Prostate indeterminate lesions on magnetic resonance imaging. Biopsy *versus* surveillance. A literature review.

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ABSTRACT

Context: The indeterminate multiparametric prostate magnetic resonance image (mpMRI) lesion is one which cannot be classified as “positive” or “negative” for suspected cancer. Currently, there is no consensus on how to manage patients with indeterminate mpMRIs, where areas cannot be classified as positives or negatives (PI-RADS 3 or Likert 3).

Objective: to define the concept of the indeterminate lesion and describe what management strategies may be adopted for these patients.

Evidence acquisition: A literature search of the PubMed database was carried out including the search terms “prostate indeterminate lesions”, “PIRADS 3”, “Likert 3”, “magnetic resonance imaging”, “prostate cancer”.

Evidence synthesis: There is no universally accepted definition of what constitutes an indeterminate lesion on mpMRI. This is in part due to the experience of the reporting radiologist and their willingness to call a lesion indeterminate, knowing that this may have consequences for biopsy decisions. This is also in part due to the significant variation in mpMRI acquisition parameters used between different sites. Strategies for managing the indeterminate lesion include: 1) Biopsy, where there is a highly variable prevalence of prostate cancer (PCa), reflecting the differences in clinically significant PCa definitions, mpMRI protocols and inter-observer variability in characterization of indeterminate lesions and 2) Surveillance, where early results suggest that this strategy may be of value for some selected patients with PSA monitoring and/or interval mpMRI. The use of pre-biopsy MRI, in conjunction with traditional clinical parameters and secondary biomarkers-nomograms, may allow a more accurate selection of patients who can avoid biopsy.

Conclusion: A strategy of close surveillance based on PSA monitoring and interval mpMRI is a feasible management option for motivated patients with the indeterminate mpMRI. This surveillance strategy could result in fewer men needing to undergo biopsy and though early results are promising, long-term results for such a strategy are awaited.

Patient summary: In some patients who have an MRI scan of their prostate, the scan may identify an area that we are not sure contains cancer or not. This area is typically called the “indeterminate” lesion. In this report we looked to define the concept of the indeterminate lesion on multiparametric magnetic resonance (mpMRI) and describe what strategies may be carried out for these patients. The use of mpMRI, in conjunction with traditional clinical parameters, may allow more accurate risk stratification and assessment of the need for prostate biopsy.

INTRODUCTION

Prostate specific antigen (PSA) testing is the main triage test for detection of prostate cancer (PCa). However, PSA has limited specificity and sensitivity in determining the presence of PCa, leading to unnecessary biopsies and the diagnosis of potentially indolent PCa. The current standard of care diagnostic procedure for men with suspected PCa is transrectal ultrasound guided biopsy (TRUS-bx). For a prostate volume of 30–40 mL, 10–12 core biopsies are recommended (1). Unlike many other solid tumours for which image-guided biopsy is common, PCa has traditionally been detected by randomly sampling the organ.

However, the recent introduction of multiparametric magnetic resonance imaging (mpMRI) allows for image-based identification, which may improve diagnostic accuracy for high risk PCa. Advances in imaging have led to the development of fusion biopsy platforms in which mpMRI images are electronically superimposed in real time on transrectal ultrasound (TRUS) images. Numerous targeted biopsy platforms exist and can perform biopsies of suspicious regions seen on the prostate mpMRI. (2-6)

The translation into clinical practice of the results on mpMRI findings is important. A mpMRI which does not identify any suspicious areas is associated with a high negative predictive value (NPV) for clinically significant disease and could avoid many unnecessary biopsies (7). A positive finding allows a suspicious area to be targeted with higher sampling density, which may result in a greater proportion of men diagnosed with clinically significant disease (8).

Currently, there is no consensus on what to do in the case of the appearance of indeterminate lesions on mpMRI, where areas cannot be classified as positives or negatives

(e.g. PI-RADS score of 3 or Likert score of 3). A recent retrospective study of men with indeterminate lesions on MRI shows that when offered a choice of immediate biopsy or surveillance, men preferred surveillance, with 57% choosing this option. The overall proportion of men with clinically significant PCa in this cohort was 14%. Whilst immediate biopsy is an option for these men, surveillance of the lesion is another possibility. (9)

The objective of this review is to define the concept of the indeterminate lesion and describe what strategies may be carried out for these patients.

EVIDENCE ACQUISITION

A literature search was carried out using the PubMed database, including the following search terms “PI-RADS 3”, “LIKERT 3”, “magnetic resonance imaging”, “prostate cancer”, “prostate indeterminate lesions”. Relevant original articles and reviews were identified. Abstracts presented congresses were excluded. Studies with the highest level of evidence and relevance to the discussed topics were selected with the consensus of the authors.

EVIDENCE SYNTHESIS

CONCEPT OF THE INDETERMINATE LESION AND PERCENTAGE OF INDETERMINATE LESIONS DETECTED ON mpMRI.

mpMRI is increasingly being used in the detection and management of PCa. This technique is able to detect both high grade and large tumours (i.e. clinically significant cancer) accurately. There is growing evidence that mpMRI has the potential to discriminate between low-and intermediate/high-grade PCa (10).

However, mpMRI faces a number of challenges, one of which is determining the definition of the *indeterminate* lesion on mpMRI (11). The learning curve in prostate MRI interpretation is well recognized and recent findings have noted improvements over time in the accuracy of clinical interpretations after the implementation of prostate MRI at various centres (12,13). There is also variation in the reporting radiologists' willingness to assign an indeterminate status to a lesion, knowing that this might influence the decision to perform a biopsy. This can change for a particular radiologist over time, as experience changes. Despite continual progress in prostate MRI interpretation within the radiologic community, achieving accurate and consistent interpretations continues to provide a challenge. Although PI-RADS is intended to facilitate education and improve reader performance, the system itself requires training. The overall importance of reader experience for radiologists' performance in prostate MRI interpretation has been well characterized (14,15). However, the optimal strategy for educating radiologists in prostate MRI and reducing this learning curve is yet to be identified.

It is well known that an accurate mapping of cancer foci is crucial to evaluate tumour burden accurately, in order to allow an adequate treatment for men with PCa. In this regard, there is consensus among radiologists that the usage of a 5-point scale (Likert or PI-RADS) is very important to assess the likelihood of having clinically significant cancer, with a score of 3 out of 5 representing an *indeterminate* area that is *suspicious* for clinically significant cancer (16-17). The Likert score, rather than providing fixed criteria, is a subjective scale which is strictly linked to the overall impression of the reporting radiologist (Figure 1 and 2). Conversely, the PI-RADS criteria represent an attempt to overcome such variability, as they give the possibility to generate a score applying fixed criteria in order to

improve the agreement between different radiologists. Both approaches have been shown to be comparable (18-19). The criteria chosen might also depend on the technical standard of the MRI-scanner; the pulse sequences/scanning time and the parameters used. PI-RADSv2 made an attempt to define diagnostic parameters, but there is variation in clinical practice is common due to variation in MRI scanners used and local resources available.

The current definition of *indeterminate lesion* on mpMRI is not well described in literature, although PI-RADSv2 classification defines it as a heterogeneous signal intensity or non-circumscribed, rounded with moderate hypointensity in the T2-weighted imaging in the peripheral zone; a heterogeneous signal intensity with obscured margins in transition zone and focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value in the diffusion-weighted imaging. Also, PI-RADS classification states that *indeterminate lesions* include others that do not qualify as 2, 4, or 5. (17)

In summary, there is no universally accepted definition of what criteria constitute an *indeterminate* lesion on mpMRI as this can vary according to a number of factors. However scoring systems such as PIRADSv2 have been developed to overcome the variability in ascribing scores and future versions of this scoring system may help provide further clarity on this matter (13, 20).

The PROMIS study has recently shown that in a group of biopsy-naïve men, the likelihood of having an *indeterminate* lesion is 28% (18). There is also evidence that an accurate strategy for targeting mpMRI lesions that have been scored as *indeterminate* but might have a real likelihood of harbouring clinically significant PCa is of utmost importance, as this may reduce the burden of overdiagnosis and overtreatment (21).

INDETERMINATE LESIONS: WHAT TO DO?

a) Biopsy

Currently, a random systematic 10 to 12 core transperineal or TRUS-bx is the standard of care for the diagnosis of PCa in men with rising PSA and/or suspicious digital rectal examination (DRE) (1). However, standard TRUS-bx performs poorly for detecting clinically significant PCa, particularly in the anterior part of the prostate, and up to 70% of patients undergoing initial prostate biopsy have negative results. (22-23)

After an initial negative biopsy and in the persistent clinical suspicion of PCa, contemporary guidelines recommend performing a mpMRI before repeat biopsy (1). mpMRI targeted biopsies may detect clinically significant PCa in up to 54% of patients, having a higher detection rate comparing to standard systematic biopsies. (2-6). In this group of men, systematic plus imaging-targeted biopsies for PI-RADS 4-5 lesions (at least two cores from each MRI defined target) were recommended, while it was recommended that biopsy could be avoided for PIRADS 1-2 lesions (2). However, PI-RADS 3 lesions are indeterminate for the presence of clinically significant PCa which may lead to challenging situation to manage.

Sonn et al. (24) prospectively reviewed 105 patients with ≥ 1 prior negative prostate biopsy and clinical suspicion of PCa who underwent mpMRI and mpMRI-ultrasound fusion biopsy. Eighty-four PI-RADS 3 lesions were identified of which only 5% had PCa (4% significant PCa). In the same setting, a retrospective analysis from Kaufmann et al. (25) demonstrated a detection rate of PCa of 33% (5/15) among patients with PI-RADS 3 assessment. In the literature, there is a highly variable prevalence of PCa associated with PI-RADS 3 lesions, reflecting the differences in clinically significant PCa definitions, mpMRI protocols and inter-observer variability in characterization of PI-RADS 3 lesions.

There is increasing evidence on the use of pre-biopsy mpMRI in biopsy-naïve patients and mpMRI is increasingly being performed as a triage test to avoid unnecessary biopsies and to improve detection of clinically significant PCa while avoiding detection of low-grade disease (21,26). In this setting, some studies report detection rates of PCa among biopsied PI-RADS 3 lesions from 6.5% to 22%, with significant PCa being detected in 4.4% to 11.3% (27-29). In a study by Porpiglia et al (30), patients with PI-RADS score 3 lesions who underwent mpMRI/transrectal ultrasound fusion software-guided targeted biopsy had 12.5% (3/24) overall detection of PCa and 3/24 (12.5%) detection of clinically significant PCa.

Some available adjuncts may be of additional value in the presence of an indeterminate MRI to help make a decision as whether to proceed with prostate biopsy (31). When PI-RADS score and PSA density were combined, PI-RADS 3 score or greater and PSA density of ≥0.30 ng/mL/mL (high-risk group) was associated with the highest clinically significant PCa detection rates (86%). On the other hand, PI-RADS 3 and PSA density of <0.15 ng/mL/mL (low-risk group) detected 0% of clinically significant PCa, which may suggest that these patients could have avoided unnecessary initial biopsies (32).

b) Surveillance of the lesion

There is a paucity of literature and evidence regarding surveillance on PI-RADS 3 lesions on mpMRI of the prostate. Although a prostate biopsy is generally recommended, follow-up mpMRI may be an alternative option in the management of these patients.

Hauth et al. (33) retrospectively determined the rate of malignancy after follow-up mpMRI of the prostate in 46 patients with suspected PCa and PI-RADS 3 assessment in a baseline prostatic mpMRI without core biopsy. Follow-up mpMRI was performed, on average, after 22.6 months. Forty eight percent (22/46) of lesions had smaller diameter

and/or decreased suspicious functional parameters, being down-graded to a PI-RADS score of 2 with subsequent clinical follow up in one year. Forty eight percent (22/46) of PI-RADS 3 lesions remained stable with a second follow-up mpMRI recommended in two years. Only 4% (2/46) were progressive lesions (defined as an increase in diameter and/or in suspicious functional parameters), re-assessed to PI-RADS 4. TRUS-bx was performed and revelled PCa Gleason score 7 in both patients. Compared to patients with PI-RADS 4 score and an initial negative prostate biopsy, which had a rate of malignancy of 69% in re-biopsy, PI-RADS 3 lesions had a low malignancy rate, meaning that follow-up these patients seemed to be a reasonable alternative to biopsy.

In a study published by van der Sar et al (9), 168 patients with Likert score 3/5 lesions on mpMRI, without a previous prostate biopsy, were able to choose between immediate biopsy and surveillance on the lesion with delayed biopsy if necessary. The majority of patients (57%; 95/168) chose surveillance with PSA and/or mpMRI at 6-12months intervals. During follow-up, biopsy was performed in 11% (10/95) due to rising PSA and/or progression on mpMRI. Of these, 4% (4/95) had PCa, all Gleason 3+4, and underwent treatment with curative intent. In the immediate biopsy group PCa was detected in 45% (33/73) and clinically significant PCa in 26% (19/73). In this study, indeterminate lesions on mpMRI did not have features of high-risk disease and risk profile for cancers detected was similar between both groups.

Although early results suggest that a surveillance strategy may be of value for some selected patients, long-term outcomes and large cohorts are needed before firm recommendations can be made.

HELPFUL TOOLS IN THE SETTING OF PATIENTS WITH INDETERMINATE LESIONS ON mpMRI (NOMOGRAMS-BIOMARKERS)

Nomograms and biomarkers have been enhanced to incorporate mpMRI findings to predict both overall and clinically significant cancer risk, which allows for counseling men on the need for biopsy. New biomarkers, such as kallikrein panels (4K Score® and Prostate Health Index®) and urine biomarkers (PCA3 and TMPRSS2-ERG), may improve further upon existing PCa screening, detection, and risk assessment tools (31). The implementation of these biomarkers as secondary tools in conjunction with mpMRI could improve specificity markedly, sparing as many as half of men with an elevated PSA the need to undergo biopsy.

Fenstermaker et al. (34) evaluated whether a combination of PCA3 and mpMRI suspicion score could further optimize the detection of PCa on MRI fusion- targeted biopsy among men with no history of biopsy. Their results showed that PCA3 <35 demonstrates a high NPV among MRI suspicion score 2-3. However, in the case of high-suspicion mpMRI, PCA3 was not associated with cancer detection on mpMRI-ultrasound-fusion targeted biopsy, not adding value to cancer diagnosis. By biopsying men with a mpMRI suspicion score of 4-5 and obtaining PCA3 on men with a mpMRI suspicion score of 2-3, followed by biopsy only in men with PCA3 score >35, 36.1% of biopsies would be avoided, and 4.9% of Gleason score ≥3+4 cancers would have been missed. Other ancillary markers may help select patients with a negative/low-suspicion MRI for systematic biopsy.

Recently, nomograms have substantially improved predictive accuracy for both endpoints, even in diverse populations as well as in patients with no prior biopsy or with a prior negative biopsy. Bjurlin et al. (35) developed a nomogram to predict the probability of

Gleason score 7 on mpMRI targeted and systematic prostate biopsy in biopsy naive patients. mpMRI-utrasound fusion targeted biopsy was performed on approximately 1,140 men with suspicious regions identified on pre-biopsy 3T mpMRI along with systematic 12 core biopsy, utilizing the ProFuse|Artemis system™. Logistic regression model was used to evaluate predictors of Gleason score ≥7, and corresponding nomograms were generated. A total of 389 men with no previous biopsy and complete records were included for analysis (median age 66 years, PSA 4.8 ng/ml, prostate volume 46 cc, PSA density 0.09 ng/ml-cc). PSA density, age, and MRI suspicion score predict PCa on mpMRI-targeted and systematic biopsy.

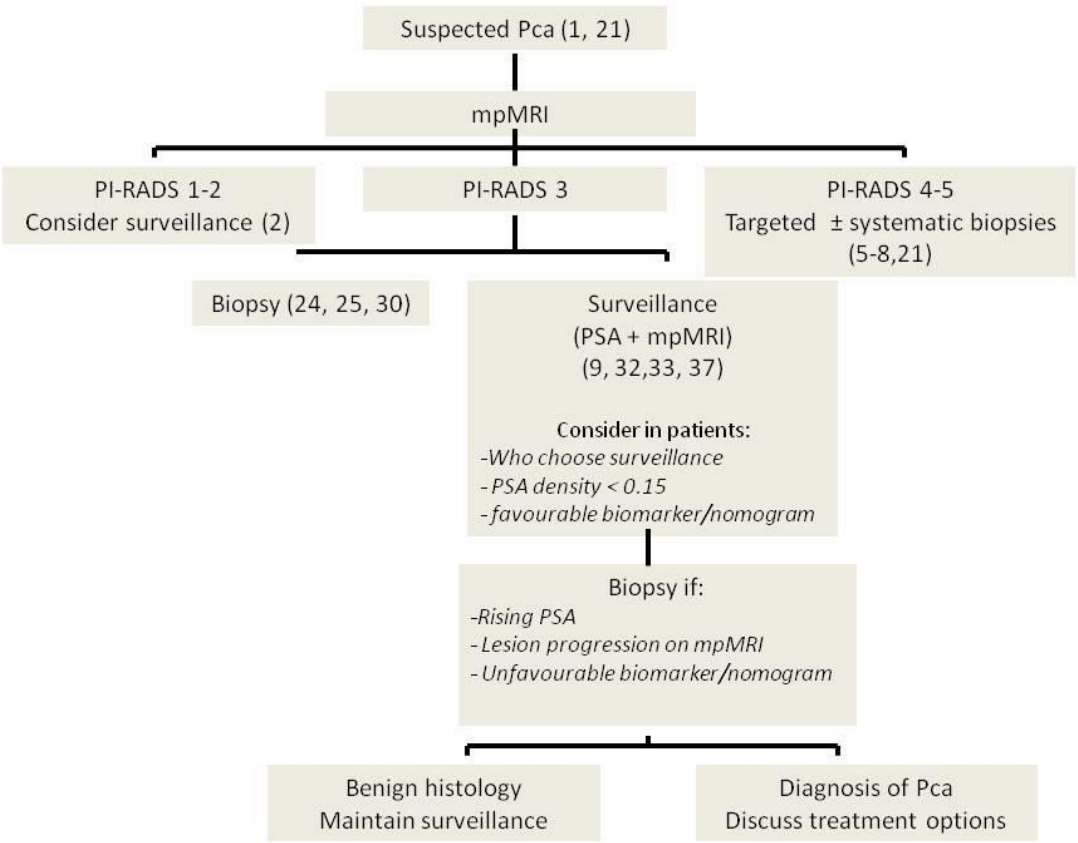
Niu et al. (36) established that patient age, PI-RADS v2 score and adjusted-PSA density were independent predictors for high grade PCa. They validated a nomogram based on mpMRI for forecasting high grade PCa, which they felt could reduce unnecessary prostate biopsies in patients with PSA 4–10 ng/mL.

Other work has identified the important role of clinical information as a predictor of significant PCa, especially PSA density (37). Logistic regression analyses were performed to test different clinical factors as predictors of PCa and build nomograms. An overall of 451 men were diagnosed with significant PCa, including 187 with a Gleason score of 4 + 3 or greater. On ROC curve analyses the predictive power of the developed nomogram from the authors for significant PCa showed a higher AUC than that of PI-RADS alone (0.79 vs 0.75, $p < 0.001$). The NPV of harbouring PCa increased in men with unsuspicious mpMRI from 79% up to 89% when PSA density was 0.15 ng/ml/ml or less. In the repeat biopsy setting the NPV of significant PCa increased from 83% to 93%. The NPV to harbour high grade PCa increased from 92% up to 98% in the entire cohort.

The use of pre-biopsy mpMRI, in conjunction with traditional clinical parameters and secondary biomarkers-nomograms, may allow more accurate risk stratification and assessment of need for prostate biopsy. The construction of nomograms can provide clinicians with simple tools capable of predicting the presence of PCa in the wide spectrum of individuals with suspicion of PCa and reduce the number of unnecessary biopsies.

Table 1 summarises some of the current literature regarding intermediate lesions, scale used in the analysis (PI-RADS vs Likert score), percentage of PCa and percentage significant PCa.

MANAGMENT OF INDETERMINATE LESIONS ON mpMRI (authors proposal)



CONCLUSIONS

The indeterminate MRI is a common finding in men with suspected PCa and management of this result is controversial. PI-RADSv2 made an attempt to define *indeterminate lesions* giving fixed criteria, such as moderate hypointensity in the T2-weighted imaging and focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value in the diffusion-weighted imaging, but there is variation in clinical practice. Men with an indeterminate lesion on mpMRI who undergo biopsy have PCa in 12-33 %; of these, 4-12 % is clinically significant. A strategy of close surveillance based on PSA monitoring and mpMRI may be offered. This surveillance strategy could result in fewer men needing to undergo biopsy, and though early results are promising, long-term results for such a strategy are awaited. The use of mpMRI, in conjunction with traditional clinical parameters such as PSA density and secondary biomarkers-nomograms, may allow more accurate risk stratification and assessment of the need for prostate biopsy in men with indeterminate MRIs. Future scoring systems or new version of current systems may also affect the outcomes seen for patients. Also, prostate MRI is an expert skill that has a learning curve. The threshold required to declare a lesion as indeterminate can vary between radiologists of different experience level. Therefore, dedicated training sessions should be provided to radiologists reporting prostate MRI so that clinicians can make appropriate management decisions based on reliable information.

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FIGURE LEGENDS

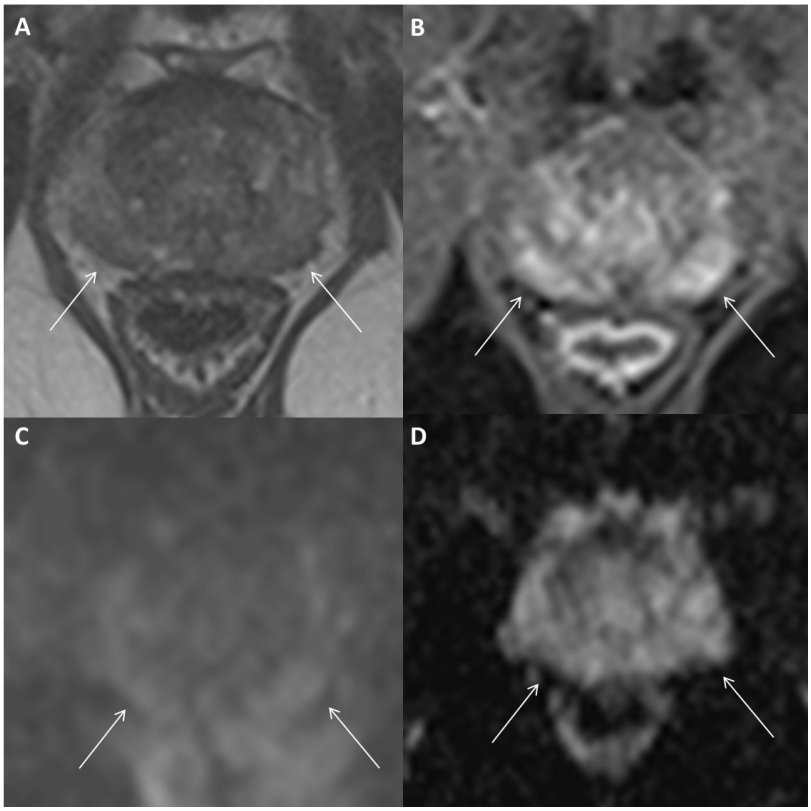

Figure 1: Fifty-one-year-old man presenting with prostate specific antigen of 1.6 ng/ml and a suspicious digital rectal examination. The arrows indicate the peripheral zone of the prostate on multi-parametric magnetic resonance imaging. There is diffuse, bilateral low signal on T2-weighted imaging (A), with blush and diffuse enhancement on dynamic contrast enhanced imaging (B). There is only minimal associated restricted diffusion on diffusion-weighted imaging (C) and on the apparent diffusion coefficient map (D). The area was scored as 3/5 on a Likert scale.

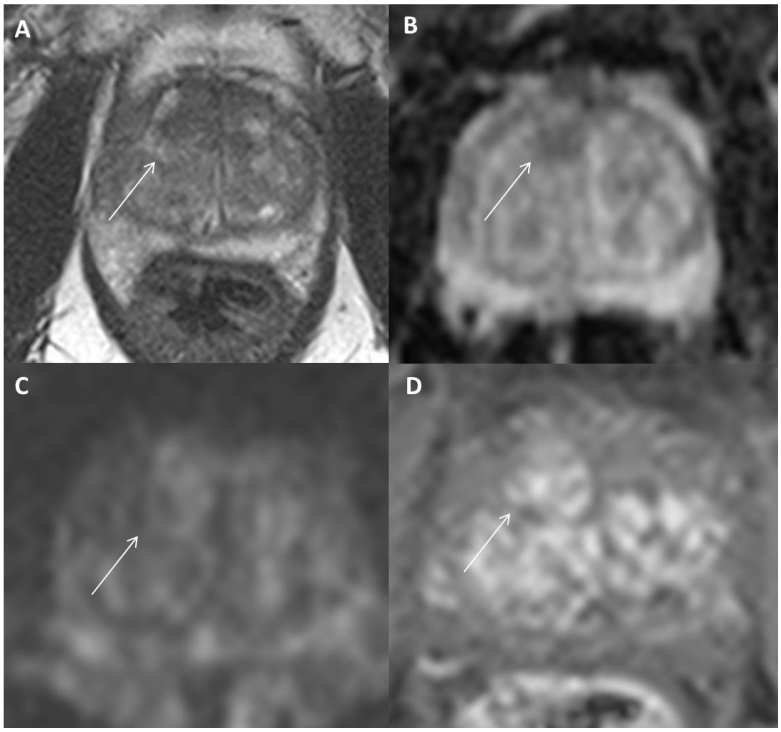

Figure 2: Sixty-eight-year-old man presenting with increasing prostate specific antigen (from 6 to 12 ng/ml) and three sets of negative biopsies. The arrows indicate an area in the right para-sagittal anterior transition zone characterised by low signal on T2-weighted imaging (A) and moderate enhancement on dynamic contrast enhanced imaging (B). The lesion is not conspicuously bright on long b value sequences on diffusion-weighted imaging (C), but there is some associated restricted diffusion on the apparent diffusion coefficient map (D). The area was scored as 3/5 on a Likert scale. The subsequent targeted biopsy did not show any cancer