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Biparametric 3T Magentic Resonance Imaging for prostatic cancer detection in a biopsy-naïve patient population: a further improvement of PI-RADS v2?

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ABSTRACT

Objectives: To prospectively determine the diagnostic accuracy of a biparametric 3T magnetic resonance imaging protocol (BP-MRI) for prostatic cancer detection, compared to a multiparametric MRI protocol (MP-MRI), in a biopsy naïve patient population.
Methods: Eighty-two untreated patients (mean age 65 ± 7.6 years) with clinical suspicion of prostate cancer and/or altered prostate-specific antigen (PSA) levels underwent a MP-MRI, including T2-weighted imaging, diffusion-weighted imaging (with the correspondent apparent diffusion coefficient maps) and dynamic contrast enhanced sequence, followed by prostate biopsy. Two radiologists reviewed both the BP-MRI and the MP-MRI protocols to establish a radiological diagnosis. Receiver operating characteristics curves were obtained to determine the diagnostic performance of the two protocols.
Results: The mean PSA level was 8.8 ± 8.1 ng/ml. A total of 34 prostatic tumors were identified, with a Gleason score that ranged from 3 + 3 to 5 + 4. Of these 34 tumors, 29 were located within the peripheral zone and 5 in the transitional zone. BP-MRI and MP-MRI showed a similar performance in terms of overall diagnostic accuracy, with an area under the curve of 0.91 and 0.93, respectively (p = n.s.).
Conclusions: BP-MRI prostate protocol is feasible for prostatic cancer detection compared to a standard MP-MRI protocol, requiring a shorter acquisition and interpretation time, with comparable diagnostic accuracy to the conventional protocol, without the administration of gadolinium-based contrast agent.

1. Introduction

Prostate cancer (PCa) is one of the most common types of tumor and the second highest cause of cancer-related mortality in males [1]. In 75%–85% of cases, PCa occurs in the peripheral zone (PZ); however, it has been shown that the transitional zone (TZ) harbors cancer in up to 25% of radical prostatectomy specimens [2]. Early diagnosis, targeted therapy and accurate monitoring following the radical prostatectomy have a significant impact on the prognosis of these patients. Clinical suspicion of PCa is typically based on digital rectal examination (DRE) and/or the finding of elevated prostate-specific antigen (PSA), and patients are typically referred for prostate biopsy, most commonly performed under transrectal ultrasound (TRUS) biopsy guidance [3–5].

Multiparametric magnetic resonance imaging (MP-MRI) is currently considered the most promising imaging modality to evaluate patients with suspicion of PCa, providing high quality imaging of the prostate [6–11].

In 2012, the Prostate Imaging Reporting and Data System (PI-RADS) was created to standardize the interpretation and systematic reporting of prostate MR imaging [12]. Since the first introduction of PI-RADS version 1 by the European Society of Urogenital Radiology, researchers have shown the clinical utility of PI-RADS in localizing PCa, classifying the risk groups, and improving the yield of target biopsy [13,14]. More recently, a simplified score system (i.e. PI-RADS v2) has been proposed to categorize and summarize the levels of suspicion or risk of having prostatic carcinoma and

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to reduce variability in imaging interpretations [15]. Despite the improvements and usefulness of PI-RADS v2, controversies still exist in particular on the real benefit of contrast material administration [16]. Nonetheless, PI-RADS v2 suggests that all prostate MRI examinations should include a dynamic contrast enhanced (DCE) sequence for detection of PZ prostatic lesions [15].

A new modality for imaging of patients with PCa has been recently proposed, based on a biparametric (T2-weighted and diffusion-weighted imaging −DWI–) magnetic resonance imaging (BP-MRI) protocol for PCa detection [16–18]. However, to the best of our knowledge, a prospective study aimed to evaluate the diagnostic accuracy of MP-MRI compared to the one achieved with the use of BP-MRI has not yet been performed, since all the published studies evaluated only the diagnostic accuracy of BP-MRI in combination to clinical and/or laboratory findings [17,18].

Therefore, the aim of the present exploratory study was to prospectively determine the diagnostic accuracy of a BP-MRI protocol for the PCa detection, compared to a standard MP-MRI protocol that included T2-weighted imaging, DWI and DCE, using a 3T scanner and without the use of an endorectal coil.

2. Material and methods

2.1. Subjects

From an initial group of 125 subjects admitted to our Urology Department, 82 untreated patients (mean age 65 ± 7.6 years, age range: 43–84) were entered into this study. Inclusion criteria was the clinical suspicion of PCa, derived from either elevated PSA levels or abnormal findings on DRE. All patients enrolled had a serum PSA assessment, DRE and finally underwent MP-MRI at 3 T. Within one month from the MRI study all patients underwent a systematic 12-core TRUS guided biopsy, to establish a final diagnosis. Informed consent, a requirement of the protocol approved by the Institutional Clinical Research Subpanel on Human Studies at our Institute, was obtained in all patients. Patient's demographics and clinical variables are shown in Table 1.

Table 1
Patients demographics and clinical variables of the subjects included in the study.

	All group	Patients with positive biopsy	Patients with negative biopsy
Number of patients	82	34	48
Age (mean ± SD)	65 ± 7.6 (range 43–84)	66 ± 5.3 (range 43–84)	63 ± 7.4 (range 53–78)
PSA levels (mean ± SD)	8.8 ± 8.1	9.9 ± 11.1	8.0 ± 5.0
Prostate volume (mean ± SD)	62.9 ± 28.6	51.0 ± 19.3	72.8 ± 30.8
Tumor size (mean ± SD)	n.a.	12.0± 6.1	n.a.
Gleason Score = 6 (3 + 3) ISUP Group 1	n.a.	12	n.a.
Gleason Score = 7 (3 + 4) ISUP Group 2	n.a.	12	n.a.
Gleason Score = 7 (4 + 3) ISUP Group 3	n.a.	5	n.a.
Gleason Score = 8 (4 + 4) ISUP Group 4	n.a.	4	n.a.
Gleason Score = 9 (5 + 4) ISUP Group 5	n.a.	1	n.a.

PSA = Prostate Specific Agent; SD = Standard Deviation; Ages are expressed in years; PSA levels are expressed as nanograms/milliliters; Prostate volume is expressed in cubic centimeters; Tumor size is expressed in millimeter; ISUP = International Society of Urological Pathology.

2.2. MRI acquisition protocol

All MRI scans were acquired on the same 3 T scanner (MAGNETOM Trio, Siemens Medical Solutions, Erlangen, Germany), equipped with a surface phased array coil (Body Matrix, Siemens Medical Solutions).

Acquisition protocol included for all subjects the following sequences: T2-weighted turbo spin echo (TSE) imaging acquired with axial, sagittal and coronal orientations (repetition time [TR], 4000 ms; echo time [TE], 101 ms; field of view 200 × 200 mm; thickness 3 mm, no gap), a DWI-sequence (TR, 4900 ms; TE, 89 ms; b-factor 0, 400, 2000; field of view 200 × 200 mm; thickness 3 mm, no gap, axial orientation) and a 3D fast low-angle shot (FLASH) T1-weighted spoiled gradient-echo sequence on the axial plane (TR, 4.91 ms; TE, 1.74 ms, field of view 200 × 200 mm, thickness 3 mm, no gap) to perform measurements in rapid succession, immediately following completion of an intravenous bolus injection of 0.1 ml/kg gadopentetate dimeglumine, using a power injector (Medtron) at 3 ml/s followed by a 30 ml saline flush, 54 contrast-enhanced sets of images were acquired sequentially without a delay between acquisitions, therefore time resolution was 7 s. All these sequences were evaluated for the MP-MRI protocol. For the BP-MRI protocol were evaluated only four sequences extrapolated from the above-mentioned MP-MRI acquisition protocol, namely the three T2-weighted TSE sequences, along with the DWI sequence.

A summary of all the sequences evaluated in this study, along with the corresponding acquisition times, is shown in Table 2.

2.3. Image analysis

Images were reviewed separately by two radiologists (M.I. and A.B.) with respectively 14 years and 10 years experience in prostate MR imaging. The two radiologists read independently the BP-MRI first, followed by the full MP-MRI scans, after an interval between 20 and 30 days, both blinded to the clinical indication and to the PSA values.

MRI criteria suggestive for malignancy were based on the PI-RADS v2 criteria, as previously described [15]. Briefly, all detected lesions were classified giving a score from 1 to 5, where, 1 was considered very low probability of PCa (clinically significant prostatic carcinoma was highly unlikely to be present); 2, as low probability (clinically significant prostatic carcinoma was unlikely to be present); 3, as intermediate probability (the presence of clinically prostatic carcinoma disease was equivocal); 4, as high probability (clinically significant prostatic carcinoma was likely to be present)

Table 2
Comparison of the MP-MRI vs the BP-MRI protocol.

Multiparametric MR protocol (~24 min)	*B*iparametric MR protocol (~17 min)
TSE T2-weighted sequence, axial planes (AT = 4'11")	TSE T2-weighted sequence, axial planes (AT = 4'11")
TSE T2-weighted sequence, sagittal planes (AT = 3'46")	TSE T2-weighted sequence, sagittal planes (AT = 3'46")
TSE T2-weighted sequence, coronal planes (AT = 3'38")	TSE T2-weighted sequence, coronal planes (AT = 3'38")
DWI sequence, axial planes (AT = 6'28")	DWI sequence, axial planes (AT = 6'28")
Dynamic contrast enhanced 3D T1-weighted spoiled gradient-echo sequence, axial planes (AT = 6'30")	

AT = Acquisition Time.

5, as very high (clinically significant prostatic carcinoma was highly likely to be present).

2.4. Prostate biopsy procedure

An urologist with over 10 years of experience in TRUS guided biopsy performed all the prostate biopsies in the study. All biopsies were performed with peri-prostatic local anesthetic (10 ml Lidocaine 1%) and pre-procedural antibiotic prophylaxis (Ciprofloxacin). Using a BK ultrasound scanner, endorectal probe, a needle guide, and an 18-Gauge 25-cm biopsy needle. After MRI examination, all patients underwent a standard 12-core TRUS guided sextant biopsy. Biopsies were obtained from each of 6 sagittal regions (3 per side) moving from prostatic base to apex with 2 cores from each zone for a total of 12 cores. In particular, 1-cm in length TRUS biopsies cores were taken from 12 prostatic regions and marked separately. Other samples were taken from the suspicious area if clear TRUS lesions were present. The procedure was well tolerated in all patients included in the study, with no major complications after the procedure. All biopsy samples were sent to the pathology laboratory of our institution, where they were analyzed and reported according to the International Society of Urological Pathology (ISUP) 2005 modified Gleason score grading system [19].

2.5. Statistical analysis

For each prostate MR imaging protocol, the diagnostic performance was assessed by measuring the area under the curve (AUC) of the free-response receiver operating characteristic analysis (ROC) [20]. Diagnostic accuracy, sensitivity, specificity, with corresponding 95% confidence intervals, were determined and compared between the MP-MRI and the BP-MRI. The differences in the AUC were statistically analyzed using the Chi-squared test. In particular, we tested whether there was a statistically significant difference between results provided by the two MR imaging protocols, as confirmed by the reference standards. The κ statistics were also performed to assess the inter-reader agreement. The degree of inter-reader agreement was interpreted with the following interval of κ values: 0–0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, and 0.81–1 = excellent agreement. All analyses were performed with the Statistical Package for Social Science (SPSS) (SPSS Inc, v. 17.0, Chicago, Ill). A *p*-value lower than 0.05 was considered as statistically significant.

3. Results

The mean PSA level of all subjects included in the study was 8.8 ± 8.1 ng/ml. A total of 34 PCa were identified in 82 patients. Among these, 29 patients proved to have a PCa of the PZ, while in 5 patients PCa was identified as belonging to the TZ.

As suggested by the PI-RADS v2 [15], for the 29 patients with PCa of the PZ, average dimension of the tumor was measured on axial plane on the ADC map, and it proved to be 12 mm (ranging from 5 to 24 mm). On the other hand, the 5 patients with PCa of the TZ showed an average dimension of the tumor of 20 mm (ranging from 10 to 31 mm), measured on axial plane on the T2-weighted images, slightly higher compared to the one measured on the images of PZ patients.

Mean volumetric value of the entire gland of patients with positive biopsy was 51.0 ml (ranging from 25 to 90 ml), measured as:

$$(\text{axialdiameter} \times \text{sagittaldiameter} \times \text{coronaldiameter}) \times 0.52$$

When considering the overall diagnostic accuracy, independently from the zonal anatomy, the two readers assigned a PI-RADS score discordant in seven cases (all in the assignment of a score of 1 rather than 2, and vice versa). The inter-reader agreement by using quadratic κ coefficients proved to be excellent (κ = 0.866).

The AUC obtained from the ROC analysis were 0.91 and 0.93 for BP-MRI and MP-MRI, respectively (*p* = n.s.). In particular, the BP-MRI analysis demonstrated an overall diagnostic accuracy of 92.7% (76/82 cases) in the detection of PCa, with a sensitivity of 85.3% (29/34 cases) and a specificity of 98.1% (52/53 cases). Similarly, the MP-MRI analysis proved an overall accuracy of 93.9% (77/82 cases), with a sensitivity of 91.1% (31/34 cases) and a specificity of 96.2% (51/53 cases).

We then moved to compare the diagnostic accuracy of the two approaches with regard to the zonal anatomy. For the PCa of the PZ, the AUC obtained from the ROC analysis were 0.90 and 0.92 for BP-MRI and MP-MRI, respectively (*p* = n.s.). In particular, the BP-MRI analysis demonstrated a diagnostic accuracy of 92.2% (71/77 cases) in the detection of PCa of the PZ, with a sensitivity of 82.8% (24/29 cases) and a specificity of 97.9% (47/48 cases). Similarly, the MP-MRI analysis proved an overall accuracy of 93.5% (72/77 cases), with a sensitivity of 89.7% (26/29 cases) and a specificity of 95.8% (46/48 cases).

In particular, MP-MRI showed a slighter, but not significant, better performance when identifying the true positive, by identifying 26 out of 29 patients with PCa, compared to the 24 out of 29 of the BP-MRI. Indeed, according to BP-MRI in three cases it was assigned a PI-RADS score of 3, which was later modified to 4 after the additional evaluation of DCE sequences in MP-MRI, leading to the identification of two more true positive, with an additional false positive.

Finally, for the diagnostic accuracy of PCa of the TZ, BP-MRI and MP-MRI showed an identical performance both in terms of sensitivity and specificity, correctly classifying all of the lesions.

All differences in terms of diagnostic accuracy proved to be statistically not different at the Chi-squared test.

Table 3 shows the overall diagnostic performance of MP-MRI compared to BP-MRI in the total number of patients included in the study, while Figs. 1 and 2 show two examples of PCs.

After TRUS biopsy, 12/34 (35.3%) patients underwent radical prostatectomy, that confirmed the diagnosis.

4. Discussion

In this exploratory study we have shown for the first time the clinical feasibility and the similar diagnostic accuracy of a BP-MRI protocol compared to a MP-MRI protocol for the detection of PCa by using an high field 3T MR scanner, without the use of an endorectal coil, in a biopsy-naïve patient population.

MP-MRI of the prostate consisting of both anatomic T1-weighted and T2-weighted MRI sequences as well as functional

Table 3
Overall diagnostic accuracy, sensitivities, specificities and areas under the curve for MP-MRI and BP-MRI protocol.

	Overall diagnostic accuracy		Sensitivity	Specificity	AUC
BP-MRI	92.7%	(76/82)	85.3%(29/34)	98.1%(52/53)	0.91
MP-MRI	93.9%	(77/82)	91.1%(31/34)	96.2%(51/53)	0.93

MP-MRI = Multiparametric MRI protocol; BP-MRI = Biparametric MRI protocol; AUC = area under the curve.

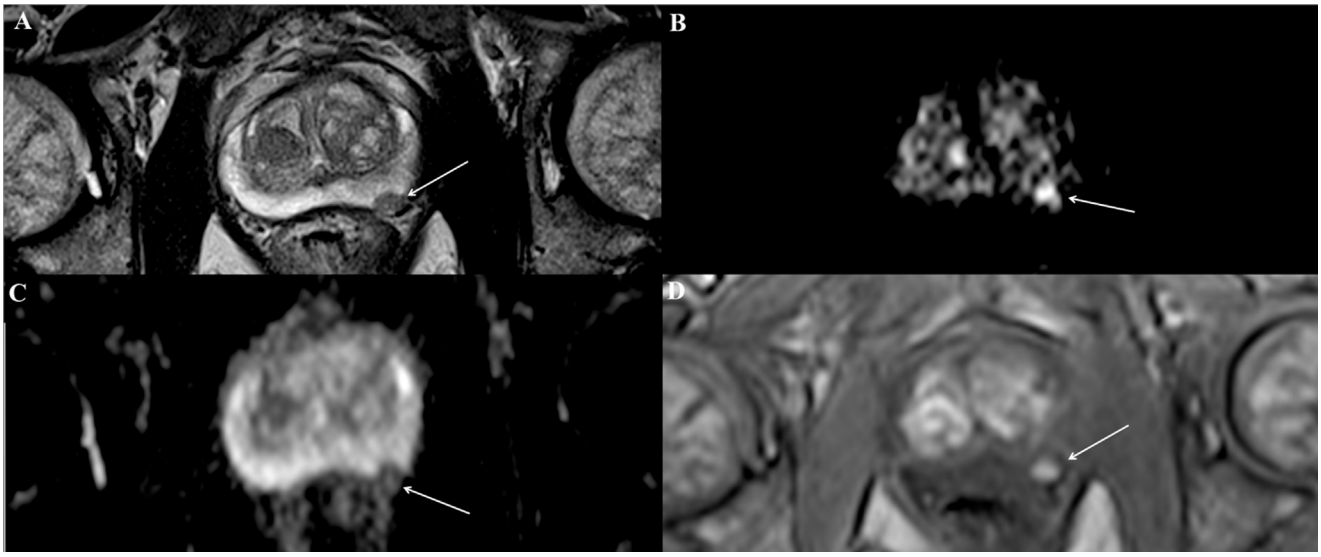

Fig. 1. Images in a 58 years old patient with prostatic adenocarcinoma of the left peripheral zone (Gleason score 7, 4 + 3 – ISUP Group 3).
A: T2-weighted axial image; B: diffusion-weighted image, along with the corresponding ADC map (C) showing a focal hypointense lesion of 7 mm of diameter, characterized by diffusion restriction (arrows). D: dynamic contrast enhancement image shows the same focal area of early enhancement (arrow). The PI-RADS score of dynamic contrast enhancement imaging was positive according to both readers. Nonetheless, the score assigned by both readers on the diffusion-weighted image was 4, so that the dynamic contrast enhancement did not change the overall PI-RADS score of 4, which was suggestive of a high probability of clinically significant cancer.

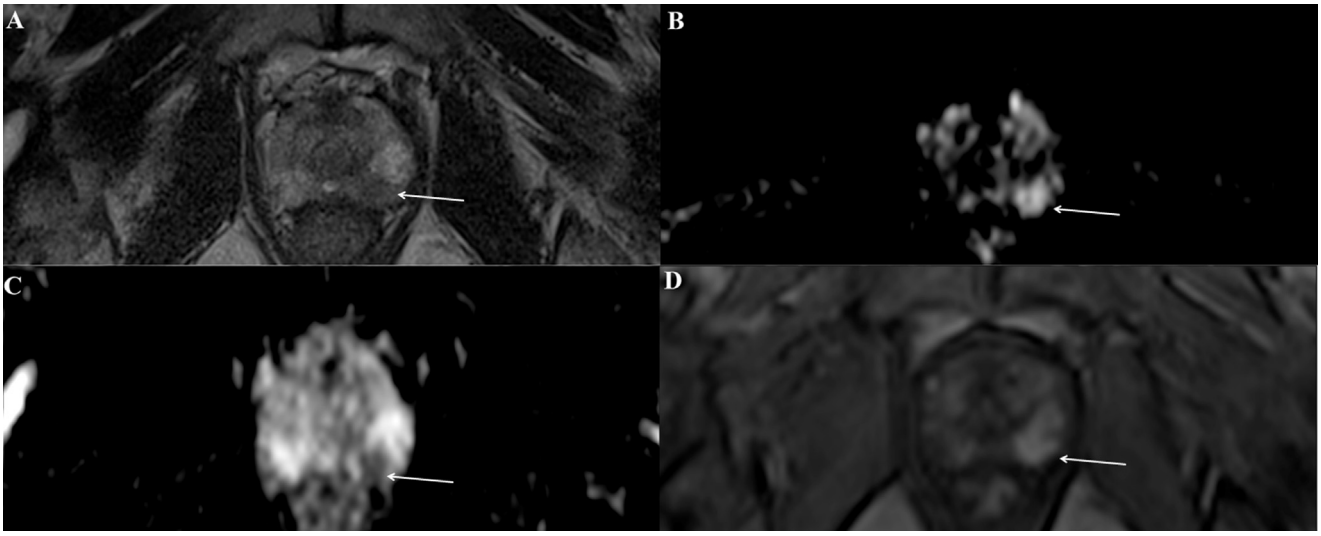

Fig. 2. Images in a 65 years old patient with prostatic adenocarcinoma of the left peripheral zone (Gleason score 7, 3 + 4 – ISUP Group 2).
A: T2-weighted axial image; B: diffusion-weighted image, along with the corresponding ADC map (C) showing a focal hypointense lesion of 10 mm of diameter, characterized by diffusion restriction (arrows). D: dynamic contrast enhancement image shows a blurrier, larger focal area of enhancement, less circumscribed than the one visible on the ADC map (arrow). Similarly to what shown in Fig. 1, the PI-RADS score of dynamic contrast enhancement imaging was positive according to both readers. However, the score assigned by both readers on the diffusion-weighted image was 4, so that the dynamic contrast enhancement did not change the overall PI-RADS score of 4.

sequences, including DWI MRI and DCE sequences has been proposed as the method of choice to image patients with suspicion of prostatic carcinoma [6,7,11]. This MP-MRI technique is able to provide valuable information in a variety of clinical settings [21–23]. Furthermore, endorectal coils at both 1.5T and 3 T scanner, have been shown to improve prostate MR image quality and staging performance compared with those of pelvic phased-array coils, although the necessity of an endorectal coil at 3 T is still questionable and under debate [23,24].

Although MP-MRI is considered the technique of choice for studying patients with suspicion of PCa, this approach is prone to different problems, mainly accountable to the use of contrast agents. Indeed, it is known how gadolinium-based contrast agents are relatively expensive, therefore adding significant costs to the healthcare system; furthermore, recent evidences suggest that their use could lead to possible accumulation in deep cerebral structures, such as dentate nuclei [25,26].

For all this reasons, several groups in the past few years have suggested to develop a more feasible, simple and less invasive imaging method for identifying PCa. In particular, in a recent paper, Rais-Bahrami and colleagues showed the usefulness of using only T2-weighted and DWI images in the detection of PCa [18]. The authors showed that when a BP-MRI was combined with PSA level and PSA density, even higher sensitivity and specificity were achieved, providing greater diagnostic accuracy in detecting clinically significant disease. These data provide support for a limited non-contrast MRI as a potential adjunct tool to optimize PCa detection [18]. More recently, Fascelli et al. validated the use of the

BP-MRI protocol along with the use of PSA or PSA density, in a biopsy-naive cohort of 59 patients at risk for PCa. The authors concluded that the combined use of a BP-MRI, PSA, and PSA density results in improved diagnostic accuracy for detecting clinically significant prostatic carcinoma [17].

Furthermore, in December 2014, a joint steering committee of the American College of Radiology, ESUR, and AdMeTech Foundation agreed to collaborate on the development of an improved PI-RADS v2. The PI-RADS v2 has been officially released in December 2014 [15], with the specific aims of PI-RADS v2 to establish simplified guidelines for minimum acceptable technical parameters for prostate MP-MRI, in order to develop assessment categories that summarize the levels of suspicion or risk of having prostatic carcinoma and to reduce variability in imaging interpretations [15]. To summarize, according to PI-RADS v2, for evaluation of lesions of PZ, DWI is the dominant sequence, while for the TZ the T2-weighted sequence plays a primary role. Consequently, a secondary role has been assigned to DCE sequence, with its application solely conducible in providing additional information in cases of a PZ lesion with a score of 3. Therefore, DCE imaging plays a role as the minor sequence when PZ cancer is equivocally suspected at DWI imaging [15].

These simplified interpretation criteria for patients with suspicion of PCa corroborate the findings of our manuscript. Indeed, we have demonstrated the feasibility of a BP-MRI protocol as a powerful diagnostic tool for detection of PCa compared to the MP-MRI protocol. In particular, we speculate that our results could represent a further improvement of PI-RADS v2. Here, we demonstrated how the sole evaluation of two parameters was sufficient in our population for an accurate detection of PCa, in particular of the PZ, compared to the evaluation of the entire MP-MRI protocol. Indeed, the role of DCE has already been limited by the current PI-RADS v2 to the detection of doubtful PCa of the PZ, with no indications in the detection of lesions of the TZ [15]. As a consequence, our results allow us to hypothesize the future elimination of contrast agent administration in the radiological suspicion of PCa, with obvious advantages for both patients and healthcare systems. In addition, it should be noted that the total acquisition time for the BP-MRI protocol was ~17 min, compared to ~24 min for MP-MRI standard protocol, with a slight reduction in the total acquisition time and patient preparation for MR examination. Nevertheless, a further reduction in costs and patient discomfort was obtained without the use of an endorectal coil, without achieving a significant loss in the overall diagnostic accuracy, due the high field of the MR scanner.

We acknowledge several limitations in the present study, firstly related to the relatively limited sample size of our group of patients. We are aware that such a small sample, especially if compared to other previous works [27,28], could lead to a misinterpretation and/or overestimation of our data. In particular, this small sample size could be somehow responsible for the extremely elevated diagnostic accuracy of PCa of the TZ. However, it should be noted that PCa of the TZ are known to be less common than the ones affecting the PZ [21], and that these patients usually show an higher tumor size compared to patients with PCa of the PZ [21], with our results being in agreement with these previous findings. Nonetheless, for all this reasons future investigations in a larger patient population are warranted to validate the findings of this exploratory manuscript.

Another limitation that should be considered is that the gold standard in our series was 12-core biopsy rather than radical prostatectomy that was performed only in 12 out of 34 patients (35.3%); however in the clinical practice TRUS biopsy is usually recommended as the first line diagnostic procedure in patients with suspicion of prostatic cancer, with all the known limitations [7,11].

In conclusion, we supported the hypothesis that a BP-MRI protocol for the study of the prostate, performed at 3 T without the use of an endorectal coil or the administration of contrast agent, is a feasible tool for the PCa detection, especially of the PZ, compared to a standard MP-MRI protocol, requiring a shorter acquisition and interpretation time and with comparable diagnostic accuracy. The implementation and validation of a BP-MRI protocol in larger patient population could further simplify the PI-RADS v2 scoring system, improving the standardization of prostate MR image interpretation and for a better stratification of patients with suspicion of prostatic cancer.

Conflict of interest

All authors do not have any financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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