Multi-parametric MRI for prostate cancer diagnosis: current status and future directions

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Abstract | The current diagnostic pathway for prostate cancer has resulted in overdiagnosis and consequent overtreatment as well underdiagnosis and missed diagnoses in many men. Multiparametric MRI (mpMRI) of the prostate has been identified as a test that could mitigate these diagnostic errors. The performance of mpMRI can vary depending on the population being studied, the execution of the MRI itself, the experience of the radiologist, whether additional biomarkers are considered and whether mpMRI-targeted biopsy is carried out alone or in addition to systematic biopsy. A number of challenges to implementation remain, such as ensuring high-quality execution and reporting of MRI and ensuring that this diagnostic pathway is cost-effective . Nevertheless, emerging clinical trial data support the adoption of this technology as part of the standard of care for the diagnosis of prostate cancer.

[H1] Introduction

Prostate cancer is the most common solid organ malignancy among men worldwide[1,2]. The lifetime probability of a man developing prostate cancer is 1 in 9 and the number of estimated deaths caused by prostate cancer in the USA during 2018 was 29,430[2]. To date, the use of serum PSA level and/or an abnormal digital rectal examination followed by random transrectal ultrasonography (TRUS)-guided prostate biopsy has been the traditional diagnostic pathway for prostate cancer[3].

The evidence regarding the benefit of population-based serum PSA screening for prostate cancer is contradictory [4–6]. However, the US Preventive Services Task Force (USPSTF) recommendations against PSA screening[7], issued in 2012, were followed by a subsequent increase in the incidence of high-grade and locally advanced tumours[8]. Results from two meta-analyses of subsequent randomized studies demonstrated that PSA screening leads to a small reduction in the risk of dying from prostate cancer over 10 years [9,10]. Taken together, these findings led USPSTF to update its recommendation in 2018, now allowing men aged between 55 and 69 years old a choice to undergo PSA-based screening[11]. This also led the European Association of Urology in supporting the use of PSA as a screening tool in 2019 [12]. The current gold-standard test for prostate cancer diagnosis —12-core TRUS-guided biopsy for men with elevated serum PSA levels[13] — is affected by sampling error, which can lead to failure to detect clinically

significant prostate cancer, imprecise risk stratification and detection of clinically insignificant prostate cancer[14] with a considerable rate of false negative results[15]. Prostate cancer mortality has rapidly declined[2] in the past few decades, but this reduction in deaths from prostate cancer is probably only partly related to the extensive use of PSA screening and random biopsies and other factors (such as advances in therapeutic strategies) have contributed to increased survival[16]. These factors combined suggest that the standard-of-care approach to prostate cancer diagnosis — serum PSA screening followed by TRUS-guided biopsy — has led to overdiagnosis (of up to 45% of men diagnosed with prostate cancer) and overtreatment of low-volume and indolent tumours [5,17]. Moreover, the use of TRUS-guided biopsy is associated with missed diagnosis of clinically significant prostate cancer in up to 30% of cases[18]. Altogether, this suggest as an improvement in the diagnostic pathway for prostate cancer is needed in order to decrease both misdiagnosis of significant prostate cancer and overdiagnosis of insignificant prostate cancer.

Abnormal mpMRI is positively associated with increased tumour volume and high tumour grade[19]; thus the introduction of this modality into the diagnostic pathway would hopefully assist in the mitigation of both overdiagnosis and underdiagnosis. This purpose was the intended role of mpMRI when it was introduced in the early 1980s for improving staging of prostate cancer [20] . However, through the refinement in the use of mpMRI sequences and the development of reporting systems[21], owing to the use of mpMRI-targeted biopsies[22], mpMRI soon gained an important role in prostate cancer detection[19], conferring information on the cancer, that had to date been missing, such as volume, location and multifocality.

This Review, will describe the current status of the role of mpMRI in prostate cancer diagnosis, starting with the basic principles of MRI, and its clinical application and finally considering the future direction of this technology in prostate cancer.

[H1] Basics of multiparametric MRI

[H2] Principles and sequences

When mpMRI was first considered for prostate cancer diagnosis, in the middle 1980s, its use was focused on to T1-weighted and T2-weighted sequences[23]. The rapid improvement of mpMRI technology has led to the addition of further sequences such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCEI) (Fig 1, 2), and/or magnetic resonance spectroscopy imaging (MRSI)[23] (Fig 2, 3). These advances resulted in a multitude of contrast mechanisms that can be considered together for improved diagnostic accuracy for prostate cancer[24].

[H3] T1-weighted imaging

T1-weighted imaging is used mainly for evaluation of regional lymph nodes and bone structures[25]. In the context of prostate evaluation, its utility is the ability to detect biopsy-related haemorrhage that can obscure or mimic cancers[26] . In order to reduce postbiopsy artifacts, a delay of at least 6-8 weeks after biopsy is typically recommended. Currently, no consensus exists concerning this clinical practice, indeed haemorrhage artifacts can still persist beyond this time period.[25]. This sequence is of limited value for detection of prostate cancer foci as presence of prostate cancer is not associated with notableT1-weighted imaging changes[21].

[H3] T2-weighted imaging

T2-weighted imaging is a fundamental sequence in mpMRI of the prostate, providing a highly defined anatomical image of the zonal architecture of the prostate gland with excellent soft-tissue contrast[27] (Fig 4). T2-weighted imaging reflects the water content of the tissue, which is related to the cellularity[21].

In the normal prostate, the peripheral zone — the part of the prostate present at birth — appears homogeneously hyperintense on T2-weighted imaging owing to its high glandular ductal tissue content[21]. Prostate cancer is characterized by high cellularity and low water content and, therefore, will appear hypointense on imaging [21] (Fig 2Aa, 2Ba). The decrease in intensity is positively associated with the aggressiveness of cancer[28]. The transition zone, which starts to form after puberty through the process of prostatic epithelial and stromal hyperplasia, tends to exhibit high cellular density, and appears heterogeneously hypointense [25]. For this reason, and because there is no nonmalignant prostate against which to reference (as every prostate is morphologically unique), cancer detection on T2-weighted imaging within the transition zone is challenging. Moreover, other changes such as acute and chronic prostatitis, scars, irradiation, hormonal treatment effects and postbiopsy haemorrhage might mimic prostate cancer on T2-weighted imaging[26]. The utility of this sequence in prostate cancer diagnosis is in discerning prostatic zonal anatomy and identifying suspicious areas through the analysis of anatomical characteristics and hypointensity level.

[H3] Diffusion-weighted imaging Diffusion-weighted imaging (DWI)

quantifies the degree of random movement of water molecules within tissue[29]. Within nonmalignant prostatic tissue, the water molecules move relatively freely, but in cancerous prostate tissue the motion of water molecules is strongly inhibited owing to the increased volume of glandular epithelium and high cellularity[29]. Thus, the apparent diffusion coefficient (ADC), which reflects the capability of water to move, will be lower for areas affected by prostate cancer than in healthy tissue. The ADC map is obtained by performing DWI with multiple magnetic gradient strengths (b-values). Increased b-values (minimum highest b-values of 1400 s/mm^2 and 2000s/mm^2 for 1.5T and 3.0T, respectively[25]), obtained by reducing the background signal from the nonmalignant prostate tissue, have been demonstrated to increase the sensitivity and the accuracy of prostate cancer detection (88% versus 71% and 89% versus 86%, respectively)[30]. Suspicious areas appear as a bright spot surrounded by low signal tissue on DWI[25] (Fig 2Ab, 2Bb), conversely, on the ADC map, prostate cancer will appear as a low-signal area (Fig 2Ac, 2Bc) with the degree of signal decrease, positively associated with increasing Gleason score[31].

The use of DWI in combination with T2-weighted imaging results in higher sensitivity (0.76) and specificity (0.82) than T2-weighted imaging alone for detecting prostate cancer [24] and also improved characterization of transition-zone tumours[32]. The transition zone is more likely to harbour benign prostatic hyperplasia nodules than other prostate zones and is often hypointense at T2-weighted sequences. The addition of DWI considerably helps in discerning malignant nodules [25].

[H3] Dynamic contrast-enhanced imaging

The aim of using the DCEI sequence is to assess the status of tumour angiogenesis on the basis of the evaluation of differences in the velocities and intensities of contrast agent uptake and washout by malignant and nonmalignant prostatic tissue[33]. DCEI is generated by rapid acquisition of a series of T1-weighted images after intravenous injection of a Ga-based contrast agent. This modality enables the evaluation of both the intensity and the dynamics of contrast enhancement. Early enhancement (appearance in the T1-weighted images obtained) of increased intensity is the hallmark feature of cancer[33] (Fig 2Ad, 2Bd). Nonetheless, as with other sequences, other benign conditions (such as hyperplastic nodules, prostatitis) might have these characteristics and lead to false positive results. DCEI alone has a reported sensitivity and specificity for detection of prostate cancer of 46-90% and 74-96%, respectively[34]. Even though the use of DCEI is currently debated, mainly owing to the increased costs and the duration of MRI related to the use of gadolinium, as well as the reported data supporting the value of biparametric-MRI (on the basis of only T2 and DWI) [35,36] , DCEI seems to be particularly useful when T2-weighted and DWI are equivocal or degraded by artifacts. In this context, DCEI has demonstrated an important role in the evaluation of local recurrence after prostate interventions (such as transurethral resection of the prostate and focal therapy) that change prostate morphology creating a setting in which standard reporting systems (for example, PI-RADS score) are not applicable[25,37,38].

[H3] Magnetic resonance spectroscopy imaging

MRSI sequences visualize the pattern of expression of specific metabolites, such as citrate and choline[39]. Citrate is normally produced by

nonmalignant prostatic tissue but its expression is decreased in prostate cancer cells. Conversely, choline (an important constituent of cell membrane) levels are low in nonomalignant tissue but highly expressed in prostate cancer[39]. Evaluating the relative change in these metabolites enables detection of areas of the prostate areas likely to harbour cancer. The sensitivity of MRSI alone ranges from 75% to 89% and the specificity from 77% to 91%, [40]. MRSI is not currently widely used in routine clinical practice and is primarily used in academic centres or research studies primarly owing to related costs, availability and lack of evidences supporting its extensive use. Dedicated software is required for signal analysis. In the context of functional sequences, a quantitative correlation between prostate cancer aggressiveness and MRSI, ADC, and DCEI has been shown[31,41–43] (Fig 3). Although not currently used, these sequences could have a specific role in providing a noninvasive tool for risk stratification. Further prospective studies assessing the role of MRSI in combination to other mpMRI sequences are needed in order to clarify its role in prostate cancer diagnosis

[H2] Interpretation

One of the most considerable challenges in prostate mpMRI has been the development of a standardized reporting system. mpMRI is typically reported using a Likert scale, which reflects the probability of the presence of prostate cancer. Initially, the criteria used to ascribe a Likert score was most often based on the radiologist's subjective opinion [23]. When a Likert score of suspicion was derived in this manner the scoring system used was often termed the Likert scoring system. As this reporting system was based on the experience of the radiologist reporting the mpMRI, this method was

inevitably affected by a high rate of variability in interpretation and lack of reliability. In order to reduce the inter-reader disagreement, decrease the gap between differently skilled radiologists and centres and improve communication between radiologists and urologists, the Prostate Imaging Reporting and Data System version 1 (PI-RADS v1) was developed in 2012, which applied a set of rigid criteria to ascribe specific scores of suspicion[21]. This classification system was the first attempt to standardize prostate mpMRI reporting. PI-RADS v1 consisted of a five-point suspicion scale (PI-RADS 1 = very low suspicion to PI-RADS 5 = very high suspicion) for each sequence used, including T2-weighted imaging, DWI, DCEI and MRSI, and the total score depended on how many sequences were used. This scoring system provided an acceptable accuracy in detecting prostate cancer (sensitivity 0.78 and specificity 0.79)[44], but it had some limitations such as a complex and time-consuming scoring flow-chart and, consequently, poor reproducibility.

In 2014, PI-RADS version 2 (PI-RADS v2) was published[25] in an attempt to overcome the issues related to the PI-RADS v1. First, a specific algorithm was provided to assign a final score to detected lesions. Second, the interpretation of each sequence was substantially simplified, particularly for DCEI. These first two changes were intended to overcome poor reporting reproducibility and improve time-efficiency. Third, to improve mpMRI diagnostic accuracy, dominant sequences for different prostatic areas were defined (such as T2-weighted imaging for the transition zone and DWI for the peripheral zone). Finally, MRSI was no longer included in the scoring workflow, to make PI-RADS score even more widely applicable. A meta-analysis reported a significant improvement in prostate cancer detection

using PI-RADS v2 compared with PI-RADS v1 in terms of sensitivity (0.95 versus 0.88, P=0.04) but no significant differences in specificity (0.73 versus 0.75, P=0.90)[45] suggesting an improvement in the ability of mpMRI in detecting prostate cancer but stability in the rate of false positives..

The PI-RADS scoring systems are widely used in clinical practice, but some experienced radiologists prefer the subjective Likert scoring system as they value the ability to score outside of the rigid criteria of PI-RADS scoring system because not all situations fit the PI-RADS scoring criteria perfectly. For example, the DWI sequence could be suboptimal or lesions might only be identified using contrast-enhanced sequences, which would lead to a low score of suspicion using PI-RADS v2, but a higher score of suspicion using the Likert scoring system. In a 2018 multicentre analysis [46], the central quality control of mpMRI identified that, despite using PI-RADS v2 for scoring mpMRI, the agreement between central reading and local site reading was similar to that of a multicentre study using the Likert scoring system [47]. This observation might suggest that inter-reader agreement of Likert and PI-RADS score are comparable, but this assumption needs to be confirmed with a dedicated prospective study.

In studies comparing the performance of PI-RADS scoring systems with the Likert scoring system, some have shown that the Likert scoring system performs similarly[48] or better than PI-RADS scoring systems[49,50] , but these studies were carried out in centres with experienced radiologists and might not be reproducible in centres in which the radiologists have less experience[49,50]. Some room for improvement clearly exists in the standardization of reporting of prostate MRI, the PI-RADS v2 scoring system provides a good starting point for radiologists learning how to interpret

prostate MRI. Future improvements need to cover interobserver agreement, clarification and simplification of the scoring workflow and refinement of technical issues concerning mpMRI acquisition.

[H1] Indications

The introduction of mpMRI to the clinical pathway of prostate cancer diagnosis is an ongoing process and international guidelines have been updated. For example, the European Association of Urology (EAU) guidelines on prostate cancer suggest that mpMRI could be used in two different ways: first, to improve the detection of clinically significant prostate cancer by adding targeted biopsy to systematic biopsies in instances of positive mpMRI results and performing systematic biopsies alone when mpMRI is negative. Second, as a triage test before biopsy, in which a targeted biopsy alone would be performed when mpMRI is positive, and patients with a negative mpMRI would not undergo any prostatic biopsy[3].

The role of mpMRI is slightly different for each biopsy setting. In biopsy-naive patients, a positive scan would improve the definition the suspicious area and enable a targeted biopsy to be performed. Conversely, a negative mpMRI might enable men to defer or avoid biopsy. In the setting of a previous negative biopsy, a positive mpMRI could help in sampling a lesion that might have been missed at the previous biopsy. In patients with a previous diagnosis of low-risk prostate cancer, mpMRI might improve the risk assessment and help in decision-making between active surveillance and definitive treatment.

The EAU guidelines on prostate cancer[3] and the National Comprehensive Cancer Network (NCCN) guidelines on early detection of

prostate cancer [51] state that evidence is insufficient to recommend routine use of mpMRI in biopsy-naive men. Nonetheless, agreement exists regarding the helpful role of mpMRI in this setting with EAU guidelines on prostate cancer strongly recommending the use of the combination of targeted and TRUS-guided biopsies in instances of positive mpMRI[3]. Both guidelines agree, with a strong grade of recommendation[52], on performing mpMRI before a repeat biopsy when clinical suspicion persists. Regarding active surveillance, the EAU guidelines do not recommend the use of mpMRI as a standalone tool to trigger biopsy, nonetheless, its use before confirmatory biopsy is suggested with a strong grade of recommendation[3,52] . Similarly, the NCCN guidelines for prostate cancer support the use of mpMRI and MRI-targeted biopsy but the inclusion of mpMRI in active surveillance protocol still considered controversial[51].

A further use of mpMRI is for local staging of prostate cancer; mpMRI can be useful in assessing T stage to help determine whether disease is confined to the gland or has spread beyond it. The PI-RADS v2 guidelines highlight involvement of the neurovascular bundle, asymmetry of the bundles, bulging of the contour of the prostate, irregular margin and loss of the rectoprostatic angle as signs suggestive of extraprostatic involvement[25]. mpMRI can also be used to assess seminal vesicle involvement, with low T2-weighted signal, restricted diffusion or contrast enhancement suggesting seminal vesicle involvement[25]. mpMRI might also help to identify abnormal lymph nodes and pelvic skeletal metastasis, specifically through anatomical cross-sectional evaluation and DCEI sequence. Nonetheless this specific evluations are not included in a standardized reporting method such as PI-RADS system.

Notably, current guidelines do not typically necessitate mpMRI in patients with low-risk disease and predominant Gleason score 3 pattern for local staging[3]. The main reason is the low sensitivity for extracapsular extension (ECE) (0.49-0.64), particularly for focal ECE[53]. However, in patients with low-risk disease, mpMRI might be used if nerve-sparing surgery is considered to rule out any eventual macroscopic area of ECE, although evidence that conclusively demonstrates the benefit of mpMRI over existing staging tools is still awaited. Indeed, evidence suggests that patients with low-risk disease do not benefit from preoperative mpMRI[54] with this test having no incremental value compared with other standard staging tools[55]. Moreover, the use of preoperative mpMRI does not seem to affect the rate of positive surgical margins [56]. However, in patients with high-risk disease the high specificity of mpMRI makes of this test a useful tool in the preoperative assessment, given the increased probability of ECE [55].

[H1] Current role of mpMRI in diagnosis

When assessing the diagnostic performance of mpMRI in the detection of prostate cancer, two main factors must be taken into account: first, the reporting system used has changed and developed over time and is often different in different studies making comparison challenging. Second, the reference standard considered to prove the presence of cancer (such as systematic biopsy, systematic plus targeted biopsy, radical prostatectomy) needs to be considered when comparing different diagnostic strategies.

De Rooij and colleagues[57] published the first meta-analysis investigating the accuracy of the combination of T2-weighted imaging and two functional techniques, DWI and DCEI, before publication of PI-RADS v1. The authors evaluated seven studies summarizing results from 526

patients. The studies in which the whole prostate was analysed showed a pooled sensitivity of 0.78 (95% CI, 0.65–0.87) and a pooled specificity of 0.88 (95% CI, 0.80–0.94). The reference standard was standard TRUS biopsy or transperineal biopsy without any targeted approachin five studies and radical prostatectomy in the other two and the scoring systems used considerably varied [57].

The first meta-analysis of studies analysing PI-RADS v1 included 14 studies and 1,785 patients[44]. The majority of studies included a targeted biopsy approach as the reference standard with one exception that used radical prostatectomy. The pooled sensitivity and specificity were 0.78 and 0.79, respectively. Negative predictive value (NPV) and positive predictive value (PPV) ranges were 0.58-0.96 and 0.50-0.83, respectively. Studies with low risk of bias regarding PI-RADS applicability showed better performance than those with high risk of bias (sensitivity of 0.82 versus 0.73 and specificity of 0.82 versus 0.75). Moreover, mpMRI sensitivity was increased (0.84) and specificity reduced (0.75) when clinically significant prostate cancer was considered as the outcome instead of any prostate cancer, suggesting an increased rate of false-positive and a reduced false-negative rate [44].

After the release of PI-RADS v2 in 2015, Woo *et al.*[45] published a meta-analysis in which the performance of mpMRI was evaluated and compared with PIRADS v1. For all the 21 studies included (3,857 men), the pooled sensitivity and specificity were 0.89 (range 0.73-1.00) and 0.73 (range 0.80-1.0respectively. Direct comparison of PI-RADS v1 with v2 showed PIRADS V2 had increased pooled sensitivity (0.95) but no differences in specificity. In terms of choosing a cut-off PI-RADS score for

indicating a suspicious mpMRI, regardless of the PI-RADS version used, a score of ≥4 provided acceptable sensitivity (0.89) and specificity (0.74); however, a cut-off score of ≥3 provided an excellent sensitivity (0.95) but a poor specificity (0.47)[45]. The authors suggested that use of ≥4 as a cut-off value could be adequate for general use of PI-RADS , and the latter PI-RADS ≥3? might be considered in men with previous negative biopsies, in whom missing as few cancers (that were potentially missed during the previous prostate biopsy) as possible is desirable. For localizing prostate cancer, PI-RADS v2 had better sensitivity for cancers in the peripheral zone than the transition zone (0.93 versus 0.88) but specificity was lower (0.68 versus 0.75)[45] underlining the more challenging interpretation characterizing transition zone at mpMRI images

Another systematic review that assessed the accuracy of mpMRI for detection of clinically significant prostate cancer reported a detection rate ranging from 44% to 87%[19], which is considerably higher than for random TRUS biopsies, even when extended sampling is taken into account (detection rate of any cancer of 42.5% using 21-core TRUS-guided biopsies) [58].

Evaluating the diagnostic yield of mpMRI-targeted biopsies compared with systematic biopsies is important when assessing the performance of mpMRI for detecting prostate cancer. In the past four years several studies have compared targeted biopsy and systematic biopsy approaches. In a systematic review including 14 studies (involving 2,293 patients), median detection of clinically significant prostate cancer was 24% for TRUS-guided biopsy and 33% for mpMRI-targeted biopsy and median detection of any prostate cancer

was 43% for TRUS-guided biopsy and 51% for mpMRI-targeted biopsy[59]. In 10 out of 14 studies, mpMRI-targeted biopsy detected less clinically insignificant disease than TRUS-guided biopsy. Moreover, a targeted approach was more efficient, detecting more clinically significant disease with fewer cores (9 versus 37). The proportion of clinically significant prostate cancer missed using TRUS-guided biopsy and detected by mpMRI-targeted biopsy was 9% (range 5-16%). Conversely, use of mpMRI-targeted biopsy resulted in 2% of clinically significant prostate cancers being missed (range: 0-12%)[59].

Schoots *et al.*[22] performed a meta-analysis of 16 strictly-selected studies (all men included had a positive mpMRI and received TRUS-guided biopsy and mpMRI-targeted biopsy) in order to provide reliable results regarding pooled benefit of mpMRI-targeted biopsy compared with TRUS-guided biopsy in prostate cancer detection. Use of mpMRI-targeted biopsy resulted in 20% more clinically significant prostate cancers being identified than TRUS-guided biopsy ($P < 0.001$)[22]. Furthermore, mpMRI-targeted biopsy was almost twofold better at avoiding detection of insignificant disease (relative sensitivity of 0.56)[22]. These observations show the high accuracy of mpMRI and, importantly, its superiority compared with the standard of care (TRUS-guided biopsy) in detecting clinically significant prostate cancer and avoiding overdiagnosis of insignificant disease.

[H2] mpMRI in biopsy-naive patients

The role of a prebiopsy mpMRI in biopsy-naive men might be to identify those with a low risk of harbouring clinically significant prostate cancer who could avoid a biopsy, therefore, reducing the number of biopsies

performed on a population level, and decreasing overdiagnosis and overtreatment. Evidence is conflicting in this group of men: a subgroup analysis by Schoots and colleagues[22] showed that mpMRI-targeted biopsy and TRUS-guided biopsy had a similar detection rate for clinically significant prostate cancer (relative sensitivity 0.97) . Thus, the authors reasoned that systematic sampling alone might be sufficient to detect prostate cancer. Results of a systematic review showed that use of mpMRI-targeted biopsy was associated with reduced detection of prostate cancer [60]. However, the PROMIS study[47] provided level 1 evidence for diagnostic accuracy of an upfront mpMRI and took a major step towards the introduction of this radiological test in the diagnostic pathway of men in whom prostate cancer is suspected. In this study, mpMRI-targeted biopsy had higher sensitivity than TRUS-guided biopsy (87% versus 60%) and a higher NPV (72% versus 65%) for detecting Gleason score prostate cancer ≥3+4 or cancer core length ≥4 mm[47].

In 2018, Kasivisvanathan *et al.*[46] published the randomized controlled PRECISION study. In this trial, 500 men in whom prostate cancer was suspected were randomly assigned to receive either to mpMRI (group 1) or to TRUS-guided biopsy (group 2). Men assigned to group 1 underwent an mpMRI-targeted biopsy alone if their mpMRI was positive but did not undergo any biopsy if their mpMRI was negative. In group 1, 28% of patients avoided biopsy owing to the absence of any suspicious areas on mpMRI. mpMRI-targeted biopsy aided diagnosis of clinically significant prostate cancer in 38% of men compared with 26% for TRUS-guided biopsy (P=0.005)[46]. (Table 1)

Porpiglia *et al.*[61] performed a randomized controlled trial (RCT)

comparing the combination of TRUS-guided biopsy and mpMRI-targeted biopsy (arm A) with TRUS-guided biopsy alone (arm B) in 212 biopsy-naive men. Men with a negative mpMRI in arm A underwent a TRUS-guided biopsy. Detection of any prostate cancer and clinically significant prostate cancer were higher in arm A than arm B (50.5 versus 29.5% and 43.9 versus 18.1%, respectively, all P<0.002). Interestingly, within the arm A, detection of clinically significant prostate cancer was 56.8% for mpMRI-targeted biopsy alone (in patients with positive mpMRI) and 3.8% for TRUS-guided biopsy alone (in patients with negative mpMRI). These results demonstrated the utility of adding mpMRI to the diagnostic pathway and also the low probability of missing clinically significant prostate cancer and avoiding biopsy when mpMRI is negative[61]. Panebianco *et al.*[62] conducted a similarly designed RCT in 1,140 patients. In this study patients underwent either a TRUS-guided biopsy (Group A) or mpMRI and TRUS-guided biopsy plus eventual subsequent mpMRI-targeted biopsy (Group B). Dectection of any prostate cancer was higher in the mpMRI group than in the TRUS-guided biopsy group (73% versus 38%)[62]. However, other RCTs have shown different results. Tonttila *et al.* [63] randomly assigned 113 men to either mpMRI with subsequent TRUS-guided biopsy plus eventual mpMRI-targeted biopsy or to TRUS-guided biopsy. Cancer was detected in 64% of men in mpMRI arm and in 57% of men in TRUS-guided biopsy arm. Clinically significant prostate cancer was detected in 55% of men in the mpMRI arm and in 45% of men in the TRUS-guided biopsy arm. The differences between the two groups were not statistically significant, but the comparison is likely to be underpowered owing to the small number of patients included [63] (Table 1). Baco *et al.* [64] randomly assigned 175 men

476 either to TRUS-guided biopsy and targeted biopsy of suspicious lesions (at
477 either DRE or ultrasonography) or to TRUS-guided biopsy combined with
478 mpMRI-targeted biopsy. No significant differences were found for detection
479 of any prostate cancer between the control group and the mpMRI group
480 (54% versus 59%, respectively, P = 0.4) or for clinically significant prostate
481 cancer (49 versus 44%, respectively, P = 0.5)[64]. Boesen *et al.*[35] assessed the
482 value of biparametric MRI in 1,020 patients referred for suspicion of prostate
483 cancer. A combined approach (mpMRI-targeted biopsy plus TRUS-guided
484 biopsy) was restricted to men with suspicious mpMRI findings. The
485 combination improved detection of clinically significant prostate cancer by
486 11% and reduced detection of insignificant disease by 40% compared with
487 TRUS-guided biopsies in all men (Table 1). Rouviere *et al.*[65] published a
488 prospective multicentre paired cohort study enrolling 275 men with a
489 suspicion of prostate cancer. Each patient received mpMRI and underwent
490 subsequently to TRUS-guided biopsy plus eventual mpMRI targeted biopsy
491 in instances of positive mpMRI. No differences were reported in the
492 detection of clinically significant prostate cancer between mpMRI targeted
493 and TRUS-guided biopsy (32.3% versus 29.9% P = 0.38). However, the
494 highest detection of clinically significant prostate cancer was reached by the
495 combination of the two techniques (37%)., In a similar paired-cohort study,
496 van der Leest *et al.*[66] compared the detection of clinically significant prostate
497 cancer in an MRI pathway versus a “RUS-guided biopsy pathway in a cohort
498 of 626 men with suspicion of prostate cancer receiving mpMRI and
499 subsequent TRUS-guided biopsy plus eventual mpMRI targeted biopsy. The
500 MRI pathway (in which patients with a positive mpMRI undergo only
501 mpMRI targeted biopsy and patients with negative mpMRI do not receive

any form of biopsy) resulted in a dectection rate of 25.4% for clinically significant prostate cancer. The TRUS-guided biopsy pathway (in which all patient receive a TRUS-guided biopsy) resulted in a detection rate of 23.3% for clinically significant prostate cancer (P = 0.17) Detection of insignificant prostate cancer was significantly different between groups (14.1% for mpMRI versus 24.8% for TRUS-guided biopsy P < 0.0001). Thus, the MRI pathway would have avoided biopsy in 49% of men at the cost of missing 4% of clinically significant prostate cancer.

In key studies with a paired cohort design in the biopsy-naive setting (Table 1), four paired cohort and one RCT studies showed higher detection of clinically significant prostate cancer using mpMRI-targeted biopsy than the TRUS-guided biopsy[35,46,67–70] However, two prospective paired-cohort studies[65,66] showed no significant differences among these two biopsy techniques, underlining that the combination of mpMRI targeted and TRUS-guided biopsy is the most accurate strategy for detecting clinically significant prostate cancer.

In summary, both EAU[3] and NCCN[51] guidelines on prostate cancer are cautious in suggesting routine use of mpMRI in in the biopsy-naive population, but the majority of high-quality evidence supports the addition of mpMRI-targeted biopsy in the diagnostic pathway. Specifically, EAU guidelines on prostate cancer suggest the use of mpMRI before prostate biopsy in this population (but the grade of recommendation is weak), supporting the use of mpMRI targeted biopsy in addition to TRUS-guided biopsy and avoiding biopsy when mpMRI is negative only in patients in whom clinical suspicion of prostate cancer is low[3].

[H2] mpMRI after previous negative biopsy

Much effort has been made in the past decade to improve the management of patients with previous negative biopsies and a persistent clinical suspicion of prostate cancer. The addition of anterior apical cores, performing sampling of areas adjacent to previously biopsied sites, and generally increasing the number of cores taken, have been the most commonly used techniques to decrease the risk of missing prostate cancer during a repeat biopsy[71–74]. Saturation biopsy has a higher prostate cancer detection rate than standard 12-14 core TRUS-guided biopsy (32.7% versus 24.9%, P = 0.0075)[71] but the majority of additional cancers identified are clinically insignificant (40% of all prostate cancers detected) [75]. Moreover, the increased rate of complications needs to be considered when further biopsy approaches are being contemplated[76].

The role of mpMRI in this setting is to detect suspicious areas that might have been missed by previous biopsy and enable targeted biopsies of these suspicious areas to be performed. In the PICTURE study, Simmons et al.[77] evaluated the accuracy of mpMRI in the repeat biopsy setting in a cohort of patients referred for a 5-mm template transperineal biopsy as the reference test. mpMRI-targeted biopsy had a sensitivity of 94% and a NPV of 69% for detecting Gleason score ≥3+4 prostate cancer and/or maximum cancer core length ≥4mm using a Likert score ≥3 as cut-off value. Notably, only 30% of the patients in this cohort had not had a previous detection of cancer; the remaining men previously had low-risk prostate cancer identified using TRUS-guided biopsy. Owing to this population heterogeneity, the results regarding mpMRI accuracy in this study should be interpreted with caution. In a meta-analysis of 14 studies including 698 patients with previous

554 negative biopsy, mpMRI-targeted biopsy had a pooled sensitivity of 88% and
555 specificity of 69% [78]. A meta-analysis and a systematic review[22] evaluating
556 the use of targeted biopsy in the population with a previous negative biopsy[60]
557 both reported that mpMRI improved the detection rate of any prostate cancer
558 and that mpMRI-targeted biopsy was noninferior to even saturation biopsy
559 techniques for detecting clinically significant prostate cancer[79] (Table 1).
560 Another study showed that use of mpMRI-targeted biopsy resulted in
561 detection of less prostate cancer overall than TRUS-guided biopsy (34% of
562 patients versus 39%) but of more clinically significant disease (26% of
563 patients versus 17%)[80] . Arsov *et al.*[81] randomly assigned 267 patients to
564 either mpMRI-targeted biopsy (arm A) or a combination of mpMRI-targeted
565 biopsy and TRUS-guided biopsy (arm B). In arm B, mpMRI-targeted biopsy
566 alone identified a similar proportion of clinically significant disease to
567 TRUS-guided biopsy (26% versus 25% P = 0.6). Furthermore, detection of
568 clinically significant prostate cancer was similar in arm A and arm B (29%
569 versus 32% P = 0.7) . The authors concluded that an mpMRI-targeted biopsy
570 alone strategy should be evaluated in patients referred for repeat biopsy after
571 previous negative biopsy.

572 In summary, the use of mpMRI in the repeat biopsy setting is strongly
573 recommended by the EAU and NCCN guidelines on prostate cancer [3,51]to
574 reduce the proportion of clinically significant prostate cancer that is missed
575 using standard biopsy modalities. Performing targeted biopsy alone in this
576 setting could be considered to reduce the potential harm of repeated
577 sampling, as is suggested in the EAU guideliens on prostate cancer[3].

578

579 **[H1] Available biopsy strategies**

Different techniques and strategies to perform mpMRI targeted biopsies have been developed and refined alongside the development of mpMRI. This process has involved software and device development as well as the assessment of different approaches (such as transrectal and transperineal) and strategies (including mpMRI-targeted biopsy alone or combined with the TRUS-guided approach).

[H2] Targeted biopsy strategies

An mpMRI-targeted biopsy is defined as any biopsy technique in which an MRI scan is used to determine the location of a suspicious target before biopsy and the resulting information is used to alter the biopsy technique[82]. To date, three approaches of MRI-targeted biopsy have emerged: visual registration (also referred to as cognitive registration); software-assisted registration (also referred to as image fusion registration) and direct in bore biopsy[83].

[H3] Visual registration

In the visual registration MRI-targeted biopsy technique a real-time transrectal ultrasound probe is used to image the prostate and biopsy needle. The locations of the suspicious lesions detected on mpMRI are used by the operator to direct the biopsy needle during the targeted sampling to parts of the prostate on the ultrasonography image that relate to the suspicious area on the mpMRI[14]. The visual registration approach is the simplest method of performing mpMRI-targeted biopsy as it does not require any additional equipment to that needed to perform a prostate biopsy without targeting. However, in order to accurately target the suspicious area, the operator needs to be skilled in estimating the location of the lesion on the ultrasonography

images. This particular technique is affected by a learning curve effect[84]. Moreover, the operator needs either a multidisciplinary radiologist-urologist approach or a previous training in mpMRI interpretation in order to be able to transpose the radiological information on ultrasonography images.

[H3] Software registration

Efforts to improve targeted biopsy strategies have led to the development of a software registered targeted technique. This technique enables the contouring of the suspicious lesion and the prostatic gland on mpMRI images by using specific software. The contours are then superimposed on to the ultrasonography images, enabling the operator to identify the area to target. The aim of software registered targeted biopsy is to overcome the limitations of the visual registered strategy, helping the operator to easly identify the mpMRI suspicious lesion on ultrasonography images of the prostate and providing improved reproducibility. However, a learning curve effect related to the use of software registration seems to still be present [84–86]. One disadvantage of this technique is related to the cost of the software platforms, which make it less cost-effective than the visual registration approach[87]. To date, several platforms have been developed (UroNav, InVivo; Artemis, Eigen; Urostation, Koelis; Biopsee, Medicom; Virtual Navigator, Esaote; BioJet, BK Ultrasound), but direct comparisons of the effectiveness of available platforms have not been carried out[88,89].

[H3] In bore biopsy

The in bore biopsy technique is performed inside the MRI scanner itself using sequential mpMRI images to guide the needle into the suspicious

area. One advantage of this strategy is that it reduces some of the registration error associated with real-time transrectal ultrasonography that is used in the other mpMRI-targeted biopsy techniques. Both visual-registration and software-registration targeted biopsy can fail to sample the target for several reasons (such as prostate movement and/or deformation, patient movement, incorrect image registration or mismatch image planes) in up to 40% of mpMRI-targeted biopsies negative for the presence of prostate cancer [90,91]. In addition, the needle can actually be seen inside the lesion on MRI, giving increased likelihood of sampling the correct area. However, this approach is subject to increased costs and scanner use time, and requires the involvement of radiologists with expertise in the technique[14].

[H3] Comparative studies

To date, no consensus has been reached regarding which mpMRI-targeted biopsy strategy has the highest rates of detection of clinically significant cancer. A meta-analysis including 43 studies reported no significant differences in detection of clinically significant prostate cancer between the three different MRI-targeted biopsy techniques; however, a trend towards the superiority of software registered and in bore techniques over the visual registered technique was observed (pooled sensitivity for clinically significant prostate cancer 0.89 and 0.92, respectively, versus 0.86, P $\geq$0.42) [83]. Stabile et al.[84] reported superiority of software registered targeted biopsy to visual registered targeted biopsy in detecting clinically significant prostate cancer. Software registered targeted biopsy had a 2.4-fold higher probability of detecting clinically significant prostate cancer than visual registered targeted biopsy. The results of the FUTURE study, in which

234 men were randomized to undergo one of the three strategies showed no differences in detection of clinically significant cancer between strategies[92]. However, these results must be cautiously considered as this study was probably unpowered owing to the small sample sizeand the number of targeted cores taken differed among groups, possibly affecting the detection of prostate cancer. The SmartTarget Biopsy Trial reported similar results, showing no differences between visual registration and software registration techniques. In this within-person randomized paired study, 141 men with a previous prostate biopsy and a positive mpMRI received, in a randomized order, both a visual-registration and a software-registration targeted biopsy in the same session. [93]. Nevertheless, considering the reported Gleason grade concordance between mpMRI-targeted biopsy and prostatectomy specimens being good but not perfect (88-90%)[94,95], a proper and reliable comparison between different mpMRI-targeted biopsy techniques should be conducted using final pathology as the reference standard.

[H3] The transrectal versus the transperineal approach

Each mpMRI-targeted biopsy technique can be performed using either a transrectal or transperineal approach (Fig 5), although the most commonly used approach for mpMRI-targeted biopsy is currently transrectal[59]. Some of the factors influencing choice of a specific approach include likelihood of infection, diagnostic accuracy and feasibility. The transrectal approach has a non-negligible risk of sepsis and prophylactic fluoroquinolones are currently recommended[96,97]. Worryingly, rates of resistance to fluoroquinolones are rising in rectal flora and increasing evidence shows that their use has a detrimental effect in the long term (such

as disabling and potentially permanent adverse effects on tendons, muscles, joints, nerves and the central nervous system, and increased rate of sepsis owing to bacterial resistance)[98]. However, rates of hospitalization related to sepsis from a transperineal approach are extremely low compared with those related to the transrectal approach (0%-0.7% versus 0.5-6.9%) [96].

Both the transrectal and transperineal approach have acceptable accuracy for mpMRI-targeted biopsy[83]. Pepe et al.[99] conducted a direct comparison of transrectal and transperineal mpMRI-targeted biopsy . Transperineal fusion biopsy resulted in more clinically significant prostate cancer being detected than transrectal cognitive biopsy (93% versus 67% of the total number of clinically significant prostate cancer that was detected by the reference standard) with the former detecting more anterior cancers (94% versus 25% of all anterior cancers diagnosed. However, as different mpMRI-targeted biopsy strategies (fusion and cognitive) were compared, concluding whether the results were caused by the different strategy or the different approach is difficult. Stabile et al.[84] reported the results of a comparison between the transperineal or transrectal approach using software registered targeted biopsy. The transperineal approach had a higher detection rate of clinically significant prostate cancer than the transrectal approach (transperineal approach odds ratio for detection of clinically significant prostate cancer was 4.1 with transrectal approach as reference) with the latter being subject to a more evident learning curve effect. However, transrectal mpMRI-targeted biopsy has been shown to have excellent detection rates of clinically significant prostate cancer and can detect anterior tumours when performed by an experienced clinician[46,68].

The feasibility of delivering these different approaches is another

factor that requires consideration. Biopsies carried out transrectally are traditionally performed under local anesthesia within the office or outpatient setting, and most centres can deliver this approach without too much difficulty. However, transperineal biopsy is more time consuming than transrectal biopsy, is resource intensive and is usually done under general anaesthesia, requiring operating room time. These factors reduce the feasibility of performing transperineal mpMRI-targeted biopsy for the average centre. However, with the increasing use of local anaesthetic in transperineal biopsy and the advantages with respect to infection risk and diagnostic accuracy, this approach is likely to become increasingly popular[100].

In summary, the evidence is not strongly in favour of one approach over another for mpMRI-targeted biopsy; however, software registration and in bore targeted biopsy might provide good detection of clinically significant prostate cancer when relying on locally available equipment and expertise.. One method of targeting might have advantages over others for particular lesions in particular locations, although these indications remain to be elucidated. Regarding the access route, in presence of risk factors for urinary infections (such as indwelling catheter or need for saturation biopsy), a transperineal approach can be considered to reduce the risk of infectious complications.

[H2] mpMRI alone or in combination

One of the most debated questions regarding the use of mpMRI-targeted biopsy is whether, in the presence of a positive mpMRI, a targeted approach alone might be sufficient. mpMRI-targeted biopsy alone was

shown to have superior efficacy to TRUS-guided biopsy in the PRECISION study[46]. mpMRI-targeted biopsy alone detected more clinically significant prostate cancer than TRUS-guided biopsy (38% versus 26%) and fewer insignificant cancers (9% versus 22%) with a fewer number of cores (median: 4 versus 12). Moreover, the rate of complications at 30 days was lower in the mpMRI-targeted biopsy group[46]. However, most studies seem to show that the combination of systematic and targeted biopsy increases the detection both of any prostate cancer and clinically significant prostate cancer [59,83,101,102].

Supporters of an mpMRI-targeted biopsy alone strategy argue that the proportion of clinically significant prostate cancer missed is low, as the systematic approach detects approximately double the number of insignificant cancers as mpMRI-targeted biopsy[22,83,103], which highlights an advantage of avoiding systematic biopsy, reducing overdiagnosis and potentially overtreatment. Overdiagnosis and overtreatment in prostate cancer is major problem and biopsy techniques that reduce this must be taken into consideration when deciding on the optimal approach[4,104]. Other advantages of the mpMRI-targeted biopsy alone approach include the reduction in core number, operative time, pathologist time and patient-reported complications (which can lead to considerable morbidity, particularly for transperineal systematic biopsies). [46,77].

Supporters of the combined approach argue that obtaining histological information about prostate areas that are not suspicious on mpMRI is important as it can influence the margins and nerve sparing approach in radical surgery[105]. Furthermore, as prostate cancer is a multifocal disease[106] supporters of the combined approach argue that not sampling outside of the

area targeted using mpMRI can result in smaller prostate cancer foci that surround the index lesion being missed[107,108], although the clinical significance of these lesions is debated. Stabile *et al.*[109] reported that the probability of finding clinically significant prostate cancer foci outside the lesion detected using mpMRI is directly related to the PI-RADS score obtained[109], ranging from 25% for a PIRADS score of 3 to 70% for a PI-RADS score of 5 [109].. In summary, the decision to perform a targeted alone approach omitting systematic sampling must be discussed with the patient, taking into account the risk (ranging from 5% to 20%) of misdiagnose significant disease but at the same time significantly decrease the risk of insignificant cancer overdiagnosis[65,103]. What is clear is that patient preferences should be considered when deciding on which biopsy approach to adopt, bearing in mind the advantages and limitations.

[H1] The role of mpMRI as a triage test

In order to use mpMRI as a triage test in the prostate cancer diagnostic pathway, it needs to reliably predict the presence or the absence of cancer; a high NPV might help to avoid prostate biopsies. In the biopsy-naive population included in the PRECISION trial[46], the use of an upfront mpMRI enabled 28% of patients (in the investigative arm) to avoid biopsy, although follow-up monitoring of these patients is ongoing. In the PROMIS study[47], 27% of patients had a negative mpMRI and the authors suggested that these patients could have avoided biopsy. The introduction of mpMRI as triage test might change the traditional diagnostic pathway of prostate cancer (Fig 6).

[H2] Using a negative mpMRI

The role and the clinical utility of a negative mpMRI is strictly related to its NPV;, hence its reliability for the absence of clinically significant prostate cancer. The NPV of mpMRI has been assessed, but it varies widely among the published series. This wide variation reflects the differences in the prevalence of cancer-free prostates in different populations. In the PROMIS study[47], which was designed to provide level 1 evidence on the diagnostic accuracy of mpMRI , the performance of mpMRI was compared with TRUS-guided biopsy in 576 biopsy-naive men using a 5mm-template transperineal biopsy as the reference standard. The NPV of mpMRI for Gleason score ≥4+3 and/or a maximum cancer core length ≥6 mm of any cancer was 89%. Notably in this multicentre study , a negative MRI was not associated with any primary Gleason pattern 4 disease or worse. Most of the thresholds for declaring a miss were triggered by maximum cancer core length rather than grade. However, the NPV dropped to 76% when the *a priori* threshold of any pattern 4 or a maximum cancer core length ≥4mm was used. Despite these results, mpMRI had a better NPV than the traditional standard-of-care modality of TRUS-guided biopsy, which had an NPV of 63% ($P < 0.0001$). Nonetheless, the limitations of the PROMIS study[47] should be acknowledged: first, no information was provided regarding tumour location. This omission might have created a mismatch of tumours detected by mpMRI and by transperineal biopsy. Indeed, some mpMRI-suspicious lesions might have been negative for prostate cancer and vice versa some negative areas on mpMRI might have been positive for the presence of cancer. Second, the diagnostic accuracy of TRUS-guided biopsy might have been decreased owing to it being performed after a 5-mm template transperineal biopsy, which might have considerable modified the

prostate parenchyma owing to upto 70 cores being taken.

Panebianco et al.[110] assessed the value of a negative mpMRI after 48 months of follow-up monitoring in 1,545 patients. The probability of being free of clinically significant prostate cancer at 48 months was 95% in biopsy-naive men and 96% in men with a previous negative biopsy[110]. However, in this study, which was a reflection of clinical practice, not all patients had routine prostate biopsies carried out as part of follow-up monitoring so the true prevalence of clinically significant prostate cancer might have been higher than reported.

A meta-analysis[111] evaluating the NPV of mpMRI NPV in 48 studies (including 9,613 patients) reported a median NPV for any prostate cancer of 82.4%, (IQR 69-92) and of 88.1% (IQR 86-92) for clinically significant prostate cancer. The large variability in the NPV was a result of the lack of standardization in definition of clinically significant disease and differences in the prevalence of clinically significant prostate cancer, which ranged from 14% to 51%. The authors concluded that, should it be possible to risk stratify men into those with a high and low pre-test probability of having clinically significant prostate cancer, mpMRI could be used as a triage test in patients at low risk.

A negative mpMRI should not considered enough to omit prostate biopsy owing to the wide variability of mpMRI NPV. However, a negative mpMRI should be used as a further clinical tool to help in the decision-making process for prostate cancer diagnosis. The combination of negative mpMRI with nomograms predicting the presence of prostate cancer should be supported in order to identify those patients who might safely avoid a biopsy. The decision making needs to be shared with the patient.

[H2] Using a positive mpMRI

A positive mpMRI can also be used to influence the biopsy technique. Notably, the positive predictive value (PPV) of mpMRI ranges from 48% to 82% for any prostate cancer using a cut-off value of a Likert score of ≥3 and a PPV of 42-92% when using a cut-off value of a Likert score of ≥4[111]. Similarly, using the PI-RADS score, PPV ranges from 50% to 83%, using a cut-off value of ≥3[44]. The PROMIS study reported a PPV of 65% for Gleason score ≥3+4[47]. These results highlight the large number of false positives obtained using mpMRI, which means that a positive mpMRI alone cannot currently replace prostate biopsy. One of the main causes of the false positives are suspicious areas on mpMRI that mimic prostate cancer but are, in fact, indicative of benign conditions such as prostatitis[26,112]. The development of clinical adjuncts to a positive mpMRI that help differentiate between areas likely and not likely to be clinically significant prostate cancer are important areas of research. Further risk stratifying mpMRIs scored as indeterminate or a Likert or PI-RADS score of 3 is a particularly important area of focus to enable a definitive management plan to be implemented.

[H1] Adjuncts to mpMRI , Several aspects and factors of mpMRI are subject to continuous development and refinement. Some of these (such as magnetic field strength, endoretal coil, spectroscopy, and mpMRI cost effectiveness), are still debated, others mostly concern different strategies and settings in which mpMRI can be used (for example, active surveillance of prostate cancer and combined use with biomarkers).

[H2] Magnetic field strength

Current clinical practice uses mpMRI scanners with magnetic field

strengths of either 1.5 or 3 T are typically used in current clinical practice. An increased signal:noise ratio is provided by 3T scanning, which enables increased spatial and temporal resolution[113]. However, increased field strengths might cause more artefacts. Initial studies comparing 1.5 with 3T mpMRI reported comparable accuracy in cancer localization and local staging[114,115]. Moreover, 1.5T, performed using both endorectal and surface coils, seemed to be superior in image quality and tumour delineation to 3T. Direct comparisons in homogeneous cohorts without the use of endorectal coil showed that the use of 1.5 T did not compromise the diagnostic accuracy of mpMRI in terms of PI-RADS scoring, achieving excellent NPV and moderate PPV (94% and 52%, respectively) [116,117]. Furthermore, no significant differences between the two field strengths were observed in a meta-analysis[45]. Further data is needed, but the PI-RADS v2 recommendations state that, overall, the advantages of 3T substantially outweigh any disadvantages and the authors prefer and recommend use of 3T systems. A 3T system is not deemed mandatory for prostate mpMRI,but using such systems seems reasonable for prostate mpMRI when available in a given practice.

[H2] The use of an endorectal coil

Prostate mpMRI can be performed using two types of coil: endorectal and external (surface) phased array coil. The combination of both or a surface coil alone are commonly used in clinical practice (Fig 7). The addition of an endorectal coil is associated with increased costs, duration for examination, and is uncomfortable for patients. Evidence is conflicting on the benefit of an endorectal coil in the diagnosis and staging of clinically

significant prostate cancer. Some systematic reviews and meta-analyses show no clear benefit of using an endorectal coil [45,53,22]. However, other studies have shown that the addition of an endorectal coil to a surface coil can improve the accuracy of mpMRI in the detection, localization and staging of prostate cancer[118–121]. Specifically, Turkbey et al.[119] demonstrated an increase in sensitivity from 0.45 to 0.76 and in PPV from 0.64 to 0.80 with the addition of an endorectal coil. Nevertheless, these studies were affected by several limitations, such as nonblinding of radiologists, variable quality in surface coils and small cohorts. Owing to the aforementioned issues and the controversial clinical benefit, the use of an endorectal coil is not considered mandatory in guidelines[25].

[H2] Utility of spectroscopy

A number of studies have evaluated the value of MRSI in the diagnosis of prostate cancer. Contradictory results have been reported on the diagnostic benefit of MRSI [78,122–125]. The majority of studies assessed MRSI in combination with PI-RADS v1 scoring, although one study evaluated the effect of integration of MRSI to PI-RADS v2 and reported improvement in detection of high-grade prostate cancer (accuracy of 0.65 versus 0.72) [126]. MRSI is a complex technique, with low availability, high costs, long acquisition time, need for experienced radiologists and dedicated software. Owing to these limitations and the unclear clinical benefit, MRSI is not currently mandated in clinical guidelines [25].

[H2] The use of quantitative assessment

Despite the development of standardized reporting systems, accurate

interpretation of mpMRI remains challenging, particularly for inexperienced radiologists. To overcome this issue, a quantitative approach for mpMRI interpretation has been developed, which has been established by defining thresholds for quantitative radiological parameters indicative of prostate cancer. Potential parameters include the 10^{th} percentile of ADC, the time to peak, the T2 signal intensity skewness and the T2 value in the peripheral zone[127–129]. However, investigation of these associations is still at the experimental stage. The main concern about the applicability of quantitative sequences is their generalizability for different protocols and mpMRI vendors. In conclusion, a need for improvement remains in standardization and mpMRI reproducibility. Futher assessment and development of quantitative mpMRI will result in an improved and standardized mpMRI interpretation.

The specific role and advantages behind the use of mpMRI adjuncts, particularly the role of quantititative analyses, still need to be clarified. Further dedicated, well-designed studies will help in making mpMRI an extensively usable test.

[H1] Active surveillance and mpMRI

Active surveillance (AS) has been increasingly adopted as a conservative management approach for patients with low-risk prostate cancer and selected men with intermediate-risk prostate cancer to avoid or delay unnecessary treatment until higher-risk disease is evident[130]. Several AS programmes are available, with different selection criteria[131–133]. Growing evidence suggests that mpMRI in the setting of AS is being increasingly used [134–136]. A systematic review showed that mpMRI is useful for detecting

clinically significant prostate cancer in men eligible for AS, reporting that 70% of these men have a positive mpMRI[134]. Interestingly, a 2018 systematic review, including men with low-risk prostate cancer (Gleason score 3+3), showed that, at confirmatory biopsy, a diagnostic pathway including a combination of mpMRI-targeted biopsy and TRUS-guided biopsy yielded a higher rate of cancer upgrading (27%) than either strategy alone (upgrading for mpMRI-targeted biopsy alone versus TRUS-guided biopsy was 17% versus 20%). Nonetheless, no pathway was more favourable than the other (relative risk: 0.92). The authors concluded that both biopsy techniques were complementary in detecting prostate cancer upgrading and that a prebiopsy mpMRI should be performed before a confirmatory biopsies for men on AS[135]. However, at present no robust data support the use of mpMRI instead of repeat standard biopsy for monitoring men on AS[137,138]. Many studies reporting the utility of mpMRI as a monitoring tool for men on AS lack rigor and do not readily enable comparison of outcomes. Thus, the European School of Oncology convened a task force to establish the PRECISE guidelines for the reporting of serial mpMRI on AS[139]. The key points of these recommendations are that the likelihood of mpMRI change over time (such as mpMRI sequences and scoring) from the previous or baseline mpMRI scan must be assessed , and that absolute measurements of eventual visible lesion size must be taken at each time point to enable accurate assessment of change, using a dedicated pictorial representation.

[H1] Role of biomarkers to improve mpMRI

The use of biomarkers in combination with mpMRI information to improve the accuracy of mpMRI is being investigated. Prostate-specific

antigen density (PSAd), PCA3 and prostate health index (PHI) are the most commonly studied biomarkers in combination with mpMRI (Table 2). PSA density is known to be related to the presence of clinically significant prostate cancer[140,141]. Washino et al.[142] retrospectively reviewed 288 biopsy-naive patients who underwent both mpMRI and mpMRI-targeted plus TRUS-guided prostate biopsy for a suspicion of prostate cancer for whom PSAd were available. PI-RADS v2 was used for reporting.. The authors reported an accuracy of mpMRI alone and PSAd alone in predicting prostate cancer of 0.82 and 0.84, respectively. The combination of PI-RADS score ≤3 plus PSAd <0.15ng/ml/ml, yielded no clinically significant prostate cancer. However, a PI-RADS score ≥4 and a PSAd ≥0.15 ng/ml/ml, or a PI-RADS score =3 and a PSAd ≥0.30ng/ml/ml yielded the highest clinically significant prostate cancer detection rates (ranging from 76 to 97%)[142].

The addition of PSAd increased the accuracy of mpMRI alone from 0.75 to 0.79 in a cohort of 1,040 patients with suspicion of prostate cancer[143]. The NPV of PI-RADS score 3 as a cut-off increased from 92% to 98% using a PSAd of 0.15ng/ml/ml as the threshold, potentially avoiding 20% of unnecessary biopsies[143]. Hansen et al.[144] reported similar findings in the repeat biopsy setting using a PSAd threshold of 0.20ng/ml/ml using Likert score threshold of 3. Appayya et al.[49] assessed the performance of PSAd in patients with indeterminate lesions (a Likert score of 3). Overall, clinically significant prostate cancer was detected in 21 of 76 men (27%). A PSAd cut-off value of 0.17ng/ml/ml resulted in a sensitivity, specificity and NPV of 0.67, 0.75 and 0.85, respectively [49]. According to these results, the PSAd is a cost-free, useful clinical tool when used in combination with mpMRI in order to improve the accuracy of detecting clinically significant prostate cancer,

helping in the decision-making process before prostate biopsy.

Another biomarker that has been assessed in combination with mpMRI is urinary *PCA3* level. *PCA3* is a biomarker that can be detected in urine, which showed a good sensitivity and specificity for identification of prostate cancer in patients with previous negative biopsies[145]. Busetto et al. [146] demonstrated that the addition of urinary *PCA3* level to mpMRI information increased the diagnostic accuracy (area under the curve (AUC)) of a multivariable model from 0.78 to 0.81 in 171 patients with previous negative biopsies[146]. However, the studies examining the use of urinary *PCA3* level for this purpose were affected by limitations such as small sample size, unclear use of PI-RADS scoring and TRUS-guide biopsy as the reference standard. Moreover, the availability and the cost effectiveness of this test should be considered.

The Prostate Health Index (PHI) is a marker incorporating pro-2PSA, free PSA and total PSA into a mathematical algorithm $((p2PSA/fPSA) \times PSA^{0.5})$ [147]. Increased PHI values are associated with an increased risk of the presence of clinically significant prostate cancer[148,149], and its use has been demonstrated to enable avoidance of up to 30% of biopsies at the cost of missing a small proportion of significant disease (10%) using a cut-off of 28.6[150]. Gnanapragasam et al. [151] evaluated the role of PHI in combination with mpMRI in a series of 279 men with a history of previous negative biopsy. The addition of PHI to mpMRI increased the predictive performance of mpMRI both for any prostate cancer (AUC 0.71 versus 0.64) and clinically significant prostate cancer (0.75 versus 0.64). Similarly, Druskin et al.[152] showed that the addition of PHI to a multivariable model including age, biopsy history and PI-RADS score, increased the AUC for

clinically significant prostate cancer detection from 0.83 to 0.90 in a cohort of 109 patients.

The use of these biomarkers in combination with mpMRI should be considered. To date, PSAd seems to be the most efficient biomarker available owing low costs and the easy accessibility,.

[H1] Cost-effectiveness

The introduction of mpMRI within the prostate cancer diagnostic pathway has advantages from a diagnostic perspective, but assessing its cost-effectiveness is important. One of the earliest studies addressing this topic was conducted by de Rooij et al.[153], who developed a model based on two diagnostic strategies: standard of care based on performing TRUS-guided biopsy in patients with a suspicion of prostate cancer and an experimental mpMRI strategy based on offering mpMRI to men referred for a suspicion of prostate cancer, with subsequent mpMRI-targeted biopsy if the mpMRI is positive, or routine follow-up monitoring if mpMRI is negative. In both arms patients underwent active treatment (radical prostatectomy or radiotherapy) when clinically significant prostate cancer was diagnosed. The outcomes were costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs). The authors concluded that, although the experimental mpMRI strategy is initially more expensive (expected costs of the mpMRI strategy were €31 higher than those for the TRUS-guided biopsy strategy) , these extra costs are compensated for by the reduction in treatment costs resulting from fewer false positives and an improved estimation of tumour aggressiveness compared with the standard of care TRUS-guided biopsy pathway. This resulted in an over-time improvement in QALYs

related to mpMRI strategy achieved by avoiding unnecessary radical treatment of diseases that are not clinically significant (with a reduced QoL without an improved survival) and decreasing the likelihood of late diagnosis of clinically significant prostate cancers (which are associated with reduced survival)[153].

A similar study was carried out by Faria et al. [154] relying on the cohort and datafrom the PROMIS study cohort. In order to establish how to best combine different diagnostic tests (i.e. TRUS-guided biopsy, template prostate mapping biopsy and mpMRI-targeted biopsy) in order to provide the most cost-effective strategy, the combination of each test and mpMRI cut-offs resulted in a total of 383 possible diagnostic strategies. The most cost-effective strategy for detecting clinically significant prostate cancer was the use of mpMRI as the first test followed by a transrectal mpMRI-targeted biopsy in men in whom the mpMRI suggests prostate cancer presence and a second transrectal mpMRI-targeted biopsy if no prostate cancer is found[154]. Similar findings in an Italian[155], Canadian[156] and US[157] healthcare setting studies highlighted that an mpMRI-based pathway can be cost-effective in a range of settings, although one of the main assumptions in these models is that a negative mpMRI is used as a triage test to avoid biopsy [155–157]. This strategy is not widely embraced owing to the proability of missing clinically significant prostate cancer in men with negative mpMRI who did not receive a biopsy. (Table 3).

[H1] Limitations in the use of mpMRI

Despite the benefits to the prostate cancer diagnostic pathway, distinct challenges remain. Interpretation remains a problem, despite

improvements in interobserver variability as a result of formal scoring systems, such as PI-RADS[158]. Entities which have similar characteristics to prostate cancer are frequently encountered. These entities can be normal anatomic structures or pathological benign conditions and include the periprostatic venus plexus, neurovascular bundles, post-biopsy haemorrhage, BPH nodules, acute or chronic prostatitis, and abscesses[26,112,159]. As not all of these entities are recognized in the PI-RADS v2 guidelines[158], the experience of radiologists becomes crucial in differentiating benign from malignant conditions. The importance of reader training in reporting prostate mpMRI has been assessed in several studies that demonstrated the presence of steep learning curve[160–163]. In all the series evaluated, a considerable improvement was observed in the diagnostic accuracy of novice readers between pretraining and post-training reports. Specifically, Rosenkrantz et al.[164] demonstrated an initial rapid improvement in accuracy seen after 40 examinations. In this study, six second-year radiology residents (with no previous experience of prostate mpMRI) reviewed 124 prostate mpMRIs. Overall, three of the six readers received feedback after each examination showing the preceding case's solution. Accuracy improved from 58.1% to 75.3% (P = 0.027) without feedback and from 58.1% to 77.4% (P = 0.046) with feedback. The effect of the feedback was not signifncantly associated with the accuracy improvement (P = 0.891) suggesting the presence of a self-guided learning mechanism. Nonetheless, the authors suggest the use of a training with feedback in order to increase reader's confidence in reporting mpMRI [164].

When evaluating the reproducibility of mpMRI, disagreement exists even amongst experienced radiologists[161,165]. In particular, in a study

evaluating the interobserver agreement among six radiologists from different institutions, the overall agreement level for PI-RADS v2 cut-off scores of ≥3 and ≥4 was 79% and 78%, respectively[161]. In the PRECISION trial, a sub-analysis focusing on mpMRI central quality control had similar results, reporting 78% agreement[46]. However, for staging purposes, for which no formal standardized reporting system has yet been provided, the level of agreement is even lower (κ coefficient = 0.36 for ECE)[166].

Currently mpMRI is used widely in academic centres but is less frequently used in non-academic centres. Evidence supporting its diagnostic performance primarily originates from academic centres and its reproducibility if used more widely is uncertain. The PROMIS trial involved non-academic centres and used only a 1.5T MRI machine in order to increase the generalizability of the findings[47]. The PRECISION trial also included some non-academic centres and allowed a range of different access routes and registration methods, increasing the generalizability of the findings to other centres[46]. A further study has been carried out in non-academic settings without the dedicated training programme used in PROMIS and a diagnostic performance similar to that seen in the PROMIS trial has been demonstrated (mpMRI sensitivity, PPV and NPV in detecting clinically significant prostate cancer were 73.2%, 41.4% and 85.4%, respectively)[167]. The results of this study are encouraging for the potential widespread use of mpMRI as the authors showed obtaining good diagnostic performance is feasible in a non academic centre[167]. Other issues include the need for increasing the capacity to deliver mpMRI, meeting the training needs of clinicians involvedand delivering an mpMRI diagnostic pathway within the varying health-care system funding models that currently exist.

An effort in overcoming these barriers to the widespread use of mpMRI is needed. Extensive training programmes for mpMRI reporting aimed at both radiologists and urologists and improved clarification of the cost-effectiveness of mpMRI are pivotal in order to increase the proportion of men who can benefit from this useful diagnostic test.

[H1] Future directions

Despite the rapid uptake of mpMRI use for diagnosis of prostate cancer, a number of outstanding issues with its use remain. First, the role of DCE in addition to other sequences is still under debate. The updated PI-RADS v2 downgraded the role of DCE to a secondary sequence within the evaluation of peripheral zone lesions; however, the panel still suggested its inclusion in a multiparametric protocol[25,158]. Issues related to the use of DCE are increased costs, the increased time required to perform the study, use of Ga, and patient discomfort. To date, many studies have demonstrated that the use of a biparametric imaging protocol (avoiding use of DCE) does not alter diagnostic accuracy and is comparable to multiparametric protocols[168–170]. Nonetheless, DCE is still proposed as a useful sequence in evaluating indeterminate lesions, cancers with small size or in challenging location and previously treated prostates. However, given the growing use of mpMRI, especially in the biopsy-naive setting, evaluating the possibility of an imaging protocol with improved efficacy is warranted. Further randomized studies might help to definitively prove the feasibility of biparametric MRI .

Second, despite the improvements in mpMRI reporting after the introduction of PI-RADS v2, the inter-reader variability remains an unsolved problem, particularly when the mpMRI is used in centres with little

experience. To overcome this issue, during the past 5 years efforts have been made to implement computer-aided diagnosis (CAD). The aim of CAD is to bypass interobserver variability through the use of machine learning algorithms based on quantitative analyses that are able to discriminate areas within the prostate gland in which are suspicious for clinically significant prostate cancer[171–176]. Results regarding the use of CAD in mpMRI of the prostate are still preliminary, but the first comparison between CAD and PI-RADS v2 showed promising results. The AUC for clinically significant prostate cancer of machine learning-based analysis of mpMRI radiomics was higher than PI-RADS v2 (0.955 versus 0.878, P<0.001 for transitional zone; 0.972 versus 0.940, P = 0.097 for peripheral zone). When radiomics was added to PI-RADS, a performance improvement in detecting clinically significant prostate cancer was observed for both peripheral zone and transitional zone of the prostate (P < 0.01)[177]. The introduction of CAD in clinical practice could lead to an improvement in the workflow of reporting and in diagnostic accuracy and also help urologists perform targeted diagnostic and therapeutic procedures.

Finally, when analysing the potential causes of overdiagnosis, serum PSA level remains the major factor related to the increased diagnosis of clinically insignificant disease[17]. PSA is affected by a low specificity and low NPV considering that one out of four patients with PSA <4.0 ng/ml can harbour clinically significant prostate cancer[178]. Most of the studies aiming to improve the accuracy of screening strategies tested the use of PSA in combination with mpMRI[179,180]. The results of these studies were promising, but relied on cohorts selected with the use of PSA; hence, selected with a low specific test that inevitably affected the prevalence of clinically significant

and insignificant prostate cancers in these populations. In order to avoid the bias that occurs in the pre-risk assessment using PSA , novel diagnostic tests aimed at reducing overdiagnosis (such as prostate mpMRI) should be used a step before the assessmrnt of PSA in the diagnostic pathway. In this context, the clinical question of whether prostate cancer screening based on the use of mpMRI alone is feasible, efficient and accurate needs addressing. One pilot study has been carried out comparing a primary screening using mpMRI with serum PSA level [181]. In a cohort of 47 patients aged between 50 and 75 years who received mpMRI irrespective of PSA level, mpMRI showed higher accuracy than PSA in predicting the presence of prostate cancer (AUC 0.81 versus 0.67)[181]. Larger prospective studies are awaited to provide evidence of the feasibility and the efficacy of an mpMRI screening strategy.

[H1] Conclusions

Over the past decade, prostate mpMRI has been an exciting development that seems likely to change the standard prostate cancer diagnostic pathway. This test is useful in a number of different patient populations and has the potential to serve as a triage test. Results of studies comparing mpMRI-targeted biopsy with systematic biopsy suggest the addition of mpMRI-targeted biopsy to systematic biopsy and strategies such as mpMRI-targeted biopsy alone are feasible. Use of biomarkers combined with mpMRI information can improve the performance of the mpMRI in identifying clinically significant cancer. Furthermore, the cost-effectiveness of an mpMRI diagnostic pathway has been demonstrated in a number of different settings. However, improvements aimed at reducing inter-reader variability and improve the standardization of mpMRI reporting are

important to support the introduction of mpMRI and optimize use of this technology.

Key points

- Multiparametric MRI (mpMRI) of the prostate is a novel promising tool for diagnosis of prostate cancer that might help in reducing overdiagnosis of insignificant prostate cancer
- mpMRI should include four sequences: T1-weighted images, T2-weighted images, diffusion weighted images (DWI) and dynamic contrast-enhanced imaging (DCEI)
- Interpretation and reporting of mpMRI must be carried out following standardized scoring systems (such as PI-RADS v2)
- The use of mpMRI is considered useful; the use of mpMRI targeted biopsy is increasing the detection of clinically significant prosate cancer in both biopsy-naive and previous negative biopsy setting
- The use of mpMRI as triage test is still controversial. In men with negative mpMRI, omitting a biopsy can only be considered when the clinical suspicion of prostate cancer is low
- Improvements in inter-reader agreement, development of computer-aided diagnostic systems and assessment of biomarkers to use in combination with mpMRI are needed

Figure 1: Multiparametric MRI of a nonmalignant prostate gland. a | The peripheral zone appears hyperintense (bright) and the glandular transitional zone appears heterogeneoulsy hypointense (dark) on T2-weighted imaging . **b |** No restricted diffusion on diffusion-weighted imaging. **c |** No restricted diffusion in the apparent diffusion coefficient map. **d |** No early enhancement on dynamic contrast enhanced imaging. Red arrows and red dashed lines indicate peripheral zone; yellow arrows and yellow dashed lines indicate transitional zone.

Figure 2: Multiparametric MRI of a cancerous prostate. A |

Multiparametric MRI (mpMRI) of an apical tumour in the right peripheral zone extending from 6 to 12 o'clock. The lesion (arrows) are hypointense (dark) on T2-weighted imaging (a) and shows restricted diffusion (bright) on diffusion-weighted imaging (b) with a corresponding hypointense (dark) signal on the apparent diffusion coefficient map (c). The lesion shows earlier enhancement than the rest of the gland on dynamic contrast-enhanced imaging (d). The lesion is scored 5 out of 5 both on PI-RADS v2 and on a Likert scale and some bulging of the capsule is evident, suggestive of early T3a disease. Targeted biopsy revealed Gleason 4+3 disease. **B |** mpMRI of a lesion in the left peripheral zone at the prostatic base. The lesion (arrows) is hypointense (dark) on T2-weighted imaging (a) and shows restricted diffusion (bright) on diffusion-weighted imaging (b) with a corresponding hypointense (dark) signal on the apparent diffusion coefficient map (c). The lesion shows earlier enhancement than the rest of the gland on dynamic contrast-enhanced imaging (d). The lesion is scored 4 out of 5 on PI-RADS v2 and 5 out of 5 on a Likert scale. Targeted biopsy revealed Gleason 3+4 disease.

Figure 3: Multiparametric MRI of a cancerous prostate using magnetic resonance spectroscopy imaging. Multiparametric MRI of a left apical lesion. This lesion scored PI-RADS 4 using a T2-weighted imaging sequence (a), a diffusion-weighted sequence (b) and an apparent diffusion coefficient map (c); red arrows indicate the lesion. Using a magnetic resonance spectroscopy imaging (MRSI) sequence, normal prostatic tissue shows low levels of choline and high levels of citrate (d). Conversely, in a suspicious

area, choline levels are high and citrate levels are low (e). Prostate biopsy showed adenocarcinoma with Gleason score 4+4 in the left apex.

Figure 4: The anatomy of the prostate and T2-weighted mpMRI imaging. The anatomy of the prostate in the prone position (a) and the upright position (b). The appearance of the prostate using T2-weighted imaging on the axial (c), frontal (d) and sagittal (e) view. On the obtained images the red dotted line indicates the peripheral zone; the yellow dotted line indicates the transition zone; the green dotted line indicates the central zone; and the blue dotted line indicates the anterior fibrouscolar zone.

Figure 5: Transrectal versus transperineal approach to biopsy.

Each mpMRI-targeted biopsy technique can be performed using either a transrectal or transperineal approach, but mpMRI-targeted biopsy is currently most commonly performed using the transrectal approach. Factors influencing choice of a specific approach include likelihood of infection, diagnostic accuracy and feasibility. A non-negligible risk of sepsis exists using the transrectal appriach and prophylactic fluoroquinolones are currently recommended, but rates of resistance to fluoroquinolones are rising in rectal flora and increasing evidence shows that their use has a detrimental effect However, rates of hospitalization related to sepsis from a transperineal approach are extremely low. Both the transrectal and transperineal approach have acceptable accuracy for mpMRI-targeted biopsy.

Figure 6: **Traditional and mpMRI-influenced prostate cancer diagnostic pathway.** The use of multiparametric MRI (mpMRI) as a triage test enables all men with negative mpMRI to be spared from receiving a biopsy, opting

for a surveillance strategy mainly based on the use of PSA and follow-up mpMRIs. Within the traditional diagnostic pathway, without the use of mpMRI, all men with a clinical suspicion of prostate cancer will undergo a TRUS-guided prostate biopsy (TRUS-Bx).

Figure 7 Comparison between T2-weighted images of a prostate with and without the use of endorectal coil. An endorectal coil as an adjunct to multiparametric MRI (mpMRI).mpMRI of normal nonmalignant prostate gland (T2-weighted sequence) performed with (a) and without (b) the use of endorectal coil. The use of the endorectal coil enables improved resolution of images and improved identification of anatomical structures. Nonetheless, the use of endorectal coil is still controversial.

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Table 1: The role of mpMRI in detecting prostate cancer in different settings

Setting	Year	Test	Study design (n)	Comparator	Key findings	Ref
Biopsy naive	2018	MRI-TBx alone and no biopsy in men with negative mpMRI	Matched cohort RCT (500)	12-core TRUS-Bx	MRI-TBx detected more csPCa than 12-core TRUS-Bx (38% versus 26%, P = 0.005) In the MRI arm, 28% of patients avoided biopsy owing to negative mpMRI.	46
Biopsy naive	2017	MRI-TBx alone and TRUS-	Matched cohort RCT (212)	12-core TRUS-Bx	Detection of csPCa was higher in MRI arm (test arm) than in standard biopsy arm (43.9% versus 18.1%, P<0.001)	61

		Bx in men with negative mpMRI			In 3.8% of men with negative MRI, TRUS-Bx detected csPCa	
Biopsy naive	2015	MRI-TBx + TRUS-Bx	Matched cohort RCT (1,140)	12-core TRUS-Bx	Detection of csPCa was higher in MRI-TBx + TRUS-Bx arm than the 12-core TRUS-Bx arm (73% versus 38%)	62
Biopsy naive	2016	10-core or 12-core TRUS-Bx + MRI-TBx	Matched cohort RCT (130)	12-core TRUS-Bx	Overall, detection of PCa and csPCa was significantly different between the two arms (64% versus 57%, P = 0.5 and 55% versus 45%, P = 0.8, respectively)	63
Biopsy naive	2015	2-core MRI-TBx + TRUS-Bx	Matched cohort RCT (175)	12-core TRUS-Bx	Overall, PCa and csPCa detection rate did not significantly differ between arms (59% versus 54%, P = 0.4 and 44% versus 49%, P = 0.5, respectively) 2-core MRI-TBx and 12-core TRUS-Bx detection rates of csPCa were similar, suggesting the increased efficiency of the former in terms of number of cores	64
Biopsy naive	2018	2-core MRI-TBx + 10-core TRUS-Bx in patients with positive biMRI	Paired cohort Prospective (1,020)	10-core TRUS-Bx in all men	Restricting combined biopsies to men with positive biMRI could avoid 30% of biopsies increasing csPCa detection by 11% and decreasing detection of clinically insignificant PCa by 40% compared with TRUS-Bx alone NPV of BiMRI for csPCa was 97%	35
Biopsy naive	2015	MRI-TBx	Paired cohort Retrospective (452)	12-core TRUS-Bx	MRI-TBx detected significantly higher proportion of csPCa than TRUS-Bx (88.6% versus 77.3%, P = 0.037) 83% of cancers missed by MRI-TBx were Gleason score 6	67
Biopsy naive	2011	2-core MRI-TBx	Paired cohort Retrospective (555)	10/12-core TRUS-Bx	Detection rate of csPCa was higher for MRI-TBx than TRUS-Bx (88% versus 72%)	68
Biopsy naive	2015	MRI-TBx	Paired cohort Prospectiv	12-core TRUS-Bx	Detection of csPCa was higher for MRI-TBx than TRUS-Bx (66% versus 56%)	69

			e (152)		MRI-TBX detected less insignificant cancers than TRUS-Bx (16% vs 30%)	
Biopsy naive	2017	MRI-TBx	Paired cohort Prospective (807)	24-core Transperineal-Bx	In patients in whom mpMRI resulted in a score of PI-RADS ≥3, MRI-TBx had lower csPCa detection than 24-core Transperineal-Bx (49 versus 52%) 20% of patients with PI-RADS score 1 or 2 had csPCa	70
Biopsy naive	2019	MRI-TBx	Paired cohort Prospective (275)	12-core TRUS-Bx	No difference was observed between MRI-TBx and TRUS-Bx in the detection of csPCa (32.3% versus 29.9%, P = 0.38) The combination of the two techniques reached the highest csPCa detection (37%)	65
Biopsy naive	2019	MRI pathway (MRI-TBx alone in men with positive mpMRI and no biopsy for men with negative mpMRI)	Paired cohort Prospective (626)	TRUS-Bx pathway (12-core TRUS-Bx for all patients)	MRI pathway resulted in a similar detection of csPCa to TRUS-Bx pathway (25.4% versus 23.3%, P = 0.17) and a significant reduction in detection of insignificant PCa (14.1% versus 24.8%, p<0.0001) MRI pathway would have avoided half of men from receiving prostate biopsy at the cost of missing csPCa in 4% of these patients	66
Previous negative biopsy	2015	MRI-TBx	Paired cohort Prospective (108)	24-core Transperineal-Bx	Use of MRI-TBx did result in any csPCa detected by 24-core transperineal-Bx being missed	79
Previous negative biopsy	2017	MRI-TBx	Paired cohort Prospective (206)	10-core TRUS-Bx	Detection of PCa was similar using MRI-TBx than10-core TRUS-Bx (34% versus 39%, p=0.155) MRI-TBx detected a more clinically significant disease than10-core TRUS-Bx (26% versus 17%, p<0.001)	80
Previous negat	2015	In-bore TBx	Matched cohort RCT	Fusion MRI-TBx +	Detection of csPCa was similar in the test and comparator arm (29 versus 32%, P = 0.7)	81

ive biopsy			(267)	TRUS-Bx	Within the comparator arm, fusion MRI-TBx detected a similar number of csPCa compared to TRUS-Bx (26% versus 25%)	

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RCT: randomized controlled trial; PCa: prostate cancer; csPCa clinically significant prostate cancer; mpMRI: multiparametric MRI; MRI-TBx: mpMRI targeted biopsy; TRUS-Bx: transrectal ultrasound-guided biopsy; PI-RADS: Prostate Imaging Reporting and Data System

Table 2: mpMRI in combination with prostate cancer biomarkers

Biomarker	Study design (n)	Year	Best informative cut-off value (ng/ml/ml)	Statistical analysis	Outcome	Key findings	Ref
PSAd	Retrospective Biopsy naive (288)	2017	0.15	MVA, risk categories	Presence of PCa and csPCa	PSAd was an independent predictor of presence of csPCa Highest NPV: PI-RADS 3 and PSAd <0.15 Highest PPV: PI-RADS ≥4 and PSAd≥0.15 or PI-RADS=3 and PSAd≥0.30	142
PSAd	Prospective Biopsy naive and previous negative biopsy (1,040)	2017	0.15	MVA, nomogram, risk categories	Presence of csPCa	Combination of PI-RADS and PSAd achieved the highest AUC of 0.79 PI-RADS <3 and PSAd <0.15 achieved a NPV of 0.98	143

PSAd	Retrospective Repeat biopsy (514)	2017	0.20	Risk categories	Presence of csPCa	PSAd ≤0.2 was associated with low detection of csPCa In men with negative mpMRI and PSAd ≤0.20, NPV was 0.91 In men with a Likert score of 4 or5 and PSAd>0.2, PPV was 0.66	144
PSAd	Retrospective Previous negative biopsy with indeterminate lesions at mpMRI (76)	2017	0.17	ROC curve AUC	Presence of csPCa	Use of a PSAd threshold of 0.17 had a sensitivity, specificity and NPV of 0.67, 0.75 and 0.85, respectively	49
PCA3	Prospective Previous negative biopsy (171)	2013	44	MVA, AUC	Presence of PCa	PCA3 cut-off value of 44 had an accuracy of 0.67 in identifying prostate cancer Combination of mpMRI and PCA3 with the same cut-off value reached the highest accuracy (0.81) in identifying prostate cancer	146

PHI	Prospective Repeat biopsy (279)	2016	35	ROC curve AUC, risk categories	Presence of PCa and csPCa	Adding PHI to mpMRI increased the AUC from 0.64 to 0.75 for predicting csPCA compared with mpMRI plus PSA In men with negative mpMRI, a PHI threshold of 35 missed only 1 of 21 csPCa, potentially sparing 42% of biopsies	151
PHI and PHI density	Prospective Biopsy naive (104)	2018	44	MVA, AUC	Presence of csPCa	PHI density was complementary to PI-RADS in predicting csPCA Addition of PHI density to PI-RADS increased AUC from 0.83 to 0.90	152

MVA: multivariable analysis; AUC: area under the curve; ROC: receiver operating characteristics curve; PCa: prostate cancer; csPCa clinically significant prostate cancer; PSAd: PSA density; PHI: prostate health index; mp MRI: multiparametric MRI; PI-RADS: Prostate Imaging Reporting and Data System

Table 3: The cost-effectiveness of mpMRI

Population investigated	Year	n	Statistical analysis	Outcome	Key findings	Ref
Men with PSA >4 ng/ml	2014	NR	Markov model	QALYs and ICER	MpMRI strategy is initially more expensive than TRUS-guided biopsy strategy. Extra costs are compensated for by reducing treatment costs resulting from fewer false positives	153
Men with clinical suspicion of PCa (from PROMIS study[45] population)	2017	576	Markov model (383 possible strategies were assessed)	QALYs and ICER	The most cost-effective strategy was mpMRI as the first test followed by a transrectal MRI-TBx in men in whom the mpMRI suggests a suspicion of PCa, and a second transrectal MRI-TBx if no PCa is found	154
Men with negative DRE, a previous negative prostate	2018	800	Simulation of scenario in which mpMRI is used as	Cost-effectiveness of mpMRI when used as triage test	The use of mpMRI as triage test would have avoided 45% of	155

biopsy and persistent suspicion of PCa			triage test	measured using Italian NHS costs	biopsies and 44% of the total cost while missing 7.3% of csPCa	
Men with PSA >4 ng/ml	2018	NR	Markov model (5 screening strategies tested)	QALYs and ICER	The most efficient strategy was the use of mpMRI, followed by combined biopsy (MRI-targeted biopsy plus TRUS-Bx) if mpMRI was positive and no biopsy if mpMRI was negative, using a PI-RADS threshold of 3.	157
Men with a clinical suspicion of PCa	2016	NR	Markov model (2 strategies compared)	QALYs and ICER	mpMRI used as triage test was a cost-effective strategy at 5, 10, 15 and 20 years after first referral for suspicion of PCa	156

QALYs: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; PCa: prostate cancer; csPCa clinically significant prostate cancer; NHS: national health service; PI-RADS: Prostate Imaging Reporting and Data System; mpMRI: multiparametric MRI