Role of MRI for the Detection of Prostate Cancer

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Abstract

The use of multiparametric MRI has been hastened under expanding, novel indications for its use in the diagnostic and management pathway of men with prostate cancer. This has helped drive a large body of literature describing its evolving role over the last decade. Despite this, prostate cancer remains the only solid organ malignancy routinely diagnosed with random sampling. Herein, we summarize the components of multiparametric MRI and interpretation, and present a critical review of the current literature supporting is use in prostate cancer detection, risk stratification, and management.

Introduction

Prostate cancer (PCa) represents the most common solid organ malignancy in men with almost 1.3 million new cases diagnosed globally in 2018[1] . However, despite a high incidence, many will be asymptomatic, and only a minority will result in PCa death.[2] Accurate identification of men who are at risk of metastasis or death remains a challenge. As such, a large proportion of men will undergo definite treatment, potentially without ever realizing long-term benefit [3].

Prostate-specific antigen (PSA) remains the gold-standard for screening and given its poor specificity, its utility has been debated [4]. A trans-rectal ultrasound (TRUS) guided systematic biopsy (SBx) is the conventional next step in the diagnostic pathway. However, TRUS itself has a limited role in detecting PCa as most hypoechoic lesions are benign with even up to 50% of palpable tumors being invisible on imaging.[5] Major concerns of SBx include sampling error by which 20-50% clinically significant (cs) PCa may be missed - the majority of which are located in the anterior gland and prostatic apex.[6] Additionally, given its random nature, SBx identifies a large number of indolent cancers and exposes the patient to the risk of additional testing and procedures which can result in unnecessary stress, morbidity and waste of resources.

Multiparametric MRI (mpMRI) has been increasingly used in a number of clinical settings. It has been employed as a particularly useful tool to help address the shortcomings of the established pathway described above. It is composed of anatomical sequences (T1-weighted [T1W] and T2-weighted [T2W] images), combined with functional sequences, including dynamic contrast-enhanced MRI (DCE-MRI) and diffusion-weighted imaging (DWI). Its application has been transformative in the detection, localization, and staging of PCa.[7,8]

After an initial rise in the incidence of PCa secondary to widespread PSA screening, it has stabilized or even declined in some high-income countries.[9] This has been partly attributed to a number of novel risk stratification tools including mpMRI which have proven to have better discriminative ability prior to prostate biopsy.[10] We aim to provide a critical appraisal of the literature with regards to the role of mpMRI in the PCa diagnostic pathway.

Principles of Multiparametric Prostate MRI

Currently, 1.5 and 3 Tesla (T) are the two most common magnet-field strengths utilized in clinical prostate MRI. A 3T MRI, in most scenarios, will provide improved spatial resolution due to the higher signal-to-noise ratio but will also amplify the presence of artefacts (Figure 1).[11] Although subjective, image quality at 1.5T is generally lower than at 3T, the Prostate Imaging – Reporting and Data System (PIRADS) scores are similar in the two groups without an endo-rectal coil (ERC).[12] Additionally, the utilization of an ERC can result in up to tenfold improvement in signal-to-noise ratio.[13] Though the use of an ERC provides better image quality and results in greater sensitivity to detect prostate cancer, the specificity can decrease and it increases unique opportunities for image degradation (e.g. air, malpositioned coil, gland deformation).[14] Further studies aiming a comparison between 1.5T mpMRI with ERC and 3T mpMRI without ERC showed no significant differences in diagnostic accuracy.[15] Furthermore, the use of ERC is associated with increased discomfort and preparation time.[11] Contemporary recommendations in PIRADS states that both 1.5T and 3T without the use of an ERC may generate satisfactory results.[16]

Anatomic T1-weighted and T2-weighted MRI

The T1W and T2W phases provide predominantly anatomic information. While the T1W images can detect hemorrhage (mostly caused by prior biopsy), T2W images provide sufficient resolution to examine the zonal anatomy and provide insight with regards to the local staging.[17] Hemorrhage will manifest as high signal intensity (SI) in T1W images and low in T2W which can obscure the diagnosis of underlying disease (Figure 2).[18] Although there is no consensus to conclude the best interval between prostate biopsy and MRI, many clinicians suggest a 6-12 week time interval for better interpretation.[19] Though there is widespread acceptance of evidence supporting MRI prior to biopsy, which can avoid the hemorrhage and post-biopsy artifact, a large proportion of biopsies are still performed without a prior MRI due to insurance coverage or access to reliable, high quality imaging.

Given its high spatial resolution, the peripheral, transitional, and central zone can be identified as high, heterogeneous and low SI in T2W images, respectively.[20] A lower heterogenous SI lesion in the peripheral zone may be considered as suspicious for tumor.[21] However, T2W alone has high sensitivity but low specificity in detecting PCa; also, many benign lesions, i.e. prostatitis and fibrosis, also generate low SI which mimic PCa.[20] Morphologic features such as non-circumscribed or lentiform structures are more likely to be malignant lesions and are used for further

differentiation. The heterogeneous SI in transitional zone makes diagnosis a greater challenge and interpretation relies more so on morphology. Functional sequences should be used in conjunction with T2W to increase the accuracy of PCa detection.

Diffusion-weighted image

DWI quantifies the random displacement of water molecules, known as diffusion or Brownian motion, which is affected by the cellular environment. The b-value is the foundation of DWI which represents the strength of the diffusion sensitizing gradient and is measured in seconds per square millimeter. A high b-value setting can suppress benign prostate tissue and increase the contrast between normal and abnormal prostatic tissue, predominantly suspicious for cancer.[22] The latest PIRADS version, v2.1, recommends image acquisition at a b-value of 1400-2000 s/mm2.[16] However, high b-value, e.g. 2000 s/mm2, has very low signal-to-noise ratio while b-value of 1000 s/mm2 has high signal-to-noise ratio but lower normal tissue suppression.[23] An apparent diffusion coefficient (ADC) map is designed to overcome this situation by calculating at least two different b-values. On the image, an area with limited diffusion coefficient showed high SI in the DWI and low SI in the ADC map. PCa tissue tends to have higher cellularity which results in impeded diffusion of water molecules, demonstrating high SI in b-value and low SI in ADC on DWI.[24] A schematic of MR images according to PIRADS is noted in Figure 3.

Dynamic contrast-enhanced MRI

DCE-MRI reflects the vascular distribution and capillary permeability of tissue, a surrogate for neoplastic neovascularization. The features of PCa presenting on DCE-MRI demonstrate an earlier intense enhancement than normal prostatic tissue.[25] A fast (2-3 cc/s) injection of gadolinium-based contrast agent and high temporal resolution acquisition (<15 s) is essential.[16] However, there are pitfalls in DCE-MRI interpretation such as prostatitis and BPH nodules that may exhibit similar DCE characteristics.[20] Although PI-RADS v2 recommends DCE-MRI as essential in every patient unless there is a contraindication, the evidence supporting its necessity is controversial.[19] Moreover, there are issues related to the utilization of gadolinium-based contrast agent as time considerations and the risk of adverse events, including nephrogenic systemic fibrosis and accumulation.[26] In response, the biparametric MRI (bpMRI) protocol was proposed to exclude the routine utilization of DCE-MRI during screening or follow-up and may serve as future standard of care protocol for screening.[27,26]

MRI Interpretation

Initial guidance for prostate MRI interpretation was limited with no standardized criteria available. Radiologists historically used Likert scale-based reports which though correlating with cancer detection and Gleason score, varied by institution. The lack of criteria resulted in inter-reader variability and made it challenging to compare outcomes across cohorts.[28]

The PIRADS document represents the current standard for image acquisition and interpretation based on expert consensus. It is a multinational, multidisciplinary consortium supported by both the American College of Radiology and European Society of Urogenital Radiology.[29] The accuracy and reproducibility of this first generation system(sensitivity and specificity f 0.78 and 0.79 respectively) has been validated in a meta-analysis.[30] Although PI-RADS provided a common reporting language, several issues remained. The overall score was not standardized, with some studies publishing a summary score from each sequence, from 3 to 15 while others using a 1 to 5 overall score.[31,32] Version 2 was released in 2015 to address these deficiencies.[33] The major changes included the introduction of the dominant sequence in different anatomical zones: DWI and T2W in peripheral and transitional zone, respectively. This version also limited the weight of DCE imaging.[34] A recent meta-analysis reported a pooled sensitivity and specificity of 0.89 and 0.73 with a significant sensitivity increasing when it comes to head-to-head comparison.[35]

A less costly and abbreviated acquisition protocol termed bpMRI which requires only T2W images and DWI parameters, high b-value DWI and ADC maps, has been proposed.[26] Validation studies have shown there are benefits to bpMRI alone, or in combination with clinical variables such as PSA and/or PSA density to detect csPCa in a biopsy-naive cohort.[36]

Inter-observer variability has been previously reported at 80%, likely impacts the accuracy of diagnosis. [37] The initial learning curve can affect inter-observer disagreement and prior work demonstrates rapid improvement in the first 40 cases. [38] In the hope of reducing inter-observer variability and simplifying assessment, PIRADs version 2.1 was introduced which maintained the majority framework of version 2 while incorporating some minor adjustments.[16] Critical changes focused on transition zone interpretation including upgrading of PIRADS 2 lesions to PIRADS 3 based on DWI scores. Given the low cancer detection rate of PIRADS 2 and PIRADS 3 lesions and the limited evidence to support it, adoption of PIRADs version 2.1 has been variable and the changes remain controversial. Five radiologist read a 355 patients cohort to concrete this concept that version 2.1 has better inter-observer agreement, especially in transitional zone. [39]

Clinical Utility of Multiparametric MRI in Prostate Cancer Diagnosis

The introduction of mpMRI and its evolving indications have transformed the diagnostic paradigm for prostate cancer. The growing body of evidence supporting its use has facilitated its inclusion in guidelines supporting its increased use and influencing coverage decisions to ensure reimbursement. Following MRI, targeted biopsy (TBx) can be directly biopsied under MRI guidance (in-bore MRI TBx), with software-based fusion biopsy platforms, or visual registration/cognitive fusion biopsy. [40] One-stop MRI TBx was also feasible for patient to receive TBx right after the mpMRI was performed which shows not inferior to traditional TBx at the second visit and provides shorter diagnosis time. [41] **Table 1.** summarizes selected studies verifying the role of mpMRI and its accuracy in different clinical scenarios in recent years.

Biopsy naïve population

Prostate ultrasound has limited discriminative value for benign and malignant lesions. Additionally, given its random nature, sampling is not directed to areas of highest yield for clinically significant disease. PSA-detected indolent PCa captured by SBx had no survival benefit with treatment in the ProtecT trial at 10 years follow-up.[3] Given the poor specificity of PSA alone, men are unnecessarily exposed to the risks of biopsy including infectious hospitalizations/sepsis(1-4%), hematuria, hematochezia, lower urinary tract symptoms, and urinary retention, amongst others. [42] At the same time, a considerable proportion of significant PCa is overlooked. The ability to better identify a priori which men should undergo biopsy to detect significant PCa, and ensure that biopsy will provide the most accurate and useful result is improved by the mpMRI.

A systematic review assessing the diagnostic accuracy of mpMRI showed sensitivities of 58-96%, specificities of 23-87%, and negative predictive value of 63-98%.[10] And a more recent review showed mpMRI had a pooled sensitivity of 91% with a pooled specificity 37%.[43] Although results were overall promising, the wide ranges reflect study limitations including single-center series and retrospective design.

The Prostate MR Imaging Study (PROMIS), was a prospective paired validation cohort study that aimed determine whether mpMRI before biopsy can be beneficial to patients.[44] This study used transperineal template mapping biopsy as the reference standard, of which technique reported to have the negative predictive value (NPV) of mpMRI for PCa was 92%; and the NPV for csPCa was 89% for Gleason score ≥4+3/any cancer core length ≥6 mm and 72% for Gleason score ≥3+4 / any cancer core length ≥4 mm.[45,46] This PROMIS study proposed diagnostic pathway with mpMRI pre-

biopsy could avoid biopsy in 27% of patients while identifying 17% more clinically significant cancers if only those with MR-visible lesions required biopsy.[37] Fusion biopsy has been shown to add diagnostic value compared to conventional TRUS biopsies alone in meta-analysis and further supported by more recent single institution, prospective studies.[47-49] The PRECISION trial was a multi-national trial randomizing 500 biopsy-naïve patients into two groups: mpMRI with or without TBx alone versus standard TRUS biopsy. [50] The primary endpoint of the trial was to compare the proportion of csPCa, grade group (GG) ≥ 2, detected by both diagnostic pathways. It ultimately demonstrated that mpMRI and TBx was superior to TRUS biopsy, with the csPCa detection rate being 36% and 26% in mpMRI and standard pathway, respectively. Consistent with prior studies, detection of clinically insignificant PCa was lower in the mpMRI group. Given that men with a negative mpMRI did not undergo biopsy, the NPV was not determined.

The primary endpoint of a recent prospective, multicenter, and paired diagnostic study (MRI-FIRST trial), in men undergoing SBx alone if mpMRI was negative or SBx and TBx if a lesion noted, was detection of ≥GG2.[51] SBx alone identified 30% of significant cancers, while TBx alone found 32%. There was no difference in detection of clinically significant cancer between the groups, highlighting the need to both systematic and targeted sampling.

The PRECISION and PROMIS trials reported about that a quarter of patients, 28% and 27% respectively could potentially avoid biopsy completely. van der Leest et al. reported the avoidance rate was almost half, 49%; and for those patients without a suspicious lesion on MRI, 3% harbored csPCa at immediate biopsy, increasing only to 4% at 1 year follow-up.[52,37] This was a head-to-head prospective multicenter trial using GG ≥ 2 in any core as csPCa and double expert consensus reading which minimizing the PI-RADS 3 diagnosis (6%) which was notable less prevalent than prior studies (22%-32%).[53] Moreover, the clinically insignificant PCa detected rate was reported to be 14% and 23% in MRI and TRUS biopsy pathway respectively.[52]

MRI has been studied as a triage tool to aid in selection of men who would benefit the most for biopsy. Immediate biopsies can be selectively avoided in patients with negative mpMRI study and favorable PSA values/density.[54] While the identification of targets for sampling has improved the diagnosis of csPCa, there appears to be a continued role for systematic sampling. The optimal screening MR protocol and cost-effectiveness require further study.

Repeat biopsy setting

Prostate MRI initially established its role in men with a prior negative biopsy and continued suspicion for occult disease. [47,48,55] Historically, a high proportion (60-75%) of 'blind' biopsies in men with elevated PSA/abnormal DRE resulted in benign pathology[56,57] A false negative on SBx may lead to delay in treatment and often requires additional biopsies with additional core sampling to achieve an accurate diagnosis.[58]

MpMRI with fusion biopsy can identify areas outside of the conventional template (anterior, midline, distal apex). The PICTURE trial [59], a paired-cohort validating confirmatory study, examined patients requiring repeat biopsy using transperineal template mapping biopsies as reference standard. It showed that the most patient with negative MRI can avoid immediately biopsy according to its high NPV, 91% in Likert score $\geq$ 3 and 83% in Likert score $\geq$ 4 group respectively. Another multi-institutional review concretes this concept with a result that all TBx are more accurate than standard biopsies despite the numbers of prior negative biopsy results.[55] The consensus statement by American Urological Association and Society of Abdominal Radiology also advised the patient warrant repeat biopsy when MRI detected PIRADS 3-5 lesions and at least two cores should be sampled at each lesion.[60]

Utility of MRI in Active surveillance

Active surveillance (AS) should be the standard of care in low and very-low risk PCa. It has been widely adopted as maturing data of long-term AS series and the ProtecT trial have demonstrated favorable outcomes.[3] Despite this, a number of men and physicians still elect for definitive treatment due to ongoing patient and physician uncertainty regarding patient's disease status. Historical tools for risk stratification (PSA, DRE, and Gleason score) have been insufficient although, recently serum, tissue, and imaging-based biomarkers have shown significant promise. The concept of MRI as a confirmatory test during the consideration phase of AS was introduced to gain additional information into disease risk prior to selecting a management strategy or initiation of AS.[61] Using MRI based scoring system, prostate cancer radiological estimation of change in sequential evaluation (PRECISE) for example, showed the evidence to reduce the disqualified rate compared with 12-core based AS candidate.[62] MRI can help identify suspicious lesions that can be targeted during confirmatory biopsy.[63,48] Though MRI is imperfect, it has been shown with alternative confirmatory tests to reduce the incidence of adverse pathology in men who proceed to radical prostatectomy.[64]

The ASIST trial randomized 273 men to either confirmatory SBx alone, or MRI with systematic and TBx in men initially diagnosed with GG1 PCa. TBx did not demonstrate a significantly higher upgrading risk than SBx, however, each modality identified unique cases of upgrading, highlighting the value of both systematic and TBx information. [65] Additionally there were differences in TBx cancer detection rates between sites despite centralized MRI interpretation, potentially underscoring differences in experience or technique with fusion biopsy. Importantly, at 2-year follow-up there was a 50% reduction of AS failure in the MRI pathway, demonstrating a role for better long-term risk stratification.[66]

Incorporation of mpMRI for decision making seems reasonable to avoid unnecessary and frequent protocol biopsies due to reported high NPV.[60] Further studies for implementing mpMRI into current protocol for AS are still required.

Utility of MRI in target focal therapy

The morbidity of definitive treatment is a legitimate concern given the historical propensity of overdiagnosis and overtreatment of indolent cancers. Approximately half of patients are eligible candidates for focal therapy (FT). [67] As evidence demonstrates limited benefit from definitive treatment of favorable-risk prostate cancers, FT has become an appealing alternative. [68]
FT can ablate defined volumes of cancer while minimizing the collateral damage to vital structures, e.g. sphincter, bladder neck, and neurovascular bundle, and better preserve functional outcomes. [69] MRI with TBx help clinicians localize the lesion and accurately define the focal ablative volume to be treated. [70,71] MRI is also critical in post FT follow-up, where the DCE sequence becomes the dominant sequence although the number of studies is few. [72]
FT has achieved good short-term outcomes but still lacks long-term evidence, is composed of relatively small cohorts and lack comparative treatment outcomes. [73] Further high level trials providing evidence of outcomes and patient selection is requisite before FT becoming widely adopted.

Utility of MRI in pre-prostatectomy

MRI has adequate spatial resolution to characterize most prostate cancer location, size, adverse features. [74] The surgeon can use this information to stratify risk of extracapsular, plan bladder neck dissection and margins/nerve-sparing. A randomized control trail showed the benefit of reducing the positive margin rate in

cT1 cases only. [75] Further meta-analysis reported the surgical positive rate dose not associate with the MRI although surgeons still planning the neurovascular bundle depend on the image finding. [76] However, the MRI features such as tumor size and PIRADS score has additional value to predict post-prostatectomy biochemical recurrence which can provide further information to support clinical decision-making in intermediate and high-risk disease. [77]

Use of MRI in post-treatment follow-up

A number of options are available for the management of localized PCa including radical prostatectomy and radiation (EBRT and brachytherapy) in selected patients. Despite early diagnosis and treatment, biochemical recurrence can occur in up to 40%.[78] MRI can characterize locally recurrent disease after both surgery or radiation therapy and help guide salvage treatment options.
The acquisition and reporting system, including both anatomic and functional data, of mpMRI, is similar to PI-RADS version 2.[33] Although using similar sequences in the post-treatment setting, the anatomic changes after surgery, radiation and ablation represent unique challenges. Therefore, the functional information provided by dynamic contrast enhanced MRI and DWI, play a greater role in this setting. Some studies suggest that a complete mpMRI with endorectal coil, acquired at 3T with contrast injection, may help improve sensitivity and specificity.[79,80] While DWI can be useful for the differentiation between inflammation and post focal therapy or radiotherapy residual benign prostatic tissue from malignancy, image interpretation can be affected by artifacts generated from metal clips in the post-operative setting.[81] Additionally, perfusion characteristics on DCE MRI can provide diagnostic value especially in the post-radiation or ablation setting.[82]

Overall, recurrent tumors display similar characteristics to tumors diagnosed in the primary setting. However, the changes in post-treatment tissue that may mimic residual disease can be informed by clinical history and PSA kinetics.

Conclusions

Since its introduction into the diagnostic pathway, mpMRI and targeted biopsy have shown value in multiple clinical settings. Use of pre-biopsy mpMRI has the advantage of limiting the diagnosis of small volume, low risk cancers while simultaneously increasing the sensitivity to detect clinically significant prostate cancer. Currently, the combination of both systematic and targeted biopsies improves the diagnostic accuracy. As rapid adoption increase, a focus on quality assurance is imperative to ensure that similar outcomes are achieved outside of expert academic centers.

Conflicts of interest

Boris A. Hadaschik reports personal fees from ABX, Bayer, Lightpoint Medical, Inc., Janssen R&D, Bristol-Myers-Squibb and Astellas and travel from AstraZeneca, Janssen R&D and Astellas.

Acknowlegement

Mark Emberton receives research support from the United Kingdom's National Institute of Health Research (NIHR) UCLH / UCL Biomedical Research Centre.

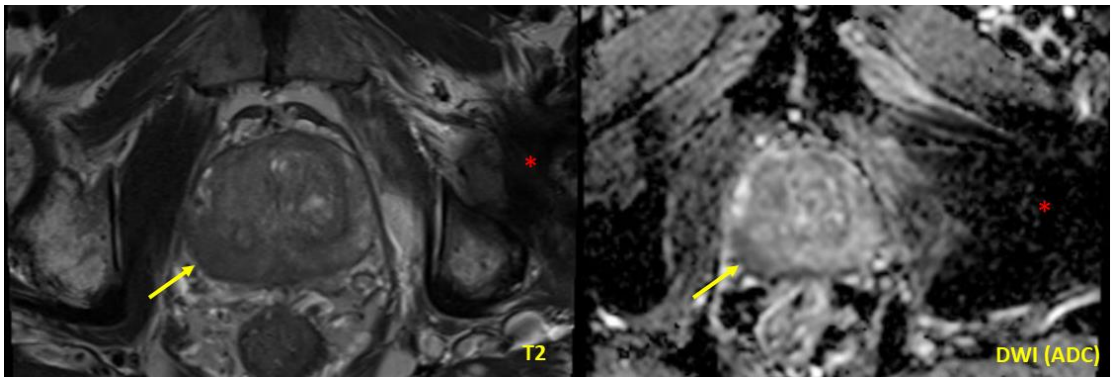


Figure 1. Granulomatous prostatitis mimicking high grade prostate cancer may manifest as a PIRADS 5 lesion on MRI. The arrow denotes a 2.2cm diffuse area of low signal intensity at the right mid peripheral zone that corresponds to restricted diffusion on the ADC map. The star denotes image artefact introduced by a left hip prosthesis. Despite the presence of a prosthesis, the images are diagnostic and can still provide important information for detection and staging.

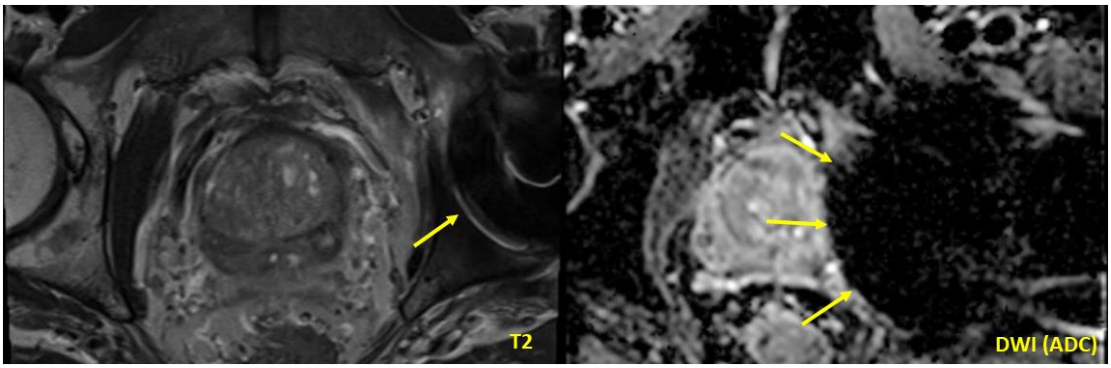
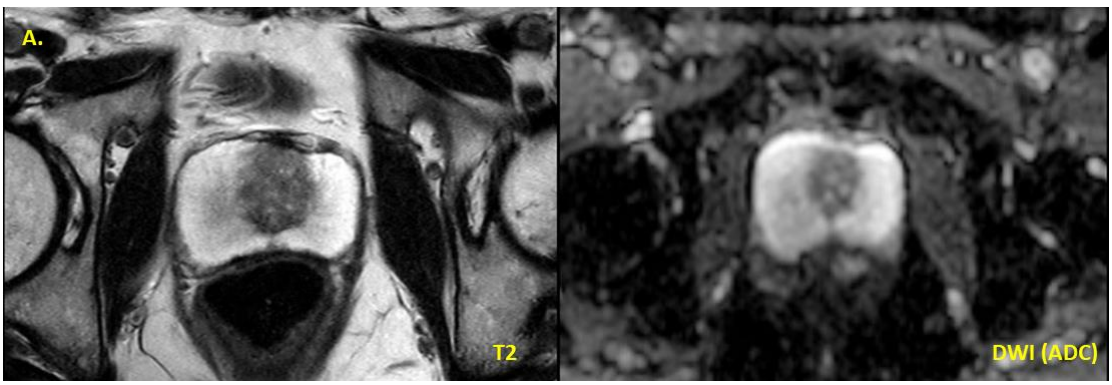
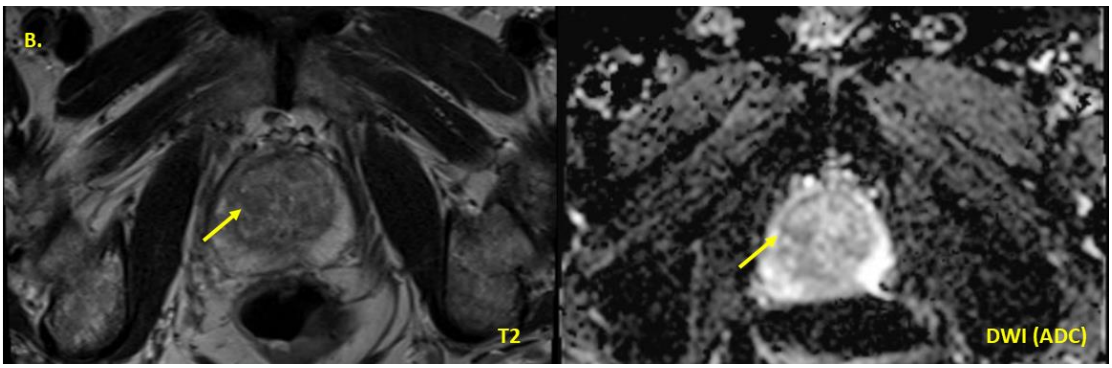
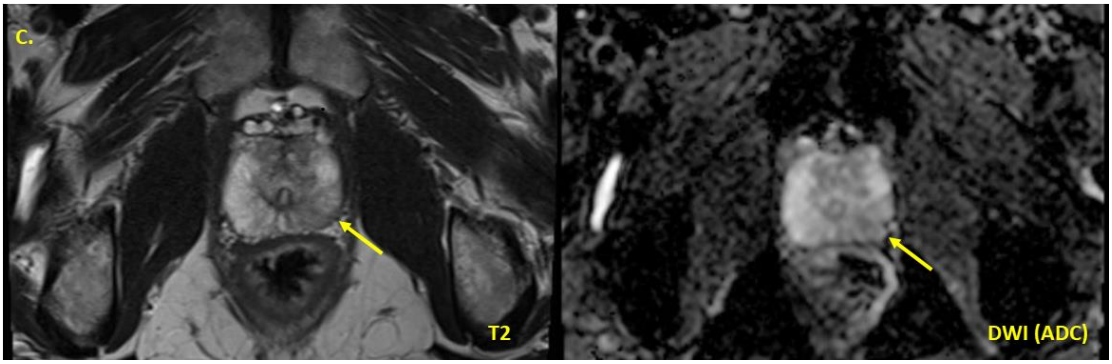


Figure 2. Imaging artefact introduced by the presence of a left hip prosthesis. On T2 weighted imaging the distortion does not obscure the prostate image, however on diffusion weighted imaging the prosthesis renders interpretation of the left lateral aspect of the prostate non-diagnostic.




B.
T2
DWI (ADC)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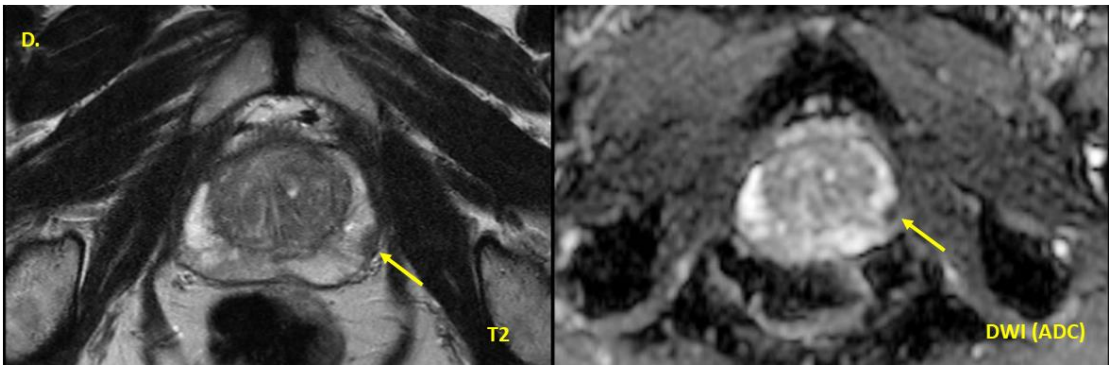
T2
DWI (ADC)


D.
T2
DWI (ADC)

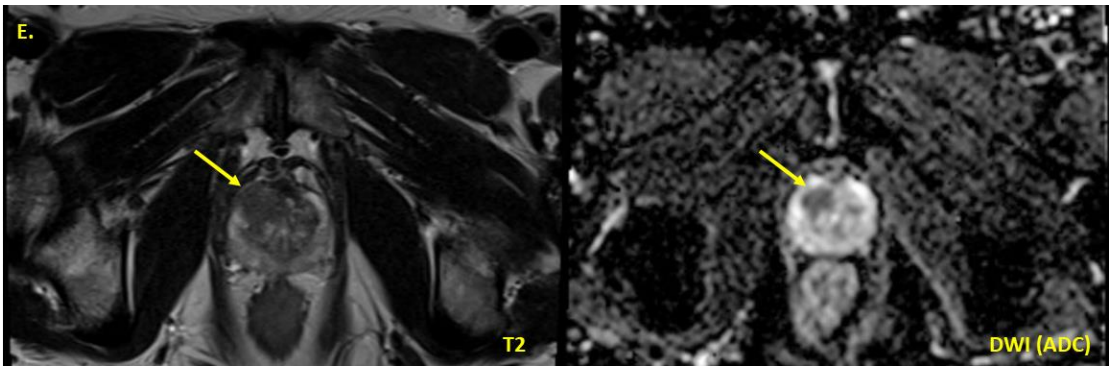

E.
T2
DWI (ADC)

Figure 3. PIRADS v2.1 provides standardization of image interpretation of multiparametric Prostate MRI. A) T2-weighted and ADC map of PIRADS 1 demonstrating a peripheral and transition zone without evidence of low signal intensity or restricted diffusion. B) PIRADS 2 lesion of the right anterior transition zone. T2-weighted imaging demonstrates low signal intensity within a well-circumscribed nodule consistent with BPH and ADC map demonstrates mildly restricted diffusion. C) PIRADS 3 finding consistent with prostatitis. Regional/diffuse low signal intensity of the left mid peripheral zone which corresponds to mildly restricted diffusion. D) PIRADS 4 lesion of the Left mid posterior lateral peripheral zone. There is an 8mm region of low signal intensity and corresponding restricted diffusion. E) PIRADS 5 lesion of the right apical anterior transition zone. The lesion demonstrates a classic “erased charcoal” appearance with indistinct border. The 1.7cm lesion exhibits capsular bulge concerning for extracapsular extension and corresponds to severely restricted diffusion on the ADC map.

Study	Level of evidence	Case number	Finding	Definition of significant Prostate Cancer
Biopsy naïve				
Kasivisvanathan et al. (**PRECISION**) [50]	1b Multicenter Randomized Noninferiority trail	500	PIRADS csPCa vs insignificant 3: 12% vs 22% 4: 60% vs 9% 5: 83% vs 11% TBx is superior to SBx	GG≥2
Ahmed et al. (**PROMIS**)	1b	576	Inter-observer agreement 80% Sens: 93%, Spec: 41% PPV: 51%, NPV: 89% Patient can avoid biopsy safely if MRI was negative	Likert score GG ≥ 3 (there are two other definitions)
Rouviere et al. (**MRI-FIRST**) [51]	1b 16 France centers prospective, multicenter, paired diagnostic study	251	no difference between SBx and TBx in csPCa (29.9% vs 32.3%). Improve after combination. MRI before biopsy is helpful but SBx is still essential.	Likert score GG ≥2
Porpiglia et al.[49]	1b	212	Both cancer and csPCa detection rate of TBx is better than SBx: PCa (50.5% vs 29.5%, respectively; p=0.002) and csPCa (43.9% vs 18.1%, respectively; p<0.001).	(biopsy GG ≥3 or maximum CCL ≥5 mm

van der Leest et al. [52]	2	626	Biopsy performed in-bore. csPCa 23% of TRUS biopsy and 25% of MRI guided biopsy. Biopsy in PIRADS 1-2 MRI found 3% (10/309) csPCa.	GG≥2
Prior negative/ Repeat biopsies				
Simmons et al. (**PICTURE**) [59]	1b prospective diagnostic validating cohort	249	Repeat biopsy can be avoided by mpMRI. But still some csPCa may be missed	Likert GSG≥3 Cancer core length ≥ 6mm
Wegelin et al. (**FUTURE**) [83]	1b? Multicenter randomized controlled trial	665	The additional value of SBx was limited, and only 1.3% of csPCa would have been missed when SBx had been omitted	GG≥2
Sidana et al. [55]	2	779	Total csPCa was 30.7% and TBx csPCa was 26.3%. TBx is outperforming SBx in prior negative patient.	GG≥2
Truong et al. [84] (aim for benign lesion)	2	285	In prior negative patients, false positive MRI may occur in up to 46.3%.	GG≥2
Active surveillance				
Klotz et al. (ASIST) [65]	1b prospective randomized multicenter open-label	273	No difference in upgrading rate. Both TBx and SBx missed 8% and 6% csPCa. In the most experience sites, TBx is superior to SBx.	GG ≥2
Tran et al. [85]	2	207	40% experienced any upgrading, including 24% on systematic sampling,	Upgrading: GG2

			14% on MRI-targeted cores, and 2% on both. upgrading also occurred in areas outside TBx, suggesting that systematic sampling should be offered to men with AS	Major upgrading: GG3
Jayadevan et al[86]	2	332	Confirmatory biopsy with MRI guidance is significantly associated with future disease upgrading of prostate cancer, especially when combined with PSA density. Upgrade to at least GG3 rate 7.9% vs 11.4 vs 23.3% in confirmatory normal, GG1 and GG2, respectively.	Upgrading GG3
Frye et al. [87]	2	166	TBx alone identified 44.9% of patients who progressed compared to 30.6% identified by systematic 12-core biopsy alone 81% NPV in detecting pathological progression Multiparametric magnetic resonance imaging progression predicts the risk of pathological progression.	Upgrading GG 1 to 2 Or GG 2 to 3
Miscellaneous				
Siddiqui et al. [48]	2	1003	TBx diagnosed 30% more high-risk cancers vs SBx (173 vs 122 cases, P <.001) and 17% fewer low-risk cancers (213 vs 258 cases, P <.001).	High volume GG2 and ≥GG3
Ahdoot et al. [91]	2	2103	TBx alone found 12.7% ≥GG2 cancers vs SBx (5.8%) TBx found 3.5% new GG1 cancers vs SBx (7.8%) Combined TBx and SBx can provider more accurate diagnosis which is 9.9% more than either technique alone.	GG2

Table 1. Studies of mpMRI with or without targeted biopsy for detection prostate cancer. csPCa: clinically significant prostate cancer; GG: grade group; TBx: targeted biopsy; SBx: systematic biopsy.

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