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Original Article

Impact of commonly used medications on the detection of clinically significant prostate cancer in the targeted biopsy era

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Abstract: Objectives: To compare prostate cancer rates in magnetic resonance imaging (MRI)-detected lesions for patients who are chronically taking beta-blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), or immunosuppressors. Methods: This cohort consisted of 897 Prostate Imaging Reporting & Data System (PI-RADS)v2 3-5 lesions from 590 MRI-targeted fusion prostate biopsies (UroNav). Baseline characteristics and clinicopathological data were collected. A matching cohort was analyzed, and multivariate analysis was completed for each medication group. Matching analysis accounted for age, prostate-specific antigen (PSA), and PI-RADS score. Multivariate analysis additionally considered lesion size. Results: Of the 897 lesions, 261/897 (29%) of lesions were identified as PI-RADS 3, 373/897 (42%) were PI-RADS 4, and 263/897 (29%) were PI-RADS 5. In the patient cohort, 16% were taking a beta-blocker, 3.9% were taking an NSAID, and 5.4% were taking an immunosuppressant. An equal number of lesions in controls were matched to 148 lesions in males taking beta-blockers, 37 lesions in males taking NSAIDs, and 46 lesions in males taking immunosuppressants. Matching was based on age, PSA, and PI-RADS score. In the matched cohort, neither beta-blockers, NSAIDs, nor immunosuppressants altered clinically significant prostate cancer (csPCa) identification on MRI (OR 1.11, CI 95% 0.6, 1.9; OR 0.70, CI 95% 0.32, 1.66; OR 1.73, CI 95% 0.59, 5.35, respectively). Conclusion: This pilot study shows no difference in csPCa detection rates in patients using anti-inflammatories or drugs that alter prostate blood flow.

Keywords: Prostate cancer, multiparametric magnetic resonance imaging (mpMRI), magnetic resonance imaging (MRI) targeted fusion biopsy

Introduction

The widespread use of multiparametric magnetic resonance imaging (mpMRI) and mpMRI-transrectal ultrasound (TRUS) fusion-targeted prostate biopsies has changed the diagnostic pathway of prostate cancer (PCa). Targeted biopsies can improve the detection of clinically significant PCa (Gleason score ≥ 7, Grade Group ≥ 2) while reducing the detection of clinically insignificant PCa [1-3].

Men undergoing magnetic resonance imaging (MRI) for suspicion of PCa often present with other associated comorbidities for which different classes of medications are prescribed, both for urological and nonurological conditions, such as benign prostate hyperplasia, hypertension, and diabetes [4, 5]. Some medications have been proposed to potentially alter prostate vasculature (5-alpha reductase inhibitors, beta-blockers), change prostate smooth muscle tone (α-antagonists, phosphodiesterase inhibitors), reduce inflammation (nonsteroidal anti-inflammatory drugs (NSAIDs)), or change the prostate immune microenvironment (systemic immunosuppressors) [6-8]. However, the precise ways in which these medications may affect prostate cancer detection via MRI have not been thoroughly investigated.

No study to date has evaluated the effect of chronic use of such medicines within a cohort of MRI-targeted fusion biopsies. Therefore, the association between potential changes in prostate inflammation or blood flow and the detec-

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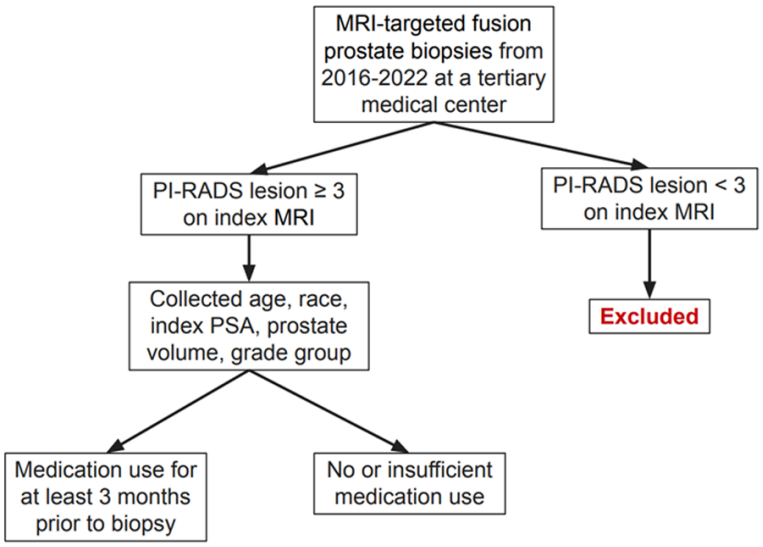

Figure 1. Data Collection Flowchart. Patients with a magnetic resonance imaging (MRI)-targeted prostate biopsy and at least one PI-RADS lesion ≥ 3 were included in the study. Multiple variables, including age, race, index PSA, prostate volume, and grade group, were collected for each patient. Patients were then screened for the use of a beta-blocker, NSAID, or immunosuppressant for at least 3 months prior to UroNav. MRI = magnetic resonance imaging, PI-RADS = Prostate Imaging Reporting & Data System, PSA = prostate specific antigen.

tion of clinically significant prostate cancer remains unclear. In this study, we aim to compare prostate cancer detection rates stratified by different Prostate Imaging Reporting & Data System (PI-RADS) scores with MRI-TRUS fusion biopsy in patients using chronic beta-blockers, NSAIDS, and immunosuppressors.

Materials and methods

Patient population

Clinical, imaging, and pathologic data were collected for patients who underwent an MRI-targeted fusion prostate biopsy from 2016 through 2022 at the University of Wisconsin, a single tertiary medical center. Biopsies that solely included Prostate Imaging Reporting & Data System Version 2.1 (PI-RADSv2.1) lesions < 3 were excluded from the cohort. Biopsies that contained at least one lesion of at least PI-RADS 3 on index MRI were included in the study.

Clinical data collected included age, race, index prostate-specific antigen (PSA), and prior biopsy history (**Figure 1**). Prostate volumes were calculated and recorded from index MRI. Pathology results were used to elucidate the grade group for each biopsied lesion.

Patients in each medication cohort (beta-blocker, NSAID, immunosuppressant) were actively taking the respective medication at least three months prior to the index MRI. Inhaled and oral immunosuppressants of any dose were included; topical and nasal immunosuppressants were excluded. This was based on the immunosuppressant's systemic absorption. Patients who were on 81 mg daily of aspirin were not included in the NSAID cohort.

Analysis was performed on a per-lesion basis. Comparative analysis was performed using RStudio (Boston, MA). Baseline variables between the groups were compared using either a Student's T-test, Mann-Whitney Test, or Chi-Square Test. Multivariable logistic regression analyses adjusting for age, PSA, and PI-RADS lesion score were performed, with final pathology identified on targeted biopsy as the dependent variable.

Biopsy protocol and histopathology

All patients underwent targeted biopsies. Fellowship-trained abdominal radiologists manually contoured the prostate and PI-RADSv2.1 score 3, 4, and 5 lesions (DynaCAD, Philips Healthcare, Massachusetts, USA) and imported them to ultrasound (bk3000, BK Medical, Massachusetts, USA) with image-fusion software (UroNav, Philips Healthcare), fellowship-trained Urologists performed the biopsies. Tissue cores were fixed in a 10% formalin solution and re-reviewed by a subspecialty urologic pathologist. Tissue cores obtained from the targeted and template biopsies were labeled and fixed separately. Biopsies with no associated Gleason Score due to non-malignant designation are referred to as "negative biopsies".

Prostate volume calculation

Prostate volume was measured using T2-weighted MRI images acquired on a 3T scanner

with axial, sagittal, and coronal orientations. A radiologist blinded to outcomes manually contoured the prostate on axial slices. Volume was calculated using the ellipsoid formula, where length was the cranio-caudal dimension on sagittal view, width the maximal transverse diameter on axial view, and height the anteroposterior dimension on sagittal view. In cases where segmentation software with exponential signal modeling was used, volume was computed by summing cross-sectional areas across slices, adjusting for signal decay to enhance boundary detection. Measurements were recorded in mL.

Statistical analysis

Given the numerical imbalance between all three medication cohorts and the non-medicated cohort, lesions in patients on each medication with lesions in non-medicated patients were subsequently matched. All matching analysis was performed using the MatchIt package in R, which calls functions from the Matching package [9, 10]. Several matching methods were tested, including coarsened exact matching (CEM), nearest neighbor matching with and without replacement, and genetic matching. The balance of each matching method was assessed by evaluating standardized mean differences (SMD) and variance ratios. Pre-matching and post-matching SMD are shown in the Love Plot's. Lesions were matched based on age, corrected PSA, and PI-RADS score. The genetic matching algorithm ultimately provided the most balanced results, with all SMDs less than the threshold of 0.1. Logistic regression was performed to estimate the marginal treatment effect on the pathologic outcome.

Results

Characteristics of cohort

590 MRI-targeted fusion patient prostate biopsies (UroNav) were reviewed, and 897 of the biopsied lesions (36%) met inclusion criteria and were identified as clinically significant prostate cancer (csPCa) (defined as PI-RADSv2.1 3-5). Of these 590 UroNavs, 94 (15.9%) of patients were taking a beta-blocker, 23 (3.9%) were taking an NSAID, and 32 (5.4%) were taking an immunosuppressant. Patients had an average of 1.52 lesions found on UroNav. The average age was 66.4 years, and the average PSA was 10.4 ng/mL. 55.4% of patients were found to have clinically significant prostate cancer (Supplementary Table 1). Analyzing the 897 individual lesions, 29% of lesions were identified as PI-RADS 3, 42% were PI-RADS 4, and 29% were PI-RADS 5. 16% of PIRADS lesions were found in patients on a beta-blocker, 4.1% in patients on an NSAID, and 5.1% in patients on an immunosuppressant. As indicated by the pathology report, 45.5% of lesions were negative, 32.9% were Grade Group (GG)1-2, and 21.6% were GG3-5 (**Table 1**).

Characteristics of medication sub-groups

The baseline characteristics of the NSAID and immunosuppressant subgroups were not significantly different from their respective non-NSAID and non-immunosuppressant groups when considering age, PI-RADS score, PSA, number of csPCa lesions identified on targeted biopsy, and pathological Grade Group (**Table 1**).

In the beta-blocker sub-group, PI-RADS scores were significantly different between the two groups. 31% of lesions were PI-RADS 3 in the non-beta-blocker group compared to 18% in the beta-blocker group. Conversely, 28% of lesions were PI-RADS 5 in the non-beta-blocker group compared to 35% in the beta-blocker group. Significantly more lesions were found to be clinically significant on targeted prostate biopsy in the beta-blocker group (44%) compared to the non-beta-blocker group (35%). Grade Groups were not significantly different between the two groups (**Table 1**).

There were no significant differences found in age, PI-RADS score, PSA, presence of csPCa on targeted biopsy, or pathology of targeted biopsy between the beta-blocker, NSAID, nor immunosuppressant groups and their associated matched groups (**Table 2**).

Analysis of medication sub-groups

Multivariate analysis of the medication subgroups, adjusting for age, PSA, lesion size, and PI-RADS lesion score, showed that medication use was not significantly associated with the detection of csPCa on targeted biopsy: beta-blocker use (P = 0.93, **Table 3**), NSAID use (P = 0.34, **Table 3**), and immunosuppressant use (P = 0.33, **Table 3**).

Table 1. Baseline characteristics of the overall cohort and medication subgroups on a per-lesion basis

Characteristic	Total Cohort	Beta-Blocker	NSAID	Immunosuppressant
Number of Lesions	897	148 (16%)	37 (4.1%)	46 (5.1%)
PI-RADS Score				
3	261 (29%)	27 (18%)	10 (27%)	18 (39%)
4	373 (42%)	69 (47%)	17 (46%)	18 (39%)
5	263 (29%)	52 (35%)	10 (27%)	10 (22%)
(*p*-value)	---	(0.006)	(0.9)	(0.3)
csPCa on Targeted Biopsy	324 (36%)	65 (44%)	13 (35%)	18 (39%)
(*p*-value)	---	(0.03)	(0.9)	(0.7)
Pathology of Targeted Biopsy				
No cancer	408 (45.5%)	60 (40.5%)	14 (37.8%)	19 (41.3%)
GG1-2	295 (32.9%)	47 (31.8%)	13 (35.1%)	19 (41.3%)
GG3-5	194 (21.6%)	41 (27.7%)	10 (27.0%)	8 (17.4%)
(*p*-value)	---	(0.13)	(0.58)	(0.44)

Each medication group was compared to the remainder of the total cohort to avoid duplicative comparison. PI-RADS = Prostate Imaging Reporting & Data System, csPCa = clinically significant prostate cancer, GG = grade group.

Table 2. Baseline characteristics of the matched medication subgroups

Characteristic	Beta-Blocker	No Beta-Blocker	NSAID	No NSAID	Immuno-suppressant	No Immuno-suppressant
Match Size (N)	148	148	37	37	46	46
Age (years)*	67	67	66	66	67	68
(*p*-value)	> 0.9		> 0.9		> 0.9	
PSA (ng/mL)*	8.6	8.7	8.3	8.2	7.5	7.7
(*p*-value)	> 0.9		> 0.9		> 0.9	
PI-RADS Score*						
3	27 (18%)	27 (18%)	10 (27%)	10 (27%)	18 (39%)	18 (39%)
4	69 (47%)	69 (47%)	17 (46%)	17 (46%)	18 (39%)	18 (39%)
5	52 (35%)	52 (35%)	10 (27%)	10 (27%)	10 (22%)	10 (22%)
(*p*-value)	> 0.9		> 0.9		> 0.9	
csPCa on Targeted Biopsy	65 (44%)	62 (42%)	13 (35%)	15 (41%)	18 (39%)	14 (30%)
(*p*-value)	0.7		0.6		0.4	
Pathology of Targeted Biopsy						
No cancer	73 (49%)	76 (51%)	19 (51%)	21 (57%)	24 (52%)	29 (63%)
GG1	10 (6.8%)	10 (6.8%)	5 (14%)	1 (2.7%)	4 (8.7%)	3 (6.5%)
GG2	31 (21%)	42 (28%)	6 (16%)	7 (19%)	12 (26%)	5 (11%)
GG3	12 (8.1%)	9 (6.1%)	2 (5.4%)	5 (14%)	3 (6.5%)	3 (6.5%)
GG4	9 (6.1%)	6 (4.1%)	4 (11%)	1 (2.7%)	2 (4.3%)	3 (6.5%)
GG5	13 (8.8%)	5 (3.4%)	1 (2.7%)	2 (5.4%)	1 (2.2%)	3 (6.5%)
(*p*-value)	0.3		0.3		0.5	

* Indicates matching criteria. NSAIDs = Nonsteroidal anti-inflammatory drugs, PSA = prostate-specific antigen, PI-RADS = Prostate Imaging Reporting & Data System, csPCa = clinically significant prostate cancer, GG = grade group.

In the matched cohorts, beta-blockers, NSAIDs, nor immunosuppressants were associated with enhanced or detracted csPCa identification on MRI (OR 1.11, CI 95% 0.6, 1.9; OR 0.70, CI 95% 0.32, 1.66; OR 1.73, CI 95% 0.59, 5.35, respectively).

Discussion

The use of multiparametric magnetic resonance imaging (mpMRI) combined with MRI-transrectal ultrasound (TRUS) fusion-targeted prostate biopsies has enhanced the detection

Table 3. Multivariate analysis of medication sub-groups (OR = Odds Ratio, CI = Confidence Interval)

Medication	Characteristic	OR	95% CI	*p*-value
Beta-blocker	Age (years)	1.05	1.03, 1.08	--
	PSA (ng/mL)	1.03	1.01, 1.06	--
	Lesion size (cm)	1.05	0.80, 1.38	--
	PI-RADS score			
	3	--	--	--
	4	2.41	1.71, 3.39	--
	5	4.32	2.74, 6.82	--
	Beta-blocker use	1.02	0.69, 1.50	0.93
NSAID	Age (years)	1.05	1.03, 1.08	--
	PSA (ng/mL)	1.03	1.01, 1.06	--
	Lesion size (cm)	1.05	0.80, 1.38	--
	PI-RADS score			
	3	--	--	--
	4	2.41	1.71, 3.38	--
	5	4.34	2.75, 6.84	--
	NSAID use	1.42	0.69, 2.91	0.34
Immunosuppressant	Age (years)	1.05	1.03, 1.08	--
	PSA (ng/mL)	1.03	1.01, 1.06	--
	Lesion size (cm)	1.05	0.80, 1.38	--
	PI-RADS score			
	3	--	--	--
	4	2.43	1.73, 3.42	--
	5	4.38	2.78, 6.92	--
	Immunosuppressant use	1.38	0.72, 2.66	0.33

No drug was shown to have an impact on the detection rate of clinically significant prostate cancer (*p*-value 0.93, 0.34, and 0.33 for beta-blocker, NSAID, and immunosuppressant use, respectively). NSAIDs = Nonsteroidal anti-inflammatory drugs, PSA = prostate-specific antigen, PI-RADS = Prostate Imaging Reporting & Data System.

of clinically significant prostate cancer (PCa) while reducing the identification of clinically insignificant cancer. In our research, we reviewed 590 patients undergoing targeted biopsies, correlating the radiological findings with histopathology in patients using drugs with potential effects on prostate blood flow and inflammation. Despite variations in lesion detection rates and characteristics between medication sub-groups, multivariate analysis, and matching analysis revealed that chronic use of beta-blockers, NSAIDs, and immunosuppressants was not significantly associated with changes in the detection rate of clinically significant PCa on MRI-targeted biopsies. This provides additional evidence that imaging protocols should not be interpreted differently when these medications are present.

Beta-blockers bind to beta-1 and beta-2 adrenergic receptors, thereby counteracting the actions of catecholamines like epinephrine and norepinephrine. These medications are most commonly prescribed for their effects on slowing the heart rate and reducing blood pressure by decreasing renin and cardiac output [11]. Studies have shown that the prostate has a high density of adrenergic nerves, which helps the prostate smooth muscle contract to expel prostatic fluid [12]. Murine models have revealed that adrenergic nerve density increases in early prostate cancer, and human studies have shown higher adrenergic nerve density correlates with more aggressive pathology and poorer prognosis [13, 14]. Because beta-blockers reduce blood flow and there is a high adrenergic nerve density in early prostate cancer, this blood flow reduction could be particularly pronounced in lesions where prostatic cancer is present. Since mpMRI relies on blood flow changes to detect lesions, this reduction of blood flow in prostate cancer lesions could potentially alter imaging properties associated with lesion identification and grading. Several research articles have explored how beta-blockers can affect prostate cancer mortality and their effect on the incidence of prostate cancer. Still, none have addressed how beta-blockers could alter the detection of clinically significant prostate cancer on imaging [14-17]. We find that PI-RADS 3 lesions are found less commonly in patients on beta-blockers (**Table 1**), potentially reflecting alterations in vascular flow. However, our results suggest that despite the physiological potential for beta-blockers to alter properties within the prostate, these changes are not consequential enough to change the ability to detect clinically significant

prostate cancer using mpMRI on a per-lesion basis. It is not clear if there is a dose-dependent effect, or whether a time-dependent effect would show any differences.

NSAIDs primarily reduce inflammation by inhibiting cyclooxygenase-2, which is inducibly expressed during an inflammatory response [18]. In contrast, immunosuppressants can reduce inflammation by inhibiting the release of immune mediators and reducing cytokine production [19]. Prior studies have shown that prostatic inflammation can confound the ability to accurately detect prostate cancer on MRI [20, 21]. However, no studies have explored how NSAID or immunosuppressant use may alter the detection of clinically significant prostate cancer on imaging. By reducing prostatic inflammation through either NSAIDs or systemic immunosuppressants, cancerous prostatic lesions may have higher visibility on imaging and decrease the rate of false positives. However, our results did not show that using systemic NSAIDs or immunosuppressants reduced inflammation in the prostate enough to enhance the detection of clinically significant prostate cancer using mpMRI, which leads us to believe the cumulative effect is not substantial enough to change radiological findings, altering accuracy for prostate cancer detection.

Although the retrospective acquisition of the data is a limitation to the interpretation of the findings, the database analyzed has few missing data points, as the prostate MRIs were reread by fellowship-trained radiologists, which also reduces the interobserver variability. Our per-lesion analysis method guided by MRI has both strengths and limitations. This approach provides insight into our primary aim of understanding how an individual MRI lesion may be affected by medications. We did not focus this analysis on accounting for multiple lesions in a patient and did not assess the overall clinical impact of medication use on cancer detection given that this analysis would be confounded by nontargeted biopsies done concurrently.

Conclusion

Based on multivariate analysis and analysis of a matched MRI-targeted fusion biopsy cohort, no differences in lesion detection rates of clinically significant prostate cancer were seen across different medication subgroups. These results suggest that the long-term use of beta-blockers, NSAIDs, and immunosuppressants do not significantly alter the detection rates of clinically significant prostate cancer on MRI-targeted biopsies, and such findings support no changes in the current reporting protocols in case of the presence of these medications.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Baseline characteristics of the overall cohort and medication subgroups on a per-patient basis

Characteristic	Total Cohort	Beta-Blocker	NSAID	Immunosuppressant
Sample size (N)	590	94 (15.9%)	23 (3.90%)	32 (5.42%)
Lesions per patient	1.52	1.57	1.61	1.44
Age (years)	66.4	68.6	67.3	67.6
PSA (ng/mL)	10.4	9.42	9.03	9.41
Highest PI-RADS Score				
3	114 (19.3%)	10 (10.6%)	3 (13.0%)	10 (31.3%)
4	234 (39.7%)	39 (41.5%)	10 (43.5%)	12 (37.4%)
5	242 (41.0%)	45 (47.9%)	10 (43.5%)	10 (31.3%)
csPCa on Targeted Biopsy	327 (55.4%)	58 (61.7%)	15 (65.2%)	19 (59.4%)
Pathology of Targeted Biopsy				
No cancer	263 (44.6%)	36 (38.3%)	8 (34.8%)	13 (40.6%)
GG1-2	197 (33.4%)	33 (35.1%)	9 (39.1%)	13 (40.6%)
GG3-5	130 (22.0%)	25 (26.6%)	6 (26.1%)	6 (18.8%)

NSAIDs = Nonsteroidal anti-inflammatory drugs, PSA = prostate-specific antigen, PI-RADS = Prostate Imaging Reporting & Data System, csPCa = clinically significant prostate cancer, GG = grade group.