Prostate Cancer Prostatic Dis. Author manuscript; available in PMC 2014 September 01.

Published in final edited form as:
Prostate Cancer Prostatic Dis. 2014 March ; 17(1): 40–46. doi:10.1038/pcan.2013.43.

Performance of multi-parametric MRI in men at risk of prostate cancer prior to first biopsy: a paired validating cohort study using template prostate mapping biopsies as reference standard

Mohamed Abd-Alazeez[1], **Alex Kirkham**[2], **Hashim U. Ahmed**[1,3], **Manit Arya**[1,7], **Eleni Anastasiadis**[5], **Susan C. Charman**[4], **Alex Freeman**[6], and **Mark Emberton**[1,3]

[1]Department of Urology, University College London Hospitals NHS Foundation Trust, London, UK

[2]Department of Radiology, University College Hospitals NHS Foundation Trust, London, UK

[3]Division of Surgery and Interventional Science, University College London, London, UK

[4]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine

[5]Clinical Effectiveness Unit, Royal College of Surgeons of England, London, UK

[6]Department of Histopathology, University College Hospitals NHS Foundation Trust, London, UK

[7]Barts Cancer Institute

Abstract

Background—Multi-parametric MRI (mp-MRI) has the potential to serve as a non-invasive triage test for men at risk of prostate cancer. Our objective was to determine the performance characteristics of multi-parametric MRI (mpMRI) in men at risk prior to first biopsy using 5mm template prostate mapping (TPM) as the reference standard.

Methods—One hundred and twenty nine consecutive men with clinical suspicion of prostate cancer that had no prior biopsy, underwent mpMRI (T1/T2-weighted, diffusion-weighting, dynamic-contrast enhancement) followed by TPM. The primary analysis used: a) radiological scores of suspicion of ≥3 attributed from a 5-point ordinal scale, b) a target condition on TPM of any Gleason pattern ≥4 and/or a maximum cancer core length of ≥4mm and c) two sectors of analysis per prostate (right and left prostate halves). Secondary analyses evaluated the impact of: a) changing the mpMRI score threshold to ≥4 and b) varying the target definition for clinical significance.

Results—141/258 (55%) sectors of analysis showed “Any cancer”; 77/258 (30%) had the target histological condition for the purpose of deriving the primary outcome. Median (with range) for age, PSA, gland volume and number of biopsies taken were 62 years (−41-82), 5.8ng/ml (1.2-20), 40ml (16-137) and 41 cores (20-93). For the primary outcome sensitivity, specificity, positive and negative predictive values and area under the receiver operating curve (with 95% CI) were 94% (88-99%), 23% (17-29%), 34% (28-40%), 89% (79-98%) and 0.72 (0.65-0.79), respectively.

Address for correspondence: Mohamed Abd-Alazeez, 67-73 Riding House Street, Division of Surgery and Interventional Science, University College London, London, W1W 7EJ, London, UK, Tel 020 3447 9194, Fax 020 3447 9303, mohamed.azeez.10@ucl.ac.uk.

Conflict of interest:
None of the funding sources had any role in the data acquisition, analyses and production of this manuscript.

Europe PMC Funders Author Manuscripts

Conclusion—MpMRI demonstrated encouraging diagnostic performance characteristics in detecting and ruling-out clinically significant prostate cancer in men at risk who were biopsy naive.

Keywords

Clinically significant disease; multi-parametric MRI; pre-biopsy; prostate cancer; Template prostate mapping; triage test; transrectal ultrasound guided biopsy

Introduction

There are a number of problems with the current prostate cancer diagnostic pathway that relies on serum prostate specific antigen (PSA) and transrectal ultrasound (TRUS) guided biopsy. Over-diagnosis and over-treatment have been a recognized consequence, but missed diagnosis and poor risk stratification also occur[1,2]. The only widely accepted correction has been to adopt the strategy of increased sampling [3].

An alternative strategy is to identify an area or volume of tissue at high probability of being cancer and target this area at biopsy, either exclusively or at a higher sampling density than the rest of the tissue. Multi-parametric MRI (mpMRI) currently holds the most promise for meeting the requirements of an imaging test which may be able to discriminate clinically significant cancer from areas with no cancer or clinically insignificant cancer within the prostate [4].

Most of the studies to date have used transrectal biopsy as a reference test (which is limited in accuracy), targeted biopsies (which prevents systematic interrogation of negative areas) or radical prostatectomy (which introduces a selection bias in that men have to be histologically diagnosed with cancer and then choose surgery rather than radiotherapy or active surveillance). Transperineal template prostate mapping (TPM) biopsies offer a robust reference standard as the sampling frame is fixed at every 5mm of the whole prostate, allow systematic interrogation of the whole prostate, blinded to the imaging, can be applied to most men undergoing the index imaging test and therefore limit the selection bias. Recently, TPM biopsies have been shown to have little to no miss-classification error when compared to whole-mount radical prostatectomy pathology in the detection of lesions 0.5cc or greater in volume with or without the presence of Gleason pattern 4 or greater[5], reinforcing earlier simulation studies [6].

In this study, we aimed to answer the following question: In men with no previous biopsy who present with a clinical suspicion of prostate cancer (based on high PSA, positive family history and/or abnormal digital rectal examination), to what extent can mpMRI detect and rule-out clinically significant prostate cancer using TPM biopsies as the reference standard, in a real practice setting?

Patients and methods

Research ethics committee exemption was granted.

In the period 01/01/2007 to 31/01/2011, men with a clinical suspicion of prostate cancer underwent a mpMRI; those with mpMRI scores of 3 or greater were offered a template mapping biopsy. One hundred and twenty-nine consecutive men were eligible for inclusion in this study as they all had an overall MRI score of ≥3 followed by TPM.

Exclusion criteria included: a) prior biopsy, b) previous treatment for prostate cancer, c) PSA >20ng/ml (TPM would have been too invasive for such patients where limited TRUS

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

sampling would suffice), d) >12 months between MRI and TPM, e) patients that did not have TPM, and f) patients that had inconclusive TPM where only limited numbers of biopsies were taken.

MRI

We aimed to determine the performance of real-practice mpMRI prior to biopsy and therefore did not select cases based on type of MRI scanner used or whether certain radiology reporters were involved. The index test, mpMRI, comprised T2 weighted (T2W), Diffusion-weighted (DW) and Dynamic contrast enhanced (DCE) imaging with either 1.5 Tesla (Siemens Avanto, n=113) or 3.0 Tesla (Phillips Achieva n=16) magnetic field strengths (Table 1). A multi-channel (at least 8) pelvic phased array coil, but no endorectal coil, was used. The detailed scan parameters for the 1.5T machine are shown in Table 1; the slice thickness at 3T was identical, but the in-plane resolution was slightly better. The contrast used was 20ml of Gadoteric Acid 0.5mmol/ml (Dotarem, Guerbet, France) given by an automated injector coincident with the start of the third dynamic sequence. Our practice for the last 8 years has been to use only a pelvic phased array coil rather than an endorectal coil. This is in keeping with a number of other centres which undertake mpMRI for prostate cancer detection [7].

Five radiologists (each one is reporting at least 100 prostate mpMRIs per year) reported all the mpMR images using a score from 1 to 5 as in the recent European Consensus Guidelines [7], which have recently been validated [8]: 1= Clinically significant disease is highly unlikely to be present, 2= Clinically significant disease is unlikely to be present, 3= Clinically significant disease is equivocal, 4= Clinically significant disease is likely to be present, 5= Clinically significant disease is highly likely. MRI Images from each patient were reviewed by one radiologist. The index test was conducted in a blinded manner to the reference test as all mpMRI reports were committed to the electronic medical record prior to the biopsy result becoming available. Some reports (n=38) did not contain numerical scoring data and for these, one designated reporter (AK) provided numerical scores based only on the report text and blinded to histology. Whenever a suspected lesion crossed the midline, both prostate halves (right and left) were attributed the same scoring for that lesion. As the role of mpMRI in future may be to triage men and thus select those that could avoid a biopsy, we incorporated the uncertainty score of '3' to confer a positive index test; thus, mpMRI scores of ≥3 were designated positive for the purpose of the primary outcome. The effect of varying this threshold to ≥4 was also evaluated as a secondary outcome. If the mpMRI was positive in an area proven to harbor clinically insignificant disease, according to the definition used, this area was deemed as false positive.

Biopsy

All patients underwent TPM biopsies using a 5mm sampling frame under general anesthesia in the method previously described by Barzell [9]. Urologists doing TPM biopsies were not blinded to MRI results however all 20 zones of the prostate were systematically biopsied.

Target conditions

The pathological outputs from the reference test were grouped into a number of definitions of clinical significance, or target conditions, in order to reflect the fact that no universally accepted definition currently exists.

These "Target Conditions" are:

1. UCL definition 1: Gleason ≥ 4+3 and/or maximum cancer core length (CCLmax) ≥ 6mm

2. UCL definition 2: Gleason ≥ 3+4 and/or maximum cancer core length (CCLmax) ≥ 4mm
3. Gleason score ≥ 4+3
4. Gleason score ≥ 3+4
5. CCLmax ≥ 6mm
6. CCLmax ≥ 4mm

The target histological condition for the purpose of deriving our primary outcome is one that is used in other large-scale multicenter level I evidence validating cohort studies in which mpMRI is being compared to TPM[10,11]. The histological reporting in our institution follows the classic scheme of interpreting the Gleason grading, the one used before the International Society of Urological Pathology 2005 guidelines [12]. In other words, Gleason scoring was based on the most frequent pattern, and not the highest grade, detected on histological analysis (although the latter was always available for each TPM zone). Further, the cancer core length was reported as the actual amount of cancer seen in each core without counting the intervening areas of benign glands [13]. Our target condition definitions is based on the only system that has been validated for a parallel sampling strategy and is based on the traditional volume and grade thresholds for individual lesions that are centred on 0.2cc and 0.5cc in combination with dominant and non-dominant Gleason pattern 4 [14].

Statistical considerations

Analysis was done at half prostate level (right and left). This was done via drawing an imaginary sagital line that passes through the patient urethra and divides the prostate in two halves. This resulted in 258 sectors of analysis out of the 129 patients. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) and the area under the receiver operating characteristic curve (AUROC) are presented with 95% confidence intervals (95% CI). Confidence intervals were obtained by bootstrapping using 500 bootstrap samples in order to account for the fact that these sectors of analysis were not independent of each other [15].

Our predefined primary objective was to assess the ability of mpMRI (with a score of ≥3/5 considered positive) to detect and rule-out clinically significant disease, defined as any cancer with Gleason pattern 4 or greater (≥3+4) and/or maximum cancer core length (CCLmax ≥4mm]) (UCL definition 2), in one prostate half (right or left).

Our predefined secondary objectives were to examine the performance of the index test by a) changing the mpMRI score threshold to ≥4 and b) varying the target histological definition for clinical significance .

Results

Baseline demographic data are presented in Table 2.

Primary outcome

In ruling-out UCL definition 2 clinically significant cancer, mpMRI had a sensitivity and NPV of 94% (95% CI, 88-99%) and 89% (95% CI, 79-98%), respectively (Table 3). In ruling in UCL definition 2 cancer, mpMRI had a specificity and PPV of 23% (95% CI, 17-29%) and 34% (95% CI, 28-40%), respectively.

Secondary outcomes

The performance of the test for different levels of clinical significance on TPM at mpMRI threshold of ≥3 is shown in Table 3. The sensitivity for the detection of Gleason 4+3 disease using an mpMRI score of ≥3 was 100%.

When using an mpMRI score of ≥4 to rule-out UCL definition 2 cancer, we had lower sensitivity of 68% (95% CI, 56-78%) with reduction in NPV (83% [95% CI, 77-89%]) (this is not a significant decrease). In ruling-in UCL definition 2 cancer at an mpMRI score of ≥4, both specificity (69% [95% CI, 61-76%]) and PPV (48% [95% CI, 38-58%]) improved. The results for other definitions of significance are shown in Table 4.

Table 5 shows AUROC curve values for different definitions of clinically significant disease at mpMRI scores 1-5.

Discussion

Summary of Results

The accuracy of mpMRI at detecting clinically significant prostate cancer varied with the mpMRI threshold that was used to declare a lesion as being present or absent. If the indeterminate score of 3 was included as a positive mpMRI, high sensitivity (93-100%) and NPV (89-100%) were achieved, but with low specificity (19-23%) and PPV (6-34%). When the indeterminate state was omitted and mpMRI scores of 4 and 5 only were used, specificity (61-69%) and PPV (11-48%) improved substantially whilst only marginally compromising sensitivity (68-92%) and NPV (83-99%).

The choice of threshold depends on the purpose of the test. Some have argued that the greatest clinical utility for mpMRI is as a triage test to rule-out clinically significant prostate cancer so that men can avoid biopsies or reduce the burden of biopsy in areas that are negative on imaging. For this purpose, the NPV of 89-100% that we have demonstrated (with negative defined as a radiological score of 1 or 2) would add some weight to this argument.

The low specificities that we have demonstrated are in part a consequence of applying our definitions of clinical significance on histology rigidly. In other words, even if cancer was found in the mpMRI suspicious area it would be discounted as a false positive if the amount or grade did not meet the pre-specified threshold for clinical significance; others have considered *any* cancer detected in MRI suspicious areas as true positives regardless of burden of disease found. [16]. As a result, our method will inevitably lead to an overestimate of false positives: small lesions correctly scored as likely tumours on mpMRI will count as false positives because they did not meet the histological criteria for significance.

Comparison with other studies

Figures for NPV depend greatly on the population being studied and the method of analysis. It is, however, reassuring that another group found a very high NPV for high grade (dominant Gleason 4) tumours of 98.4% [17] using T2 and spectroscopy sequences. Other studies using whole-mount prostatectomy as reference standard support the proposition that mpMRI has encouragingly high performance characteristics for detecting and ruling-out clinically significant prostate cancer [18].

Controversy continues on the use of endorectal coils, 3T machines and the relative value of the different components of a ‘multi-parametric’ scan. However, there is increasing evidence that both DW and DCE improve the performance of the test [19-22]. In our institution, we

achieved similar results to groups using endorectal coil. According to the recently published ESUR guidelines [7], Barentsz et al. recommended 3 different protocols for detection, staging and for nodes and bone metastases. In the detection protocol they advised with T2W + DW + DCE imaging without an endorectal coil. They added that this can adequately be done at 1.5T using 8-16 channel pelvic phased array.

Most studies of MRI in the prostate have divided up the prostate into numerous sectors for analysis. While this has the advantage of increasing the number of data points, and enables the assessment of the performance of MR in different regions, it has fundamental drawbacks: edge effects increase with the number of sectors, and figures for specificity and NPV are not easy to interpret when reapplied to the level of the whole prostate [23]. We analysed the prostate in halves rather than wholes because of the high prevalence of disease in our cohort, but did not divide further into sectors, and the results are therefore directly relevant to some important clinical questions [24]. We do believe however that with dividing the gland into further sectors for analysis, more selective ablation of the gland could be undertaken. However this is better performed through using TRUS-MRI image fusion with accurate localization of the targeted prostate cancer disease [25].

Further, we accounted for adjacency by conducting boot-strap analyses.

Clinical implications

Most studies have used a dichotomous result to declare whether mpMRI is normal or abnormal. By applying an ordinal 5-point scale we can begin to explore the impact of incorporating indeterminate results within our definition of normal or abnormal. Our observation that the test result is sensitive to the probability threshold used may allow us to use mpMRI in a more intelligent manner than we had previously contemplated.

What is the implication of a negative scan of one half of the prostate – in other words, an MRI score of 1-2, which occurred in 18% of prostate halves? In our population, the implication was a very high chance of that half being free of Gleason dominant 4 tumour (none were missed), a 93% chance of being free of any Gleason pattern 4 and a 98% chance that the CCLmax would be <6mm. If both prostate halves are negative, a decision to defer biopsy might seem reasonable if these data are substantiated in larger multicentre studies in which the unit of analysis is the whole prostate. We are currently conducting such a study.

In contrast, if a mpMRI is attributed a score of 4 or 5 (Figure 1) then the probability of clinically significant disease will be around 50%, (though for any tumour 73%). Accounting for this apparently low figure are many tumours correctly identified on mpMRI but falling below the thresholds for clinical significance: in practice the level of PPV is useful with encouragingly high positive hit-rates with targeted biopsies using a limited number of cores[26-28].

The indeterminate mpMRI remains a problem (Figure 2), though is an under-reported phenomenon [29]. We usually see a score of 3 as a positive signal to biopsy, with the mpMRI findings still useful for targeting the equivocal area. However, if the aim of the scan is to rule-out large volume or high grade (Gleason dominant 4) disease, a score of 3 might prompt deferring the biopsy after a period of surveillance. Such decision-making will depend on a balance of patient factors such as age, comorbidity and competing mortality risk assessment as well as anxiety.

Overall, if mpMRI can be used to defer or reduce the burden of biopsy in some patients, and to target suspicious foci in most others, it might serve as a rational triage test [4]. In addition,

in the case of a positive diagnosis of tumour, the pre-biopsy mpMRI is immediately available for staging, and is free of post-biopsy artefact, which can reduce its accuracy.

Our study had some limitations. The first relates to the nature of our study. We chose to analyze and report our real-life practice experience. We did this as one of the major critiques of mpMRI is that it can only be done within specialist units and rigid protocols. This criticism, if correct, compromises the external validity of some of the studies that have been published to date.

Second, our cohort incorporated some work-up bias. Patients with an mpMRI score of 1 or 2 throughout the prostate tended not to choose TPM over TRUS biopsy. We could therefore not include them. Adding more to that is the use of TPM as a reference standard rather than TRUS biopsy. These factors lead to high prevalence of disease in our cohort.

Since prevalence was high, one would expect to see a low NPV. However our NPV was 89-100% for different definitions of clinically significant disease. It is also known that the prevalence does not directly affect sensitivity and specificity whereas it affects positive and negative predictive values. Our sensitivity amongst different definitions of clinically significant disease was 93-100%.

Third, despite the fact that template biopsies perform well for the detection of significant disease (both in theoretical studies and in practice [30], with figures of up to 87% for the detection of significant tumour), they are arguably less accurate than radical prostatectomy, and we used a core biopsy technique to estimate tumour significance. Although the technique for doing so has been validated [14], it introduces another potential source of error.

Finally, although it is widely recognized that not all prostate cancer requires treatment [31], the definitions of clinically significant disease are inevitably contentious. We attempted to include as many as possible to allow for the differences of opinion that currently exist, especially with regard to Gleason 4 disease [32,33].

Conclusion

A normal multi-parametric MRI – that is, one with a score of 1 or 2 - confers a high probability (89-100%) of freedom from clinically significant prostate cancer and as a result, may allow some men to defer or reduce the burden of prostate biopsy. The positive predictive value for clinically significant disease – that is, lesions scoring 4 or 5 on mpMRI – was approximately 50%, something which may allow these patients to benefit from targeted biopsy.

Acknowledgments

Mohamed Abd-Alazeez receives funding from the Egyptian government. Hashim Uddin Ahmed and Mark Emberton receive funding from the Medical Research Council, the NIHR-HTA, NIHR-i4i, the US NIH/NCI, Pelican Cancer Foundation, Prostate Cancer UK and St Peter's Trust. This work was part funded by research support for Mark Emberton and Alex Kirkham from the UK National Institute of Health Research UCLH/UCL Comprehensive Biomedical Research Centre, London, UK. Manit Arya would like to acknowledge Orchid (male cancer charity) and Barts and London charity.

Other sources of funding

Mark Emberton and Hashim U Ahmed receive funding from USHIFU and Advanced Medical Diagnostics for clinical trials. Mark Emberton is a paid consultant to Steba Biotech, USHIFU and Sanofi-Aventis. Mark Emberton has received research support by GSK for a study evaluating the role of MRI in men with prostate cancer. Mark Emberton and Hashim Ahmed have previously received medical consultancy fees from GE Healthcare/Oncura and Hashim Ahmed previously from Steba Biotech. Mark Emberton is a medical director of Mediwatch PLC.

References

1. Schroder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009; 360(13):1320–1328. [PubMed: 19297566]
2. Hugosson J, Carlsson S, Aus G, Bergdahl S, Khatami A, Lodding P, et al. Mortality results from the Goteborg randomised population-based prostate-cancer screening trial. Lancet Oncol. 2010; 11(8): 725–732. [PubMed: 20598634]
3. Taylor JA, Gancarczyk KJ, Fant GV, McLeod DG. Increasing the number of core samples taken at prostate needle biopsy enhances the detection of clinically significant prostate cancer. Urology. 2002; 60(5):841–845. [PubMed: 12429312]
4. Ahmed HU, Kirkham A, Arya M, Illing R, Freeman A, Allen C, et al. Is it time to consider a role for MRI before prostate biopsy? Nature reviews Clinical oncology. 2009; 6(4):197–206.
5. Crawford ED, Rove KO, Barqawi AB, Maroni PD, Werahera PN, Baer CA, et al. Clinical-pathologic correlation between transperineal mapping biopsies of the prostate and three-dimensional reconstruction of prostatectomy specimens. The Prostate. 2013; 73(7):778–787. [PubMed: 23169245]
6. Hu Y, Ahmed HU, Carter T, Arumainayagam N, Lecornet E, Barzell W, et al. A biopsy simulation study to assess the accuracy of several transrectal ultrasonography (TRUS)-biopsy strategies compared with template prostate mapping biopsies in patients who have undergone radical prostatectomy. BJU Int. 2012; 110(6):812–820. [PubMed: 22394583]
7. Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, et al. ESUR prostate MR guidelines 2012. European radiology. 2012; 22(4):746–757. [PubMed: 22322308]
8. Portalez D, Mozer P, Cornud F, Renard-Penna R, Misrai V, Thoulouzan M, et al. Validation of the European society of urogenital radiology scoring system for prostate cancer diagnosis on multiparametric magnetic resonance imaging in a cohort of repeat biopsy patients. Eur Urol. 2012; 62(6):986–996. [PubMed: 22819387]
9. Barzell WE, Melamed MR. Appropriate patient selection in the focal treatment of prostate cancer: the role of transperineal 3-Dimensional pathologic mapping of the prostate—a 4-year experience. Urology. 2007; 70(Suppl 6A):27–35. [PubMed: 18194708]
10. Simmons, L.; Ahmed, HU.; Moore, CM.; Emberton, M. Imaging for Significant Prostate Cancer Risk Evaluation (PICTURE). 2011. ClinicalTrials.govClinicalTrials.gov
11. Emberton, M. PROMIS - Prostate MRI Imaging Study - Evaluation of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis and Characterization of Prostate Cancer. 2011. ClinicalTrials.govClinicalTrials.gov
12. Epstein JI, Allsbrook WC, Amin MB, Egevad LL. The 2005 international society of urological pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol. 2005; 29(9):1228–1242. [PubMed: 16096414]
13. Karram S, Trock BJ, Netto GJ, Epstein JI. Should intervening benign tissue be included in the measurement of discontinuous foci of cancer on prostate needle biopsy? Correlation with radical prostatectomy findings. The American journal of surgical pathology. 2011; 35(9):1351–1355. [PubMed: 21836493]
14. Ahmed HU, Hu Y, Carter T, Arumainayagam N, Lecornet E, Freeman A, et al. Characterizing clinically significant prostate cancer using template prostate mapping biopsy. The Journal of urology. 2011; 186(2):458–464. [PubMed: 21679984]
15. Efron, B.; Tibshirani, RJ. An Introduction to the Bootstrap. Chapman & Hall/CRC Monographs on Statistics & Applied Probability; 1993.
16. Puech P, Potiron E, Lemaitre L, Leroy X, Haber GP, Crouzet S, et al. Dynamic contrast-enhanced-magnetic resonance imaging evaluation of intraprostatic prostate cancer: correlation with radical prostatectomy specimens. Urology. 2009; 74(5):1094–1099. [PubMed: 19773038]
17. Villeirs GM, De Meerleer GO, De Visschere PJ, Fonteyne VH, Verbaeys AC, Oosterlinck W. Combined magnetic resonance imaging and spectroscopy in the assessment of high grade prostate carcinoma in patients with elevated PSA: a single-institution experience of 356 patients. European journal of radiology. 2011; 77(2):340–345. [PubMed: 19740617]

18. Turkbey B, Mani H, Shah V, Rastinehad AR, Bernardo M, Pohida T, et al. Multiparametric 3T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol. 2011; 186(5):1818–1824. [PubMed: 21944089]
19. Tanimoto A, Nakashima J, Kohno H, Shinmoto H, Kuribayashi S. Prostate cancer screening: the clinical value of diffusion-weighted imaging and dynamic MR imaging in combination with T2-weighted imaging. Journal of magnetic resonance imaging: JMRI. 2007; 25(1):146–152. [PubMed: 17139633]
20. Isebaert S, Van den Bergh L, Haustermans K, Joniau S, Lerut E, De Wever L, et al. Multiparametric MRI for prostate cancer localization in correlation to whole-mount histopathology. Journal of magnetic resonance imaging: JMRI. 2013; 37(6):1392–1401. [PubMed: 23172614]
21. Akin O, Gultekin DH, Vargas HA, Zheng J, Moskowitz C, Pei X, et al. Incremental value of diffusion weighted and dynamic contrast enhanced MRI in the detection of locally recurrent prostate cancer after radiation treatment: preliminary results. European radiology. 2011; 21(9): 1970–1978. [PubMed: 21533634]
22. Delongchamps NB, Beuvon F, Eiss D, Flam T, Muradyan N, Zerbib M, et al. Multiparametric MRI is helpful to predict tumor focality, stage, and size in patients diagnosed with unilateral low-risk prostate cancer. Prostate cancer and prostatic diseases. 2011; 14(3):232–237. [PubMed: 21423266]
23. Kirkham A, Emberton M, Allen C. How Good is MRI at Detecting and Characterising Cancer within the Prostate? European Urology. 2006; 50(6):1163–1175. [PubMed: 16842903]
24. Ahmed HU, Hindley RG, Dickinson L, Freeman A, Kirkham AP, Sahu M, et al. Focal therapy for localised unifocal and multifocal prostate cancer: a prospective development study. Lancet Oncol. 2012; 13(6):622–632. [PubMed: 22512844]
25. Vourganti S, Rastinehad A, Yerram NK, Nix J, Volkin D, Hoang A, et al. Multiparametric magnetic resonance imaging and ultrasound fusion biopsy detect prostate cancer in patients with prior negative transrectal ultrasound biopsies. The Journal of urology. 2012; 188(6):2152–2157. [PubMed: 23083875]
26. Haffner J, Lemaitre L, Puech P, Haber GP, Leroy X, Jones JS, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU international. 2011; 108(8 Pt 2):E171–178. [PubMed: 21426475]
27. Kasivisvanathan V, Dufour R, Moore CM, Ahmed HU, Abd-Alazeez M, Charman SC, et al. Transperineal magnetic resonance image targeted prostate biopsy versus transperineal template prostate biopsy in the detection of clinically significant prostate cancer. The Journal of urology. 2013; 189(3):860–866. [PubMed: 23063807]
28. Delongchamps NB, Peyromaure M, Schull A, Beuvon F, Bouazza N, Flam T, et al. Prebiopsy magnetic resonance imaging and prostate cancer detection: comparison of random and targeted biopsies. The Journal of urology. 2013; 189(2):493–499. [PubMed: 22982424]
29. Rouse P, Shaw G, Ahmed HU, Freeman A, Allen C, Emberton M. Multi-parametric magnetic resonance imaging to rule-in and rule-out clinically important prostate cancer in men at risk: a cohort study. Urologia internationalis. 2011; 87(1):49–53. [PubMed: 21701136]
30. Bittner N, Merrick GS, Butler WM, Bennett A, Galbreath RW. Incidence And Pathologic Features Of Prostate Cancer Detected On Transperineal Template-Guided Mapping Biopsy Following Negative Transrectal Ultrasound-Guided Biopsy. J Urol. 2013
31. Ahmed HU. The index lesion and the origin of prostate cancer. N Engl J Med. 2009; 361(17): 1704–1706. [PubMed: 19846858]
32. Ploussard G, Epstein JI, Montironi R, Carroll PR, Wirth M, Grimm M-O, et al. The contemporary concept of significant versus insignificant prostate cancer. Eur Urol. 2011; 60(2):291–303. [PubMed: 21601982]
33. Wolters T, Roobol MJ, Leeuwen PJv, Bergh RCNvd, Hoedemaeker RF, Leenders GJLHv, et al. A Critical Analysis of the Tumor Volume Threshold for Clinically Insignificant Prostate Cancer Using a Data Set of a Randomized Screening Trial. JURO. 2011; 185(1):121–125. [PubMed: 21074212]

Europe PMC Funders Author Manuscripts

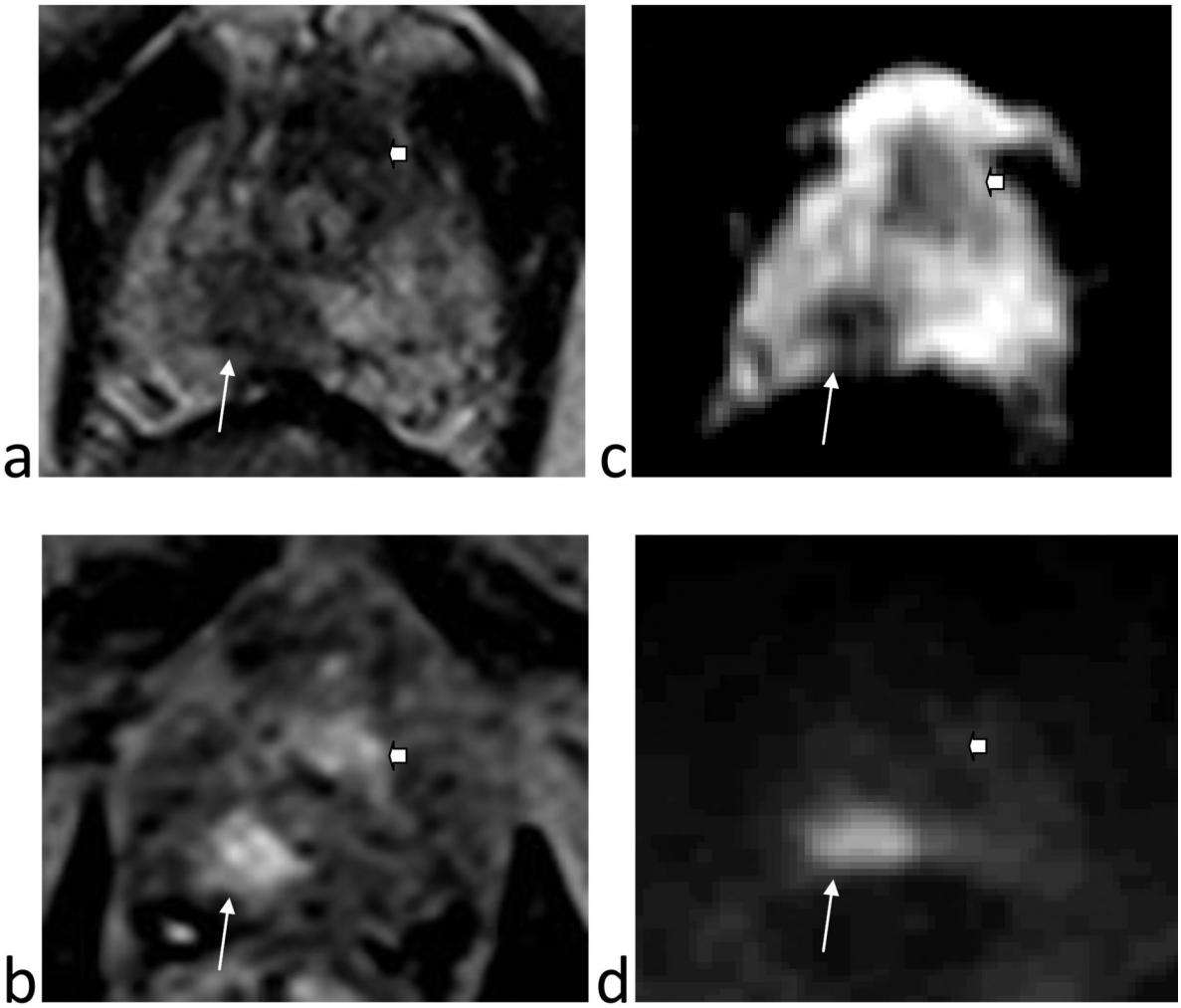

Figure 1.
Axial images from a positive MRI (scoring 5/5) with a maximum of 5 mm, 50%, of Gleason 3+4 found at template biopsy in the right posterior apical parasagittal zone. The T2 image (a) shows a low signal focus on the right (arrow), the contrast-enhanced image (b) shows corresponding focal enhancement (arrow), the Apparent Diffusion Coefficient (ADC) map (c) shows significantly restricted diffusion (arrow) and there is a focus of high signal on the long b diffusion image (b-1400) (arrow, d). Note that although the transition zone (arrowhead) enhances moderately and shows mildly restricted diffusion, it is not of high signal on the long b value images (d).

Europe PMC Funders Author Manuscripts

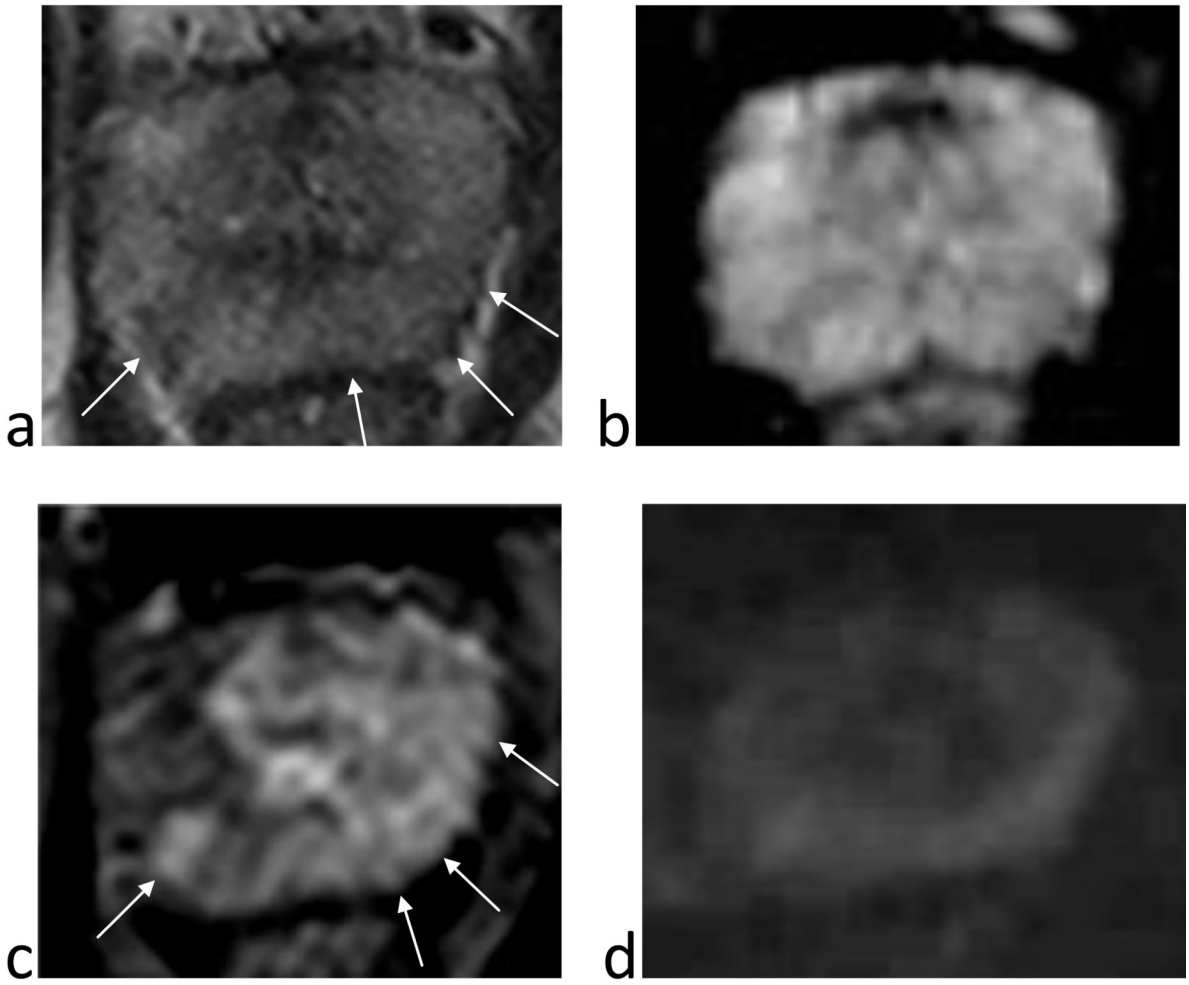

Figure 2.

Axial images from an indetermnate MRI (scoring 3/5) with no tumour found at biopsy. The T2 image (a) shows diffuse, but slightly heterogenous, moderate reduction in signal in the peripheral zone on each side (arrows). The contrast-enhanced image (b) shows moderate enhancement in a similar distribution (arrows). No significantly restricted diffusion is seen on the ADC map (c) and long b diffusion image (d).

Europe PMC Funders Author Manuscripts

Table 1

Detailed MRI scan parameters at 1.5T

	TR	TE	Flip angle/degrees	Plane	Slice thickness (gap)	Matrix size	Field of view/mm	Time for scan
1. T2 TSE	5170	92	180	Axial, coronal	3mm (10% gap)	256×256	180×180	3m 54s (ax), 4m18s (cor)
2. VIBE fat sat	5.61	2.52	15	axial	3mm	192×192	260×260	7m (17s per acquisition)
3. Diffusion (b values: 0, 150, 500, 1000)	2200	Min (<98)		axial	5mm	172×172	260×260	5m 44s (16 averages)
4. Diffusion (b=1400)	2200	Min (<98)		axial	5mm	172×172	320×320	3m 39s (32 averages)

Europe PMC Funders Author Manuscripts

Table 2

Detailed MRI scan parameters at 3T

	TR	TE	Flip angle/degrees	Plane	Slice thickness (gap)	Matrix size	Field of view/mm	Time for scan
1. T2 TSE	7340	101	150	Axial, coronal	3mm (10% gap)	320 × 310	200×200	5 min (ax), 5 min 20s (cor)
2. VIBE fat sat	4.1	1.5	10	axial	3mm	256×256	250×250	5 min (20 15s repititions)
3. Diffusion (b values: 0, 100, 300, 800, 1000)	4300	80		axial	5mm	126 × 81	25 × 21	5m 58s (6 averages)
4. Diffusion (b=2000)	7500	79		axial	5mm	126 × 81	25 × 21	5m 34s (14 averages)

Europe PMC Funders Author Manuscripts

Table 3

Baseline demographics of 138 men undergoing mp-MRI followed by template prostate mapping

Age, years (median, range)	62 (41-82)
PSA (median, range)	5.8 (1.2-20)
Prostate volume (median, range)	40 (16-137)
Number of sectors with no cancer on TPM, N (%)	117/258 (45%)
Number of sectors with “Any cancer” on TPM, N (%)	141/258 (55%)
Number of biopsies at TPM (median, range)	41 (20-93)
Gleason Score on TPM, N (%)	
6	87/141 (62%)
7 (3+4)	41/141 (29%)
7 (4+3)	8/141 (6%)
8	3/141 (2%)
9 (4+5)	2/141 (1%)

Europe PMC Funders Author Manuscripts

Table 4

The performance characteristics of mp-MRI with a radiological score of ≥ 3 to detect and rule-out clinically significant cancer on TPM defined by a number of thresholds at half prostate level (Primary outcome) (95% confidence intervals in parentheses)

Classification	ROI	TP	FN	TN	FP	SEN	SPEC	PPV	NPV
UCL2	**258**	**72**	**5**	**42**	**139**	**94 (88-99)**	**23 (17-29)**	**34 (28-40)**	**89 (79-98)**
UCL1	258	45	1	64	166	98 (93-100)	22 (16-27)	21 (15-27)	98 (93-100)
Gleason 4+3	258	13	0	47	198	100 (100-100)	19 (14-24)	6 (3-10)	100 (100-100)
Gleason 3+4	258	50	4	43	161	93 (85-100)	21 (15-27)	24 (18-30)	92 (83-100)
CCLmax ≥6	258	39	1	46	172	98 (91-100)	21 (15-27)	19 (13-24)	98 (93-100)
CCLmax ≥4	258	59	4	43	152	94 (87-99)	22 (16-28)	28 (23-34)	91 (82-98)
Any cancer	258	127	14	33	84	90 (86-95)	28 (20-37)	60 (53-67)	70 (55-84)

Europe PMC Funders Author Manuscripts

Table 5

The performance characteristics of mp-MRI with a radiological score of ≥ 4 to detect and rule-out clinically significant cancer on TPM defined by a number of thresholds at half prostate level (secondary outcomes) (95% confidence intervals in parentheses)

Classification	ROI	TP	FN	TN	FP	SEN	SPEC	PPV	NPV
UCL2	**258**	**52**	**25**	**124**	**57**	**68 (56-78)**	**69 (61-76)**	**48 (38-58)**	**83 (77-89)**
UCL1	258	37	9	140	72	81 (68-91)	66 (60-73)	34 (25-44)	94 (90-97)
Gleason 4+3	258	12	1	148	97	92 (73-100)	61 (54-67)	11 (5-17)	99 (97-100)
Gleason 3+4	258	38	16	133	71	70 (57-81)	65 (58-71)	35 (25-44)	89 (84-994)
CCLmax ≥6	258	32	8	141	77	80 (66-92)	65 (58-72)	30 (21-39)	95 (91-98)
CCLmax ≥4	258	45	18	131	64	71 (58-83)	67 (60-75)	42 (32-51)	88 (82-93)
Any cancer	258	79	62	87	30	56 (48-64)	75 (65-83)	73 (64-81)	58 (50-67)

Europe PMC Funders Author Manuscripts

Table 6

Area under the receiver operating characteristic curves for different definitions of clinically significant cancer at mpMRI score 1-5

	AUROC
UCL1	0.78 (0.71, 0.84)
UCL2	0.72 (0.65, 0.79)
Any cancer	0.70 (0.63, 0.76)
Gleason 4+3	0.79 (0.69, 0.87)
Gleason 3+4	0.71 (0.63, 0.78)
CCL max ≥ 6	0.78 (0.69, 0.84)
CCL max ≥ 4	0.73 (0.66, 0.80)