HHS Public Access

Author manuscript

Prostate Cancer Prostatic Dis. Author manuscript; available in PMC 2017 October 18.

Published in final edited form as:

Prostate Cancer Prostatic Dis. 2017 September ; 20(3): 339–342. doi:10.1038/pcan.2017.16.

Longitudinal Assessment of Urinary PCA3 for Predicting Prostate Cancer Grade Reclassification in Favorable Risk Men during Active Surveillance

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Abstract

Background—To assess the utility of urinary prostate cancer antigen 3 (PCA3) as both a one-time and longitudinal measure in men on active surveillance (AS).

Methods—The Johns Hopkins AS program monitors men with favorable-risk prostate cancer with serial PSA, digital rectal examination (DRE), prostate MRI, and prostate biopsy. Since 2007, post-DRE urinary specimens have also been routinely obtained. Men with multiple PCA3 measures obtained over ≥3 years of monitoring were included. Utility of first PCA3 score (fPCA3), subsequent PCA3 (sPCA3), and change in PCA3 were assessed for prediction of Gleason grade reclassification (GR, Gleason score>6) during follow-up.

Results—In total, 260 men met study criteria. Median time from enrollment to fPCA3 was 2 years (IQR 1–3) and from fPCA3 to sPCA3 was 5 years (IQR 4–6). During median follow-up of 6 years (IQR 5–8), 28 men (11%) underwent GR. Men with GR had higher median fPCA3 (48.0vs. 24.5, p=0.007) and sPCA3 (63.5vs.36.0, p=0.002) than those without GR, while longitudinal change in PCA3 did not differ by GR status (log-normalized rate 0.07vs.0.06, p=0.53). In a multivariable model including age, risk-classification, and PSA density, fPCA3 remained significantly associated with GR (log[fPCA3] odds ratio=1.77, p=0.04).

Conclusions—PCA3 scores obtained during AS were higher in men who underwent GR, but the rate of change in PCA3 over time did not differ by GR status. PCA3 was a significant predictor of GR in a multivariable model including conventional risk factors, suggesting that PCA3 provides incremental prognostic information in the AS setting.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Keywords

prostate cancer; active surveillance; PCA3; biopsy reclassification

INTRODUCTION

Active surveillance (AS) has emerged as a widely accepted management strategy for men with low risk and very low risk prostate cancer (PCa) [1]. While methods of monitoring and triggers for curative intervention vary among AS programs, the majority of protocols require serial prostate biopsy, a procedure associated with patient discomfort and risk of complications [2]. As such, alternative methods of monitoring are needed. One potential option is prostate cancer antigen 3 (PCA3), a noncoding mRNA first described in 1999 that is highly overexpressed in PCa tissue [3]. A urinary assay was subsequently introduced in 2006 and has consistently demonstrated high informative rates [4,5]. Since its introduction to clinical use, several studies have exhibited a significant association of PCA3 with PCa [5]. One National Cancer Institute Early Detection Research Network (EDRN) validation trial conducted at 11 centers found that a PCA3 value >60 at initial biopsy had a positive predictive value of 80% for detecting PCa, and a score <20 at repeat biopsy was associated with negative predictive value of 88% [6]. In another cohort of men with a history of negative biopsy, PCA3 values obtained during follow-up were associated with a subsequent diagnosis of PCa [4].

To this point, however, evaluation of PCA3 in the AS population remains quite limited. In the Canary Prostate Active Surveillance Study (PASS), urinary PCA3 was associated with increased Gleason score on biopsy (p=0.02), but PCA3 was no better than prostate-specific antigen (PSA) in predicting Gleason score ≥7 (>Grade Group 1) cancer (area under the receiver operator characteristic curve: 0.63 vs. 0.68, p=0.51) [7]. Based on urinary samples obtained during the course of AS, our group previously demonstrated higher mean PCA3 scores in men who underwent biopsy reclassification as compared to those who did not (60.0 vs. 50.8, p=0.131), although this finding did not meet conventional levels of statistical significance [8]. Interestingly, PCA3 scores were highest among men who underwent reclassification based on Gleason score upgrading (mean 72.0). Together, these findings suggest potential utility of PCA3 in the AS setting but remained limited by small sample size and short-term follow-up. Furthermore, the utility of repeated PCA3 measures has yet to be demonstrated. Therefore, we sought to assess the utility of PCA3 as both a one-time measure and longitudinal measure among men with pathologically-confirmed favorable-risk cancer who have stayed on AS for several years.

MATERIALS AND METHODS

Since 1995, the institutional review board approved Johns Hopkins AS program has enrolled 1511 men with favorable risk (low risk or very low risk) PCa with informed consent. Very low risk criteria include clinical stage T1c disease, PSA density <0.15 ng/mL/cm^3, Gleason score ≤ 6 (Grade Group 1), ≤ 2 biopsy cores with cancer, and ≤ 50% involvement of any core with cancer [9]. Low risk disease includes clinical stage ≤T2a, PSA < 10 ng/ml, and

Gleason score ≤ 6 (Grade Group 1). Monitoring included semiannual PSA and digital rectal exam (DRE) as well as annual prostate biopsy and/or more recently prostate MRI for most men. Since 2007, urine samples were obtained at clinic visits after standard DRE and were subsequently mixed with a stabilization buffer prior to storage at −80C. Copy numbers of PCA3 and PSA mRNA were calculated with the Progensa PCA3 assay using transcription mediated nucleic acid amplification. The PCA3 score is generated as a ratio of PCA3 mRNA to PSA mRNA in the urine multiplied by 1,000. The informative rate of study samples was 95.2%.

In order to assess for longitudinal changes in PCA3, the study cohort was limited to subjects with at least two urine samples obtained over three or more years of follow-up (i.e. at least 3 years apart) and a prostate biopsy within 6 months of each PCA3 assessment (n=294). Further, due to variable effect of 5-alpha reductase inhibitor (5-ARI) medications on PCA3, 34 men who were on 5-ARI at the time of PCA3 assessment were excluded (final n=260) [10]. The sample size is similar to a prior analysis of the AS cohort [8]. The chosen outcome of interest was grade reclassification (GR) defined as any Gleason score >6 (Grade Group 2 or greater) cancer detected on follow-up biopsy.

Statistical Analysis

Patient demographics as well as first (fPCA3) and subsequent (sPCA3) PCA3 scores were compared between men who did and did not undergo GR using the t-test, Mann-Whitney test, or chi-squared test, as appropriate. PCA3 scores were transformed into logarithmic scale to correct for skew and stabilize variance. A linear mixed effects model with random effects was used to assess the longitudinal changes in PCA3 over time and also to evaluate its association with the outcome of interest [11]. This model accounts for the correlated nature of repeated PCA3 measures on the same patient and also allows for individual variations in baseline intercept and changes in PCA3 over time. Unstructured correlation structure was used to model these data. Additionally, the utility of a single PCA3 value for independently predicting high-grade disease was assessed using a multivariable logistic regression model adjusting for age, disease volume (very low risk or low risk status), and PSA density. Model accuracy was assessed by measuring the area under the receiver operating characteristic curve (AUC), and the goodness-of-fit of the multivariable model was evaluated using Hosmer-Lemeshow goodness-of-fit test [12]. One-sided tests were used for a priori hypotheses that were directional, and statistical significance was set at $p<0.05$. Analyses were performed using SAS (Version 9.4, Cary, NC, USA) and STATA (Version 13.1, College Station, TX, USA).

RESULTS

Patient Characteristics

A total of 260 men met study inclusion criteria. The median time from enrollment in AS to the fPCA3 measurement was 2 years (IQR 1–3 years), median time from fPCA3 to sPCA3 measurement was 5 years (IQR 4–6 years), and the median number of biopsies performed after fPCA3 was 2 (IQR 1–3). All men underwent a 12–14 core prostate biopsy within 6 months of each PCA3 assessment. During follow-up, 28 men (10.8%) demonstrated GR

(Supplemental Table 1). The median overall follow-up from diagnosis was 6 years (IQR 5–8 years), and the median time from diagnosis to GR among those who underwent GR was 7 years (IQR 5–9 years). Demographic information by GR status is listed in Table 1. Men who underwent GR were significantly older (69 vs. 66, p=0.03), had higher PSAD (0.11 vs. 0.08, p=0.03), and were less likely to be categorized as very low risk (79% vs. 95%, p=0.004) as compared to men without GR. Only 21 (8%) men underwent radical prostatectomy, with too few events to allow for a meaningful analysis of surgical pathology.

fPCA3, sPCA3, and Grade Reclassification

As compared to patients who did not undergo GR, those who underwent GR during follow-up had significantly higher PCA3 scores at both the first (48.0 vs. 24.5, p=0.007) and subsequent (63.5 vs. 36.0, p=0.002) measures (Figure 1). The normalized rate of change of PCA3 (average increase in log[PCA3]/year) was 0.07 in men who underwent GR and 0.06 in those who did not. Linear mixed effects modeling did not demonstrate a significant association between longitudinal increase in PCA3 and subsequent identification of high-grade cancer (p=0.53; Table 2).

On univariable analysis, fPCA3 was significantly associated with GR (odds ratio [OR] log[fPCA3] = 1.88, 95% CI 1.13–3.13, p=0.02). In a multivariable model including baseline age, PSA density, and risk strata (low-risk vs. very-low-risk disease), fPCA3 remained significantly associated with GR (OR = 1.77, 95% CI 1.17–3.08, p=0.038; Table 3). The multivariable model demonstrated good discriminative ability for grade reclassification (AUC without PCA3 = 0.70 (95% CI 0.63–0.76; AUC with fPCA3 = 0.74, 95% CI 0.68–0.79). The final model showed no evidence of lack of fit based on the H-L statistic (p=0.3). Notably, similar findings were obtained when sPCA3 was considered instead of fPCA3 (Table 3). We also attempted to investigate the relationship between PCA3 and prostate MRI findings. However, the majority of men did not undergo MRI around their fPCA3 assessment (2007–2009), though sPCA3 values were done in alongside prostate MRI in a subset of men in this study (N=74). Analysis of this subset did not reveal any significant associations between MRI findings and GR (Supplemental Table 2).

DISCUSSION

We sought to assess the utility of urinary PCA3 in a cohort of men with favorable-risk PCa undergoing monitoring on a stringent AS protocol over time. In this highly-selected population, we found that urinary PCA3 was significantly associated with subsequent identification of Gleason score 7 (>Grade Group 1) cancer. Interestingly, this relationship was observed using PCA3 scores obtained early (1–3 years) during the course of surveillance as well as several years (4–6 years) into surveillance. In a multivariable model accounting for conventional prognostic factors such as PSA density and risk classification, PCA3 score remained a significant predictor of grade reclassification during follow-up. While PCA3 scores increased over time among the overall cohort, the rate of change in PCA3 did not differ between those who did and did not undergo GR, suggesting there may be limited utility in monitoring changes in PCA3 over time.

A number of studies have evaluated the potential utility of PCA3 in diagnosing PCa among both biopsy-naïve cohorts and those with previous negative biopsies [4,6,13–15]. For men with elevated PSA scheduled for initial biopsy, institutional studies have shown improved discriminative ability for diagnosing PCa when PCA3 was added to a baseline model [13,14]. Moreover, the EDRN validation trial demonstrated improved detection of any PCa and high-grade PCa based on PCA3 score at initial biopsy. The trial furthermore provided thresholds to reduce the frequency of unnecessary biopsies, including potential avoidance of 15% of biopsies at a cost of missing 5% of high-grade cancers (PCA3 <20, PSA <4), or avoidance of 38% of biopsies at a cost of missing 11% of high-grade cancers (PCA3 <20, PSA <10) [4]. Several other studies have similarly demonstrated improved discrimination using a PCA3 threshold of 20 in the setting of repeat biopsy [4,6,15].

Notably, studies performed in the diagnostic setting inherently capture men with a range of PCa risk classifications, from those without PCa to those with high-grade PCa. Such populations would be expected to represent an extensive range of PCA3 values. On the other hand, men participating in AS uniformly carry a diagnosis of PCa and are of favorable-risk in the vast majority of cases. As such, the variability of PCA3 is reduced in the AS setting, potentially limiting its predictive utility. The Canary AS cohort, which does not restrict enrollment by Gleason score (8% of patients had Gleason score ≥7), found that PCA3 increased with higher volume disease and with higher Gleason score, but these relationships were not statistically significant when PCA3 was added to a baseline model accounting for PSA [7]. Notably, this study did not consider disease progression over a longitudinal interval with multiple biopsies, but rather at a single time-point during the course of surveillance.

In a previous assessment of our AS population, we observed a higher mean PCA3 score among men who underwent biopsy reclassification over short-term follow-up as compared to those who did not, but this difference was not statistically significant (60.0 vs. 50.8, p=0.131) [8]. In that study, the mean PCA3 score was 72.0 among the 16 men who underwent grade reclassification, as compared to 51.2 among the 22 men who underwent reclassification by cancer volume (p=0.174). Given the importance of Gleason score in predicting PCa outcomes and the emphasis placed on pathologic grade in the contemporary AS setting, we more specifically focused on GR as an outcome in the current study [1,16]. Indeed, while our previous assessment was limited by sample size and follow-up, the current study revealed a significant association between PCA3 and grade reclassification, even among a homogenous population of men with favorable risk cancer that had remained stable over multiple surveillance biopsies. Interestingly, elevated PCA3 was associated with increased risk of GR when considering either the first or subsequent urinary samples, suggesting that a single PCA3 value provides independent prognostic information whether obtained early or late in the course of surveillance. On the other hand, acknowledging the uniform risk categorization of our AS population, obtaining longitudinal PCA3 values over time did not appear to augment predictive ability.

There are methodological aspects of this study that deserve mention. First, although routinely collected in our program since 2007, practical limitations were such that urine samples could not be obtained at each AS visit. Importantly, these limitations are random in nature and are unlikely to pose a systematic bias to the study population. Second, this

analysis did not initially account for the use of MRI, which has become increasingly utilized in the setting of PCa detection and monitoring. On the other hand, we have found that the utility of MRI during AS is limited [17]. Most notably, inclusion for the present study was limited to AS patients with multiple urine samples obtained over at least three years. Therefore, men in our program who underwent reclassification within three years of enrollment were not considered, resulting in a relatively homogeneous study population with very favorable-risk disease (Table 1) that has been confirmed over multiple biopsies prior to study inclusion. Prior analyses have suggested a need for closer surveillance during the initial three years to quickly identify those men who may have been undersampled at the time of diagnosis [18]. Such an approach would be expected to limit the range of disease risk and therefore PCA3 values contained in the study cohort, potentially blunting the predictive effect of the marker observed. Therefore, it is notable that individual PCA3 values were indeed predictive even in this cohort, and a lack of utility of longitudinal PCA3 measures in such a favorable-risk cohort does not preclude their possible utility in other populations. Indeed, a marker capable of distinguishing men in a highly-selected AS cohort would be expected to have even better discriminatory value in a broader population.

A number of emerging biomarkers, including PCA3, have been introduced in the last decade to improve upon the performance characteristics of PSA [5,19]. Individualized risk assessment at diagnosis is possible using validated risk calculators such as that from the Prostate Cancer Prevention Trial [20]. In this setting, urinary biomarkers have been shown to augment individualized prediction of PCa and high-grade PCa [21]. However, the association of PCA3 with longitudinal outcomes, such as PCa-specific mortality, have not been evaluated. The evidence is even more sparse in the setting of AS, where previous studies have not demonstrated utility of PCA3 for improving predictive ability for a longitudinal outcome. Importantly, the present study is the first to report an association of urinary PCA3 with biopsy reclassification during prolonged surveillance rather than with biopsy features at a single time point [7,8]. A combination of conventional and emerging metrics may prove most useful in the long-term to identify AS patients at the highest risk of adverse outcomes.

CONCLUSIONS

In a population of men with favorable-risk prostate cancer monitored on AS for several years, the first and subsequent urinary PCA3 scores were significantly higher in men who underwent GR during follow-up. Notably, however, the change in PCA3 over time was not associated with GR. Inclusion of PCA3 score improved model prediction for GR, suggesting PCA3 may have utility as part of a multivariable tool to risk-stratify men on AS and reduce the burden of repeat biopsies over extended follow-up.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Reagent support for PCA3 was provided by Hologic, Inc. This project was supported by grant NCI U24CA115102 from the National Cancer Institute of the National Institutes of Health.

Financial Disclosures/Funding Source: This project was supported by grant NCI U24CA115102 from the National Cancer Institute of the National Institutes of Health.

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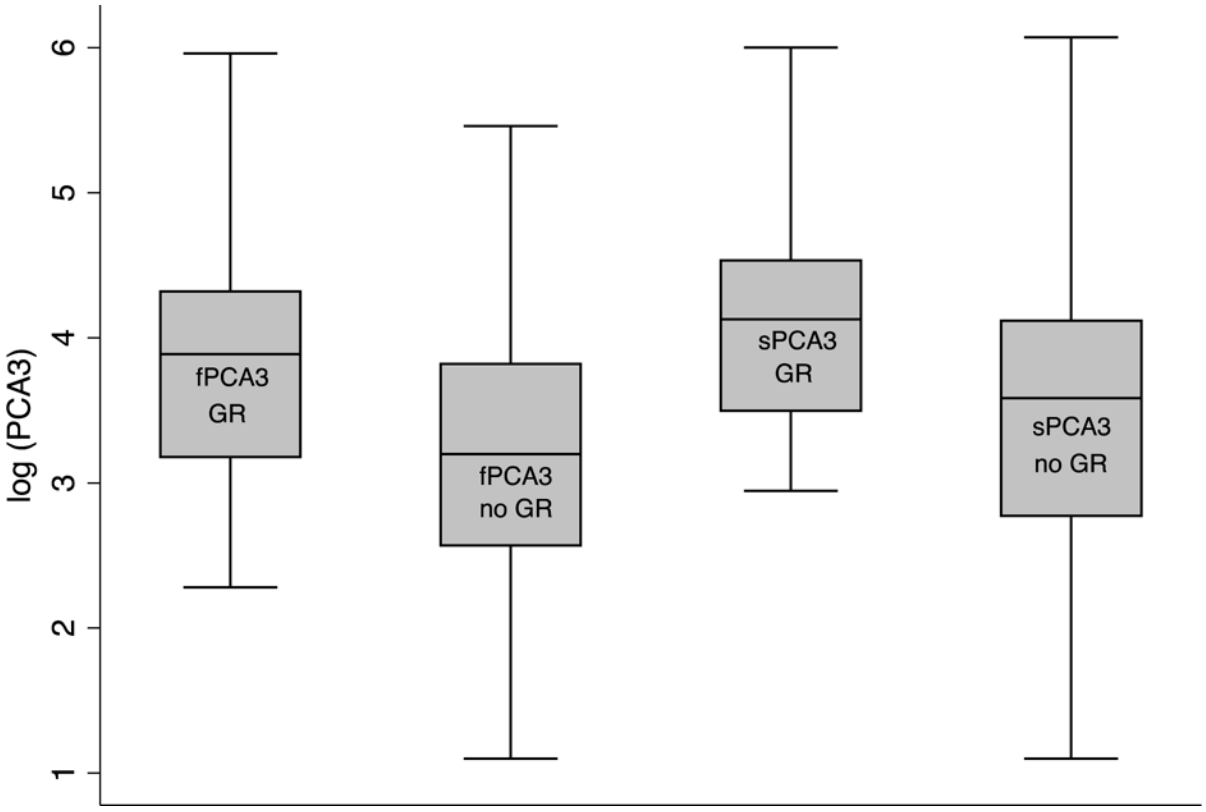

Fig 1.

Box plots comparing first PCA3 (fPCA3) and subsequent PCA3 (sPCA3) values between men with and without grade reclassification (GR). Horizontal lines in boxes represent medians; vertical lines represent 1.5- times interquartile ranges

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Table 1

Demographics

	Grade Reclassification (n= 28)		No Grade Reclassification (n = 232)		*P value*
Patient characteristics at baseline	**Median**	**IQR**	**Median**	**IQR**	
Age, yrs	69	66 – 74	66	63 – 69	0.03
PSA, ng/ml	5.3	3.0 – 6.9	4.0	2.8 – 6.3	0.50
PSAD, ng/ml/ml	0.11	0.06 – 0.16	0.08	0.05 – 0.11	0.03
fPCA3, ng/ml	48.0	24 – 75	24.5	13.1 – 45.7	0.007
sPCA3, ng/ml	63.5	37 – 93	36.0	18 – 59	0.002
Year of PCa diagnosis	2006	2004 – 2008	2007	2005 – 2008	0.18
Time from PCa diagnosis to fPCA3, yrs	2	1–3	2	1–3	0.33
No. of biopsies at time of fPCA3	2	1–3	2	1–3	0.24
Risk strata, n(%)[1]					
Very-low-risk	22 (79)		221 (95)		0.005
Low-risk	6 (21)		11 (5)		
Race, n(%)					
Caucasian	26 (93)		223 (96)		0.21
African-American	1 (3.5)		9 (4)		
Other	1 (3.5)		0 (0)		

[1]Risk strata = Very low-risk (T1c, Gleason score of 6 or less, PSA<10 ng/mL, 2 or fewer positive biopsy cores with cancer, 50% or less cancer in each core, PSA density <0.15 ng/mL/g) or Low-risk (men who did not meet very low-risk criteria but are T1-T2a, Gleason score 6 or less, PSA<10 ng/mL)

Table 2

Linear mixed effects model for fPCA3 (n=260)

Covariate	Co-efficient	*P value*
Time	0.06	< 0.001
High-grade[1]	0.05	0.04
Risk strata[2]	0.02	0.08
Age	0.04	0.01
High-grade × Time[1]	0.01	0.53
Risk strata × Time[2]	0.05	0.37

[1]High-grade = Gleason score >6

[2]Risk strata = Very low-risk (T1c, Gleason score of 6 or less, PSA<10 ng/mL, 2 or fewer positive biopsy cores with cancer, 50% or less cancer in each core, PSA density <0.15 ng/mL/g) or Low-risk (men who did not meet very low-risk criteria but are T1-T2a, Gleason score 6 or less, PSA<10 ng/mL)

Table 3

Multivariable model for association between fPCA3 (Model 1) or sPCA3 (Model 2) and grade reclassification adjusting for baseline covariates

Covariates (Model 1)	**Odds Ratio**	**95% CI**	***P value***
Age	1.04	0.96 – 1.14	0.320
PSA density (per 0.1 unit)	2.49	1.39 – 5.80	0.018
Low-risk (vs. very low risk)[1]	4.67	1.72 – 14.22	0.007
Log[fPCA3]	1.77	1.17 – 3.08	0.038
Covariates (Model 2)	**Odds Ratio**	**95% CI**	**P-value**
Age	1.03	0.94 – 1.12	0.579
PSA density (per 0.1 unit)	1.59	1.28 – 3.36	0.022
Low-risk (vs. very low risk)[1]	3.45	1.28– 9.30	0.014
Log[sPCA3]	1.74	1.03 – 2.94	0.042

[1]Very low-risk (T1c, Gleason score of 6 or less, PSA<10 ng/mL, 2 or fewer positive biopsy cores with cancer, 50% or less cancer in each core, PSA density <0.15 ng/mL/g) or Low-risk (men who did not meet very low-risk criteria but are T1-T2a, Gleason score 6 or less, PSA<10 ng/mL)