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BRIDGING GAP BETWEEN PRE AND POSTOPERATIVE PROSTATE BIOPSIES: PI RADS CORRELATION WITH FINAL HISTOPATHOLOGICAL DATA

Tsisitso Abakelia*, Ketevan Lashkhi, Sophio Kakhadze

Introduction.

Prostate cancer (Pc) is the second most commonly diagnosed cancer in men population. According to the global cancer observatory (GCO), there were over 1,414,259 new cases of Pc and 375,304 men have died of prostate cancer in 2020 [1]. In clinical practice treatment strategy and therefore survival outcomes of Pc depend on histopathological grade of the tumor evaluated by Gleason scoring system; it involves five histological growth patterns defining tumor grade [2]. In the recent past transrectal ultrasound (TRUS) guided biopsy was the most popular tool to derive Gleason score (Gs). However, TRUS biopsy showed differences in Gs with prostatectomy specimens; moreover, sextant biopsies under sample most prostates and may miss small index lesion, leading to the false negative results, which causes to late cancer detection and overly intensive treatment (in up to 40%) [3-6]. Multiparametric magnetic resonance imaging (mpMRI) and MRI-targeted biopsy demonstrated potential to solve this problem, with high accuracy in prostate cancer diagnosis [7].

In this paper the matter for consideration is mpMRI in Pc diagnosis with risk stratification system- Prostate Imaging Reporting and Data System (PI RADS). This system was established by European society of urogenital radiology (ESUR) as scoring system with strict criterions for categorization of suspected lesions in prostate gland, whereby a score level 1 to 5 corresponds to the like hood of clinically significant cancer. With this system mpMRI noninvasively predicts tumor grade [8]. Score level 1 to 5 are applied to lesion for each single mpMRI sequences considering zonal location of suspected lesion. PI RADS involves several mpMRI sequences: T2 weighted imaging (T2W)-for structural representation of lesion; Diffusion weighted imaging (DWI) with apparent diffusion coefficient (ADC) - correspond with micro-architecture of tissue and dynamic contrast enhanced imaging (DCE) -to assess tumor vascularity [9]. At the time of primary diagnosis high diagnostic accuracy is crucial for an optimal Pc management. Preoperative prediction of Pc grade with high accuracy and evaluation of tumor extension at the time of diagnosis may modulate treatment strategy and therefore impact on cancer prognosis: survival rate, quality of life-especially in patients with indolent tumor, for whom potential risks of surgery outweighs the survival benefit. We hypothesize that pre-biopsy mpMRI with PI RADS as valuable tool among pre and postoperative Pc grading can show high reliability in preoperative Pc grading, thus modulating Pc management. Existing literature regarding discrepancy between the pre- and post-operative pathological Gleason scores strengthens this hypothesis [10]. There are limited number of published studies in total evaluating possibilities of mpMRI in preoperative Pc grading, defining strength of PI RADS correlation with Gs, finding compliance of Pc grades generated from PI RADS and Gleason scoring system. Existing literature revealed PI RADS as strong predictor for significant Pc detection, however with different results and conclusions [11-15]. Studies investigating reliability of mpMRI in Pc preoperative grading, by evaluating the correlation of PI RADS with Gs are needed. The purpose of this study was to find the strength of correlation between mpMRI and histopathological data in prostate cancer diagnosis. Our approach allowed us to directly compare MRI features of Pc to histological features and provide a model to reconcile our findings and those of others.

Materials and methods.

Study population: In Acad. F. Todua Medical Centre from June 2020 to September 2022 203 consecutive patients suspected of Pc who underwent preoperative mpMRI were included in this study prospectively. Inclusion criteria were
patients suspicious for Pc (on ultrasound sonography, on digital rectal examination, or with elevated blood PSA levels) and consecutive positive biopsy with Gleason scoring. Exclusion criterions: prostate cancer positive patients who underwent any type of Pc treatment: radical prostatectomy, Trans-urethral resection of the prostate (TURP), radiotherapy, hormone therapy or chemotherapy. Among the patients enrolled in this study (n=203) who underwent histopathological examination with Gleason scoring 50 patients were excluded due to the negative biopsies for Pc on follow up. In total 153 patients were included in the final analysis (Figure 1).

Radiological technique: mpMRI was performed on a 3T scanner-Magnetom Skyra, Siemens AG, Erlangen, German; using 18-channel phased array body coil. mpMRI examination included: T2W; DWI; ADC and DCE-MRI sequences covering the entire pelvic region. DWI sequences were taken in transverse plane with three values (50; 400; 1000 s/mm²); restricted diffusion was measured by the ADC map [16]. DCE images were obtained using fast T1 weighted imaging (gradient echo sequence) in transverse plane. Contrast medium-Gadovist was used with a dose of 0,1mL/kg body weight [17].

Image interpretation: mpMRIs were interpreted by board-certified two experienced radiologists independently. Firstly, the three single scores from 1 to 5 were defined for T2W, DWI, ADC and DCE sequences according to the ESUR guidelines PIRADS v2.1 and then overall PI RADS scores were calculated [9,18]. In order to limit biased image interpretation, performing mpMRI reports and PI RADS scoring were done before biopsy or surgery, so radiologists were blinded to the morphological outcomes.

Biopsies were derived by TRUS guided biopsy (137 patients) and MRI/Ultrasound fusion guided biopsy in 16 patients. Biopsy samples were examined and analyzed by experienced pathologists who were blinded to MRI findings. During a follow up Gleason score of TRUS and MRI/Ultrasound fusion guided biopsies were compared with prostatectomy specimens. Discrepancy of histopathological grades between biopsies and radical prostatectomy was found in 18 patients. Upgraded Gleason scores of prostatectomy specimens were considered for the final data analysis.

Statistical analysis: SPSS, version 27.0 was used for all statistical analysis. Baseline characteristics of patients with pathological outcomes were compared using a chi-square test for categorical data (PIRADS score) and a Student t-test or ANOVA for continuous data. Linear regression analysis was performed to analyze the correlation between the rising PI RADS scores and prognostic factors. Pearson’s correlation coefficient was calculated for PI RADS and Gs, ADC and Gs. P values less than 0.05 were considered statistically significant. A receiver operating characteristic (ROC) analysis was used to evaluate sensitivity and specificity of the scoring system with regard to tumor incidence. Linear regression analysis was used to predict Gleason grades with regards to different ADC values. Concordance of pre and postoperative Gleason scores was verified by Bland-Altman plot.

Results.

patients age ranged from 54 to 89 (mean age 69 SD 7,0); the preoperative mean total PSA value was 17.6899ng/ml (range:4.30-1134.00ng/ml. SD 156.33) When mpMRI data was analyzed mean tumor volume was defined as 6.5cm³; Tumor sizes showed low positive correlation with Gs (r=0.210 p=0.009) and PI RADS sum scores (r=0.215 p=0.008); low negative correlation with ADC (R=-195 P=0.16); Most frequent location of tumor was detected in right peripheral zone (47.1% n=72). mpMRI evaluated spread of each lesion: 54.9% n=84 was defined with extracapsular extension. Mean PI

![Figure 1. Flow chart of materials and methods.](image-url)
RADS sum score for tumors with extracapsular extension was defined as 14; Mean sum score for tumors with no extracapsular extension was 12. Conducted T test showed statistically reliable differences between them: t=6.40 and p=0.000.

Overall, PI RADS score distribution was as follows: in total PI RADS 3 was given to 54 patients (47 with negative biopsies and the rest of 7 patients with positive biopsies (4.6% out of 153), PI RADS 4 to 35.9% and PI RADS 5 to 59.5%. Low grade tumors (Gs 6) were found in cutoff between PI RADS sum score 8-13; intermediate grade tumors (Gs 7) in cutoff between 10-14; Gs 8 in cutoff 8-15 and very high-grade tumors (Gs9-10) in cutoff of 12-15. All PI RADS 3 lesions were associated with different grades (PI RADS sum score range from 8 to 13). Grade group 5(Gs9 and Gs10) were linked to overall PI RADS 5 (sum score range:12-15). The relationship of Gleason grades and PI RADS sum scores is demonstrated in cross-tabulation analysis (Chi-Square is 147.9 P=.000) (Table 1).

Regarding tumor malignancy: 9.8% were cancers with Gs 6(3+3); 16.3% with Gs 7(3+4); 14.4% with Gs 7(4+3); 17% with Gs 8(4+4); 18.3% with Gs8(3+5); 3.3% with Gs8(5+3); 12.4% with Gs9(4+5); 5.2% with Gs9(5+4); 3.3% with Gs10(5+5) (Table 2).

Mean ADC values were calculated for each Gleason grade and illustrated by box plot analysis (Figure 2). Grade 1 with mean ADC 0.88 and grade 5 with mean ADC 0.67. ADC values decreased relative to Gleason score upgrade. 50 patients with negative biopsies received mean ADC value 1.34. Fisher’s test determined statistically reliable difference between Gleason groups (F=89.85 and P=0.000). In accordance to linear regression analysis (R Square=0.74), with Gleason upgrade by one group- ADC decreases by 0.046 unit (B=−27.3 da p=0.000).

Dynamic Contrast-Enhanced MRI was assessed by observation on enhancement curves for each patient, deriving single scores from algorithm-based approach. In summary 19 patients (12.4%) received type 1 enhancement curve; 56 patients(36.6%) with type 2 enhancement curve and 78 patients (51%) with type 3 curve. DCE curves Correlation with Gs was as follows: high positive correlation with Gleason scores (r=0.689 p=0.000); intermediate positive correlation with PI RADS sum scores: r=0.435 p= 0.000; high negative correlation with ADC values: r=−0.592 p=0.000. Type 1 enhancement curve was associated with Gleason grade group 1,2 and 3; while Type 3 enhancement curve was associated with Gleason grade group 2,3 ,4 and 5 (Table 3).

### Table 1. Cross-tabulation analysis demonstrates the relationship of Gleason grades and PI RADS sum scores.

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The relationship of Gleason grades and PI RADS sum scores is demonstrated in cross-tabulation analysis (Chi-Square is 147.9 P=.000) (Table 1).

### Table 2. Cross-tabulation analysis shows the relationship of Gleason scores and PI RADS sum scores.

| Dynamic contrast-enhanced MRI (DCE) curve distribution with regard to histopathological outcome. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Dynamic contrast-enhanced MRI                   | Gleason score                                  | Total                                           | Type 1 enhancement curve                         | Type 2 enhancement curve                         | Type 3 enhancement curve                         | Total                                           |
| 6(3+3)                                          | 7(3+4)                                          | 8(3+5)                                          | 9(4+5)                                          | 9(5+4)                                          | 10(5+5)                                         | 100.0%                                          |
| 31.6%                                           | 47.4%                                           | 21.1%                                           | 100.0%                                          | 100.0%                                          | 100.0%                                          | 100.0%                                          |
| 16.1%                                           | 26.8%                                           | 28.6%                                           | 10.7%                                           | 12.5%                                           | 1.8%                                            | 3.6%                                            | 100.0%                                          |
| 1.3%                                            | 2.6%                                            | 25.6%                                           | 26.9%                                           | 5.1%                                            | 21.8%                                           | 10.3%                                           | 6.4%                                            | 100.0%                                          |
| 9.8%                                            | 16.3%                                           | 14.4%                                           | 17.0%                                           | 18.3%                                           | 3.3%                                            | 12.4%                                           | 5.2%                                            | 3.3%                                            | 100.0%                                          |
Strength of correlation between PI RADS, Gleason and ADC values were determined by Pearson’s correlation. According to this analysis: there is strong positive correlation between PI RADS sum scores and Gleason scores (r=0.646 and p=0.000.) which means that higher PI RADS sum scores are associated with higher Gleason scores. In summary each of the single scores showed a tendency to higher tumor incidence (Figure 3). ADC correlates with Gleason score with high negative correlation (r=-0.604 and p=0.000)- lower ADC value is associated with higher Gs.

Receiver operation characteristic (ROC) analysis revealed large area under the curve of 0.80 (95% CI 0.74 to 0.87) regarding tumor incidence (p=0.000); when analyzing the balance between sensitivity and specificity to calculate reliable threshold for prostate cancer incidence for the PI RADS sum-score, the score level of ≥ 9 was the highest possible threshold with more sensitivity than specificity(94%/67%) for the predictions of cancers with Gleason score ≥3+4. (Figure 4).

**Figure 2.** Box plot analysis of mean ADC values with regard to Gleason scores.

**Figure 3.** Scatter plot demonstrates strength of correlation between PI RADS sum scores and final diagnose-postoperative Gleason scores.

**Figure 4.** Receiver operation characteristic (ROC) curve for the PI RADS sum-score, regarding threshold for tumor incidence.

**Figure 5.** Gleason score upgrade from TRUS biopsy to radical prostatectomy.

**Figure 6.** Bland-Altman plot shows limitation of agreement between TRUS biopsy and prostatectomy specimen.

With regards to Gleason score upgrade from biopsy to radical prostatectomy: In presented study we evaluate agreement between preoperative and prostatectomy final Gleason
groups. 153 patients with positive biopsies underwent radical prostatectomy. 18 cases out of 153 (11.7%) (7 patients with PI RADS 3 and 9 patients with PI RADS 4) showed discrepancies with Gleason score upgrade (Figure 5).

Bland-Altman plot shows limitation of agreement between biopsy and prostatectomy specimen. All values along the zero are cases with the same Gleason groups at pre and postoperative histology. Red line represents mean difference of pre and postoperative Gleason scores (p=0.000 t=4,233); green line represents lower edge of both Gleason scores. Below green line are distributed findings with significantly big differences (Figure 6).

Discussion.

With this study we could demonstrate good reliability of the PI RADS risk stratification system with regards to tumor malignancy: all single scores, sum scores of 3-15 points and overall PI RADS scores showed clear association with tumor malignancy and incidence. Our research suggests growing potential of mpMRI in pretreatment stage of prostate cancer management avoiding unnecessary interventions, reducing side effects, providing determination of precise treatment approach; all of these shall improve quality of life in patients with prostate cancer. PI RADS component: DWI coupled with ADC; dynamic enhancement curves are making it easier to predict tumor aggressiveness. These features have the potential to uncover tumor patterns and characteristics that fail to be appreciated by the naked eye. PI RADS as a risk stratification system could provide valuable information for stakeholders regarding grade of tumor, extension and staging. It should be used as the clinical selection criterion for active surveillance. PI RADS sum score calculation by summing up each single score derived from mpMRI sequences should be mandatory for each clinical report of individual patients suspicious for Pc; it could provide recommendations for further management. In clinical routine PI RADS assessment based on overall PI RADS derived from subjective impression of radiologists seems to be less reliable than separate classification of sum scores based on algorithm strict criterions [8]. Accordingly, PI RADS sum score calculation preferably should be in line with MRI report (Figure 7).

Some studies regarding radiological and morphological correlation of Pc in concordance with our findings showed an important correlation of PI RADS with histopathology. Unlike to us authors of multicenter study conducted in Turkey placed emphasis on radical prostatectomy features-histopathological factors in prostatectomy specimen and did correlate postoperative extracapsular extension, lymphovascular invasion and seminal vesicle involvement with PI RADS scores. All of these prognostic factors showed significant correlation with PI RADS score [12]. Similar to our study authors concluded that PI RADS high scores were associated with adverse histological features [19]. Other study in retrospective analysis results showed that PI RADS correlates with Pc defined as Gs >3+4 [14]; In a prospective analysis of Pc prediction from biopsy to radical prostatectomy, authors concluded that PI RADS V2.0 score was an independent predictor of postoperative Gs upgrading [5]. Hectors et al. published data with slightly different approach in comparison with our study with following conclusion: machine learning prediction models showed fair performance to predict a Gleason score of 8 or greater (AUC 0.72) [20]. Similar to our study is Rayn et al.’s publication with larger sample size comparing mpMRI features and preoperative biopsies to prostatectomy specimen. Conclusion was as follows: mpMRI alone or in addition to existing validated risk stratification tools, provides significant additional predictive ability for adverse pathological features at the time of radical prostatectomy [21]. Important multicenter study was performed in 2019, in aim to assess the accuracy of mpMRI for the detection of prostate cancer in men undergoing radical prostatectomy. Similar to our study MRI data was compared to final histopathology; however, with slightly different approach: mpMRI cases were analyzed by using PI-RADS version 1 and version 2. Conclusion was
considerable: in patients who underwent radical prostatectomy, an abnormal mpMRI is highly predictive (95% PPV) of significant prostate cancer, with an index lesion concordance of 75%. There has been a significant improvement in accuracy after the adoption of PI-RADS version 2 technical specifications and reporting criteria [22].

The moderate correlation of PI RADS with Gs was defined in Heister et al. study concluding low risk Pc have lower PI RADS sum scores than intermediate and high-risk tumors [23]. Recently conducted prospective study also found moderate correlation of PI RADS with Gs(Kendall Tau 0.354). In this study methods, especially inclusion criteria were different to our study [13]. In contradistinction to these results in their retrospective study Slauoi et al. concluded that PI RADS score was not associated with significant differences regarding Gleason score distribution within target. Methods were similar to our study; exact match of Gs in pre and postoperative biopsies were found in 62%, which is lower than we observed in our series-88.31%. In their series all diagnosed cancers assigned with PI RADS 3 corresponded to Gs 7 [15]. In our research we had different findings: PI RADS 3 lesions were defined as Gs6(3+3) n=4; Gs 8(4+4) n=2 and Gs8(5+3) n=1.

Research of Katz et al. revealed that mpMRI and PI RADS alone are not sufficient to determine clinically significant prostate cancer since both high- and low-grade tumors were found in PI RADS 4 and 5 [11]. To overcome related problems, we placed emphasis on PI RADS sum score calculation, by summing up each single score and this enhances credibility of diagnostic test.

With regards to PI RADS 3, defined as equivocal cancer suspicion, could lead to certain management challenges and cause uncertainty in PI RADS diagnostic accuracy. To solve this problem Junker et al. in their article recommended to lift the threshold between PI RADS 2 and from sum score levels ≥ 7 to ≥ 8 [8]. This issue still remains in contention. In our study 54 patients were assigned to PI RADS 3, 47 patients were cancer negative in preoperative biopsies and only 7 of them had positive biopsies; these falsely high initial PI RADS scores mainly corresponded to the presence of benign adenomas. Need of new approaches is obvious to reduce this false positive rate-difficulties with MR differentiation between benign and malignant lesions. This observation emphasizes the importance of PI RADS 3 as reported previously [24].

Latest work of Ono et al. showed that from following parameters: Age, prostate volume, transition zone volume, and mean and minimum apparent diffusion coefficients only the minimum apparent diffusion coefficient value (odds ratio: 0.994; p < 0.001) was an independent predictor of clinically significant prostate cancer. Minimum ADC provided additional value to indicate the presence of clinically significant prostate cancer in the transition zone for the PI RADS 4/5 lesions. This will be valuable data to consider the need for subsequent biopsies in patients with Prostate Imaging Reporting and Data System 4/5 lesions and an initial negative targeted biopsy [25].

Prostate biopsy Gs upgrading remains a challenge for clinicians managing localized Pc [5]. In our study out of 153 patients who underwent preoperative TRUS (n=137) biopsy and MRI/Ultrasound fusion guided biopsy(n=16), 18 patients (11.7%) all with history of TRUS biopsy showed discrepancies with Gleason score upgrade.

The need for improved understanding of the role of pre-biopsy mpMRI is obvious. MpMRI with PI RADS risk stratification system has potential to bridge this gap existing between pre and postoperative biopsies, in this most important stage this technique could avoid unnecessary treatment reducing side effects through precise approach thus improving quality of life with it. In summary our findings indicate a significant advantage of using the prediction model as PI RADS. We envisage that the growing field of artificial intelligence, machine learning and scrupulous approach of radiologists may take us closer to precise prediction of final Gs by mpMRI.

Limitations.

In our study PI RADS sum score of several cases were generated retrospectively, subsequently and uniformly after collection of whole radiological data while overall PI RADS scores were calculated consecutively, this might have led to some verification bias, however, sum scores were calculated independently, radiologists were blinded to morphological reports. Additionally, this is a single centre study; performance of our model needs further validation in an external data set. Further multicentre studies with data based on larger sample size will be necessary to assess contribution of mpMRI to clinical practice.

Conclusion.

PI RADS demonstrated a highly positive correlation with Gleason scores. It showed strong relation with histopathological adverse prognostic features. mpMRI with PI RADS risk stratification system is a reliable approach in prediction of Pc grade in preoperative period with high accuracy. Considering discrepancy between pre and postoperative Gleason grades which still remains as challenge PI RADS has capacity to avoid unnecessary invasion, providing precise treatment strategy, especially for low-risk tumors.

Conflict of interest disclosure.

Authors declare no potential conflicting interests related to this paper.

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