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MRI in the Management of Prostate Cancer

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Multiparametric MRI has a changing role in prostate cancer diagnosis. Internationally recognized consensus documents such as prostate imaging reporting and data system version have been developed and adapted to standardize the acquisition and reporting of prostate MRI. The improvement in scanning techniques and development of highly sensitive functional sequences have improved the detection of clinically significant prostate cancer as well as treatment planning and follow up. This has led to a recent NICE recommendation to use prostate MRI as the initial investigation in men with clinically suspected localized disease. The results of several recent international MRI prostate trials are influencing the way imaging is used to stratify which patients require a prostate biopsy as well as how MRI guidance is used to target biopsies.
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Prostate cancer is the second most common cancer in men, accounting for up to 15% of all cancer diagnosed worldwide with autopsy studies demonstrating that up to 38.5% of men have some measurable prostate cancer, increasing incrementally with age.[1] With advancing awareness, and screening for prostate cancer, there has been a reduction in disease-specific mortality and aggressive cancer. Simultaneously there has been an increase in detection of indolent cancer that would likely never have become clinically apparent in the patients' life times. Subsequent overtreatment of these cancers has associated morbidity especially regarding continence, and potency.[2] Definition of a "clinically significant" prostate tumor is variable but Gleason grade of ≥7 (International Society of Urologic Pathologists ≥2) and/or >0.5 mL are generally considered to be the most accepted criteria.[3]

The role of multiparametric magnetic resonance imaging (mpMRI) of the prostate has changed in the last 20 years, from its initial use to stage biopsy proven prostate cancer, to a diagnostic and risk stratification tool in men with a clinical suspicion of prostate cancer. Currently mpMRI has an increasing role as a triage test to assess those men who may have clinically significant disease, and to limit the number of men undergoing unnecessary and morbid prostate biopsy. This is in addition to planning radical (radiotherapy, prostatectomy) or focal treatments, and as a follow up test.

MRI is the best imaging technique to visualize the prostate with excellent resolution and contrast between the prostate gland and surrounding structures, as well as the anatomical zones of the gland. mpMRI is the combination of anatomical (T2-weighted) and functional sequences (Diffusion weighted [DWI] and dynamic contrast enhanced [DCE]). Additional, less commonly used, sequences include MR spectroscopy.

No single MR sequence performs as well as a combination of sequences to diagnose significant prostate cancer (as defined by Gleason score ≥7). This has been consistently shown in studies comparing stand-alone sequences (T2, DWI, DCE) with mpMRI, against prostatectomy and biopsy histology specimens. T2-weighted sequences alone detected prostate cancer with a sensitivity of 0.36-0.63, DWI sequences 0.38-0.53 and DCE 0.38-0.43, whilst in combination, superior cancer detection rates were achieved with sensitivities of 0.74-0.8, specificity of 0.8-0.93, and positive predictive value of 0.9.[4-7] Moreover mpMRI has been shown to be more sensitive in detecting clinically significant lesions (0.72-0.75)[8,9] and has a reported negative predictive value of between 0.63 and 0.98 for ruling out these lesions.[9,10]

Standardized Conduct and Reporting of Prostate mpMRI

There are now several consensus and guideline documents that aim to standardize the conduct and reporting of prostate

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Table Prostate Imaging-Reporting and Data System (PIRADS) Showing Different Scores (1-5) Depending on T2, DWI, and Dynamic Contrast Enhancement Findings

	Peripheral Zone		PI-RADS		Transition Zone	
	DWI/ADC = Primary sequence				T2 = Primary sequence	
1	DWI/ADC normal		1	1	Completely encapsulated nodule	
2	DWI/ADC indistinct		2	DWI ≤ 3 DWI ≥ 4	2	Homogenous circumscribed nodule with no capsule "atypical nodule" or majority encapsulated circumscribed nodule inc. cystic change and nodule in nodule appearance
3	ADC → focal mild/moderate hypointense DWI → focal iso/mild hyperintense	DCE –ve DCE +ve	3	DWI ≤ 4 DWI 5	3	Heterogeneous signal intensity with obscured margins
4	ADC → focal marked hypointense DWI → focal marked hyperintense		4		4	Lenticular or noncircumscribed, homogeneous lesion, moderately hypointense and <1.5 cm
5	Same as 4 *but* >1.5cm or extraprostatic extension		5		5	Same as 4 *but* >1.5 cm or extraprostatic extension

mpMRI, in order to improve its diagnostic ability and reproducibility.[11] Some recommend the use of a Likert-type system, whereby the radiologist assigns a score between 1 and 5 on the basis of the likelihood of the presence of clinically significant cancer. The PIRADS system, which was first published in 2012 and subsequently updated in 2016 [12-14] provides a structured basis for scoring.

PIRADS

The Prostate Imaging Reporting and Data System version 2 (PIRADS v2 — Table) is a consensus document that aims to standardize the techniques of mpMRI acquisition, reporting and communication of results. The framework of PIRADS is designed to help radiologists decide whether a lesion is likely to represent clinically significant cancer or not, using a scoring system of 1-5. Unlike Likert scoring, which does not have a framework or structure, PIRADS attempts to categorise specific imaging features on each MRI sequence. This allows for a more objective assignment of likelihood and/or score in an attempt to reduce variability in interpretation. It is validated in men that have not undergone surgery or targeted therapy. The "dominant" most useful sequence to diagnose malignancy differs for lesions in the peripheral or transition zones (TZs). The framework is summarized in Table and described in more detail below.

Small field of view multiplanar T2 weighted-sequences allow exquisite resolution of the zonal anatomy of the prostate (Fig. 1), seminal vesicles, bladder, and other pelvic structures. The most commonly used T2 sequences in mpMRI are fast-spin-echo or turbo-spin-echo with a field of view between 12 and 20 cm and 3 mm slice thickness.

Prostate tumors, particularly in the peripheral zone (PZ), are conspicuous on T2 imaging as low signal foci compared to intermediate to high signal in the healthy background PZ (Fig. 2). More linear and wedge shaped low-signal foci in the PZ can be attributed to areas of scarring from infection, or fibrosis, therefore functional data from DWI (and to a lesser extent DCE sequences) is key in interpreting PZ changes.

The prostatic TZ is comprized of stromal and glandular tissue with benign nodules recognized in almost all patients undergoing mpMRI.[15] These can return heterogeneous T2 signal and varying degrees of restricted diffusion and enhancement. Benign nodules within the TZ are characterized by a continuous surrounding low signal capsule, which is best identified on axial T2. The addition of a second orthogonal plane can increase the radiologist's confidence for identifying the nodule as benign. The presence of microcystic

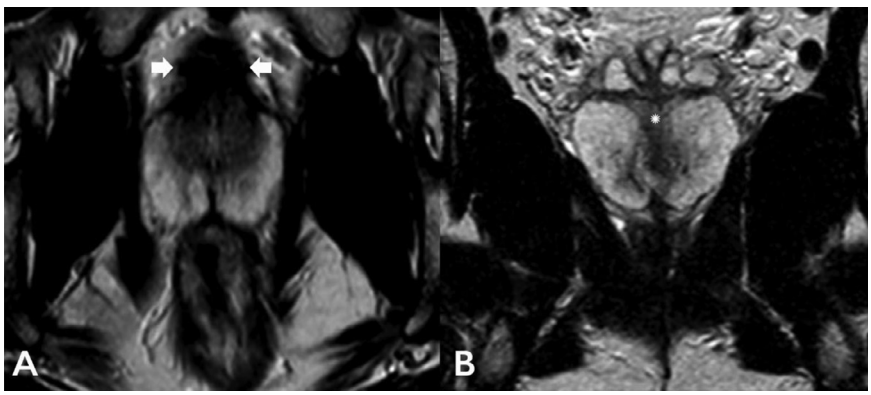

Figure 1 Normal prostate zonal anatomy. (A) Axial T2w image of the prostate. Normal appearances of the peripheral zone that returns uniform high signal. Low signal stroma is seen within the Transitional zone. Arrows indicating the normal anterior fibromuscular stroma. (B) Coronal T2W image of the same prostate. The normal Central zone is marked by an asterisk.

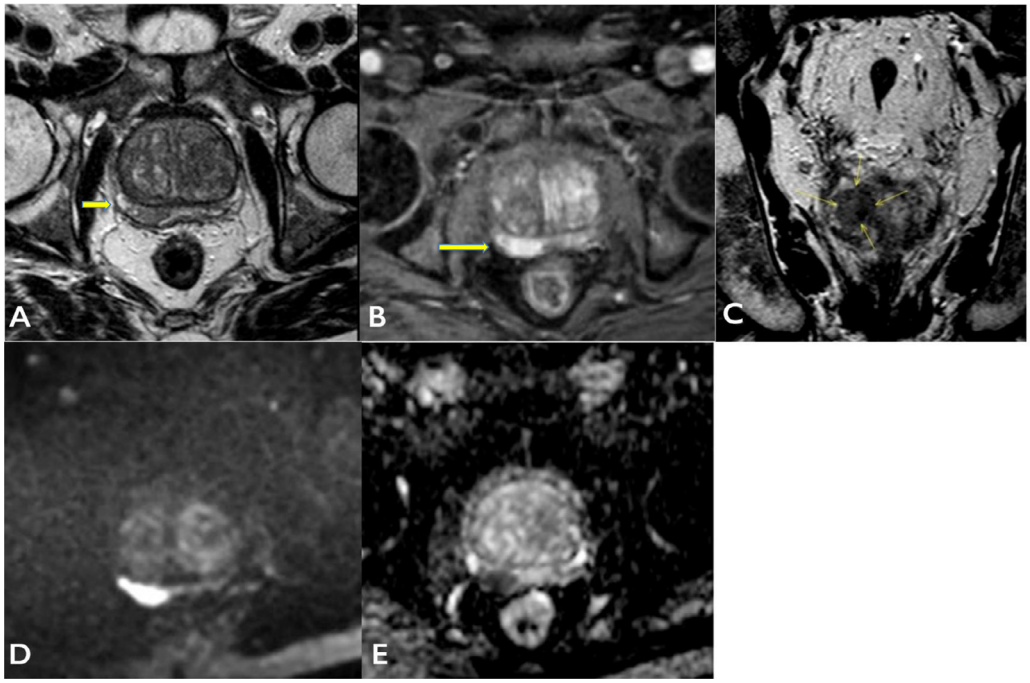

Figure 2 PIRADS 5/5 lesion in the right peripheral zone. (A) Axial T2w image of the prostate. Ill distinct low T2 region in the right peripheral zone (PZ) (arrow). (B) DCE 2 minutes image of the prostate shows avid enhancement in this right PZ (arrow). (C) Coronal T2w image that better demonstrates the focal low T2 lesion (arrows). This is a good example of how an alternative plane can help interpret a low signal area. (D) B1400 DWI image with high signal in the right PZ lesion that indicates marked restricted diffusion, confirmed in the corresponding ADC map E.

change also suggests a non-malignant pathology.[13] Adenocarcinoma in the TZ is less common than in the PZ (30% vs 70%)[16] and can be difficult to detect amongst background change; PIRADS v2.1 has been updated to specifically help with assessment of the TZ.[13,17]

An entirely encapsulated TZ nodule is scored as a 1 within the PIRADS framework, whilst an incomplete capsule around a nodule (atypical nodule) or a focal area of mild hypointensity within the TZ, interspersed between nodules, is scored a 2. If an atypical nodule demonstrates markedly restricted diffusion then this should be upgraded to a score 3. It is important to consider, however, that if several discrete, similarly appearing nodules within the TZ all demonstrate restricted diffusion, then this might be a feature of the background TZ and each nodule should not be individually scored a 3.

On T2 imaging, TZ tumors (Fig. 3) are often described as having a smudge like or "erased charcoal sign" appearance, with a lack of defined capsule. In addition, they can typically take a lenticular shape, particularly anterior tumors and those abutting the "surgical capsule" between the PZ and TZ.[18] PIRADS 3 lesions within the TZ include areas of ill-defined, heterogenous low T2 intensity that may demonstrate restricted diffusion, and measure less than a 1.5 cm. If the region of restricted diffusion measures more than 1.5 cm this is upgraded to a PIRADS 4 lesion. Abnormal T2 areas that measure greater than 1.5 cm, or those with clear extra-prostatic extension are scored PIRADS 5.

The normal central zone (CZ) can be tricky to differentiate from tumor as its dense stromal tissue returns low signal on T2. The CZ, in particular, can be prone to misinterpretation, particularly when the prostate is large, with distorted and asymmetrical anatomy. Clues to the identification of the normal CZ are its close relationship to the ejaculatory ducts at the base of the gland and its cone-shape confluence of fibres at the verumontanum; this is in combination with symmetrical DWI signal and enhancement. The anterior fibromuscular stroma refers to the tissue that lies anterior to the prostate. The anterior fibromuscular stroma returns low signal on T2 imaging and should be interrogated carefully, particularly in cases with anterior TZ tumors, which can invade anteriorly into this region.

DWI

DWI produces a visual representation of the movement of water molecules in tissue. Water molecules can freely move within healthy prostatic tissue (several hundred microns), compared to more limited flow within highly cellular tumor where diffusion is restricted to submicron to tens of microns in range.[19]

Imaging at successive imaging points with different gradient strengths (b-values) allows the discrepancy in diffusion between healthy tissue and tumor to become evident. On "high b-value" images the tumor is conspicuous as a bright focus on a dark background of normal tissue. The calculated apparent diffusion coefficient maps (ADC), extrapolated from the DWI data, shows tumors as a low ADC signal. Both the high b-value and ADC images need to interpreted together, to ensure true presence of an abnormality. B-values of at least 1000 s/mm^2 are required to nullify the DWI signal

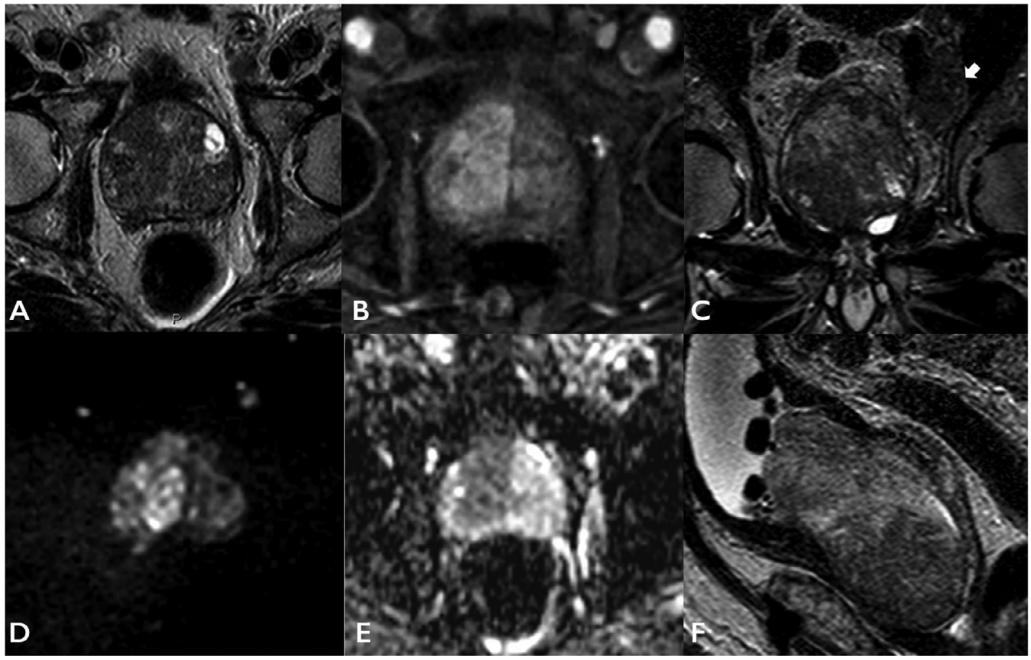

Figure 3 PIRADS 5/5 lesion in the right transitional zone. (A) Axial T2w image of the prostate showing an ill distinct low T2 region in the right TZ. This is also well seen in images C (coronal) and F (sagittal) T2 planes. (B) DCE 2 minutes image showing marked early enhancement of the entire right TZ compared to the left. (C) coronal T2W image showing tumor but also metastatic left pelvic side wall lymph nodes (arrow). (D) B1400 DWI image showing high signal in the right TZ in keeping with restricted diffusion as evidenced by low signal in image E (ADC map).

retained by healthy tissue[20] and several studies have shown even higher b-values of up to 2000 s/mm^2, could provide higher sensitivity of identifying tumors particularly in the PZ.[21] The PIRADS framework suggests B value of at least 1400 s/mm^2.[13] The trade-off is the higher the b-value the greater the geometric distortion and poorer resolution from reduced signal-to-noise ratio.

There is growing evidence that DWI imaging can differentiate between low and higher grade cancers, predicting Gleason $\geq$4 disease in the PZ using semi-quantitative analysis of signal intensity.[22,23]

DCE

DCE exploits the differences in vascularity and permeability of tumor vessels. Tumors demonstrate exuberant proliferation of abnormal friable blood vessels due to vascular endothelial growth factor secretion. Higher grade prostate cancer (particularly in the PZ) correlates with increased intratumoral microvessel density histologically.[24] T1-weighted fast gradient-echo images are acquired pre-contrast and then at multiple time points following intravenous gadolinium injection, with a recommended temporal resolution of less than 15 seconds, and overall time period between 2 and 5 minutes. Pre-contrast T1 images should be assessed for the presence of postbiopsy haemorrhage, which can be misinterpreted as enhancement. Normal PZ tissue will tend to enhance slowly and uniformly after approximately 30 seconds, whilst tumor enhances promptly and homogenously in the arterial phase. Benign adenomatous nodules will also commonly enhance early post contrast,[25] albeit more heterogeneously, but highlighting the importance of considering all the mpMRI sequences together.

Both quantitative assessment of enhancement using washout curves and qualitative interpretation of DCE sequences have been described in the literature. In recent years the PIRADS steering committee have concluded that there is insufficient evidence to recommend semiquantitative DCE analysis, which is partly due to the variability in the techniques to quantify enhancement and the inconsistency in DCE protocols between different institutions. Instead the PIRADS recommendation is to describe focal enhancement corresponding with abnormal T2 or DWI findings as positive DCE (DCE +ve) whilst normal enhancement pattern *or* diffuse multifocal enhancement is defined as negative (DCE −ve).

Overall Approach to Scoring Using PIRADS

DWI and/or ADC is the dominant sequence in scoring PZ lesions within the PIRADS framework. Normal or ill-distinct signal abnormality on DWI and/or ADC images with homogenous high T2 or minimal linear or wedge-shaped T2 changes are designated as PIRADS 1 or 2 respectively. Abnormal focal high signal on high-b value DWI and low signal on ADC map must be correlated with T2 sequences and assigned a score of 3 or 4 (mild or marked hypointensity on ADC and mild or marked hyperintensity on DWI). In lesions that score 3 on DWI and T2 sequences, if there is focal early

enhancement post contrast (DCE positive) this lesion is upgraded to a PIRADS 4. A PIRADS 5 lesions would consist of a larger nodule (>1.5 cm) of marked DWI and/or ADC abnormality and corresponding T2 change, including evidence of clear extraprostatic extension (EPE).[12]

T2 is the dominant sequence in PIRADS scoring of the TZ, with DWI and/or ADC sequences useful in specific scenarios to help characterize atypical nodules.[13]

It is clear that, with PIRADS, DCE has a limited role in the assessment of prostate for cancer (the only formal role is in upgrading PIRADS 3 lesions on DWI and/or ADC and T2 in the PZ). However, DCE can be crucial when the DWI imaging is inadequate (eg, rectal gas artefact) and it has a useful role in postoperative and postradiotherapy assessment.[26,27] Moreover the addition of DCE-MRI can often be useful in establishing a non-malignant diagnosis (such as prostatitis and/or atrophy) and can improve confidence in reporting lesions seen on T2 and DWI.

There have been several single-centre prospective trials that describe the use of biparametric MRI (ie, T2 and DWI without DCE) to help risk stratify men pre-biopsy; negative predictive values have been reported as high as 97% and without significant discrepancy in cancer detection compared to mpMRI protocols that include DCE.[28-30]

DCE may take a more limited role as a troubleshooting sequence in the future. However, the results of prospective trials evaluating biparametric MRI accuracy are awaited.

Use of mpMRI for Guiding Biopsy

The conventional diagnostic pathway of prostate cancer detection has until recently been based on a combination of elevated Prostate-Specific Antigen, digital rectal examination and transrectal ultrasound guided, systematic 10 to 12-core biopsies to "sample" the gland. There are significant limitations to this non-targeted approach to biopsy, including reduced sampling of the anterior periurethral and extreme apical gland (of up to 20%), which may miss clinically significant disease, and conversely, the potential for overdiagnosing clinically indolent cancers. Transrectal biopsy is a morbid procedure, with the small but significant risk of sepsis.[31,32]

In recognition that in virtually no other solid organ malignancy is a blind biopsy carried out without prior imaging, mpMRI now plays a more routine role in diagnosing and locating lesions, with targeted biopsy of those identified.[3,33]

Indeed, the 2019 UK The National Institute for Health and Care Excellence guidelines now recommend mpMRI as the first-line investigation for people with suspected clinically localized prostate cancer, with the results reported using a 5 point Likert scale.[34]

They further recommend that those scoring Likert 3 or more should be offered an mpMRI "influenced" prostate biopsy, and that biopsy can be omitted in those scoring 1 or 2, after appropriate counselling. This is a significant shift from previous guidance towards use of mpMRI only for those with a previous negative biopsy with an ongoing suspicion of cancer, or those undergoing active surveillance.

MRI-directed biopsy can be performed using MRI-ultrasound fusion software, or visual registration (ie, cognitive targeting of the MRI lesion by the clinician), or "in-bore" within the MR scanner. Currently there is no evidence to favour 1 technique over another.[35] All MR directed prostate biopsy techniques consistently offer increased detection of significant disease and reduced detection of clinically insignificant disease.[36]

The PROMIS trial evaluated the diagnostic accuracy of mpMRI in 576 biopsy naïve men who underwent both transperineal template mapping (comprehensive sampling of the entire prostate at 5 mm intervals) and standard systematic transrectal 12-core biopsies. mpMRI was found to be significantly more sensitive than transrectal systematic biopsy in detecting significant cancer (93% vs 48%) against template biopsy as the reference standard. In addition, the study suggested that up to 27% of men could avoid an unnecessary biopsy where mpMRI is used a diagnostic triage test. Furthermore there would be an improved detection of clinically significant cancer by 18%.[37]

Subsequent studies, including Prostate Evaluation for Clinically Important Disease: Sampling Using Image Guidance or Not? (PRECISION), have corroborated the improved detection rate of clinically significant prostate cancer using MRI directed biopsy.[38] PRECISION randomized 500 men to standard transrectal systematic biopsy, or mpMRI with MRI-targeted biopsy (in those with a lesion). PRECISION reported 12% more clinically significant cancer in those men randomized to MRI-targeted biopsies 13% fewer men diagnosed with clinically insignificant disease, additionally,28% of men receiving MRI avoided biopsy entirely.

Although the role of mpMRI in the detection of prostate cancer has been established, one needs to remember that both mpMRI and targeted biopsy will fail to detect clinically significant prostate cancer in a proportion of men. In a population where the prevalence of prostate cancer is 30%, a MRI-pathway can be expected to miss 84 significant cancers for every 1000 men.[39] Although this false-negative rate of MRI pathway is favourable compared to systematic biopsy alone (which would have missed 111 cancers in the same 1000 men) it highlights the need for follow up and safety-netting for men with a negative MRI.[36,39]

mpMRI for Staging

Prostate cancer spreads through the condensation of fibromuscular stroma surrounding the gland (known as the "capsule") into the periprostatic fat (stage T3a) and can extend into the seminal vesicles (stage T3b) or into local structures such as the rectum, bladder and pelvic side-wall (stage T4). mpMRI can identify gross EPE (Fig. 4), as well as assessment of abnormal pelvic lymph nodes. However, a meta-analysis review of mpMRI to stage local T3 disease revealed a low sensitivity of 0.66 and specificity of 0.88. The sensitivity was improved when using 3T MRI scanners with higher resolution T2 images. Overall, mpMRI did not perform well in predicting microscopic EPE.[40] Objective measures to predict microscopic EPE have been investigated, most commonly the length measured on T2 images of

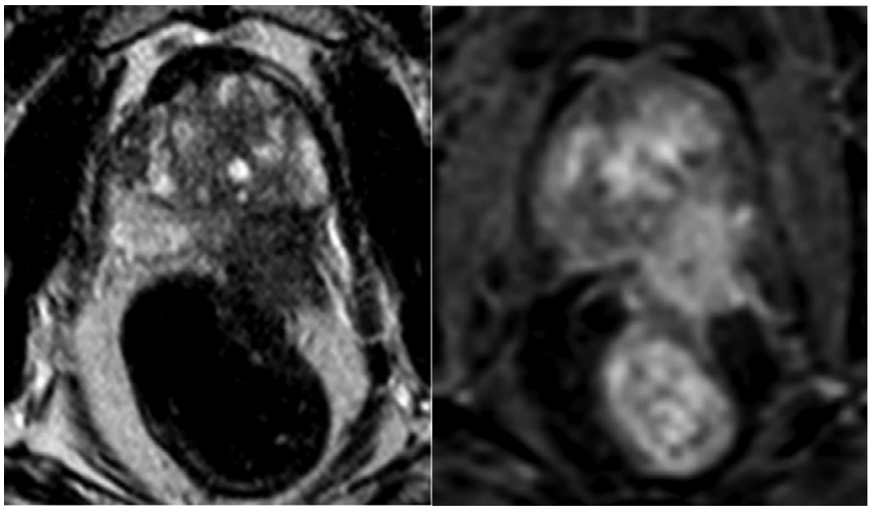

Figure 4 T4 Left peripheral zone lesion. (A) Axial T2W image of the prostate showing a large exophytic tumor erupting posteriorly from the left PZ and invading the rectum causing it to tent anteriorly. (B) DCE image shows abnormal tumoral enhancement and enhancing tissue extending laterally into the mesorectal fat.

curvilinear tumor capsular abutment. Tumor capsular abutment of 6-15 mm has been proposed as predictive for EPE, in combination with other features such as capsular bulging, with sensitivities of 0.7 and specificity of up to 0.72.[41-43] Local staging with mpMRI, with assessment of tumor volume and location, can impact the surgical approach, including in making the decision whether to spare the neurovascular bundles and/or bladder neck, both of which can impact on post-operative morbidity.[44,45] No method is superior to mpMRI in local staging of prostate cancer so future work will focus on validating and improving current mpMRI staging assessments.

Conclusions

MpMRI of the prostate has developed hugely since its conception. Improvements in MRI resolution and the adoption of functional images has led to high accuracy rates for ruling out clinically significant disease, with improved sampling on targeted biopsy, and lower rates of overdiagnosis of clinically indolent disease. PIRADS has been adopted internationally as an evidence based consensus for standardising the acquisition and interpretation of prostate mpMRI. Evolution of its recommendations, as new evidence becomes available, should lead to further improvements in the use of mpMRI within the diagnostic pathway, and for planning treatment and follow-up. Recently updated guidelines have further elevated the diagnostic role of mpMRI. The challenge will be to provide and maintain imaging standards sufficient to accurately rule out the presence of clinically significant disease, if men with a "negative" MRI are to safely avoid biopsy altogether.

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