

Review Article

Is contrast enhancement needed for diagnostic prostate MRI?

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Abstract: Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) provides clinical guidelines for multiparametric magnetic resonance imaging (mpMRI) [T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)] of prostate. However, DCE-MRI seems to show a limited contribution in prostate cancer (PCa) detection and management. In our experience, DCE-MRI, did not show significant change in diagnostic performance in addition to DWI and T2WI [biparametric MRI (bpMRI)] which represent the predominant sequences to detect suspected lesions in peripheral and transitional zone (TZ). In this article we reviewed the role of DCE-MRI also indicating the potential contribute of bpMRI approach (T2WI and DWI) and lesion volume evaluation in the diagnosis and management of suspected PCa.

Keywords: Prostate cancer (PCa); biparametric magnetic resonance imaging (bpMRI); Prostate Imaging Reporting and Data System version 2 (PI-RADS v2)

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Introduction

Recent Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) using multiparametric magnetic resonance imaging (mpMRI) [T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)], established the guidelines to promote global standardization of prostate imaging, to improve detection, localization, characterization and risk stratification of prostate cancer (PCa) as well as to improve communication with referring urologists (1).

PI-RADS v2 determines the role of each sequence (T2WI, DWI and DCE) and, by combining and assessing on a 5 point category scale the findings on each sequence, correlates with the presence of clinically significant PCa and its localization.

Among potential ambiguities and gaps (2), an unclear guidance on clinical management for each one of the five categories has emerged. Particularly, the PI-RADS score 3 is insufficient for decision-making (biopsy or not biopsy) and the positive DCE upgrading this category to a score 4 is irrelevant (3,4).

In this scenario, some Authors have recently proposed

a standardization and simplification of PI-RADS v2 using the bpMRI approach (5-7). Diagnosis of PCa is histological. BpMRI typically meets the objective of detection and localization of PCa suspected foci as well as the execution of MRI-targeted or MRI-TRUS-guided fusion prostate biopsy. Depiction of index lesion and its volume by bpMRI could represent a potential alternative tool to determine PCa presence and severity, to guide patient's management and to defeat the use of contrast material in patients suspected of PCa.

We here reviewed the role of DCE-MRI. The potential contributes of bpMRI (T2WI and DWI) and lesion volume in the diagnosis and management of suspected PCa were reported as well.

Current state of MRI sequences in the diagnosis of PCa

Despite the detailed information provided by the American College of Radiology (ACR) (8), the working group of the European Society of Urogenital Radiology (ESUR) (9) and the latest version of PI-RADS 2.0 (1), the "gold standard" for evaluating PCa aggressiveness is the Gleason score (GS), measured after prostate biopsy or radical prostatectomy.

Since the correlation between mpMRI and PCa aggressiveness remains controversial (1), the main objective of mpMRI is the detection and localization of suspicious PCa.

In the PI-RADS v2 spectroscopy has been omitted and DCE has assumed a minor role; DWI and T2WI are respectively considered the predominant sequences for lesion detection in peripheral zone (PZ) and transitional zone (TZ) (1). T2WI and DWI seem to be sufficient for co-registration of MRI-TRUS images and then for guidance of subsequent biopsy of suspicious lesions identified by bpMRI.

DCE-MRI potential and drawbacks

According to PI-RADS v2, a lesion in PZ assigned to PI-RADS 3 score is upgraded to PI-RADS 4 when it shows enhancement by DCE (1). Since the addition of DCE does not actually seem to alter the clinical implications (7), the role of T2WI and DWI has been emphasized. DCE may potentially be useful:

- (I) to help the detection of some subtle tumors which, due to small size, poor visual contrast, compared to adjacent benign tissue, or a challenging location

within prostate, tend to be missed using the combination of T2WI and DWI alone;

- (II) to aid imaging when imaging quality of T2WI and DWI is impaired;
- (III) to assist the scoring level of suspicion for clinical significant cancer in case of equivocal lesions;
- (IV) to assess recurrent disease in patients who received treatment (2). DCE-MRI can monitor the response to treatment and increase the diagnostic accuracy of locoregional recurrence in patients who underwent radical prostatectomy (sensitivity 46–90%; specificity 74–96%) (10). Moreover, it has been suggested as a promising biomarker for assessing and predicting therapeutic response in PCa providing information about the action of therapeutics and potentially helping to distinguish responders from non-responders (11);
- (V) to assess tumor microvascularization and angiogenesis (11). On DCE-MRI, PCa shows earlier and stronger enhancement of vessels than surrounding normal prostate tissue does (12).

Contrary to the above mentioned potential values, DCE in PCa exhibits the following defective features:

- (I) DCE is a not-specific sequence to detect PCa in the peripheral, transitional and central zone and to determine tumor aggressiveness correlated with the type of enhancement curve. Moreover, it is often difficult to differentiate small areas of enhancement, especially in the transitional area, from the adjacent normal prostate tissue (10);
- (II) DCE sequences and curve type play a secondary role in the accurate determination of lesion category using PI-RADS providing the assessment of a positive or negative score (1);
- (III) the enhancement curves are not-specific and have low sensitivity in identifying suspicious PCa foci. Therefore, the role of the DCE should ensure the enhancement of suspicious lesions identified on T2WI or DWI, compared to the surrounding glandular tissue (10);
- (IV) DCE score depends on variability in reader interpretations, mainly due to ambiguity in the definition of positive and negative enhancement (2);
- (V) it is moreover not clear how to consider a multifocal early background enhancement, while diffuse enhancement is considered a negative finding. As a consequence, a future improvement of PI-RADS v2 should be necessary to overcome weaknesses about

technical aspects of the acquisition, postprocessing and interpretation of DCE (2);

- (VI) the optimum imaging period after gadolinium injection remains unknown, with subsequent lack of standardization in data acquisition protocols.

DCE additionally displays limits concerning both cost and time necessary to complete the study which are related to the use of gadolinium-based contrast agents. The potential risks of these contrast materials in patients with a glomerular filtration <30 mL/min and their accumulation in the brain have to be considered (13,14).

Biparametric MRI (bpMRI) protocol and clinical results

At our institution, MRI of the prostate is performed on a 3 T scanner (Achieva, Philips Medical Systems, Healthcare, Eindhoven, the Netherlands) without an endorectal coil. The bpMRI protocol consists of axial T1W gradient-echo sequence with fat-suppression technique (THRIVE) imaging, axial, sagittal and coronal T2W FSE imaging, axial DWI sequence with B values of 0, 750, 1,500 and 2,000 s/mm² and apparent diffusion coefficient (ADC) maps calculation.

On bpMRI data we calculated volumes of both prostate and index lesion using the ellipsoidal formula (maximum anterior posterior diameter × maximum transverse diameter × maximum longitudinal diameter × 0.52) and/or by a software with 3D reconstruction. A freehand region of interest (ROI) around the seminal vesicles, TZ and PZ of the prostate and urethra, from base to the apex is drawn and then around the index lesion; the software reproduced, automatically and in real-time, 3D volumetric graphic their representation in different transparent colors after applied translation and rotation. In the meanwhile, the volume values, expressed in cm³, were automatically calculated and registered.

The knowledge of the value of the individual sequences is essential in the detection, localization and management of suspicious PCa.

Several studies demonstrate that DCE has a limited contribution to the information provided by T2WI and DWI alone or in addition to T2WI and DWI (15-22) and with reported sensitivities and specificities of 71–84% and 33–79%, respectively, for PCa of any grade, and 80–90% and 47–86% for high-grade PCa (2,15,17,18,23-32).

The diagnostic value of bpMRI in men with or without prior biopsy and combined with prostate-specific antigen

(PSA) has been validated, resulting an improved accuracy for detecting clinically significant PCa and to direct biopsy needles under TRUS guidance, after MRI-ultrasonography fusion (6,15,33-36). Recently, De Visschere *et al.* (7) demonstrated that the role of DCE is limited for diagnosis of clinically significant PCa in patients with elevated PSA before biopsy and that DCE should be reserved only to those patients with a score 3 lesion on DWI in PZ and no suspicious lesion in TZ. The authors demonstrated that DCE was redundant in 80.8% of patients while in the 19.2% of patients, the supplementary information (enhancement or not) was incorrect in approximately 30% resulting contrast medium not necessary in the vast majority of patients when using PI-RADS v2; in the remaining 19.2% of patients, the additional information (enhancement or not) was incorrect in approximately 30% of the cases, resulting in an unnecessary use of DCE in the majority of patients evaluated by PI-RADS v2.

In accordance with previous reports, in our experience we found that bpMRI and mpMRI have similar diagnostic accuracy in the detection of PCa index lesions (*Figure 1*).

For our study we examined patients with PSA abnormalities, with or without previous negative biopsies, submitted to radical prostatectomy. The histological findings were considered as standard reference (37).

For the index lesion detection, we measured the diagnostic performance of T2WI, DWI and DCE MRI alone or combined in bpMRI (T2WI and DWI) or mpMRI (T2WI, DWI and DCE). Compared to the standard reference, the sensitivity of DWI, T2WI and DCE, alone, was in the order: DWI > T2WI > DCE. For DWI, it was 97.6%, 100% and 94.7% in the whole prostate or for PZ and TZ, respectively. The sensitivity of T2WI and of DCE-MRI was low, assuming values of 68.3%, 47.4% and 86.4% or of 39.02%, 31.6% and 45.4% for the whole prostate, TZ and PZ, respectively. Both types of combined MRI (bpMRI and mpMRI) exhibited same level of sensitivity which corresponded to DWI value (100% in PZ, 97.6% and 94.7% in the entire prostate or TZ, respectively). Analogous trends were observed by assessing the agreement (measured by Cohen's k coefficient) between the MRI approaches and the reference standard. As for sensitivity, the agreement of bpMRI and mpMRI (which corresponded to the value of DWI alone) were identical, indicating that DCE sequence in mpMRI did not contribute to index lesion detection in PZ and in TZ (37). Evaluating both index and non-index lesions by bpMRI, we found 27.6% false-positives and 3.3% false-

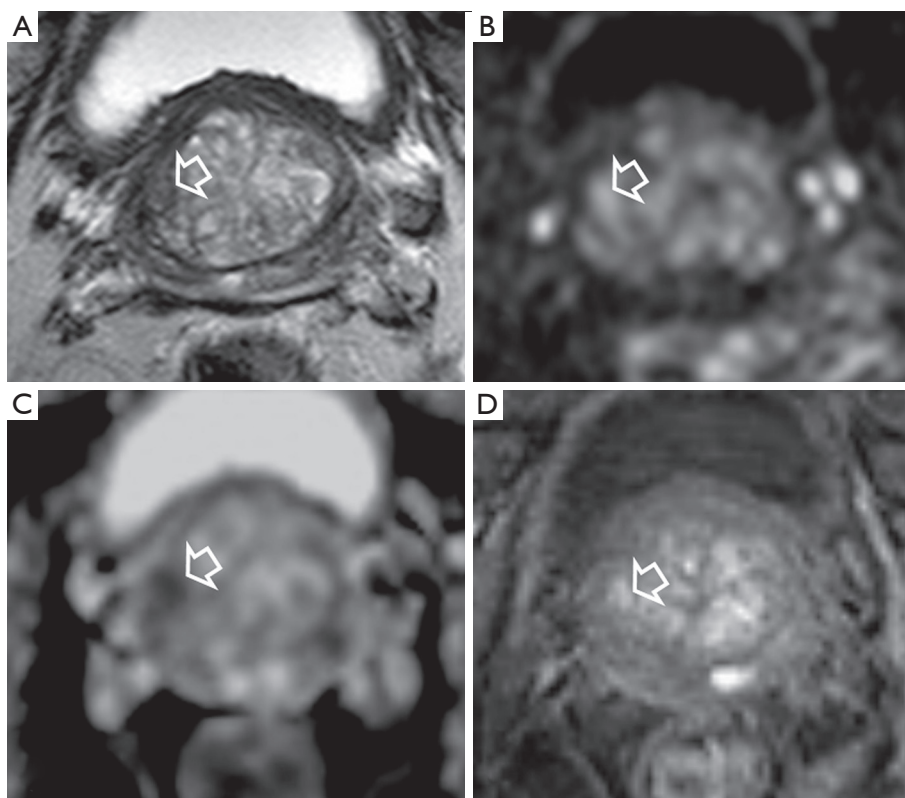


Figure 1 A 72-year-old patient with PSA of 7.3 ng/mL but without previous prostate biopsy. Focal lesion of 10 mm (arrow) in the base in the right side of the TZ with moderately low signal intensity on T2WI (A), high signal intensity on high b-value image of the DWI (B), low signal on ADC map (C) and moderately contrast enhancement on DCE (D). The lesion was assigned a PI-RADS v2 score of 3. The enhancement on DCE was considered irrelevant and biopsy was required because of the suspicious lesion. Targeted biopsy revealed a Gleason 3+3 prostate cancer. PSA, prostate-specific antigen; TZ, transitional zone; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced, PI-RADS, prostate imaging reporting and data system.

negatives. However, the diagnostic performance of bpMRI increased with the size of lesion and, interestingly, assumed high values for lesions ≥ 10 mm, which can only mean a reduced risk of both false-positives and false-negative, for bpMRI, in the group of the clinically significant lesions ($GS \geq 7$) (37).

bpMRI and lesion volume as alternative to multiparametric MRI

Although DCE-MRI quantitative parameters have the potential to assess PCa aggressiveness (low grade from intermediate and high grade) in PZ (38), to date no definitive studies have been reported about the correlation between DCE and cancer aggressiveness. MRI has the greatest potential to depict volumes in clinical relevant lesions (2,39-49), and several studies have reported a

sufficiently reliable correspondence between volume of the suspicious lesion (measured on T2WI and DWI) and tumor volume measured at histological examination of the prostate (50-52).

In this perspective, the bpMRI could be considered a reliable tool for estimating volume of PCa as in the case of other solid tumors.

PCa is considered a clinically significant neoplasia if Gleason score is ≥ 7 and tumor volume > 0.5 mL (53). According to the findings mentioned above, the volume of the suspicious lesion may have a discriminating role in the management of the patients with MRI evidence of suspicious lesion at risk for PCa. Since the most effective way to reduce overtreatment of PCa is to limit its detection in men with low-risk disease, assessment of the aggressiveness of the PCa is crucial in identifying appropriate patient-tailored management.

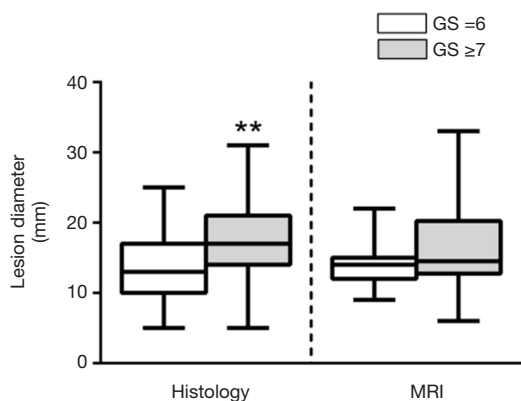


Figure 2 Variability of index tumor and index lesion diameter measured by histology and MRI respectively for GS =6 and GS ≥7 groups. In horizontal graph lines, boxes and whiskers represent the median, interquartile range, and range values respectively. Comparison between GS =6 and GS >7 was performed using the nonparametric Mann-Whitney test. **, P=0.008. MRI, magnetic resonance imaging.

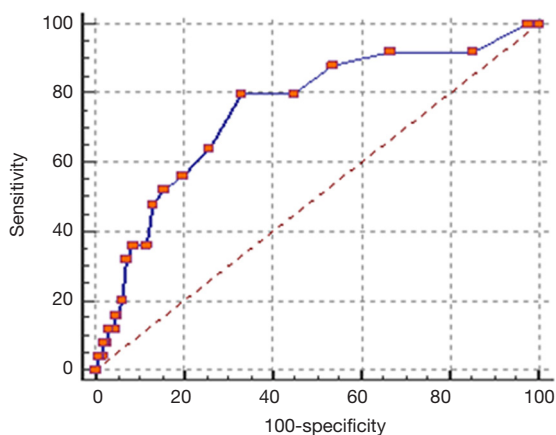


Figure 3 The area under the ROC curve (performed by comparing values of tumor lesion volume in GS ≥7 and GS =6 groups) was 0.752 (P<0.0001) and lesion volume showed a sensitivity and specificity of 80% and 67% respectively in significant PCa prediction.

In clinical practice, when we take into the account an appropriate decision-making (biopsy or active surveillance), the main weakness emerging from the PI-RADS v2 is the lesion diameter. According to PI-RADS v2, a lesion with a PI-RADS score of 4 is upgraded to the higher score when its diameter is >15 mm (1). To our knowledge, no studies demonstrated a relationship between the lesion diameter

and cancer aggressiveness. Additionally, in our recent experience we found that lesion diameter detected by MRI seems not to be able to predict tumor aggressiveness. In contrast with histology, indeed, no statistical differences of tumor lesion diameter between GS =6 and GS ≥7 groups (37) were seen (Figure 2).

PCa often is a solid tumor with a defined three dimensional shape. Our recent data demonstrated the potential diagnostic power of MRI lesion volume for PCa and tumor aggressiveness (differentiation of clinically significant cancer >0.5 versus <0.5 mL) (52). Detection of aggressive PCa (GS ≥7) increased with the increase of lesion volume by 13.8% to 40% or to 55% considering a lesion volume <0.5 mL or between 0.5 and 1 mL or >1 mL, respectively (P=0.008). In addition, the area under the ROC curve (performed by comparing values of tumor lesion volume in GS ≥7 and GS =6 groups) was 0.752 (P<0.0001) and the cut-off lesion volume was >0.5 mL with a sensitivity and specificity of 80% and 60% respectively (52) (Figure 3).

Moreover, although the gold standard for assessment of PCa clinical significance are the Gleason score and tumor volume, obtained from prostate biopsy and/or radical prostatectomy specimens, several studies demonstrated that MRI has the greatest potential to depict volumes in clinical relevant lesions (50-52).

However, the lesion volume has some limits: (I) volume calculation of suspected lesion requires the use of an appropriate software (because estimation with the ellipsoid model might be too rough); (II) although there are several studies that show a correlation between volume of neoplasia (measured at the final histological examination) and volume of suspected lesion (measured with the appropriate software), this evidence is not definitive (multicenter, prospective studies, etc.).

A new risk stratification system as alternative to PI-RADS v2: clinical management and lesion categories correlation

PI-RADS v2 score does not offer a clear guidance on the clinical management for each one of the five categories. In particular, a consensus was reached regarding the need of not performing the biopsy for score 1 and 2 lesion and to perform biopsy for score 4 and 5 lesion. Conversely, there is still no consensus for the management of PI-RADS 3 lesions (equivocal for the presence of clinical significant cancer and/or indeterminate for biopsy). DCE plays a limited role

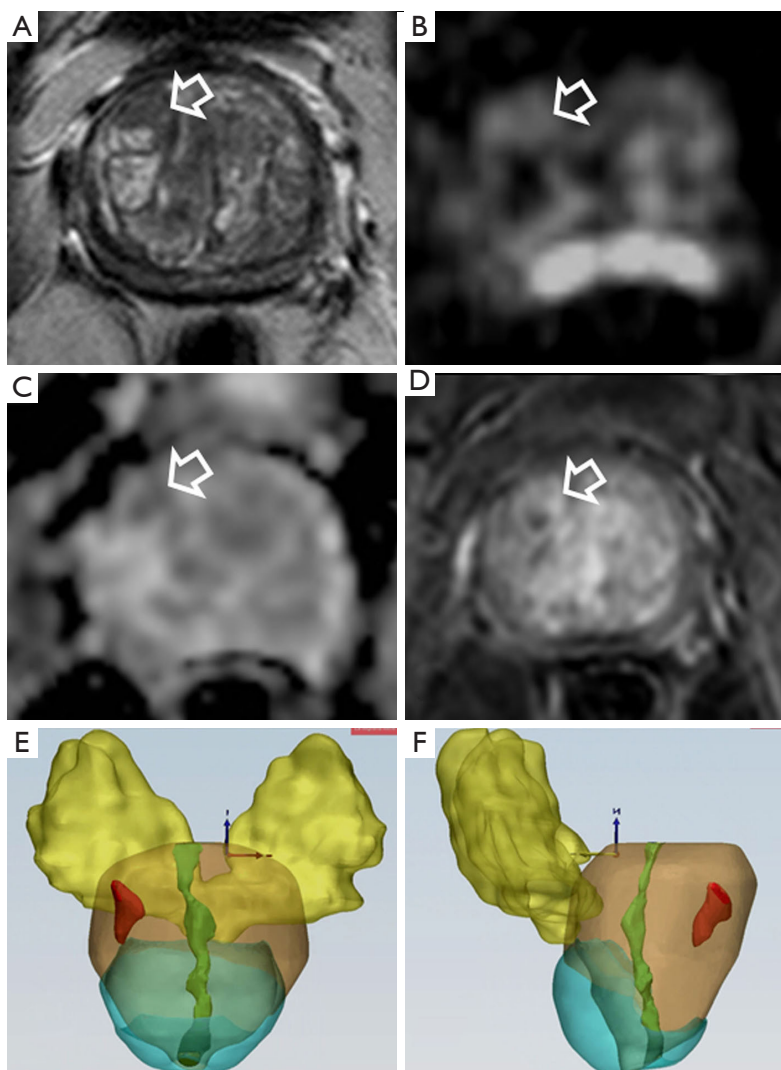


Figure 4 A 67-year-old patient with PSA of 4.1 ng/mL but without previous prostate biopsy. Focal lesion of 12 mm (arrow) in the anterior TZ of the base of the prostate in the right side with moderately low signal intensity on T2WI (A), high signal intensity on high B value image of the DWI (B), low signal on ADC map (C) and moderately contrast enhancement on DCE (D). 3D reconstructions (E,F) showed a lesion volume <0.5 mL. The lesion was assigned a PI-RADS v2 score of 3. The enhancement on DCE was considered irrelevant and biopsy was required because of the suspicious lesion. Targeted biopsy revealed fibrous hyperplasia. PSA, prostate-specific antigen; TZ, transitional zone; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; PI-RADS, prostate imaging reporting and data system.

and is ignored in TZ and in PZ, except when DWI has been assigned a score, then the overall assessment category may be upgraded to a score 4 of a positive DCE that in many cases may be result redundant. As a consequence, recently an alternative overall assessment score by T2WI and DWI yielded similar performance as PI-RADS v2 (7).

According to the criteria and lexicon of the PI-RADS v2 guidelines (1), in our experience, the image analysis was

based on the recognition of lesion pattern on DWI (lesion hyperintense) and ADC map (lesion moderately/markedly hypointense), at first, and on T2WI (lesion moderately hypointense/hypointense) sequences, later. DWI, with high b values, together with ADC images represented the predominant sequence to detect the lesion both in PZ and TZ.

Although the most important limitation for the adoption of bpMRI in clinical practice is the lack of a standardized

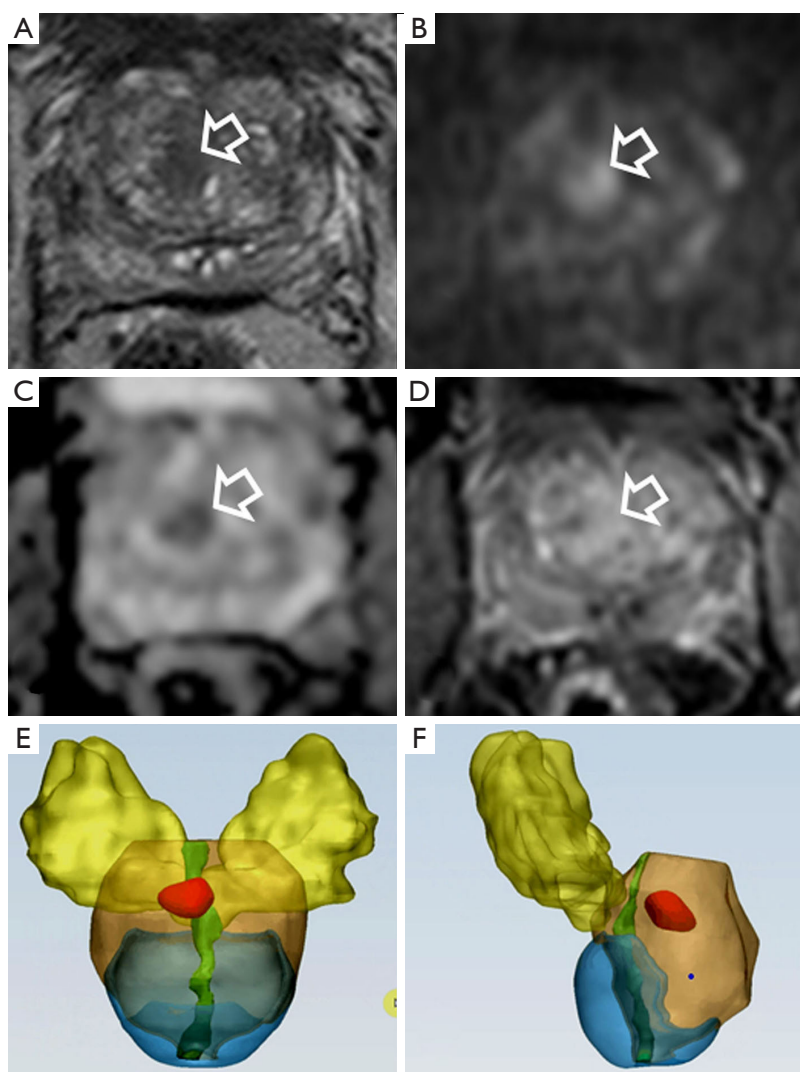


Figure 5 A 59-year-old patient with PSA of 7.6 ng/mL but without previous prostate biopsy. Focal lesion of 12 mm (arrow) in the anterior and posterior TZ in the base of the prostate on the right side with moderately low signal intensity on T2WI (A), high signal intensity on high B value image of the DWI (B), low signal on ADC map (C) and moderately contrast enhancement on DCE (D). 3D reconstructions (E,F) showed a lesion volume >0.5 mL. The lesion was assigned a PI-RADS v2 score of 4. The enhancement on DCE was considered irrelevant and on the basis of lesion volume biopsy was required. Targeted biopsy revealed a Gleason 3+3 prostate cancer. PSA, prostate-specific antigen; TZ, transitional zone; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; PI-RADS v2, prostate imaging reporting and data system version 2.

scoring system for risk assessment of suspicious lesions, in our experience, the bpMRI and lesion volume calculation represent potential tools to manage suspected PCa (biopsy in >0.5 mL volume and <0.5 mL volume or no biopsy), in particular in PI-RADS 3 lesions.

Representative cases of bpMRI and lesion volume in patients with suspicious PCa are reported in *Figures 4-6*.

According to others (7), omitting DCE in all patients

seems reasonable in the clinical situation where prostate MRI is used as a method of risk stratification of clinical significant PCa in patients with elevated PSA. In addition, bpMRI reveals to be a valid tool in the detection of local recurrence after prostatectomy.

In our experience bpMRI (DWI sequences and ADC maps in association with T2WI), without endorectal coil, as an alternative approach to mpMRI examination, is justified

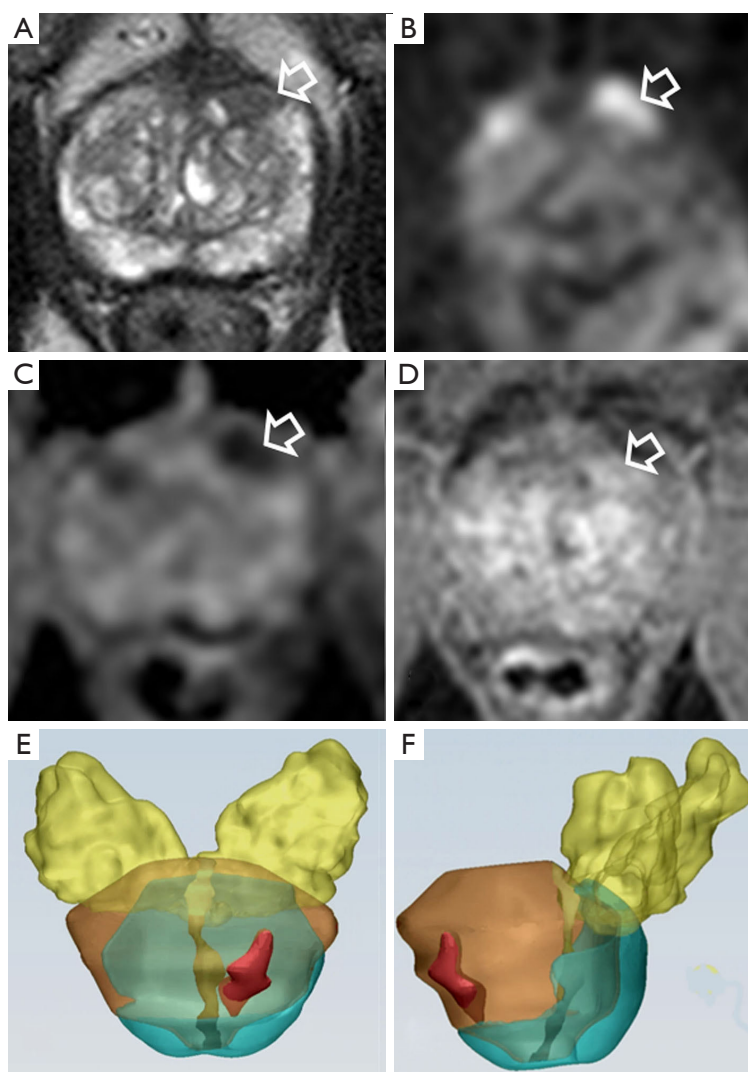


Figure 6 A 60-year-old patient with PSA of 6.8 ng/mL but without previous prostate biopsy. Focal lesion of 15 mm (arrow) in the anterior fibromuscular stroma of the mid-prostate on the left side with moderately low signal intensity on T2WI (A), high signal intensity on high B value image of the DWI (B), low signal on ADC map (C) and moderately contrast enhancement on DCE (D). 3D reconstructions (E,F) showed a lesion volume >0.5 mL. The lesion was assigned a PI-RADS v2 score of 4. The enhancement on DCE was considered irrelevant and on the basis of lesion volume biopsy was required. Targeted biopsy revealed a Gleason 3+4 prostate cancer. PSA, prostate-specific antigen; TZ, transitional zone; T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast-enhanced; PI-RADS v2, prostate imaging reporting and data system version 2.

(I) to identify and localize lesions in the PZ, TZ and in the anterior fibromuscular stroma; (II) by no use of gadolinium-based contrast agent; (III) by reduction of examination time and costs.

A comparative study between mpMRI and bpMRI and volume of the lesion measurement is underway. Our preliminary data show a higher predictive value of lesion volume compared to DCE in terms of overall cancer detection

rate and cancer aggressiveness. In this perspective, the bpMRI and lesion volume index calculation, result more appropriate than mpMRI for cancer diagnosis and clinical decision making (biopsy or not biopsy) in patients suspected of having PCa.

Conclusions

In clinical practice, the development of imaging techniques,

examination protocols and 3D software improved diagnosis of usual and unusual malignancies (54-56). Particularly, mpMRI modified the approach to the patient with suspicious of PCa and became a useful tool to detect clinical significant cancer. However, gadolinium, long test times and higher costs represent limits for mpMRI. By demonstrating similar diagnostic accuracy of bpMRI and mpMRI in the detection of PCa, gadolinium-based contrast agent seems not to be strictly necessary in the detection and localization of PCa, and bpMRI and lesion volume calculation are sufficient for these purposes. We emphasize the clinical use of the bpMRI considering the use of no gadolinium, reduction of the costs and time required to complete the study.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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