The diagnostic accuracy of T2-w, DWI and perfusion kinetics in PI-RADS: do we need gadolinium enhancer for the diagnosis of prostate cancer?

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**Aims and objectives**

Magnetic resonance imaging (MRI) is an established diagnostic method with rapidly increasing popularity and availability in radiological diagnostic centers. Improved image reconstruction methods and new generation devices with faster scanning times and higher static field are some of the technical features supporting the current role of MRI as the standard of care for many organs and diseases, including the prostate diagnostics. MRI analyzes the physical properties of hydrogen magnetization to convey not only anatomical but also functional information such as the cellularity, the extracellular space restriction and the vascularization of the tissue of interest. The combination of anatomical and functional sequences has been established with the term "multiparametric MRI", or mpMRI (Figure 1).

In the last 3 years, mpMRI is gaining ground as the standard of care for the early diagnosis of prostate cancer, while still maintaining its established position in follow up during active surveillance and for the staging of diagnosed disease. The American College of Radiology (ACR) introduced in the latest guidelines of 2017 the innovative recommendation of mpMRI in biopsy-naïve patients in view of an MR-guided or magnetic resonance - transrectal ultrasound (MR-TRUS) fusion biopsy [1,2]. The 2017 guidelines if the European Association of Urology along with the European Society for Radiotherapy and Oncology and the International Society of Geriatric Oncology (EAU/ESTRO/SIOG), on the other hand, still acknowledge the TRUS biopsy as the standard of care for biopsy-naïve patients with prostate cancer suspicion [3]. EAU/ESTRO/SIOG guidelines propose the role of mpMRI in view of an MR-guided or an MR-TRUS biopsy in clinical scenarios with persistent suspicion for malignity after at least one negative TRUS biopsy [3]. This is the most acceptable approach, supported also by the European Society of Medical Oncology (ESMO) and the British organization National Institute for Health and Care Excellence (NICE) [4-6]. The American Urological Association (AUA) is more conservative about the role of mpMRI in the early prostate cancer diagnosis, however, in the latest guidelines 2017 recommends mpMRI in clinical scenarios of repeated prostate biopsy and considers mpMRI in the early screening process as an investigational tool [7-9](Figure 2).

Dealing with diagnosis and treatment of prostate cancer is an interdisciplinary and quite often inter-regional challenge. In order to normalize the image interpretation language to a common denominator, the European Society of Urogenital Radiology (ESUR) released in 2012 for the first time a structured reporting system, the Prostate Imaging Reporting And Data System version 1 (PI-RADS™ 1) [10]. PI-RADS is a structured, unifying mpMRI-based score for malignancy prediction. According to PI-RADS™1, T2w images, DWI with ADC maps, DCE and optionally magnetic resonance spectroscopy (MRS) are evaluated with a score 1 to 5. The final summation product, ranging from 3 to 15 (without MRS) or 4-20 (with MRS), is classified in the PI-RADS scale from 1 to 5. Prostate scored PI-RADS 1 and 2 is a candidate for active surveillance and for lesions scoring PI-RADS 4 and
5 an MR- or MR-TRUS targeted biopsy is indicated. Lesions scored as PI-RADS 3 are potential biopsy candidates, the decision being dependent on the global patient’s profile.

PI-RADS™ 1 was evaluated by a meta-analysis summarizing 14 studies (1785 patients) [11]. The PI-RADS Steering European Society of Uroradiology (ESUR) committee in combination with the ACR has published a new, revised version PI-RADS™2 in 2015 [12,13] in order to simplify reporting and reducing the inter-observer gap. The core changes in PI-RADS™2 are summarized in (Figure 3):

i. Instead of the symmetrically balanced contribution of all sequences in the final scoring, PI-RADS™2 prioritizes the dominant sequences for each prostate region: Diffusion-weighted imaging (DWI) for the peripheral zone and T2weighted imaging (T2w) for the transitional zone. The dominant sequence determines the final PI-RADS score as it can be only minimally affected by other sequences.

ii. Dynamic Contrast Enhancement (DCE) in PI-RADS™2 is drastically restricted to a dichotomous role, influencing only the decision between PI-RADS 3 and 4 in the peripheral zone (Figure 4) [14].

After an experience of 2 years with PI-RADS™2, we aimed to assess the effectiveness of sequence prioritization as well as the predictive value of the DCE (Figure 5). The retrospective evaluation of our databank has revealed equal diagnostic accuracy for T2w and DWI in the transitional and peripheral zones. Moreover, the gadolinium enhancer and DCE perfusion kinetic analysis did not significantly increase the diagnostic accuracy of PI-RADS in our series. Based on these results and similar studies we provide hints for possible implications towards the common target, to improve the early prostate cancer diagnosis and at the same time minimize the potential harm through the screening process.
**Fig. 1:** Features of the multiparametric MRI (mpMRI). Sample images of a PI-RADS 5 lesion (white arrow) from (a) the transitional and (b) the peripheral prostate zone. mpMRI combines (ai, bi) anatomical T2weighted (T2w), high-resolution sequences with functional sequences such as (aii, bii) Diffusion Weighted Imaging (DWI) and (aiii, biii) T1-weighted series with Dynamic Contrast Enhancement (DCE). Panels (iv) show the corresponding dynamic analysis of the suspect lesion (white arrow).

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**Fig. 2:** Recommendation of mpMRI in the current guidelines for early prostate diagnosis and treatment. According to the American College of Radiology, mpMRI has an indication for biopsy-naive patients in the view of a first MRI-guided or MR-TRUS biopsy. The majority of European and British guidelines define TRUS as the standard of care and recognize the role of mpMRI by persisting clinical suspicion despite a negative first TRUS biopsy.

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**mpMRI scoring: PI-RADS™2**

**Updates PI-RADS™2**

- **Prioritization**
  
  T2w dominance in the transitional zone and DWI dominance in the peripheral zone

- **Dichotomous DCE** role in the peripheral zone only

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**Fig. 3:** Main updates of PI-RADS™2.

**mpMRI evaluation with PI-RADS™2**

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<thead>
<tr>
<th>DWI</th>
<th>T2w</th>
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**Fig. 4:** Dichotomous role of the DCE in PI-RADS™2 only for PI-RADS 3 lesions in the peripheral zone.

Fig. 5: Aims and Objectives.

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Methods and materials

The study was retrospective for 312 lesions from 221 patients aged 64±7 years (mean/#), scanned in our department between 4/2010 and 11/2017. All patients were examined with suspicion for prostate cancer based on elevated PSA assay and in the vast majority on basis of an inconclusive TRUS biopsy. An MR-guided biopsy followed within 3 months post-diagnosis. All patients were examined with 3.0T static field strength (Philips Ingenia, Philips Medical Systems, Böblingen, Germany). The lesion sample is well balanced between different prostate zones with 164 lesions (52.56%) in the transitional and 148 lesions (47.44%) in the peripheral zone. The following mpMRI dataset has been applied as the standard of diagnosis with an average duration of 35 - 40 min:

i. T2w tse HR paracoronal, paraxial and parasagittal in 2mm resolution
ii. Diffusion-weighted Echo Planar Imaging (DWI EPI) at 5 different b-values (b0-100-500-800-1000 s/mm$^2$)
iii. T1 weighted Fast Field Echo (T1-FFE) with dynamic contrast enhancement (DCE) in 25 repetitions with 13.35 s temporal resolution and 7 s delay. A body weight-adjusted bolus of gadoteridol (ProHance®, Bracco Imaging S.p.A., Konstanz, Germany) 0.1mmol/kg was injected at 3 ml/s flow rate.

All lesions were graded by 2 radiologists; one with intermediate experience and a board-certified radiologist according to PI-RADS™2 (Figure 6).

Logistics and descriptive statistical data processing were performed with LibreOffice™ 4.4.7.2 (The Document Foundation, Berlin, Germany) and the Microsoft© Office suite 2010 (Microsoft Ireland Operations Limited, Dublin, Ireland. Graphical processing was accomplished using the free source platform Inkscape (License name: GPL v2+, https://inkscape.org). Percentages are rounded up to the closest integer unless specifically stated otherwise.

Ethical statement

All patient data derived from the prostate database of the Suedharz Hospital Nordhausen. Data were analyzed retrospectively, fully anonymized, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its amendments as well as with the guidelines of the Ethical Committee for clinical studies of the University of Jena. Due to the retrospective character of the study, the ethical committee has waived the mandate from obtaining a legally effective informed consent from the included subjects.
Material and Methods

- Retrospective study of diagnostic accuracy
- 312 MRI-guided biopsied lesions
- 221 patients 64±7 y.o.
- 148 (47%) peripheral, 164 (53%) transitional
- 164 (53%) malignant (including ASAP) and 148 (47%) benign
- 3T MRI (Philips Ingenia), superficial coil (without endorectal coil)
- T2w tse transversal, DWI b 0-100-500-800-1000 s²/mm, ADC and DCE (gadoteridol)

Fig. 6: Materials and Methods.

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Receiver Operating Characteristic (ROC) statistical analysis was implemented in order to estimate the optimized diagnostic accuracy for T2w, DWI, and DCE for each prostate subregion (Figures 7, 8, 9).

In the peripheral zone, the optimized sensitivity (Se) / specificity (Sp) was 83%/57% with a corresponding Area Under Curve of 0.72. The Se/Sp of DWI was for the same lesions 90%/41% with AUC 0.69, respectively. Thus, in our settings, both sequences show a moderate performance, without any statistically significant dominance to one another (P 0.61, chi-squared test) (Figure 7). In the transitional zone, the Se/Sp of the T2w is 79%/61% and 87%/49% for the DWI. The AUC on the ROC curve diagram is calculated 0.75 for the T2w and 0.72 or the DWI, respectively, hence revealing a moderate diagnostic accuracy for both sequences in the transitional zone with no significant difference to each other (P 0.68, chi-squared test) (Figure 8). All in all, this retrospective analysis reveals a moderate diagnostic accuracy for T2w and DWI without any outstanding dominant performance in the transitional or peripheral zone.

The standalone PI-RADS scoring of the DCE performed poorer than T2w and DWI (Figure 9). With a Se/Sp of 70%/42% in the peripheral zone and 80%/49% in the transitional zone with corresponding AUC values of 0.61 and 0.62, the DCE is significantly less accurate parameter compared to the T2w (P 0.02) and the DWI (P 0.04) especially in the transitional zone (Figure 9). Thus, the current study suggests that DCE is less accurate malignancy predictive marker compared to the non-enhanced mpMRI sequences in the standalone setting.

Furthermore, we aimed to assess the predictive value of DCE as a secondary PI-RADS feature for the classification of ambivalent lesions (Figure 4). For this reason, we analyzed the dignity of lesions being over-called or under-called based on the DCE scoring. The positive predictive value (PPV) of the DCE turned out to be 49% for the peripheral and 46% for the transitional zone (Figure 9). Amongst the over-called lesions, the vast majority corresponded to prostatitis and benign prostate hyperplasia, with no predilection towards a particular benign type. Summarizing the above, this dataset provides evidence that the DCE does not significantly increase the diagnostic accuracy of the T2w and DWI PI-RADS.
Fig. 7: Diagnostic accuracy of T2w and DWI PI-RADS in the peripheral zone. (Left) ROC curves for T2w (red line) and DWI (red dashed line). (Right), tabulated sensitivity (Se), specificity (Sp) and Area Under Curve (AUC). Both modalities show equal diagnostic accuracy, $P \leq 0.01$ chi/square test.
Fig. 8: Diagnostic accuracy of T2w and DWI PI-RADS in the transitional zone. (Left) ROC curves for T2w (red line) and DWI (red dashed line). (Right), tabulated sensitivity (Se), specificity (Sp) and Area Under Curve (AUC). Both modalities show equal diagnostic accuracy, P 0.68 chi-square test.
Fig. 9: Diagnostic accuracy of DCE in the peripheral (right) and transitional (left) zone. ROC curves for DCE (green dashed line). On the same graph, the corresponding T2w and DWI (gray line and dashed line) are left for comparison. (Below), tabulated sensitivity (Se), specificity (Sp) and Area Under Curve (AUC). In the transitional zone, the diagnostic accuracy of DCE is significantly reduced compared to the other modalities, P 0.02 and 0.04 versus T2w and DWI, chi-square test.

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Conclusion

In this study, we implement a retrospective evaluation setting of MRI-guided prostate biopsies to assess the diagnostic accuracy of the current mp-MRI scoring system, PI-RADS™2, in its individual parameters. T2w and DWI PI-RADS performed with equal diagnostic accuracy in the transitional and peripheral zone. Hence, the prioritization of T2w for the transitional and DWI for the peripheral zone as implemented in PI-RADS™2 does not reflect on this dataset (Figure 10). Moreover, the DCE series did not significantly increase the diagnostic accuracy of PI-RADS either in the transitional or peripheral zone. Similar data from independent groups [15-17] suggest the necessity for prospective, case-control or randomized controlled studies in order to strengthen the evidence level for the use of gadolinium prostate mpMRI.
Take-home message

The diagnostic accuracy for T2-w and DWI is equal in the transitional and peripheral prostate zone
→ Re-evaluate prioritization?

Gadolinium contrast and DCE perfusion kinetic analysis do not significantly increase the diagnostic accuracy of T2-w and DWI in PI-RADS
→ Do we need Gadolinium?

Fig. 10: Take-home message

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References


