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Utilizing lesion diameter and prostate specific antigen density to decide on magnetic resonance imaging guided confirmatory biopsy of prostate imaging reporting and data system score three lesions in African American prostate cancer patients managed with active surveillance

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Utilizing lesion diameter and prostate specific antigen density to decide on magnetic resonance imaging guided confirmatory biopsy of prostate imaging reporting and data system score three lesions in African American prostate cancer patients managed with active surveillance

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Abstract

Objective The objective of the study is to identify the rate of significant prostate cancer (PCa) detection in PI-RADS3 lesions in AA patients stratified by PSAD threshold of <0.15 vs. ≥ 0.15 ng/ml^2 and lesion diameter of <1 cm vs ≥ 1 cm.

Methods We analyzed our institutional database of MRI-TB to identify the rate of significant prostate cancer (PCa) detection in PI-RADS3 lesions in AA patients stratified by PSAD threshold of <0.15 vs. ≥ 0.15 ng/ml^2 and lesion diameter of <1 cm vs ≥ 1 cm. Significant prostate cancer was defined as Gleason grade group 2 or higher on MRI-TB of the PI-RADS 3 lesion.

Results Of 768 patients included in the database, 211 (27.5%) patients identified themselves as AAs. Mean age of AA patients was 63 years and mean PSAD was 0.21. Sixty nine (32.7%) AA patients were found to have PI-RADS 3 lesions. Mean PSAD of AA patients with PI-RADS 3 lesions was 0.21 ng/ml^2 as well. Fifty percent of AA patients with PI-RADS 3 lesions had PSAD ≥ 0.15 ng/ml^2. Significant PCa detection rate for AA patients with PI-RADS 3 lesions was 9% for PSAD of ≥ 0.15 vs. 0.03% percent for AA patients with PSAD <0.15 ng/ml^2 (OR 7.056, CI 1.017–167.9, $P=0.04$). Stratification by lesion diameter (<1 cm vs. >1 cm) resulted in missing 0% of significant PCa when only AA patients with PSAD ≥ 0.15 ng/ml^2 and lesion diameter ≥ 1 cm received MRI-TB.

Conclusions We report on the performance of a reported PSAD density threshold in detecting significant PCa in one of the largest series of AA patients receiving MRI-TB of the prostate. Our results have direct clinical implications when counseling AA patients with PI-RADS 3 lesion on whether they should undergo MRI-TB of such lesions.

Keywords Active surveillance · African American · Prostate cancer · PI-RADS 3 · Prostate specific antigen density · Lesion diameter

Introduction

About 50% of all patients diagnosed with prostate cancer (PCa) have a low-risk disease [1]. In low-risk prostate cancer, active surveillance (AS) is the recommended option for the initial management [2]. Monitoring in AS used to be based on repeated PSA measurements, clinical T-staging, and repeated random systematic transrectal ultrasound (TRUS)-guided biopsies. More recently, magnetic resonance imaging (MRI) and MRI-targeted biopsies (MRI-TB) were increasingly used in the management of patients with clinically low-risk PCa to reduce the risk of missing clinically significant disease and overcome the shortcomings of systemic prostate biopsy [3]. The Prostate Imaging Reporting and Data System version 1 (PI-RADS v1) was then developed in 2012 for use with multiparametric magnetic resonance imaging and was updated to PI-RADS version 2 (PI-RADS v2) in 2015 due to the increased utility of mpMRI in PCa characterization, surveillance, and therapy [4]. In PI-RADS v2, lesions are categorized into five score groups with an increased risk of detecting cancer in any

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lesion; the higher is the PI-RADS score 5 [5]. A study using PI-RADS to predict biopsy outcomes had excellent results [6]. Receiver operating characteristic (ROC) curve analysis for clinically significant PCa yielded an area under the curve (AUC) of 0.89, and the negative predictive value (NPV) of a PI-RADS score of ≤ 2 was 0.98. However, the PI-RADS score suffered from a low positive predictive value (PPV) for clinically significant PCa (0.58 using a threshold PI-RADS score of ≤ 3). Therefore, researchers explored combining the PI-RADS v2 score with classical parameters, including PSA level, prostate volume, PSA density, and DRE findings to improve the PPV of MRI lesions in the lower spectrum of the PI-RADS score. While literature is growing around the utility of these parameters in the general population, very little has been done to test their validity among African Americans (AA). This population has the highest incidence of PCa globally, and their PCa-related mortality rate is twice that of Caucasians [7]. This study evaluated the clinically significant PCa detection rate with MRI-TB at a community health organization serving as the destination for the care of a large AA population. It aimed to examine the validity of the PSA density (PSAD) threshold of < 0.15 ng/ml^2 as a tool to avoid unnecessary biopsies in AA men when their MRI shows lesions of PI-RADS score of 3.

Methods

We performed a retrospective review of MRI-targeted biopsy (MRI-TB) from October 2015 to February 2018 at a large healthcare organization treating a diverse population in a metropolitan area. The urology department at this institution manages 1800 patients with PCa every year, 35% of whom identify as AA. A single radiology group read the prostate MRI and followed PI-RADS v2 algorithms to categorize lesions into one of five risk strata. Lesions categorized as PI-RADS 3 or higher were considered for MRI-TB.

The selection criteria were AA patients with lesions on MRI of PI-RADS score 3 done in the course of their management with active surveillance. All MRI-transrectal ultrasound fusion-guided biopsies were performed by a single urologist with several years of experience in MRI-transrectal ultrasound targeted biopsy using the DynaCAD MRI-transrectal ultrasound fusion biopsy system UroNav (Invivo, Gainseville, Florida, US). The biopsies were conducted using a local anesthetic in the outpatient setting. Three target biopsy cores were taken from each lesion and were immediately followed by a 12-core systematic biopsy where one core was taken from each of the 12 sectors.

Patients undergoing MRI-TB had up to five lesions included for biopsy. Biopsies were scored by a fellowship-trained genitourinary pathologist using Gleason criteria. The pathological assessment of Gleason 3 + 3 = 6 was used as the minimum positive cutoff for PCa following biopsy.

After institutional review board approval, data were extracted from the electronic medical record (EMR) with a case-by-case review by researchers to confirm the accuracy of the data. mpMRI studies were reviewed to obtain the PI-RADS score of lesions sampled via MRI-TB, as well as prostate volume. Descriptive variables collected include the date of MRI-TB, date of birth, ethnicity, previous prostate biopsy reports, and PSA before MRI-TB. Patient age was calculated from the date of birth and the date MRI-TB was performed. PSAD was calculated as the quotient of PSA level and prostate volume. Exclusion criteria for analysis included no lesion diameter and incomplete descriptive information in the EMR.

Clinically significant PCa was defined as the percent of lesions with Gleason 3 + 4 or higher PCa detected by MRI-TB. All analyses were done using SAS 9.4. Tests were two-sided with an alpha value of 0.05.

All patients were imaged on one of two 3-Tesla MRI systems: a GE Discovery 750 3.0 T (GE Healthcare, Waukesha, WI, USA), using a 32 channel torso phased array coil, and Philips Ingenia 3.0 T (Philips Healthcare, Best, the Netherlands) using a 32 element anterior torso phased array coil coupled with an integrated posterior 20 element array in the tabletop. All patients underwent a highly similar imaging protocol on one of these two machines, consisting of: large field of view (FOV) (32 cm or greater) 2D fast spin-echo (FSE) T2-weighted images with fat suppression and 3D T1 gradient-echo (GRE) with Dixon fat–water separation (fat, water, in-phase, out-of-phase reconstructions); small field of view (18 cm) FSE T2 images of the prostate in the axial, sagittal and coronal planes; axial diffusion weighted images (DWI) in small FOV (Philips, 18 cm) and larger FOV (GE, 30 cm); small (22 cm) FOV bolus IV gadolinium chelate dynamic contrast enhanced T1 GRE series (20 successive post-contrast phases, temporal resolution < 10 s); and a final large FOV pelvic post-contrast T1 GRE Dixon (water reconstruction) series. Examinations were interpreted and analyzed using DynaCAD (InVivo, Gainesville, FL, USA). IV contrast employed: before Sept. 2017, 0.075 mmol/kg gadobenate dimeglumine (MultiHance®, Bracco Diagnostics Inc., Princeton, J); subsequently, 0.1 mmol/kg gadobutrol (Gadavist®, Bayer Healthcare Pharmaceuticals, Wayne, NJ).

Results

Patient data and biopsy outcomes

Of 768 patients included in the database, 211 (27.5%) patients identified themselves as AA. The mean age of AA patients was 63 years, and the mean PSAD was 0.17 ng/

Table 1 Characteristics of African American male population presenting with PI-RADS 3 lesion on magnetic resonance imaging of the prostate

	PSAD < 0.15 ng/ml^2 (n = 35)	PSAD ≥ 0.15 ng/ml^2 (n = 34)	Lesion diameter < 1 cm (n = 37)	Lesion diameter ≥ 1 cm (n = 32)
Mean age in years (STD)	62.8 (8.82)	61.95 (9.06)	64.24 (8.75)	60.90 (8.45)
Mean PSA density in ng/ml^2(STD)	0.07 (0.035)	0.31(0.17)	0.12 (0.09)	0.21 (0.19)
Any cancer detection rate in PI-RADS3 lesion	20%	44%	31%	33%
Significant cancer detection rate in PI-RADS3 lesion	3%	11%	6%	10%

Table 2 (a) Odd of detecting any cancer stratified by the presence of risk factors of large lesion diameter and high PSA density in African American men undergoing magnetic resonance imaging of the prostate for PI-RADS 3 lesions in the course of active surveillance (b) odd of detecting clinically significant cancer stratified by the presence of risk factors of large lesion diameter and high PSA density in African American men undergoing magnetic resonance imaging of the prostate for PI-RADS 3 lesions in the course of active surveillance

Risk factor	Odds ratio	95% Confidence interval	*P* value
a			
Lesion diameter ≥ 1 cm	0.6937	0.151–3.218	0.3176
PSAD ≥ 0.15	1.217	0.2401–5.796	0.4002
Lesion diameter > 1 cm and PSAD ≥ 0.15 ng/ml^2	1.595	0.31–7.838	0.5631
b			
Lesion diameter ≥ 1 cm	1.048	0.0325, 15.21	0.4715
PSAD ≥ 0.15	1.215	0.03746, 17.73	0.4311
Lesion diameter ≥ 1 cm and PSAD ≥ 0.15 ng/ml^2	1.322	0.09172, 42.43	0.4353

ml^2. Sixty nine (32.7%) AA patients were found to have PI-RADS 3 lesions. The mean PSAD of AA patients with PI-RADS 3 lesions was 0.21 ng/ml^2 as well. Fifty percent of AA patients with PI-RADS 3 lesions had PSAD ≥ 0.15 ng/ml^2. Any cancer detection rate and significant cancer detection rate were 3% vs. 11% and 20% vs. 44% in AA patients with PI-RADS3 lesions and PSAD of < 0.15 and ≥ 0.15, respectively (Table 1).

Risk factor evaluation and cancer prediction

The univariate logistic regression analysis results for the association between risk factors (lesion volume ≥ 1 cm, PSAD ≥ 0.15 ng/ml^2, and combined lesion volume ≥ 1 cm and PSAD ≥ 0.15 ng/ml^2) and cancer detection in PI-RADS 3 lesions are shown in Table 2a and b.

We divided the patients who underwent MRI-TB biopsy of PI-RADS3 lesions into four groups: (1) PI-RADS v2 scores of 3, lesion diameter < 1 cm, and PSAD < 0.15, (2) PI-RADS v2 scores of 3, lesion diameter < 1 cm, and PSAD ≥ 0.15, (3) PI-RADS v2 scores of 3, lesion diameter ≥ 1 cm, and PSAD < 0.15, and (4) PI-RADS v2 scores of 3, lesion diameter ≥ 1 cm, and PSAD ≥ 0.15. We then compared the prediction characteristics of the four groups for detecting significant PCa (Table 3). The results of this analysis are operationalized into a decision tree in Fig. 1. As illustrated, high PSAD was the strongest predictor of detecting significant cancer in PI-RADS 3 lesions. Lesion

Table 3 Test performance characteristics for different combinations of lesion diameter and PSA density for predicting clinically significant PCa in African American males presenting for MRI-targeted biopsy of PI-RADS3 lesion in the course of PCa management with active surveillance

Risk factor grouping	Sensitivity	Specificity	Negative predictive value	Positive predictive value
PI-RADS v2 scores of 3 + lesion diameter < 1 cm + PSA density < 0.15 n = 28	0%	67.74%	87.50%	0%
PI-RADS v2 scores of 3 + lesion diameter < 1 cm + PSA density ≥ 0.15 n = 9	33.33%	90.32%	93.33%	25%
PI-RADS v2 scores of 3 + lesion diameter ≥ 1 cm + PSA density < 0.15 n = 7	33.3%	79.49%	93.94%	11.11%
PI-RADS v2 scores of 3 + lesion diameter ≥ 1 cm + PSA density ≥ 0.15 n = 25	60%	75%	91.3%%	30%

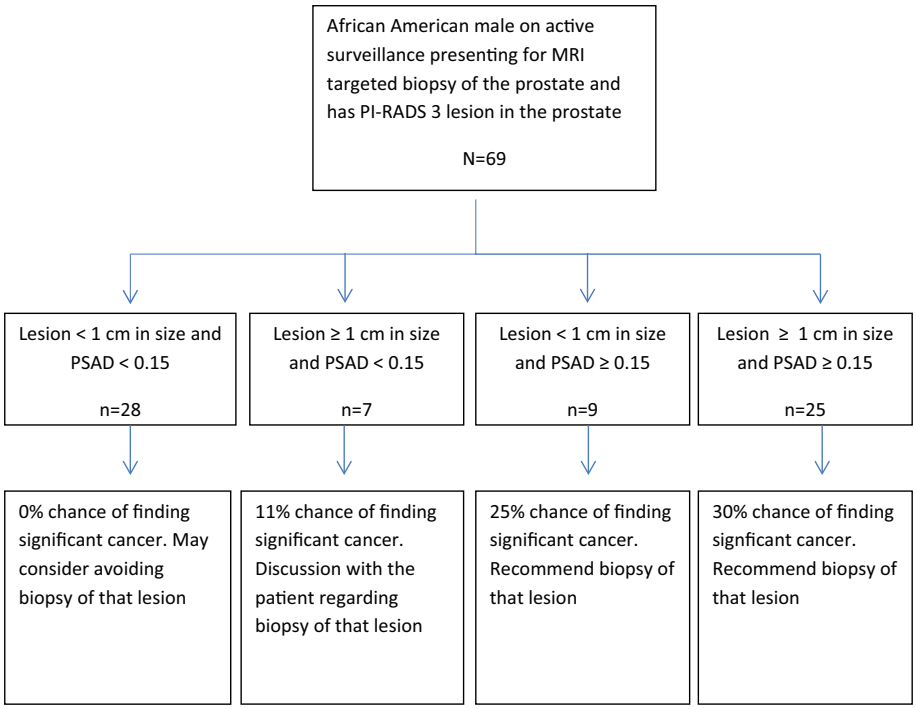

Fig. 1 Decision tree for managing PI-RADS 3 lesions in African American men presenting for MRI—targeted biopsy of the prostate in the course of active surveillance of their prostate cancer

diameter ≥ 1 cm was also a predictor of finding significant PCa in PI-RADS 3 lesions, but not to the extent of high PSAD. When combined, these two factors acted synergistically rather than canceling the effects of each other. In our patients, no single patient with significant PCa presented with a lesion < 1 cm in diameter and PSAD < 0.15 ng/ml^2.

Discussion

In this study, we present our experience with the outcomes of MRI-TB of PI-RADS v2 3 lesions in AA men during active surveillance, and we attempt to refine the selection of patients who should have such biopsy using the risk factors of lesion diameter and elevated PSAD. Our results include findings that help decide what to do with PI-RADS 3 lesions in AA patients without the limitation of generalizing data from studies built on Caucasians. Overall, elevated PSAD and large PI-RADS 3 lesion volume go hand in hand, and in fact, only 20% of our patients with PSAD ≥ 0.15 had PI-RADS 3 lesions < 1 cm in size. The larger lesion diameter plausibly increases the probability that the lesion is the source of the elevated PSAD. We also find that elevated PSAD has a higher positive predictive value for diagnosing clinically significant PCa in PI-RADS 3 lesions in African American men compared to lesion size. Finally, we show that our targeted biopsies are not detecting clinically significant PCa in AA patients with PI-RADS3 lesions < 1 cm in diameter and whose PSAD is < 0.15 ng/ml^2. Therefore, we can use the criteria of small lesion diameter and PSAD < 0.15 to select a group of AA patients on active surveillance who may safely avoid a repeat confirmatory biopsy of their PI-RADS 3 prostate lesions.

Different thresholds of PSAD have been used and validated in previous literature to select which lesions to target in the course of prostate biopsy. Washino et al. found PSAD to be an independent predictor for total and clinically significant PCa. The authors set the PSA density threshold value to 0.15 ng/ml^2 and showed the sensitivity, specificity, PPV, and NPV of that threshold for clinically significant PCa to be 0.99, 0.34, 0.59, and 0.96, respectively [8]. Boesen et al. examined 808 biopsy-naïve men with clinical suspicion of localized PCa and detected significant PCa in 283/808 (35%) men. The authors then suggested that the best way to avoid unnecessary biopsy was to restrict biopsies to men with highly suspicious MRI findings (score _4) or PSAd < 0.15 ng/ml^2.Their NPV for PSAD < 0.15 in a PI-RADS 3 lesion was 0.93 [9]. In both of these studies, the patients were biopsy nieve. Our group of patients was an "MRI-targeted biopsy" nieve and had received only random ultrasound-guided biopsy of the prostate before their inclusion in our study database. However, our conclusion for the importance of PSAD in detecting significant cancer in PI-RADS 3 lesions is also supported by findings from studies that examined patients previously diagnosed with ultrasound-guided prostate biopsy. Schoots et al. examined the role of PSAD in reducing MRI-targeted prostate biopsy in patients with active surveillance and reported that upgrading to GS ≥ 3 + 4 in PI-RADS 3 lesions was limited to men with a PSA density of ≥ 0.15 ng/ml^2 [10].

Our results also agree with previous studies that larger lesion diameter indicates a higher likelihood that a lesion would contain significant prostate cancer [11]. However, the value of considering lesion diameter in PI-RADS 3 foci may be limited in patients with low PSAD. In our study, most patients with PSAD of < 0.15 had a lesion diameter of < 1 cm and did not harbor clinically significant PCa.

Our study was possible because our hospital serves a large population of AA patients and can close the gaps in our knowledge about PCa in these patients. Also, considering barriers or obtaining MRI in AA, we present a relatively large series of AA with PI-RADS 3 lesions [12]. Finally, the concentration of imaging read, biopsy performance, and pathology reporting in the hands of a few trained providers reduces the inter-reader variability and increases the accuracy of our results.

Our study has limitations; first, its retrospective design increases the risk of selection bias. Second, clinicians involved were not blinded to clinical data and MRI results. Third, the findings of clinically significant cancer were done through biopsy and not through the gold standard post-prostatectomy pathology. However, the availability of post-prostatectomy pathology is limited in a cohort of men with a low-risk disease managed with AS and not radical prostatectomy [13]. Finally, multiple radiologists were involved in reading the MRI studies included in this research, and we did not control for the possible disagreement in PI-RADS assignment among these radiologists. Moreover we did not use the newer (2019) revision of PI-RADS criteria (version 2.1), which includes significant changes in the criteria and has clarified some of the controversial characteristics of prostate nodules.

Conclusion

African American patients with a PI-RADS v2 score of 3 and a PSA density of < 0.15 ng/mL and lesion diameter < 1 cm may avoid unnecessary confirmatory biopsies.

Declarations

Conflict of interest The authors have no conflict of interest to disclose.

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