Current role of multiparametric magnetic resonance imaging for prostate cancer

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Abstract: Multiparametric magnetic resonance imaging (mp-MRI) has shown promising results in diagnosis, localization, risk stratification and staging of clinically significant prostate cancer, and targeting or guiding prostate biopsy. mp-MRI consists of T2-weighted imaging (T2WI) combined with several functional sequences including diffusion-weighted imaging (DWI), perfusion or dynamic contrast-enhanced imaging (DCEI) and spectroscopic imaging. Recently, mp-MRI has been used to assess prostate cancer aggressiveness and to identify anteriorly located tumors before and during active surveillance. Moreover, recent studies have reported that mp-MRI is a reliable imaging modality for detecting local recurrence after radical prostatectomy or external beam radiation therapy. Because assessment on mp-MRI can be subjective, use of the newly developed standardized reporting Prostate Imaging and Reporting Archiving Data System (PI-RADS) scoring system and education of specialist radiologists are essential for accurate interpretation. This review focuses on the current place of mp-MRI in prostate cancer and its evolving role in the management of prostate cancer.

Keywords: Prostate cancer; multiparametric-MRI; functional imaging; diffusion imaging; active surveillance

Introduction

Currently, the diagnostic pathway for prostate cancer detection is initiated on prostate-specific antigen (PSA) level and digital rectal exam (DRE). Use of PSA as a screening tool followed by systematic transrectal ultrasound (TRUS)-guided biopsy has resulted in increased detection of prostate cancer with stage migration toward low-risk disease. About 233,000 new prostate cancers are estimated to be diagnosed in 2014 in the USA (1). This has come with the risk of overdiagnosis and overtreatment, as many of these are clinically insignificant low-risk prostate cancer. On the other hand, anterior tumors tend to be missed by TRUS biopsy until they grow to a substantial size and reach

within 15-20 mm from the posterior margin of the prostate, leading to delayed diagnosis. Systematic TRUS biopsy has historically shown to underestimate the final Gleason grade of tumor on histology following radical prostatectomy, leading to inaccurate risk stratification and selection of therapeutic options. For all these reasons, the US and the Canadian Task Force on Preventive Health Care recently released independent statements arguing that the risks of PSA tests outweigh the benefits (2).

Multiparametric magnetic resonance imaging (mp-MRI), combining the morphological assessment of T2-weighted imaging (T2WI) with diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCEI) perfusion and
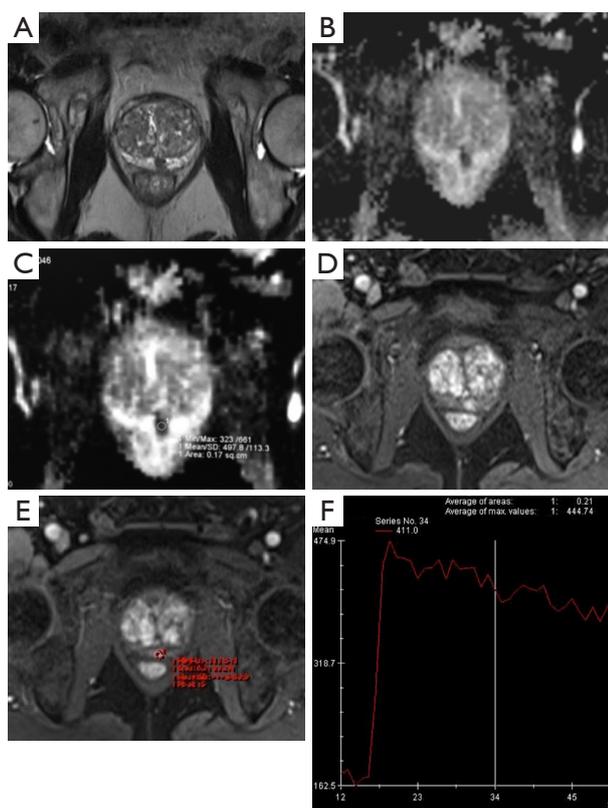
Figure 1 A 66-year-old patient, with PSA of 19.8, Gleason 3+4 on multiple cores, undergoing post-biopsy staging mp-MRI. (A) Axial T2-weighted MRI shows a small posterior mid-peripheral zone hyposignal lesion; (B,C) on multiparametric map of apparent diffusion coefficient (ADC) from axial diffusion-weighted MRI, prostate cancer shows significantly decreased values; (D,E) axial dynamic contrast-enhanced imaging (DCEI) shows early enhancement in the posterior mid-peripheral zone; (F) typical post-contrast wash-in/wash-out curve of the tumor lesion. PSA, prostate-specific antigen; mp-MRI, multiparametric magnetic resonance imaging.
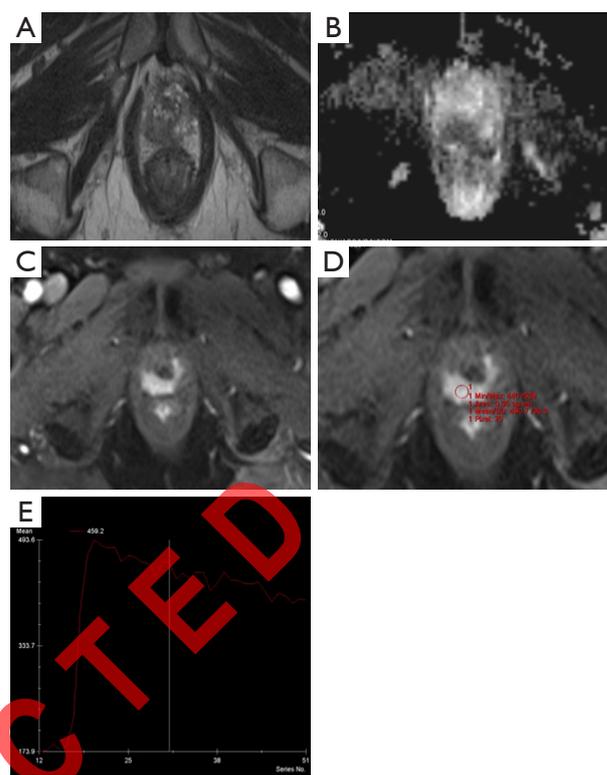
Figure 2 A 55-year-old patient with a PSA of 12.3, previously diagnosed with Gleason 3+3 cancer on 12-core template biopsy. (A) Axial T2-weighted image shows a large hypointense signal in right apical peripheral zone with capsular bulge; (B) apparent diffusion coefficient (ADC) map from axial diffusion-weighted imaging (DWI) showing hypointense signal and restricted diffusion of the lesion; (C,D) axial dynamic contrast-enhanced imaging (DCEI) showing strong early enhancement in the right apical peripheral zone; (E) typical post-contrast wash-in/wash-out curve of the tumor lesion. PSA, prostate-specific antigen.

magnetic resonance spectroscopic imaging (MRSI), has been extensively studied in recent years (3-6). In particular, T2WI and DWI have shown considerable promise in the detection, localization, risk stratification and staging of prostate cancer (7-13). This review will provide an overview of the different imaging sequences and discuss the current role of mp-MRI in the different aspects of management of prostate cancer.

Multiparametric MRI technique

Currently, mp-MRI is regarded as the reference standard

imaging modality for prostate cancer because a single MRI sequence cannot adequately detect and characterize prostate cancer. Although the ideal set of sequences for prostate mp-MRI has not been determined, mp-MRI is composed of high-resolution T2WI, DWI, and DCEI with optional MRSI (*Figures 1-3*) (13-15). T1-weighted Imaging (T1WI) is of limited use in assessing prostate morphology or in identifying tumor within the gland. Its main use is in detecting post-biopsy hemorrhage. Bowel motion artifacts should be reduced by administering anti-peristaltic agents. Prostate imaging at 3T benefits from higher signal to noise ratio (SNR). Use of endorectal coil (ERC) is not an absolute
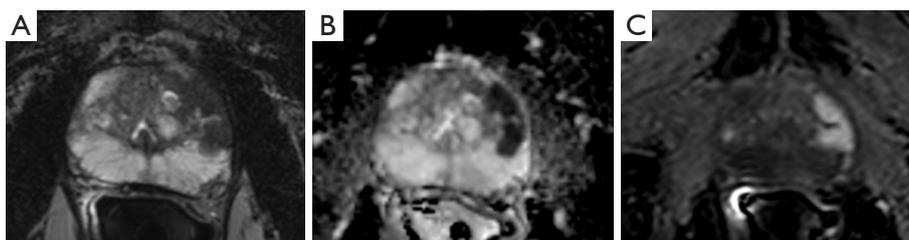
Figure 3 Multiparametric magnetic resonance imaging (mp-MRI) detects significant prostate cancer. This 63-year-old man had a doubling of serum PSA in less than 2 years. (A) A pseudonodular mass of the anterolateral part of the left mid-peripheral prostate with low signal on T2-weighted imaging (T2WI) is shown; (B) this mass is associated with low signal on the apparent diffusion coefficient (ADC) map signifying restricted diffusion; (C) focal asymmetric early enhancement on the arterial phase of the dynamic contrast-enhanced perfusion imaging. Targeted biopsies of this area revealed high volume Gleason 4+3=7 cancer. PSA, prostate-specific antigen.

Table 1 Principles and characteristics of T2WI and functional sequences

Sequence	Principle	Finding of prostate cancer	Advantages	Drawbacks
T2WI	Water content of tissue	Low signal intensity	High resolution; sharp demarcation of the prostate capsule	Central or transition zone tumor detection
DWI	Proton diffusion properties	High signal intensity on DWI; low signal intensity on ADC map	Central or transition zone tumor detection; assessment of tumor aggressiveness	Poor resolution and image distortion
DCEI	T1WI with contrast medium	Enhance and wash out rapidly	Local recurrence detection after definite treatment	Long acquisition time
MRSI	Concentration of metabolites	Increased choline plus creatinine/citrate	Assessment of tumor aggressiveness	Needs more expertise; long acquisition time

T2WI, T2-weighted imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient; DCEI, dynamic contrast-enhanced imaging; T1WI, T1-weighted imaging; MRSI, magnetic resonance spectroscopy imaging.

requirement for cancer detection protocol, but is preferable at 1.5T (14). ERC use is recommended for staging purposes, although patient acceptability and increased costs remain its drawbacks. The principle, strong and weak points of each mp-MRI sequence are summarized in *Table 1*.

T2WI

T2WI, which reflects the water content of tissue, is the basis of mp-MRI. Because of the high resolution and sharp demarcation of the prostate capsule, T2WI can be used to determine prostate zonal anatomy and prostate cancer staging. In contrast to cancer in other organs, prostate cancer presents low signal intensity compared with adjacent glandular tissue because the abundant amount of water in the normal gland demonstrates high signal intensity on T2WI. This signal difference between normal and cancer tissue helps in cancer detection in the gland-rich peripheral zone. However, cancer identification on T2WI may be limited in the transitional zone, which does not contain a large amount of water. Moreover, the T2 shortening effect by biopsy-induced hemorrhage decreases signal intensity even in noncancerous tissue. Therefore, despite satisfactory performance as reported by early studies, recent literature has demonstrated the limitations of T2WI for prostate cancer detection. Therefore, the sensitivity and specificity of T2WI show significant variation in studies, 55-88% for sensitivity and 67-82% for specificity (15,16). Furthermore, such potential drawbacks of T2WI have introduced the need for mp-MRI.

DWI

Diffusion-weighted MRI is a functional imaging tool that measures the random Brownian motion of water molecules in tissue. The apparent diffusion coefficient (ADC) on MRI or the net displacement of molecules quantifies the restriction of water diffusion and is measured by acquiring

at least two set of images with different magnetic field gradient durations and amplitudes (b value). Performing DWI requires at least two b factors for the calculation of ADC. Multipoint b value analyses increase the accuracy of the calculated ADC at the expense of increased scanning time and decrease in SNR. Earlier studies reported use of maximal b value of 1,000 s/mm^2, but more recently it has been shown that a value of up to 2,000 s/mm^2, which can be obtained on 3T scanners, may help to suppress signal from background normal prostate tissue and highlight the cancerous areas as hyperintense (17). Interpretation with high b values >1,000 s/mm^2 is advocated for DWI in combination with ADC, with the hallmark of cancer being low ADC and iso to high signal on high b value DWI images ($\geq$1,400 s/mm^2). Limitations of DWI include increased noise and anatomic distortion of the image, especially at higher b values.

Studies have also shown an inverse correlation between quantitative ADC values and Gleason score, and may therefore help in assigning accurate risk stratification for selection of therapeutic options (18,19). But, there is significant overlap in confidence intervals that ADC cannot be used as a surrogate for Gleason score at this time, although most clinically significant cancers have a ADC value of <1,000 (20). DWI is a widely available technique and is considered to be the most important functional imaging sequence in mp-MRI. Functional imaging (DWI, DCE and MRSI), and in particular DWI, may help to differentiate cancer from benign abnormalities such as prostatitis, fibrosis, scar tissue, post-biopsy hemorrhage or post-irradiation in the peripheral zone. Therefore, DWI is considered as the dominant sequence for identifying tumors in the peripheral zone (21). It is also the most useful of all the functional imaging sequences for tumor detection in the transition zone. Multiple studies have shown DWI to be the most effective of the mp-MRI sequences for detecting prostate cancer, thereby improving the diagnostic performance of mp-MRI (16,22-25).

DCEI

DCEI is an imaging modality that is designed to evaluate the status of tumor angiogenesis. DCEI requires the acquisition of repeat gradient echo images before and after injection of contrast materials such as chelated gadolinium. Owing to rapid imaging, DCEI provides the time-intensity curve in each voxel. Because tumors are evidently associated with neoangiogenesis that induces an

increase in the blood volume and transvascular permeability, tracing the dynamic flux of the contrast agent with DCEI shows strong and rapid contrast enhancement. Therefore, DCEI helps to monitor treatment effects as well as cancer detection. Recently, studies have also reported that DCEI can improve diagnostic performance for detecting local recurrence in patients who undergo radical prostatectomy (15,26). However, DCEI may cause false-positive diagnosis because inflammation is also accompanied by increased vascularity. Patient motion and peristalsis of the rectum during imaging may cause misregistration in imaging series, thereby disturbing the analysis of the time-intensity curve. The reported sensitivity and specificity of DCEI alone for prostate cancer detection also varies by reports (46-90% for sensitivity and 74-96% for specificity) (26).

MRSI

Among the sequences which comprise the mp-MRI, proton MRSI is the least frequently used and is mostly limited to the research setting. MRSI provides information about specific metabolites within prostatic tissue. The analysis is performed by measuring the resonance peaks of various biochemical metabolite levels such as citrate, creatine, and choline. Normal prostate tissue contains an abundant supply of zinc which inhibits aconitase and produces high levels of citrate. Citrate exhibits a unique peak on MR spectroscopy. On the other hand, in prostate cancer down regulation of the zinc transporters causes a decrease in zinc levels (27). This reduction in zinc decreases citrate levels by inducing oxidation. Choline levels correlate with cell turnover, as seen in prostate cancer. Thus, as cancers arise, citrate is expected to decline while choline is expected to rise. This ratio of choline to citrate is therefore an indicator of malignancy (*Figure 4*) (28-31). While MRSI is, in theory, a promising imaging sequence, it requires additional software expertise, training, and support and increases the overall mp-MRI scan time. In a multi-institutional study, it was determined that MR imaging alone was just as effective as MR imaging with MRSI and did not improve tumor localization in the peripheral zone, where most cancers occur. Also, out of the 110 patients in the final study group, only 50% were considered to have achieved good or excellent spectral quality notwithstanding the fact that the study was largely performed in excellent academic centers (32). For these reasons, MRSI has yet to become widely accepted in standard clinical practice; as a result, research has also slowed down with regard to
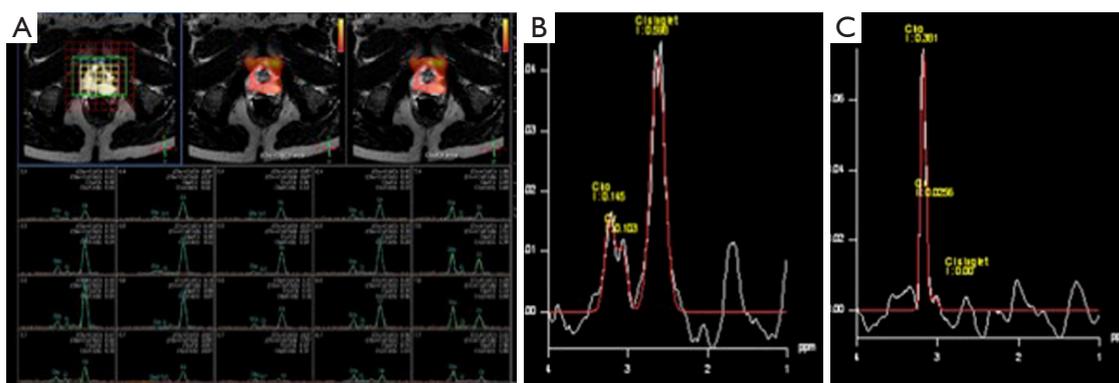
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Figure 4 Typical graphics obtained from magnetic resonance spectroscopic imaging (MRSI). (A) Multivoxel spectroscopic imaging on the prostate; (B) normal prostatic tissue: (Ch + Cr)/Ci <0.5; (C) prostate cancer: (Ch + Cr)/Ci >0.8.

MRSI. In a recent study of active surveillance in low-risk prostate cancer, it was determined that only T2W and DWI were independent predictors of biopsy upgrade (33). Spectroscopy was therefore not contributory. This study supports the argument against the routine use of MRSI in clinical practice and raises question about the future of MRSI as a component of mp-MRI.

Role of mp-MRI in detection

Although the individual sequences are useful, T2WI in combination with two functional sequences has been shown to provide better characterization of tumor in the prostate (34,35). In a diagnostic meta-analysis of seven studies, de Rooij *et al*. revealed a high overall sensitivity and specificity on accuracy of mp-MRI using T2WI, DWI and DCEI. Pooled sensitivity and specificity were 0.74 and 0.88, respectively, with negative predictive value (NPV) ranging from 0.65 to 0.94 (36). In another study, mp-MRI showed good performance at detecting and ruling out clinically significant cancer, following at least one previous biopsy, with a NPV of 95% using transperineal template systemic biopsy as the gold standard (37). The authors concluded that mp-MRI can therefore be used as a triage test following a negative biopsy and thereby identify patients who can avoid further biopsies. A recently published study reported clinical NPV of mp-MRI at 89.6% for significant cancer over a longitudinal follow-up period of 5 years (38). Shakir *et al*. demonstrated that the benefit of MRI and targeted biopsy increases with increasing PSA levels and that the diagnostic usefulness and upgrading to clinically significant disease on biopsy occurred above a PSA threshold of 5.2 ng/mL (39).

While several studies have shown the benefit of functional imaging in detection of prostate cancer in the peripheral zone, functional imaging may have a limited role in evaluating cancers in the transition zone on mp-MRI because of the heterogenous appearance and enhancement secondary to benign prostatic hyperplasia (40). Hoeks *et al*. reported that DCE-MRI in particular did not show any additional benefit over T2WI for detection of cancer in the transition zone (41). In their study, accuracy of mp-MRI for detecting Gleason grades 4 and 5 in the transitional zone was 79% for T2WI and 72% when combined with DWI and DCEI. For low-risk disease, the accuracy levels were 66% for T2WI and 62% when combined with functional imaging. In another study, the authors reported that adding DWI to T2WI improved the accuracy of detecting prostate cancer in the transition zone (42).

Tumor volume is a documented prognostic factor for prostate cancer outcome, and is its correct estimation is mandatory for success of focal therapy, the new organ-sparing treatment technique that aims to selectively ablate locally confined, clinically significant index lesions, while sparing the rest of the prostate gland and the surrounding structures (43). Histologic architecture of the tumor affects quantitative MRI findings and is known to be a major predictor of tumor visibility on mp-MRI (44). Sparse or infiltrative tumor mixed with normal tissue may be present at the periphery of the MRI-visible "dense" tumor. Studies have shown that the greatest tumor volume on mp-MRI determined from images on any of the individual sequences provided a fairly accurate estimation of the tumor volume on whole-mount histology, although estimation was more accurate for larger tumors over 10 mm and >0.5 cc in volume than for small tumors (45-47).

Because prostate MRI interpretation can be subjective and inconsistent, suspicion scores for prostate cancer on MRI [Prostate Imaging and Reporting Archiving Data System (PI-RADS)] have been developed on a 1- to 5-point scale (based on fixed criteria) for improved standardization of MRI interpretation and reporting (13). The Likert scoring system is based on an overall impression of the reader and is a more subjective form of evaluation. Studies have shown higher interobserver reproducibility in the experienced readers than for less-experience readers for both the PI-RADS and the Likert scoring systems (48). A recent meta-analysis of 14 studies evaluating use of the PI-RADS scoring system for prostate cancer detection on mp-MRI showed good diagnostic accuracy (49). However, the PI-RADS scoring system is work in progress and PI-RADS version 2 has recently been published.

Role of mp-MRI in negative biopsy patients

In a meta-analysis including 14 studies and 698 patients, the mean cancer detection rate following a negative biopsy was 37.5% (range, 19.2-68.3%) (50). The pooled sensitivity and specificity by site analysis was 57% and 90%, respectively. The positive predictive value of mp-MRI in these studies ranged from 17 to 92. However, in many of these studies, biopsies were obtained by visual/cognitive assessment following mp-MRI. Hoeks *et al.* reported a cancer detection rate of 25% (108/438) in patients who had at least one previous negative biopsy for increased PSA and underwent subsequent mp-MRI and MRI guided in bore biopsy, with 87% of these cancers found to be clinically significant (51). The positive predictive value of mp-MRI in this study was 41% (108/265) by patient analysis and 33% (123/368) by site analysis. Similarly, Vourganti *et al.* reported a cancer detection rate of 37% (73/195) following a previous negative biopsy and suspicious mp-MRI (52). In their study, targeted biopsy using MRI-TRUS fusion upgraded in 28 patients and detected additional significant cancer in 12 patients, not detected by systematic biopsy. Recently, Sonn *et al.* also detected cancer in 34% (36/105) of patients using MRI-TRUS fusion following initial negative biopsy, with 72% of these being clinically significant. The positive predictive value of mp-MRI for highly suspicious lesions (PI-RAD scores of 4 and 5) was 50% (24/48 patients) (53).

Role of mp-MRI in active surveillance

Active surveillance is being utilized more frequently in the

management of prostate cancer. The goal is to minimize the harm caused by overtreatment of low-risk disease while providing a means of identifying men with disease progression who require definitive treatment. A significant number of men on active surveillance protocols have a suspicious lesion that is identifiable on MRI (54). mp-MRI may prove to be particularly useful in this setting because suspicious lesions can be targeted with fusion biopsy leading to preferential sampling of prostate cancer tissue. This means that prostate cancer progression can be detected more efficiently and accurately. Growing evidence supports the role of repeat mp-MRI of the prostate and fusion biopsy to improve monitoring of men on active surveillance. In a retrospective analysis, Abdi *et al.* (n=603) demonstrated that mp-MRI of the prostate with the option of subsequent fusion biopsy improves the detection of prostate cancer progression for men under active surveillance (55). Walton Diaz *et al.* (n=152) demonstrated that stable mp-MRI findings were associated with Gleason score stability on biopsy (56). Importantly, only 2.9 fusion biopsies were needed to detect one case of Gleason progression compared with 8.74 saturation biopsies. According to the authors, mp-MRI may be a promising means of reducing the number of biopsies for men on active surveillance.

Siddiqui *et al.* (n=85) found that mp-MRI could reduce the number of repeat biopsies by up to 68% for men on active surveillance (57). A tumor that is not detected on mp-MRI is more likely to be low risk, and according to Johnson *et al.*, the risk of biologically significant disease in patients with a negative mp-MRI result is low enough to justify deferring definitive treatment without biopsy (58). The findings in these studies are promising and certainly warrant evaluation in large prospective trials. The Prostate Cancer Research International: Active Surveillance (PRIAS) study, which is the largest prospective study evaluating active surveillance, has commenced recruiting eligible patients to have mp-MRI incorporated into the surveillance data. This will provide reliable information with regards to the feasibility of mp-MRI in the context of active surveillance (59).

Role of mp-MRI in detection of recurrence after radical prostatectomy

Most post-prostatectomy recurrent prostate cancer is diagnosed by PSA elevation. Once PSA increment is detected, it is essential to identify whether prostate cancer has recurred at a local or a distant site to determine the treatment modalities. In current practice, imaging or

pathological evidence of local recurrence is not necessary to initiate local salvage treatment because current imaging techniques cannot adequately detect small-sized local recurrence.

In a recent meta-analysis, mp-MRI was reported to have sufficient accuracy for detecting local recurrence in patients with low PSA and small-sized recurrence (60). Recently, an increasing number of studies have been published reporting the acceptable diagnostic accuracy of mp-MRI for detecting local recurrence. Among the functional sequences, DCEI has been regarded as the most reliable sequence in detecting local recurrence after prostatectomy (61,62). However, it must be taken into account that vascularity and contrast enhancement can be reduced in patients who have received androgen deprivation therapy. In this regard, the accuracy of DCEI might be reduced in patients who undergo androgen deprivation therapy. Sensitivity and specificity of DCEI alone for detecting local recurrence after radical prostatectomy range from 88% to 100% and from 45% to 97%, respectively (63-66). Moreover, DCEI increased interobserver agreement and addition of DCEI to T2WI significantly increased accuracy for detecting local recurrence (63).

Recently, some studies have shown that DWI is also a reliable sequence in detecting local recurrence (64,65). Moreover, the combination of DWI and DCEI seemed to have more consistent specificity of 82% to 87% compared with DCEI alone (65,66). Accuracy of combined functional sequences has not been sufficiently reported (67,68). According to a recent study, T2WI plus DCEI has the highest sensitivity of 97% followed by DCEI alone and T2WI plus DWI plus DCEI (62).

Conclusions

The current literature indicates that mp-MRI of the prostate is a promising technology within prostate cancer management. Robust data to confirm many of these findings are still needed. Despite promising data indicating that Gleason score can be predicted without a tissue sample (particularly with DWI), such findings should be interpreted cautiously in the clinical setting, particularly in the scenario of an elevated PSA test and negative mp-MRI of the prostate. The clinical confidence in this aspect of the technology is justifiably more guarded compared with the academic excitement. The largest benefit may come from reduction of unnecessary biopsies which could in turn prevent overdiagnosis and overtreatment. It also has

the potential to decrease the number of missed clinically significant cancers. Like any new technology, it should be treated judiciously and used in combination with current clinical tools for risk stratification. More likely than not, the gold standard for evaluating mp-MRI is direct comparison of radiology to histopathology. The development of a more sophisticated, standardized model for correlating radiological parameters with histopathology in addition to higher volumes of good quality data is the logical next research pathway.

Acknowledgements

Footnote

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