Research Article

Temporal changes of PIRADS scoring by radiologists and correlation to radical prostatectomy pathological outcomes

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ABSTRACT

Purpose: To assess temporal improvement of prostate image reporting and data system (PIRADS) 3-5 lesion correlation to histopathologic findings from radical prostatectomy (RP) in prostate cancer (PCa).

Materials and methods: A total of 1481 patients who underwent RP for biopsy-proven PCa between 2015 and 2019 were divided into 14 groups of 100 sequential readings for the evaluation of histopathologic correlation with PIRADS readings. Temporal trends of PIRADS distribution and predictive performance for RP pathology were evaluated to assess underlying changes in prostate magnetic resonance imaging (MRI) interpretation by radiologists.

Results: PIRADS 4-5 lesions were significantly correlated with the increasing rates of Gleason Group (GG) upgrade (p = 0.044) and decreasing rate of GG downgrade (p = 0.016) over time. PIRADS ≥3 lesions read after median 2 years of experience were shown to independently predict intermediate–high-risk (GG ≥3) PCa (odds ratio 2.93, 95% confidence interval 1.00–8.54; P = 0.049) in RP pathology. Preoperative GG ≥3 biopsy lesions with PIRADS 4-5 lesions were significantly more susceptible to GG upgrade (P = 0.035) and GG ≥ 4 RP pathology (p = 0.003) in experienced reads, in contrast to insignificant findings in early readings (p = 0.588 and 0.248, respectively).

Conclusion: Preoperative MRI reports matched with RP pathology suggest an improved prediction of adverse pathology in PIRADS 3-5 lesions over time, suggesting a temporal change in PIRADS interpretation and predictive accuracy. Institutions with low volume experience should use caution in solely relying on MRI for predicting tumor characteristics. Future prospective trials and larger scale assessments are required to further validate our results.

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1. Introduction

With the introduction of the prostate imaging reporting and data system (PIRADS) guidelines in 2012 and its revision in 2015, multiparametric MRI (mpMRI) has gained widespread acceptance as a standard method of diagnosis for suspicion of clinically significant prostate cancer (PCa), 1–4 with the rate of prebiopsy mpMRI rates increasing from 3.8% in 2011–2012 to 89.4% in 2015–2016. 5 Additional technical changes and clarifications for interpretation criteria were set forth in the PIRADS version 2.1 in September 2019. 6 The PRECISION trial showed that in biopsy-naïve patients, PIRADS evaluation with mpMRI could assist 28% to avoid unnecessary biopsy, as well as increase detection of Gleason Grade (GG) ≥2 cancer when MRI-targeted biopsy was used for PIRADS 3-5 lesions (38% vs. 26% with standard biopsy, P = 0.005). 7 This was in line with previous findings from the PROMIS trial which was published prior to the PIRADS system, where mpMRI allowed 27% patients to avoid biopsy with 5% fewer clinically insignificant cancer detected. 8

Although promising, whether these results can be reproduced in actual practice settings where radiologist experience with the PIRADS system requires further validation. Interobserver agreement showed considerable variability across radiologists, with significant cancer detection rates for PIRADS 3, 4, and 5 lesions in actual practice settings where radiologist experience with the PIRADS system requires further validation. Interobserver agreement showed considerable variability across radiologists, with significant cancer detection rates for PIRADS 3, 4, and 5 lesions...
being 3–27%, 23–65%, and 40–80%, respectively. Novice readings have unreliable PIRADS diagnostic accuracy, with significant intra-reader improvement over time. Management of equivocal PIRADS 3 lesions remains to be elucidated, with conflicting results in PCa detection reported for this ‘gray zone’ in PIRADS reading, with even more limited literature accessing correlation to radical prostatectomy (RP) pathology, complicating decisions for active surveillance or early intervention. In this study, we evaluated the changes of PIRADS 3-5 histopathological outcomes over time based on RP specimens.

2. Materials and methods

This was an institutional review board approved (no. SNUBH-B-2003/600-108), single-center retrospective study comprised of 1481 men who underwent RP (open or robotic) from February 2015 to December 2019. All patients were biopsy-proven for PCa and were routinely checked for cancer extent and clinical staging through mpMRI prior to surgery, with all available MRI reassessed by two experienced uro-radiologist, each with over 15 and 20 years of experience. Any readings done with inadequate MRI protocols (e.g., no ADC or DWI), incomplete patient data, or PIRADS assessment were excluded for analysis. For temporal trend and histopathological correlation analysis, patients were sequentially divided into 14 groups of 100 men. Groups 1–2 and 6–7 were further compared to assess changes in diagnostic accuracy for intermediate to high-risk PCa, defined as any \( \geq GG4 \) (GS 8 (4 + 4)) and/or \( \geq pT3a \) (extending to or outside the prostate capsule). Median interval between groups 1–2 and 6–7 was 24 months.

All reviewed data were collected from our prospectively maintained database. Biopsy and RP specimen were reviewed by our uropathologist according to standard pathological procedures using the modified definition of the 2005 International Society of Urological Pathology Consensus conference. Tumor stage and grading were evaluated according to the 2010 American Joint Committee on Cancer/Union Internationale Contre le Cancer tumor, node, metastasis (TNM) classification. Chi-squared test for categorical variables and an independent t-test for continuous variables were used for the statistical analysis of clinicopathological variables. One-way analysis of variance (ANOVA) was used to assess inter-group differences, and linear-by-linear association (Mantel-Haenszel) test was performed for overall trend. Statistical analysis was performed with IBM SPSS software package version 22.0 (Statistical Package for Social Sciences™, Chicago, IL, USA). A 2-tailed \( P \)-value \( < 0.05 \) was considered significant for all analyses.

3. Results

3.1. Clinical characteristics and perioperative outcomes

Mean and median age of all patients included in the study were 66.7 and 67.0, respectively (Table 1). Mean prostate-specific antigen (PSA), PSA density (PSAD), and prostate volume (PV) were 14.41 ng/ml, 36.2 cc, and 0.43 ng/ml/cc for all men. Preoperative digital rectal examination was positive in 17.6% overall. Bioysy GS were similarly distributed, with 18.7% in biopsy GG1 and 25.7% in \( \geq GG4 \) (GS 8). No inter-group differences were observed for mean age, PSA, PSAD, and PV.

Mean operative time and estimated blood loss were 167.5 min and 163.9 ml, respectively. High pathologic \( \geq GG4 \) was observed in 21.9% overall, with GS upgrading and pathologic upstaging in 42.9% and 72.2%, respectively. Biochemical recurrence occurred in 12.3%, with 10.9% undergoing adjuvant radiation and 12.7% hormonal therapy.

3.2. PIRADS distribution

The radiological evaluation of preoperative mpMRI identified PIRADS 3-5 lesions in 96.5% of the study population, with 12.1% PIRADS 3, 36.9% PIRADS 4, and 47.5% PIRADS 5 overall and a mean score of 4.3 \( \pm \) 0.9. Analysis for temporal change in sequential overall PIRADS readings found no significant change in mean PIRADS (\( p = 0.096 \)) nor in PIRADS 4-5 (\( p = 0.344 \)).

3.3. Temporal changes of PIRADS correlation to RP pathology

In sequential analysis for consecutive groups of 100 reads, tumors identified as PIRADS 4-5 showed consistently decreasing rates of GG downgrading in RP pathology (\( p = 0.016 \)), from 18.2% in the first group to 8.6% in the last 100 reads (Fig. 1). MR reads also showed significant increasing correlation to GG upgrade (\( p = 0.044 \)), with 42.9% and 49.4% upgraded in groups 1 and 14, respectively. Linear-by-linear association for overall trend was not statistically significant (\( P = 0.472 \) and 0.835 for GG downgrade and upgrade, respectively).

### Table 1

| Baseline clinical characteristics | Perioperative outcomes |
|----------------------------------|------------------------|
| Age (yr)                         | 66.7 ± 7.0             |
| BMI (kg/m²)                      | 24.6 ± 2.8             |
| PSA (ng/ml)                      | 14.6 ± 25.0            |
| Prostate volume (ml)             | 36.2 ± 14.5            |
| PSA density (ng/ml/ml)           | 0.43 ± 0.63            |
| Biopsy Grade Group (%)           |                        |
| GG1                              | 266 (19.2)             |
| GG2                              | 444 (32.0)             |
| GG3                              | 316 (22.8)             |
| GG4                              | 286 (20.6)             |
| GG5                              | 75 (5.4)               |
| Overall PIRADS score (%)         |                        |
| 1-2                              | 40 (2.9)               |
| 3                                | 173 (12.4)             |
| 4                                | 513 (36.7)             |
| 5                                | 673 (48.1)             |
| Operation time (min)             | 168.1 ± 47.3           |
| EBL (ml)                         | 168.3 ± 284.5          |
| Clavien-Dindo complication ≥3    | 20 (1.5)               |
| Pathologic Gleason Score (%)     |                        |
| GG1                              | 11 (0.8)               |
| GG2                              | 493 (35.2)             |
| GG3                              | 592 (42.3)             |
| GG4                              | 126 (9.0)              |
| GG5                              | 177 (12.7)             |
| GG concordant (%)                | 636 (45.3)             |
| GG upgrading (%)                 | 596 (42.6)             |
| GG downgrading (%)               | 167 (11.9)             |
| Pathologic upstaging (%)         | 1015 (72.6)            |
| Extracapsular extension (%)      | 530 (37.9)             |
| Seminal vesicle invasion (%)     | 213 (15.2)             |
| Bladder neck muscle infiltration (%) | 75 (5.4)              |

Data is presented as mean ± SD and n (%).

BMI, body mass index; PSA, Prostate-specific antigen; GG, Grade group; PIRADS, Prostate Imaging Reporting and Data System; EBL, estimated blood loss.
Favorable RP pathology tumors (GG ≤ 2) were increasingly interpreted as PIRADS 1–2 (\(P < 0.001\)) with 2.3% in group 1 increasing to near 2-fold (13.2%) in group 14. PIRAD 3 distribution in favorable tumors also showed sequential increase, from 11.6 in group 1 to 15.8% in group 14 (\(P = 0.029\)). Overall PIRADS 1–3 distribution in pGG≤2 increased by two-fold over time (14.0% in group 1 to 28.9% in group 14, \(P = 0.037\)) (Fig. 2a). The percentage of very-high-risk tumors (GG = 5) identified among PIRADS 4–5 modest but consistent increase (\(P = 0.038\)) (Fig. 2b). In PIRADS 3–5 cases, the percentage of PIRADS 3 and GG ≤ 2 at RP showed a decreasing trend, whereas GG ≥ 3 detection showed a sequential increase (Fig. 3a–c).

### 3.4. Comparison of diagnostic accuracy and pathological correlation in early and later PIRADS

Groups 1–4 and 11–14 were analyzed for diagnostic accuracy and pathological outcome comparisons. No significant differences were observed in clinical variables including age, BMI, PSA, PSAD, and pathologic GG at RP. Median time span between the early and late read groups were 24 months.

In both early and later subgroups, age, PSA, and PSAD were significant for predicting intermediate–high grade RP pathology (GG ≥ 3) (Table 2). However, whereas only PIRADS 4–5 lesions accurately predicted GG ≥ 3 in early 400 reads (odds ratio (OR))
3.63, 95% confidence interval (CI) 1.94-6.77; \(P < 0.001\), both PIRADS 3-5 (OR 2.93, 95% CI 1.00-8.54; \(P = 0.049\)) and PIRADS 4-5 (OR 2.61, 95% CI 1.34-5.10; \(P = 0.005\)) readings were able to independently predict intermediate–high grade pathology. Further subgroup analysis for high-risk pathology found similar results, with preoperative PIRADS 4-5 lesions as independent predictors of GG ≥ 4 lesions in both groups, but with increasing OR in the most recent 400 reads (OR 4.67 vs. 9.78 in early and late reads, respectively). Interestingly, sub-analysis in preoperative biopsy GG ≥ 3 lesions found PIRADS 4-5 tumors to be more susceptible for GG upgrade at RP (p = 0.035), especially to pGG≥4 (p = 0.003) compared to PIRADS 1-3 lesions in experienced reads. Such risk for upgrade to any GG and pGG≥4 was not identified in early reads (\(P = 0.588\) and 0.248, respectively). AUROC of overall PIRADS for pGG≥4 showed modest improvement after median 2 years of PIRADS experience, with 0.702 (0.645–0.759) in the latest 400 readings compared to 0.698 (0.639–0.760) in the early readings. Predictive accuracy of PIRADS for GG 5 showed more significant improvement over time, with AUC 0.734 (0.666–0.803) vs. 0.637 (0.548–0.725) in later and early reads, respectively. Sensitivity and specificity of PIRADS 4-5 for pGG≥4 tumors were improved from 95.2% and 17.4% in early MRI to 97.6% and 22.0% in later readings.

3.5. MRI-based prediction of extracapsular extension, seminal vesicle invasion, and bladder neck muscle infiltration

Improvement in the pathologic correlation of PIRADS 5 lesions to pathologic extracapsular extension (ECE), seminal vesicle invasion (SVI), and bladder neck muscle infiltration (BNI) were assessed. No overall increasing trend in ECE (p = 0.707) prediction was observed, whereas SVI and BNI both showed significant increase over time, from 13.2% to 28.3% for SVI (p = 0.018) and 3.8% to 6.5% for BNI (p = 0.041) in the first and last 100 reports, respectively. ECE was accurately predicted in all sequential groups of 100 reads, whereas SVI and BNI were accurately predicted from groups 4 and 5, respectively. Overall trend in PIRADS 3-5 lesions showed a temporal increase for ECE, SVI, and BNI, despite statistical significance for only BNI (\(P = 0.033\)) (Figs. 3d–f). The modest upward trend in these adverse pathologic findings can be best related to the increase of pGG≥3 tumor rather than to an improvement in MRI interpretation.

4. Discussion

In this retrospective study, temporal changes in PIRADS scoring within a single institution were correlated with RP pathology. The analysis of 1400 readings divided by 14 sequential groups of 100 showed sequential decrease in GG downgrading and increase rates of GG upgrade, with favorable risk tumors (GG ≤ 2) more likely to be interpreted as PIRADS 1–3 than 4–5 over time. Subgroups of early and later reads of 400 cases each showed PIRADS 4–5 readings to independently predict intermediate–high grade pathology (GG ≥ 3) at RP, with a diagnostic accuracy of PIRADS for pGG≥4 and pGG 5 significantly improving after median 2 years of PIRADS experience. Pathological correlation of PIRADS 5 lesions to SVI and BNI were significant only after 400 and 500 respective RP cases, implying a potential learning curve for reliable PCa evaluation in MRI interpretation.

While mpMRI is the mainstay of imaging for PCa, considerable inter-reader variability is noted in multiple studies.16,17 Despite excellent inter-reader agreement for any index lesion detections, categorization via PIRADS are only moderately consistent, with a significant variability for PIRADS 3 lesions and even PIRADS 4 in TZ lesions.18 Significant tumor detection is inevitably susceptible to radiologist experience with high volume and adequate training, with variable accuracy in correlation to pathologic findings. Temporal improvements in favorable pathology (pGG<2) prediction in PIRADS 1–3 and increasing correlation of PIRADS 4-5 to GG upgrade are in line with literature in with MRI-guided fusion biopsy.

Figure 3. PIRAD 3–5 subgroup analysis. (a) percentage of PIRAD 3, (b) percentage of pathologic GG ≤ 2, (c) percentage of pathologic GG ≥ 3, (d) percentage of extracapsular extension, (e) percentage of seminal vesicle invasion, (f) percentage of bladder neck muscle infiltration.
where csPCa detection increased by 26% over time in PIRADS4–5 lesions, with more GG ≥ 3 detected in recent biopsies compared to the initial 200 cases. Greer et al. (2017) showed an increase of positive predictive values (PPV) from moderate to highly experienced readers in both PIRADS ≥ 3 and 4 lesions (0.84 to 0.87, 0.88 to 0.93, respectively), a trend that was replicated in our study with AUC of pGG≥4 moderately increasing from 0.698 to 0.702 after median 2 years of experience, with more significant increase in PIRADS accuracy for pGG 5 tumors (AUC 0.637 to 0.734). PIRADS prediction for pGG≥3 and 4–5 subgroups found PIRADS 4–5 to be independent predictors, with RP upgraded biopsy GG ≥ 3 lesions to be more likely to be read as PIRADS 4–5 than 1–3 after experience, a result that was similar in fusion biopsy with a significantly better sampling of GG ≥ 3 over time.

Generally lower sensitivity and PPV are found for PIRADS 3 lesions, ranging from 59 to 61% sensitivity and 90 to 93% PPV. PIRADS 3 lesions suffer most from the experience of radiologists, possibly as the lesion is to be indeterminate or equivocal for csPCa, whereas PIRADS 4–5 lesions are proven to accurately detect significant and adverse pathology, ranging from 40 to 55% and 80 to 90% for PIRADS 4 and 5 lesions, respectively. As such, the prevalence of PIRADS 3 lesions vary significantly among studies, from one in three (32%) to one in five (22%), and experts are more likely to confidently reclassify lesions categorized as PIRADS 3 as 1–2 or 4–5, leading some to caution immediate biopsy in PIRADS 3. In this study, we found that within the same group of radiologists, low risk tumors (GG ≤ 2) were nearly twice more likely to be interpreted as PIRADS 1–2 in cohorts separated by two years. One interesting finding is PIRADS 3 lesions in the same period were increasingly more likely to harbor favorable tumors (P = 0.029) despite overall decrease in PIRADS 3 categorization rates over time (14% vs. 10% in groups 1–4 vs. 11–14), cautioning the use of PIRADS 3 lesions as reference for early aggressive intervention in institutions with low volume experience. Similarly, PIRADS 4–5 were less likely to be downgraded in RP pathology and more likely to be upgraded, suggesting that PIRADS prediction for even more visible 4–5 lesions may have significant diagnostic variability, requiring at least 400 reads to independently predict pGG≥3.

ECE, SVI, and BNI prediction based on MRI and confirmation by RP pathology is heavily dependent on reader experience, with nearly 30% difference in interobserver sensitivity. In the revision from PIRADS version 1 to version 2, tumor-prostatic capsule contact length (CL) was newly added to the ECE criteria with up-scoring to 5 if definite ECE on T2, with SVI and BNI additionally reported for accurate local staging. Our study failed to substantiate previous literature noting improved sensitivity for ECE when read by subspecialized radiologists (66% vs. 24%, p < 0.001), with little temporal difference in the confirmed ECE detected at RP over time, accurately detected in all sequential groups of 100 cases. However, significant improvement in PIRADS 5 correlation to SVI and BNI was reported, with two-fold increase in both cases in the first and last group of 100 readings, suggests that adverse pathological features can be more accurately predicted on MRI by experienced radiologists. A multicenter study similarly reported PIRADS scores with significant association for poor pathologic prognosis including ECE and SVI, a finding that was paralleled in our study, requiring at least 400 and 500 respective cases for accurate prediction. While no other significant perioperative or oncological outcomes were noted between the two groups, there was a decrease in estimated blood loss in the experienced reading group, which may reflect the surgeons’ improved surgical skill and experience with robot-assisted laparoscopic RP, as 97.2% (1439) cases were performed via robot-assisted laparoscopic RP using da Vinci systems.

Our study is limited by its retrospective design and likelihood of selection bias, the latter of which minimized the bias by selecting serial cases of all patients with RP and with adequate MRI protocols within the set time frame. Also, 23 patients with androgen deprivation therapy prior to surgery were still included for analysis, and while previous reports have identified neoadjuvant androgen deprivation therapy to decrease PSA and positive margin rates at RP; these patients constitute only 3.5% of total patients, making a significant effect size unlikely. MRI fusion-targeted biopsy (MRDITB) was not routinely done for preoperative biopsies, and it is unclear whether the positive biopsy cores correspond to index lesions identified on MRI. In the FUTURE trial, MRI-guided biopsy, either fusion, cognitive, or MRI-targeted, was shown to have a mean detection rate of 33% to 34% without significant differences in the

Table 2
Univariate and multivariate regression analysis for pGG≥3 and pGG≥4

| Pathologic Grade Group ≥3     | Group 1–4 |          | P value | Group 11–14 |          | P value |
|-------------------------------|-----------|----------|---------|-------------|----------|---------|
|                               | Univariate | Multivariate | OR (95% CI) | P value | OR (95% CI) | P value |
| Age                           | 1.04 (1.01–1.07) | 0.008 | 1.05 (1.02–1.09) | 0.003 |          |         |
| BMI                           | 1.09 (1.00–1.18) | 0.050 | 1.07 (0.98–1.17) | 0.140 |          |         |
| PSA                           | 1.03 (1.01–1.05) | 0.003 | 0.96 (0.92–1.00) | 0.056 |          |         |
| PSA density                   | 4.56 (2.00–10.40) | <0.001 | 20.00 (3.16–126.63) | 0.001 |          |         |
| PIRADS ≥3                     | 3.55 (0.32–39.52) | 0.302 |          |         |          |         |
| PIRADS 4–5                    | 4.32 (2.41–7.77) | <0.001 | 3.63 (1.94–6.77) | <0.001 |          |         |

Pathologic Grade Group ≥4

| Group 1–4 |          | P value | Group 11–14 |          | P value |
|-----------|----------|---------|-------------|----------|---------|
| Univariate | Multivariate | OR (95% CI) | P value | OR (95% CI) | P value |
| Age       | 1.09 (0.98–1.06) | 0.290 |          |         |          |
| BMI       | 1.10 (1.00–1.22) | 0.050 | 1.08 (0.97–1.20) | 0.156 |          |         |
| PSA       | 1.02 (1.01–1.03) | 0.005 | 1.02 (0.99–1.05) | 0.247 |          |         |
| PSA density | 1.85 (1.20–2.85) | 0.005 | 1.02 (0.39–2.65) | 0.974 |          |         |
| PIRADS ≥3 | 4.15 (1.46–11.80) | 0.008 | 4.67 (1.41–15.5) | 0.012 |          |         |
| PIRADS 4–5 |          |         |          |         |          |         |

Data is presented as mean ± SD and n (%). BMI, body mass index; PSA, prostate-specific antigen; PIRADS, prostate imaging-reporting and data system.
detection of clinically significant PCa. Further analysis correlating PIRADS lesions to actual RP tumor locations may be required. Also, interobserver variability of PIRADS interpretation to the same tumor lesion was not assessed, and while only two high volume radiologists were included, potential variability between readers may have influenced our results. Mechanical changes over the study timeframe were not assessed, and subtle modifications to MRI sequence parameters and potential mechanical degradation of the scanners were not evaluated in this study. Further research into technical details is warranted and may provide different results, although no differences were noted in a previous study comparing biparametric to mpMRI. Despite these limitations, our study is one of few studies comparing temporal improvement in PIRADS reads at a single institution correlated with pathological results from RP with over 1000 patients included for analysis.

5. Conclusion

Over the past few decades, significant changes have been made to the treatment and diagnosis of PCa, fueled by the introduction of mpMRI and PIRADS. In our study, low risk tumors confirmed at RP were correlated with increasing categorization as PIRADS 1–3 and intermediate–high-risk tumors as PIRADS 4–5 with increased experience over time, with improvements in PIRADS 5 for SVI and BNI detection. These results suggest that high PIRADS in experienced centers can more accurately predict poor pathologic features after RP and caution against MRI-dependent clinical decision making in low volume institutions, especially when considering candidates for active surveillance.

Further large-scale prospective trials are required to validate our results.

Conflict of interest

All authors have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2022.07.001.

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