



Update on the ICUD-SIU consultation on multi-parametric magnetic resonance imaging in localised prostate cancer

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Abstract

Introduction Prostate cancer (PCa) imaging is a rapidly evolving field. Dramatic improvements in prostate MRI during the last decade will probably change the accuracy of diagnosis. This chapter reviews recent current evidence about MRI diagnostic performance and impact on PCa management.

Materials and methods The International Consultation on Urological Diseases nominated a committee to review the literature on prostate MRI. A search of the PubMed database was conducted to identify articles focussed on MP-MRI detection and staging protocols, reporting and scoring systems, the role of MP-MRI in diagnosing PCa prior to biopsy, in active surveillance, in focal therapy and in detecting local recurrence after treatment.

Results Differences in opinion were reported in the use of the strength of magnets [1.5 Tesla (T) vs. 3T] and coils. More agreement was found regarding the choice of pulse sequences; diffusion-weighted MRI (DW-MRI), dynamic contrast-enhanced MRI (DCE MRI), and/or MR spectroscopy imaging (MRSI) are recommended in addition to conventional T2-weighted anatomical sequences. In 2015, the Prostate Imaging Reporting and Data System (PI-RADS version 2) was described to standardize image acquisition and interpretation. MP-MRI improves detection of clinically significant PCa (csPCa) in the repeat biopsy setting or before the confirmatory biopsy in patients considering active surveillance. It is useful to guide focal treatment and to detect local recurrences after treatment. Its role in biopsy-naïve patients or during the course of active surveillance remains debated.

Conclusion MP-MRI is increasingly used to improve detection of csPCa and for the selection of a suitable therapeutic approach.

Keywords Prostate · Prostate cancer · Multiparametric MRI · Prostate MRI

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Introduction

Over the past few years, many independent groups from all over the world have reported excellent results in the detection of clinically significant prostate cancer (csPCa) using multi-parametric Magnetic Resonance Imaging (MP-MRI). As a result, MP-MRI has become highly integrated into the diagnostic workup of patients at risk for prostate cancer (PCa). However, despite its growing use, MP-MRI is not always performed in a uniform manner and it is important that standardized imaging guidelines be produced so that patients get the best diagnostic value from the examination they undergo [1]. This article presents current guidelines for imaging acquisition, reporting and scoring, and MP-MRI results in PCa detection and staging. Finally, it reviews the potential role of MP-MRI in the management of clinically localised PCa.

Methodology

A committee was nominated by the ICUD to review the current literature covering the role of MP-MRI in localised PCa management. A literature search was performed through PubMed database which focussed on the following topics: MP-MRI detection and staging protocols, reporting and scoring systems, the role of MP-MRI in diagnosing PCa prior to biopsy, in active surveillance, in focal therapy and in detecting local recurrence after treatment. The results of this analysis were first presented during a joint international consultation of the ICUD and the Société Internationale d'Urologie (SIU) held in Melbourne (Australia) on October 2015. The PubMed search was updated to add most recent publications.

Review

In an effort to harmonize practices, several professional societies have published guidelines describing how to perform, interpret and report prostate MP-MRI [2, 3]. Those guidelines include technical recommendations on how to perform the examination properly, how to localize and describe a suspicious image on all MRI sequences using unified terminology and how to summarize its likelihood of malignancy on a standardized five-point scale. They also describe how to communicate these findings to the requesting physician in a satisfactory manner.

Optimizing imaging protocols for localised prostate cancer

Detection protocol

For PCa detection, MP-MRI can be obtained at 1.5 Tesla (T) or 3T, using either a combination of an endorectal coil

(ERC) and a pelvic phased-array coil, or a pelvic phased-array coil only. The use of an ERC and/or examination at high field strength (3T) provides higher signal-to-noise ratio, and this extra signal can be used to improve resolution, speed of acquisition and/or diffusion imaging [4]. Nonetheless, good results for PCa detection have been published at 1.5T without using an ERC. The use of ERC and 3T imaging is, therefore, optional. Imaging at low field strength (< 1.5T) is discouraged [3].

The imaging protocol should include at least T2-weighted (T2W), diffusion-weighted (DW) and dynamic contrast-enhanced (DCE). T2W imaging should include images acquired along the axial, coronal and sagittal planes. DW imaging should be obtained along the axial plane and include at least three *b* values with reconstruction of an Apparent Diffusion Coefficient (ADC) map (Fig. 1). It is essential to obtain a maximal *b* value ≥ 1400 s/mm². DCE imaging should be acquired along the axial plane, with a temporal resolution ≤ 15 s and preferably ≤ 7 s. MR spectroscopy imaging (MRSI) is currently considered optional and has been relegated to the research setting.

One important challenge with DW imaging when an ERC is not used is the presence of rectal gas that may generate susceptibility and distortion artefacts, which can potentially limit lesion detection. A proper preparation of patient, including inserting small intrarectal tubes to expel rectal gas is fundamental.

When MP-MRI is obtained after prostate biopsy, a delay of at least 6–8 weeks must be observed to minimize the risk of bleeding artefacts. Haemorrhage is indeed responsible for hyperintense signal on T1-weighted (T1 W) images and hypointense signal on T2W images that may mimic prostate cancer and decrease MP-MRI positive predictive value. Axial T1-weighted images may be added to the imaging protocol to detect residual bleeding artefacts when MP-MRI is performed after biopsy.

Staging protocol

The purpose of local staging is to detect extra-capsular extension (ECE; T3a disease) and seminal vesicle invasion (SVI; T3b disease). Currently, MP-MRI is the most promising method for local staging prior to treatment although it has limitations in sensitivity.

The main features used to assess ECE are either overt/direct findings (direct extension visible in the periprostatic fat, obliteration of the rectoprostatic angle) or secondary features (capsular bulge, irregularity, broad capsular contact with the tumour, etc.) that are strongly associated with ECE. Features of SVI include focal low-signal intensity on T2W images and/or focal enhancement on DCE imaging.

The evaluation of the prostatic capsular invasion requires very high spatial resolution and high image quality. Better

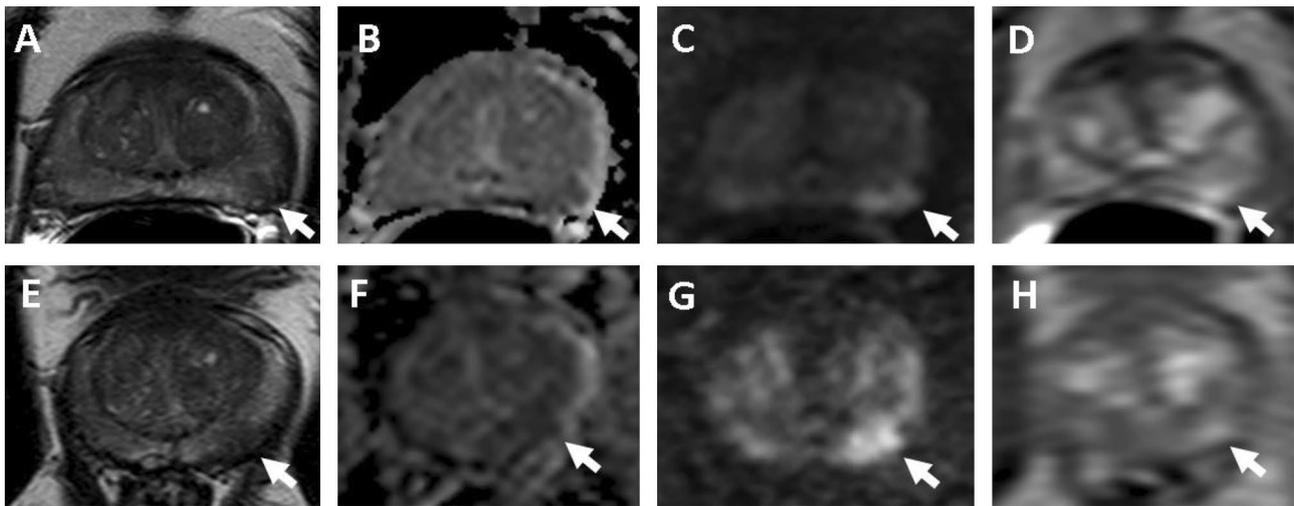


Fig. 1 63-year-old man with a PSA=4.7 ng/ml. Multi-parametric MRI obtained with combined use of an endorectal coil including axial T2W MRI (a), ADC map of DW-MRI (b), b2000 s/mm² DW-MRI (c) and DCE MRI (d) shows a lesion in the left mid-peripheral zone (arrows). The same patient underwent a multi-parametric MRI

with 32-channel-phased-array surface coil a year after the initial MP-MRI, which again localizes the same lesion on axial T2W MRI (e), ADC map of DW-MRI (f), b1500 s/mm² DW-MRI (g), DCE MRI (h) (arrows). The lesion was biopsied via TRUS/MRI fusion guidance and found to include Gleason 3 + 3 prostate cancer

spatial resolution can be achieved with combined use of ERC and a pelvic phased-array coil at 3T [5]. However, Park et al. [6] reported that MP-MRI with an ERC at 1.5T had comparable accuracy in local staging compared to no ERC MP-MRI at 3T (70 vs. 72% for with ERC vs. no ERC protocols, respectively). On the other hand, the use of the ERC significantly increased staging performance, and sensitivity for detection of locally advanced disease by experienced readers was increased from 7% (1 of 15) to a range of 73% (11 of 15) to 80% (12 of 15) ($p < 0.05$), whereas a high specificity of 97% (30 of 31) to 100% (31 of 31) was maintained [7]. SVI is less sensitive to the need for an ERC and can be detected with either ERC or non-ERC MP-MRI protocols especially if the SVs are well distended.

Critical pulse sequences for optimizing a staging MP-MRI protocol include axial T1 W imaging (for depiction of biopsy-related haemorrhage), tri-plane T2W imaging, DW imaging and DCE imaging. This multi-parametric approach not only enables staging, but also aids in predicting the aggressiveness of the lesions [8]. Moreover, DCE imaging is useful for SVI as enhancement of a seminal vesicle mass is highly suggestive of invasion [9]. Staging ability of MRSI is limited by the requirement of a large voxel size [10].

MRI reporting and scoring

The first step of the interpretation process is to detect suspicious lesions within the gland. Reading has to be performed methodically and should independently assess each of the three main compartments of the gland: the peripheral zone

(PZ), the transition zone (TZ), and the anterior fibromuscular stroma (AFMS), because diagnosis of csPCa relies on different criteria in these three zones [11]. Such analysis allows faster review of the entire gland, without omission. This task is easier when the multi-parametric protocol is respected because DCE imaging allows quick detection of foci of increased vascularization that usually matches with cancer in the peripheral zone, or foci of cancer difficult to detect on T2W or DW imaging.

Because there is a large overlap between appearances of PCa and benign findings at MP-MRI, each visible lesion must receive a five-level score of likelihood of malignancy, ranging from the lowest (1/5) to the highest (5/5) degree of suspicion for malignancy [2].

Initial guidelines recommended an entirely subjective scoring that was based only on the radiologist experience (so-called Likert score) [12]. A score of 1/5, depicting completely normal peripheral (bright and homogeneous on T2W images, without restriction or enhancement) or transition zone tissue, has a high likelihood of being benign, whereas on the contrary, a score of 5/5, depicting a typical cancer (PZ nodule with marked low-signal intensity on T2W images, marked restriction of diffusion and early enhancement), has the highest likelihood of corresponding to a csPCa. In practice, many benign areas of tissue show some abnormalities (scars and abnormal enhancement) accounting for the majority of scores of 2/5. The majority of csPCa show discordant findings on different pulse sequences, with either atypical DW or DCE imaging findings, or non-nodular appearance, accounting for the majority of scores of 4/5. Remaining lesions (scoring of 3/5, “equivocal”) show moderate signal

changes and/or atypical morphology, and can either be malignant or benign.

In an effort to harmonize practices, the European Society of Uro-Radiology (ESUR) published professional recommendations in 2012 and introduced the Prostate Imaging Reporting and Data System version 1 (PI-RADS v1)². This scoring system described five-level scores for T2W, DW and DCE imaging, and for MRSI. However, it did not clearly define if the “final” PI-RADS score of a suspicious image had to be a sum of the three or four individual scores (ranging from 3 to 15 or 4 to 20), an average score (ranging from 1 to 5), or just a decision support to let the radiologist allocate the definitive score subjectively, with knowledge of additional criteria the PI-RADS system did not take into account (clinical information, lesion size, etc.).

An updated version of the PI-RADS scoring system (PI-RADS v2) has been published in 2016 [3]. It clarifies how to assign an individual score to the different pulse sequences (T2W, DW and DCE imaging), how to describe the findings using a glossary of terms, and finally, how to build the final five-point-scaled PI-RADS v2 score of the lesion, using a detailed scoring algorithm (Tables 1 and 2).

PI-RADS v2 is specifically aimed at providing a likelihood of malignancy for clinically significant cancer (defined as Gleason score ≥ 7 and/or volume ≥ 0.5 cc and/or extraprostatic extension). It introduces the concept of a “dominant” sequence depending on the location of the image in the gland. DW imaging is thus the dominant sequence for PZ lesions, with a minor contribution of DCE imaging. InTZ, T2W imaging is the dominant sequence, with a minor contribution of DW imaging. Thus, T2W imaging has no influence on the score in PZ, and DCE has no influence on the score in TZ.

This new version states that PI-RADS score assessment should be strictly based on objective MP-MRI findings, and not incorporate factors such as the PSA, DRE, or other clinical information.

Several studies have demonstrated good performance of the PI-RADS v1 score for the classification of suspicious lesions, and moderate-to-good inter-reader agreement between readers. In a prospective two-center study that included 118 patients, Renard-Penna et al. [13] showed in 2015 that a summed PI-RADS v1 score of 9/15 or greater, achieved a sensitivity and a specificity of 86.6 and 82.4%. Sensitivity and specificity of a subjective Likert scale score of 3/5 or greater were 93.8 and 73.6%, respectively. In another series of 215 patients, Vaché et al. [14] observed respective areas under the ROC curve (AUC) of 0.80 and 0.74 in PZ for subjective Likert scoring and objective PI-RADS v1 scoring, respectively. In TZ, the AUC were 0.87 vs. 0.82, respectively, with statistically significant differences in both cases. Other studies also suggest that PI-RADS v1 criteria did not completely reflect all the components of

Table 1 Semiology criteria used for scoring peripheral (PZ) or transition (TZ) zone lesions on the T2-weighted images and on the diffusion-weighted series (DWI) in the 2015 PI-RADS v2 scoring system

Series score	DWI	
	PZ	TZ
1	Uniform hyperintense signal intensity (normal)	Homogeneous intermediate signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin	Circumscribed hypointense or heterogeneous encapsulated module(s) (BPH)
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity includes others that do not qualify as 2, 4, or 5	Heterogeneous signal intensity with obscured margins include others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and ≤ 1.5 cm in greatest dimension	Lenticular or non-circumscribed, homogenous, moderately hypointense, and ≤ 1.5 cm in greatest dimension
5	Same as 4, but ≥ 1.5 cm in greatest dimension or definite extraprostatic extension/invasive behaviour	Same as 4, but ≥ 1.5 cm in greatest dimension or definite extraprostatic extension/invasive behaviour

Table 2 Semiology criteria used for scoring peripheral (PZ) and transition (TZ) zone lesions on the dynamic contrast-enhanced, T1-weighted series (DCE) in the 2015 PI-RADS v2 scoring system

Series score	PZ or TZ DCE
Negative (–)	No early enhancement, or diffuse enhancement not corresponding to a focal finding on T2W and/or DW imaging or focal enhancement corresponding to a lesion demonstrating features of BPH on T2W imaging
Positive (+)	Focal, and earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and; corresponds to suspicious finding on T2W and/or DW imaging

Note that series score is not ranging from 1 to 5 like in other sequences, but only “positive” or “negative”

an expert’s judgement, or did not include significant criteria described in other scoring systems (e.g. size of the lesion, anterior or inferior location of TZ cancers, posterolateral location of PZ cancers, specific AFMS cancers, etc.).

The recent introduction of the PI-RADS v2 score did improve the accuracy of the scoring, with an increased sensitivity and a similar specificity, as compared to the PI-RADS v1 score [15].

MP-MRI and prostate biopsy

Pre-biopsy MP-MRI aids in prostate cancer identification, localization, characterization of aggressiveness, estimation of volume and contour. Furthermore, biopsy targeting lesions seen on MP-MRI improves the diagnostic yield of clinically significant (cs) PCa detection rate and reduces the number of insignificant PCa diagnosed in patients [16]. Another advantage of pre-Bx MRI is that it avoids post-biopsy bleeding artefacts that restrain accuracy for PCa detection.

Franiel et al. [17] investigated whether MP-MRI was helpful in differentiating low-grade (Gleason score ≤ 6) and high-grade (Gleason score > 7) PCa. Using DCE kinetic models, low-grade PCa had significantly higher mean blood volume (1.76 vs. 1.64%, $p=0.039$), longer mean transit time (6.39 vs. 3.25 s, $p<0.001$), and lower mean permeability (2.57 vs. 3.86 min $^{-1}$, $p=0.011$) than high-grade PCa. These features, achieved using 1.5-T MP-MRI, could be used to properly assess tumour aggressiveness and better manage the patient.

Pre-biopsy MP-MRI may improve csPCa detection by directly targeting suspicious areas during the subsequent biopsy procedure. In the systematic review by Moore et al. [18], PCa was detected in 30% of targeted cores (375 out of 1252) versus 7% of systematic cores (368 out of 5441). On a per patient basis, the cancer detection rate was 36% (526 of 1442) for standard biopsy and 48% (650 of 1345) for targeted biopsy. A meta-analysis by Schoots et al. [19] including 16 studies did not find any significant difference in the overall PCa detection by systematic and targeted

biopsy [sensitivity of 0.81 (95% confidence interval (CI) 0.70–0.88) versus 0.85 (95% CI 0.80–0.89)]. Targeted and systematic biopsy missed the diagnosis of prostate cancer in 15 and 19% of cases, respectively. However, targeted biopsy had a higher detection rate for csPCa [sensitivity of 0.91 (95% CI 0.87–0.94) versus 0.76 (95% CI 0.64–0.84)] and a lower detection rate of insignificant PCa [sensitivity of 0.44 (95% CI 0.26–0.64) versus 0.83 (95% CI 0.77–0.87)]. Therefore, targeted biopsy may not only improve the detection of csPCa. It may also diminish subsequent overtreatment by reducing the detection of indolent PCa (over diagnosis). This was further confirmed by a randomized trial recently published by Panebianco et al. [20].

It is of note, however, that in the meta-analysis by Schoots et al. [19], the increased detection of csPCa due to targeted biopsy was significant only in the repeat biopsy setting. In patients with history of negative prior biopsy, the relative sensitivity between targeted and systematic biopsy was 1.54 (95% CI 1.05–2.57). It was only 1.10 (95% CI 1.00–1.22) in biopsy-naive patients. This can be explained by the fact that the repeat biopsy group is more favourable for target biopsy, with an increased prevalence of anterior tumours that are well detected by MP-MRI, but tend to be missed by systematic biopsy.

Whether pre-biopsy MP-MRI can improve csPCa detection in biopsy-naive patients remains unclear. A recent randomized trial performed by Baco et al. compared two methods (12-core random biopsy versus 2-core MRI-targeted biopsy plus 12-core random biopsy) and reported no difference between those for diagnosing csPCa (defined as maximum cancer length ≥ 5 mm in Gleason 6 cancers or any Gleason ≥ 7 cancer) [21].

The role of MP-MRI in active surveillance

The literature on the role of MP-MRI in patients considering active surveillance (AS) or already enrolled in an AS program is scarce. Because it has a high sensitivity for csPCa, MP-MRI could assist in the appropriate selection of

patients for AS [22]. Its role during the follow-up period of AS remains unclear. Particularly, it is still unclear whether a negative MP-MRI could obviate the need for prostate biopsy in patients under AS. The ideal frequency of MP-MRI follow-up is already unknown.

The role of MP-MRI in focal therapy

Determining prostate cancer volume and contours is of paramount importance for targeting focal therapy. Thus far, some studies evaluated tumour volume estimation at MP-MRI. Tumour volume tends to be underestimated by all MP-MRI pulse sequences [23, 24]. Thus, it is advised to destroy a much larger region of the gland than the one indicated by MP-MRI in to allow full tumour destruction. It seems that this discrepancy in boundary may be most significant at the non-capsular side of the lesion given the tendency for tumours to originate close to the capsule and exhibit centripetal growth within the gland [25]. These findings have a key implication in planning and performing focal therapy procedures and would suggest the respect of a security margin to be confident of full tumour destruction in view of the larger histologic volume [26].

During treatment, MP-MRI provides two key advantages for an effective focal ablation over other imaging modalities. First, its excellent soft tissue contrast and multi-planar imaging capabilities allow for clear visualization and localization of the tumour and for accurate probe placement into the lesion. Second, if the procedure is performed under MR guidance, MR thermometry can be used to non-invasively monitor and control the ablation in real time by measuring the spatial distribution of tissue temperature during the thermal ablation. Finally, MRI can also be used to assess the ablation size and validate the completeness of the focal therapy covering the target lesion [27].

In thermal ablation, tissue heating induces coagulative necrosis in the target area, which becomes completely devascularized and surrounded by inflammation and edema [28]. MR images within days after high-intensity focussed ultrasound may show a significant increase of the prostate volume, presumably due to transient edema, with slightly hyperintense areas on T1-weighted images, most likely representing interstitial haemorrhage, and a central hypointense and ill-defined lesion on T2-weighted images. Similar findings are seen after photodynamic therapy, T2 heterogeneous signals are seen that are related to the edema and ischemic modifications induced by phototherapy.

After 3–5 months, the prostate shrinks and the parenchyma becomes diffusely hypointense and ill-defined, with loss of the normal zonal anatomy on T2-weighted images. This MRI appearance of HIFU and laser ablation-induced

changes is identical to those associated with cryotherapy (which induces cell death by hypothermic coagulation necrosis, direct cellular toxicity due to disruption of the cell membrane by formation of “ice ball crystals” and gene regulated cell death) [29]. At 6 months after photodynamic therapy, important changes of the prostate shape and signal are found [30]. Small areas of residual necrosis may still be present in the treated lobe, corresponding to coagulation necrosis.

The role of MP-MRI in detecting local recurrences after treatment

The goal of imaging in biochemical relapse after treatment is to detect local and/or metastatic recurrence. Technical improvements of prostatic MRI allow early detection of local recurrence after radical treatments (radical prostatectomy and radiation therapy) or focal therapy (high-intensity focussed ultrasound (HIFU), cryosurgery, and photodynamic therapy).

The most common site of postoperative local recurrence after radical prostatectomy is the urethrovesical anastomosis around the bladder neck and the membranous urethra (40–55%) [31]. MP-MRI can discriminate local relapse from residual glandular healthy tissue, scar/fibrosis, and granulation tissue. The presence, on T2W images, of a lobulated nodular-like or mass-like soft tissue thickening in the prostatectomy bed that appears slightly hyperintense compared to pelvic muscles should be considered to be strongly suggestive of local recurrence.

Recurrent tumours tend to enhance faster and more avidly after gadolinium administration in the early arterial phase, followed by a plateau or washout during the venous phase, while postoperative fibrosis tends to show either no enhancement or mild enhancement in the venous phase [32]. DCE imaging has been reported to increase diagnostic sensitivity from 48 to 88% and specificity from 52 to 100% compared with T2W MRI alone, and allows the detection of recurrent tumours measuring more than 5 mm, for a PSA level of less than 2 ng/mL, with a negative predictive value of 95% [33]. As a result, DCE imaging can be considered as the most reliable MRI technique for the detection of local prostate cancer recurrence after RP.

After external radiation beam radiotherapy (EBRT), the prostate appears decreased in volume, diffusely hypointense on T2 W images, with a loss of zonal anatomy. The seminal vesicles also appear globally hypointense.

Recurrences are most commonly located in the original tumour site [34]. T2W imaging alone is of a limited diagnostic accuracy because the recurrent tumour and the normal surrounding parenchyma both appear hypointense

[35]. Cancer can be detected under such circumstances if its signal intensity is lower than adjacent prostate tissue, and if it appears nodular or with a mass-like effect. Recurrent tissue appears as hypervascular early enhancing homogeneous nodule, with an early washout, whereas in fibrosis the enhancement is homogeneous, slow, and less intense. So, the combination of T2W and DW-MRI appears to be the optimal approach.

Brachytherapy induces a decrease in volume of the prostate gland and seminal vesicles, as does EBRT. The prostate gland appears globally hypointense on T2W images, with loss of zonal anatomy. The capsule appears irregular, and the seminal vesicle appears hypointense on T2 weighted images as well. Brachytherapy seeds can be seen on all sequences but more particularly during DCE imaging. However, sensitivity of DW imaging in detecting recurrent tumour was significantly higher than that of T2W MRI. MP-MRI achieved the highest sensitivity (77%), but with slightly decreased specificity (92%) [36].

After HIFU, MP-MRI is recommended to detect recurrence at 6 months follow-up. However, prostatic parenchyma is heterogeneously and diffusely hypointense on T2W images with a loss of normal zonal anatomy, which makes it difficult to analyze [37]. Therefore, it is essential to combine T2W MRI with DCE MRI and DW-MRI to differentiate residual/recurrent cancers (which are usually hypervascular) from post-HIFU fibrosis (which is rather homogeneous and hypovascular).

After cryotherapy, DCE imaging, DW imaging, and MRSI allow for the detection of recurrence in the same way as for HIFU ablation [38].

Conclusion

A large body of the literature suggests that MP-MRI has become a reliable tool for assessing the presence and size of aggressive cancer in the prostate. By improving the detection of significant prostate cancer, MP-MRI could be used for the selection of a suitable therapeutic approach and its evaluation. Recent initiatives have been made by the international radiological community to define a standardized way to interpret MR images. This raises the hope that the good results obtained with prostate MP-MRI by specialized academic groups will be soon reproduced in less-experienced centers.

Author contributions EB: project development, data collection, manuscript writing. BT: manuscript writing. PP: manuscript writing, MD: manuscript writing, VP: manuscript writing, JJF: manuscript writing. RR-P: manuscript writing, OR: project development, data collection, manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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