Oncologic Imaging REVIEW

The role of MRI in prostate cancer management: pushing the diagnostic frontier

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ABSTRACT

The role of Magnetic Resonance Imaging (MRI) in prostate cancer (PCa) diagnostic work-up has drastically changed over the last 40 years. Years of innovations have produced outstanding advances in diagnostic imaging and MR-guided interventional procedures. In early 2019, the updated version of the PI-RADS score system was released. The same year a real breakthrough occurred when the updated version of the European Association of Urology (EAU) guidelines was released: MRI is currently recommended as the first line imaging modality for biopsy-naive patients. Among all the published studies supporting the use of MRI in the diagnostics of PCa, robust trials have played a pivotal role: The PROMIS study, the MRI-FIRST study, the PRECISION study and the 4M trial. The success of MRI is heavily dependent on high-quality image acquisition and interpretation to minimise the number of equivocal cases, standardise negative MRIs, reduce overdiagnosis and overtreatment and promote biopsy improvement and focal therapeutic approaches. Future perspectives include the spread of non-contrast MRI as the most efficient way to face the expected upcoming large number of MRI requests for PCa diagnosis and the application of artificial intelligence-based tools that might profoundly shape modern imaging, with major implications for medical practice. The goal is to review PCa natural history and management, with an insight on MRI applications and future perspectives.

KEY WORDS

Prostate MRI; PI-RADS; MRI-directed biopsy; Artificial intelligence; Prostate cancer screening

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Background

The role of Magnetic Resonance Imaging (MRI) in prostate cancer (PCa) diagnostic work-up has evolved greatly during the last 40 years. The first prostate MRI was performed in 1982 by Steyn and Smith [1]. At that time the quality of MRI images was very poor, as was the MRI clinical impact, with MRI playing a supporting role for prostate management, primarily for staging patients with high risk of PCa (prostate-specific antigen, PSA≥20 ng/ml). Since then, the introduction of high-field magnets and phased-array coils and the advance in MRI technologies such as Diffusion Weighted Imaging (DWI), Dynamic contrast-enhanced MRI (DCE-MRI) and MR spectroscopy (MRS) allowed a significant improvement of image quality [2, 3]. The clinical implications have meaningfully grown since the publication of a milestone article by Barentsz et al. who introduced the original version of Prostate Imaging Reporting and Data System (PI-RADS) as prostate MR guidelines by the European Society of Urogenital Radiology (ESUR) in 2012 [4] and later the updated PI-RADS version 2 by the joint collaboration of the ESUR and the American College of Radiology (ACR) in 2015 [5]. In 2017, Woo et al. [6] published a systematic review and meta-analysis on the diagnostic performance of PI-RADSv2 for the detection of PCa. Authors found that PI-RADSv2 showed a higher pooled sensitivity of 0.95 (95% confidence interval [CI] 0.85-0.98) compared to 0.88 (95% CI 0.80-0.93) for PI-RADSv1 (p=0.04). Instead, the pooled specificity was not significantly different (0.73 [95% CI 0.47-0.89] vs 0.75 [95% CI 0.36-0.94], respectively; p=0.90). The analysis of the selected studies included data on experience in prostate multiparametric MRI (mpMRI) reading; the results were heterogeneous, with the level of experience of the radiologists ranging from 4 to 22 years. Since then, the role of MRI has taken over PCa diagnostics as an avalanche, basically thanks to its accurate standardisation and robust results in terms of performance. Up to 2019, MRI was recommended in patients with persistent clinical suspicion of PCa despite prior negative biopsies. The goal is to review Pca natural history and management, with an insight into MRI applications, clinical implications and future perspectives.

Current Developments and Applications

In 2019, the updated version 2.1 of PI-RADS was published [7] and a cornerstone event occurred, when the European Association of Urology (EAU) published the updated version of relevant guidelines. As a result, MRI is currently recommended as the golden standard imaging modality for biopsy-naive patients [8].

Prostate MRI Achievements

Four trials, among a very intense and proficient research on prostate MRI performance for the detection of clinically significant PCa (csPCa), have set the standard and allowed to reach the abovementioned achievements. As wisely pointed out by Rodriguez Sanchez et al. [9], the acronyms of the main MRI studies, put together, send a clear message: for most (4M), one can promise (PROMIS) precision (PRECISION) if you perform MRI first (MRI-FIRST).

The PROMIS study [10] is a paired validating confirmatory study that presented blinded data on the diagnostic accuracy of mpMRI and transrectal ultrasonography-guided biopsy (TRUS-GB) against a reference test (template prostate mapping biopsy) in biopsy-naive men. The images were acquired at a 1.5 Tesla scan and the acquisition protocol included T1-weighted (T1W), T2W, DW and DCE imaging sequences. mpMRI was more sensitive for csPCa detection (93%, 95% CI 88-96%) than TRUS-GB (48%, 42-55%; p<0.0001), but less specific (41%, 36–46% for mp-MRI vs 96%, 94-98% for TRUS-GB; p<0.0001). The use of mpMRI to triage men allowed 27% of patients to avoid a primary biopsy and to diagnose 5% fewer clinically insignificant cancers.

Kasivisvanathan et al. [11], in the PRECISION multicenter randomised trial, compared MRI-targeted biopsy with standard TRUS-GB. Patients were randomly assigned in a 1:1 ratio to either the MRI-targeted biopsy group or the standard biopsy group. Clinically significant cancer was detected in 95 patients in the MRI-targeted biopsy group and in 64 patients in the standard-biopsy group (95% CI, 4-20; p=0.005). Twenty-eight percent of patients had negative MRI and avoided biopsy. Among men with negative results on MRI that did not undergo prostate

biopsy (71), 3 were discharged, 62 were referred for monitoring of the PSA level, 3 underwent further prostate biopsy (all had negative results), 1 underwent an additional multiparametric MRI and 2 had missing information. Main limitation of the study was that the radiologists involved in the trial were experienced radiologists with a median of 300 MRIs per year.

In the paired diagnostic MRI-FIRST study, Rouvière et al. [12] investigated the use of MRI for the detection of csPCa in biopsy-naive patients. Among 275 enrolled patients, 14% were diagnosed by systematic biopsy only, 20% by targeted biopsy only, and 66% by both techniques. Authors did not find differences between systematic biopsy and targeted biopsy in the detection of csPCa according to the grading group of the International Society of Urological Pathology (ISUP) superior or equal than 2 (Gleason score 3+4). However, csPCa detection was improved by combining both techniques. Due to negative MRI results, 18-21% of biopsies were avoided (11% of csPCa were missed).

In the 4M trial [13] the Dutch group compared and evaluated the MRI pathway and the TRUS-GB pathway in biopsy-naive men with PSA levels of 3 ng/ml. Results showed a relative sensitivity of the MRI pathway versus the TRUS-GB pathway: 1.09 for csPCa ($p=0.17$) and 0.57 for clinically insignificant PCa (ciPCa) ($p<0.0001$). The total number of biopsy cores decrease was about 89%. The MRI pathway enabled biopsy avoidance in 49% patients due to nonsuspicious mpMRI (3-4% of csPCa were missed).

Prostate MRI Performance Predictive Factors

Despite the revolutionary accomplishments, the widespread use of MRI still bears some caveats. Most of them are strictly related to factors predicting MRI performance: (1) Quality control in terms of images acquisition according to PI-RADS recommendations (**Figs. 1 and 2** are high quality images and **Fig. 3** is a low-quality image); (2) MRI reading in terms of images interpretation, learning curve, training and reporting expertise; (3) Team working focused on patient's selection and management.

Recently, a systematic review of literature on the factors influencing variability in the performance of MRI in detecting csPCa was published. Among the potential influencing factors, authors included in the analysis the magnetic field strength, the use of an endorectal coil (ERC), the assessment system used by the radiologist, the inter-reader variability, the experience of the radiologists and urologists, the use of biparametric MRI (bpMRI), and the use of computer aided detection (CAD) or deep learning or machine learning for mpMRI. No reliable information was obtained regarding the detection of csPCa according to field strength, the use of ERC (improved signal reception but increased costs, artefacts, organ deformation and patient discomfort), and regarding the inter-reader variability of less experienced radiologists. Robust considerations were obtained regarding the assessment systems used and the radiologist and urologists experience. Authors recommended to refer to the latest PI-RADS guidelines for prostate MRI acquisition and interpretation, especially for less experienced radiologists and suggested that less experienced readers and biopsy operators should be supervised. Also, bpMRI showed reliable results in terms of csPCa detection, compared to mpMRI, in large volume centers with experienced radiologists, where DWI acquisition is of high quality. All considered, only 22% of the included studies had low risk of bias and applicability concerns. Indeed, across 77 included studies a high heterogeneity was found, mostly related to different MRI protocols, outcomes, mpMRI indications, csPCa prevalence, variable readers' experience, and pathological reference standards [14].

Prostate MRI Performance Results

Several meta-analyses have been published on performance of prostate MRI, confirming that a well-performed and well-interpreted negative MRI might be sufficient to avoid prostate tissue sampling. Prostate MRI performance results are focused on the technique's negative and positive predictive value (NPV, PPV), and accuracy of mpMRI in detecting csPCa.

Sathianathen et al. [15] published a systematic review and meta-analysis on prostate MRI negative predictive value. Authors reported very high pooled values for two different definitions of negative MRI and csPCa. Definition one being a PIRADS score of 1–2, and csPCa as GGG≥2 (Gleason score≥3+4). Definition

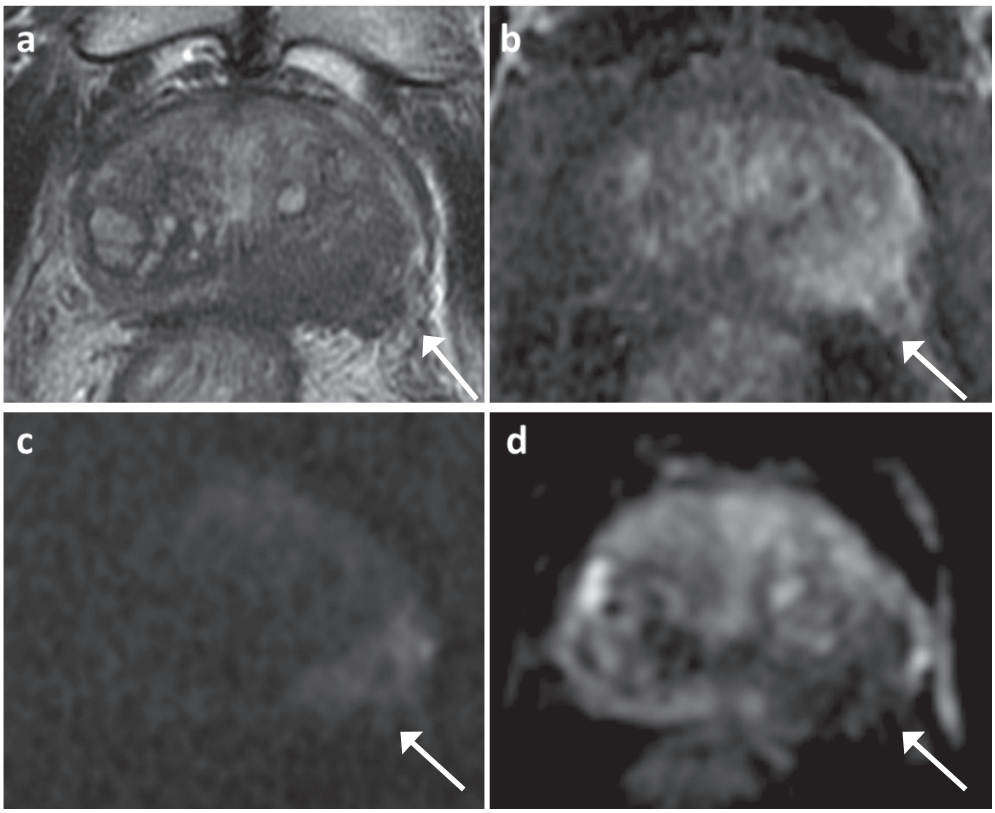

Fig 1. *High-quality MRI. (**a**) T2WI, left peripheral zone posteromedial/lateral lesion. (**b**) at the same level focal enhancement on DCE MRI. (**c-d**) at the same level hyperintensity on DWI (b=2000) and corresponding hypointensity on ADC map. The lesion was classified as PI-RADS 5 (arrow). T2WI, T2-weighted image; DCE, Dynamic Contrast -Enhanced; DWI, Diffusion-weighted image; ADC, Apparent diffusion coefficient.*

two being a PIRADS score of 1–3, and csPCa as GGG≥3 (Gleason score≥4+3). Pooled NPVs for biopsy-naive men were respectively 90.8% (95% CI 88.1-93.1%) vs. 96.1% (95% CI 93.4-98.2%). Calculation using definition two for negative MRI and definition one for csPCa yielded a pooled NPV of 86.8% (95% CI 80.1-92.4%); Calculation using definition one for negative MRI and definition two for csPCa yielded a pooled NPV of 97.1% (95% CI 94.9-98.7%). The investigation demonstrated that MRI of the prostate is generally an accurate test for ruling out csPCa [16].

The PPV of prostate MRI proved to be generally lower than NPV. Westphalen et al. [17] reported an estimated PPV of 35% (95% CI: 27-43%) for a PI-RADS score ≥3 and 49% (95% CI: 40-58%) for a PI-RADS score ≥4 across 26 centers. Authors proposed several reasons for the disparity, such as inaccurate targeting of MRI lesions, mischaracterisation of cancer grade and differences in prevalence of disease across centers. They concluded that the variation of PPV is most likely multifactorial, related to the abovementioned factors and other considerations, such as prostate MRI pitfalls (hence radiologist experience) (**Figs. 4, 5**) [18, 19] or the number of samples obtained from each biopsy target. In 2019, Barkovich et al. [20] showed similar results, stratified according to single PI-RADS score: the pooled PPVs were 6%, 12%, 48%, and 72% of lesions classified as PI-RADS scores of 2, 3, 4, and 5, respectively.

In a recently published study, Park et al. [21] aimed to determine csPCa and overall PCa detection rates in each PI-RADSv2 category. They found that the pooled

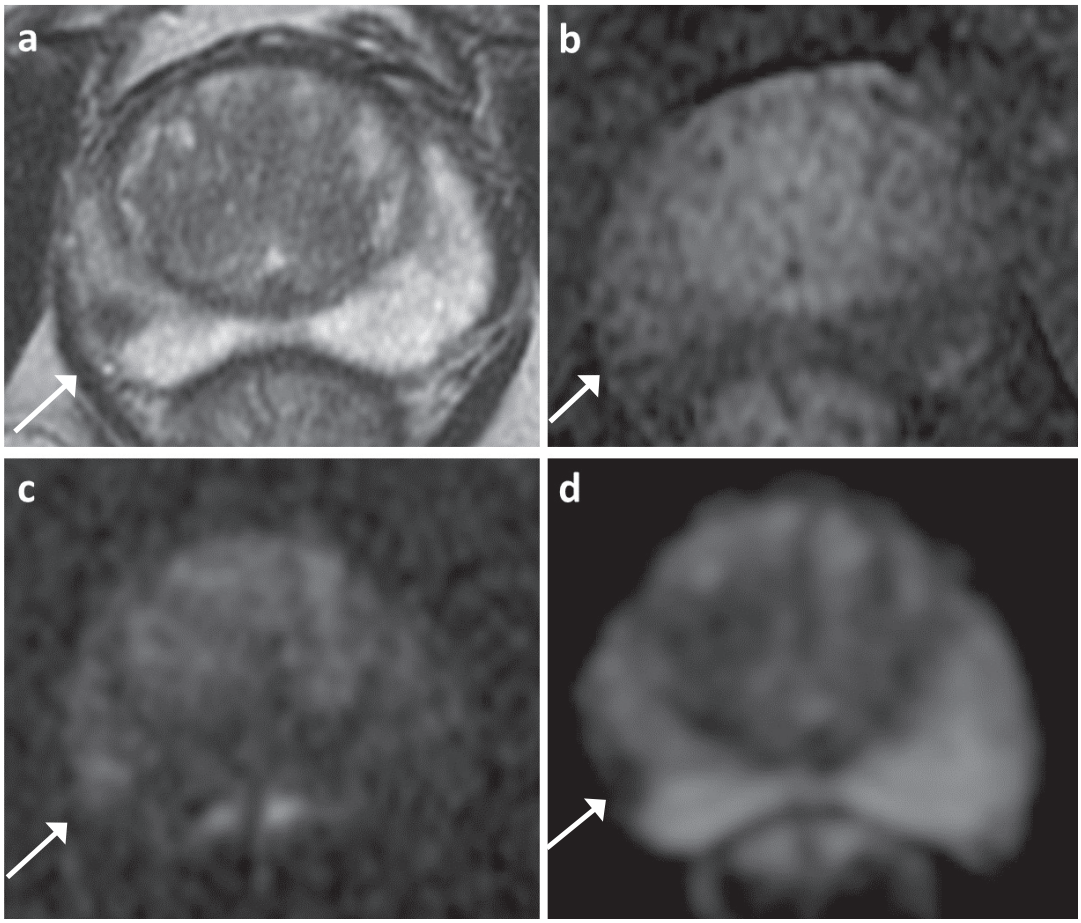

Fig 2. *High-quality MRI. (**a**) T2WI, right peripheral zone posterolateral lesion. (**b**) at the same level no early enhancement on DCE MRI. (**c-d**) at the same level hyperintensity on DWI (b=2000) and corresponding hypointensity on ADC map. The lesion was classified as PI-RADS 4 (arrow). T2WI, T2-weighted image; DCE, Dynamic Contrast -Enhanced; DWI, Diffusion-weighted image; ADC, Apparent diffusion coefficient.*

detection rates of csPCa monotonically increased for each PI-RADSv2 category, i.e., 4% (95% CI, 2-8%) for category 1-2; 17% (95% CI, 13-21%) for category 3; 46% (95% CI, 38-55%) for category 4; and 75% (95% CI, 73-78%) for category 5. However, substantial heterogeneity was noted in csPCa detection rates for categories 1-2 and 4. The very high NPV of prostate MRI was confirmed also in this meta-analysis. The clinical benefit of prostate MRI comes from its high NPV to rule out csPCa, which allows biopsy avoidance and reduces the detection of Gleason grade group (GGG) 1 prostate cancer.

The described results are in line with the latest Cochrane systematic review and meta-analysis data published in 2019, by Drost et al. [22]. The primary endpoint of this systematic review and meta-analysis was to determine the diagnostic accuracy of the index tests MRI only, MRI-targeted biopsy, MRI pathway (MRI with or without MRI targeted biopsy) and systematic biopsy compared to template-guided biopsy, considered as the reference standard in detecting csPCa (GGG≥2). Among others, they found that the pooled sensitivity and specificity for the detection of PCa GGG≥2 by the MRI pathway were 0.72 (95% CI: 0.60-0.82) and 0.96 (95% CI: 0.94–0.98), respectively.

MRI-Directed Biopsy: Prostate MRI Pathway

Along to the growth of prostate MRI requests the need of MRI-directed biopsy (MRDB) has followed, with the definition of the MRI pathway. Two main MRDB techniques exist: In-bore MR targeted biopsy (MR-TB) (**Fig. 6**) and MR-transrectal ultrasound fu-

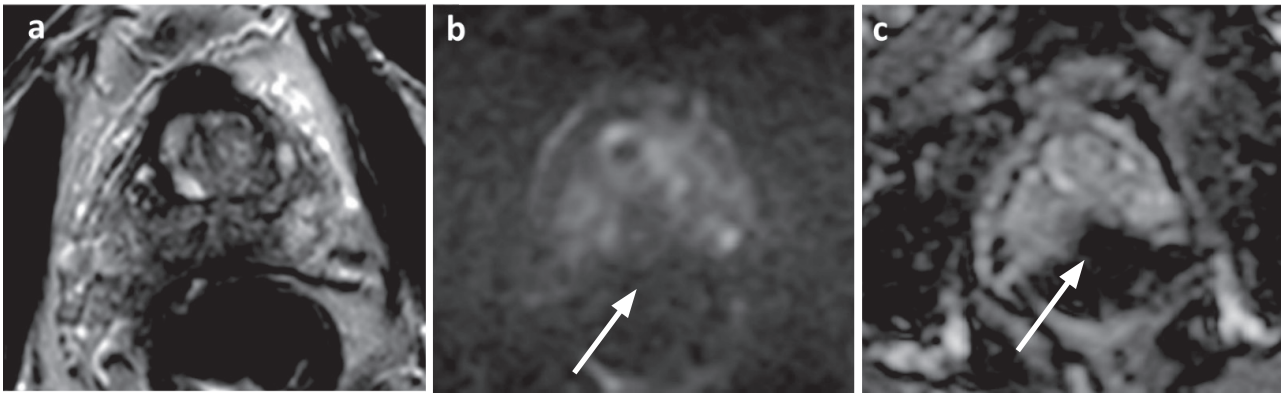

Fig. 3. *Low quality MRI.* ***(a)*** *T2WI with evidence of air-filled rectum.* ***(b-c)*** *DWI (b=1500) and ADC map with evidence of architectural distortion (arrow). T2WI, T2-weighted image; DWI, Diffusion-weighted image; ADC, Apparent diffusion coefficient.*

sion biopsy (FUS-TB) [23]. In a recent meta-analysis, Kasivisvanathan et al. [24] demonstrated that MRDB detects more men with csPCa than systematic biopsy (detection ratio [DR] 1.16 [95% CI 1.09-1.24], p<0.0001) and lower proportion of men with ciPCa than systematic biopsy (DR 0.66 [95% CI 0.57-0.76], p<0.0001). Also, the proportion of positive cores for PCa was greater for MRDB than for systematic biopsy (relative risk 3.17 [95% CI 2.82-3.56], p<0.0001). Up-to-date, no data show significant advantage of MR-TB for overall PCa and csPCa detection compared to FUS-TB (p=0.13) [25]. A question mark still exists on the exact number of samples that should be performed per-lesion.

The MRI pathway achieves higher performance outcomes, and it does so with fewer biopsy and fewer number of sample cores, reducing overtreatment and promoting minimally invasive focal therapeutic approaches, such as high intensity focused ultrasound (HIFU). Most significant goals of the MRI pathway are to target the index lesion, to precisely classify tumour grading and to reduce the detection of ciPCa (GGG 1).

Prostate MRI without contrast media injection

The potential spread of prostate MRI without contrast media injection (commonly referred to as biparametric MRI) could represent the most efficient way to face the expected upcoming large number of MRI request for PCa diagnosis. Multiparametric MRI protocol includes T2WI, DWI and DCE MRI. Biparametric MRI includes only T2WI and DWI sequences. Radiologists considering the non-contrast MRI as the default approach should acknowledge a list of advantages and disadvantages for different patients' risk groups and clinical scenarios.

Recently, a position paper on MRI without contrast medium in men with suspected prostate cancer was released by the PI-RADS steering committee [26]. Authors described in detail the potential role of bpMRI in biopsy-naive patients, comparing it to contrast MRI, with the discussion on the operational aspects and impacts on clinical practice, on the image assessments and on MRI diagnostic performance. Among the principal advantages of applying non-contrast MRI, authors mentioned the lack of contrast media side effects, the lack of impact in MRI negative and positive cases and on clinical decision-making for prostate biopsy, with an increase of operational and procedural efficacy. Main disadvantages are the lower reading performance of less experienced radiologists, the need of patient monitoring (safety net), the need of adjustments of biopsy decision and the potential of delayed diagnosis and treatment. Prerequisite to bpMRI as default approach were also enlisted: high-quality imaging, high reader expertise, adjustments of biopsy decision, diagnostic safety-net and patients monitoring. An essential requisite for the use of bpMRI is the stratification of patients in risk groups, that allows to decide in advance the need for contrast injection. The majority of published meta-analyses have demonstrated that the injection of contrast media has a marginal role in csPCa detection [27-31]. However, PI-RADS recommendations suggest the use of bpMRI to be reserved for select clinical sce-

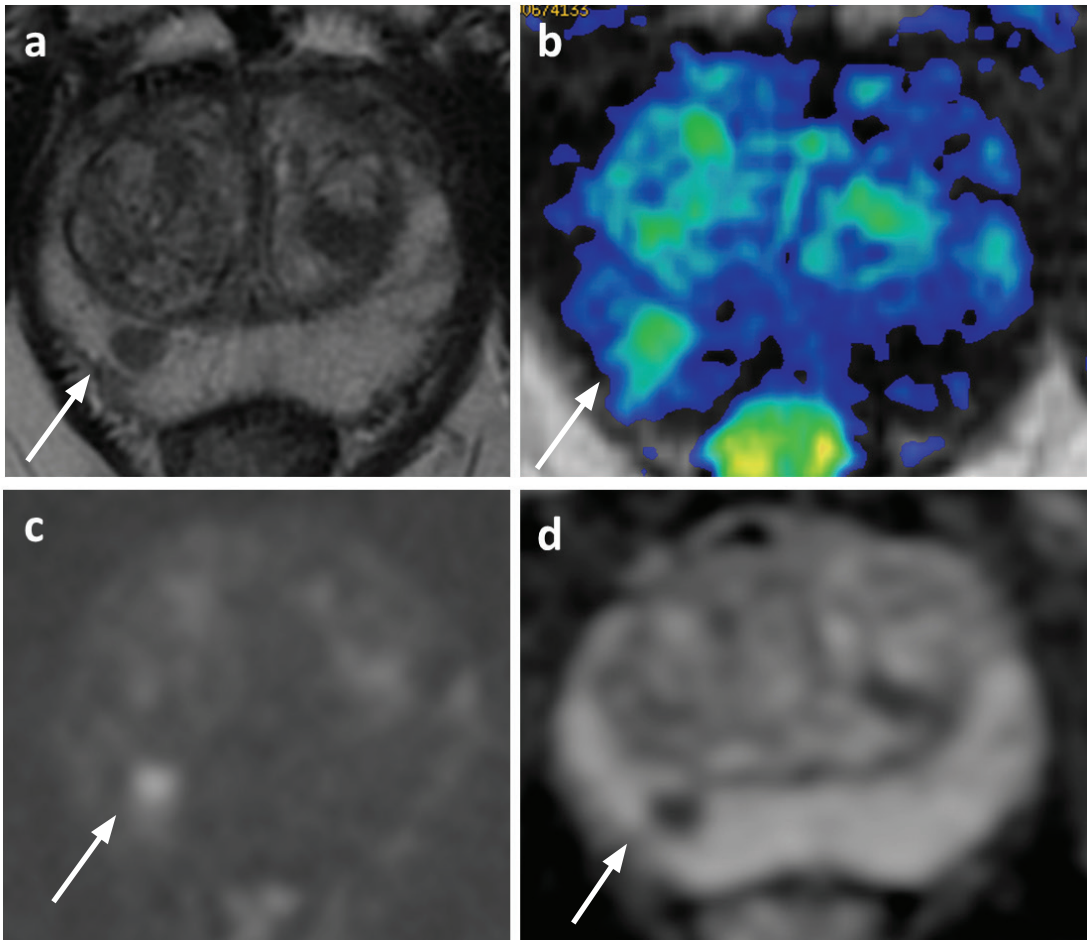

Fig. 4. *Prostate MRI pitfall: ectopic BPH nodule (arrow).* ***(a)*** *T2WI, right peripheral zone posterolateral lesion with sharply-defined margins, round shape and surrounded by a subtle pseudocapsule.* ***(b)*** *at the same level early enhancement on colorimetric map of DCE MRI.* ***(c-d)*** *at the same level hyperintensity on DWI (b=2000) and corresponding hypointensity on ADC map. The lesion was classified as PI-RADS 2. BPH, Benign Prostatic Hyperplasia; T2WI, T2-weighted image; DCE, Dynamic Contrast -Enhanced; DWI, Diffusion-weighted image; ADC, Apparent diffusion coefficient.*

nario, such as in patients with prior negative biopsies and persistently elevated PSA levels, in patients in active surveillance, in patients with a prior negative bpMRI and persistent suspicion of csPCa, in patients previously undergone interventions and/or medical therapy (e.g. hormonal therapy) and in patients with high-risk of developing PCa (e.g. family history, elevated urinary genomic scores and risk calculator scores [32].

Future Perspectives

Prostate MRI and the PI-RADS score have become the gold-standard imaging modality for PCa detection and EAU guidelines recommended MRI as first line study for biopsy-naive patients. The MRI approach can provide essential clinical benefits spanning from early diagnosis to potential biopsy avoidance and reduction of indolent cancer detection.

Nonetheless, open issues and question marks still exist. The first being the large number of MRI requests expected in the near future and the lack of quality control and certification that could mine the widespread reliability of MRI in PCa diagnostics. The second being the increasing development and diffusion of Artificial Intelligence (AI)-based tool that, if supervised, could meet the increasing demands for MRI-directed PCa diagnosis, especially for MRI without contrast media.

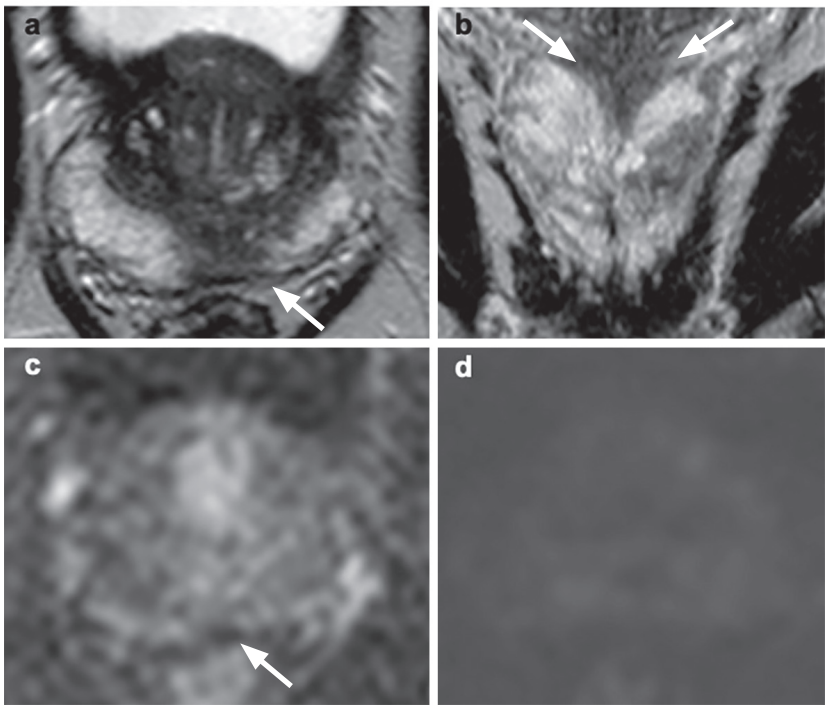

Fig 5. *Prostate MRI Reversed Teardrop sign. (**a-b**) Axial and coronal T2WI with evidence of a median low signal intensity area at the middle third of the posterior zone (arrow). This posterior nodular-shaped area shows late contrast enhancement on perfusion sequences (**c**) and no hyperintensity on DWI (**d**). This sign represents the central zone compressed between the transition and peripheral zone. The use of the coronal plane is very important to demonstrate the continuity and symmetry of this area with the rest of the central portion. T2WI, T2-weighted image; DWI, Diffusion-Weighted Image.*

Artificial Intelligence Developments

At the present time, the past utopian visions of MR-guided procedures, standardised scores and staging systems have become reality. Years of innovations have produced outstanding advances in diagnostic imaging and MR-guided interventional procedures. If, in the past, the main concern of global consensus was about the appropriateness of MRI as the first-line technique for PCa diagnosis, nowadays its role in guiding the management of PCa has been fully established. On the other side, AI is profoundly shaping modern imaging with major implications for medical practice.

Today, significant evidence exists in the field of radiomics. Radiomics extracts and analyses large number of quantitative imaging features from medical images using high throughput methods [33]. Radiomics has been applied to PCa MRI diagnostics to mainly address cancer detection and the issue of cancer heterogeneity. Among the many investigations on radiomics and machine learning application to PCa diagnostics, few are worth mentioning. Recently, Stoyanova et al. [34] clearly described the radiomic process. Radiomics' features are extracted from prostate mpMRI images related to volume/shape and intensity volume histogram (first order features); texture features (second order features) and transform analysis features. The extracted features are then integrated with clinical and molecular data to develop diagnostic, predictive or prognostic models, and to potentially guide quantitative MRI-directed biopsy, to further reduce the number of underdiagnosis, lowering morbidity. In 2018 Bonekamp et al. [35] published a study on the role of biparametric radiomic machine learning (RML) compared to ADC quantification and radiologic qualitative assessment. On a cohort of 361 patients authors showed that quantitative measurement of the mean ADC, when compared to clinical assessment, is able to significantly

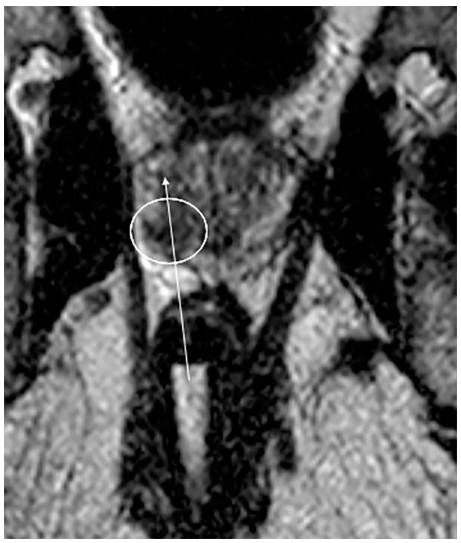

Fig. 6. *Coronal T2WI acquired during in-bore MR directed prostate biopsy, targeting the hypontense lesion on the right lobe of the prostate. T2WI, T2-weighted image.*

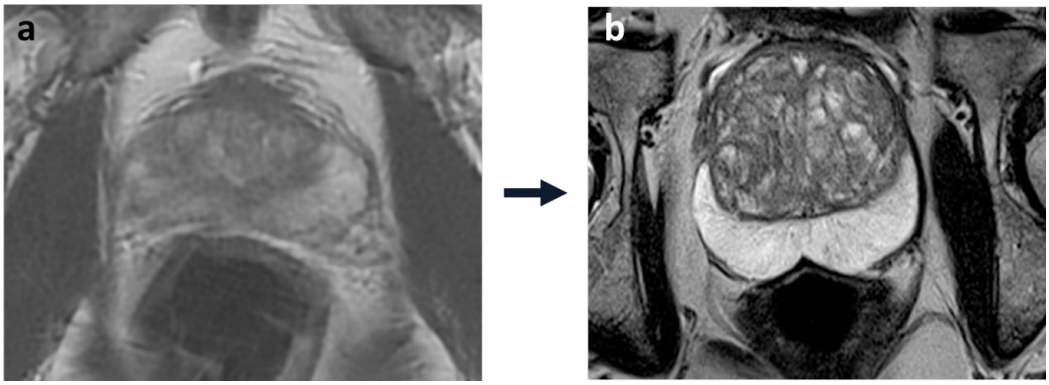

Fig. 7. *T2-weighted axial image. (**a**) low quality image. (**b**) high resolution quality image. The images are not from the same patient and ideally represent what artificial intelligence algorithm might allow in the future.*

reduce the misclassification of MRI-detected lesions. Instead, the RML did not add significant performance improvements compared to mean ADC quantifications. However, such results need to be considered acknowledging that the use of radiomics was used for lesion characterisation, not for lesion detection and that the RML analysis was based on biparametric MRI. In 2019, Varghese et al. [36] proposed a systematic rigorous machine learning and radiomics classifier applied to prostate MRI as an objective patients' risk stratification method. Authors divided the patients' cohort (68) into two categories: high risk and low risk according to the National Comprehensive Cancer Network guidelines. The classifier in both subgroups performed well in an independent validation set; also, it performed equivalently to PI-RADS v2 in in terms of AUC but better in terms of the class-specific measures, especially for the high-risk class.

As for prostate imaging, AI might be considered as the evolution and integration of all the innovative information technology (IT) techniques, becoming a problem-solving tool rather than a replacement of the radiologist. Indeed, AI might meet multiple PCa diagnostic open issues: (1) image quality and inter-reader reproducibility. The delivery of diagnostic benefits is highly dependent on good-quality images and high reader expertise. AI might perform image quality control and artefact reduction, according to scans and software type (**Fig. 7**). High quality data sets are needed to optimise image quality and improve consistency among exams. (2) MRI reading optimisation. AI might work as second reader for intermediate/difficult cases; might evaluate and assess

quantitative MRI metrics (T2WI, DWI/ADC and DCE MRI); might reduce variability of negative and positive predictive values for csPCa. (3) Non-contrast vs. contrast-MRI. AI might have a role in determining when to perform contrast-MRI and support the MRI role for opportunistic screening as triage test [37]. (4) Multivariate risk prediction tools to personalised PCa diagnoses. AI might adapt MRI performance to match patient clinical priorities and to manage multiple imaging time point. (5) Patients Monitoring. AI might support radiologists in follow-up MRI for disease monitoring. Multiple imaging timepoints when training AI systems should be considered, as temporal changes provide valuable information for analyses.

Prostate Cancer Screening

Among the most promising upcoming prostate MRI applications, the opportunistic screening covers a paramount position. The need of a more sensitive test to early diagnose PCa follows the lack of serum PSA threshold recommendation in international guidelines [8]. The Prostate Cancer Prevention Trial (PCPT) showed that, at a PSA threshold of 3 ng/ml, the sensitivity for GGG≥2 was 58%; the threshold, if lowered to at least 1.6 ng/ml, achieved an adequate sensitivity of 84% [38].

Foundations steps have been made in 2016 by Nam et al. [39] who performed a pilot study to evaluate the feasibility of prostate MRI as the primary screening test for PCa. Of the 47 recruited patients, 18 (38.3%) had cancer while 29 (61.7%) had no evidence of cancer. The adjusted odd ratio of PCa was significantly higher for MRI score than for PSA level (2.7, 95% CI 1.4–5.4, p=0.004 vs 1.1, 95% CI 0.9–1.4, p=0.21). Another pilot study, incorporated into the Gothenburg arm [40, 41], part of the ERSPC screening study, reported MRI diagnostic performance at different PSA thresholds. In this study, MRI was used in addition to PSA and participants did not reflect a medium risk screened population as they were recruited from the final screening round and screened up to nine times using serum PSA, with 1/3 of the participants undergone to prior biopsy. Under these circumstances, when MRI was combined with a PSA threshold>1.8 ng/mL, sensitivity was 73% with a negative predictive value of 92% in the detection and exclusion of GGG≥2.

The first large on-going trial is run in the United Kingdom (UK) by the group of Prof. A. Ahmed at the University College of London. Recently, in a discussion session at the American Society of Clinical Oncology 2020 Virtual Annual Meeting, Evans et al. presented the preliminary results of the IP1-PROSTAGRAM clinical trial evaluating the performance of non-contrast MRI for prostate cancer screening compared to PSA. In a prospective, population-based cohort study, the authors recruited men aged 50 to 69 in the UK for PCa screening through seven primary care practices and community-based recruitment. All participants underwent non-contrast MRI. Among 400 recruited patients, 4% had csPCa, with 82% found by PROSTAGRAM [41]. The authors concluded that its use, compared to PSA-based screening, was associated with increased rates of csPCa detection.

In a recently published perspective article, Eldred-Evans et al. [42] described different approaches to MRI screening, such as abbreviated MRI protocols, targeted MRI screening, longer rescreening intervals and a multi-modal screening pathway. Authors concluded that MRI might represent an attractive screening test with sufficiently high sensitivity for csPCa, able to reduce overdiagnosis.

Also, Panebianco et al. [43] proposed an emerging innovative method to meet PCa screening needs, using the Network Medicine (NM) approach. The basic tenet of NM, that sees the disease as a perturbation of a network of interconnected molecules and pathways, might fit as good candidate to explore complex computational and clinical biomarkers to face the challenges of PCa early detection, to advance towards a more reliable and noninvasive technique.

Summary

MRI of the prostate and the PI-RADS score cover a leading role in the diagnostic pathway of PCa (MRI pathway). MRI allows a highly accurate detection of PCa foci and allows to direct prostate targeted biopsies. However, prostate MRI requires high image quality and reader expertise to reach its diagnostic potential. It also requires full integration of predictive data to reach its full capability.

A large number of MRI requests for PCa diagnosis is expected in the upcoming years. Accordingly, radiologists should engage in the clinical development of AI systems for PCa diagnosis, in order to meet the increasing demands for MRI-directed PCa diagnosis. AI application could also implement prostate MRI critical issues among which we acknowledge inter-reader agreement, improvement of diagnostic accuracy in less experienced readers and reduction of report-

ing time. Standardisation and personalised diagnostic and therapeutic approaches for patients are warranted. Finally, MRI is suited to detect PCa in a screening setting, especially if integrated in a wider approach as part of the NM. R

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References

1. Steyn JH, Smith FW. Nuclear Magnetic Resonance Imaging of the Prostate. *Br J Urol* 1982; 54: 726-728.
2. Giganti F, Rosenkrantz AB, Villeirs G, et al. The evolution of MRI of the prostate: The past, the present, and the future. *AJR Am J Roentgenol* 2019; 213: 384-396.
3. Valerio M, Zini C, Fierro D, et al. 3T multiparametric MRI of the prostate: Does intravoxel incoherent motion diffusion imaging have a role in the detection and stratification of prostate cancer in the peripheral zone? *Eur J Radiol* 2016; 85: 790-794.
4. Barentsz JO, Richenberg J, Clements R, et al. ESUR prostate MR guidelines 2012. *Eur Radiol* 2012; 22: 746-757.
5. Weinreb JC, Barentsz JO, Choyke PL, et al. PI-RADS prostate imaging – reporting and data system: 2015, version 2. *Eur Urol* 2016; 69: 16-40.
6. Woo S, Suh CH, Kim SY, et al. Diagnostic performance of prostate imaging reporting and data system version 2 for detection of prostate cancer: A systematic review and diagnostic Meta-analysis. *Eur Urol* 2017; 72: 177-188.
7. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol* 2019; 76: 340-351.
8. Mottet RCN, van den Bergh N, Brier E, et al. EAU Guidelines: Prostate Cancer. EAU Guidel 2019. 10.1016/j.eururo.2020.09.042.
9. Rodríguez Sánchez L, Macek P, Barbé Y, et al. Re: MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *Eur Urol* 2020; 78: 469-470.
10. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *The Lancet* 2017; 389: 815-822.
11. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med* 2018; 378: 1767-1777.
12. Rouvière O, Puech P, Renard-Penna R, et al. Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. *Lancet Oncol* 2019; 20: 100-109.
13. van der Leest M, Cornel E, Israël B, et al. Head-to-head comparison of transrectal ultrasound-guided prostate biopsy versus multiparametric prostate resonance imaging with subsequent magnetic resonance-guided biopsy in biopsy-naïve nen with elevated prostate-specific antigen: A large prospective multicenter clinical study. *Eur Urol* 2019; 75: 570–578.
14. Stabile A, Giganti F, Kasivisvanathan V, et al. Factors influencing variability in the performance of multiparametric magnetic resonance imaging in detecting clinically significant prostate cancer: A systematic literature review. *Eur Urol Oncol* 2020; 3: 145-167.
15. Sathianathen NJ, Omer A, Harriss E, et al. Negative predictive value of multiparametric magnetic resonance imaging in the detection of clinically significant prostate cancer in the prostate imaging reporting and data system era: A systematic review and meta-analysis. *Eur Urol* 2020; 78: 402-414.
16. Panebianco V, Barchetti G, Simone G, et al. Negative multiparametric magnetic resonance imaging

for prostate cancer: What's next? *Eur Urol* 2018; 74: 48-54.
17. Westphalen AC, McCulloch CE, Anaokar JM, et al. Variability of the positive predictive value of PI-RADS for prostate MRI across 26 centers: Experience of the society of abdominal radiology prostate cancer disease-focused panel. *Radiology* 2020; 296: 76-84.
18. Panebianco V, Barchetti F, Barentsz J, et al. Pitfalls in interpreting mp-MRI of the prostate: A pictorial review with pathologic correlation. *Insights Imaging* 2015; 6: 611-630.
19. Panebianco V, Giganti F, Kitzing YX, et al. An update of pitfalls in prostate mpMRI: a practical approach through the lens of PI-RADS v. 2 guidelines. *Insights Imaging* 2018; 9: 87-101.
20. Barkovich EJ, Shankar PR, Westphalen AC. A systematic review of the existing prostate imaging reporting and data system version 2 (PI-RADSv2) literature and subset meta-analysis of PI-RADSv2 categories stratified by Gleason scores. *AJR Am J Roentgenol* 2019; 212: 847-854.
21. Park KJ, Choi SH, Lee JS, et al. Risk stratification of prostate cancer according to PI-RADS version 2 categories: Meta-analysis for prospective studies. *J Urol* 2020; 204(6): 1141-1149.
22. Drost F-JH, Osses D, Nieboer D, et al. Prostate magnetic resonance imaging, with or without magnetic resonance imaging-targeted biopsy, and systematic biopsy for detecting prostate cancer: A Cochrane systematic review and meta-analysis. *Eur Urol* 2020; 77: 78-94.
23. Panebianco V, Barchetti F, Manenti G, et al. MR imaging-guided prostate biopsy: technical features and preliminary results. *Radiol Med (Torino)* 2015; 120: 571–578.
24. Kasivisvanathan V, Stabile A, Neves JB, et al. Magnetic resonance imaging-targeted biopsy versus Systematic biopsy in the detection of prostate cancer: A systematic review and meta-analysis. *Eur Urol* 2019; 76: 284-303.
25. Wegelin O, van Melick HHE, Hooft L, et al. Comparing three different techniques for magnetic resonance imaging-targeted prostate biopsies: A systematic review of in-bore versus magnetic resonance imaging-transrectal ultrasound fusion versus cognitive registration. Is there a preferred technique? *Eur Urol* 2017; 71: 517-531.
26. Schoots IG, Barentsz JO, Bittencourt LK, et al. PI-RADS committee position on MRI without contrast medium in biopsy naive men with suspected prostate cancer: A narrative review. *AJR Am J Roentgenol* 2020: AJR.20.24268.
27. Woo S, Suh CH, Kim SY, et al. Head-to-head comparison between biparametric and multiparametric MRI for the diagnosis of prostate cancer: A systematic review and meta-analysis. *AJR Am J Roentgenol* 2018; 211: W226-241.
28. Alabousi M, Salameh JP, Gusenbauer K, et al. Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naïve patients: a diagnostic test accuracy systematic review and meta-analysis. *BJU Int* 2019; 124: 209-220.
29. Liang Z, Hu R, Yang Y, et al. Is dynamic contrast enhancement still necessary in multiparametric magnetic resonance for diagnosis of prostate cancer: a systematic review and meta-analysis. *Transl Androl Urol* 2020; 9: 553-573.
30. Niu X, Chen X, Chen Z, et al. Diagnostic performance of biparametric MRI for detection of prostate cancer: A systematic review and meta-analysis. *AJR Am J Roentgenol* 2018; 211: 369-378.
31. Kang Z, Min X, Weinreb J, et al. Abbreviated biparametric versus standard multiparametric MRI for diagnosis of prostate cancer: A systematic review and meta-analysis. *AJR Am J Roentgenol* 2019; 212: 357–365.
32. Turkbey B, Rosenkrantz AB, Haider MA, et al. Prostate imaging reporting and data system version 2.1: 2019 update of prostate imaging reporting and data system version 2. *Eur Urol* 2019; 76: 340-351.
33. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images are more than pictures, they are data. *Radiology* 2016; 278: 563-577.
34. Stoyanova R, Takhar M, Tschudi Y, et al. Prostate cancer radiomics and the promise of radiogenomics. *Transl Cancer Res* 2016; 5: 432-447.
35. Bonekamp D, Kohl S, Wiesenfarth M, et al. Radiomic machine learning for characterization of prostate lesions with MRI: Comparison to ADC Values. *Radiology* 2018; 289: 128–137.
36. Varghese B, Chen F, Hwang D, et al. Objective risk stratification of prostate cancer using machine

learning and radiomics applied to multiparametric magnetic resonance images. *Sci Rep* 2019; 9: 1570.
37. Boesen L, Nørgaard N, Løgager V, et al. Assessment of the diagnostic accuracy of biparametric magnetic resonance imaging for prostate cancer in biopsy-naive men: The biparametric MRI for detection of prostate cancer (BIDOC) study. *JAMA Netw Open* 2018; 1: e180219.
38. Thompson IM. Operating characteristics of prostate-specific antigen in men with an initial PSA level of 3.0 ng/mL or lower. *JAMA* 2005; 294: 66.
39. Nam RK, Wallis CJD, Stojcic-Bendavid J, et al. A pilot study to evaluate the role of magnetic resonance imaging for prostate cancer screening in the General Population. *J Urol* 2016; 196: 361-366.
40. Grenabo Bergdahl A, Wilderäng U, Aus G, et al. Role of magnetic resonance imaging in prostate cancer screening: A pilot study within the Göteborg randomised screening trial. *Eur Urol* 2016; 70: 566-573.
41. Alberts A, Schoots I, Drost FJ, et al. Value of magnetic resonance imaging in population-based prostate cancer screening: Comparison of 3 biopsy strategies in the 5th screening round of the ERSPC Rotterdam. *Eur Urol Suppl* 2017; 16: e867-8. https://doi.org/10.1016/S1569-9056(17)30560-2.
42. Eldred-Evans D, Tam H, Sokhi H, et al. Rethinking prostate cancer screening: could MRI be an alternative screening test? *Nat Rev Urol* 2020; 17: 526-539.
43. Panebianco V, Pecoraro M, Fiscon G, et al. Prostate cancer screening research can benefit from network medicine: an emerging awareness. *Npj Syst Biol Appl* 2020; 6: 13.

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Panebianco V, Pecoraro M, Catalano C. The role of MRI in prostate cancer management: pushing the diagnostic frontier. *Hell J Radiol 2020*; 5(4): 45-57.