MRI in prostate cancer diagnosis, surgical or radiation treatment, focal therapy, active surveillance and follow-up

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SUMMARY

Serum prostate-specific antigen, digital rectal examination and transrectal ultrasound, supplemented with biopsy, are conventionally used for the screening, diagnosis, staging and surveillance of prostate cancer (PCa). However, their sensitivity and specificity are limited with diagnosis of clinically insignificant cancer and a potential risk of overtreatment as a result. Multiparametric MRI combines anatomical and functional pulse sequences, including diffusion-weighted imaging and dynamic contrast-enhanced MRI, and has evolved out of its limited role in PCa staging. The ability to visualise the prostate accurately and to detect or exclude clinically significant PCa makes multiparametric MRI a great tool to improve the diagnosis, staging, treatment planning and follow-up of patients with PCa. Multiparametric MRI can rule out clinically significant PCa and therefore has the potential to reduce the need for biopsies or to determine whether active surveillance or immediate treatment is appropriate.

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INTRODUCTION

Prostate cancer (PCa) remains the most commonly diagnosed cancer and the third leading cause of cancer death among men in the Western world. However, the vast majority of men diagnosed with PCa will die from other causes.[1] Therefore, the differentiation between life-threatening versus indolent PCa is important. Historically, digital rectal examination (DRE), serum prostate-specific antigen (PSA) screening, transrectal ultrasound (TRUS) and TRUS-guided biopsy are used for screening, diagnosis and surveillance despite their limited sensitivity and specificity. Multiparametric MRI (mpMRI) combines anatomical and functional pulse sequences, including diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) and has evolved out of its limited role in PCa staging. This review discusses the role of mpMRI in screening and detection of clinically significant disease, biopsy guidance, active surveillance, surgery planning, radiotherapy or focal therapy and follow-up after therapy. Furthermore, it briefly discusses the technique of mpMRI acquisition and the uniform reporting using the Prostate Imaging Reporting and Data System (PI-RADS).

MULTIPARAMETRIC-MRI

PATIENT PREPARATION AND TIMING

To avoid image artefacts, patients should empty the rectum

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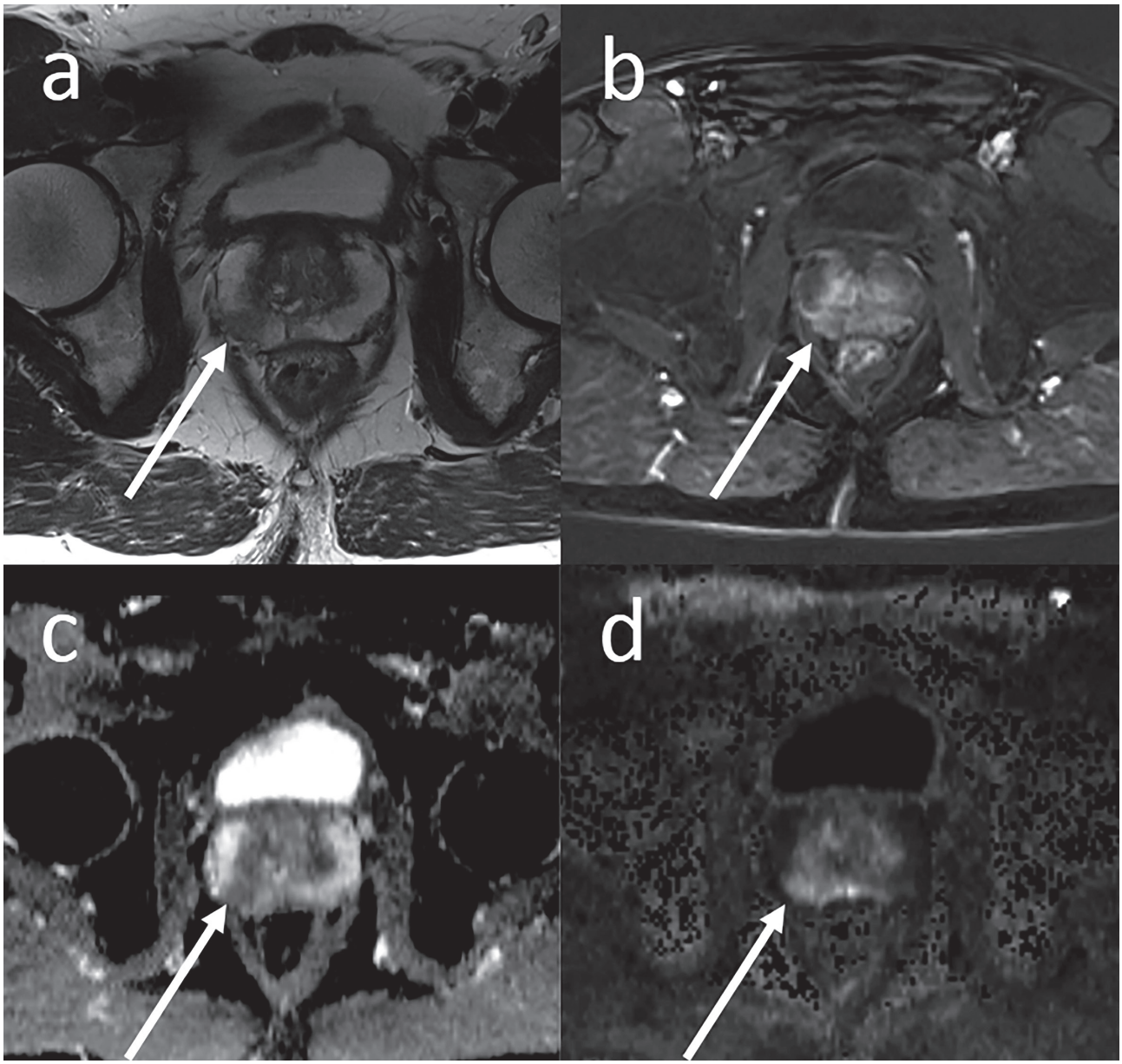

FIGURE 1. Multiparametric MRI of a focal prostate carcinoma in the right peripheral zone of the mid prostate.
a: Axial T2-weighted MR image with a right sided 1.5 cm hypointense lesion (white arrow).
b: Axial dynamic contrast-enhanced MR image shows higher contrast uptake in this lesion than in surrounding normal tissue (white arrow).
c and d: Axial diffusion weighted MR image shows an area of lower apparent diffusion coefficient (c, white arrow) with a corresponding high signal on high b-value image (d, white arrow).

and bladder just before the MRI examination. Depending on institutional preference, an antispasmodic agent can be used to reduce motion artefacts. As post-biopsy changes such as haemorrhage and inflammation can affect the interpretation of mpMRI in staging, MRI is best performed before biopsy. If not, an interval of at least six weeks between biopsy and MRI is recommended.[2] For diagnosis, however, such a delay is not necessary.

MRI EQUIPMENT

A 3.0 tesla (T) MRI is considered the most optimal platform for high spatial and temporal resolution imaging of the prostate, although state-of-the-art multichannel 1.5 T machines with optimised gradients can produce comparable image quality. On older 1.5 T machines, the use of an endorectal coil (ERC), preferable in combination with a multichannel pelvic phased-array coil, is recommended for optimal im-

TABLE 1. Prostate Imaging Reporting and Data System (PIRADS) v2 overall assessment score.

Prostate imaging reporting and data system (PI-RADS)	
PI-RADS 1	clinically significant cancer is highly unlikely to be present
PI-RADS 2	clinically significant cancer is unlikely to be present
PI-RADS 3	the presence of clinically significant cancer is equivocal
PI-RADS 4	clinically significant cancer is likely to be present
PI-RADS 5	clinically significant cancer is highly likely to be present

age resolution. When an ERC is used, a saline laxative enema three hours before the examination is advised to facilitate coil placement and reduce artefacts. Because of cost, time and patient discomfort, the routine use of ERC is not established.

SEQUENCES OF MULTIPARAMETRIC MRI

MpMRI is composed of high-resolution T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) and DCE-MRI (*Figure 1*).

T2-WEIGHTED IMAGING

T2WI provides the best depiction of the prostatic zonal anatomy and capsule. T2WI is used for PCa detection, localisation and staging. PCa typically presents as a low-signal-intensity focus in an inherently high-signal-intensity peripheral zone. Transitional zone PCa is characterised by a homogeneous, hypointense signal with indistinct margins. T2WI is sensitive but not specific for PCa detection, and various 'benign' conditions such as benign prostatic hyperplasia (BPH), prostatitis, haemorrhage, atrophy and post-treatment changes can mimic cancer on T2WI.[2,3] Therefore, findings should be correlated with other functional techniques such as DWI and DCE-MRI.

DWI

DWI assesses the random mobility of protons in an aqueous environment. Restriction of such mobility is typical for PCa and is displayed as high signal-intensity on high b-value images and low signal-intensity on apparent diffusion coefficient (ADC) maps.[2] Several studies reported that the ADC inversely correlates with Gleason score, therefore ADC is useful in the assessment of aggressiveness and hence in the identification of clinically significant PCa.[2,4]

DCE-MRI

DCE-MRI assesses the tissue enhancement. However, the kinetics of PCa enhancement are heterogeneous, and at present, the added value of DCE is not firmly established. Most data show rather modest added value over and above the combination of T2W and DWI.[2-4]

PROSTATE IMAGING REPORTING AND DATA SYSTEM

In 2012, PI-RADS was introduced by the European Society of Urogenital Radiology (ESUR) to improve the quality and consistency of the mpMRI procedure and reporting. A revised version, PI-RADS v2, was published in 2015.[2] It consists of a detailed scoring system for imaging findings on T2WI, DWI and DCE-MRI, which are subsequently integrated into a five-point overall assessment score that indicates the likelihood of clinically significant disease in both the peripheral and transition zones (PI-RADS 1= highly unlikely, PI-RADS 5= highly likely; *Table 1*). Clinically significant prostate cancers (csPCa) were defined as a Gleason score ≥7 (including 3 + 4 with prominent but not predominant Gleason 4 component) and/or volume ≥0.5 cc and/or extra-prostatic extension. Prostate biopsy is advised for PI-RADS' assessment categories 4 and 5, while for PI-RADS' assessment category 3, biopsy may or may not be appropriate depending on other clinical variables. DWI is considered as the 'dominant' sequence in the peripheral zone, as is T2WI in the transition zone. Certain benign and malignant conditions may display similar characteristics on DWI and T2WI, so mpMRI diagnosis requires expertise and experience on the reader's part. DCE plays a minor role in PI-RADS v2, as it can only upgrade an equivocal finding (score 3) on DWI in the peripheral zone into a score 4. Each report should include a total prostate volume calculation and an adequate lesion measurement and localisation on a sector map. Vargas *et al.* showed that these integrated PI-RADS scores resulted in correct classification of approximately 95% of the tumours with a pathological volume >0.5 ml, with less good results for tumours with volume ≤0.5 ml.[5]

ROLE IN SCREENING AND DIAGNOSIS OF CLINICALLY SIGNIFICANT DISEASE

PCa screening using serum PSA testing continues to be controversial. It can reduce morbidity and mortality from PCa, but it also increases the risk of overdiagnosis and overtreatment with resultant morbidity. In current practice, nomograms that combine demographic details, DRE findings and

PSA results are used to identify patients at an increased risk of csPCa. Using PI-RADS criteria, mpMRI has been shown to be a very useful tool in such patient risk stratification.[6,7] In patients with elevated PSA and previous negative prostate biopsy, a new biopsy can be performed with the needle targeted to one or more lesions on a positive mpMRI, while a negative mpMRI can effectively obviate a new biopsy on the basis of its high negative predictive value (NPV).[7,8] In a recent meta-analysis, the median mpMRI NPV was 82.4% for exclusion of prostate cancer (both significant and insignificant) and 88.1% for csPCa.[6] The use of mpMRI as a triage test as compared with TRUS-biopsy in biopsy-naive men with elevated PSA was recently studied in two large trials. In the pivotal PROMIS trial was shown that mpMRI as a triage test was more sensitive for csPCa (93% *vs* 48%) and might allow 27% of patients to avoid a primary biopsy.[9] Also, 5% fewer clinically insignificant cancers were detected. These findings were endorsed by the recent PRECISION trial in which biopsy was avoided in 28% of patients, and also more csPCa and less insignificant disease was detected.[10]

ROLE IN STAGING

Currently, mpMRI is the best imaging technique available to determine whether the tumour is organ-confined or shows extra-glandular invasion. In the most recent European Association of Urology (EAU) guidelines, mpMRI is included as a local staging technique in high-risk disease, intermediate-risk disease with predominantly Gleason pattern 4 and in low-risk disease if mpMRI is considered necessary for treatment planning.[11] Also, the use of whole-body-MRI is recognised as an alternative technique to detect possible metastases in intermediate- and high-risk patients. In a recent meta-analysis, however, MRI showed a good specificity but a poor and heterogeneous sensitivity in the detection of extra-capsular extension (ECE), seminal vesicle invasion and overall stage T3.[12] Higher field strengths and the use of additional functional techniques seem to increase the accuracy of local staging. To further optimise the use of mpMRI in the staging of PCa, refinement is needed for both clinicopathologic and imaging criteria of ECE (especially focal ECE); an international language should preferably be used for reporting (similar to PI-RADS for PCa detection), and techniques should be standardised using high field strengths and additional functional imaging.

ROLE IN MRI-GUIDED PROSTATE BIOPSY

In conventional systematic TRUS biopsy, approximately 20% of csPCa are missed, especially the anterior tumors.[13] Furthermore, TRUS biopsy has shown to underestimate the final Gleason grade and is associated with the detection of microfocal cancer lesions that may not be clinically significant. Several prostate targeted biopsy methods using mpMRI have been introduced to overcome these limitations. There are three categories: (1) visual estimation MRI targeted TRUS biopsy ('cognitive fusion'); (2) MRI/TRUS fusion guided biopsy using dedicated rigid or elastic fusion software; and (3) in-bore MRI guided biopsy. Currently, there is no consensus on which type of MRI-targeted biopsy is superior in cancer detection or other areas. A large randomised, controlled trial comparing the three techniques is currently ongoing. So far, in general, MRI-targeted biopsy has shown to significantly improve risk stratification by reducing sampling error, and evidence is accumulating in recommending mpMRI as a tool of directing either initial or repeat biopsies following a previous negative TRUS-guided biopsy.[14]

ROLE IN ACTIVE SURVEILLANCE

Active surveillance (AS) has grown in popularity as a way to manage patients with low risk PCa without the morbidity of definitive treatment and the risk of overtreatment of indolent disease. This approach is supported by good long term cancer control in multiple studies.[15]

PATIENT SELECTION

MpMRI has the potential to accurately identify patients who are candidates for AS. With its high NPV, a negative mpMRI can rule out csPCa and hence corroborate the biopsy finding of a low risk cancer. A mpMRI result concordant with the initial biopsy (PI-RADS 1-2) has a low reclassification rate, while a result discordant with the initial biopsy (PI-RADS ≥3) is typically seen as a trigger for repeat (targeted) biopsy.[16-18] Furthermore, mpMRI demonstrates good specificity for evaluation of extra-prostatic extension.

MONITORING AS

Approximately one-third of AS patients progress to active treatment within a median follow-up of 2.5 years.[16-18] There are data suggesting that disease stability on MRI can predict Gleason score stability.[19] Other early data suggest a potential role for non-invasive monitoring of patients with serial mpMRI at set intervals and prostate biopsies only performed if changes occur on mpMRI. With this strategy, the number of repeat biopsies could decrease to 68%.[17,18] The incorporation of mpMRI in AS remains, however, a new concept and robust data on the use of repeat MRI in AS are lacking. The appearance of new lesions or an increase in TNM staging on mpMRI is clear evidence of progression. However, significant change in an existing lesion may be harder to define and MRI-occult lesions are impossible to compare. Therefore, the European School of Oncology con-

KEY MESSAGES FOR CLINICAL PRACTICE

1. Multiparametric MRI can be used to detect or exclude clinically significant cancer.
2. Multiparametric MRI may be used as a triage test to avoid or to support biopsy.
3. Multiparametric MRI is not only useful in the diagnosis of prostate cancer but also for active surveillance, staging and recurrence detection.
4. PI-RADS v2 provides a detailed scoring system that indicates the likelihood of clinically significant disease.

vened the Prostate Cancer Radiological Estimation of Change in Sequential Evaluation (PRECISE) panel to develop recommendations for MRI in men on AS for PCa.[20]

ROLE IN PLANNING OF RADICAL PROSTATECTOMY, RADIOTHERAPY AND FOCAL THERAPY

In radical prostatectomy (RP), the neurovascular bundle-sparing technique aims to preserve sexual potency and urinary continence. Additional mpMRI combined with clinical variables increased prediction accuracy for recurrence after RP, and mpMRI has shown to improve decision-making to preserve the neurovascular bundle.[21,22] However, as previously discussed, the NPV for excluding ECE was not sufficiently high in other studies.[23] Also, the sensitivity for detecting lymph node invasion is low.[21-23] In radiotherapy (RT), the use of mpMRI allows for more accurate risk-grouping, more appropriate selection of radiotherapeutical approach and a more patient-specific dose plan.[24] More accurate contouring with mpMRI can help to avoid under- or overestimation of the RT target volume. Focal therapy is the targeted destruction of an index cancer lesion (the most aggressive or largest cancer focus) while preserving the surrounding, normal and healthy parenchyma. Despite the prevalence of multifocality, the index lesion appears to be responsible for the natural history of that cancer.[25] The role of focal therapy in the management of PCa is, however, still uncertain.[26] Focal therapy success relies upon accurate tumour detection, localisation, tumour boundary definition and delineation and effective ablation targeting with adequate margin control. In various studies in different clinical settings, mpMRI has proven to be able to provide useful information on these requirements.

ROLE IN RECURRENCE DETECTION

After earlier definite therapy, the diagnosis of PCa recurrence is defined as two consecutive values of serum PSA >0.2 ng/mL after RP and >2 ng/mL above the nadir value after RT. A rapidly rising PSA and short PSA doubling time (PSAdt) indicate metastatic recurrence, whereas a moderately rising PSA and long PSAdt suggest local relapse.[27] After RP, recurrent disease is most frequent at the vesicourethral anastomosis, whereas after RT, recurrent disease is most often seen at the site of the prior tumour. MpMRI has proven to be very useful in the differentiation between residual glandular healthy tissue, scar/fibrotic tissue, granulation tissue and local tumour recurrence.[28] DCE-MRI can be considered as the most reliable MRI technique for the detection of local PCa recurrence after RP.[28,29] However, it must be taken into account that vascularity and contrast enhancement can be reduced in patients who have received androgen deprivation therapy, and in some cases T2WI and DWI could be sufficient.[28] Finally, ^{68}Gallium-prostate-specific membrane antigen positron-emission tomography (^{68}Ga-PSMA PET), in combination with CT/MRI, has shown promising results regarding its ability to detect recurrent or metastatic PCa.[30] However, the impact of ^{68}Ga-PSMA PET on the management of patients with prostate cancer needs further research.

CONCLUSION

The ability to visualise the prostate accurately and to detect or exclude csPCa makes mpMRI a great tool to improve the diagnosis, staging, treatment planning and follow-up of patients with PCa. MpMRI can rule out csPCa and therefore has the potential to reduce the need for serial biopsies and to determine whether AS or immediate treatment is most appropriate.

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