



## Systematic Biopsy Does Not Contribute to Disease Upgrading in Patients Undergoing Targeted Biopsy for PI-RADS 5 Lesions Identified on Magnetic Resonance Imaging in the Course of Active Surveillance for Prostate Cancer

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<b>OBJECTIVE</b>	To compare the utility of the systematic 12-core prostate biopsy (SB) combined with magnetic resonance imaging (MRI)-targeted lesion biopsy (MRI-TB) vs MRI-TB alone in the diagnosis of high PI-RADS lesions.
<b>MATERIALS AND METHODS</b>	Patients undergoing MRI-TB + SB for suspicious MRI lesions were retrospectively reviewed. These patients had a previous prostate biopsy and were evaluated with MRI to assess the need for a repeat biopsy. Pathologic findings of MRI-TB combined with a SB were compared to those of the patients' previous SB. An upgrade was defined as an increase in the Gleason Score of any prior biopsy. A no-upgrade (NU) MRI-TB was defined as a MRI-TB that did not lead to disease upgrading when compared to SB.
<b>RESULTS</b>	A total of 148 patients were analyzed in this study. Of the 255 total lesions (247 lesions with PI-RADS $\geq 3$ ), 141 were upgraded from the previous biopsy (55.3%). Of these, 104 were upgraded by the MRI-TB (40.8%), and 87 lesions were upgraded by the SB (34.1%). The MRI-TB had a NU rate of 26.2% for all lesions. On subanalysis, the NU rates of PI-RADS 3, 4, and 5 MRI-TBs were 39.3%, 21.2%, and 3.4%, respectively.
<b>CONCLUSION</b>	The NU rate for the MRI-TB in a PI-RADS-5 lesion is meager. Men with a PI-RADS 5 lesion may be safely managed with the MRI-TB alone without combining with SB. Men with PI-RADS 3 and 4 lesions should benefit from SB in addition to MRI-TB for accurate management of their disease. UROLOGY 134: 168–172, 2019. © 2019 Elsevier Inc.

Prostate biopsy techniques evolved from the open perineal and transperineal needle biopsies in the 1920s to the fusion of MRI and ultrasound imaging to target lesions in modern prostate biopsies. The systematic approach to the prostate biopsy was first discussed in a landmark paper in 1989 and became the gold-standard throughout the 1990s.<sup>1</sup> The sampling size of the systematic biopsy (SB) evolved from the initial 6-core, or sextant

method, to the extended 12-core biopsy in the late 1990s when multiple studies found that 12-core patterns that added cores lateral to the sextant pattern detected 31% more cancers, without an increase in adverse events.<sup>2,3,4</sup>

In the late 2000s, significant improvements in MRI imaging technologies have expanded the role of MRI to be used in the clinical evaluation of prostate cancer. In 2012, the International MRI Working Group released Prostate Imaging Reporting and Data System (PI-RADS) to standardize the reporting and mapping of all prostate lesions.<sup>5</sup> PI-RADS allows the radiologist to score the lesion on a scale of 1 to 5, depending on suspicion of malignancy.

The use of MRI guidance to target lesions for prostate biopsy was also established in the late 2000s. The most popular method in which this is done is via the MRI/ultrasound fusion-guided technique. Multiple studies have

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found that the MRI-targeted biopsy (MRI-TB) appears to be superior to the standard sextant and extended-core biopsies in detecting higher risk cancers, as well as avoiding diagnosis of lower risk, clinically insignificant cancers, with fewer core samples.<sup>6,7</sup>

Although they have been shown to be inferior in cancer detection, standard biopsies (SB) are currently recommended in conjunction with MRI-TB. There is a lack of guidance on when MRI-TB alone is sufficient. This retrospective analysis reviews whether MRI-TB alone is sufficient to decide on the management of prostate cancer in men with MRI findings of PI-RADS 3, 4, and 5 lesions, without the need for an additional SB.

## METHODS

### Study Design

We performed a retrospective review of the results of MRI-Targeted biopsy with accompanying systemic biopsy in patients with a prostate MRI showing at least one PI-RADS 3, 4, or 5 lesion. Each lesion was analyzed separately. The patients were being evaluated with MRI to assess the need for a repeat biopsy for restaging for men on active surveillance. Every MRI-targeted biopsy was combined with repeat systemic biopsy (MRI-TB + SB). Pathologic findings of the MRI-TB + SB were compared to those of the previous SB. An upgrade was defined as an increase in the Gleason score of any prior biopsy. A no-upgrade (NU) MRI-TB was defined as a MRI-TB that did not lead to disease upgrading when compared to SB.

Prostate lesions of patients were graded on mpMRI by a single fellowship-trained radiology group. All patients were imaged on one of two 3-T MRI systems: a GE Discovery 750 3.0 T (GE Healthcare, Waukesha, WI), 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 1 of these 2 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 FOV (18 cm) FSE T2 images of the prostate in the axial, sagittal and coronal planes; axial diffusion weighted images 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 serial postcontrast phases, temporal resolution <10 seconds); and a final large FOV pelvic post contrast T1 GRE Dixon (water reconstruction) series.

Examinations were interpreted and analyzed using DynaCAD (InVivo, Gainesville, FL). IV contrast employed: before September 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). All standard and MRI/ultrasound fusion-guided target biopsies were performed by a single fellowship trained urologist using the UroNav Fusion Biopsy System (UroNAV). MRI-TB of all lesions was done prior to the SB. Pathology was reviewed by a fellowship-trained genitourinary pathologist as part of a specialized genitourinary pathology service. Simple frequencies and percentages were reported for the analysis. The analysis was performed per lesion for purposes of calculating no upgrade rate. Mean prostate specific

antigen (PSA) and mean lesion volume were used as cutoff for the no upgrade rate analysis.

## RESULTS

One hundred and forty-eight patients were reviewed in this study and found to have a total of 255 lesions on MRI. [Tables 1](#) and [2](#)

**Table 1.** Characteristics of the study population stratified by ethnicity

Parameter	Value
All patients	148
Mean ± SD Age (range)	65.7 ± 7.0 (49-83)
Mean ± SD (ng/mL) PSA (range)	9.3 ± 8.8 (0.5-61.3)
Mean ± SD (mL) prostate volume (range)	57.5 ± 33.4 (15-195)
Mean ± SD (mo) from previous biopsy (range)	28.7 ± 26.2 (1-132)
Total number of lesions	255
Number of PIRADS 3 lesions (%)	136 (53.3%)
Number of PIRADS 4 lesions (%)	74 (29.0%)
Number of PIRADS 5 lesions (%)	37 (14.5%)
Final pathology = BENIGN (%)	113 (44.3%)
Final pathology = 3 + 3 (%)	36 (14.1%)
Final pathology = 3 + 4 (%)	47 (18.4%)
Final pathology = 4 + 3 (%)	19 (7.5%)
Final pathology = 4 + 4 (%)	9 (3.5%)
Final pathology = 4 + 5 (%)	9 (3.5%)
Final pathology = 5 + 4 (%)	1 (0.4%)
ETHNICITY = AFRICAN AMERICAN (%)	36 (24.3%)
Mean ± SD Age (Range)	64.5 ± 7.3 (49-81)
Mean ± SD (ng/mL) PSA (Range)	9.7 ± 5.6 (1.9-21.3)
Mean ± SD (mL) prostate volume (Range)	67.0 ± 42.8 (17-195)
Mean ± SD (mo) from previous biopsy (range)	28.2 ± 20.9 (7-73)
Total number of lesions	54
Number of PIRADS 3 lesions (%)	28 (51.9%)
Number of PIRADS 4 lesions (%)	18 (33.3%)
Number of PIRADS 5 lesions (%)	6 (11.1%)
Final Pathology = BENIGN (%)	19 (35.2%)
Final Pathology = 3 + 3 (%)	9 (16.7%)
Final Pathology = 3 + 4 (%)	10 (18.5%)
Final Pathology = 4 + 3 (%)	6 (11.1%)
Final Pathology = 4 + 4 (%)	2 (3.7%)
Final Pathology = 4 + 5 (%)	3 (5.6%)
Final Pathology = 5 + 4 (%)	0 (0.0%)
ETHNICITY = WHITE (%)	90 (60.8%)
Mean ± SD Age (range)	66.1 ± 6.9 (51-83)
Mean ± SD (ng/mL) PSA (range)	7.5 ± 6.1 (0.6-26.6)
Mean ± SD (mL) prostate volume (range)	57.5 ± 31.7 (15-180)
Mean ± SD (months) from previous biopsy (range)	30.1 ± 28.7 (1-130)
Total number of lesions	155
Number of PIRADS 3 lesions (%)	85 (54.8%)
Number of PIRADS 4 lesions (%)	42 (27.1%)
Number of PIRADS 5 lesions (%)	26 (16.8%)
Final pathology = BENIGN (%)	73 (47.1%)
Final pathology = 3 + 3 (%)	20 (12.9%)
Final pathology = 3 + 4 (%)	30 (19.4%)
Final pathology = 4 + 3 (%)	8 (5.2%)
Final pathology = 4 + 4 (%)	6 (3.9%)
Final pathology = 4 + 5 (%)	5 (3.2%)
Final pathology = 5 + 4 (%)	1 (0.6%)

**Table 2.** Characteristics of the study population stratified by the PI-RADS score of the lesions seen on magnetic resonance imaging of the prostate

Parameter	Value
PIRADS 3 LESIONS (%)	136 (53.3%)
Mean ± SD Age (range)	64.4 ± 7.1 (50-83)
Mean ± SD (ng/mL) PSA (range)	9.5 ± 8.1 (1.4-61.3)
Mean ± SD (mL) prostate volume (range)	61.1 ± 31.8 (15-195)
Mean ± SD (mo) from previous biopsy (range)	27.7 ± 25.8 (1-132)
Final pathology = BENIGN (%)	83 (61.0%)
Final pathology = 3 + 3 (%)	12 (8.8%)
Final pathology = 3 + 4 (%)	15 (11.0%)
Final pathology = 4 + 3 (%)	5 (3.7%)
Final pathology = 4 + 4 (%)	3 (2.2%)
Final pathology = 4 + 5 (%)	2 (1.5%)
Final pathology = 5 + 4 (%)	0
PIRADS 4 LESIONS (%)	74 (29.0%)
Mean ± SD Age (range)	64.7 ± 6.4 (50-81)
Mean ± SD (ng/mL) PSA (range)	6.2 ± 4.9 (0.6-26.6)
Mean ± SD (mL) prostate volume (range)	51.3 ± 25.6 (15-134)
Mean ± SD (mo) from previous biopsy (Range)	30 ± 28 (2-132)
Final pathology= BENIGN (%)	20 (27.0%)
Final pathology = 3 + 3 (%)	16 (21.6%)
Final pathology = 3 + 4 (%)	19 (25.7%)
Final pathology = 4 + 3 (%)	8 (10.8%)
Final pathology = 4 + 4 (%)	5 (6.8%)
Final pathology = 4 + 5 (%)	3 (4.1%)
Final pathology = 5 + 4 (%)	0
PIRADS 5 LESIONS (%)	37 (14.5%)
Mean ± SD Age (Range)	66.5 ± 8.8 (49-83)
Mean ± SD (ng/mL) PSA (Range)	14.6 ± 13.3 (1.3-61.3)
Mean ± SD (mL) prostate volume (range)	59.1 ± 32.7 (26.3-180)
Mean ± SD (mo) from previous biopsy (range)	29.0 ± 27.9 (1-120)
Final pathology = BENIGN (%)	4 (10.8%)
Final pathology = 3 + 3 (%)	6 (16.2%)
Final pathology = 3 + 4 (%)	13 (35.1%)
Final pathology = 4 + 3 (%)	7 (18.9%)
Final pathology = 4 + 4 (%)	1 (2.7%)
Final pathology = 4 + 5 (%)	4 (10.8%)
Final pathology = 5 + 4 (%)	1 (2.7%)

list patient characteristics grouped by ethnicity and PI-RADS scoring. The number of all lesions was 255 (any lesion seen on

MRI). There were 136 PI-RADS 3 lesions, 74 PI-RADS 4 lesions, and 37 PI-RADS 5 lesions (number of lesions assigned PI-RADS 3 and higher = 247). Repeat biopsy of patients with 141 lesions led to cancer upgrade when compared with the initial diagnostic biopsy (55.3%). Of these, patients with 104 lesions were upgraded by the MRI-TB (40.8%), and 87 lesions were upgraded by the SB (34.1%). There were a total of 33 lesions (12.9%) upgraded on both the MRI-TB and SB (8 PI-RADS 3, 14 PI-RADS 4, and 11 PI-RADS 5 lesions).

The MRI-TB had a NU rate of 26.2% for all lesions. On subanalysis, there were a total of 136 PI-RADS 3 lesions, of which 56 were in patients who were upgraded after the new combined (MRI-TB + SB) biopsy (41.2%). Of these, 34 were upgraded by the MRI-TB, and 39 were upgraded by the SB. The NU rate of PI-RADS 3 MRI-TBs is 39.3%.

There were a total of 74 PI-RADS 4 lesions, of which 52 were in patients who were upgraded after the new combined (MRI-TB + SB) biopsy (70.3%). Of these lesions, 41 were upgraded by the MRI-TB and 31 were in patients who were upgraded by the SB. Of the 31 lesions in patients upgraded by the SB, 20 were also upgraded by the MRI-TB. The NU rate of PI-RADS 4 MRI-TBs is 21.2%.

There were a total of 37 PI-RADS 5 lesions, of which 29 were in patients upgraded after the new combined (MRI-TB + SB) biopsy (78.4%). Of these, 28 lesions were upgraded by the MRI-TB and 13 were in patients who upgraded by the SB. Of the 13 lesions in patients who upgraded by the SB, 2 of them were not also upgraded by the MRI-TB. In 1 of these 2 lesions, however, the patient had a second, PI-RADS 3 lesion that was upgraded by the MRI-TB. The NU rate of PI-RADS 5 MRI-TBs is 3.4%. Twenty-five of the 28 lesions upgraded by the MRI-TB had a Gleason score ≥7. Of the cancers not upgraded by the SB, 82.4% (14/17) had a Gleason score ≥7. Table 3 compares MRI-TB vs SB cancer upgrade rates in each PI-RADS lesion groups.

Data on lesion size were limited and reported for only 70 of the 255 total lesions. The multivariate analysis presented in Table 4 shows that the NU rates for lesions ≤10.5 mm are 57.1%, compared to 13.6% in lesions >10.5 mm. For PI-RADS 5 lesions, however, the NU rate of the MRI-TB was low, regardless of size.

## DISCUSSION

Our results suggest that the MRI-TB alone may be sufficient for patients with a PI-RADS 5 lesion on MRI, without the need for a SB. SBs are currently recommended in conjunction with MRI-TB in all men with a clinically significant prostate lesion. However, the need for the SB in addition to MRI-TB has been called into question in recent years for many reasons. First, MRI-TB is superior to

**Table 3.** Rates of Gleason grade upgrade by systematic biopsy and MRI targeted biopsy stratified by PI-RADS score

	Number of Patients	Number of Lesions	Same Grade Detected by New Combined Biopsy	Downgrade in New Combined biopsy	Upgraded by MRI-targeted Lesion Biopsy	Upgraded by Standard 12-core Biopsy
PI-RADS 3	95	136	69 50.7%	12 8.8%	34 25.0% 39.3% NU RATE	39 28.7%
PI-RADS 4	62	74	19 25.7%	3 4.1%	41 55.4% 21.2% NU RATE	31 41.9%
PI-RADS 5	36	37	5 13.5%	0 0.0%	28 75.7% 3.4% NU RATE	13 35.1%

NU, no upgrade.

**Table 4.** Upgrade rates by systematics and magnetic resonance imaging targeted biopsies stratified by patient's race, PSA, and lesion volume

	Number of Patients	Number of Lesions	Same Grade Detected by New Combined Biopsy	Downgrade in New Combined Biopsy	Upgrade in New Combined Biopsy	Upgraded by MRI-targeted Lesion Biopsy		Upgraded by Standard 12-core Biopsy
ALL LESIONS	148	255	97 38.0%	15 5.9%	141 55.3%	104 40.8%	26.2% NU RATE	87 34.1%
WHITE	90	155	60 38.7%	11 7.1%	84 54.2%	61 39.4%	27.4% NU RATE	50 32.3%
PI-RADS 3	57	85	43 50.6%	10 11.8%	32 37.6%	19 22.4%	40.6% NU RATE	22 25.9%
PI-RADS 4	35	42	13 31.0%	1 2.4%	28 66.7%	20 47.6%	28.6% NU RATE	17 40.5%
PI-RADS 5	26	26	4 15.4%	0 0.0%	22 84.6%	22 84.6%	0.0% NU RATE	9 34.6%
AA	36	54	16 29.6%	4 7.4%	34 63.0%	23 42.6%	32.4% NU RATE	25 46.3%
PI-RADS 3	21	28	13 46.4%	2 7.1%	13 46.4%	7 25.0%	46.2% NU RATE	10 35.7%
PI-RADS 4	17	18	1 5.6%	2 11.1%	15 83.3%	13 72.2%	13.3% NU RATE	10 55.6%
PI-RADS 5	6	6	2 33.3%	0 0.0%	4 66.7%	2 33.3%	50.0% NU RATE	3 50.0%
PSA≤8.5	39	65	26 40.0%	2 3.1%	37 56.9%	27 41.5%	27.0% NU RATE	21 32.3%
PI-RADS 3	23	31	17 54.8%	1 3.2%	13 41.9%	7 22.6%	46.2% NU RATE	10 32.3%
PI-RADS 4	17	23	7 30.4%	1 4.3%	15 65.2%	12 52.2%	20.0% NU RATE	6 26.1%
PI-RADS 5	9	10	2 20.0%	0 0.0%	8 80.0%	8 80.0%	0.0% NU RATE	4 40.0%
PSA>8.5	14	21	8 38.1%	0 0.0%	13 61.9%	8 38.1%	38.5% NU RATE	11 52.4%
PI-RADS 3	8	11	4 36.4%	0 0.0%	7 63.6%	4 36.4%	42.9% NU RATE	5 45.5%
PI-RADS 4	4	4	2 50.0%	0 0.0%	2 50.0%	1 25.0%	50.0% NU RATE	2 50.0%
PI-RADS 5	6	6	2 33.3%	0 0.0%	4 66.7%	3 50.0%	25.0% NU RATE	4 66.7%
LOI ≤10.5 mm	37	41	21 51.2%	6 14.6%	14 34.1%	6 14.6%	57.1% NU RATE	10 24.4%
PI-RADS 3	24	28	17 60.7%	5 17.9%	6 21.4%	1 3.6%	83.3% NU RATE	5 17.9%
PI-RADS 4	12	12	4 33.3%	1 8.3%	7 58.3%	4 33.3%	42.9% NU RATE	4 33.3%
PI-RADS 5	1	1	0 0.0%	0 0.0%	1 100.0%	1 100.0%	0.0% NU RATE	1 100.0%
LOI > 10.5 mm	28	29	7 24.1%	0 0.0%	22 75.9%	19 65.5%	13.6% NU RATE	10 34.5%
PI-RADS 3	13	14	7 50.0%	0 0.0%	7 50.0%	6 42.9%	14.3% NU RATE	4 28.6%
PI-RADS 4	8	8	0 0.0%	0 0.0%	8 100.0%	6 75.0%	25.0% NU RATE	5 62.5%
PI-RADS 5	7	7	0 0.0%	0 0.0%	7 100.0%	7 100.0%	0.0% NU RATE	1 14.3%

NU, no upgrade.

SB as it detects significant cancers while minimizing the number of cores needed to make the diagnosis. Second, the risk of rectal bleeding and infection increases with increasing numbers of cores sampled.<sup>8,9</sup> Also, the combination of the SB with MRI-TB has also been reported to lead to overtreatment of prostate cancer. For every 1 additional clinically significant cancer diagnosed by adding SB to MRI-TB, another 17 low-risk cancers would be diagnosed.<sup>7</sup>

Many of these low-risk lesions will never become clinically significant to require intervention during the patient's lifetime.<sup>10</sup> Our study supports the need for systemic biopsy in PI-RADS 3 and 4 lesions to accurately manage patient's prostate cancer. We also show that omitting SB in patients with a PI-RAD 5 lesion on mpMRI may be possible because MRI-TB had a low NU rate and provided the grading information needed to treat these patients.

The NU rate for the MRI-TB in a PI-RADS 5 lesion is meager.<sup>11</sup> In our study, 28 of the 29 PI-RADS 5 lesions upgraded on the new combined biopsy were upgraded by the MRI-TB, compared to only 13 by the SB alone. It, therefore, appears that the MRI-TB has its most significant use in patients with a PI-RADS 5 lesion. This pattern was similar with PI-RADS 4 lesions, in which the MRI-TB upgraded more lesions than the SB. The MRI-TB and the SB upgraded the same number of PI-RADS 3 lesions. There was also not much overlap in the lesions that were upgraded between the 2, meaning that they have low individual upgrade rates and the combined biopsy would provide higher detection rates in PI-RADS 3 lesions.

The MRI-TB NU rate for lesions  $\leq 10.5$  mm in size is 57.1%, which is a high rate. However, on subanalysis, looking at PI-RADS 5 only lesions  $\leq 10.5$  mm, the NU rate was 0%, meaning all lesions upgraded by the SB were also upgraded by the MRI-TB, and that MRI-TB could still be utilized as the only modality of prostate biopsy in PI-RADS 5 lesions that are  $\leq 10.5$  mm

This study has limitations; only patients with lesions found in their mpMRI were selected for this study. This is an impending selection bias for this study. A study performed in 2016 reviewing cancer detection rates in men with negative prebiopsy mpMRI results; however, found that a negative prebiopsy MRI had a negative predictive value of 98% for Gleason score  $\geq 7$  cancer.<sup>12</sup> Hence, including patients with negative prebiopsy MRIs would not have significantly changed the outcome of this study. Also, comparing the previous SB alone to the new combined (MRI-TB + SB) biopsy created a dilemma for the design of this study, due to the inability for lesion-to-lesion comparison in patients with multiple lesions on mpMRI. Grouping the data by patient resulted in nonupgraded lesions that were forcibly counted as upgraded because the patient had another lesion that was upgraded. We made the decision to group the data by lesion rather than by patient. An upgraded lesion is a lesion with a higher GS from any location on the previous SB.

## CONCLUSION

Men with a PI-RADS 5 lesion may have a similar cancer upgrade rate with targeted biopsy of the lesion alone without combining with SB. If validated, these results call for using MRI-TB only in managing patients with PI-RADS 5 lesions, which promises to reduce the numbers of cores sampled to make the diagnosis, minimizing bleeding, and infection risks.

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