and sensitivity, total and free PSA, urine samples for PCA3 examination, and TRUS prostatic biopsy (at least 10 core biopsies from the peripheral zone). First-catch urine sample was collected (20-30 ml) after DRE and doing three strokes for each prostate lobe, doing them from the base to the apex and from lateral to median directions, as described by Groskopf et al.[8]. The urine sample was processed and tested to quantify PCA3 and PSA mRNA concentrations using a gen-probe assay of the PROGENSA PCA3 assay [8]. The PCA3 score was calculated as [PCA3 mRNA]/[PSA mRNA] x 1000.All patient data were collected and statistically analyzed using SPSS version 20 software. After collection of the TRUS biopsy results, the data of the patients with positive biopsy results were compared with patients with negative ones. Evaluation of the diagnostic accuracy and efficiency of two different cut-off of PCA3 score (20 and 35) as an indication for repeat biopsy was carried out, using terms of sensitivity, specificity, positive predictive value, and negative predictive value in comparison.

Also, areas under the curve (AUC) of the receiver operating characteristics (ROC) curve for PSA and PCA3 were estimated to compare the diagnostic accuracy and efficiency of both markers in predicting positive biopsy result on repeat biopsy. P values were estimated and considered statistically significant if<0.05.

Results

Patients Characteristics according to biopsy results are presented in (Table 1).

	Negative TRUS biopsy result (n= 56)	Positive TRUS biopsy result (n= 22)	*P* value	Total (n= 78)
Age (Years)	66.2 ± 3.9	66.9 ± 4.3	0.8	66.1 ± 3.9
Previous biopsy One biopsy: No (%) Two biopsies: No (%)	12(54.5) 10(45.5)	18(32.1) 38(67.9)	0.03	40(51.3) 48(48.7)
Mean PSA (ng/ml)	17.8 ± 7.3	22.04 ± 10.4	0.04	22.04 ± 10.4
Mean PCA3	28.8 ± 13.4	54.2 ± 26.8	0.001	36.3 ± 21.5
PCA3 cut-off ≥ 35: No (%) <35: No (%)	8(14.3) 48(85.7)	15 (68.2) 7 (31.8)	0.02	23 (29.5) 55 (70.5)
DRE Suspicious: No (%) Not suspicious: No (%)	15 (26.8) 41 (73.2)	17 (77.3) 5 (22.7)	0.001	32 (41) 36 (59)
Mean prostate volume (gm)	67.8 ± 19.8	62.9 ± 18.2	0.3	66.5 ± 19.4

Table 1: Patients Characteristics according to biopsy results.

As regard all patients in the study, the mean age was 66.1 ± 3.9 years, the mean prostate volume was 66.5 ± 19.4 gram, 51.3% had one negative previous biopsy, and 48.7% had two previous biopsies, their mean PSA was 18.2 ± 8.1 ng/ml, and mean PSA3 scores was 36.3 ± 21.5. As regard 35 as PSA3 cut-off score, there were 23 patients (29.5%) had PSA3 score higher than 35.On DRE, 32 patients (41%) were suspicious on examination while 36 patients (59%) had no suspicion on examination.

Of the 78 patients that their urine was examined for PCA3, 22 patients were found to have prostate adenocarcinoma (positive result) in their set of TRUS prostate biopsies with a detection rate of 28.2%, and the other 56 patients had no malignancy in their biopsies (negative result). There was no statistically significant difference in age between patients with positive and negative biopsy results. The mean PSA was statistically significant higher in the patients with positive results (22.04 ± 10.4 vs. 17.8 ± 7.3, P value 0.04). Also, the mean PCA3 score was statistically significant higher in the patients with positive results than those with negative results (54.2 ± 26.8 vs. 54.2 ± 26.8, P value.0.001).in positive cas-

es according to the histopathology,18 patients(81.9%)were have Gleason score < 6 Gleason score(GS), 3 patients (13.6%) were have 7 GS and one patient (4.5%) has 8 GS. We noted that the mean PCA3 score was higher with the patients with> 7GS compared to those with < 7 GS but without statistically significant different (P= 0.3)

As regard score of 35 as PCA3 cut-off, the was statistically significant higher percent of patients with PCA3 scores more than 35 in the patients with positive result than in those with negative biopsy results (68.2% vs. 31.8%, respectively, P value 0.02). There were 17 patients (77.3%) with suspicious DRE in patients with positive results, and this percent was statistically significant higher than that in patients with negative results (26.8%) (P value. 0.001). The mean prostate volume was larger in the patients with negative biopsy results, but without statistically significant difference (P value 0.3). In the current study, another PCA3 score was evaluated as a cut-off, which was 20 and a comparison between 20 and 35 as a cut-off of PCA3 was done using terms of sensitivity, specificity, positive predictive value and negative predictive value as items of comparison are presented in (Table 2).

	PCA3 cut-off35	PCA3 cut-off20
Sensitivity	63.4%	90.9%
Specificity	83.9%	27.8%
Positive predictive value	60.9%	43.5%
Negative predictive value	85.5	83.4

Table 2: Diagnostic accuracy of PCA3 score (Cut-off 35 vs. 20).

The sensitivity of the test was increased when the PCA3 score was lowered from 35 to 20 (from 63.4% to 90.9%) however this increase in the sensitivity was on the expense of specificity which was markedly lowered from 83.9% to 27.8%.

Comparison between PCA3 a PSA in predicting the result of TRUS prostatic biopsy was assessed by using receiver operating characteristic (ROC) curve analysis by PCA3 and PSA as test variables and biopsy result as a state variable or reference variable, and this comparison is shown in (Figure 1).

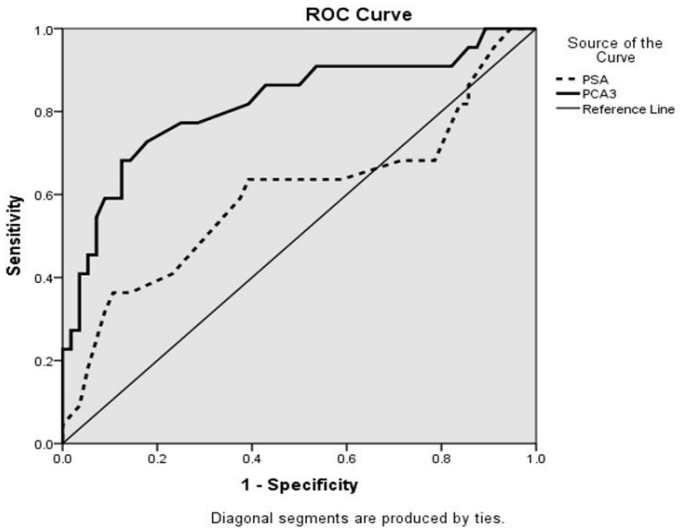

Figure 1: Receiver operating characteristic (ROC) curve showing accuracy of PCA3 and PSA as a diagnostic test variables and biopsy results as a state variable (reference method).

As regard PCA3 score the area under the curve (AUC) was 0.817 (95% confidence interval 0.442 to 0.745) and for PSA, the area under the curve was 0.598 (95% confidence interval 0.701 to 0.934). There was a statistically significant difference between the area under the curve between PSA and PCA3 score (P value 0.001).

Discussion

After more than 2 decades of introducing PSA in the clinical practice, still no specific test for cancer prostate is available. So, it is mandatory identifying new biomarkers able to distinguish with greater specificity cancer from non-cancer patients and decrease potential side effects related to unnecessary prostate biopsies., the Prostate Cancer gene 3 (PCA3) is considered as the most promising among many new biomarkers under development for the detect of prostate cancer [7,9].

Recently, after Discovered in 1999, the PCA3 gene (segment of non-coding messenger ribonucleic acid (mRNA) from chromosome 9q21-22) is overexpressed > 95% of all prostate cancers

tested. PCA3 gene is expressed in prostate cancer tissue 66-100 times more than in normal prostate tissue and 140 times more than in benign prostatic hyperplasia. Moreover, this gene is not found in non-prostate cancers [8].Our study included78 patients with history of one or more negative TRUS prostatic biopsy result. All of them still had suspicion of prostate cancer and scheduled for repeat biopsy. The mean age was 66.1 ± 3.9 years, the mean prostate volume was 66.5 ±19.4 g, 51.3% had one negative previous biopsy, and 48.7% had two previous biopsies, their mean PSA was 18.2 ± 8.1 ng/ml, and mean PCA3 scores was 36.3±21.5. As regard 35 as PCA3 cut-off score, there were 23 patients (29.5%) had PCA3 score higher than 35.On DRE, 32 patients (41%) were suspicious on examination while 36 patients (59%) had no suspicion on examination.

Of the 78 patients that their urine was examined for PCA3, 22 patients were found to have prostate adenocarcinoma (positive result) in their set of TRUS prostate biopsies with a detection rate of 28.2%, and the other 56 patients had no malignancy in their biopsies (negative result). The mean PCA3 score was statistically significant higher in the patients with positive results than those with negative results (54.2 ± 26.8 vs. 54.2 ± 26.8, P value.0.001). We noted that the mean PCA3 score was higher with the patients with >7 GS compared to those with < 7 GS but without statistically significant difference (P= 0.3) (Table 1).

In a study done by Alexandar H. et al, 2008, on 463 for repeat prostatic biopsy, they reported that 28% of their repeated biopsy patients were positive, they noted that the higher the PCA3 score, the more probability of a positive repeat biopsy. The PCA3 score had a greater diagnostic accuracy than free/ total PSA percentage. The PCA3 score was independent of age, total Prostate-Specific Antigen (PSA), and prostate volume. Moreover, the PCA3 score had high significantly different in patients with clinical stage T2 versus T1, Gleason score >7 versus GS below 7 [10].

In our study (Table 2) the reported PCA3 (cut off 35) sensitivity was 63.4%, specificity 83.9%, positive predictive value (PPV) 60.9% and a negative predictive value (NPV) of 85.5% while at cut off 20 sensitivities was 90.9%, specificity 27.8%, PPV43.5% and a NPV 83.4%.So, use of a cut off 20 improves the sensitivity on expense of the specificity.Data coming from a recent review and a lot of meta-analysis reported that test sensitivity ranged from 46.9 to 82.3%; specificity from 56.3 to 89%; PPV from 59.4 to 97.4% and NPV from 87.7 to 98%, respectively [9,10]. Our results are comparable to results obtained byHessels et al on his study on 108 patients who underwent prostatic biopsies for suspected prostate cancer reported PCA3 (cut off 35) sensitivity of 67%, specificity of 83%, positive predictive value (PPV) of 53% and a negative predictive value (NPV) of 90% 5 [11].

In Pietro et al 2012 study demonstrated 118 patients (median 62.5 years) with primary negative saturated prostatic biopsy done transperinealprostatic biopsies (median 30-35 cores) for patients with persistent suspicion of PCa. Diagnostic accuracy, sensitivity, specificity, PPV and NPV of PCA3 score cut-off of 20 vs 35 in PCa diagnosis were 44.9 vs 50%, 90.6 vs 71.9%, 27.9 vs 41.8%, 31.9 vs 31.5% and 88.9 vs 80%, respectively. ROC analysis demonstrated an AUC for PCA3 score≥20 vs ≥35 of 0.678 and 0.634, respectively. Noted that PCA3 is more helpful and useful as an exclusion test; moreover, setting a PCA3 cut-off at 20 vs 35, would have avoided 22.9% vs 38.1% of biopsies while missing 9.4% and 28% in diagnosis of PCa [12].Other studies reported that, PCA3 accuracy (cut-off ≥ 35) at repeated biopsy remains conflicting insensitivity, specificity, PPV and NPV range between 47 to 76.6%, 66.6 to 78.6%, 39 to 74%and 62.5 to 87%, respectively [13-15] in other hand, few studies considered that only NPV is satisfactory being > 80% in the evaluation of PCA3 accuracy [16,17].

On the other hand, Roobol [18] concluded that PCA3 score cannot replace the PSA test as the choice of an appropriate cut-off level with acceptable performance is debatable. and Rigau [18] suggested the usefulness of a multiplexed urine-based diagnostic test having the same sensitivity as the PSA test. In our study Comparison between PCA3 and PSA in predicting the result of TRUS prostatic biopsy was assessed by using receiver operating characteristic (ROC) curve analysis, as regard PCA3 score the area under the curve (AUC) was 0.817 (95% confidence interval 0.442 to 0.745) and for PSA, the area under the curve was 0.598 (95% confidence interval 0.701 to 0.934). There was a statistically significant difference between the area under the curve between PSA and PCA3 score (P value 0.001) (Figure 1).These results agreed with study of Alexander H. et al 2008 and study of Ploussard G et al, 2010, in which PCA3 score has been reported to be more accurate than PSA F/T ratio.by noting a better AUC of PCA3(0.68) than AUC of PSA(0.57) [19, 20] on the contrary, Aubin did not demonstrate a statistical difference in AUC ROC analysis between PCA3 and PSA F/T (0.69 vs 0.63) [21]. Recent data have underlined the lower sensitivity of PCA3 in comparison with PSA F/T (greater percentage of missed PCa) combined with a greater specificity (lower number of false positive results and unnecessary biopsy) [10, 22].

In other study by Leonard et al, 2007 which conducted with 226 patients scheduled for repeat biopsy. Their Repeat prostatic biopsies were positive in 60 cases (27%) of the 226 patients. They reported that the accuracy of PCA3 score is higher than total PSA as the receiver operating characteristic curve analysis yielded an area under the curve of 0.68 for the PCA3 score. In other hand, the area under the curve for total PSA was 0.52. with a PCA3 score cutoff of 35, the assay sensitivity was 58% and specificity 72%, with odds ratio of 3.6. At PCA3 scores of less than 5, only 12% of patients had positive repeated prostatic biopsy and confirmed as prostate cancer; but with PCA3 scores greater than 100, the possibility of positive prostatic biopsy was 50% [23]. More studies are needed to validate the predictive accuracy of the PCA3 score and to determine whether the PCA3 assay can synergize with other di-

agnostic methods such as the free/total serum PSA. In addition to providing information to guide biopsy decisions, the PCA3 score could potentially be used to monitor men with chronically elevated serum PSA levels for the development of clinically significant CaP. The results from this research study have indicated that the PCA3 assay may be a good tool to assist clinicians in the treatment of patients in the "PSA dilemma" population. The development of a nomogram incorporating the PCA3 score and other diagnostic variables may further improve the predictive accuracy of the PCA3score for its use in clinical practice.

Abbreviations

PCa = prostate cancer;

PCA3 = Prostate Cancer Gene 3;

pIPCa = pathological indolent prostate cancer;

SPBx = saturation prostate biopsy;

PPV = positive predictive value;

NPV = negative predictive value;

GS = Gleason score;

GPC = greatest percentage of cancer;

PSA F/T = free/total PSA;

ROC = receiver operating characteristic;

AUC = area under the curve.

Conclusions

PCA3 remained a good predictor of prostate cancer in patients scheduled for repeat biopsy. The use of the PCA3 score was highly correlated with the risk of having cancer on re biopsy, and could prevent unnecessary prostate biopsies if the value is low. The development of a nomogram incorporating the PCA3 score and other diagnostic variables may further improve the predictive accuracy of the PCA3 score for its use in clinical practice.

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