**Integrating MRI for the diagnosis of prostate cancer**

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**Abstract (200/200 max)**

*Purpose of review*

We review recent developments in prostate MRI for prostate cancer diagnosis.

*Recent findings*

Large series have strengthened the case for the use of MRI prior to subsequent biopsy to maximise the detection of clinically significant disease, and reduce the detection of clinically insignificant disease. This has effectively moved the discussion on from whether MRI is useful in prostate cancer detection to how best to use it, and at which time point. The PIRADS group have published a second version of the PIRADS criteria for prostate MRI, covering acquisition, interpretation and reporting both for clinical practice and data collection for research.

There is debate about the commonly used and more prescriptive PIRADS system versus the less prescriptive systems based on overall clinical impression of clinically significant disease (eg Likert or SQS scoring). Studies suggest that the Likert or SQS approach may outperform PIRADSv2. Published data are conflicting on whether software assisted fusion of MRI lesions to ultrasound used at biopsy is more effective than visual registration by a trained operator.

*Summary*

The use of prostate MRI is increasing worldwide, and the debate now focuses on how best to use it to optimise the detection of clinically significant disease.

**Keywords (3-5)**

Prostate cancer; multiparametric MRI; prostate cancer detection; screening

**Abbreviations**

Apparent diffusion coefficient (ADC) map

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI)

Diffusion-weighted imaging (DWI)

Endorectal coil (ERC)

Magnetic Resonance Imaging (MRI)

Multi-parametric MRI (mpMRI)

United Kingdom National Institute for Health & Clinical Excellence (UK NICE)

Transrectal ultrasound (TRUS)

**Introduction**

Magnetic resonance imaging (MRI) is being more widely used in the detection of prostate cancer. Its’ use is more common in the setting of an initial negative biopsy, but it is also of interest in the initial selection of men for prostate biopsy, with the aim of maximising the efficient detection of clinically significant disease, whilst reducing the detection of clinically insignificant disease.

The use of different scanning parameters (multi-parametric MRI or mpMRI) is well established. Diffusion-weighted imaging (DWI) allows an assessment of the movement of water in a given volume; this is typically restricted in cancer. This can be assessed directly from high b-value images (eg b1400, b2000), and also from assessment across a range of b values (apparent diffusion coefficient, ADC). Diffusion-weighted imaging has shown the greatest correlation with disease aggressiveness, where a lower ADC value corresponds to higher Gleason grade (1,2). Dynamic contrast enhancement (DCE) involves the rapid acquisition of images following intravenous injection of a gadolinium based contrast agent. Prostate cancer has a rapid wash-in and rapid wash-out phase, due to an enhanced blood supply, which is typically composed of leaky vessels. T1-weighted anatomical imaging is used to assess for the presence of haemorrhagic artefact in men who have had previous biopsy, whilst T2-weighted imaging gives the clearest anatomical imaging of larger tumours, which show as reduced signal on these sequences.

MR spectroscopy, which measures active metabolites within the tissue, has generally fallen out of favour, and is not recommended in the latest guidelines from the America College of Radiologists (ACR) and the European Society of Uro-radiology (ESUR) (3).

A recent study assessed the use of an endorectal coil (ERC) in men undergoing 3Tesla MRI scanning (4). Each of 49 men had an MRI examination using 1 of 2 different non-ERC protocols and an ERC protocol. This showed increased detection of cancer with and endorectal coil (78% sensitivity) versus a standard non-ERC protocol (43% sensitivity) or an augmented non-ERC protocol (60% sensitivity). However, the sensitivity of the non-ERC coil protocol was lower than is reported in many other series (5). The use of pelvic phased array coils alone is common amongst expert centres worldwide, and is within the guidelines of minimal acquisition requirements as set out by the ACR and ESUR (3).

One of the key questions currently is whether the results seen at expert centres around the world can be reproduced at other centres. A recent study compared the a series from the National Institutes of Health, USA with a propensity matched cohort at the Long Island Jewish Medical Centre (6). This showed no difference in the rates of upgrading by targeted biopsy at the two different centres, nor in the detection rate of clinically significant disease.

**New published data on MRI before biopsy**

Recent publications have shown the results of single centre series comparing standard and MRI-targeted biopsy in large cohorts of men. A prospective series of 1003 men at the National Institutes of Health, USA used a combined approach where all men with a lesion on MRI had a standard TRUS biopsy and a biopsy targeted to any MRI lesions, during the same procedure (7). The population was a mixed population of men who had prior negative or positive biopsy and some biopsy naïve men. Targeted biopsy diagnosed 30% more high risk cancers than standard biopsy (173 vs 122 men) and avoided the detection of 17% of low risk cancers (213 vs 258 men). When standard and targeted biopsies were combined, an additional 103 of men had a prostate cancer diagnosis than either approach alone. However, the majority of these additional diagnoses were of low risk disease (83% low risk, 12% intermediate risk, 5% high risk). It is important to note that this was not a typical ‘diagnostic’ population in that only 196 men had had no prior biopsy. However, a sub-group analysis showed that targeted biopsy performed similarly in both settings. The fact that all men had an MRI lesion should also be noted – this will result in a higher detection rate than a typical ‘first biopsy’ population where around 1 in 3 men will have no lesion (8).

A study of 1140 men randomised men to standard TRUS biopsy (arm A) or MRI with targeted biopsy where there was a lesion seen on MRI in addition to standard TRUS biopsy (arm B) (9). Men with a negative TRUS biopsy in arm A then underwent an MRI, with a targeted biopsy if a lesion was seen, or a saturation TRUS biopsy if no MRI lesion were seen. This study design is interesting in that it compares the two different pathways incorporating MRI that are often under discussion – to diagnose men with the most readily accessible prostate cancer using standard biopsy, and then to assess those with a negative biopsy with MRI. No men who had an MRI first had any Gleason 7 or greater cancer missed at initial biopsy; 37/130 (28%) men with a negative MRI and negative standard biopsy had Gleason 6 cancer detected on the subsequent saturation TRUS biopsy. For those who do not consider that there is clinical utility in diagnosing isolated Gleason 6 disease, then this saturation TRUS biopsy might be omitted in clinical practice.

The standard biopsy arm in this study resulted in 355/570 (62%) of men having an MRI after a negative biopsy, with 208 men having targeted biopsy plus repeat random biopsy, of whom 186 had cancer detected. Of 570 men in the MRI first arm, 130 patients had a negative MRI; none had significant cancer on TRUS, although 37/130 (28%) had Gleason 6 .

In another series of 150 men who had a 5mm transperineal template biopsy and biopsies targeted to MRI lesions, 50 men had a PIRADS score of 1 or 2 ie a ‘negative MRI’ for clinically significant cancer. Of these 50 men, two had ‘moderate risk cancer’ defined as one of Gleason 7 with < 50% cores positive or 8mm maximum cancer core length or <5% Gleason 7 but 30% or greater cores positive . (10)

The PRECISION trial has been set up to assess the detection rate of clinically significant cancer (Gleason 7 or above) between a standard TRUS biopsy (10-12 core) and an MRI-targeted biopsy (https://clinicaltrials.gov/ct2/show/NCT02380027?term=PRECISION&recr=Recruiting&type=Intr&cond=prostate+cancer&rank=2Men are randomised to either standard biopsy or an MRI scan. If the MRI is scored as unlikely to show clinically significant disease (1 or 2 on a Likert scale) then no biopsy is done. It is expected to complete recruitment in late 2017.

**The timing of MRI and prostate biopsy**

There is some debate on the most cost-efficient place for prostate MRI within the diagnostic pathway. The European Association of Urology (EAU) guidelines published in 2015 have added the recommendation to use prostate MRI in men with an initial negative standard TRUS biopsy, where a clinical suspicion of prostate cancer persists (11). Others are keen to see it as a triage test to determine which men undergo prostate biopsy, using it to reduce the number of men having an unnecessary negative biopsy. A recent cost effectiveness analysis of this triage approach has shown that an MRI-targeted biopsy strategy was dominant over (ie more cost effective than) a standard TRUS biopsy strategy at 5,10,15 and 20 years after diagnosis, when the direct medical costs of diagnosis and treatment of prostate cancer were assessed (12). This analysis assumes that men with a negative MRI do not undergo biopsy or any further tests. In practice, not all patients and urologists are content for a man with a negative MRI to avoid a standard TRUS biopsy, and none of the cost effectiveness analyses tend to take this into account.

In addition to using the MRI to direct the biopsy, an MRI prior to first biopsy will also avoid the difficulty of post biopsy artefact on image interpretation. It is generally held that any biopsy artefact will show on T1-weighted images where haemorrhage shows as increased signal intensity. Questions are raised about how long post biopsy artefact persists for. Many have assumed that once any changes on T1-weighted imaging have settled then changes on any other sequences will also have resolved. A series of 14 men who were assessed for prostate cancer using mpMRI and subsequent 10 core TRUS biopsy were evaluated for post biopsy artefact on subsequent MRI scans at 1, 2 and 6 months to assess the evolution of biopsy related MRI changes (13). This showed that T2-weighted signal changes can persist for up to 6 months following standard TRUS biopsy, although ADC imaging was not significantly affected. Resolution of visible haemorrhage on T1-weighted imaging does not necessarily correlate with resolution of T2-weighted imaging changes. These T2-weighted imaging changes can result in overstaging of disease and prompt radical treatment; for this reason pre-biopsy MRI is also attractive for the purposes of local staging as well as efficient cancer detection (14).

When the utility of MRI for staging is assessed it is dependent on whether the MRI has been done prior to biopsy, or after biopsy, as is more commonly the case. The question asked of a staging MRI is whether there is extracapsular extension or seminal vesicle invasion. The presence of extracapsular extension can be particularly difficult to assess on a post-biopsy MRI, and a recent publication of MRI for staging in community practice showed positive and negative predictive values of 36 and 77% respectively for extracapsular extension compared to radical prostatectomy (15).

The UK NICE guidelines recommend prostate MRI for all men who have a prostate biopsy showing cancer, who are potentially eligible for radical treatment. In addition, due to the known inaccuracies of standard transrectal ultrasound (TRUS) guided biopsy, NICE recommends that any man with a negative TRUS guided biopsy, who would be a candidate for radical treatment if prostate cancer were diagnosed, should have an MRI at 3-4 months after the negative biopsy to assess for missed significant cancer (16). In the UK, there are strict timelines for the cancer diagnoses, timed from the date of the GP referral to the specialist service (http://www.ncin.org.uk/collecting\_and\_using\_data/data\_collection/gfocw). Financial penalties for breaching these timelines (31 days from referral to diagnosis, and 31 days from diagnosis to treatment) have led many UK centres to place prostate MRI at the start of the diagnostic pathway, in order to reduce delays later in the pathway that can have adverse financial consequences. In other healthcare systems with different financial pressures, others will have standard TRUS biopsy as the initial diagnostic assessment, with MRI reserved for men with a subsequent negative biopsy, or for staging purposes prior to treatment initiation.

Some authors have looked at the use of PSA density to reduce the use of prostate biopsy in men with an equivocal lesion (PIRADS v2 <3) and a low PSA density. (<0.15 ng/ml). In a series of 288 men, no men with PI-RADS <3 and a PSAD <0.15 ng/ml had clinically significant cancer, defined as Gleason > 3 + 4 or > 4mm cancer core length (17).

**The conduct of the MRI-targeted biopsy**

There are a number of considerations when planning a prostate biopsy of an MRI-defined lesion. The first is whether to use the transrectal or transperineal route; transperineal biopsy has the advantage of a lower infection rate, and, because the prostate is in a similar position for the MRI and the ultrasound visualisation targeting of lesions may be easier. The transrectal biopsy route in the left lateral position using an end –fire probe is more comfortable than the transperineal route in lithotomy position using the biplanar probe, where a longer length of probe has to be held in the rectum to allow sagittal scanning.

Some groups have reported the use of transperineal biopsy under local anaesthetic (18) although it is rare for this to be the standard of care.

The use of visual registration of the MRI image showing a suspicious lesion onto the ultrasound image used for needle placement is a rapid and low cost approach for those with expertise in doing this (19). Software assisted registration will show the MRI lesion overlaid on the ultrasound image. Comparisons of the two techniques are often complicated by the expertise of an operator or team in one method or another.

Fusion systems that are currently available commercially are most commonly used in the USA are Artemis (Eigen/Hitachi) (20,21) and UroNav (Invivo/Phillips) (22, 23, 7). Others commoner in Europe are BiopSee (24, 25), UroStation (Koelis) (26, 27). This is an area of commercial development with a number of new devices coming onto the market each year.

Oberlin and colleagues have recently reported a cohort of men having either visual/cognitive registration or fusion assisted registration for targeted biopsy (28). They found no difference in the detection rate of clinically significant prostate cancer between cognitive registration and image fusion techniques. This confirms the findings of the PROFUS trial which compared two fusion assisted biopsy cores, 2 visually directed biopsy cores and a standard 12 core TRUS biopsy (29). Fusion did not increase cancer detection in PROFUS, but did show better performance for smaller targets. This is similar to a recent study from Memorial Sloan Kettering, where there was no definitive overall difference between visual targeting and software fusion, although each had advantages in different locations (30). It may be that fusion will come to have widespread use in centres new to visual targeting, and in those men with more difficult lesions.

The NIH group used a two core technique (one seen in the axial plane and one in the sagittal plane) when reporting their recent series of 1003 men (7). They then analysed a series of 893 biopsied lesions to assess whether their two core technique could be reduced further (31), but found that significant cancer could be missed if either the axial or sagittal cores were missed out. A group looking at this in the setting of in-bore targeted biopsies found similar detection rates with one or two cores and felt the number of cores could be reduced (32).

**The debate over PIRADS versus Likert scoring**

Likert scoring, developed by psychologist Rensis Likert in the context of scaling responses in survey research, assigns a score on a linear continuous scale. It has been adapted for prostate MRI reporting when radiologists give an assessment of the likelihood of clinically significant disease, either for a whole prostate or for a given lesion. This is most commonly done on a 1- 5 scale where 1 is least likely and 5 is most likely to show clinically significant disease. Some groups have used a 3 part of scale of low likelihood, equivocal and high likelihood.

The PIRADS system (versions 1 and 2 ) looks to formalise this type of scoring by giving specific anatomical and functional criteria for each of the T2, DCE and diffusion weighted sequences for a score of 1-5. A total score out of 15 is the given for the likelihood of clinically significant disease, where clinically significant disease is defined as Gleason > 3+ 4 and/or volume > 0.5cc and/or extraprostatic extension.

The Likert scale allows a reporting radiologist more freedom in assigning a score of higher or lower likelihood of clinically significant disease based on a high weighting to a given factor. For example, in a man where the diffusion sequences are subject to artefact from rectal gas, the combination of low signal on T2 and characteristic enhancement on DCE may result in a lesion being given the highest possible score.

Experienced radiologists in a study of 6 radiologists assessing 120 examinations showed fair reproducibility for use of the PIRADS v 2 lexicon. However, in a subgroup of men who had targeted biopsy of PIRADS v2 lesions scoring 4 or more, only 45% showed Gleason 3 + 4 tumour or greater, suggesting that there is still work to be done in this area (33).

A group compared the use of Likert scale (1-5) with PIRADSv1 (34) in 250 men who had radical prostatectomy pathology for comparison (35). They compared individual radiologist Likert scores with a score based on description of the lesions, and PIRADSv1, and found that the Likert score was significantly more accurate than the others for the detection of clinically significant disease. As the PI-RADS system has now been revised, further comparison would be useful.

One assessment of the PIRADSv2 in men who had targeted biopsy showed a cancer detection rate of only 30% for PIRADSv2, which was lower than expected (36).

A report of PIRADSv1 versus PIRADS v2 assessment in 82 men showed an increase in the area under the curve for the detection of prostate cancer for both an experienced reader and an inexperienced reader (37).

One group assessed the use of PIRADS v2 and compared it to a simplified quantum scoring (SQS) (38). They found that SQS had a higher area under the curve for the detection of clinically significant prostate cancer on per lesion analysis (0.729 vs 0.829 for PIRADS v2 and SQS respectively). In addition, the SQS had a more normal distribution of score than the PIRADS v2, with 80% of lesions in PIRADS v2 scoring 4 or 5. This could lead to a higher proportion of men undergoing biopsy.

Rosenkrantz and colleagues have called for further work to be done to validate the PIRAds v2 scale (33).

**Conclusion**

Prostate MRI is of use in the detection of clinically significant prostate cancer. Current debate concerns the most cost efficient place for MRI in the diagnostic pathway, the optimal way to use the MRI data to direct the biopsy, and the use of the updated PIRADSv2 reporting system for the likelihood of clinically significant disease. Whilst PIRADSv2 is commonly used, some studies suggest that Likert or SQS approach may outperform it. Future research will concentrate on validation of this and other assessment systems.

**Key points (3-5 key points/sentences)**

* Prostate MRI is recommended in the UK And European guidelines for assessment of men with a negative standard TRU biopsy and continued suspicion for prostate cancer
* The second version of PIRADS has been published which sets a framework for the acquisition, interpretation and reporting of prostate MRI for the detection of prostate cancer
* There is debate on the utility of the PIRADS reporting system compared to a less prescriptive one such as a Likert score of 1-5 for clinically significant disease based on the radiologists overall impression

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None