Validation of dominant and secondary sequence utilization in PI-RADS v2 for classifying prostatic lesions

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Introduction: *To assess the secondary sequence rule in The Prostate Imaging Reporting Data System (PI-RADS) version 2 by comparing the detection of Grade group 1+ (GG1+) and 2+ (GG2+) cancers in PI-RADS 3, an upgraded PI-RADS 4, and true (non-upgraded) PI-RADS 4 targets.*

Materials and methods: *We analyzed a total of 589 lesions scored as PI-RADS 3 or 4 obtained from 434 men who underwent mpMRI-US fusion biopsy from September 2015 to November 2017 for evaluation of GG1+ and GG2+ prostate cancer. PI-RADS 4 lesions were differentiated into those that were "upgraded" to PI-RADS 4 based on the secondary sequence and those that were "true" PI-RADS 4 based on the dominant sequence.*

Results: *The odds of detecting a GG2+ cancer was significantly higher for an upgraded 4 (peripheral zone (PZ): OR 5.06, 95%CI 2.04-12.54, p < 0.001, transitional zone (TZ): OR 3.08, 95%CI 1.04-9.08, p = 0.042) and true 4 (PZ: OR 5.82, 95%CI 3.10-10.94, p < 0.0001, TZ: OR 2.43, 95%CI 1.14-5.18, p = 0.022) lesions compared to PI-RADS 3 lesions. Additionally, we found no difference in the odds of detecting a GG2+ prostate cancer between a true PI-RADS 4 (OR 1.15, 95%CI 0.49-2.71 p = 0.746) and upgraded 4 (referent) in the PZ. Similar non-significance was noted between true 4 (OR 0.79, 95%CI 0.26-2.38 p = 0.674) and upgraded 4 lesions in the TZ for detection of GG2+ cancers.*

Conclusions: *Upgraded PI-RADS 4 and true 4 targets have a higher odds of detecting GG1+ and GG2+ compared to PI-RADS 3 in the PZ and TZ. Our findings validate the revised scoring system for PI-RADS.*

Key Words: multiparametric MRI, prostate cancer, upgraded 4, PI-RADS

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Introduction

Multiparametric magnetic resonance imaging (mpMRI) of the prostate has transpired as a preeminent method to localize and characterize cancer within the prostate

gland. The Prostate Imaging Reporting Data System (PI-RADS) has superseded other methodologies for interpretation of cancer risk in a locus. However, the original version of PI-RADS lacked clear guidelines on derivation of overall PI-RADS risk score.[1] Due to the aforementioned shortfall, numerous studies have explored various paradigms such as cumulative sum score[2-4] and 5-point scale[5-8] to obtain a MRI based risk assessment. This heterogeneity in overall scoring has been well noted in a meta-analysis analyzing the sensitivity and specificity of PI-RADS.[9] To address the lack of homogeneity and to standardize the reporting of PI-RADS scoring, in 2015, a version 2 (PI-RADSv2) was released.[10] In version 2, a 5-point risk stratification system is employed based on a dominant sequence rule, which gives priority to one particular sequence rather than weighting each sequence equally. The sequence that is used as the dominant sequence depends on the location of the tumor, with diffusion weighted imaging (DWI) being the dominant sequence for peripheral zone (PZ) targets, and T2 imaging being the dominant sequence for transitional zone (TZ) targets.[11] However, for targets that are indeterminate (PI-RADS 3 on dominant sequence) a secondary sequence is utilized to determine whether the lesion should be upgraded to a PI-RADS score of 4 or remain indeterminate as a PI-RADS 3. In the PZ a positive diffusion contrast enhancement (DCE) upgrades the score to a 4, while in the TZ, a score of 5 on the DWI upgrades the score to a 4.

In this study, we aim to validate the secondary sequence scoring system proposed in the version 2 of PI-RADS scoring among a cohort of men undergoing biopsy of the prostate for evaluation of prostate cancer.

Materials and methods

Study cohort

The data used for this study was extracted from a consecutive series of men who underwent an mpMRI-ultrasound fusion biopsy for the evaluation of an elevated PSA level or positive DRE on clinical exam between September 2015 and November 2017 at the Department of Urology, University of Miami. For this study, we selected all targets that were scored according to PI-RADSv2 guidelines as PI-RADS 3 or 4. A differentiation was made between a lesion which scored as PI-RADS 4 (true 4) on primary sequence (i.e DWI 4 in the PZ, T2I 4 in TZ) and those that were upgraded (upgraded 4) using a secondary sequence (i.e. DWI 3 & DCE+ in the PZ and T2I 3 & DWI 5 in the TZ). Volume of target lesions were derived applying the ellipsoid volume formula to the three MRI dimensions, length, width and extent, measured in centimeters. A minimum of two cores was obtained from each mp-MRI suspicious target. Additionally, every patient underwent a 12-needle core trans-rectal ultrasound (TRUS) guided extended template biopsy. Histopathological examination of biopsy specimens was performed according to the established standards at the University of Miami. Cores were classified as follows: Grade group 1 (GG1) if Gleason score 6, GG2 if Gleason score 3+4=7, GG3 if Gleason score 4+3=7, GG4 if Gleason score 8, and GG5 if Gleason score 9 or 10. Significant prostate cancer was defined as Grade Group 2 or higher (GG2+) cancer. Any cancer was defined as Grade Group 1 or higher (GG1+). All radiologists were fellowship trained in abdominal imaging with more than 10 years of experience. Informed consent was waived, due to the retrospective nature of this IRB approved study.

Statistical analysis

Patient characteristics were tabulated using descriptive statistics. Analysis of GG1+ and GG2+ prostate cancer was conducted separately for targets in TZ and PZ. Since patients might have multiple lesions, we needed to take into account the within-patient correlation in our analysis. We fitted generalized estimating equation (GEE) models with logit link for correlated binary outcome data to assess the significance of PI-RADS in predicting GG1+ and GG2+ cancer. All models adjusted for history of a previous negative biopsy (PNB), patient age at MRI and PSA (< 4, 4 to 10, > 10). Interactions between PNB×PI-RADS, age×PI-RADS, and PSA×PI-RADS were tested one at a time. However, for TZ lesions, due to sparseness of the data, interaction between PNB×PI-RADS could not be tested while modelling for GG2+ cancers. Likewise, while modelling for GG1+ cancers in the TZ, interactions between PNB×PI-RADS and PSA×PI-RADS could not be tested. We reported for each outcome an adjusted odds ratio (OR) with 95% confidence interval (95%CI) and p value for likelihood of GG1+ or GG2+ in upgraded PI-RADS 4 and in true 4 compared to PI-RADS 3, as well as true PI-RADS 4 compared to upgraded PI-RADS 4. Statistical analyses were performed by SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

A total of 586 men underwent mpMRI-US fusion biopsy during the study timeframe for evaluation of prostate cancer, and 434 patients had at least one lesion which was scored as PI-RADS 3 or 4. Among them, 295 (68%) men were biopsy naïve and 139 (34%) had a history of a prior negative biopsy. The mean age was 65.3 ± 8.4 years. Demographics and clinical characteristics of the cohort is represented in Table 1.

TABLE 1. **Patient demographics and characteristics of the target lesions**

	n (%)
Total patients	434 (100.0)
Age (mean ± SD)	65.3 ± 8.4
PSA (mean ± SD, n = 429)	8.2 ± 6.7
< 4	56 (13.1)
4 to 10	279 (65.0)
> 10	94 (21.9)
Prior negative biopsy	
No	295 (68.0)
Yes	139 (34.0)
Digital rectal exam (n = 400)	
Normal	372 (93.0)
Abnormal	28 (7.0)
Prostate volume (n=387)	
< 40	120 (28.2)
40-80	211 (49.4)
81+	95 (22.3)
Total target lesions analyzed	**589 (100.0)**
PI-RADS	
3	355 (60.3)
Upgraded 4	61 (10.4)
True 4	173 (29.3)
Location	
Transitional zone	230 (39.0)
Peripheral zone	359 (61.0)
Lesion volume (cm^3), n	573
Mean (standard deviation)	5.42 (5.37)
Median (range)	3.92 (0.10-44.60)

Out of 589 targets analyzed, 355 (60.3%) were PI-RADS 3, 61 (10.4%) an upgraded PI-RADS 4, and 173 (29.3%) a true PI-RADS 4. By location, 359 (61%) targets were in the PZ (34.5% PI-RADS 3, 18.5% true 4, and 8% upgraded 4) and 230 (39%) in the TZ (25.8% PI-RADS 3, 10.9% true 4, and 2.4% upgraded 4). The detection rates by Gleason grade group by PI-RADS 3, upgraded 4 and true 4 lesions in the PZ and TZ are reported in Table 2.

The odds of detecting GG2+ cancers was significantly higher in upgraded PI-RADS 4 (OR 5.06, 95%CI 2.04-12.54, p < .001) and true PI-RADS 4 (OR5.82, 95%CI 3.10-10.94, p < 0.0001) compared to PI-RADS 3, Table 3. Additionally, the odds of detecting GG1+ was also significantly higher in upgraded PI-RADS 4 (OR 5.18, 95%CI 2.30-11.68, p < 0.0001) and true PI-RADS 4 (OR 5.16, 95%CI 3.01-8.86, p < 0.0001), relative to PI-RADS 3. However, no difference in likehood of detecting GG2+ (OR 1.15, 95%CI 0.49-2.71, p = 0.746) and GG1+ (OR 1.00, 95%CI 0.44-2.27, p = 0.992) cancers was found when true 4 targets were compared against upgraded PI-RADS 4 targets in the PZ.

Similarly, in the TZ odds of detection of GG2+ cancer was significantly higher between upgraded 4 (OR 3.08, 95%CI 1.04-9.08, p = 0.042) and true 4 target (OR 2.43, 95%CI 1.15-5.18, p = 0.022) when compared to PI-RADS 3. Moreover, odds of detecting GG1+ was also significantly higher in upgraded PI-RADS 4 (OR 6.01, 95%CI 1.72-21.03, p = 0.005) and true PI-RADS 4 (OR 2.51, 95%CI 1.40-4.52, p = 0.002) compared to PI-RADS 3 target. Similar to PZ findings, there was no difference in likelihood of detecting GG2+ (OR 0.79, 95%CI 0.26-2.38, p = 0.674) and GG1+ (OR 0.42, 95%CI 0.12-1.50, p = 0.182) cancers when true 4 lesions were compared to upgraded 4 lesions.

TABLE 2. **Association between PI-RADS and outcome by location of target lesions (n = 589 target lesions from 434 patients)**

	Total		**Benign**		**GG1**		**GG2**		**GG3**		**GG4**		**GG5**		**GG1+**		**GG2+**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Total lesions	589	100.0	376	63.8	78	13.2	79	13.4	28	4.8	13	2.2	15	2.5	213	36.2	135	22.9
PZ	**359**	**61.0**	**227**	**63.2**	**44**	**12.3**	**50**	**13.9**	**18**	**5.0**	**10**	**2.8**	**10**	**2.8**	**132**	**36.8**	**88**	**24.5**
PIRADS 3	203	34.5	158	77.8	22	10.8	16	7.9	3	1.5	2	1.0	2	1.0	45	22.2	23	11.3
True 4	109	18.5	44	40.4	15	13.8	25	22.9	11	10.1	8	7.3	6	5.5	65	59.6	50	45.9
Upgraded 4	47	8.0	25	53.2	7	14.9	9	19.1	4	8.5	-	-	2	4.3	22	46.8	15	31.9
TZ	**230**	**39.0**	**149**	**64.8**	**34**	**14.8**	**29**	**12.6**	**10**	**4.3**	**3**	**1.3**	**5**	**2.2**	**81**	**35.2**	**47**	**20.4**
PIRADS 3	152	25.8	113	74.3	16	10.5	16	10.5	2	1.3	1	0.7	4	2.6	39	25.7	23	15.1
True 4	64	10.9	31	48.4	14	21.9	9	14.1	8	12.5	2	3.1	-	-	33	51.6	19	29.7
Upgraded 4	14	2.4	5	35.7	4	28.6	4	28.6	-	-	-	-	1	7.1	9	64.3	5	35.7

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TABLE 3. **Estimated odds ratios of GG1+ and GG2+ cancer associated to PI-RADS by location of target lesion**

	GG1+		GG2+	
	OR (95%CI)	**p value**	**OR (95%CI)**	**p value**
PI-RADS in PZ (n = 348)				
Upgraded 4 versus 3 (ref)	5.18 (2.30-11.68)	< .0001	5.06 (2.0-12.54)	< .001
True 4 versus 3 (ref)	5.16 (3.01-8.86)	<. 0001	5.82 (3.10-10.94)	< .0001
True 4 versus upgraded 4 (ref)	1.00 (0.44-2.27)	0.992	1.15 (0.49-2.71)	0.746
PI-RADS in TZ (n = 219)				
Upgraded 4 versus 3 (ref)	6.01 (1.72-21.03)	0.005	3.08 (1.04-9.08)	0.042
True 4 versus 3 (ref)	2.51 (1.40-4.52)	0.002	2.43 (1.14-5.18)	0.022
True 4 versus upgraded 4 (ref)	0.42 (0.12-1.50)	0.182	0.79 (0.26-2.38)	0.674

Analysis was performed separately for PZ and TZ target lesions. Accounting for within-patient correlation, we assume exchangeable correlation structure of data (same correlation between any two responses within a patient) and fit generalized estimating equation (GEE) models for correlated binary outcome data. For each outcome, GG1+ and GG2+, models included PI-RADS, indicator of previous negative biopsy, patient age at biopsy, PSA (< 4, 4 to 10, > 10), and lesion volume (cm^3). A total of 11 PZ and 11 TZ target lesions were excluded due to missing PSA or lesion volume.

Discussion

In this study, we validate the "secondary sequence" rule in PI-RADS v2, showing that upgraded PI-RADS 4 targets in the PZ (DWI 3/ DCE+) and in the TZ (T2 3/ DWI 5) were more likely to harbor GG1+ and GG2+ cancers compared to PI-RADS 3 (DWI 3/ DWI -) targets, but had similar detection rates to true PI-RADS 4 targets (DWI 4/T2 4).

Multi-parametric MRI is popularly being employed as a diagnostic tool for prostate cancer detection and localization. The heterogeneity in deriving overall PI-RADS scores according to version 1 has been elucidated in a meta-analysis by Hamoen et al.[9] As it points out, the two most common methods of obtaining the final PI-RADS score were semi-objective cumulative score approach (CS) and a subjective 5-point Likert scoring method. A study comparing the two methods suggested CS is appropriate for less experienced readers and conversely noted that experienced radiologists performed better on Likert based scoring.[12] However, the assumption that all sequences contributed equally in CS system was shown to be unlikely with single sequences like DWI outperforming T2 and DCE in the PZ and T2 outperforming DWI and DCE in the TZ.[12,13] This forms the foundation for the utilization of a dominant sequence for overall risk stratification in PI-RADS v2. A recent meta-analysis of studies employing PI-RADS v2 showed a pooled sensitivity of 85% and specificity of 71%.[14] Compared to PI-RADS v1, PI-RADS v2 indeed had a better sensitivity (85% versus 82%), however underachieved in specificity (71% versus 82%).[9,14]

Two previous studies have ventured to assess the "dominant sequence rule" and value of a secondary sequence as a differentiator of indeterminate lesions in the PZ as put forth by PI-RADS v2 scoring guidelines.[15,16] In the first study by Greer et al lesions scored as indeterminate on DWI with a positive DCE had a higher detection rate (67.8% versus 40%, $p < 0.02$) than DCE negative lesions, supporting the secondary sequence rule in PI-RADS v2. However, the authors found that for PZ lesions, positivity on DCE doubled their odds of being cancerous (OR 2.0 95% CI 1.08-3.7; $p = 0.02$), regardless of the PI-RADS score. However, this estimate was based on all lesions, and is driven primarily by lesions that are PI-RADS 3 or higher. For PI-RADS 2 lesions, the incremental gain in the detection of cancer was minimal. The authors also noted that 63.2% (129/204) of false positive lesions had a positive DCE. Therefore, given the minimal gain in incremental cancer detection and the increased risk of false positives, the value of DCE for PI-RAD 2 lesions may be minimal. While the study found a higher cancer detection rate in PI-RADS 4 and 5 lesions with positive DCE findings compared to those without, this may not have any impact on decision making, as PI-RADS 4 and 5 lesions have a high risk of cancer, and warrant a biopsy regardless of DCE positivity. These findings may lend support to the reasoning behind the restricted use of DCE in PI-RADS v2 to only PI-RADS 3 lesions. Finally, the radiologists involved in the above-mentioned study are considered to be experts in the interpretation of mp-MRI of the prostate. In case of a novice reader, an increased incorporation of DCE may

add more false positives. However, further research will be needed to truly understand the benefits and risks of using DCE in addition to other sequences for assigning risk in the PZ .

Similar to our results, Druskin et al noted higher rates of GG2 cancer detection in upgraded 4 (21%) and a true 4 lesions (36.5%) in contrast to PI-RADS 3 lesions (8.9%) in the PZ.[16] Unlike our study, a significant difference was noted between all three groups, suggesting there is indeed a difference in detection rates between a upgraded 4 and a true 4 lesion. This finding would call for a subclassification of PI-RADS 4 lesions into 4a and 4b lesions. However, on subsequent sub-group analysis they have noted that these differences were driven by a patient's biopsy status. In biopsy naïve patients, there was a significant increase in cancer detection between upgraded 4 and PI-RADS 3 ($p = 0.001$) lesions but not between upgraded 4 and true 4 lesions ($p = 0.9$). Alternatively, in patients who have a previous negative biopsy, the results were opposite, with a significant increase in cancer detection being noted between upgraded 4 and true 4 lesions ($p = 0.001$) and not between upgraded 4 and PI-RADS 3 lesions. As acknowledged in the study, this difference and the rationale to stratify results by biopsy status might have been driven by the fact that patients with a history of prior negative biopsy have a lower pre-biopsy probability of harboring cancer. While we agree that prior negative biopsy is an independent predictor of cancer detection, we did not find a significant interaction between biopsy status and PI-RADS score on the likelihood of detecting cancer. This would suggest that the impact of the PI-RADS score on cancer detection does not vary by the biopsy status. Clearly, given the discrepancy in results between this study and our own, further research on this topic will be imperative.

In general, TZ cancers can be more difficult to detected on mp-MRI, especially for the novice reader. Due to the hyperplastic growth that occurs in this region, a challenge can be distinguishing between real cancers and benign nodules that mimic prostate cancer. The functional sequences like DCE and DWI that provide most of the predictive power in the PZ may not be as helpful in the TZ due to false positives from benign hyperplastic nodules that also display contrast enhancement and restricted diffusion.[17,18] In PI-RADS v2 the role of functional sequences in the TZ has clearly been de-emphasized and T2 has become the dominant preferred sequence in the TZ. However, the role of the functional sequences in the TZ remains controversial.[19-21] While some studies have suggested that T2 outperforms DWI in the TZ,[13] others have suggested differently and have shown that DCE may be helpful as well.[15] We contend that T2 was chosen as the dominant sequence as a default to reduce false positives in the TZ, which can be a problem for the novice mpMRI reader. However, we believe as do others, that the functional sequences do assist in cancer detection even in the TZ. Regardless, this topic necessitates further validation. To our knowledge, ours is the first study to validate the importance of DWI as a secondary sequence in upgrading an indifferentiable lesion on a dominant sequence in the TZ to detect GG1+ and GG2+ cancers.

Our study had several limitations. First is the retrospective nature of our study cohort. Moreover, scoring was done by three different radiologists and may have some inter-reader variability. Also targeted biopsy was conducted by three different providers with varying level of expertise. Nevertheless, these limitations actually help to generalize our findings to real life clinical practice scenarios where multiple providers are involved in prostate MRI interpretation and fusion biopsy of the prostate.

Conclusion

Our findings validate the revised scoring system for PI-RADS. Indeterminate lesions on primary sequence with a positive secondary sequence have an increased risk of cancer and should be upgraded to PI-RADS 4. Furthermore, we found no difference in the detection of prostate cancer between targets that were upgraded to PI-RADS 4 (upgraded 4) and those that were reported as PI-RADS 4 (true 4) in the PZ and TZ. These findings provide further evidence validating the secondary sequence rule for indeterminate targets in PI-RADS version 2. □

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