



Biparametric (bp) and multiparametric (mp) magnetic resonance imaging (MRI) approach to prostate cancer disease: a narrative review of current debate on dynamic contrast enhancement

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Abstract: Prostate cancer is the most common malignancy in male population. Over the last few years, magnetic resonance imaging (MRI) has proved to be a robust clinical tool for identification and staging of clinically significant prostate cancer. Though suggestions by the European Society of Urogenital Radiology to use complete multiparametric (mp) T2-weighted/diffusion weighted imaging (DWI)/dynamic contrast enhancement (DCE) acquisition for all prostate MRI examinations, the real advantage of functional DCE remains a matter of debate. Recent studies demonstrate that biparametric (bp) and mp approaches have similar accuracy, but controversial evidences remain, and the specific potential benefits of contrast medium administration are still poorly discussed in literature. The bp approach is in fact sufficient in most cases to adequately identify a negative test, or to accurately define the degree of aggressiveness of a lesion, especially if larger or with major characteristics of malignancy. This feature would give the DCE a secondary role, probably limited to a second evaluation of the lesion location, for detecting small cancer or in case of controversy. However, DCE has proved to increase the sensitivity of prostate MRI, though a less specificity. Therefore, an appropriate decision algorithm is needed to standardize the MRI approach. Aim of this review study was to provide a schematic description of bpMRI and mpMRI approaches in the study of prostatic anatomy, focusing on comparative validity and current DCE application. Additional theoretical considerations on prostate MRI are provided.

Keywords: Prostate magnetic resonance imaging (prostate MRI); biparametric; multiparametric; functional magnetic resonance imaging (functional MRI); dynamic contrast enhancement (DCE)

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Introduction

Prostate cancer (PCa) is the most common malignancy found in the male population and represents one of the major causes of cancer-related death (1). Since a large number of cases can be clinically silent, there is the compelling necessity of sensitive diagnostic tools for correct diagnosis and staging.

The standard clinical approach includes prostate-specific antigen (PSA) assessment, evaluation of potentially abnormal findings on digital-rectal exploration (DRE), and trans-rectal ultrasound (TRUS)-guided biopsy. Among the limitations of these methods are the increase of PSA values also under benign conditions, and the risk of not getting enough sample through TRUS-guided prostate biopsy (2,3).

In recent years, wide visibility has gained the use of multimodality imaging in cancer diseases (4-20). Magnetic resonance imaging (MRI) has shown high diagnostic accuracy, as an independent method for adequate disease rule-out, in effectively targeting the biopsy, in association with other clinical parameters such as PSA, for the evaluation of PSA density (PSAD), to increase sensitivity in identifying clinically significant (cs) lesions or cancer recurrence after specific therapy (21-32).

In the attempt to increase MRI diagnostic and prognostic validity and to limit the evaluation variability, over the years scientific and clinical communities have tried to standardize both acquisition technique and reporting.

The European Society of Urogenital Radiology (ESUR) suggests the multiparametric (mp) acquisition of the prostate using T2-weighted (T2W), diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE) sequences for all MRI examinations (33,34). The evaluation of each of these sequences translates into an objectified numerical score leading to the formulation of the Prostate Imaging Reporting and Data System (or PIRADS) (34).

The PIRADS, initially formulated in 2012, has undergone substantial changes from version 1 to version 2 in an attempt to obtain a specific algorithm to estimate the probability of malignancy of the PCa and consequently gain clinical consideration. Though its revision, also the second version of the PIRADS, however, had some limitations represented by inter- and intragroup variability (35), as described in several studies and well summarized in the systematic review issued by Stabile *et al.* (36).

Based on these considerations, PIRADS has lately come to the revised version 2.1, which still has some limits, represented by ambiguities and potential misclassifications

of the general score, as shown by the critical analysis made by Ullrich *et al.* (37).

Among the most largely debated issues in the panorama of MRI of the prostate, the role of DCE remains. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/ggs-20-547>).

MRI of the prostate gland

MRI of the prostate is based on a zonal anatomical approach of the different glandular components (*Figure 1*). The prostate has four different areas divided as per McNeal's scheme, differentiated in peripheral zone (PZ), central zone (CZ), transitional zone (TZ) and anterior fibro-muscular stroma (AFMS). These anatomical areas have different glandular structures, which result in a wide variability of the signal intensity (38).

According to these considerations, PIRADS v2.1 proposes the analysis of specific sequences considered dominant for the evaluation of these different areas (39).

T2W sequences

The high resolution T2W sequences allow excellent morphological visualization of the gland, and accurate description of its anatomy. T2W images permit also the volumetric measurement of the gland and the lesion, an accurate identification and localization of suspected PCa, and the evaluation of the extra-compartmentalization of the PCa. T2W images are also useful in guiding any targeted biopsy (40-42).

According to PIRADS recommendation, the T2W sequences are considered dominant for the detection of PCa in the TZ, which account for only 5% of glandular tissue, identifying 5 different scores based on the characteristics of signal intensity, morphology and size of the lesion (34). However, DWI sequences and the analysis of the apparent diffusion coefficient (ADC) values increase the ability to confidently evaluate the TZ, considering that homogeneous hypointense T2W signal may also be appreciated in numerous other conditions, including atrophic alterations and benign prostatic hyperplasia, outcomes of prostatitis, and post-biopsy scar areas (43).

DWI

The DWI sequences evaluate the degree of movement or

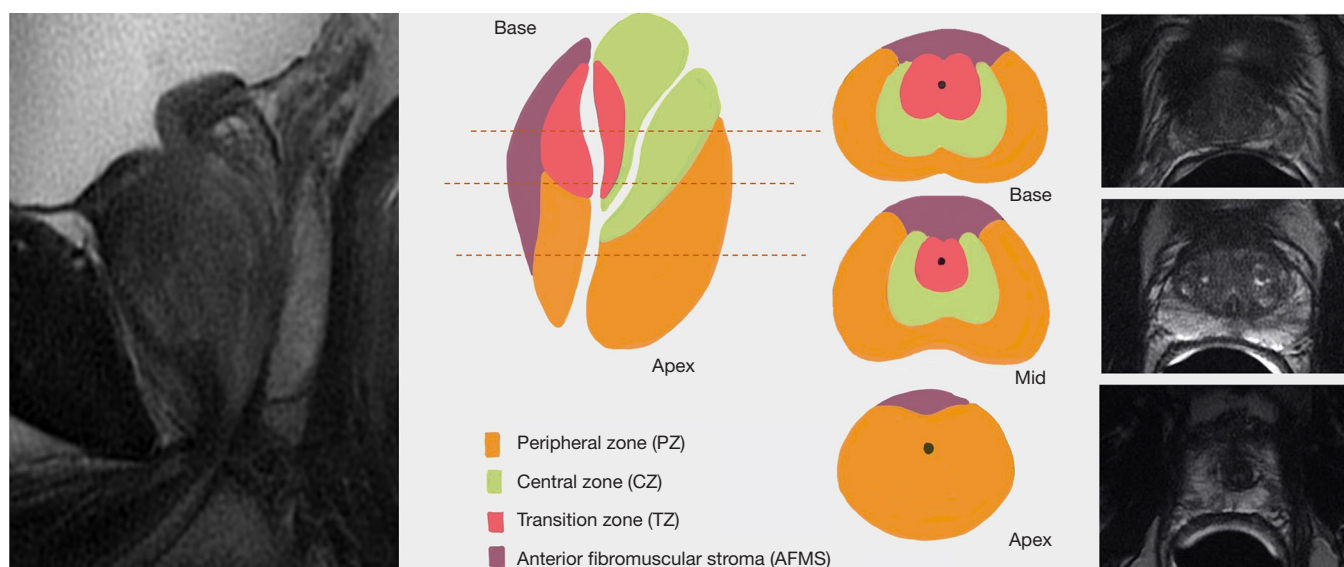


Figure 1 Zonal anatomy of prostate gland.

diffusion of water molecules, expressing it as a parameter known as ADC. A restricted diffusion of water molecules is attributed to an increase in the cellularity of malignant lesions. Therefore, the DWI sequences provide an important quantitative biophysical parameter that directly correlates with changes in extracellular space, allowing to distinguish benign alterations from malignant lesions (44).

However, the correct selection of the b-value for the DWI is critical, depending on the latter the ability to evaluate the real restriction of water molecule diffusion. High b-values are recommended by ESUR, considering that they are better correlated with hypercellular formations, sign of the strength of the diffusion sensitizing gradient (33,34,45,46).

The ADC map provides an objective value of restriction, and has demonstrated high accuracy in identifying the degree of aggressiveness of the tumor (47-51).

The quantitative method of analysis could help less experienced readers to classify lesions and stage the degree of aggressiveness of the tumor.

DWI sequences are considered dominant in the evaluation of the PZ, which accounts for 70–75% of the glandular tissue, identifying 5 scores based on the degree of restriction and the size of the restricted area.

DCE

The term “dynamic” derives from the multiple serial images that are collected after injection of contrast media.

The primary interest linked to the use of DCE sequences is related to the significant increase in the vessels supplying the lesion which could be associated to the tumor growth.

There is a disorganized and heterogeneous formation of vessels that also present different permeability. This growth is mainly due to the release of specific molecules by the tumor cells (specific growth factors including the vascular endothelial growth factor). Numerous studies demonstrate that the higher the tumor neoangiogenesis, the worse the prognosis of the lesion.

In their study that lasted more than 20 years, Mucci *et al.* identified the irregularity and size of the vessels induced by the angiogenic process as a malignancy biomarker, considering that patients with small vessels had a 6-time less chance of developing lethal cancer (52).

Also, Brawer *et al.* identified microvascular density as an independent predictor of the tumor stage. Therefore, the quantification of tumor angiogenesis can help in stratifying the patients and planning their adequate management (53).

Among the different factors, the micro vessel density has showed excellent correlation with the DCE sequences, allowing an adequate pre-operative stratification of the lesion Gleason score with MRI, as shown by Singanamalli *et al.* (54).

Therefore, the clinical application of DCE-MRI for PCa is based on data demonstrating that malignant lesions show earlier and faster enhancement and earlier contrast agent washout compared with healthy prostate tissues (55).

This requires fast bolus administration of contrast media combined with rapid acquisition methods.

DCE-MRI requires the use of serial 3D T1-weighted fast spoiled gradient-echo MRI sequence acquisitions before, during, and after a bolus of low-molecular-weight gadolinium contrast medium. Contrast agents in vessels and in the extracellular space shorten local relaxation times, leading to a rapid brightening of signal on the T1-weighted sequences. T1-weighted spoiled gradient-echo sequences provide high sensitivity to T1 changes, high signal-to-noise ratios, adequate anatomic coverage, and rapid data acquisition.

Ideally, the acquisitions should be obtained approximately every 5 seconds to allow the detection of early enhancement; however, many centers use acquisition times up to 15 seconds to increase the spatial resolution and identify csPCa. However, longer acquisitions (e.g., >15 seconds) are not recommended due to difficulties in identifying early enhancement, which may impair the analysis.

DCE imaging may be technically analyzed by means of qualitative or semi-quantitative method.

The qualitative analysis of DCE-MRI and its use for prostate imaging is based on the general assumption that malignant tumors show early rapid high enhancement after injection followed by a relatively rapid decline if compared to the slower and continuously increasing signal given by normal tissues during the first few minutes after contrast injection.

Unlike the visual approach, the semi-quantitative analysis calculates the kinetics of the lesion. The main method reported in literature is curve typing, which plots the kinetic of enhancement in a signal-time curve with a type 3 curve (decline after initial upslope) considered the most equivocal for PCa, especially in presence of focal asymmetric enhancing lesions.

Although the semi-quantitative approach is widely used in the assessment of DCE-MRI, limitations are reported in terms of generalization among acquisition protocols, sequences, and all the other factors contributing to the MR signal intensity, which, in turn, affects curve metrics (56).

Therefore, current recommendation of PIRADS Steering Committee does not include the routine adoption of curve analysis for prostate lesion (34).

PIRADS v2.1 proposes the presence of early enhancement among the distinctive signs of csPCa in the CZ, which accounts for 40% of the epithelial mass (other signs include glandular symmetry, the extension of the CZ beyond the verumontanum and anomalous T2 and DWI signals in comparison with the adjacent portions of AFMS).

Due to the structure of CZ, indeed, low T2 signal intensity and reduced ADC values can also be observed under normal conditions, as shown by Gupta *et al.*, who identified CZ ADC values overlapping with those found in malignancies of other glandular portions (57). Conversely, the contrast dynamic of CZ seems to be characteristic, which can be advantageous in identifying tumors of the base (37,38,55).

DCE may be advantageous in the evaluation of AFMS also, which is the largest portion of non-glandular tissue of the prostate. AFMS usually shows low signal intensities in T2W and DWI sequences. Besides, it appears hypovascularized. However, given the close proximity of AFMS with TZ, similar considerations on signal intensity are often applied, and little value is attributed to DCE sequences.

However, the significance of angiogenesis in PCa still remains controversial (58), thus reducing the sensitivity of DCE.

Biparametric MRI (bpMRI) vs. mpMRI

Although DCE is included in the PI-RADS v2 and v2.1 guidelines, and the ESUR suggests the acquisition of all imaging sequences for prostate MR examinations, the role of DCE sequences in diagnosis and staging of PCa is rather controversial (59-61).

Recent literature indeed focuses on the overlapping diagnostic validity using bp and mp protocols in detecting csPCa (62).

The bp approach is in fact sufficient in most cases to adequately identify a negative test, without the need of studying the contrast enhancement of the prostate gland.

Similarly, T2 and DWI sequences may accurately allow to define also the degree of aggressiveness of a lesion, especially if larger or with major characteristics of malignancy (*Figure 2*).

Moreover, the bp protocol offers several advantages, considering that it is time-saving and cost-effective, and does not bring the potential risks associated with contrast medium administration (63-66).

This feature would give the DCE a secondary role, probably limited to a second evaluation of the lesion location, for detecting small cancer or in case of controversy.

Small cancer detection

Recent evidence suggests that the use of DCE may

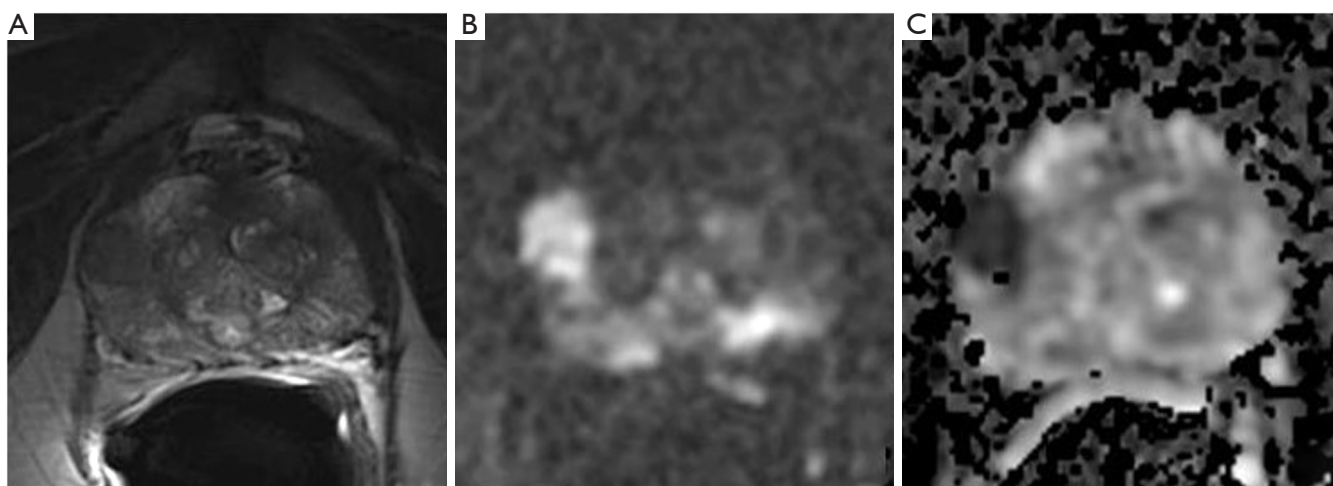


Figure 2 Biparametric MRI including axial T2W (A), DWI (B) and ADC map (C) of a Gleason Score 8 (4+4) prostate cancer. A defined rounded hypointense area is identifiable in the right anterior horn. High restriction is highlight. This finding results in a PIRADS score of 4. DCE, in this case, is not important for the final diagnosis. MRI, magnetic resonance imaging; T2W, T2-weighted; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast enhancement; PIRADS, the Prostate Imaging Reporting and Data System.

increase the accuracy of prostate MRI in identifying small tumors, considering that the discriminating ability of the sequences included in the bp protocol increases with the size of the lesion, and reaches high diagnostic validity for lesions greater than 10 mm. The DCE sequences can significantly contribute to the identification of small lesions (<7 mm), whose documentation may be limited with the bp approach (67).

The capability of DCE to adequately delimitate prostate nodular lesions, even of small dimensions, could be of particular importance also for the adequate measurement of the lesion volume, which helps improve the diagnostic yield of the targeted biopsy. To our knowledge, however, there are still no studies that quantify this aspect (68).

Equivocal lesions

DCE improves the ability of stratification of patients with a PIRADS 3 or equivocal score, and helps avoid some typical pitfalls, as in the AFMS (69).

The study carried out by Greer *et al.* proved that DCE imaging may improve PCa detection and stratification. Notably, by analyzing the PZ, Greer *et al.* showed how addition of DCE to DWI determined an increase in the probability of cancer detection of 15.7%, 16.0%, and 9.2% for PIRADS category 2, 3, and 4, respectively. Lesions

classified as PIRADS category 3 at DW MRI and as positive at DCE imaging in the PZ showed a higher probability of cancer detection than did DCE-negative PIRADS category 3 lesions (67.8% *vs.* 40.0%, $P=0.02$) (39).

This results in a more sensitive evaluation (70), but the clinical impact depends on how equivocal cases are managed, considering that the outcome of the examination does not change if a targeted biopsy for score 3 or more is adopted. In this perspective, as discussed also in PIRADS v2.1, the administration of contrast medium could be reserved to doubtful or suboptimal quality cases, ruling out its use in the routine scanning protocol.

This is of particular importance considering that the csPCa lesion rate in case of PIRADS 3 has been shown to be variable, ranging from 16% to 21%; these data underline the need for further stratification in these patients in whom DCE could play an important role together with other clinical/laboratory-related parameters, including the PSAD, given the risk of unnecessary biopsies (71,72).

A thorough reading of PICTURE study results reveals that functional imaging including DCE and DWI in addition to T2W images is capable to increase the number of men avoiding biopsies up to 8.9% (73).

Furthermore, as demonstrated by the PRECISION study, the PIRADS 3 rate reported in a center can be considered as a quality indicator. It should be less than

15%, considering that it tends to be proportionally higher in presence of less experienced readers (21,74).

These considerations highlight two key aspects of the biparameter approach: the experience of the reader and the image quality.

A clear example is presented by Gatti *et al.*, who investigated the ability of six readers with different experience, divided into three groups of two readers, evaluating 1,000, 300, and 100 cases each. They interpreted 68 examinations of PCa patients, first with bpMRI including DWI and, after 1 month, with mpMRI, adding DCE. Expert readers showed excellent agreement both in bp and mp model (sensitivity =0.91–0.96, AUC =0.86–0.93; $P \geq 0.10$). DCE increased significantly the performance of both 300 and 100 case experienced radiologists, with an AUC of 0.86 and 0.77, respectively in mp model versus 0.73 and 0.68, respectively, in bp model (75). These results give additional substance to the discussion about the routine use of contrast medium as a complement to the second read of difficult cases.

On the other hand, as stated also by the recent PIRADS Committee Position paper, MRI quality is of paramount importance in the bp approach as the image quality is sufficient for detection or exclusion of csPCa (74,76).

It must be also considered, however, that lesions defined as PIRADS 4 by means of contrast enhancement in presence of equivocal cases, could be a distinct form from native PIRADS 4 lesions defined by means of bp sequences, in terms of prevalence of disease significance (*Figure 3*) (77).

Literature on diagnostic validity

There are many studies that have investigated the diagnostic validity of the different bp and mp approaches.

In a recent meta-analysis carried out by Niu *et al.* from 2007 to 2017, in 33 studies on 2,383 patients, a significantly higher pooled sensitivity (0.85; 95% CI, 0.78–0.93) was reported on mpMRI compared to bpMRI (0.80; 95% CI, 0.71–0.90) ($P=0.01$), though evidence of a similar pooled specificity [mpMRI, 0.77 (95% CI, 0.58–0.95); bpMRI, 0.80 (95% CI, 0.64–0.96); $P=0.82$] (78).

Many authors, however, emphasize the overlapping diagnostic efficiency of both protocols (67,79,80) and, recently, two different meta-analyses have come to the same conclusions.

Notably, Woo *et al.* reported a similar pooled specificity and sensitivity between mpMRI and bpMRI in a head-to-head comparison meta-analysis including 22 studies (2,142

patients) (bpMRI: sensitivity and specificity of 0.74 and 0.90, respectively; mpMRI: sensitivity and specificity of 0.76 and 0.89, respectively) (81).

Similar accuracy was reported in the meta-analyses carried out by Alabousi *et al.* in 31 studies on 9,244 patients. In these studies, significant differences are reported with reference to sensitivity and specificity, considering that more robust sensitivity (around 90%) and slightly lower specificity (around 70%) were described (82).

This difference between accuracy parameters expressed in sensitivity and specificity reveals a significant variability even though the conclusions are similar (*Figure 4*).

High sensitivity is the true positive, because it expresses the proportion of positiveness properly identified as such, while specificity is the true negative, implying a greater likelihood of false positives with a positive test and the possible need of additional biopsies.

It is clear, therefore, that the discrepancy between the results may deeply affect the future clinical management of the patients. It is likely, however, that the described bias depends on the high heterogeneity of the studies, and recent paper of PIRADS Committee also advise caution on pooled test accuracies (77).

A different impact may have the results of the recent PROMIS study, a multicenter multi-reader trial including 497 biopsy-naïves undergoing mpMRI, which revealed no significant differences between bpMRI and mpMRI in the exclusion of csPCa, with a similar negative predictive value (90% and 91% for bpMRI and mpMRI, respectively) and sensitivity (94% and 95% for bpMRI and mpMRI, respectively), though presence of a slightly higher number of equivocal cases obtained with the bp evaluation *vs.* the mp one (32% *vs.* 28%, $P=0.031$). The validity of this study is mainly related to the application of the trans-perianal mapping biopsy performed independently of the MRI results, that allowed avoiding potential bias related to the use of biopsy to confirm MR findings. Moreover, even the poor comparability with other PIRADS-based studies, the use of a five-point Likert scale (as in the PROMIS study) allowed also detecting any potential advantages of DCE, unlike the PIRADS, which currently define DCE only as a dichotomous variable (68).

Recent PIRADS Committee consideration on MRI approach to naïve men with suspected PCa

Recently, the PIRADS Committee edited a narrative review including current position about MRI approach in patients

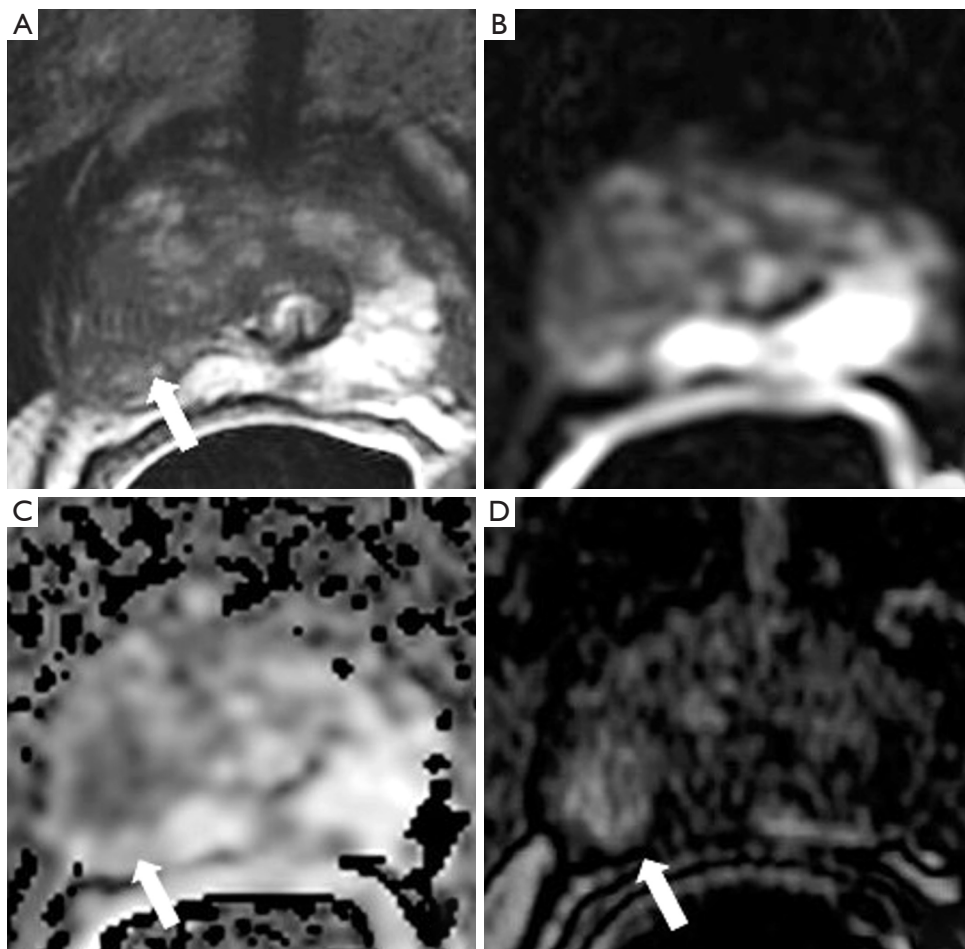


Figure 3 MpMRI examination including axial T2W (A), DWI (B), ADC map (C) and DCE (D) images of a Gleason Score 7 (3+4) prostate cancer (white arrow). A faint hypointensity signal is evidenced in the right side of PZ at apex gland; moderate restriction is observed in DWI and ADC map. Significant early enhancement is qualitative evidenced in DCE sequences. MpMRI approach allows to correctly stratify a PIRADS 3 in PIRADS 4 lesion. MpMRI, multiparametric magnetic resonance imaging; T2W, T2-weighted; DWI, diffusion weighted imaging; ADC, apparent diffusion coefficient; DCE, dynamic contrast enhancement; PIRADS, the Prostate Imaging Reporting and Data System; PZ, peripheral zone.

with suspected PCA.

The increase in demand for prostate MRI has recently led to questioning about the preparation of the medical structures facing the increased requests (availability of scanners and experienced radiologists, able to provide accurate examinations, potentially time- and cost-sparing facilities).

Since the diagnostic performance of the bp approach was not inferior to the mp, with some exceptions, the bp model seems to be one of the possible solutions although, as overmentioned, the bp approach requires some fundamental prerequisites (i.e., high image quality and reader expertise).

As suggested by the PIRADS Committee, the current role of DCE could be limited to type 3 lesions, to determine the nature of equivocal lesions, increasing their degree and therefore the probabilities of non-benignity. Although the higher sensitivity, lower specificity may result, considering how DCE is of help in identifying a greater number of lesions, including the indolent ones.

The need therefore focuses on identifying a specific threshold of disease, which clarifies when to increase the sensitivity of the method through DCE, or when to increase the specificity, thus avoiding useless biopsies.

An adequate model to identify the clinical risk is

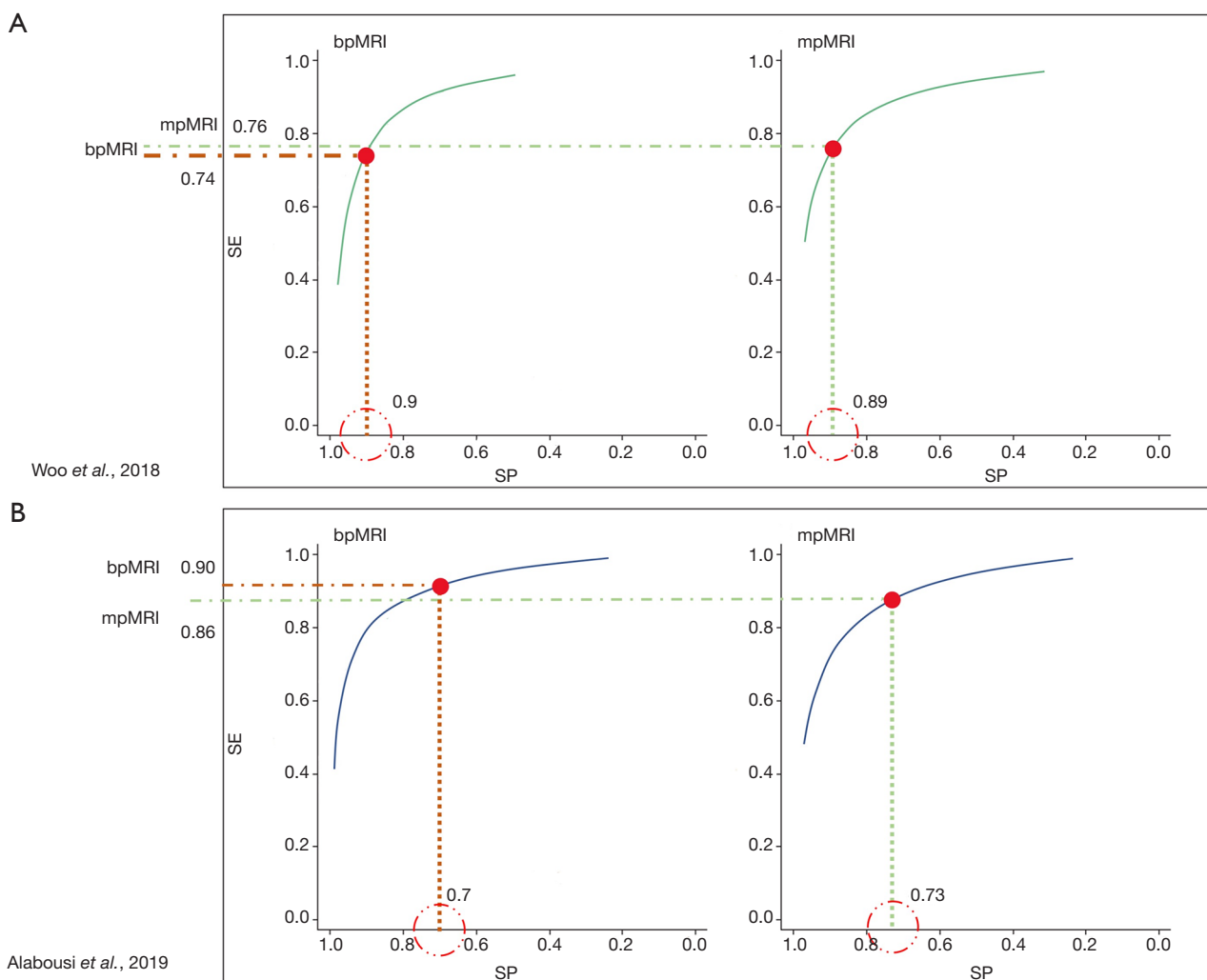


Figure 4 Figurative representation of results reported by Woo *et al.* (81) (A) and Alabousi *et al.* (82) (B). Images reproduce diagnostic test accuracy in terms of sensitivity and specificity in different meta-analysis. SE, pooled sensitivity; SP, pooled specificity.

therefore of paramount importance and include all current clinical and instrumental parameters such as PSA, anomalous findings in DRE, PSAD, or, more recently, some genomic biomarkers.

A risk model capable of determining pre-test probability of disease should allow the standardization of the MRI approach to prostate gland disease.

Low risk patients: rule-out of disease and reduced overdiagnosis of prostatic lesions are the target for low risk patients, given the low risk of PCa and therefore the high probability of negative examination. The bp approach alone may be useful once the threshold for biopsy has been established to PIRADS 4–5. In these cases, the DCE can be

useful as a safety net also to evaluate low quality images.

Intermediate-to-high risk patients: including all patients with genetic predisposition or high clinical scores, patients in active surveillance for fast doubling of PSA values or with persistently elevated PSA values despite negative biopsies; for this class of patients, a mp approach should be preferred to increase the sensitivity of the method, unless in presence of lesions with typical features of malignancy. In these cases, however, the presence of the radiologist is mandatory during the acquisition.

Very high-risk patients: including patients with very high PSA values and known anomalies on DRE, suggesting a clinically significant lesion; the bp approach alone could be

useful in the definitive evaluation (77).

DCE in post-treatment evaluation

DCE imaging can be used to evaluate response to therapy after radical prostatectomy (83). DCE-MRI proved to be adequate in detecting cancer recurrence when PSA begins to increase after a nadir in radical-prostatectomy patients. Detection of tumor recurrence after radical treatment can be difficult due to the lack of normal landmarks and the presence of scar tissue. In this regard, Panebianco *et al.* evaluated 84 patients with suspected local recurrence after prostatectomy using conventional MRI with MR spectroscopy and DCE-MRI as well as ¹⁸F-choline PET/CT and concluded that accuracy was greater for mpMRI than for PET/CT (area under the curve of MRI and PET/CT, 0.971 and 0.837, respectively) (84).

DCE-MRI is also useful in detecting recurrence after radiation therapy or ablation. Biochemical recurrence can occur in 20–40% of patients undergoing external-beam radiation therapy. Detecting recurrence after radiation therapy can be clinically challenging because the PSA level may not be a reliable marker, and the digital rectal examination can be non-specific due to fibrotic changes in the irradiated prostate gland. MpMRI with DCE sequences have shown the capacity to identify tumor recurrence with high accuracy in post-radiotherapy patients (84–86).

Conclusions

Prostate MRI is essential for detection, staging and treatment planning of csPCa. In the latest years many studies have investigated on the diagnostic accuracy of the bp approach *vs.* the mp one, and a debate has risen about the usefulness of DCE sequences as concrete discriminator for a definite diagnosis of csPCa.

BpMRI has proved to be non-inferior to mpMRI, although the relative superior sensitivity of mpMRI, recognizing DCE as a valuable complement in equivocal cases or smaller lesions. The bp approach needs high standard of image quality and level of expertise. Therefore, the current recommendations suggest to have both bp and mpMRI approaches available.

It remains essential to codify an appropriate decision algorithm that includes imaging and clinical-laboratory findings of the lesions, patient history and potentially promising genomic biomarkers, allowing modelling the pre-test risk of the patients and therefore standardization of the

MRI approach. Further studies are necessary to investigate the DCE additional role in proper discrimination of csPCa.

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