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Evaluating the Role of mpMRI in Prostate Cancer Assessment

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Abstract

Prostate cancer is the most common malignancy among American men. The role of multiparametric MRI has recently gained more importance in detection of prostate cancer, its targeted biopsy, and focal therapy guidance. In this review, uses of multi-parametric MRI in prostate cancer assessment and treatment are discussed.

Keywords

prostate cancer; MRI; biopsy; focal therapy; PIRADS

Introduction

In the United States, approximately one in seven men will be diagnosed with prostate cancer (PCa) in his lifetime. The American Cancer Society estimates that 220,800 American men will be newly diagnosed and 27,540 men will die of the disease in 2015 [1]. Traditionally, PCa is discovered by an abnormal digital rectal exam (DRE) and/or elevated serum prostate-specific antigen (PSA) followed by systematic transrectal ultrasound (TRUS)-guided biopsy, typically obtained with 12 needles distributed symmetrically in the gland. The combination of PSA screening and TRUS guided biopsy can lead to overdiagnosis and overtreatment of indolent cancers, resulting in psychological and physical damage to the patient without tangible benefit. At the same time that the current system results in overdiagnosis of indolent disease, systematic biopsies can easily miss or under-grade aggressive lesions that lie outside the standard 12-core template. These conventional approaches to detecting PCa thus, both over diagnose low-risk disease and underdiagnose high-risk disease [2].

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Recently, multiparametric magnetic resonance imaging (mpMRI) has emerged as a promising imaging tool for assessment of the prostate, allowing clinicians to localize possible cancerous lesions. This information can be utilized to guide prostate biopsies, limiting their number while producing more accurate assessments of tumor grade. This information can be used to tailor treatment for patients. Moreover, mpMRI tends to detect clinically significant cancers while not detecting small, insignificant tumors [3]. Meanwhile, a negative mpMRI provides the patient excellent assurance that they do not harbor a clinically significant PCa. Reports have shown mpMRI to have a negative predictive value of 95% for clinically significant cancer when performed before biopsy [3]. As valuable as mpMRI is, there is still room for optimization of mpMRI to further reduce false negatives for significant disease. Additionally, the standardized scoring systems for mpMRI, known as Prostate Imaging and Reporting and Data System (PI-RADS), are undergoing continuous review and revision [3–5].

Combined with image guided biopsy, pre-mpMRI of the prostate is helpful in early detection of clinically significant disease [6]. Today, mpMRI is becoming a routine diagnostic tool in prediction, assessment, and localization of PCa and disease management [4,7]. This article will discuss the present uses of mpMRI in PCa assessment and treatment.

What is mpMRI?

MRI is a highly flexible imaging modality that is capable of producing images based on ‘anatomic’ or ‘functional’ features. mpMRI consists of both anatomic and functional scans also known as sequences [8]. Specifically, mpMRI of the prostate is comprised of four key sequences: T1-weighted (W), T2W, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) MRI. T1W and T2W are generally considered ‘anatomic’ and DWI and DCE are generally considered ‘functional’. The combination of these sequences provides a more accurate diagnosis than any individual sequence [9,10].

T1W and T2W sequences make up the anatomical portion of mpMRI. T1W MRI allows postbiopsy hemorrhage to be identified. As hemorrhage can interfere with the diagnostic accuracy of mpMRI, it is generally advised that the patient wait 8–10 weeks after a biopsy to perform an MRI. This is not possible in all cases; hence, the T1W scan can be obtained to identify any sites of hemorrhage, denoted by high-signal regions; if the hemorrhage is sufficiently severe, the MRI should be delayed to allow for resolution. T2W imaging primarily demonstrates the distribution of free water and readily depicts prostate zonal anatomy; (peripheral zone (PZ) is generally brighter than the transition zone (TZ), the central zone, or the fibromuscular zone) as well as prostatic and periprostatic features including the urethra, prostatic capsule, and seminal vesicles (SV) at high resolution. The high resolution of the T2W sequence can be used to stage PCas for extraprostatic extension (EPE) or seminal vesicle invasion (SVI) [11].

DWI is the key functional sequence of mpMRI. This modality depicts restricted diffusion of water molecules within the prostate by acquiring images at different magnetic gradient strengths, or b-values. Using the Stejskal–Tanner diffusion decay model, apparent diffusion coefficient (ADC) maps are obtained from DW images on a voxel-by-voxel basis [12–14].

ADC values inversely correlate with Gleason grade in PCa (low ADC values are associated with higher-grade PCa), and DWI is most useful for distinguishing between normal parenchyma and abnormal tissues since tumor tissue has high cellular density and therefore restricted water diffusion [8]. At higher b-values, cancers with restricted water diffusion appear as high signal intensity focus while normal tissue appears hypointense. Quantitative and qualitative analysis of DWI at b-values >1000 demonstrates improved MRI sensitivity for distinguishing between low- and high-grade PCa in the PZ [15]. The disadvantage of high b-value DWI is that it suffers from low signal and high noise creating a low signal-to-noise ratio (SNR) [16–19]. An alternative to directly acquiring high b-value DWI is to calculate high b-value imaging based on an extrapolation model from images at lower b-values. The calculated high b-value image is presented as if it had been directly acquired at a high b-value, thereby retaining a high SNR [15]. DWI, using both high b-value imaging and ADC maps, increases both sensitivity and specificity in mpMRI when compared to T2W imaging alone [9] and is considered the best MR sequence to distinguish between malignant and indolent cancers of the prostate regardless of region [8].

DCE-MRI is another functional sequence of mpMRI. This sequence visualizes the inflow and outflow of contrast media in suspicious lesions by capturing early and delayed enhancement of tumors after the bolus infusion of an intravenous contrast agent. Scans are acquired before, during, and after injection of a low-molecular-weight gadolinium chelate [20] and is comprised of fast 3D T1W sequences that are sensitive to the change in T1 as a result of the arrival of the gadolinium chelate. Because tumor vessels are more leaky and tortuous than normal vessels, the contrast media, which normally does not enhance the prostate significantly, washes in with more enhancement and also washes out of tumors more quickly than normal tissue. There is no consensus on the proper way to evaluate DCE-MRI. Possible methods include qualitative, semiquantitative, and quantitative analyses. Qualitative analysis of DCE-MRI is the subjective assessment of early enhancing focal areas and/or early washout. This is generally simple to perform and is fairly consistent among readers, but requires training. Semiquantitative analysis involves tracking the time-intensity curves over a region of interest and measuring features such as the time of contrast uptake, time of peak enhancement, maximum slope of initial enhancement, percent of peak enhancement compared to normal, and area under the curve (AUC) [21]. The advantage of these measurements is that they do not require special software but they also do not yield physiologically meaningful results and are subject to variation on different scanners, variations in injection and cardiac output, and may not be comparable at different time points. The most complex but quantitative method of DCE-MRI analysis involves compartmental modeling and requires additional software. This method utilizes a two-compartment pharmacokinetic (typically the Tofts model is used) to compute rate constants of inflow and outflow of contrast. The Tofts model does not depend on signal intensity, but rather on a calculated concentration of gadolinium. This is obtained by acquiring a 'T1 map' prior to injection of contrast. Based on changes in calculated concentration, rate constants such as K^{trans} , k_{ep} , and v_e are derived by fitting the time-concentration curve [22]. An advantage of this method is that it is less dependent on injection rate and inter-vendor variations. The parameters K^{trans} , k_{ep} , and v_e in theory should be consistent across time points and different scanners. In practice, errors can be introduced in the T1 map, the arterial

input function, and in the curve fitting process. Moreover, the value of DCE-MRI, which is generally seen as modest, does not currently warrant the investment in time and resources that the quantitative approach demands.

One of the reasons that DCE-MRI is less useful than the other sequences is that increased enhancement may also be seen in benign prostatic hyperplasia and prostatitis. Therefore, DCE-MRI must always be interpreted in conjunction with the other mpMRI sequences. DCE-MRI is most useful when T2W and DWI are unclear. DCE is also the most important sequence in detecting recurrent cancer post-treatment [23]. However, it is also important to note some additional disadvantages of DCE imaging including its susceptibility to motion artifacts, its wide range of sensitivity and specificity compared to T2W and DW imaging [24], its difficulty in reproducibility, and limitations in the use of contrast media in patients with impaired renal function [25].

Another functional imaging sequence that has historically been part of mpMRI, but is no longer widely used, is proton magnetic resonance spectroscopic imaging (MRSI). This MR sequence allows readers to assess specific levels of creatine, citrate, and choline in the prostate [22,26–30]. Normal tissue demonstrates high citrate and low choline levels, whereas cancers demonstrate lower citrate and higher choline levels. Thus, the choline-to-citrate ratio has been established as a measure of the likelihood of cancer. Moreover, the higher the ratio, the more likely the cancer is of high grade. A major problem with MRSI is that it is technically challenging. In a study by the American College of Radiology Imaging Network, mpMRI with MRSI was not found superior to mpMRI without MRSI and also did not improve tumor localization [31]. Polanec et al. also found that adding MRSI to T2W, DWI, and DCE imaging did not improve the detection or grading of PCa [32]. Additionally, MRSI requires longer acquisition time, extra software expertise, and training [22]. Thus, as there is no added benefit of acquiring MRSI as it produces limited if any improvements in accuracy while adding costs and time, few centers still include this sequence in their mpMRI.

The use of the endorectal coil (ERC) during an mpMRI remains a point of controversy. The ERC provides better scan quality with excellent SNR and is helpful in staging PCa, but it involves patient discomfort and increased cost. Studies obtained at 3T with or without the ERC produce similar results. No direct randomized studies utilizing the ERC have been performed. Historically, to achieve the same results as a 3T scanner, 1.5T scanners have required an ERC. Recent improvements in MR technology at 1.5T raise the question whether ERC is necessary even at 1.5T. Thus, the ERC can be viewed as an optional tool to improve mpMRI quality. It has also been shown that tailoring the use of the coil to the individual may reduce the unnecessary use of ERC; for example, an ERC mpMRI may be used for staging purposes but not simply for following a patient on active surveillance.

PI-RADS: standardizing the performance and interpretation of prostate MRI

Although many studies of mpMRI for PCa detection and staging have been performed, results vary considerably. Some of the main reasons for this are differences in the acquisition and interpretation of mpMRI. One of the first attempts to standardize prostate imaging reporting was made by Dickinson et al. in 2011 [33]. However, overall agreement for

optimal acquisition and evaluation was not reached. Thus, the European Society for Urogenital Radiology (ESUR) established the initial version of the PI-RADS [34] in 2012, and these guidelines have now been evaluated by multiple groups. For example, Roethke et al. concluded that PI-RADS v1 was beneficial in identifying lesions for biopsy and that it outperformed the 5-point Likert scale used by many other groups [35]. Most importantly, however, is that it introduced the concept of standardization to prostate MRI.

Due to advances in technology, in 2015, the ACR and ESUR revised PI-RADS. PI-RADS v2 lays out the recommended technical parameters for obtaining mpMRI and guidelines for scoring each sequence [5]. Readers provide an overall PI-RADS score for each lesion on a 1–5 scale (extremely low to high likelihood of harboring clinically significant cancer). The overall score is derived from rules based on the findings of each individual MRI sequence (Figure 1). For instance, in the PZ, the DWI sequence is considered dominant. Therefore, the overall score usually reflects what the DWI score is. The only exception to this rule is when the DWI score is a '3' in which case the DCE-MRI sequence can increase the overall score by one point to a '4' if it is positive. In the TZ, T2W is considered the dominant sequence, meaning that overall scoring is based on the score of the T2W image. The only exception is a T2W score of '3' that can be raised to a '4' by a clearly positive DWI. Indicators of aggressiveness, such as EPE, SVI, and large lesion size (>1.5 cm), raise the PI-RADS score of any lesion to 5 (Figure 1).

However, PI-RADS scores are simply an indicator of suspicion and do not necessarily indicate tumor aggressiveness. The PI-RADS score should give an indication of the likelihood of cancer and therefore the need for biopsy but are not necessarily employed to confer tumor aggressiveness.

Though there is minimal literature evaluating PI-RADSv2 at present, a recent study suggested additional benefits to the guidelines. Schieda et al. demonstrated the PI-RADS v2 criteria improved sensitivity without reducing specificity and may improve the performance of inexperienced readers compared to experienced readers [36]. Muller et al. reported that PI-RADS v2 results in moderate interobserver agreement for detecting clinically significant disease [37] indicating the continuing need for training in prostate MRI.

Clinical uses of mpMRI

Biopsy guidance

Following abnormal PSA results, urologists usually perform a TRUS-guided systematic biopsy as standard of care. During TRUS-guided biopsy, 12 systematic cores are acquired from the prostate. Because PCa is not easily seen on TRUS, urologists primarily use ultrasound (US) to guide the needle to the medial and lateral parts of the right and left PZ at apical, mid, and base levels of the prostate. This results in 6 right-sided and 6 left-sided biopsies for a total of 12 biopsy cores. Therefore, TRUS-guided biopsies concentrate on the posterior PZ and can miss cancers in the prostate's anterior PZ, TZ, distal apex, and subcapsular regions [38–43].

The random nature of TRUS-guided biopsies results in the overdetection of small low-grade PCas that are common in men over 50. Meanwhile the posterior bias of TRUS biopsies leads to missing significant lesions located anteriorly. To address this issue, MR-image-guided biopsies were proposed. However, performing biopsies in the MR magnet is difficult and time-consuming. Importantly, converting from TRUS to MR guidance would take the biopsy from urologists and transfer the procedure to radiologists, which would have been a disruptive change in workflow for both specialties. This led to the concept of MRI-TRUS-fusion-guided biopsies. An mpMRI would be performed at one time and the information from the MRI would be superimposed or fused to a TRUS performed at another time and place. Urologists would retain the biopsy procedure but the biopsy would be informed by the mpMRI. The first step of the MRI-TRUS fusion is thus fusing the MRI image to the US image. Then the US is tracked (either with a mechanical arm or by using optical or radiofrequency tags on the US probe) so that as the TRUS probe is moved the MRI image is moved in exactly the same way, a process that has been likened to ballroom dancing. During MRI-TRUS-fusion-guided biopsies, the needle is guided directly into a lesion previously determined to be suspicious on mpMRI. This method is becoming more prevalent and is improving the detection of cancer throughout the prostate. Recent technologies using TRUS/MRI fusion can register TRUS to a patient's most recent mpMRI, allowing the operator to benefit from both the real-time TRUS for guiding the needle and the diagnostic accuracy of mpMRI without having to perform the biopsy inside the MRI gantry. These targeted fusion-guided biopsies have led to more accurate localization and characterization of PCa. For example, Siddiqui et al. compared the MRI-TRUS fusion biopsy to the standard TRUS biopsy in a cohort of 1003 men, demonstrating that MRI-TRUS resulted in a 30% increase in the detection of high-risk PCa as well as a 17% decrease in the detection of low-risk cancer [44]. Furthermore, Volkin et al. reported that fusion-guided biopsy found significantly more anteriorly located PCa than standard TRUS biopsy [43]. It is clear that MR-TRUS-fusion-guided biopsy leads to greater detection of clinically significant cancer along with less overtreatment of indolent lesions.

Although MRI-TRUS fusion biopsies are most common, there are several other methods for making use of mpMRI during a prostate biopsy [2]. One is the inbore MRI-guided prostate biopsy, during which the clinician takes biopsy samples with the patient inside the MRI gantry. Suspicious lesions are previously identified on mpMRI. Inside the MRI gantry, at least one diagnostic MRI sequence is obtained for visualization of the target lesion(s). The needle is then inserted transrectally or transperineally. Before taking biopsy samples, the clinician confirms that the needle has been inserted into the lesion by obtaining another MRI sequence. While in-bore-guided biopsy does provide precise lesion sampling, it is uncomfortable for the patient and is a lengthy and expensive procedure due to the need for MRI-compatible biopsy needles [45,46]. Furthermore, the number of patients requiring biopsy overwhelms the available expert clinicians and MRI machines, and the procedure is not popular with urologists because it must be performed in the radiology department. For these reasons, centers have not widely adopted the in-bore guided biopsy approach [47].

Another technique for guiding prostate biopsies is known as 'cognitive fusion.' During this procedure, the clinician guides the TRUS biopsy needle, estimating its location based on the MR images. Relative to MRI-TRUS fusion, it is simple, requiring nothing but the TRUS

apparatus and mpMRI images. Although this technique is inexpensive, it relies heavily on the experience of the operator – he or she must be able to line up the oblique US with the axial MR without a computer-generated overlay of the two images. In addition, with cognitive fusion, it is impossible to record the exact biopsy sites. This is a significant drawback, as knowledge of prior biopsy sites is valuable for planning repeat procedures and for monitoring patients on active surveillance [2,48]. Despite these drawbacks, current literature demonstrates that cognitive fusion biopsies are more accurate than systematic TRUS biopsies [49–51], and they may be an option for centers without computer-aided fusion technology.

Image-guided focal therapy

The rising prevalence of MRI-TRUS fusion biopsies has made the development of image-guided focal therapy (FT) of PCa possible. FT uses a combination of imaging techniques and minimally invasive ablative methods to eradicate tumor cells while leaving surrounding normal tissue relatively unharmed [52]. Its goal is to minimize side effects of treatment while still treating the tumor successfully [53]. This makes FT an attractive alternative to radical prostatectomy (RP) in addition to being a strategy that could potentially reduce the complications of overtreatment of indolent disease [54]. Multiple FT techniques have been paired with MRI and/or US and have gained increasing popularity as effective targeted treatment options [55]. The advancement of imaging technologies allows for better image quality and thus the possibility for more focused treatments. An important caveat is that a ‘radiologic margin’ is not necessarily the same as a ‘pathologic margin.’ There is considerable evidence that cancer cells extend beyond what is seen on the image as the tumor’s edge. Thus, focal therapies should aim to overlap the edges of the visualized tumor. Combined with the use of MRI guidance, precision treatment is possible with low risk of altering the patients’ quality of life.

Unlike with biopsy, where there is no advantage to working in the MR gantry, with FT, MRI provides an additional important guidance tool. As tissue heats, its MR properties change and this can be measured in near-real time, a process known as MR thermometry. For instance, high-intensity-focused ultrasound (HIFU) can be used to direct thermal energy to cancerous tissue with high precision [56]. HIFU works by directing focused US waves to the targeted area of tissue, heating the lesion to a temperature where coagulative necrosis is induced [57]. This process can be measured with MR thermometry. The neighboring tissue is left relatively unharmed, which makes HIFU a promising treatment method. mpMRI is useful during HIFU procedures and is used to monitor HIFU-treated lesions for recurrence [55]. In a study by Ahmed et al., 20 patients with unilateral localized PCa underwent HIFU hemiablation. After 12 months, 89.5% of the patients had no histological evidence of remaining PCa, and only three patients reported adverse effects from the treatment [58]. In another study by Ahmed et al., 42 patients were treated with MRI-guided HIFU and 30 of 39 patients had no histological evidence of PCa at six months post-treatment. After retreatment in four of the patients, 39 of the 41 had no evidence of PCa on mpMRI [59]. Recently, HIFU was approved by the US FDA for prostatic tissue ablation by Sonablate 450 (SonaCare Medical) and studies are underway to test this FT treatment method in low-risk, organ confined disease, and in recurrent PCa [55,60,61]. As a result, HIFU is a promising FT

option since it is a minimally invasive procedure, and MRI-guided HIFU can be monitored nearly in real-time using MR thermometry, thus giving the procedure more precision [55].

Another focal thermal treatment for PCa is MRI-guided focal laser ablation (FLA). During FLA therapy, an optical fiber is placed within the lesion using MRI guidance and a high-energy laser rapidly heats cancerous tissue and induces coagulation [55]. Normal structures such as the rectum can be protected from ablation by hydrodissecting the tissue plane between the prostate and the rectum, thus permitting peripheral lesions to be treated without damaging the rectum. FLA uses an in-bore MRI-guided approach. In a study by Linder et al. in 2010, FLA was found to be successful in ablating tumors and MRI accurately determined the ablated region on post-treatment in four men who underwent FLA, MRI, and subsequent RP. Whole mount histopathology was compared to the MRI calculated ablated volume and was found to correlate [62]. In a phase I trial by Oto et al. in 2013, nine men were successfully treated with MR-guided FLA and followed at six months post-treatment. Post-treatment MR image-guided biopsy showed no disease in 78% of patients, while in the remainder, low-grade cancer was detected at the treatment site (Gleason 6(3 + 3)). This study demonstrates MR-guided FLA to be a feasible and safe FT method for low-risk PCa [63]. However, these studies also point out that the ablated zone does not always completely cover the tumor and recurrences occur in up to 22%. By increasing the ablation zone, Lepor et al. showed in a study of 25 patients that 96% of targeted sites were completely treated with MR-guided FLA with almost no negative impact on quality of life [64]. With the aid of MRI, FLA appears to be a safe and viable FT option in treating PCa producing few side effects.

Cryoablation (CA) is another ablative technique that relies on coagulative necrosis via rapid cycles of thawing and freezing [55]. CA employs a combination of cyroprobe settings, distribution, and freezing intensities that can be used to treat focal lesions [65]. The destruction of cancers results from rapid thermal expansion and the formation of lethal ice crystals that rupture the cell membrane during thawing. MR guidance permits definition of the field to be ablated, thereby protecting the contiguous healthy prostatic tissue and vital structures. One problem with cryotherapy is that it is relatively difficult to control the size of the frozen region (also known as the 'ice ball'), and MRI does not adequately reflect the damaged region in real time.

In a study by Gangi et al., 11 patients underwent percutaneous MR-guided CA and MR guidance allowed visualization of the ice ball growth although accurate control of tissue damage was not possible [66]. In a study by Bomers et al. in 2013, 10 patients underwent MRI-guided focal CA to treat recurrences after radiation therapy. CA was found to be safe and feasible; however, 3 of the 10 patients had recurred by one year [67]. At present, there is a paucity of data on the success of MR-guided CA over the long term. Nerve damage affecting erectile dysfunction is commonly reported as a side effect of cryotherapy as well as incontinence reflecting the inability to control the ice ball with accuracy [66,68,69]. Thus, the future of MR-guided CA awaits more mature data.

mpMRI in active surveillance

Patients found to have low-risk PCa are often placed on active surveillance. This management strategy consists of serial PSA testing and biopsies, enabling clinicians to monitor disease progression while avoiding overtreatment [70]. Active surveillance has proven successful in managing low-risk disease [71,72]; however, it requires repeated biopsies and active surveillance fatigue is a known phenomenon.

mpMRI has been increasingly used to identify candidates for active surveillance. Both mpMRI and MRI/ TRUS-fusion-guided biopsy have been shown to be successful in screening patients for clinically significant disease. For patients diagnosed with low-grade cancers by 12 core systematic TRUS biopsies, mpMRI can be useful in confirming that no other lesions are present. For those patients in whom no suspicious lesion is seen, mpMRI can be used to follow patients in place of biopsy provided that other parameters (PSA and rectal examination) remain stable. A study by Park et al. demonstrated that patients with no visible tumor on mpMRI are less likely to have unfavorable disease, thus making them better suited to active surveillance [73].

mpMRI can act as a noninvasive method for monitoring patients on active surveillance. Rather than performing serial 12 core systematic TRUS biopsies that risk missing significant cancer and pose the risk of infection, clinicians may be able to use mpMRI to accurately visualize the status of the prostate. A study by Rais-Bahrami et al. showed that small index lesions (≤ 7 mm) on mpMRI are either pathologically benign or represent low-grade Gleason 6 cancer on MRI-TRUS fusion biopsy [74]. These lesions showed no significant progression over a mean imaging period of 2.3 ± 1.6 years (≤ 7 mm lesions) and 2.4 ± 1.7 years (≤ 5 mm lesions). Thus, mpMRI is an effective method for monitoring patients with low-grade cancers, and can therefore be a powerful screening tool for patients on active surveillance provided that an mpMRI is obtained before the patient is selected for AS. mpMRI, however, does not replace serial PSA testing and DRE. If either of these demonstrates changes, the patient should be biopsied again whether or not the MRI has changed in characteristics. However, in most cases, MRI can provide confidence, in the absence of sudden increases in PSA, that the patient is safe to remain on AS, thus reducing the total number of lifetime biopsies that a patient has to experience [70].

mpMRI in biochemical recurrence

PCa patients, although receiving the best possible treatment with curative intent by means of surgery or radiation, can still face disease recurrence. This is first detected by rising PSA values and, in the absence of any other imaging findings, is termed 'biochemical recurrence' (BCR). BCR occurs in 27–53% of patients, after RP or radiation therapy [75]. mpMRI can be helpful in detecting foci of recurrence [76]. However, early detection of local recurrent disease could result in more focal therapies for recurrence [77]. mpMRI is useful in detecting local recurrences in the prostatic bed post-RP (Figure 2) [75]. Since the prostate is no longer present, the normal anatomy is disrupted and postprostatectomy imaging is critical for detecting sites of recurrence. Since the recurrences tend to be small, an ERC is important to increase SNR and image resolution (Figure 2). DCE is the best imaging modality within the mpMRI repertoire to detect BCR after RP as it can detect recurrences even with PSA

values <1 ng/mL [20,76,78,]. However, in some cases, the ERC is not necessary. For instance, Cha et al. showed that mpMRI at 3T with a surface array coil but no ERC enabled detection of recurrent disease [79]. The AUC for the combination of T2W, DWI, and DCE gave a value of 0.918, compared to T2W alone with an AUC of 0.773 [79]. In a recent study by Muller et al., mpMRI-guided TRUS fusion biopsy was found to be successful in diagnosing local recurrence in 8/10 patients suspected of recurrence after RP [6]. Most importantly, Muller et al. found that abnormalities on DCE imaging and T2W imaging were strong indicators of recurrence [6].

Several studies on recurrent disease after radiotherapy have shown mpMRI to be valuable in achieving levels of accuracy between 80% and 90% [80,81]. mpMRI's role in BCR not only implies improved detection of post-treatment failure, but also aids in further treatment planning decisions. Barchetti et al. reported that DCE is better for detecting BCR in postradiation patients since DWI is prone to artifacts [76]. Yet, in a study by Donati et al. in 2013, the diagnostic accuracy of DCE was found to have no added benefit when combined with T2W and DWI after radiation therapy [82]. There is considerable amount of debate over which sequence is best to determine BCR in postradiation patients; however, the majority of studies suggest that mpMRI is the most dependable imaging biomarker for recurrence [76].

Limitations of mpMRI

Some of the major roadblocks in the implementation of mpMRI into routine practice include cost, reimbursement, patient acceptability, and training. More efficient MR imaging could reduce cost and removing the ERC could improve patient acceptability. Automated computer-assisted diagnosis could reduce the need for intensive training. However, notwithstanding these improvements, some patients cannot undergo MRI. Patients with an implant or internal metallic prosthesis cannot undergo MRI, although increasingly, medical device manufacturers are designing their products to be used in MRI environments. Additionally, limitations regarding registration errors in MRI-TRUS fusion are of concern during image-guided biopsy procedures. Commercial systems, such as Uronav® (Invivo) or Artemis® (Eigen), try to address this limitation, yet issues remain and the development of better registration tools are needed to combine MRI with US.

An important caveat is that MRI can miss significant cancers. At this point, it is unclear how common this is, but it cannot be entirely relied upon and is thus not a replacement for biopsy. Finally, larger multi-institutional studies need to be conducted to confirm the cost-benefit ratio of mpMRI and establish its limitations [83].

A limitation of the role of mpMRI in FT relates to this tissue preserving treatment method's primary end points. The primary conclusion of FT is a negative biopsy 12 months post-treatment; however, the end points of FT are still under controversy. Detection of PCa recurrence on mpMRI compared to histologic grading is regarded as secondary to biopsyproven recurrent disease. Additionally, PSA levels are not advised accurate since these methods have not been established in focal treatments [84]. Furthermore, an editorial to the European Association of Urology in 2012 commented on the increasingly difficult

decision towards FT of PCa due to the ‘burden of harm’ put on patient. Yet, it was stated that advances in MRI would provide the key to disease management [85].

Future directions of mpMRI include upcoming multi-institutional studies validating whether mpMRI preceding initial biopsy veritabily improves diagnostic accuracy of clinically significant prostatic disease and further investigation into hyperpolarized MRSI to increase the sensitivity of mpMRI [86,87]. Hyperpolarized MRI uses hyperpolarized probes that increase SNR and allows for better molecular functional imaging [88]. Studies utilizing ¹³C-pyruvate as a hyperpolarization conjugate to visualize tumors have been performed in prostate and are continuously underway [89]. ¹³C-pyruvate magnetic resonance spectroscopy is a newly developing technology and can be used as a delineator for advancing PCa [90].

Conclusion

mpMRI is useful in the detection, monitoring, and treatment planning of PCa. Though it still must be complemented by traditional detection and treatment methods such as DRE, PSA, and biopsy, mpMRI has the potential to reduce the number of unnecessary biopsies, to reduce overdiagnosis and overtreatment of indolent cancers, and to aid in patient management. The goal of mpMRI is to provide a noninvasive method of screening, assessing, and treating clinically significant cancers, as well as to identify patients who would benefit from active surveillance. When used in conjunction with the traditional detection and monitoring methods, mpMRI imaging has proven to be a successful technique for assessing PCa.

Expert commentary

mpMRI is useful in the detection, monitoring, and treatment planning of PCa. mpMRI has the potential to reduce the number of unnecessary biopsies, to reduce overdiagnosis and overtreatment of indolent cancers, and to aid in patient management. When used in conjunction with the traditional detection and monitoring methods, mpMRI imaging has proven to be a successful technique for assessing PCa. Use of mpMRI is more common recently; however, some challenges are still present in its acquisition and interpretation. Prospective and randomized multicenter trials will enable us to understand the real impact of mpMRI on management of PCa.

Five-year view

Several advances in the MRI of PCa have been made during the past decade. In particular, important clinical developments have been reported in imaging and image-guided biopsy of localized PCa. mpMRI will continue to be explored in several research studies and will be more commonly used in PCa management. More effort is needed in the standardization of image acquisition and interpretation.

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Key issues

- T2W MRI, DW-MRI (including ADC maps and high b-value DW-MRI), and DCE-MRI are key pulse sequences of mpMRI.
- Use of endorectal coil provides the best possible scan quality, but involves patient discomfort and increased cost. Studies obtained at 3T with or without the ERC produce similar results.
- PI-RADS v2 guidelines lay out the recommended technical parameters for obtaining mpMRI and guidelines for interpretation and scoring of each pulse sequence.
- Including mpMRI information in guiding biopsies (cognitive, in bore, TRUS/MRI fusion guided) improves the biopsy yield compared to systematic TRUS-only-guided biopsies.
- Although a relatively new approach, combined with the use of MRI guidance, focal treatment of PCa is possible with low risk of altering the patients' quality of life.
- Use of mpMRI in active surveillance is a new approach, but it has been shown to be effective in monitoring patients with low-risk PCa. Further evidence with larger scale studies is needed for this use.
- Early detection of local residual/recurrent disease focus in patients with biochemical recurrence after definitive therapy (surgery or radiotherapy) is critical and difficult. mpMRI has promising results in localizing disease foci in this patient population.
- When used in conjunction with the traditional detection and monitoring methods, mpMRI has proven to be a successful technique for assessing PCa.

Figure 1. 69 year old male with serum PSA=9.59ng/mL. Axial T2W MRI (A), ADC map of DW MR (B), b2000 DW MRI (C) and DCE MRI (D) shows a PI-RADS 5 lesion in the midline anterior transition zone of the prostate (arrows). Targeted biopsy revealed Gleason 3+4 in this lesion.

Figure 2.

62 year old, male S/P radical prostatectomy with a serum PSA=1.73ng/mL. Axial T2W MRI shows a periurethral lesion on the left (arrow) (A), this lesion has positive diffusion restriction on ADC map (arrow) (B), additionally, DCE MRI shows hypervascularity within the lesion (arrow) (C). Targeted biopsy revealed prostate cancer within this lesion.