Multiparametric magnetic resonance imaging: Current role in prostate cancer management

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Abstract: Digital rectal examination, serum prostate-specific antigen screening and transrectal ultrasound-guided biopsy are conventionally used as screening, diagnostic and surveillance tools for prostate cancer. However, they have limited sensitivity and specificity. In recent years, the role of multiparametric magnetic resonance imaging has steadily grown, and is now part of the standard clinical management in many institutions. In multiparametric magnetic resonance imaging, the morphological assessment of T2-weighted imaging is correlated with diffusion-weighted imaging, dynamic contrast-enhanced imaging perfusion and/or magnetic resonance spectroscopic imaging. Multiparametric magnetic resonance imaging is currently regarded as the most sensitive and specific imaging technique for the evaluation of prostate cancer, including detection, staging, localization and aggressiveness evaluation. This article presents an overview of multiparametric magnetic resonance imaging, and discusses the current role of multiparametric magnetic resonance imaging in the different fields of prostate cancer management.

Key words: active surveillance, MR-guided biopsy, multiparametric MRI, prostate cancer, prostate cancer detection, radical prostatectomy.

Introduction

Prostate cancer is the second most common cause of cancer-related deaths for men in the USA, with more than twice as many new cases in 2014 compared with its nearest contender, lung cancer.1 The incidence of prostate cancer in Japan has also increased after implementation of Western diet and lifestyle elements.2 Early detection and accurate characterization of prostate cancer helps to reduce mortality rates. Prostate mp-MRI, combining the morphological assessment of T2WI with DWI, DCE-MRI perfusion and/or MRSI, has been shown to be valuable in the detection, localization and characterization of prostatic tumor.3,4 A recent meta-analysis of seven studies (526 patients) by de Rooji et al. showed a high overall sensitivity (74%, 95% CI 0.66–0.81) and specificity (88%, 95% CI 0.82–0.92) of mp-MRI for prostate cancer detection.5 Although the routine use of mp-MRI has not been established, recently published guidelines from the European Association of Urology,6 the American Urological Association7 and the National Comprehensive Cancer Network mention the potential role of mp-MRI in several aspects of prostate cancer management, including prostate biopsy, AS and recurrent prostate cancer detection.8 This review aimed to present an overview of mp-MRI and discuss the current role of mp-MRI in the different fields of prostate cancer management.

mp-MRI acquisition

Patient preparation

To avoid any artifactual distortion from stools, bowel gas and the bladder, the patients should empty the rectum and bladder just before the MRI examination. The antispasmodic agent (e.g. scopolamine butylbromide or glucagon) is beneficial to reduce motion artifacts from bowel peristalsis.9 However, because of the cost and potential drug reactions, the use of an
antispasmodic agent is subject to institutional preference, and there is still no consensus for its routine use.\(^\text{10}\)

**MR equipment**

A magnetic field of 1.5 T is adequate for scanning the prostate, although optimized images at 3 T are superior.\(^\text{10,11}\) The biggest benefit of 3 T is an increased signal-to-noise ratio, which leads to better image quality. The use of ERCs can improve image resolution on a standard 1.5-T scanner; however, similar image quality can be achieved with multichannel pelvic phased-array coils. On 3 T, ERCs might not provide the same advantages as on 1.5 T.\(^\text{10–12}\) The benefit of ERCs for routine use is not necessarily superior in terms of the cost, patient discomfort and extra time for examination.

**Timing of post-prostate biopsy MRI**

There is no consensus over the time-period for post-biopsy changes, such as hemorrhage and inflammation. These changes can be seen in some patients for several months with diagnostic difficulty and artifact on MRI.\(^\text{10,13}\) The degree of post-biopsy hemorrhage is lower in cancerous lesions than in non-cancerous lesions, therefore the detection capability is not likely to be substantially compromised by post-biopsy hemorrhage, and there might be no need to delay MRI after prostate biopsy, if the primary purpose of the examination is staging of the prostate cancer.\(^\text{12,14}\) However, post-biopsy changes could affect the interpretation of prostate MRI for staging in some instances. According to the guideline published by the committee of the ACR and the ESUR in 2015, an interval of at least 6 weeks or longer between biopsy and MRI should be considered for staging.\(^\text{10}\)

**Sequences of mp-MRI**

Mp-MRI is composed of high-resolution T2WI, DWI and DCE-MRI with optional MRSI.

**T2WI**

T2WI provides the best depiction of the prostatic zonal anatomy and capsule. T2WI is used for prostate cancer detection, localization and staging. Prostate cancer is typically shown as a round or ill-defined, low-signal-intensity focus in an inherently high-signal intensity PZ.\(^\text{15,16}\) TZ cancer is often seen as a homogeneous hypointense signal mass with indistinct margins or can have a lenticular or water-drop shape.\(^\text{16,17}\) However, various conditions, such as BPH, prostatisitis, hemorrhage, atrophy and post-treatment changes can mimic cancer on T2WI. T2WI alone is sensitive, but not specific for prostate cancer detection, and should be correlated with other functional techniques, such as DWI, DCE-MRI and/or MRSI.\(^\text{16}\)

**DWI**

DWI is a powerful functional technique, as it allows ADC maps to be calculated, enabling qualitative and quantitative assessment of prostate cancer aggressiveness. Cancer shows a higher signal intensity on DWI, and a lower ADC value as compared with normal prostatic tissue.\(^\text{16,18}\) For qualitative assessment, the ACR and ESUR guideline recommended the use of a high b-value (\(\geq 1400\) s/mm\(^2\)), as it suppresses the signal of normal prostatic tissue effectively, thus the contrast between cancerous and non-cancerous lesions can be emphasized better on DWI. If the MR scanner yields an adequate SNR, the use of a very high b-value (e.g. 2000 s/mm\(^2\)) is more advantageous for cancer detection.\(^\text{19,20}\) For quantitative assessment, a considerable number of studies reported ADC values to correlate with Gleason scores.\(^\text{21–24}\) ADC values can be useful for the characterization of clinically significant cancer.

**DCE-MRI**

DCE-MRI allows the evaluation of the enhancement pattern of a tumor, which is thought to be related to tumor angiogenesis. Prostate cancer shows early and more pronounced enhancement than surrounding normal prostate tissue on DCE-MRI.\(^\text{16,21}\) In addition, DCE-MRI can also help to monitor treatment effects as well as cancer detection, because tumors are evidently associated with neoangiogenesis that induces an increase in the blood volume and transvascular permeability.\(^\text{25–28}\) Tracing the dynamic flow of the contrast agent with DCE-MRI, prostate cancer shows strong and rapid contrast enhancement. Meanwhile, DCE-MRI has a limitation that it is non-specific, because angiogenesis can also be seen in prostatitis in the PZ and in highly vascularized BPH nodules in the TZ.\(^\text{25}\)

**MRSI**

MRSI provides information about the specific metabolites within prostatic tissue. It is able to show lower levels of citrate, and higher levels of choline in prostate cancer as compared with benign tissue.\(^\text{29}\) MRSI can be used for cancer detection and monitoring therapy response, but does not give staging information owing to its poor spatial resolution.\(^\text{30–32}\) This technique is currently used mainly in a research setting, and the latest guideline published by ACR and ESUR no longer suggests its routine use.\(^\text{10}\)

**Prostate Imaging Reporting and Data System**

In 2012, the first PIRADS was introduced by the ESUR to improve the quality and consistency of the MR procedure and reporting.\(^\text{16}\) For the purpose of further improving the risk stratification in patients with suspected cancer, and improving the communication between practicing radiologists and clinicians, the PIRADS steering committee of ACR and ESUR prostate MRI working group have developed a revised version, PIRADS v2.0, which was made public in 2015.\(^\text{10,33}\) It described a detailed recommendation on integrating mp-MRI scores according to prostatic zonal anatomy, and suggested a simplified approach for the DCE-MRI interpretation scheme. It also included a pathological definition of clinically significant prostate cancer, which should be used for comparison with mp-MRI. Integration of MR scores, and summary of MRI features on T2WI, DWI and DCE-MRI in PIRADS v2.0 are shown in Tables 1 and 2. A representative case is shown in Figure 1. A recent study by Vargas et al. showed that the integrated scores suggested by PIRADS v2.0 resulted...
in correct classification of 94–95% of the tumors with a pathological volume ≥0.5 mL (any GS), but was limited for the assessment of tumors with volume ≤0.5 mL (GS ≥ 4 + 3).34

**Clinical applications of mp-MRI**

**Clinically significant cancer detection**

The efforts to reduce prostate cancer mortality by screening and early detection have come with a risk of overdiagnosis and overtreatment of clinically insignificant low-risk prostate cancer. For this reason, there is increasing emphasis on a diagnostic strategy towards detecting only “clinically significant” tumors; such tumors are often defined as those with a pathological volume ≥0.5 mL, although other definitions, including the presence of any cancer with a GS ≥ 4 + 3, have also been proposed.35,36

The conventional diagnostic pathway using PSA screening and digital rectal exam followed by a systematic TRUS-guided biopsy is related to the detection of low-risk prostate cancer, leading to overdiagnosis of clinically insignificant cancers, and a potential risk of overtreatment.37,38 In contrast, mp-MRI can detect high-grade and larger tumors accurately, which means it might perform particularly well for detection of clinically significant disease.39 Furthermore, the functional techniques might be used to differentiate between low- and intermediate- to high-grade cancer. Given that, MRI can be a useful tool for detecting clinically significant disease.4 A recent study reported that the negative predictive value of mp-MRI was 89.6% to rule out clinically significant prostate cancer over a longitudinal follow-up period of 5 years.40

**MR-guided prostate biopsy**

Conventional systematic TRUS biopsy has been reported to miss approximately 20% of clinically significant prostate cancer,41 especially the anterior tumors until they grow to a substantial size and reach within 15–20 mm from the posterior margin of the prostate, leading to a delay in treatment.42 Systematic TRUS biopsy has also historically shown to underestimate the final Gleason grade of the tumor on histology after RP, leading to inaccurate risk stratification and selection of therapeutic options. Furthermore, TRUS biopsy is associated with detection of microfocal cancer lesions (tumor volume ≤0.5 mL) that might be clinically insignificant and are unlikely to require treatment.43 To overcome the limitation of standard TRUS biopsy, several prostate targeted biopsy methods using MRI have been introduced. There are three broad categories of targeted biopsy: (i) visual estimation MRI targeted biopsy; (ii) in-bore MRI guided biopsy; and (iii) MRI/TRUS fusion guided biopsy.

**Visual estimation MRI targeted biopsy**

Visual estimation MRI targeted biopsy is where the physician carrying out the TRUS-guided biopsy reviews the MR imaging results before the procedure, and uses this knowledge to select the most appropriate area for targeted biopsy under ultrasound guidance. Visual estimation allows the adaptation of MRI targeted biopsy in clinical practice without significant
Although this method lacks real-time feedback regarding accuracy, Puech et al. showed that MRI examination before biopsy improved the clinically significant cancer detection rate compared with systematic biopsy.\textsuperscript{38}

\textbf{In-bore biopsy}

This is a targeted biopsy technique directly carried out within the MRI bore. The in-bore biopsy approach has the advantages of accurate depiction of needle placement, fewer sampled cores and lower likelihood of missed targets if they are MRI-visible.\textsuperscript{45} Multiple studies have shown that in-bore MRI-guided biopsy is a feasible diagnostic technique in patients with prior negative biopsy. Epstein et al. reported in-bore MRI-guided biopsy offered a significantly higher cancer detection rate than reported detection rates for repeat systematic biopsy.\textsuperscript{46} Pokorny et al. showed that an MRI-guided biopsy reduced the diagnosis of low-risk prostate cancer by 89.4\%, and increased the detection of intermediate-risk/high-risk prostate cancer by 17.7\% compared with systematic biopsy.\textsuperscript{47} Disadvantages of this method are longer procedure time (1–2 h) and higher costs for software/devices.

\textbf{MRI/TRUS fusion-guided biopsy}

MRI/TRUS fusion biopsy is the method that combines TRUS of the prostate with a pre-procedural MRI overlay showing the suspicious areas delineated by the operator. This method allows the operator to visualize the cancer in real-time while guiding the biopsy needle to the targeted area by TRUS. This can be carried out at the bedside similar to a conventional TRUS biopsy. According to the previous reports, MRI/TRUS fusion after an initial negative biopsy can detect a clinically significant cancer more precisely than a systematic biopsy.\textsuperscript{48,49} Meanwhile, Wysock et al. found MRI/TRUS fusion-guided biopsy as compared with visual targeting to be more often histologically informative, but did not increase the cancer detection rate.\textsuperscript{50} Potential disadvantages of this method are the indirect approach and the higher cost for the software/device, dependence on the software for accurate image fusion, and operator training.

\textbf{Management of patients with AS}

AS is a way of monitoring prostate cancer that involves the postponement of immediate therapy. Definitive treatment is only used if there is evidence that the patient is at increased risk for disease progression. AS is an accepted option for the initial management of carefully selected men with low-risk prostate cancer.\textsuperscript{51} Challenges in this field include improving patient selection, optimizing follow-up strategies and identifying appropriate triggers for definitive therapy.
Patient selection for AS

Multiple criteria have been proposed for identifying patients with a favorable prognosis who are candidates for AS, which is usually decided based on PSA, clinical stage, amount of cancer in the biopsy and GS. Although controversial, several sites have recommended a repeat prostate biopsy before committing to a plan for AS, in order to identify patients in whom the original biopsy might have missed evidence of increased risk.\textsuperscript{52} Mp-MRI could eventually be useful as a supplemental tool to optimize patient selection for AS. Previous studies have shown that clinically significant prostate cancer could be more precisely excluded before AS enrollment if a lesion is not seen on mp-MRI.\textsuperscript{53} In their study, when no cancer was identified on mp-MRI, a confirmatory biopsy was able to reclassify just 3.5\% of cases as requiring definitive therapy.\textsuperscript{53} An ongoing international study called Prostate Cancer Research International: Active Surveillance, which is the largest prospective study evaluating AS, has commenced recruiting eligible patients to have mp-MRI incorporated into the surveillance data.\textsuperscript{54} That study will provide reliable information with regard to the feasibility of mp-MRI in AS.

Monitoring AS

For monitoring AS, repeat prostate biopsy is usually recommended based on the concern that the histological grade might worsen. Siddiqui \textit{et al.} reported that mp-MRI-based nomograms could decrease the number of repeat biopsies in patients under AS by as much as 68\%.\textsuperscript{55} In addition, Diaz \textit{et al.} showed that just 2.9 MRI/US fusion biopsies were required to detect one case of Gleason progression compared with 8.74 systematic biopsies.\textsuperscript{56} That study also showed that stable findings on mp-MRI are associated with GS stability. If the mp-MRI findings are stable over a time since the prior mp-MRI and the previous biopsy showed low-risk disease, it is reasonable to postpone the biopsy. According to the study reported by Abdi \textit{et al.}, patients with a visible lesion on mp-MRI are reported to be more likely to show radiological progression than patients with no visible lesion.\textsuperscript{57} In summary, mp-MRI scans on AS can be a substitute for the biopsy procedure and help to identify low-risk lesions, which might have progressed to intermediate- to high-grade lesions. A representative case is shown in Figure 2.

Radical prostatectomy planning

Mp-MRI has a potential to provide useful information to determine whether the tumor has penetrated the capsule. The goals of radical prostatectomy include cancer control and minimization of postoperative complications, such as incontinence and erectile dysfunction.\textsuperscript{58} The neurovascular bundle-sparing technique aims to preserve patient sexual potency. However, sparing the neurovascular bundle when ECE is present increases the probability of a positive surgical margin with a need for postoperative additional therapy, and chances of local cancer recurrence.\textsuperscript{59} McClure \textit{et al.} reported that preoperative prostate MRI data changed the decision to use a nerve-sparing technique during robot-assisted RP in 27\% of patients in this series.\textsuperscript{60} In their study, for the patients whose surgical plan was

\textbf{Fig. 2} A 69-year-old patient under AS for prostate cancer. (a) T2WI shows the non-circumscribed low signal intensity area in the right PZ (arrow). (b) The lesion is shown as an indistinct hypointense area on the ADC map (arrow). Biopsy after MRI confirmed a Gleason score of 3 + 3 of the lesion in the right PZ. Follow-up MRI after 1 year showed (c) an increased size of the tumor on T2WI (arrow) and (d) a decreased signal on the ADC map (arrow). A second biopsy carried out after MRI revealed that that right PZ lesion showed a worsening of Gleason score to 3 + 4.
changed to a nerve-sparing technique, there were no positive margins on the side of the prostate cancer, so there was no need to change the treatment plan. More recently, Petralia et al. found that the use of mp-MRI-directed intraoperative frozen section analysis can reduce the rate of positive surgical margins in patients undergoing nerve-sparing robot-assisted RP. Positive surgical margins were found less frequently in the patients who underwent MRI and intraoperative frozen section analysis than in control patients (7.5% vs 18.7%).

On MRI, the presence of low signal intensity in the PZ of the prostate with irregular bulging, bowing of the prostate capsule, disruption of the low-signal-intensity periprostatic band on T2WI, direct involvement of the neurovascular bundle or obliteration of the retroprostatic angle are considered as useful findings for ECE. In addition to these visual findings, several studies have shown that ADC could also be useful for ECE prediction. Woo et al. reported the mean ADC values for patients with ECE (0.77 ± 0.11 × 10⁻³ mm²/s) were significantly lower than those without ECE (1.01 ± 0.34 × 10⁻³ mm²/s).

**Detection of local recurrence after therapy follow up post-RP**

The diagnosis of local recurrence is generally based mainly on PSA level above a threshold or on PSA kinetic values, and it is called BF. Still, BF does not always mean local recurrence in the prostatic bed, because BF can also be caused by distant metastases. Additionally, if there is a residual normal prostate tissue in the post-prostatectomy bed, a persistently elevated PSA serum level could be observed. BF after RP develops in approximately 50% of high-risk patients, and in approximately 10% of low-risk patients within 15 years from surgery.

In recent years, a large number of studies on mp-MRI for the detection of post-RP recurrence have been carried out, and many authors reported DCE-MRI as the most useful sequence for the detection of local recurrence. Wu et al., in a meta-analysis of the 14 studies carried out to assess the effectiveness of mp-MRI in detecting local recurrent prostate cancer after RP, found that DCE-MRI as compared with T2WI showed higher pooled sensitivity (85%, 95% CI 0.78–0.90) and specificity (81%, 95% CI 0.64–0.82), and when it was combined with MRSDI had an even higher pooled specificity (90%, 95% CI 0.56–1.00). In addition, several groups showed that DCE-MRI and/or DWI in combination with T2WI were useful in evaluating suspected soft tissue lesion of the prostatic bed after RP. Apart from that benefits of DCE-MRI, it should also be taken into account that vascularity and contrast enhancement of the lesion can be reduced in patients who have received hormone therapy. A representative case is shown in Figure 3.

**Follow up after RT**

In regard to RT, BF ranges from 15% for low-risk patients to 67% for high-risk patients during a 5-year follow-up period. However, serum PSA concentration does not always decrease in a consistent manner, even if the patient has been successfully treated. PSA bounce, which is characterized by a temporary post-treatment increase in PSA concentration, is common with all forms of RT. MP-MRI is considered to be additional data to help evaluate whether a suboptimal PSA response or PSA bounce reflects local failure of RT or a false positive PSA result.

After RT, the entire prostate decreases in size and signal intensity on T2WI, because RT causes glandular atrophy and

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**Fig. 3** A 65-year-old patient with a recent elevation of PSA level to 2.1 ng/mL at 5 years after RP. (a) On T2WI, a focal area with slightly high intensity is seen within the right posterolateral bladder neck (arrow). (b) Dynamic contrast-enhanced T1-weighted image shows early enhancement corresponding to the finding on T2WI (arrow). This lesion shows (c) high signal on diffusion weighted images (arrow) and (d) low signal on apparent diffusion coefficient map (arrow). These findings suggest localized recurrence of prostate cancer.
fibrosis. Prostate cancer also shows changes, which might include decreased size, reduced capsular bulging, capsular irregularity or decreased extracapsular extension. Recurrent prostatic cancer can be recognized as hypervascular early enhancing homogeneous nodule, while the normal prostatic tissue will be hypovascular and delayed enhancing.\(^7\)\(^5\) Haider et al. reported that DCE-MRI performs better than T2WI in the detection and localization of prostate cancer in the peripheral zone after external beam RT.\(^7\)\(^3\) In their study, DCE-MRI had significantly better sensitivity (72% vs 38%), specificity (85% vs 80%) and accuracy (83% vs 74%) than T2WI. Tamada et al. showed that combined T2WI, DWI and DCE-MRI provide a sensitive method to detect local recurrence after high-dose rate brachytherapy (sensitivity 77%, specificity 92%, accuracy 90%).\(^7\)\(^7\) It is suggested that DCE-MRI should be carried out at least 3 months after RT because of an increase in perfusion and blood volume due to inflammatory changes of the tissue as a result of radiotherapy seen immediately after treatment.

**Conclusion**

Mp-MRI can detect clinically significant prostatic cancer with high accuracy; therefore, risk stratification, treatment planning and follow up can be better yielded. It can also reduce the unnecessary biopsies and prevent overdiagnosis as well as overtreatment. Based on the previous studies, we believe that mp-MRI will play a more important role in a wide variety of management options for prostate cancer.

**Conflict of interest**

None declared.

**References**
