Prospective evaluation of the correlation between Prostate Imaging –Reporting and Data System (PI-RADS) version 2.1 and International Society of Urological Pathology (ISUP) score, and inter-observer Reproducibility of the New Version

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Abstract

Purpose: To evaluate the correlation between PI-RADSv2.1 and International Society of Urologic Pathologists (ISUP) score for patients who underwent multiparametric-MRI(MpMRI) prior to transrectal ultrasound (TRUS) guided cognitive fusion biopsy (CF-Bx). And to investigate inter-observer agreement of PI-RADSv2.1. Methods: Patients who underwent MpMRI of prostate prior to first TRUS-guided CF-Bx, were included in this prospective study. MpMRI examinations were evaluated by two radiologists before biopsy according to the PI-RADSv2.1. Interobserver agreement was recorded and the final PI-RADS categorization was performed by consensus. Correlation of histopathological results with PI-RADSv2.1 score was evaluated. Lesions with Gleason Score(GS)[?]6 were considered as prostate cancer (PCa). Results: A total of 84 patients with 106 lesions were included in the study. The ratio of PCa in the PI-RADS groups 1,2,3,4,5 was 0%, 0%, 22.2%, 56%, 94.45%, respectively. There was a positive correlation with a value of 0.814 between the PI-RADSv2.1 and the ISUP score. When PI-RADS[?]3 is accepted as the cut-off value in peripheral zone(PZ) and the whole gland, the NPV for malignancy was 100.00%. For PI-RADS [?]4, it was 76.47% for PZ, and 80.65% for the whole gland. For the whole gland; sensitivity, specificity, and PPV of the PI-RADS[?]3 were 100%, 12.9%, and 44.33%, respectively; for PI-RADS[?]4, these values were 72.09%, 80.65%, and 72.09% respectively. Without applying cut-off values, the interobserver agreement for PI-RADS score was ϰappa:0.562. Conclusions: PI-RADSv2.1 was created in the framework of v2 to facilitate to evaluate MpMRI and to increase interobserver agreement. We believe that further studies will be necessary.

INTRODUCTION

Prostate cancer(PCa) is the most commonly observed cancer in men in the world and the 3rd most common cause of cancer-related deaths[1]. An autopsy study of 1056 men, who died from causes other than prostate cancer, found 68-77% of men aged 60-79 years had not received a diagnosis but had asymptomatic PCa identified. This result shows the prevalence of this silent disease[2,3]. However, the mortality and morbidity of advanced stage PCa are very high. Recent studies have focused on distinguishing lesions expressed as “silent disease” with almost no fatality potential, such as tumors with a Gleason score(GS) of 6, and high-grade cancers[4]. Due to limited sensitivity and specificity of serum PSA screening, digital prostate examination,

and TRUS-bx, advanced imaging methods are required to reduce biopsy numbers and to perform target-specific biopsies[5]. With advanced imaging methods, diagnosis and treatment of prostate cancer can be chosen specifically to the person or active surveillance may be performed. To ensure standardization and reduce differences emerging in the selection of parameters and interpretation of images on prostate MRI, the ESUR published a guideline in 2012[5,6]. Rapid developments in this field and limitations encountered during the use of the PI-RADSv1 led to an update of the PI-RADS system and PI-RADSv2 was published in 2015 by a committee[7]. In 2019, PI-RADSv2.1 was published including changes ensuring more accurate and reproducible interpretations can be made[8,9].

The aim of this prospective study is; to investigate the correlation of the PIRADSv2.1 score with the histopathological result and the ISUP score in patients with suspected prostate cancer in MpMRI examinations guided PI-RADSv2.1 and diagnosed with TRUS-guided cognitive fusion biopsy(TRUS-guided CF-Bx) and to assess the compatibility between different experience levels of the radiologists.

MATERIAL AND METHODS

In this prospective single-center study, 166 consecutive patients who underwent MpMRI for prostate cancer diagnosis between April'19 and December'19 were evaluated. Ethical approval was obtained from a local committee. Oral and written consents were obtained from all patients. Twelve patients with unsuitable image quality for evaluation, 26 patients with bx performed previously, without cognitive fusion biopsy in our hospital and with prostate cancer treatment before testing, and 44 patients with no tissue diagnosis due to PI-RADS-1 or refusing biopsy were excluded from the study. A total of 106 lesions of 84 patients diagnosed with TRUS-guided CF-Bx in our hospital were included in the final study group. Patient age, serum PSA value, PSAd, and prostate volume were recorded. The prostate MpMRI examined in the study was performed with a 1.5T Siemens Magnetom Aera MRI device with 18 channels pelvic coil according to the protocols shown in below *Table-1* . All sequences were assessed on a SYNGO.VIA-workstation.

Assessment of images and histopathological correlation

MpMRI images were evaluated before biopsy according to the PI-RADSv2.1 guidelines by two radiologists with 25-years of experience(reader-1) and 2-year of experience(reader-2) in abdominal MRI. The appearance, localization, and dimensions of lesions were first independently assessed by the two radiologists. Lesion localization was defined according to the sector map in the PI-RADSv2.1 guidelines. Lesions exceeding zonal anatomy (both PZ and transitional zone(TZ) spread) or lesions with extraprostatic extension were defined as diffuse cancer. Lesions were scored according to PI-RADSv2.1 criteria on T2 weighted images(T2W) and diffusion weighted imaging(DWI). DCE-MRI was defined as 'negative' or 'positive' and each lesion was given a PI-RADSv2.1(category 1-5) score. These scores were recorded to evaluate the interobserver agreement. Due to the different PI-RADS scores in between the readers, the final PI-RADS categorization was performed by consensus for 28 lesions *(Table-2).*

Interobserver agreement of these variables and histopathological correlation with PI-RADSv2.1 score were evaluated. Negative MpMRI findings were assigned to PI-RADS-1.

Based on MpMRI findings and clinical suspicion of prostate cancer, a biopsy was performed on the patients. While MpMRI cognitive fusion TRUS-bx was applying with the 18G automatic tru-cut biopsy needle, the hypoechogenic-hyperechogenic foci were considered, 2 samples were taken from each lesion by correlating them with the foci defined in MpMRI and marked on the sector map[7]. In addition to cognitive fusion, 12-core systematic bx was performed. The TRUS-bx procedure was performed by one of 3 experienced urologists. A total of 84 patients diagnosed with using TRUS-guided CF-Bx had 106 lesions identified. Biopsy specimens were evaluated by a urogenital pathologist. Malignant lesions were grouped according to the ISUP scoring (ISUP1, GS3+3; ISUP2, GS3+4; ISUP3, GS4+3; ISUP4, GS4+4; ISUP5, GS[?]9)[10]. On MpMRI, lesions that have PI-RADSv2.1 score [?]3 were recorded as positive, while lesions have <3 score were recorded as negative lesions.

Statistical Method

In descriptive analyzes, continuous variables are presented as mean±standard deviation or median (25th-75th percentile) and categorical variables as a percentage(%). The compliance of the data to normal distribution was evaluated using the Shapiro-Wilk test. If the data has a normal distribution, a t-test was used to compare two groups; under non-parametric conditions, the Mann-Whitney U test was used. Comparison of continuous variables between three and more categories was used the one-way ANOVA or the non-parametric equivalent of the Kruskal-Wallis test. The power of the correlation between two continuous variables was assessed with the Spearman correlation analysis. Accordingly, the correlation coefficient(r) values <0.2 show very weak or no correlation, values from 0.2-0.4 show weak correlation, from 0.4-0.6 show moderate correlation, 0.6-0.8 show a high correlation, and values>0.8 are interpreted as very high correlation. Interobserver agreement was evaluated by using kappa coefficients($\varkappa$), were computed and assessed as follows: 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–0.99, almost perfect agreement. To evaluate the success of the obtained variables, to diagnose prostate cancer and to determine cut-off points, ROC analysis was used with the area under the curve(AUC) used to calculate sensitivity, specificity, positive predictive value(PPV), and negative predictive value(NPV). SPSS 22.0 and MEDCALC programs were used for statistical analyses. p<0.05 was accepted as statistically significant.

RESULTS

The mean age, PSA, prostate volume and mean PSAd values for the 84 cases included in the study were 63.5±7.5 years, 11.68±17.34ng/ml, 62.4±38.08cm^3, and 0.23±0.39ng/ml^2, respectively. There were no statistically significant differences between malignant and benign diseases for age and PSA values. Prostate volume in the malignant group was found to be significantly lower and PSAd higher than the benign group (p<0.001,p<0.001)(*Table-3*).

Of the 106 lesions examined in this study from the 84 patients, 26(24.5%) were benign prostatic tissue, 36(33.96%) were prostatitis, 43(40.46%) were malignant lesions and 1(0.94%) was high-grade prostatic intraepithelial neoplasia. Among malignant lesions, 65.1% were localized in the PZ, 14% in the TZ, and 20.9% were diffuse cancers.

In the PI-RADS groups 1, 2, 3, 4, and 5, there were 5, 4, 54, 25, and 18 lesions identified respectively. No malignancy was detected in any of the 9 lesions who had PI-RADS-1 and 2. Systematic biopsy was performed to these patients with the decision of the clinician due to the increase in PSA, rectal examination findings and the age of the patient. Of the PI-RADS-3, 4, and 5 lesions, the PCa ratios were 22.2%, 56% and 94.45%, respectively.

Table-4 shows the statistical parameters in PZ and TZ when the cut-off value PI-RADS[?]3 and PI-RADS[?]4 taken as positive for cancer detection when T2W and DWI are independently evaluated. In TZ, there was no patient with a PI-RADS<3, so the diagnostic parameters for this variable could not be calculated.

The success of the PI-RADS score to predict cancer was found to have an AUC value of 0.764 (0.646-0.882) for PZ and 0.629 (0.347-0.910) for TZ when PI-RADS[?]3 positive is considered. Evaluation by excluding the zonal anatomy and taking the PI-RADS score as [?]3 positive found the cancer prediction success had AUC values of 0.773 (0.683-0.864), 0.722 (0.621-0.824), 0.740 (0.641-0.838), 0.619 (0.514-0.724), and 0.764 (0.646-0.882) for T2W, DWI, DCE, T2W and DWI combinations (biparametric), and the T2W, DWI and DCE combination (MpMRI), respectively.

The sensitivity, specificity, NPV, and PPV values for prostate cancer detection according to PI-RADSv2.1 and regardless of the zone, for T2W and DWI independently, for biparametric and MpMRI assessment when PI-RADS[?]3 and [?]4 taken as positive are summarized in *Table-5* . When the results for cut-off value of [?]3 are compared with the results for cut-off value [?]4 in *Table-4* and *Table-5* , the differences between the two cut-off values were statistically significantly different(p<0.001). Accordingly, when the PI-RADS score cut-off value of [?]4 was taken as positive, the sensitivity and NPV moderately fall, while specificity and PPV increase.

All lesions in the ISUP>1 group (n=27) were evaluated as PI-RADS-4 or 5. While 25.47% of all lesions had

ISUP>1 observed, 40.56% of the lesions (n=43) were identified to have PI-RADS-4 and 5. When PI-RADS-3 lesions are evaluated, 22.2% of these lesions received PCa. In this group, there were no lesions with ISUP>1 diagnosis. There was a positive correlation between PI-RADSv2.1 score with ISUP score and the correlation value was 0.814(p<0.001) *(Table-6)*

In PZ, for the ISUP grades 1, 2, 3, 4, and 5, there were 4(57.1%), 2(28.6%), 0(0%), 0(0%), and 1(14.3%) lesions which upgraded to PI-RADS group 4 with DWI score 3 and DCE positivity, identified respectively*(Table-7)* . For lesions with DWI score 4 and PIRADS 4, 0(%0), 2(33.3%), 2(33.3%), 2(33.3%), and 0 lesions identified respectively for the ISUP grades 1, 2, 3, 4, and 5. Lesions that are primary PI-RADS4, were observed to have higher ISUP grades. When grouped according to ISUP grade 1 and >1, there were significant differences in terms of the DWI score 3 and 4 percentages (p:0.03)(*Figure-1* ,*Figure-2*).

The interobserver agreement kappa value($\varkappa$) for the PI-RADS score, without applying the cut-off value, was 0.562 which represents moderate agreement. When PI-RADS cut-off value of [?]3 positive is considered, kappa was 0.320, which represents fair agreement but when the cut-off value was determined as [?]4, the kappa is 0.770 which corresponds to a substantial agreement. Interobserver agreement for T2W was moderate with kappa:0.575 when PI-RADS[?]3 positive taken as the cut-off and reached the substantial agreement with kappa: 0.814 when PI-RADS[?]4 is taken. Interobserver agreement for DWI was fair with kappa:0.321, when PI-RADS[?]3 is taken as the cut-off value but reached the substantial level when PI-RADS[?]4 is taken as the cut-off($\varkappa$=0.757). For DCE investigation with positive and negative scores evaluation, interobserver agreement was at substantial levels with $\varkappa$=0.721.

DISCUSSION

In this study, the correlation of prostate gland diseases with patient age, gland volume, serum PSA value and, PSA density, the effectiveness of the MpMRI and PI-RADSv2.1 scoring system in detecting prostate gland diseases, PI-RADSv2.1 and ISUP score correlation, and interobserver agreement were assessed. In our study, serum PSA did not show a significant difference for malignant or benign disease. PSAd was observed significantly high in the malignant group. Joshua Stephen Jueve et al. reported a sensitivity of 90-95% for PSAd and considering the 0.15 ng/ml^2 threshold value, they supported that the high NPV may prevent unnecessary biopsy in patients with proportional PSA increase compared to prostate volume[11]. There was a negative correlation found between prostate volume and malignancy diagnosis. This result is similar to the results of studies by Shadi Al-Khalil et al.[12] and Tang et al.[13]. The causes for the increase of prostate volume may be interpreted as due to benign causes like hyperplasia and prostatitis. The study of Haas et al. presented that patients with prostate cancer were of advanced ages[14]. Droz et al. showed high mean age in the cancer group[15]. In our study, the mean age in the cancer group was consistent with the literature and was higher compared to benign diseases of the prostate gland; however, the difference was not statistically significant(p:0.053). PI-RADSv2 is a scoring system widely used for the detection of PCa and its reliability has been demonstrated by numerous studies. When we examine these studies in the literature, the cut-off value for detection of clinically significant prostate cancer on MpMRI of PI-RADS 3 or 4 had ranges of 85.7-94.5% for sensitivity, 23-71% for specificity, and 34-97% and 50-92% for PPV and NPV, respectively[16–21]. Venderink et al.[22] determined the clinically significant PCa rates (GS[?]3+4) for PI-RADS-3, 4, and 5 lesions were 17%, 34%, and 67%, respectively. A study by Mathur et al. found the detection rates for clinically significant PCa were 6.1%, 33.3%, and 64.4% for PI-RADS 3, 4, and 5 respectively, and increased in proportion to the score[23]. A study assessing 737 lesions with MpMRI-targeted TRUS-bx found the PCa rates for PI-RADS 1, 2, 3, 4 and 5 lesions were 0%, 10%, 12%, 22% and 72% respectively[24]. In our study, 22.2%, 56%, and 94.45% cancers were detected in PI-RADS 3, 4, and 5 groups respectively. None of the malignant lesions in the PI-RADS3 group had ISUP>1 pathology results. As in all PI-RADS versions, disease management after scoring is not specified for patients in v2.1. In PI-RADS v2.1, "Category 3 lesions are of intermediate status with an equivocal risk of presenting clinically significant prostate cancer (csPCa)" risk is stated and there are limited studies in the literature regarding the selection of follow-up-biopsy and it has not been clarified yet[9,25]. Therefore, all PI-RADS-3 lesions were biopsied with

the clinician's preference.

There was a positive correlation found between the PI-RADSv2.1 score with the ISUP score*(Table-6)* ($p<0.001$). A study by Walker et al.[26] found a positive correlation between PI-RADSv2.1 categories and ISUP groups with a correlation value of 0.5 and with the increase of the PI-RADS category, clinically significant cancer rates were shown to increase. Additionally, as shown in the study by Walker et al., also in our study, in PZ when lesions with DWI score 3 upgraded to PI-RADS4 group with DCE positivity and PI-RADS4 lesions with DWI score 4 are compared, the PI-RADS4 lesions with DWI score 4 were observed to have higher ISUP grades[26]. These results clearly show that as the PI-RADSv2.1 score increases, the clinically-significant cancer detection rate increases, and can be interpreted as the tumors have more aggressive histopathology. However, in our study, the histopathological evaluation of lesions observed 25.47% had ISUP>1, while 40.56% of lesions had PI-RADS scores of 4 or 5. It is clear that PI-RADSv2.1 also needs improvements and more objective recommendations, and further research may contribute to achieving this aim. In our study, when cut-off values for PZ and whole gland are accepted as PI-RADS[?]3, the NPV for malignancy was 100.00%. For cut-off value PI-RADS[?]4 lesions, this value was 76.47% for PZ, 83.33% for TZ, and 80.65% for the whole gland, compatible with the literature[27–29]. The high NPV is very important in terms of excluding cancer for patients without performing bx. The sensitivity, specificity, PPV, and NPV analysis in terms of PI-RADSv2.1 sequences and zones are summarized in *Table-4* and *Table-5* . However, no study in the literature separately evaluated the sequences in PI-RADSv2.1. When we compare with meta-analyses performed for PI-RADSv2, the sensitivity, specificity, PPV, and NPV values for the sequences are compatible with the previous studies[30]. A study comparing PI-RADSv2 and 2.1 calculated the diagnostic sensitivity, specificity, PPV, and NPV for PI-RADSv2.1 according to PI-RADS[?]3 are taken as positive for the detection of GS[?]7 tumors according to zones as 94.3%, 24.2%, 46.1%, and 86.1% for PZ and 93.8%, 42.1%, 45% and 93% for TZ, respectively[31]. In our study, taking the PI-RADS score cut-off value as [?]3 positive for PZ, the sensitivity for PCa was 100%, specificity was 11.11%, PPV was 46.67% and NPV was 100.00%, similar to levels to the literature for PZ was observed. Although the PI-RADSv2 system is well standardized and expanded for MpMRI use, studies have reported interobserver agreement is highly variable from low to high[32–34]. A study with 3 observers by Popita et al.[35] found the interobserver agreement kappa coefficient($\varkappa$) was 0.643, 0.664, and 0.568. A study which two radiologists examined 170 patients, determined the interobserver agreement for PI-RADS[?]3 was substantial (all zones $\varkappa$=0.63 PZ $\varkappa$=0.62, TZ $\varkappa$=0.53) and for PI-RADS[?]4 was almost perfect (all zones $\varkappa$=0.91, PZ $\varkappa$=0.91, TZ $\varkappa$=0.87)[36]. Smith et al.[37]found the interobserver agreement was fair with $\varkappa$=0.24. The compatibility degree between experienced observers was higher for the whole gland and PZ lesions compared to the observers with moderate levels of experience. When the sequence-specific interobserver agreement is assessed, values were $\varkappa$=0.24, 0.24, and 0.23 for T2W, DWI, and DCE respectively. Between two radiologists with different levels of experience, we observed moderate compatibility for the use of PI-RADSv2.1 without the cut-off value(all zones $\varkappa$=0.562) and the cut-off value of PI-RADS[?]4(all zones $\varkappa$=0.77). Our data show that the use of the new update to PI-RADSv2.1 increases interobserver agreement with more specific definitions. Increasing observers' experience and future PI-RADS updates will increase the agreement power between inexperienced observers or observers with similar experience.

Limitation

- The small sample group, and lack of equal numbers of lesions according to pathologic diagnosis and zones. Increasing the number of patients in the study may provide better results and beneficial statistical data for the literature.
- As the study was prospectively designed, there were 9/106 lesions in PI-RADS<3 group, so we could not evaluate the sensitivity and specificity of PI-RADS-3, especially in TZ.
- The main disadvantage of TRUS-guided CF-Bx is that the success of the procedure is depending on the operator's experience and lack of standardization.[38]
- Measuring interobserver agreement between radiologists before and after PI-RADS training may reveal the difference between experience and training in terms of MpMRI.

PI-RADSv2.1 was observed to be very effective for detecting lesions, for determining patient selection for biopsy, identifying risk level for patients with prostate cancer suspicion, and follow-up strategies according to risk level. When the PI-RADS[?]3 cut-off value is increased to PI-RADS[?]4, the significant increase in the specificity, PPV and interobserver agreement suggests that the PI-RADS3 criteria will be revised in new versions of the PI-RADS.

When lesions with DCE positivity and DWI score 3 upgrading PI-RADS 3 to 4 and PI-RADS 4 lesions with DWI score 4 are compared, we identified significant differences between ISUP grades. For this reason, we suggest there should be differences in the scoring of these groups.

PI-RADSv2.1 is created to increase interobserver agreement within the framework of v2 and also provides additional explanations for certain criteria. We believe that, as more data to be obtained with further studies, PI-RADS guidelines will be more accurate.

Conflict of Interest:

The authors declare no conflicts of interest.

REFERENCE LIST:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019: {Cancer} {Statistics}, 2019. *CA Cancer J Clin* . 2019;69(1):7-34. doi:10.3322/caac.21551

2. Johnson LM, Turkbey B, Figg WD, Choyke PL. Multiparametric MRI in prostate cancer management. *Nat Rev Clin Oncol* . 2014;11(6):346-353. doi:10.1038/nrclinonc.2014.69

3. Drost FJH, Rannikko A, Valdagni R, et al. Can active surveillance really reduce the harms of overdiagnosing prostate cancer? A reflection of real life clinical practice in the PRIAS study. *Transl Androl Urol* . 2018;7(1):98-105. doi:10.21037/tau.2017.12.28

4. Dinh AH, Melodelima C, Souchon R, et al. Quantitative analysis of prostate multiparametric MR images for detection of aggressive prostate cancer in the peripheral zone: A multiple imager study.*Radiology* . 2016;280(1):117-127. doi:10.1148/radiol.2016151406

5. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* . 2012;22(4):746-757. doi:10.1007/s00330-011-2377-y

6. Mottet N, Bergh RCN Van Den, Vice-chair PC, et al. EAU-ESUR-ESTRO-SIOG Guidelines on Prostate Cancer/ Guias Europeas.*Eur Assoc Urol 2018* . 2018:1-145. http://uroweb.org/guidelines/compilations-of-all-guidelines/.

7. ACR. Prostate Imaging Reporting and Data System (PI-RADS). *Am Coll Radiol* . 2015. https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2.pdf?la=en.

8. Richenberg JL. PI-RADS: Past, present and future. *Clin Radiol* . 2016;71(1):23-24. doi:10.1016/j.crad.2015.10.019

9. PI-RADS. PI-RADS v2.1 - ACR. 2019.

10. Epstein JI, Zelefsky MJ, Sjoberg DD, et al. A Contemporary Prostate Cancer Grading System: A Validated Alternative to the Gleason Score.*Eur Urol* . 2016. doi:10.1016/j.eururo.2015.06.046

11. Jue JS, Barboza MP, Prakash NS, et al. Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy. *Urology* . 2017. doi:10.1016/j.urology.2017.04.015

12. Al-Khalil S, Ibilibor C, Cammack JT, de Riese W. Association of prostate volume with incidence and aggressiveness of prostate cancer.*Res Reports Urol* . 2016. doi:10.2147/RRU.S117963

13. Tang P, Jin XL, Uhlman M, et al. Prostate volume as an independent predictor of prostate cancer in men with PSA of 10-50 ng ml -1.*Asian J Androl* . 2013. doi:10.1038/aja.2013.11

14. Haas GP, Delongchamps N, Brawley OW, Wang CY, de la Roza G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* . 2008.

15. Droz JP, Balducci L, Bolla M, et al. Management of prostate cancer in older men: Recommendations of a working group of the International Society of Geriatric Oncology. *BJU Int* . 2010. doi:10.1111/j.1464-410X.2010.09334.x

16. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* . 2017. doi:10.1016/S0140-6736(16)32401-1

17. Grey ADR, Chana MS, Popert R, Wolfe K, Liyanage SH, Acher PL. Diagnostic accuracy of magnetic resonance imaging (MRI) prostate imaging reporting and data system (PI-RADS) scoring in a transperineal prostate biopsy setting. *BJU Int* . 2015. doi:10.1111/bju.12862

18. Abd-Alazeez M, Kirkham A, Ahmed HU, et al. Performance of multiparametric MRI in men at risk of prostate cancer before the first biopsy: A paired validating cohort study using template prostate mapping biopsies as the reference standard. *Prostate Cancer Prostatic Dis* . 2014. doi:10.1038/pcan.2013.43

19. Thompson JE, Moses D, Shnier R, et al. Multiparametric magnetic resonance imaging guided diagnostic biopsy detects significant prostate cancer and could reduce unnecessary biopsies and over detection: A prospective study. *J Urol* . 2014. doi:10.1016/j.juro.2014.01.014

20. Zhang L, Tang M, Chen S, Lei X, Zhang X, Huan Y. A meta-analysis of use of Prostate Imaging Reporting and Data System Version 2 (PI-RADS V2) with multiparametric MR imaging for the detection of prostate cancer.*Eur Radiol* . 2017. doi:10.1007/s00330-017-4843-7

21. Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic Performance of Prostate Imaging Reporting and Data System Version 2 for Detection of Prostate Cancer: A Systematic Review and Diagnostic Meta-analysis.*Eur Urol* . 2017. doi:10.1016/j.eururo.2017.01.042

22. Venderink W, van Luijtelaar A, Bomers JGR, et al. Results of Targeted Biopsy in Men with Magnetic Resonance Imaging Lesions Classified Equivocal, Likely or Highly Likely to Be Clinically Significant Prostate Cancer. *Eur Urol* . 2018. doi:10.1016/j.eururo.2017.02.021

23. Mathur S, O'Malley ME, Ghai S, et al. Correlation of 3T multiparametric prostate MRI using prostate imaging reporting and data system (PIRADS) version 2 with biopsy as reference standard. *Abdom Radiol* . 2019;44(1):252-258. doi:10.1007/s00261-018-1696-8

24. Mehralivand S, Bednarova S, Shih JH, et al. Prospective Evaluation of PI-RADS^{TM} Version 2 Using the International Society of Urological Pathology Prostate Cancer Grade Group System. *J Urol* . 2017;198(3):583-590. doi:10.1016/j.juro.2017.03.131

25. Yang S, Zhao W, Tan S, et al. Combining clinical and MRI data to manage PI-RADS 3 lesions and reduce excessive biopsy. *Transl Androl Urol* . 2020;9(3):1252-1261. doi:10.21037/tau-19-755

26. Walker SM, Mehralivand S, Harmon SA, et al. Prospective Evaluation of PI-RADS Version 2.1 for Prostate Cancer Detection. *Am J Roentgenol* . 2020;215(5):1098-1103. doi:10.2214/ajr.19.22679

27. Wysock JS, Mendhiratta N, Zattoni F, et al. Predictive value of negative 3T multiparametric magnetic resonance imaging of the prostate on 12-core biopsy results. *BJU Int* . 2016. doi:10.1111/bju.13427

28. Pokorny MR, De Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance (MR) imaging with subsequent mr-guided biopsy in men without previous prostate biopsies.*Eur Urol* . 2014. doi:10.1016/j.eururo.2014.03.002

29. Itatani R, Namimoto T, Atsuji S, et al. Negative predictive value of multiparametric MRI for prostate cancer detection: outcome of 5-year follow-up in men with negative findings on initial MRI studies.*Eur J Radiol* . 2014. doi:10.1016/j.ejrad.2014.06.026

30. Chen Z, Zheng Y, Ji G, et al. Accuracy of dynamic contrast-enhanced magnetic resonance imaging in the diagnosis of prostate cancer: Systematic review and meta-analysis. *Oncotarget* . 2017. doi:10.18632/oncotarget.20316

31. Rudolph MM, Baur ADJ, Cash H, et al. Diagnostic performance of PI-RADS version 2.1 compared to version 2.0 for detection of peripheral and transition zone prostate cancer. *Sci Rep* . 2020;10(1):1-10. doi:10.1038/s41598-020-72544-z

32. Benndorf M, Hahn F, Krönig M, et al. Diagnostic performance and reproducibility of T2w based and diffusion weighted imaging (DWI) based PI-RADSv2 lexicon descriptors for prostate MRI. *Eur J Radiol* . 2017. doi:10.1016/j.ejrad.2017.05.015

33. Greer MD, Shih JH, Barrett T, et al. All over the map: An interobserver agreement study of tumor location based on the PI-RADSv2 sector map. *J Magn Reson Imaging* . 2018. doi:10.1002/jmri.25948

34. Sonn G, Fan R, Ghanouni P, et al. Prostate Magnetic Resonance Imaging Interpretation Varies Substantially Across Radiologists.*Eur Urol Focus* . 2017;5. doi:10.1016/j.euf.2017.11.010

35. Popita C, Popita AR, Andrei A, et al. Interobserver agreement in prostate cancer detection using multiparametric MRI. *J BUON* . 2018;23(4):1061-1069.

36. Purysko AS, Bittencourt LK, Bullen JA, Mostardeiro TR, Herts BR, Klein EA. Accuracy and interobserver agreement for prostate imaging reporting and data system, version 2, for the characterization of lesions identified on multiparametric MRI of the prostate. *Am J Roentgenol* . 2017;209(2):339-345. doi:10.2214/AJR.16.17289

37. Smith CP, Harmon SA, Barrett T, et al. Intra- and interreader reproducibility of PI-RADSv2: A multireader study. *J Magn Reson Imaging* . 2019. doi:10.1002/jmri.26555

38. Brown AM, Elbuluk O, Mertan F, et al. Recent advances in image-guided targeted prostate biopsy. *Abdom Imaging* . 2015;40(6):1788-1799. doi:10.1007/s00261-015-0353-8

TABLES:

Table-1: MpMRI Protocols (1.5T Siemens MagnetomAera)

MpMRI Protocols (1.5T Siemens Magnetom Aera)

T2W Coronal
T2W axial
T2W sagittal
T2W Coronal
T2W axial
DWI
T1W axial Lymph node
T1Map axial
T1W DCE-MRI***
postcontrast T1W axial
HASTE:Half-fourier acquisition single shot turbo spin echo TSE:Turbo Spin Echo TE:Time of Echo TR:Tin

*There is no currently widely accepted optimal "high b-value" beyond the requirement for a DW image set with a b-value [?]1,400 sec/mm^2.[9]

***In dynamic contrast enhancement imaging (DCE-MRI), a gadolinium-based contrast agent with an automatic injector at 0.1-0.2 mmol/kg concentration and 2-4 mL/s injection rate via IV were used and T1 axial sections were obtained over 240-300 sc. duration with one every 7 sc. before, during, and after administration including the entire prostate.

Table-2: Distribution of PI-RADS scores given to lesions by two readers.

Variables	PI-RADS Score of 1st Reader	PI-RADS Score of 1st Reader	PI-RADS Score of 1st Reader	PI-RADS Score of 1st Reader	PI-RADS Score of 1st Reader	Total
PI-RADS Score of 2nd Reader	**1**	**2**	**3**	**4**	**5**	
1	**5**	0	0	0	0	5
2	0	**2**	14	1	0	17
3	0	2	**37**	5	1	45
4	0	0	2	**17**	2	21
5	0	0	1	2	**15**	18
Final PI-RADS Score	5	4	54	25	18	106

Table-3: Descriptive statistics of patients included in the study.

Characteristics of patient	Histopathological diagnosis	Histopathological diagnosis	
	Malignant(n:43) Average±Standard Deviation Median (25p-75p)	**Benign (n:63) Average±Standard Deviation Median (25p-75p)**	**p**
Age	65.24±7.90 65.0(59.75-70.0)	62.07±6.90 62.50(57.0-66.0)	0.053
PSA	15.24±24.12 7.56(5.28-11.19)	8.75±7.52 6.94(4.00-9.71)	0.259
Prostate Volume	46.11±29.21 39.37(30.74-50.53)	75.94±39.51 72.50(44.87-100.75)	<0.001
PSAd	0.37±0.55 0.20(0.11-0.33)	0.13±0.121 0.11(0.07-0.147)	<0.001

Prostate Volume and PSAd values are statistically significant for malign and benign lesion differentation.

PSA: prostate spesific anjigen PSAd: PSA density

Table-4: Statistical parameters for the cancer detection in Peripheral Zone(PZ) and Transitional Zone(TZ).

Zone	Sequence	Cut-off Value	Sensitivity	Specificity	PPV	NPV	A
PZ	**T2W**	PI-RADS [?]3 positive	100%	27.78%	51,85%	100%	5
		PI-RADS[?]4 positive	32.14%	97.22%	90%	64.81%	6
	DWI	PI-RADS [?]3 positive	92.86%	13.89%	45.61%	71.43%	4

Zone	Sequence	Cut-off Value	Sensitivity	Specificity	PPV	NPV	A
		PI-RADS[?] 4 positive	46.43%	91.67%	81.25%	68.75%	7
	MpMRI (T2W, DWI and DCE)	PI-RADS [?]3 positive	100%	11.11%	46.67%	100%	5
		PI-RADS [?]4 positive	71.43%	72.22%	66.67%	76.47%	7
TZ	**T2W**	PI-RADS[?]4 positive	33.33%	90.91%	50%	83.33%	7
	DWI	PI-RADS[?]4 positive	33.33%	59.09%	18.18%	76.47%	5
	MpMRI (T2W, DWI and DCE)	PI-RADS[?]4 positive	33.33%	90.91%	50%	83.33%	7

Statistical parameters when the threshold value for cancer detection PI-RADS[?]3 and PI-RADS[?]4 taken as positive in PZ and TZ when T2W and DWI are independently evaluated. In TZ, there was no patient with a PI-RADS score <3, so the diagnostic parameters for this variable could not be calculated.

PZ: peripheral zone TZ: transitional zone PPV: positive predictive value NPV: negative predictive value MpMRI:multiparametric magnetic resonance imaging T2W: T2Weighted imaging DWI: diffusion-weighted imaging DCE: dynamic contrast enhancement imaging

Table-5: Statistical parameters for the cancer detection in the whole gland

	Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy
T2W	PI-RADS [?]3 positive	100%	22.58%	47.25%	100%	53.77%
	PI-RADS[?]4 positive	46.51%	93.75%	45.26%	94.04%	71.43%
DWI	PI-RADS [?]3 positive	95.35%	14.52%	43.62%	81.82%	47.62%
	PI-RADS[?]4 positive	54.55%	80.65%	23.84%	94.10%	69.81%
DCE	PI-RADS[?]3 positive	79.07%	68.85%	64.15%	82.35%	80.21%
T2W and DWI (biparametric)	PI-RADS[?]3 positive	100%	23.81%	47.25%	100%	54.85%
MpMRG (T2W, DWI and DCE)	PI-RADS [?]3 positive	100%	12.90%	44.33%	100%	49.06%
	PI-RADS[?]4 positive	72.09%	80.65%	72.09%	80.65%	77.36%

Sensitivity, specificity, negative predictive value, and positive predictive values for prostate cancer detection are shown for T2W, DWI independently and T2W-DWI (biparametric) and MpMRI, when PI-RADS [?]3 and [?]4 scores taken as positive accordingly PI-RADS v2.1.

PPV: positive predictive value NPV: negative predictive value MpMRI:multiparametric magnetic resonance imaging T2W: T2Weighted imaging DWI: diffusion-weighted imaging DCE: dynamic contrast enhancement

imaging

Table-6: Assesments of lesions' ISUP grades according to their PI-RADS category.

	BENIGN	**ISUP 1 (37.2%)**	**ISUP 2 (13.9%)**	**ISUP 3 (13.9%)**	**ISUP 4 (13.9%)**	**ISUP 5 (20.9%)**
	n					
PI-RADS 1	5	0	0	0	0	0
PI-RADS 2	4	0	0	0	0	0
PI-RADS 3	42	12	0	0	0	0
PI-RADS 4	11	4	4	3	2	1
PI-RADS 5	1	0	2	3	4	8
TOTAL	**63**	**16**	**6**	**6**	**6**	**9**

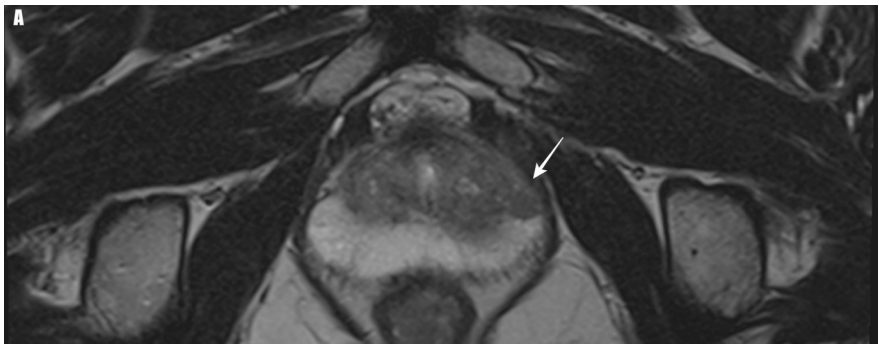
There was a positive correlation between the PI-RADSv2.1 score and the ISUP score.

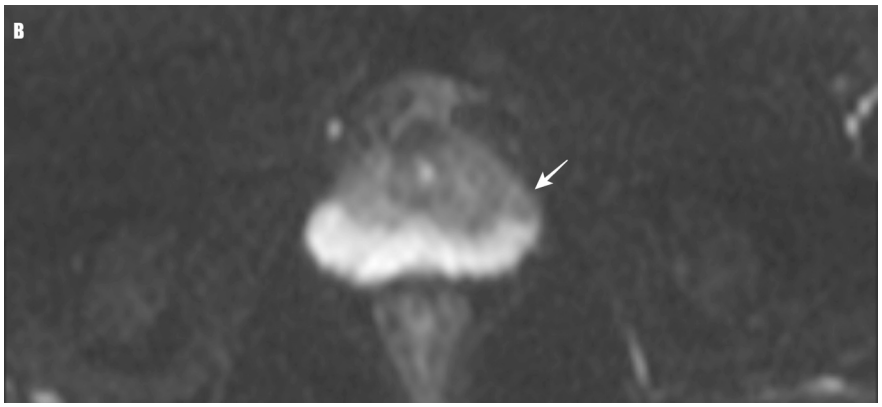
Table-7: The correlation between ISUP Grades and DWI scores of PI-RADS 4 lesions in the Peripheral Zone

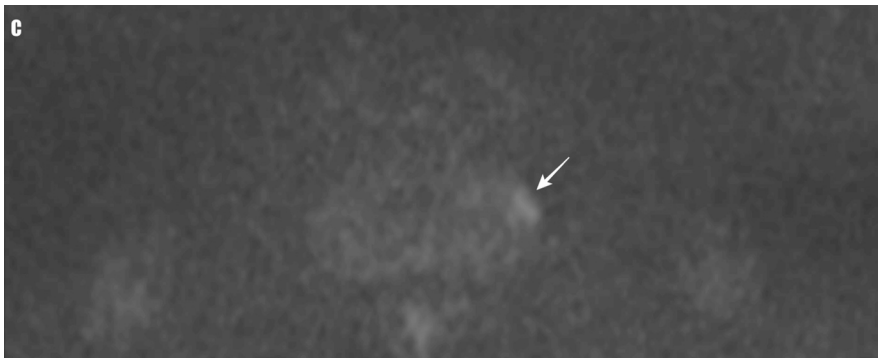
PI-RADS 4	**PI-RADS 4**	**ISUP Grade**	**ISUP Grade**	**ISUP Grade**	**ISUP Grade**	**ISUP Grade**	**I**
DWI score	**DCI Status**	**1**	**2**	**3**	**4**	**5**	**T**
3	Upgraded by +DCI	4(57.1%)	2(28.6%)	0(0.0%)	0(0.0%)	1(14.3%)	7
4	NA	0(0.0%)	2(33.3%)	2(33.3%)	2(33.3%)	0(0.0%)	6
Total		**4**	**4**	**2**	**2**	**1**	1

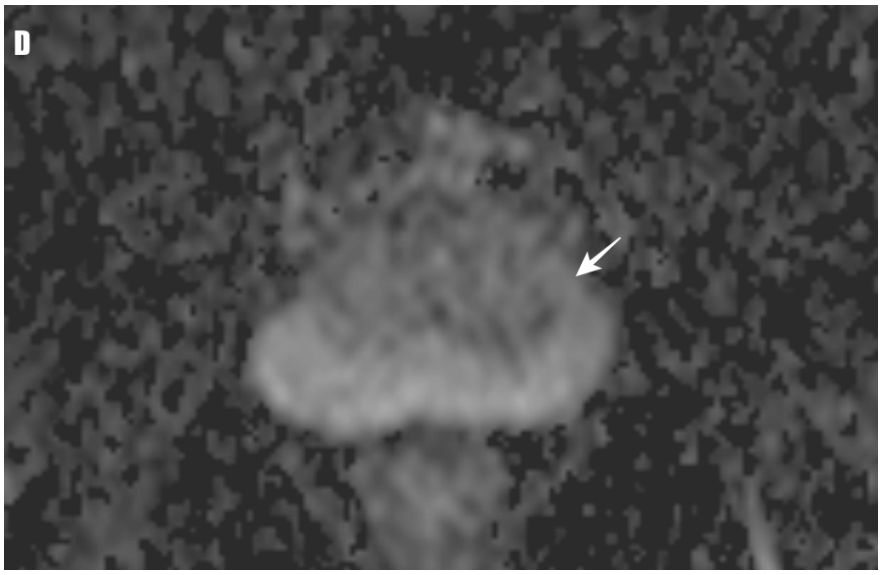
FIGURES:

Figure-1









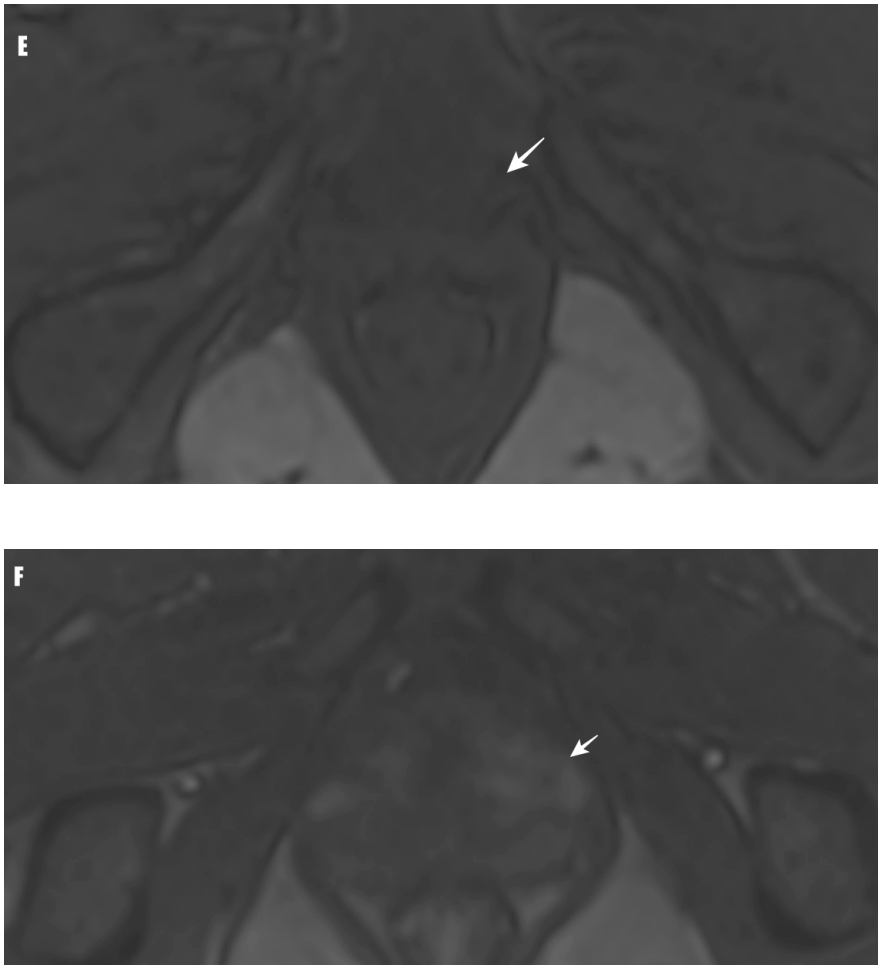
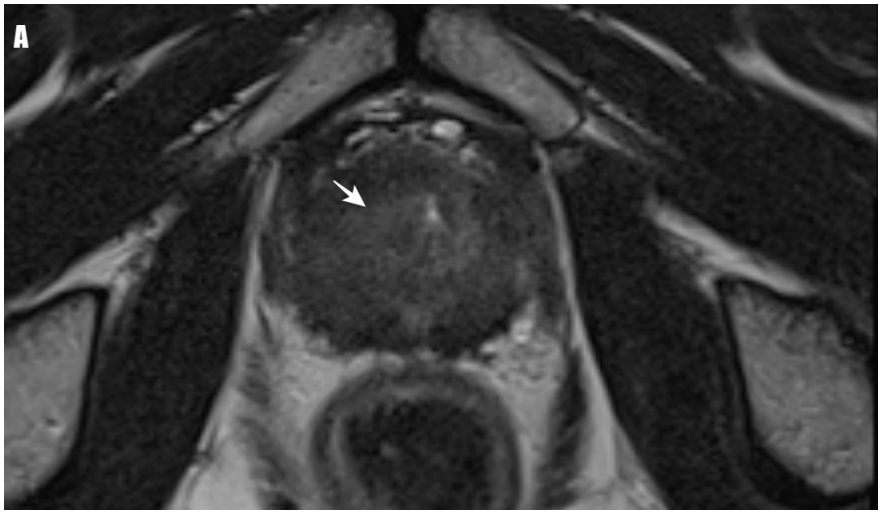
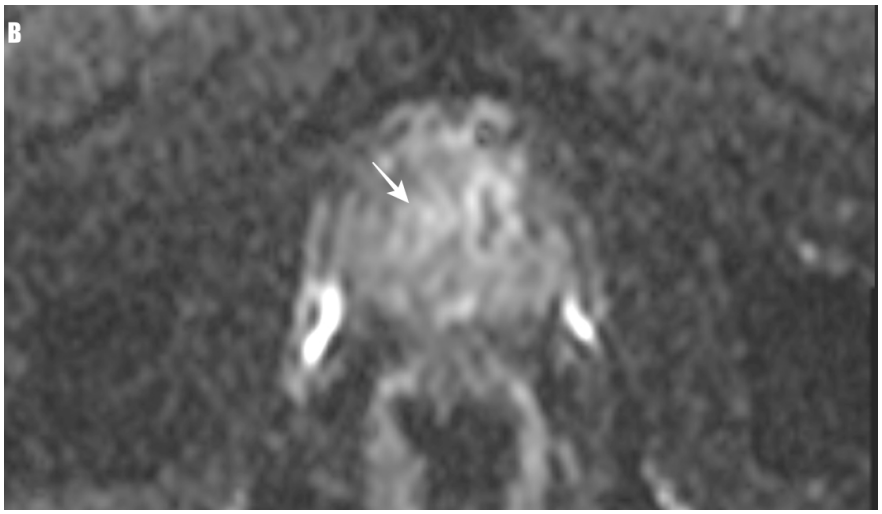
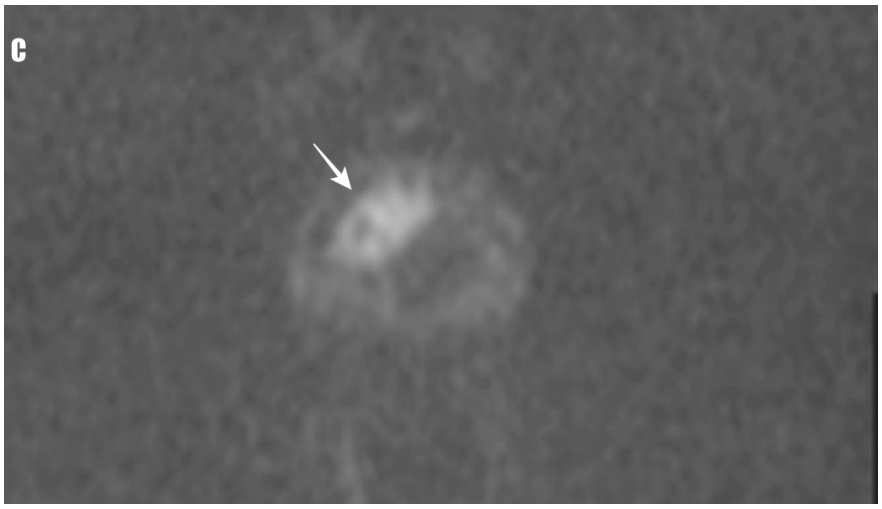


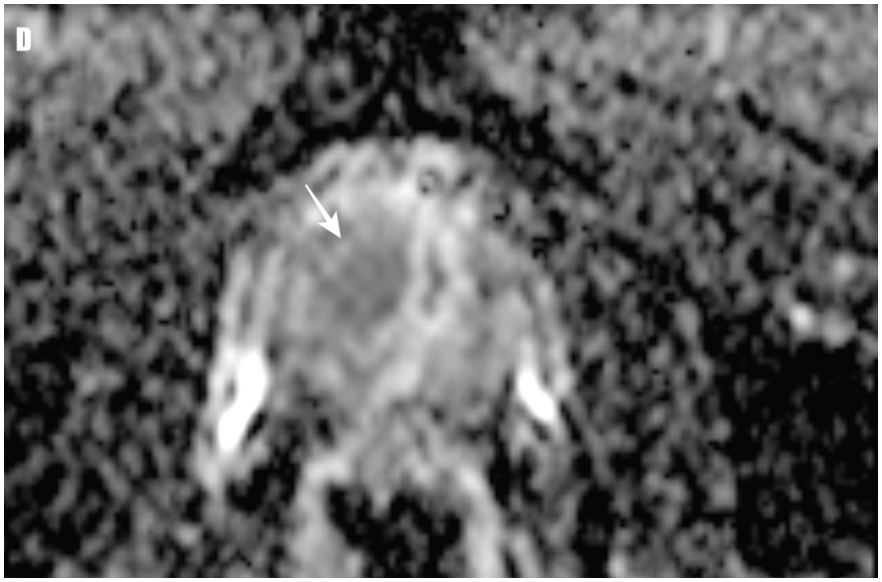
Figure.1 56-year-old man with prostate-specific antigen level of 5.6 ng/mL. Arrows present Prostate Imaging Reporting and Data and System (PI-RADS) category 4 lesions visible in the peripheral zone.**A** , Axial T2-weighted MR image shows lesion in the left-mid peripheral zone. The dimension of the lesion is 1.0 cm which is consistent with the PI-RADS score of 3 on T2-weighted image. **B** ,**C,** show that the lesion is hypointense on DWI(b=50 s/mm^2) and hyperintense, on DWI(b=1800 s/mm^2). **D** , Apparent Diffusion Coefficient map, indicates that the lesion is mildly hypointense, making it PI-RADS score of 3 on DWI. **E** (precontrast T1-Weighted) **and F,**Dynamic contrast enhancement MR image shows early enhancement within same location as lesion in **A**–**D** with early enhancement for overall PI-RADSv2.1 score of 4. TRUS-guided cognitive MRI fusion biopsy is detected prostate cancer with ISUP 1.

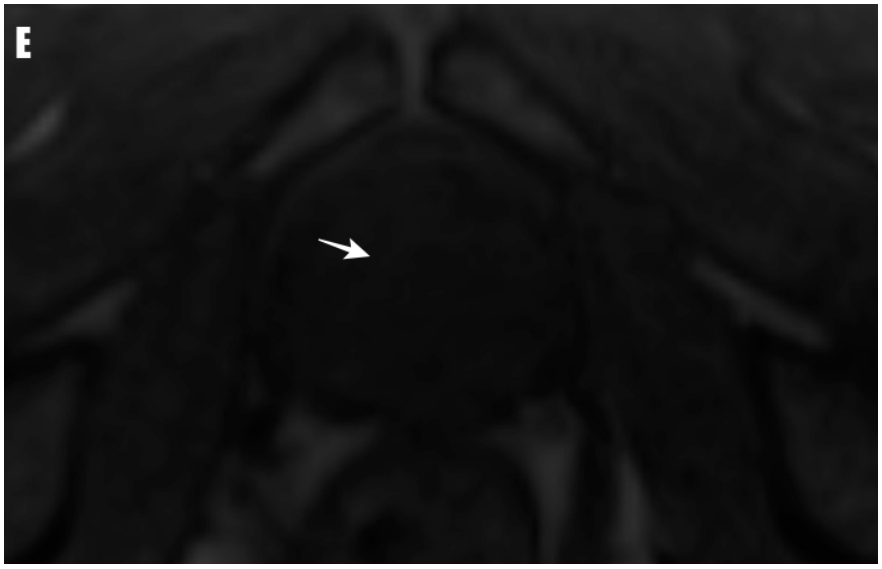
Figure.2











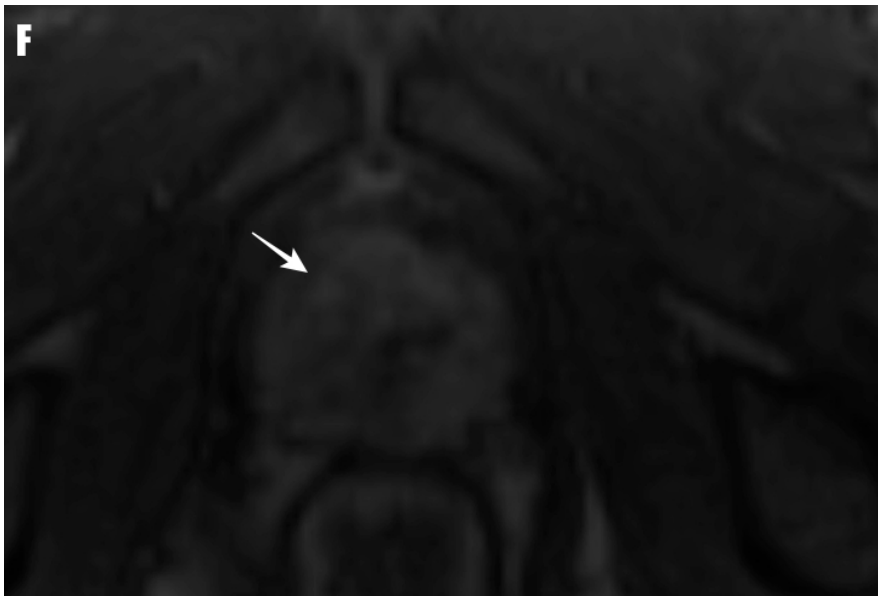


Figure.2 67-year-old man with prostate-specific antigen level of 8.31 ng/mL. Arrows present Prostate Imaging Reporting and Data and System (PI-RADS) category 5 lesions visible in the peripheral zone.**A** , Axial T2-weighted MR image shows lesion in the right-apex peripheral zone. The dimension of the lesion is 2.0 cm which is consistent with the PI-RADS score of 5 on T2-weighted image. **B** ,**C,** show that the lesion is hypointense on DWI(b=50 s/mm^2) and hyperintense, on DWI(b=1800 s/mm^2). **D** , Apparent Diffusion Coefficient map, indicates that the lesion is significantly hypointense, making it PI-RADS score of 5 on DWI. **E** (precontrast T1-Weighted)**and F,** Dynamic contrast enhancement MR image shows early enhancement within same location as lesion in **A**–**D** with early enhancement for overall PI-RADSv2.1 score of 5. TRUS-guided cognitive MRI fusion biopsy is detected prostate cancer with ISUP 5.

TABLE and FIGURE LEGENDS:

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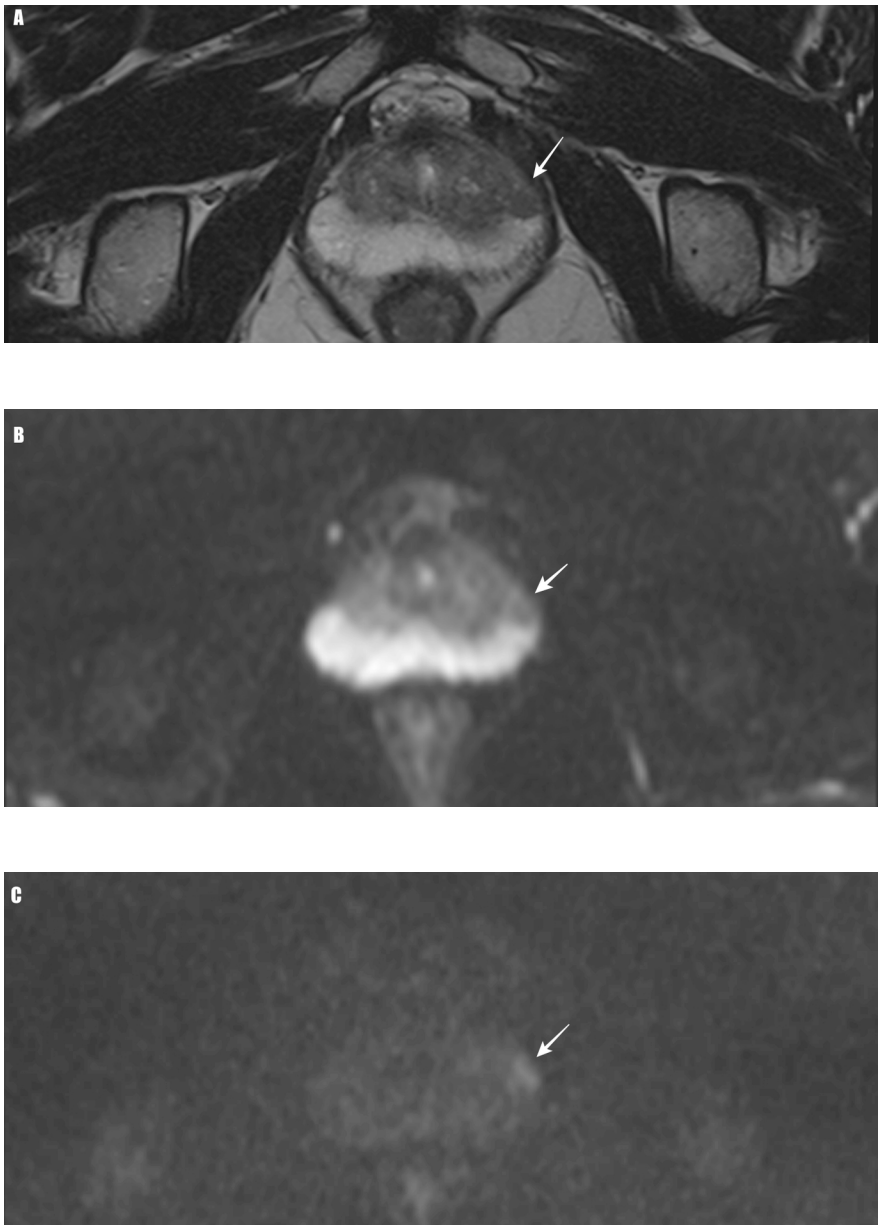

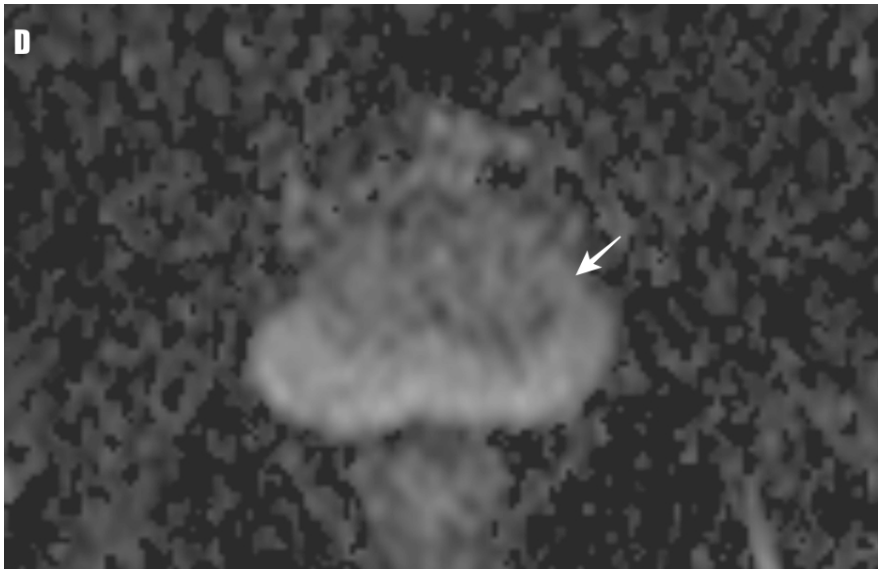

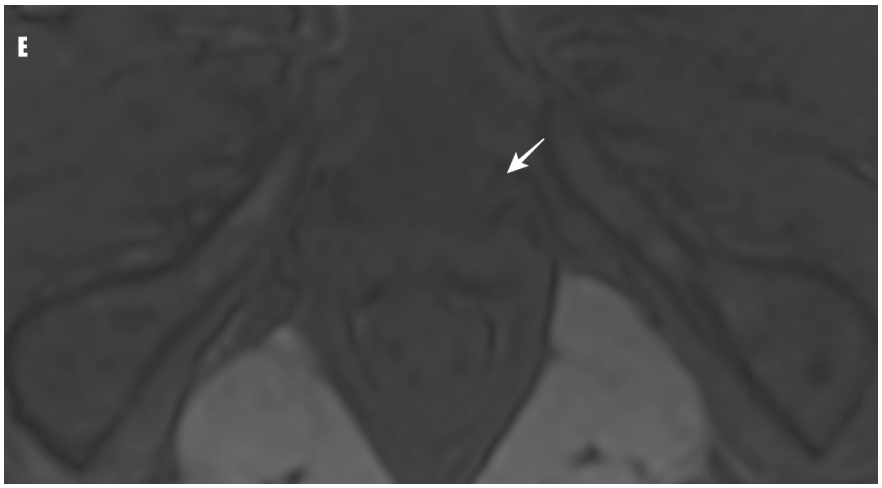

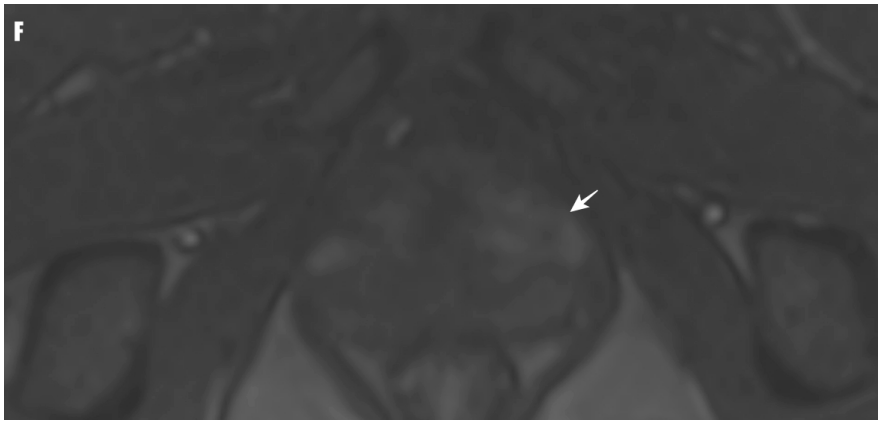

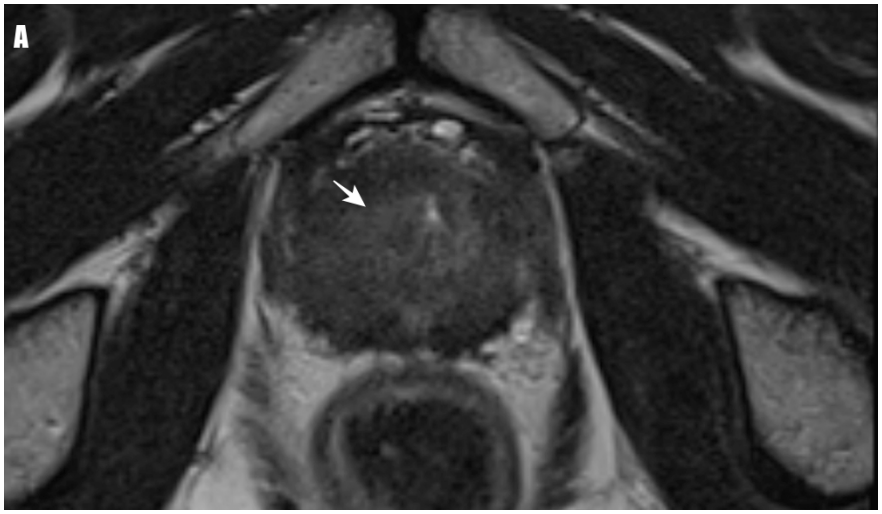

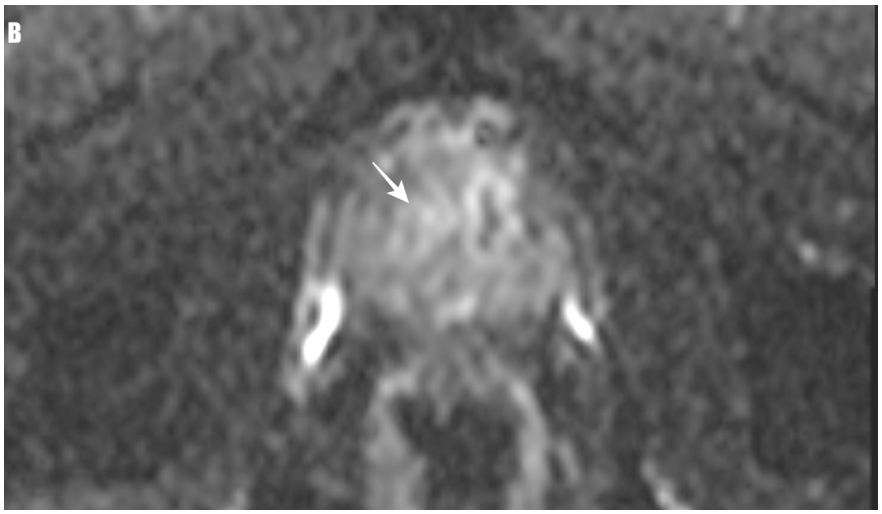

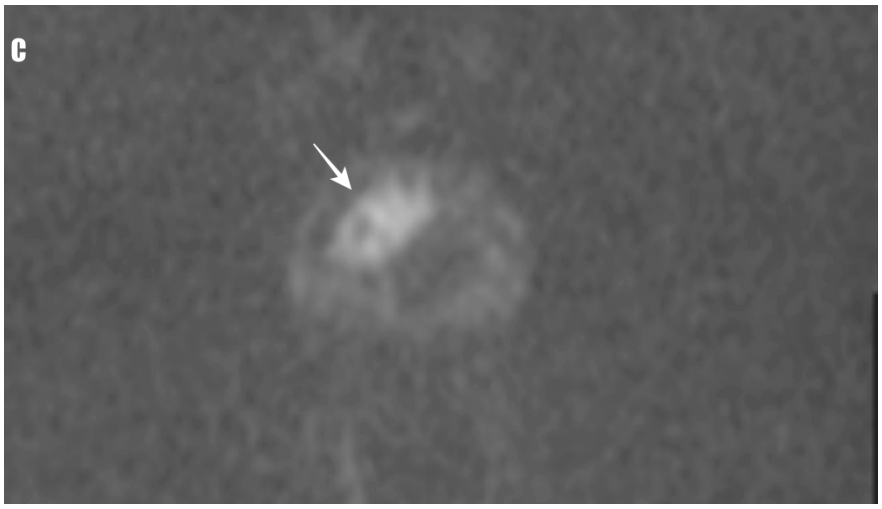

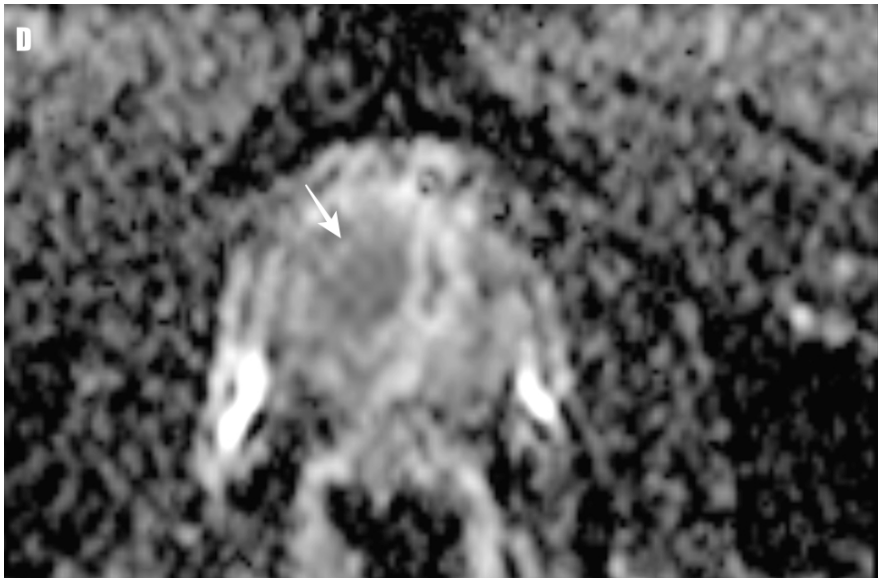

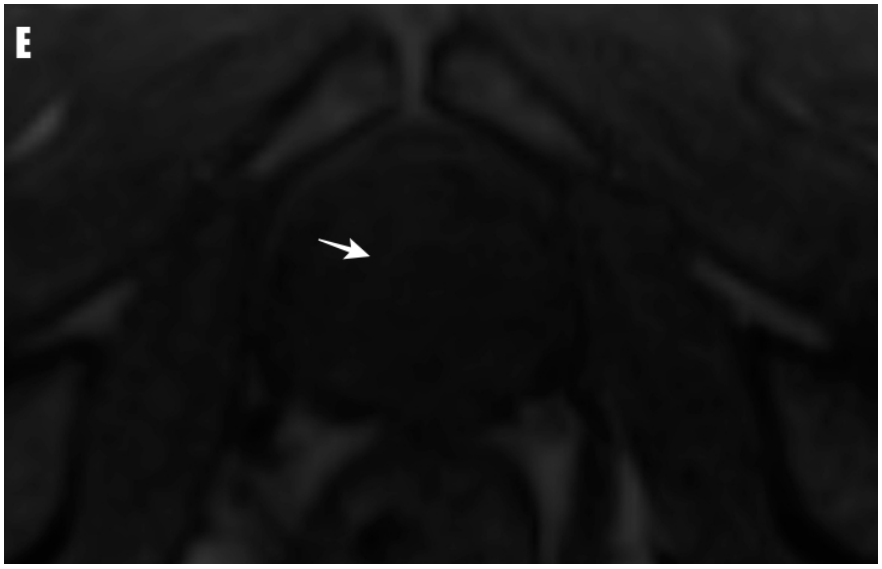

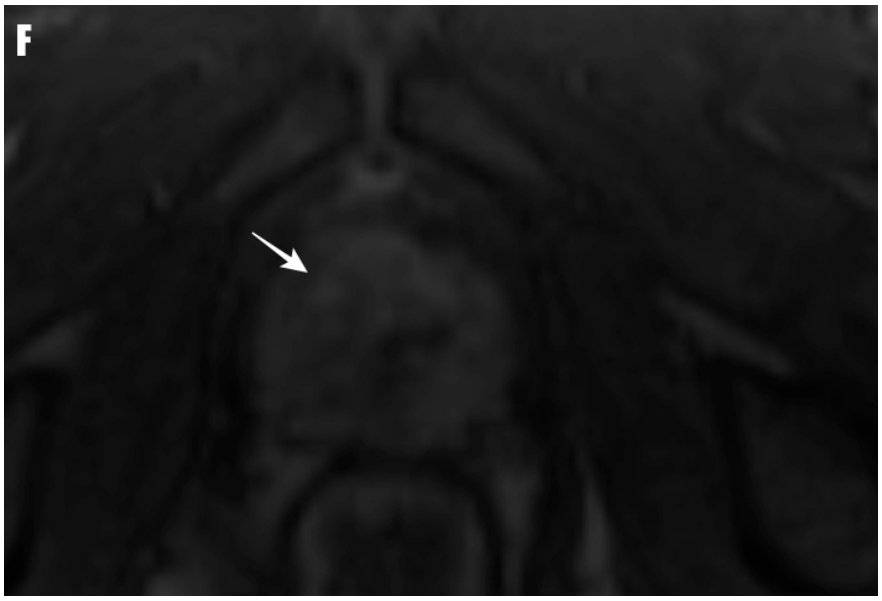

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TABLES.pdf available at https://authorea.com/users/410336/articles/519747-prospective-evaluation-of-the-correlation-between-prostate-imaging-reporting-and-data-system-pi-rads-version-2-1-and-international-society-of-urological-pathology-isup-score-and-inter-observer-reproducibility-of-the-new-version