# The Role of Multiparametric MRI in Detection, Localization and Characterization of Prostate Cancer

**by**

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**A thesis submitted in fulfilment of the requirements for the degree of MD(Res),**

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# Declaration

I, Mohamed Abd Alazeez confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed…Mohamed Abd Alazeez…… (candidate)
Date…28th July 2014…….

# Acknowledgments

I would like to express the deepest appreciation to my supervisors, Professor Mark Emberton and Dr. Alex Kirkham who helped me a lot throughout my MD project.

In addition, a special thank you to Mr Manit Arya who supported me at many stages during my MD and Hashim Ahmed who has always been giving me sincere advice and guided me on how proper research should be performed.

Finally, I would like to thank all my family members specially my wife for her support at all the times.

# Abstract

Our aim was to detect the performance characteristics of multiparametric magnetic resonance imaging (mp-MRI) in patients with clinical suspicion, or previous diagnosis, of prostate cancer. Mp-MRI (index test) comprised of T2-weighted, diffusion weighted and dynamic contrast enhanced imaging. Radiologists used Likert score 1-5 based on the likelihood of the presence of prostate cancer. Concordance was made between results of mp-MRI and template prostate mapping (TPM) biopsy (reference standard). This retrospective study included patients that had both the index test and reference standard between January 2007 to January 2011 at either University College London Hospital or London Urology Associates.. These were patients with; a) no prior prostate biopsy (n=129), b) prior negative prostate biopsy (n=54), c) previous positive prostate biopsy (n=194) and d) biochemical failure after radiotherapy (n=37). A set of target conditions was used and varied between the four groups of patients. These were either based on Gleason scoring, maximum cancer core length or a combination of both.

In the first group, mp-MRI showed encouraging diagnostic performance results in ruling out clinically significant prostate cancer with sensitivity and negative predictive value (NPV) up to 94% and 89%, respectively. Accuracy figures were similar in the second group with sensitivity and NPV reaching up to 90% and 95%, respectively. In patients that underwent mp-MRI before reclassification TPM biopsy (third group), NPV for predicting that cancer remained low risk (as detected on previous TRUS-guided biopsy) reached up to 100%. Positive predictive value for upgrade of prostate cancer disease on subsequent TPM biopsy reached up to 75% with diagnostic odds ratio up to 2.86. In the last group, a combination of T2-weighted + high b-value showed optimum mp-MRI performance.

These results suggest that mp-MRI can be used as a triage test among different patient populations, to select patients that can avoid biopsy and those that need re-biopsy before entering an active surveillance program. Time and cost can be saved by using only certain MRI sequences in patients with biochemical failure after radiotherapy.

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# Abbreviations

ADC – apparent diffusion coefficient
AUC – area under the curve
AUROC – area under the receiver operating characteristic curve

BBH – benign prostatic hyperplasia

CCLmax – maximum cancer core length
CT – Computed Tomography

DCE –dynamic contrast enhanced
DRE – digital rectal examination
DWI – diffusion weighted imaging

ERC – endorectal coil
ESUR – European Society of Urogenital Radiology

IQ – interquartile
ISUP – International Society of Urological Pathology

Mp-MRI – multiparametirc magnetic resonance imaging
MRS – magnetic resonance spectroscopy

NICE - National Institute for health and Care Excellence
NPV – negative predictive value

PIRADS - Prostate Imaging Reporting and Data System
PPA – pelvic phased array
PPV – positive predictive value
PSA – prostate specific antigen
PSAD – prostate specific antigen density

RP – radical prostatectomy

SNR – signal-noise ratio

TPM – template prostate mapping
TRUS – transrectal ultrasound

UCL – University College London

# Chapter 1

## Introduction and Hypothesis

# Introduction

## Prostate cancer epidemiology

Prostate cancer is considered to be the most widely diagnosed cancer, accounting for 25% of all cancers in males. One in six males will develop prostate cancer during his lifetime and only 3% will die from this disease (1, 2). Autopsy specimens show that the disease affects 30% of men in their fourth decade, 50% of men in their $6^{th}$ decade and climbs up to affect more than 75% of those aged 85 years or older (3, 4).

Five-year survival rate for all stages of prostate cancer is currently 99% while 10 and 15 year survival rates are 93% and 79%, respectively. The majority of patients diagnosed with prostate cancer die with, rather than from, this disease (5). Many tumours will remain indolent throughout patient's life and so not all of diseased patients will make benefit from active treatment.

As the biology of prostate cancer is still poorly understood, it remains a challenge to accurately identify patients that need treatment from those that could be over-treated. Adequate risk stratification of diseased men could help identify those at curable stage while sparing others with indolent disease. A better understanding of the disease process and accurate characterization of prostate cancer will lead to proper selection of suitable therapies and counselling patients about disease progression.

## Gleason scoring system for prostate cancer

The Gleason scoring system provides an accurate means at predicting prostate cancer outcome (6). It is based on the microscopic appearance of prostate cancer tissue expressed in two grades, e.g; Gleason 3+4. The two numbers (primary and secondary grades) are added to produce the Gleason score. Gleason grade ranges from 1 to 5, with 5 carrying the worst prognosis. Accordingly, Gleason score ranges from 2-10. Gleason 4+3 is considered more aggressive than Gleason 3+4 although both have the Gleason sum of 7. Gleason pattern of 1 and 2 are almost never seen.

At prostate biopsy, the first Gleason number is assigned to the most common tumour pattern while the second is assigned to the next most common tumour pattern if only two patterns are present. If three patterns are present, the first Gleason pattern should be the most common one while the second pattern should be the highest grade (regardless of its proportion). However if the biopsies are largely composed of grade 4/5 cancer, grade 3 cancer should be ignored if <5%. At Radical prostatectomy, Gleason score is interpreted based on the dominant (largest volume) Gleason pattern + the second most dominant. If only

one Gleason pattern is present, it is doubled to calculate the Gleason score. If a grade is less than 5%, it is not included in the final Gleason score (7).

It should be noted that there has been significant upgrade of tumours with pattern 3 towards pattern 4 based on the recommendations from the International Society of Urological Pathology (ISUP) in 2005 (7).

If there is prevalent high-grade pattern (e.g pattern 4) within the biopsy and less than 5% low grade pattern (e.g pattern 3), the overall Gleason grade should be composed of the high-grade tumour pattern only (Gl 4+4), ignoring the low grade one. Also, Gleason score should be made from the most prevalent pattern and the highest grade one (7).

In a retrospective study over 767 men diagnosed with prostate cancer, the effect of Gleason score, age and co-morbidities were examined as predictors of death from the disease (8). Gleason score was found to be the best predictor for the rate of death from prostate cancer. As the Gleason score increased, mortality rate increased.

## Prostate cancer diagnosis

### Diagnostic test

A diagnostic test is an investigation that leads to a change in the patient management. In other words, it can either be used to detect a disease condition, assess its severity, predict outcome after planned therapy, monitor response to treatment or completely rule out the presence of that disease. It can also be used for all of these purposes. Ideally, it should yield the maximum benefit with the least risk to the patient. In diagnostic studies, this is usually referred to as "index test" which is the test under evaluation. In order to test the performance of the "index test", a concordance of the results should be made with a standard test, the so-called "reference standard". The reference standard is the best available method for the detection of the disease of interest (9). Poor reference standard leads to inappropriate interpretation of the index test with potential under or over-estimation of the results (reference standard error bias) and subsequent incorrect treatment decision (10).

### Target condition

It is important to have a clear definition of the disease of interest, the so called "Target condition" (11). Different target conditions may exist with different thresholds of clinical significance. Further management could be based on the accuracy of the index test for the detection/ruling out of different target conditions. Defining the target condition should be based on the best available evidence about the threshold for the intervention that the test will be used to guide.

### Insignificant or indolent

An indolent prostate cancer has been defined as the one that will never progress to a clinically manifest disease regardless of the longevity of the patient. Whereas insignificant prostate cancer is a subtype of indolent cancer, that also factors in patient age and comorbidities (12). In other words, an insignificant prostate cancer is a silent cancer that would not have caused any morbidity or mortality throughout the patient's life if left untreated.

### Population under study

Non-random selection of the population that is subject to both the index and reference tests leads to workup bias. Another type of bias comes up if the reference standard is changed based on the results of the index test; differential verification bias. For reproducibility, a detailed description of both tests is mandatory. The methodology and protocol of both tests should be clear and applicable at more than one centre in order to obtain similar results.

The extent of agreement between the index test and the reference standard is usually referred to as accuracy. Accuracy can be expressed using sensitivity, specificity, positive and negative predictive values, likelihood ratios, odds ratio and the area under receiver-operator characteristic curve (13, 14). Index test results can be shown in several ways; dichotomous, ordinal, categorical or continuous. In the current work, the multiparametric magnetic resonance imaging (mp-MRI) results were ordinal. In other words, different cutoff points (scoring 1-5) were used to separate findings considered to be positive, equivocal or negative.

Time between the index test and reference standard must not be too long to allow for disease progression. If disease progression occurs, interpretation of the results will be inadvertently inaccurate due to the artificial underperformance of the index test (disease progression bias).

While prevalence of a disease straightforwardly affects positive and negative predictive values, it does not directly alter sensitivity and specificity (15). As the prevalence increases, one would expect high positive and low negative predictive values.

A test with high sensitivity and high negative predictive value is useful clinically to rule out the presence of a disease. That is, a negative result would in effect exclude the possibility that the patient has the disease of interest.

**Diagnostic techniques in prostate cancer**

***Drawbacks of the current diagnostic pathway***

Men aged ≥50 who present with lower urinary tract symptoms are offered prostate specific antigen (PSA) blood test and digital rectal examination (DRE). PSA is known to have a low specificity (36%, (16)), leading to many unnecessary prostate biopsies. Meanwhile, normal PSA is found in up to 25% of patients and more than 50% have normal DRE (17). If high PSA is found and/or abnormal DRE, the next step usually is to perform transrectal ultrasound (TRUS) guided biopsy (18). The patient is counseled for the procedure and explained the risks, especially the risk of septicemia. Ten to twelve needle biopsies are randomly taken from the prostate gland aiming at picking up a possible prostate cancer. If the biopsies come back as negative, the patient is usually reassured and told that he has no cancer, which is wrong in up to 30% of cases (19, 20). TRUS-guided biopsy is known to under-estimate cancer burden and Gleason grade in 27-46% of cases (21, 22).

In patients with previous negative TRUS-guided biopsy but persistently high or increasing PSA, a second biopsy is usually done. If this comes back as negative, the patient is, again, reassured and either kept under PSA observation or discharged. Recently, National Institute for Health and Care Excellence (NICE) guidelines recommended performing mp-MRI, in

patients with previous negative TRUS-guided biopsy before attempting to perform further biopsies (23). If mp-MRI is negative, another set of biopsies should not be offered unless there is continued clinical suspicion of prostate cancer (24).

Recent studies report conflicting results between Gleason scores found on TRUS-guided biopsy and radical prostatectomy in more than third of patients deemed suitable for active surveillance (25, 26). Using 6 different protocols of active surveillance programs Vellekoop et al. showed that 33-45% of patients had adverse pathology at radical prostatectomy (26). These were only the patients that chose to have radical prostatectomy as a definitive treatment for their prostate cancer after a period of active surveillance. Such patients were younger than those with similar tumours that did not have surgery, something that suggests potential increase in percentage of adverse pathology should those patients have undergone surgery. They also found that men with more extensive biopsy sampling were significantly less likely to be upgraded and/or upstaged at radical prostatectomy. NICE guidelines recently recommended performing mp-MRI on enrolment of patients into an Active Surveillance program (23).

Biochemical failure occurs in 16-67% of prostate cancer patients within 5 years of treatment with radiotherapy, depending on their initial risk status. These patients either have local or distant recurrence. Should there be a local recurrence, such patients can be managed surgically either by salvage prostatectomy (27, 28) or focal therapy (29, 30).

TRUS-guided biopsies have inherent random and systematic errors. The random errors arise from the fact that the operator is unaware where the tumour could be. TRUS is only able to visualize hypo-echoic lesions while missing 37% to 50% of malignant iso-echoic foci (31, 32). The systematic error comes from under-sampling of the anterior peripheral and transition zones (33). It has been reported that false negative rates for any cancer at TRUS-guided biopsy range between 10-38% (34) and for clinically significant disease it reaches up to 23% (35). Another problem with TRUS-guided biopsy is the detection of low-grade low-burden tumours that are considered clinically insignificant, leading to over-diagnosis of prostate cancer. This is because these tumours might not have affected the patient's life if undiagnosed (12). Over-diagnosis potentially leads to overtreatment with subsequent unjustified morbidity and economic sufferings.

***New sonographic techniques***

3-D and 4-D ultrasound have been developed to improve visualization of suspicious areas within the prostate over conventional TRUS. Localization of cancer has been improved (36, 37) however under-detection remains a problem that still warrants systematic biopsies. Other

emerging techniques include contrast-enhanced sonography, harmonic sonography and elastography (38).

***Computed Tomography (CT)***

CT has a very limited role in the diagnosis of prostate cancer due to low sensitivity. It may have a role in high-risk patients with positive lymph node disease and known metastatic disease. Bone scintigraphy is more sensitive than CT in this respect (32).

***Magnetic resonance imaging (MRI)***

Magnetic resonance imaging has shown promising results in the detection and characterization of prostate cancer. Traditionally, T1 and T2-weighted morphological sequences were used to stage the already diagnosed prostate cancer. Innovative functional sequences (e.g diffusion-weighted imaging (DWI), dynamic contrast enhanced (DCE) imaging and magnetic resonance spectroscopy (MRS)) have made a breakthrough in the diagnostic value of MRI, the so called multiparametric MRI (mp-MRI) (39). This helped better detection, localization and characterization of prostate cancer (40, 41).

Moreover, development in the imaging hardware and software (e.g 1.5T to 3.0T) improved temporal and spatial resolution and signal to noise ratio. This did not only help diagnosing clinically significant tumours, but also allowed targeting of these tumours with needle biopsies and focal treatment.

**MRI of the prostate**

***Basic MRI features of the prostate***

The prostate gland is commonly described into 3 distinctive zones on MRI. These are the base, midgland and apex. On coronal plane, the prostate looks like an inverted cone with the base towards the bladder and the apex resting over the external urethral sphincter. The midgland is sandwiched between the base and the apex. On the axial plane, four zones can be identified within the prostate: a) the anterior fibromuscular stroma, b) the transition zone, c) the central zone (which is hard to be precisely seen separate from transition zone) and d) the peripheral zone.

Ninety-five percent of prostate cancers are adenocarcinomas and arise from the peripheral zone (70%), transition zone (25%) and central zone (5%).

***MRI technique and technology***

MRI technique can simply be explained based on the water content of tissues. The signals generated by the hydrogen (H) nuclei of water, is responsible for the image that the MRI scan produces. Different sequences show the same tissues in different ways. For instance, tissues with more hydrogen content will appear white on T2-weighted images and black on T1 (42).

When the body is subjected to a powerful magnetic field of MR scanner, protons (hydrogen nuclei of water) align with the direction of the field. This alignment is altered according to the strength of the magnet. When the magnetic field is turned off, the protons return to their original alignment. It is this change in the alignment that creates a signal detected by the scanner. Certain tissue characteristics can affect how the protons return back to the original status and these properties can be used to generate contrast between different tissue types (42).

***Morphological MRI sequences***

T1 and T2-weighted imaging

Various human body tissues have certain T1 and T2 values. Depending on the timing of pulse and the strength of the magnet applied, pulse sequences are generated in favor of either T1 or T2.

T1-weighted imaging uses short echo and repetition times. It does not delineate prostate cancer, as normal prostatic and cancer tissue show the same homogenous low signal intensity. Its main use is in: a) detection of post-biopsy hemorrhage, b) evaluation of the contour of the prostate and status of neurovascular bundles, c) detection of bone metastases and enlarged nodes, d) baseline sequence for calculation of pre-contrast T1-weighted and DCE images for purposes of subtraction (5).

T2-weighted imaging uses long echo and repetition times. Tissues with high water content appear brighter. It is the basic morphological sequence to delineate the prostate zonal anatomy. Cancerous tissue appearance differs between peripheral zone and central gland. In peripheral zone, it appears as an ill defined or round dark focus of low signal intensity against bright tissue. However in central gland it is a challenge to differentiate between cancer foci and benign prostatic hyperplasia (BPH) (43). Tamada et al. found that peripheral zone cancers identified on T2-weighted imaging are either triangular or circumscribed (44). Central gland tumour is often identified as homogenous signal mass with ill-defined margins “erased charcoal sign”. Also a lenticular or “water-drop” shape is typical (45). High-grade cancers usually have lower signal intensity than low-grade ones. In a recent study over 28

patients, Hoeks et al. found that T2-weighted imaging was enough for cancer detection in central gland whereas other sequences in mp-MRI were not useful (46).

In a study of 70 patients, Turkbey et al. showed sensitivity and specificity of T2-weighted imaging at 42% and 83% for the detection of any prostate cancer, respectively. When using a less stringent methodology in correlating imaging and pathological findings, neighbouring approach, they had sensitivity and specificity of 73% and 89%, respectively (47). Neighbouring approach considered the potential misalignment between pathologic sections and MRI images, due to surgical deformation, shrinkage and non-uniform slicing of pathologic specimens.

T2-weighted imaging alone may have a greater accuracy over DRE in locating cancer within the prostate and seminal vesicles (48). It is the sequence used to evaluate the capsule, seminal vesicles and posterior bladder wall for evidence of extraprostatic tumour extension. Signal intensity is inversely proportional to the amount of mucin associated with the cancer (49). Overall, T2-weighted imaging is known to be more sensitive than specific for the detection of prostate cancer (50, 51). The overall accuracy has been recently found to be nearly 60% (52). Two additional functional sequences should be used (40, 45). The low specificity comes mainly from the image artifact that results from performing early MRI after biopsy. This artifact was found to cause overestimation of the cancer burden in 20% of cases (53). It also affects the interpretation of other sequences as DCE imaging, DWI and MRS imaging (54, 55). Thereby, a period of 6-8 weeks has been suggested to separate MRI from previous prostate biopsy (45, 53, 54, 56). This is to allow for the resorption of all blood products (32, 45). However the biopsy artifact can last up to 2-4 months (53, 57). Other causes of false positive results include prostatitis, BPH, atrophy and changes after treatment; e.g radiotherapy. Moreover, some tumours are iso-intense where T2-weighted imaging will not be able to pick them up leading to low sensitivity (5).

***Functional MRI sequences***

A) Diffusion-weighted imaging (DWI)

In normal tissues, water molecules move freely according to Brownian motion. However in malignant tissues, this movement becomes restricted due to destruction of the normal glandular structure and high cellular density resulting in tight extracellular spaces. In other words diffusion of these molecules from extra- to intra-cellular spaces becomes restricted, something that can be picked up on MRI through DWI (58). Therefore DWI provides invaluable information about the functional environment of water in tissues reflecting high cellular density formed by malignant tissue. In addition to that, quantitative biophysical

parameter can be extracted from DWI and be used to differentiate between malignant and benign tissue.

The degree of sensitivity to water diffusion is reflected in the b-value. As the b-value becomes higher, the sensitivity to diffusion increases. However there is also prolongation of the radiofrequency pulse, something that increases the echo time and reduces the quality of DWI and signal-noise ratio (SNR) (5). Although the quality of DWI and SNR are higher with lower b-value, however added effects of T2 shine-through and tissue perfusion influence DWI. For optimum scan, b-values should be: 0, 100 and 800-1000 s/mm$^2$ (45). However, very high b-values (>1000 s/mm$^2$) can be used when normal prostatic tissue, as in central gland, mimics a tumour giving high signal on DWI (45). High b-values were also found to suppress the effect of hemorrhage in the post-biopsy setting in peripheral zone (59). Overall, high b-value imaging has been found to increase the diagnostic performance of mp-MRI in the detection of prostate cancer (60).

The measureable physical parameter of DWI is the apparent diffusion coefficient (ADC). Malignant prostatic tissues have lower ADC values (20-40%) than benign tissues in peripheral zone. This is due to the fact that any increase in cellular density causes reduction in water molecules mobility and consequently lowers ADC value. This feature helps in prediction of tumour aggressiveness (higher cellular density and Gleason scoring) (61, 62). Thereby, both DWI and ADC play an essential role in characterization of prostate cancer (58). Hambrock et al. also found an inverse relationship between Gleason score and ADC values (63).

Although there has been a general agreement that post-biopsy artifact hampers the utility of DWI (64), recent data demonstrated high accuracy of ADC in discrimination between malignant tissue and haemorrhage in the peripheral zone (65). However, a significant overlap of ADC values has been found between benign and malignant tissues and so ADC findings should be used in conjunction with T2-weighted MRI and other available imaging parameters (66).

Haider et al. demonstrated that when DWI is added to T2-weighted imaging at whole gland level, sensitivity reached up to 81% (in comparison to 54% at T2-weighted imaging alone). Whereas specificity came down from 91% at T2-weighted imaging to 84%, using both sequences. (67). A more recent meta-analysis showed the sensitivity and specificity of DWI when added to T2-weighted imaging to range from 65%-84% and 77%-87%, respectively (66). DWI was also found to increase the sensitivity of T2-weighted imaging for detection of prostate cancer in patients with biochemical recurrence after radiotherapy (68).

ADC maps can be generated and analysed to provide quantitative data as well. However absolute values should be used with caution as these differ according to field strengths, b-values, models and even between patients (45).

Thereby, DWI is a very essential component of mp-MRI. It has a short acquisition time, requires no contrast injection and provides a high contrast resolution between cancer and normal tissues. Disadvantages include susceptibility to motion and magnetic field homogeneities (69).

B) Dynamic contrast enhanced (DCE) imaging

This is a T1-weighted sequence where low molecular –weight contrast agent is injected into the patient. This contrast diffuses from intravascular to extravascular space then leaks back slowly to the vascular space. Tumour tissues, unlike normal tissues, have the ability to grow new blood vessels from existing ones (angiogenesis) or de novo (vasculogenesis). These neovessels have more permeability than the normal ones. This feature helps in the detection, localization and characterization of prostate cancer. This abnormal permeability leads to early enhancement of malignant tissue before normal tissues and early washout of the contrast, a characteristic that helps in detection and localization (70). As the tumour becomes more aggressive, more neovessels are being formed and consequently brighter enhancement and quicker washout result on DCE imaging. This later feature helps predicting the aggressiveness (characterization) of the disease (71, 72). This microvessel change has been found to be more severe in prostate cancer than in BPH and prostatic intra-epithelial neoplasia (73). Thereby, in prostate cancer there is early, fast and intense enhancement with quick washout of the contrast. The quick washout is highly suggestive of the presence of cancer by itself (74).

For semi-quantitative analysis purposes, intensity versus time curves can be generated. These give information on time to peak, maximum uptake slope, peak enhancement, area under the enhancement curve and washout rates (75). Enhancement curve is composed of 3 different components; persistent increase, plateau and initial upslope then decline. The last one is most diagnostic for prostate cancer (76).

Some pharmacokinetic parameters are frequently extracted from DCE imaging to help providing quantitative analysis. These are $v_e$ (leakage space), $k_{ep}$ (efflux rate constant) and $k^{trans}$ (influx transfer constant). Amongst them, $K^{trans}$ has been identified as the most useful parameter in DCE imaging. This is because it increases proportionately with tumour neo-angiogenesis (5). The main value of using pharmacokinetic parameters of DCE imaging is to increase the specificity of the highly sensitive T2-weighted imaging. This is mainly to

confirm the presence of possible lesions seen on T2-weighted scans rather than discovering new ones (77).

DCE imaging forms an important integral part of mp-MRI. The reported sensitivity of DCE imaging in the literature varies from 46% to 96% with specificity of 75% to 96% (78). In patients with biochemical failure after radiotherapy, DCE imaging was found to have a positive predictive value of 75% (79) besides an important role in patients with previous negative biopsies (80). DCE imaging has also been shown to detect clinically significant prostate cancer in 93% of cases (81). The main challenge for DCE imaging is that it is still unable to differentiate between BPH and transition zone tumours or prostatitis from cancer in the peripheral zone. This becomes more pronounced in young men where non-malignant prostate tissue enhances. Well-differentiated prostate cancer shows less vascularity and permeability changes than poorly differentiated one does. This accounts for some of the false negative results on DCE imaging. Therefore, DCE imaging should be interpreted along with other sequences to avoid false readings.

C) Magnetic resonance spectroscopy (MRS)

In malignant tissue, the levels of cellular metabolites are changed. Choline levels are increased mostly due to the increased turnover of the cell membrane that accompanies neoplastic proliferation. Citrate and polyamines, which are found in normal prostatic tissue, decrease with malignant tissue replacement. MRS gives important information about the biochemical and metabolic environment of tissues. Ratios rather than absolute metabolite concentration can be obtained. Consequently, increased choline/citrate (or choline+creatine/citrate) ratio is used as an evidence of malignancy in MRS. The higher this ratio, the higher the Gleason grade of prostate cancer (82-84). However a multicentre study showed that the combination of MRS and T2-weighted imaging did not improve tumour detection in patients that underwent radical prostatectomy (85). Shukla-Dave et al showed that MRS is more likely to detect high grade high volume tumours (86). MRS can also help in accurate measurement of tumour volume and predict tumour aggressiveness (87).

Despite the relatively high specificity of MRS, benign conditions as prostatitis, prostatic atrophy and post-biopsy hemorrhage may still lead to false positive results. MRS is not able to accurately provide staging for prostate cancer due to its poor spatial resolution. In their consensus meeting, the European Society of Urogenital Radiology (ESUR) mentioned that MRS is time consuming, requires expertise and the use of endorectal coil (ERC) at 1.5T. The choice of using MRS depends on personal local experience and availability (45).

***Multiparametric MRI (mp-MRI)***

Currently, MRI is considered as the best imaging modality for staging prostate cancer with the highest sensitivity and specificity. This is because it is able to detect, localize and describe the volume and extent of the tumour (88-90).

In 2011, a consensus meeting of 16 European prostate cancer experts was held to give recommendations over interpretation and reporting of mp-MRI (40). Consensus was reached on 54% of 260 items related to mp-MRI interpretation and reporting. They recommended the inclusion of the three basic sequences, which are: T2-weighted, DWI and DCE imaging, as a minimum standard in mp-MRI setting. An agreement was reached on some other points including features of malignant tissues over different mp-MRI sequences and the use of scoring 1-5 system to show the likelihood of the presence of clinically significant prostate cancer (defined as Gleason ≥4 + 3 and/or lesions ≥0.5 cm3 in volume). They suggested the use of TPM biopsy as a reference standard, that can be applied to all men, rather than radical prostatectomy. No consensus has been reached in some issues like the routine use of ERC and the use of bowel relaxants. They called for prospective trials to validate the outcome of mp-MRI in the detection, localization and characterization of prostate cancer.

The ESUR MRI guidelines came out in 2012 (45). Radiologists with adequate experience in prostate MRI had consensus meetings that lead to recommendations for the use of MRI in the management of patients with prostate cancer. A minimum of 2 functional MRI sequences should be used with T2-weighted imaging. Based on D'Amico's risk assessment of prostate cancer disease (91), mp-MRI can be used for different intentions. In low risk patients, it can be used to rule out the presence of clinically significant disease, should the patient choose to have active surveillance. Mp-MRI also helps planning of nerve sparing or focal therapy in this context. In intermediate risk patients, mp-MRI can detect extracapsular disease. In high-risk group, it is helpful for the detection of nodal or bone metastases. They also advised with performing mp-MRI in patients continued to have clinical suspicion of prostate cancer after negative initial TRUS-guided biopsy. An emphasis has been specially made on the use of the scoring system, prostate imaging reporting and data system (PI-RADS). This is similar to the one previously proposed by another consensus group (40). Finally, they recommended that mp-MRI should be a basic tool in the management of prostate cancer.

Mp-MRI diagnostic criteria for prostate cancer

I. **T2-weighted imaging:** Peripheral zone: ill-defined or round dark focus of low signal intensity.

Central gland tumour: homogenous signal mass with ill-defined margins “erased charcoal sign” or “water-drop” shape.

II. **DWI:** restricted diffusion and low signal on ADC maps.

III. **DCE imaging:** early, rapid enhancement and washout of the contrast, high peak enhancement, increased area under enhancement curve, high $v_e$, $K_{ep}$ and $K_{trans}$.

IV. **MRS:** elevated choline/citrate (or choline + creatine/citrate) ratio.

Each one of the functional mp-MRI techniques adds to its final interpretation. Where DWI and MRS increase the specificity of cancer characterization, DCE imaging shows high sensitivity for cancer detection (92-94). For transition zone cancers, mp-MRI has been found to increase the accuracy of T2-weighted imaging from 64% to 79% (93).

***Mp-MRI Scoring system for prostate cancer***

MRI interpretation and reporting is crucial to deliver an accurate picture of a possible prostate cancer disease. Some authors simply report mp-MRI sequences as either being negative or positive (binary scale), and then give an overall risk stratification of disease as low, intermediate or high (95). However it was difficult to interpret cancer significance using this method and also it did not put into consideration the variation of each sequence performance depending on tumour location within the prostate (96). Recently, the 1-5 Likert scoring system is gaining more popularity between uro-radiologists (60, 97, 98). However, an overall score can be problematic when one or more of the mp-MRI sequences are diagnostic of a tumour while the other(s) is not (41).

The ESUR guidelines proposed the PI-RADS scoring system for interpreting mp-MRI after reviewing multiple previous studies (45). This has provided a detailed description on reporting using basic sequences of T2-weighted, diffusion-weighted and dynamic contrast enhanced imaging. It gives a score 1-5 for each suspected lesion on each individual MRI sequence as well as an overall 1-5 score based on the presence/absence of clinically significant disease. However no definition for clinically significant disease was given by this publication. In addition to that, it did not put into account the higher sensitivity of different sequences at either PZ or TZ. For instance, T2-weighted sequence has a high performance at TZ while diffusion-weighted imaging was found to be the best parameter used in PZ (96, 99), meanwhile dynamic contrast enhanced imaging shows a high false positive rate in TZ.

The PI-RADS scoring was then vaildated by Portalez et al. over 129 patients with at least one set of previous negative biopsy (100). They found that PI-RADS scoring was a useful tool in risk stratification of patients at risk of prostate cancer. Further studies subsequently started using this scoring system (101-104).

***Is endorectal coil (ERC) mandatory for mp-MRI?***

The use of ERC versus pelvic phased array (PPA) has been a subject of controversy between different studies. Some centres use an ERC to reduce the SNR and obtain better MR images. Heijmink et al. found that the combination of ERC with PPA showed superior rates of tumour localization than that when using PPA alone (105). A recent study performed over two groups of patients that had either ERC or PPA showed no significant difference between the two groups in terms of sensitivity, specificity and overall accuracy (106). ESUR guidelines show that the use of ERC is not mandatory at either 1.5T or 3T, however PPA is required (45). It called for studies comparing between the accuracy of mp-MRI with the use of PPA with or without ERC.

***Detection of significant versus insignificant prostate cancer disease***

As mentioned earlier, insignificant prostate cancer is a silent cancer that would not have caused any morbidity or mortality throughout the patient's life if left untreated. Most of patients that are diagnosed with prostate cancer through PSA screening have clinically insignificant disease (32).

Schmid et al. followed up 43 patients with untreated prostate cancer, through serial PSA measurements, over a period of time from 12-63 months (107). Based on the finding that cancer volume can be predicted from the PSA level (1gm of cancer causes a rise in PSA by 3.5ng/ml) (108-110), they determined the doubling time of prostate cancer volume. This was found to be more than 24 months in 34/43 (79%) of those patients. Twenty-six (60%) of those patients had organ confined disease while 8 (17%) had non-organ confined one. Gleason score of less than 7 was also associated with a longer PSA doubling time. This lead to the conclusion that, in patients with low risk disease, prostate cancer has a very slow growth rate, and that PSA doubling time and Gleason score are important clinical predictors for progression of this disease.

There is a stressing need to reassure patients diagnosed with insignificant prostate cancer disease. Despite the use of clinical and pathological predictors, it is still challenging to assure such patients that they can be safely managed conservatively. Other factors have to be considered as the patient age and life expectancy.

To set predictors for clinically insignificant disease, Epstein et al. proposed a cut-off of 0.2cc (7 mm in diameter) (111). Later on Stamey et al. upgraded this cut-off to 0.5cc (10 mm in diameter) (112). Currently the criteria that are used to define clinically insignificant disease based on the radical prostatectomy (RP) specimen are: a) Gleason score $\leq 6$ (with no 4 or 5), b) organ confined disease and c) tumour volume $< 0.5$cc (111, 113, 114). However this

definition was found to misclassify 30% of patients whose RP specimens showed unfavorable pathological features (12).

On the other hand, the criteria based on TRUS-guided biopsy for preoperative prediction of insignificant disease are: a) PSA density ≤ 0.15, b) Gleason score ≤ 6, c) <3 positive cores and d) < 50% cancer core length (115). These criteria were found to be highly predictive for favorable disease (12).

Thanks to the continuous promising results obtained by mp-MRI, clinically significant disease could be detected with adequate precision while missing the clinically insignificant one (69, 116, 117). Although prostate cancer is known to be multifocal in nature, there is a proof that the secondary cancers, and not the index one (the largest tumour or Gleason score >6), do not adversely affect the prognosis (118-121).

As discussed before, a European consensus meeting advised with T2-weighted imaging, DCE imaging and DWI to be the baseline sequences for the exclusion of clinically significant disease, defined as Gleason ≥4 + 3 and/or lesions ≥0.5 cc (40).

MRI is accurate for the detection of high-grade high volume tumours than low-grade small ones (84, 122). Some studies concluded that tumour foci of more than 0.5cc are the ones responsible for PSA failure and not the smaller sized ones (119, 123).

Potiron et al. studied the accuracy of DCE imaging using RP specimens as their reference standard over 83 patients. The sensitivity and specificity for detection of cancer foci of >0.5cc were 86% and 94%, respectively with an area under receiver operating characteristic curve (AUROC) of 0.874. Mean volumes of detected and missed cancers were 2.44 and 0.16cc respectively. Haffner et al. showed a sensitivity, specificity and accuracy for DCE MRI targeted biopsy for significant cancer detection as 95%, 100% and 98%, respectively (124). This was statistically significantly higher than that of extended systematic prostate biopsy ($p < 0.001$). Criteria of insignificant cancer included; one positive core with cancer core length <5 mm and no Gleason 4/5.

MRI has also shown good results in detection of clinically significant tumours of high Gleason grade. In a study over 93 patients, AUROC for cancer detection by DCE imaging was 0.819 (125). ADC showed high performance in discrimination between low, intermediate and high-grade cancers (126).

After the 2005 meeting of the ISUP, a significant upgrade of tumours to Gleason pattern 4 occurred at both RP specimens and biopsies. This led to a decrease in the diagnosed insignificant prostate cancer (7).

An interesting finding in some clinical studies is that patients that have radical prostatectomy for transition zone cancers are less likely to develop PSA recurrence in comparison to those having peripheral zone tumours of the same size (127). This led to the assumption that these tumours can be defined as insignificant (12). However, there is not enough data in the literature to support this argument.

In a series of 354 patients with insignificant prostate cancer managed with RP, PSA failure occurred in 13% of patients at 10 years (128). The risk of metastatic progression was 0.3% and specific death was 0%.

Overall, despite the strenuous efforts, there is still no general agreement on the best criteria to use for the prediction of clinically significant prostate cancer. The challenge continues; how to differentiate between patients that harbour a disease destined to progress and cause morbidity/mortality from those that would never be affected from their cancer disease.

**Transperineal template prostate mapping (TPM) biopsy "reference standard"**

***Developing a better sampling strategy***

As mentioned earlier, the reference standard is the best available method to detect and characterize the target condition. In order to explore the performance of the index test, population under study should undergo both the index test and the reference standard. The modern transperineal TPM biopsy was developed by Barzell and Melamed (129). This kind of biopsy showed many advantages over the existing routine TRUS-guided biopsy, such as; better sampling of the anterior, apical and peripheral zones, lower risk of urethral damage and lower risk of sepsis (130). As previously discussed, TRUS-guided biopsy has a false negative rate up to 38% due to under-sampling of the anterior and apical regions. It was found that in patients with more than two previous negative TRUS-guided biopsies and continued clinical suspicion of prostate cancer, 94% (16/17 patients) had prostate cancer in either the anterior or apical part of the prostate (131). Transperineal TPM biopsy (12 cores) was found to be more concordant, in terms of Gleason score, with radical prostatectomy histology results than 6-8 cores TRUS-guided biopsy, (69.6% versus 49.4%, p=0.037) (132).

***Cancer detection***

In a computer-simulated study using radical prostatectomy specimens, transperineal prostate biopsy using 5mm grid detected clinically significant cancers (defined as volumes ≥0.5 cc and/or Gleason score ≥7) with a sensitivity of 95%. However, detection of clinically insignificant cancer was also high, lowering down specificity to 30% (133). Using 10mm grid brought the specificity high up to 66% in the same study. In another simulation study,

transperineal TPM biopsy showed superior results in tumour detection than five different strategies of TRUS-guided biopsy (134).

In patients deemed suitable for active surveillance based on TRUS-guided biopsy, 72% were found to have clinically significant prostate cancer on transperineal TPM biopsy (using Epstein criteria (135) to define clinically insignificant disease; Gleason score ≤6, <50% cancer core involvement, PSA density <0.15 and less than 3 positive cores). Gleason score was upgraded to ≥ 7 in 44.6% of those patients (135). Another study found 38% of patients having clinically significant cancer on template prostate biopsy, 6 months from starting an active surveillance program (136). Criteria for active surveillance in this study included Gleason score ≤6, PSA <15ng/ml, clinical stage T1-2a, cancer core length <10mm in a single core with <50% cancer core length involvement. Transperineal TPM biopsy detected bilateral prostate cancer in up to 61% of patients originally diagnosed with unilateral disease on TRUS-guided biopsy (137, 138).

Sampling density is associated with higher detection rate of cancer. In a study over 1,151, 12-core transperineal biopsy had a cancer detection rate of 47% compared to 35% with 6-core transperineal approach (139). Another study found cancer detection rate at 38% versus 32% between transperineal versus TRUS-guided prostate biopsy, respectively. Sixteen percent of diagnosed cancers in this study were detected only on transperineal biopsy (140).

In patients with previous negative TRUS-guided biopsy, prostate cancer detection was found to be in the range of 35-56% using transperineal TPM biopsy (141-143). In a single study, 52.6% of patients were found to have Gleason score ≥7 on transperineal TPM biopsy after initial negative TRUS-guided biopsy (144). It has been recognized that patients exposed to repeated TRUS prostate biopsy after an initial negative one, show variable rates (14-23%) of cancer detection at saturation biopsy (145, 146). Transperineal template prostate biopsy has been recommended by NICE guidelines in such patients with continued clinical suspicion of prostate cancer and negative or equivocal results from other biopsy methods (147).

***Comparative risks to TRUS-guided biopsy***

Transrectal biopsy carries between 25-87% risk of urinary tract infections, in patients not on prophylactic antibiotics (148-150). However routine administration of antibiotics for such patients, especially those with repeated biopsies, leads to the development of multi-resistant strains of bacteria. Risk of sepsis is even higher in immune-compromised patients such as diabetics. Transperineal rout proved to be associated with less incidence of urinary tract infection than the transrectal “transfaecal” one (151, 152).

Fourteen-core transperineal biopsy was found to be associated with operative pain similar to that caused by 12-core TRUS-guided biopsy when performed under local anaesthesia (153). Denser transperineal sampling usually requires sedation or general anaesthesia. The incidence of urine retention was found to be lower if 12-core biopsies have been taken transperineally than transrectally (154). As transperineal sampling density increased to >50 cores urine retention rates increased to 8-38% especially with large prostate volumes (143, 155).

Both types of prostate biopsy were found to cause temporary erectile dysfunction (154).

***MRI-biopsy combination***

The use of mp-MRI in patients with suspicion of prostate cancer has enabled targeting specific areas within the prostate. This combination of MRI-biopsy technique can either be delivered through simultaneous registration, cognitive registration or image fusion methods. In simultaneous registration, special MRI-compatible biopsy set is used to conduct the image-guided biopsy. While in cognitive registration, the urologist/radiologist targets suspicious areas within the prostate with the knowledge of the lesion location seen on mp-MRI. The last method, image fusion, a special computer software is used to apply the image obtained from MRI on the current TRUS image.

## Hypothesis

It was hypothesized that mp-MRI has an accurate performance in the diagnostic pathway of prostate cancer. The null hypothesis was that mp-MRI has a poor performance at the four different patient populations analysed in this thesis.

In order to pursue this hypothesis we did the following:

1) In chapter 3 (patients with no prior prostate biopsy), we hypothesized that mp-MRI is accurate in detection and localization of clinically significant prostate cancer.
2) In chapter 4 (men with persistently elevated or rising PSA and negative TRUS-guided biopsies), we again hypothesized that mp-MRI is accurate in detection and localization of clinically significant disease.

   In 1 and 2, we would be able to reject the null-hypothesis if mp-MRI shows a high sensitivity and negative predictive value to rule out the presence of clinically significant prostate cancer.

3) In chapter 5 (patients with previous positive TRUS-guided biopsy), we hypothesized that a visible lesion on mp-MRI predicts upgrade of tumour size/grade at subsequent TPM biopsy. Whereas a low risk lesion on TRUS-guided biopsy, that is not visible on mp-MRI, will not be upsized/upgraded at TPM biopsy i.e characterization.

   We would be able to reject the null-hypothesis if mp-MRI shows an adequate positive predictive value and diagnostic odds ratio for predicting upgrade of low risk disease into a clinically significant one

4) In chapter 6 (patients with biochemical failure after radiotherapy) we hypothesized that mp-MRI can accurately detect and localize local recurrence of prostate cancer. We also hypothesized that not all mp-MRI functional sequences are essential in this setting.

   We would be able to reject the null-hypothesis if mp-MRI shows good accuracy in detection and localization of radio-recurrent prostate cancer using minimum mp-MRI functional imaging dataset.

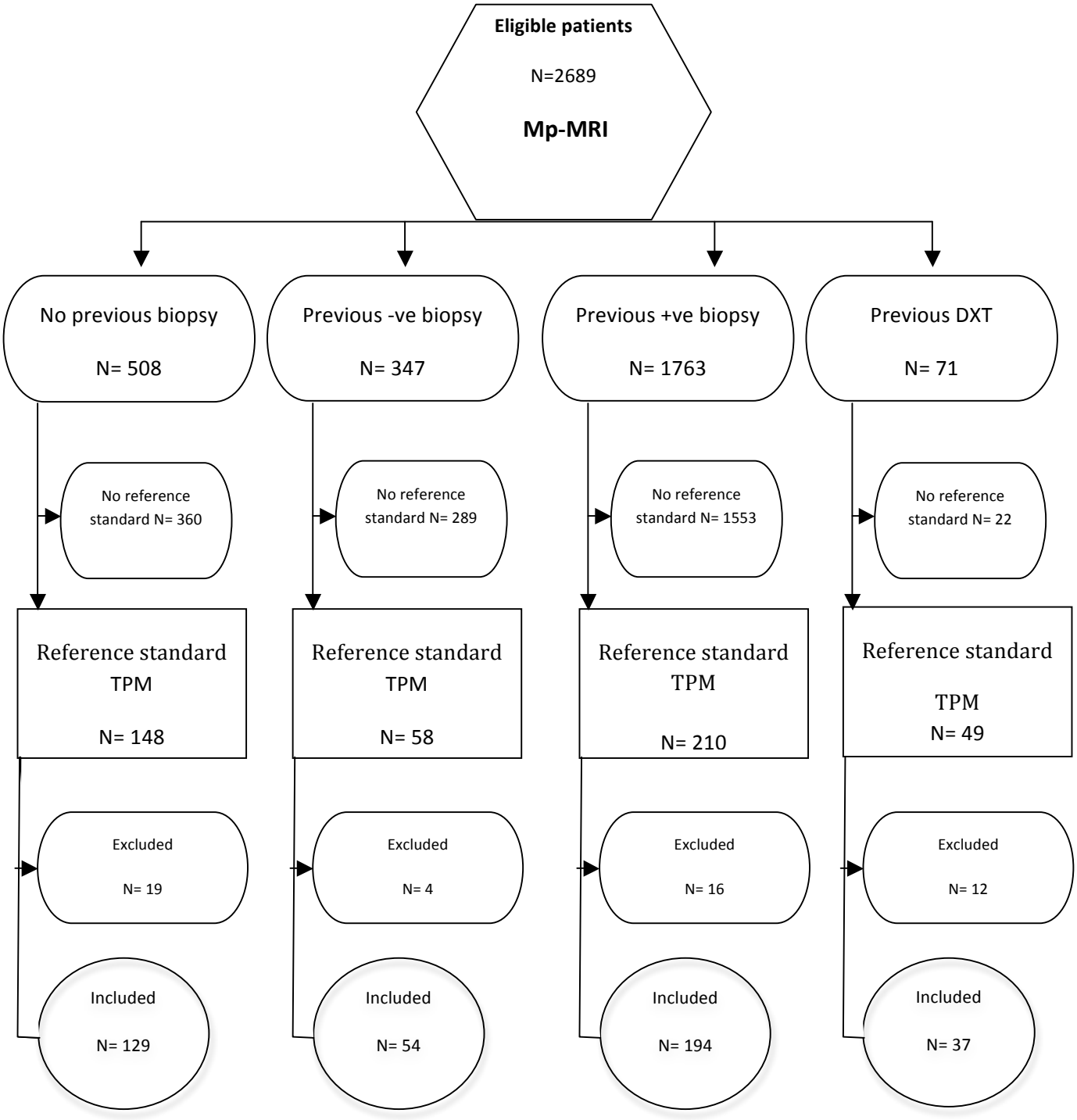



**Figure 1. Flow Chart demonstrating how patients were selected for the four main studies**

In the period from January 2007 to January 2011, 2689 patients had mp-MRI either at University College of London Hospital or at London Urology Associates (Figure 1). These patients were split into different groups of patients based on: a) whether or not they had previous prostate biopsy and b) patients that had previous radiotherapy. This lead to four different cohorts; patients with no previous prostate biopsy (n= 508), patients with prior negative prostate biopsy (347), patients with previous positive TRUS-guided biopsy (n= 1763) and those that had previous radiotherapy as treatment for prostate cancer (n= 71).

In the first group, those that had no previous TRUS-guided biopsy, 360 patients did not have our reference standard (TPM biopsy). These were patients that either went for TRUS-guided biopsy after mp-MRI or did not proceed for prostate biopsy at all. All the remaining 148 patients underwent TPM biopsy. Nineteen patients were excluded as these had either mp-MRI score 1-2 (n=9) or received less than 20 cores of systematic TPM biopsy (n= 10). This left 129 patients that constituted the final cohort in this group.

In the second group, those that had previous negative TRUS-guided biopsy, 289 patients did not have TPM biopsy. Those are either patients that had targeted TRUS-guided biopsy to an mp-MRI visible lesion, had no further prostate biopsies or went on to have PSA monitoring. Of the remaining 58 patients, 4 patients were excluded as they received less than 20 cores of systematic TPM biopsy. This left 58 patients that constituted the final cohort in this group.

In the third group, patients with previous positive TRUS-guided biopsy (n= 1763), Only 210 patients had TPM biopsy. The remaining patients either had treatment for their diagnosed prostate cancer disease on TRUS-guided biopsy, went for watchful waiting or chose to have active surveillance. Of the 210 patients that had TPM biopsy, 16 were excluded due to: a) >18 months between initial TRUS-biopsy and TPM biopsy, b) Limited TPM biopsy (< 20 zone biopsy) and c) Prostate cancer treatment started. This left 194 patients that constituted the final cohort in this group.

In the last group (patients that had previous radiotherapy for prostate cancer then developed biochemical recurrence (n= 71), 22 patients did not have TPM biopsy. These are patients that either went on to have TRUS-guided biopsy or just started hormonal treatment for prostate cancer. Forty nine patients proceeded to have TPM biopsy, of whom 12 were excluded for; a) history of brachytherapy (n=5); b) limited TPM biopsy sampling i.e less than 20 cores or non-Barzell zone sampling (n=1) and c) limited (incomplete) mp-MRI due to artifact from hip replacement (n=6). This left 37 patients that constituted the final cohort in this group.

# Chapter 2

# Techniques

## Mp-MRI protocols

We used 2 machines of different field strengths, 1.5T (Siemens Avanto, Siemens) and 3T (Phillips Achieva, Phillips, UK). In both machines mp-MRI comprised of T2-weighted, DWI and DCE imaging.

20 mg IV buscopan was administered prior to acquisition. Initially, T2-weighted images were acquired, followed by DWI and finally DCE imaging. DWI consisted of multiple b-values, the highest b-value was b=1400 s/mm$^2$ at 1.5T and b=2000 s/mm$^2$ at 3T. For DCE imaging 0.1mmol/kg megluminegadoterate (*dotarem*, Guerbet, France) was administered at 3ml/s followed by 10ml of saline chaser and T1 weighted imaging repeated through the gland volume with a temporal resolution of 13 seconds at 3T and 17 seconds at 1.5T.

A multichannel (at least eight) PPA coil, but no ERC, was used. The detailed scan parameters for the 1.5-T machine are shown in Table 1; the slice thickness at 3T was identical but the in-plane resolution was slightly better, Table 2.

Mp-MRI was reported using a Likert score 1-5, which is similar to the one published by the ESUR guidelines (45) :

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 to be present

When an mp-MRI report did not show Likert score 1-5, one radiologist interpreted the report text and gave a score based only on the text without re-reading the mp-MRI images.

Analysis was done, in most of cases, at half gland level. Data collection from radiologists' reports depended on the suspected location of the disease, right or left.

Diagnostic features for malignancy included: a) low signal intensity on T2-weighted imaging, b) restricted diffusion on DWI and c) early enhancement and washout of contrast on DCE imaging.

**Table 1.** 1.5T Siemens MRI scan parameters

| | TR (ms) | TE (ms) | Flip angle (degree) | Slice orientation | Slice thickness (mm) | FOV (mm) | b-value (s/mm$^2$) | NEX | Acquisition time (min:sec) |
|---|---|---|---|---|---|---|---|---|---|
| **T2 TSE** | 5170 | 92 | 180 | axial / coronal | 3 / 3 | 180x180 / 180x180 | n/a | 2 | 3:54 / 4:18 |
| **STIR-EPIDWI(multi-b with ADC map)** | 2200 | 98 | 90 | axial | 5mm | 260x260 | 0,150, 500,1000 | 16 | 5:44 |
| **STIR-EPIDWI (high-b)** | 2200 | 98 | 90 | axial | 5mm | 320x320 | 1400 | 32 | 3:39 |
| **3D GRE** | 5.61 | 2.52 | 15 | axial | 3mm | 260x260 | n/a | 1 | 7:00 (17s/acquisition) |

TR - repetition time

TE - echo time

TSE - turbo spin time

STIR-EPI – Short Tau Inversion Recovery Echo Planar Imaging

GRE –gradient echo

FOV – field of view

NEX – number of averages

DWI – diffusion weighted imaging

ADC – apparent diffusion coefficient

**Table 2.** 3T Philips MRI scan parameters

| | TR (ms) | TE (ms) | Flip angle (degree) | Slice orientation | Slice thickness | FOV (mm) | b value (s/mm$^2$) | NEX | Acquisition time (min:sec) |
|---|---|---|---|---|---|---|---|---|---|
| **T2 TSE** | 7340 | 101 | 150 | Axial, coronal | 3mm (10% gap) | 200x200 | n/a | 2 | 5:00/ 5:20 |
| **STIR-EPI (multi-b with ADC map)** | 4300 | 80 | 90 | axial | 5mm | 25 x 21 | 0,150, 500,1000 | 6 | 5:58 |
| **STIR-EPI (high-b)** | 7500 | 79 | 90 | axial | 5mm | 25 x 21 | 2000 | 6 | 5:34 |
| **3D GRE** | 17.07 | 3.62 | 15 | axial | 3 | 256x256 | n/a | 2 | 2:72 (13s/acquisition) |

TR - repetition time

TE - echo time

TSE - turbo spin time

STIR-EPI – Short Tau Inversion Recovery Echo Planar Imaging

GRE – gradient echo

FOV – field of view

NEX – number of averages

DWI – diffusion weighted imaging

ADC – apparent diffusion coefficient

## Template prostate mapping biopsy

### Set up

All the patients in different groups underwent TPM using a sampling frame under general anaesthesia as previously described by Barzell and Melamed (Figure 2) using their modified technique (129). In lithotomy position, the patient was draped then a spigetted urethral catheter was placed to act as a guide in order to avoid injury to the urethra during the procedure. Patient scrotum was then lifted up and temporarily fixed in place using an adhesive tape, in order to expose the perineum. Transrectal ultrasound probe with an encasing gel-filled plastic sheath was introduced then the prostate was identified in both saggital and axial planes on the TRUS screen. Using an on-screen grid, an adjustment was made in order to bring the urethra in the midline and to be able to visualize the whole prostate while moving the TRUS probe in and out of the rectum. A brachytherapy grid that is attached to the top of the TRUS probe was then applied firmly to the perineum, with adjustment to make the midline of the grid opposite the patient's urethra.

### Biopsy technique

Two 18mm gauge biopsy needles were then used to systematically sample the prostate at the 20 Barzell zones Figure 3. Depending on the prostate size, two needle prostate biopsies were deployed through the same slot on the brachytherapy grid, superficial one representing the apical core and a deep one representing the mid-gland and the basal core.

Each group of cores belonging to the same zone were put together in a formalin filled pot and labeled according to the name of this sampled zone. Minimums of 20 prostate cores were taken from each patient, covering 20 Barzell zones.

### Post-biopsy care

At the end of the procedure a local anaesthetic (20mls of 0.25% bupivacaine) was injected into the perineum and the urinary bladder was emptied through the catheter. If the drained urine was altered with dark blood, the catheter was either kept in or changed to a 3-way catheter and catheter irrigation was started. A firm perineal compression dressing was left at the end of the procedure.

In predisposed patients (those with known lower urinary tract symptoms and big prostate volume) that went into retention, an indwelling urethral catheter was left inistu for 10 days

and patient was started on an α-blocker then trial without a catheter was made. All patients were given ciprofloxacin 500mg (twice daily) for 3 days after the procedure.

Figure 3 shows the 20 different Barzel zones and the histology reporting method at University College London Hospital.

The histological reporting at our institution follows the classic scheme of interpreting the Gleason grading, the one used before the ISUP meeting in 2005 (7). 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 (156).

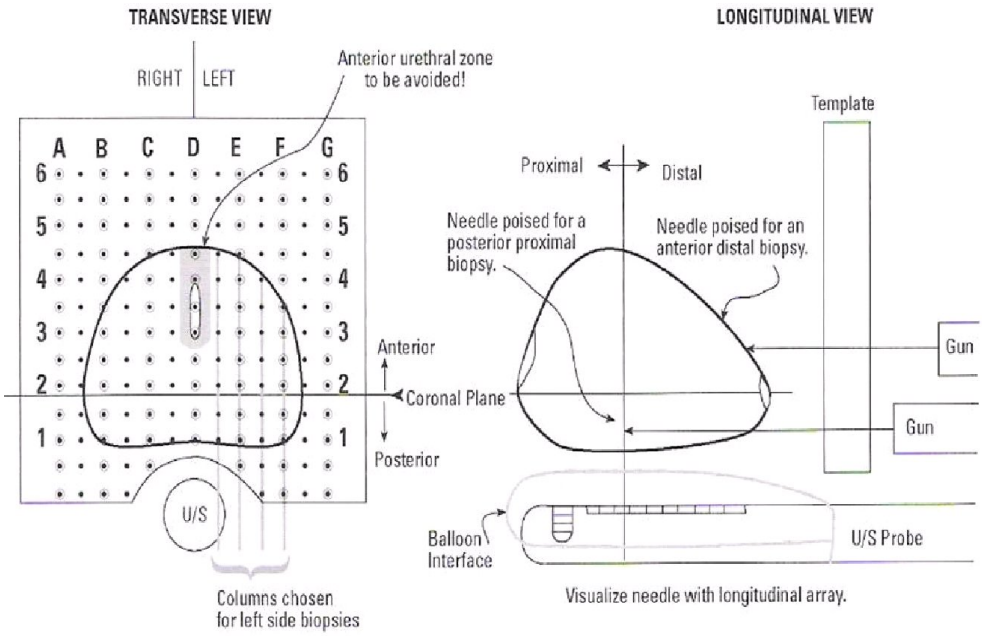



**Figure 2.** Technique of template prostate mapping biopsy.

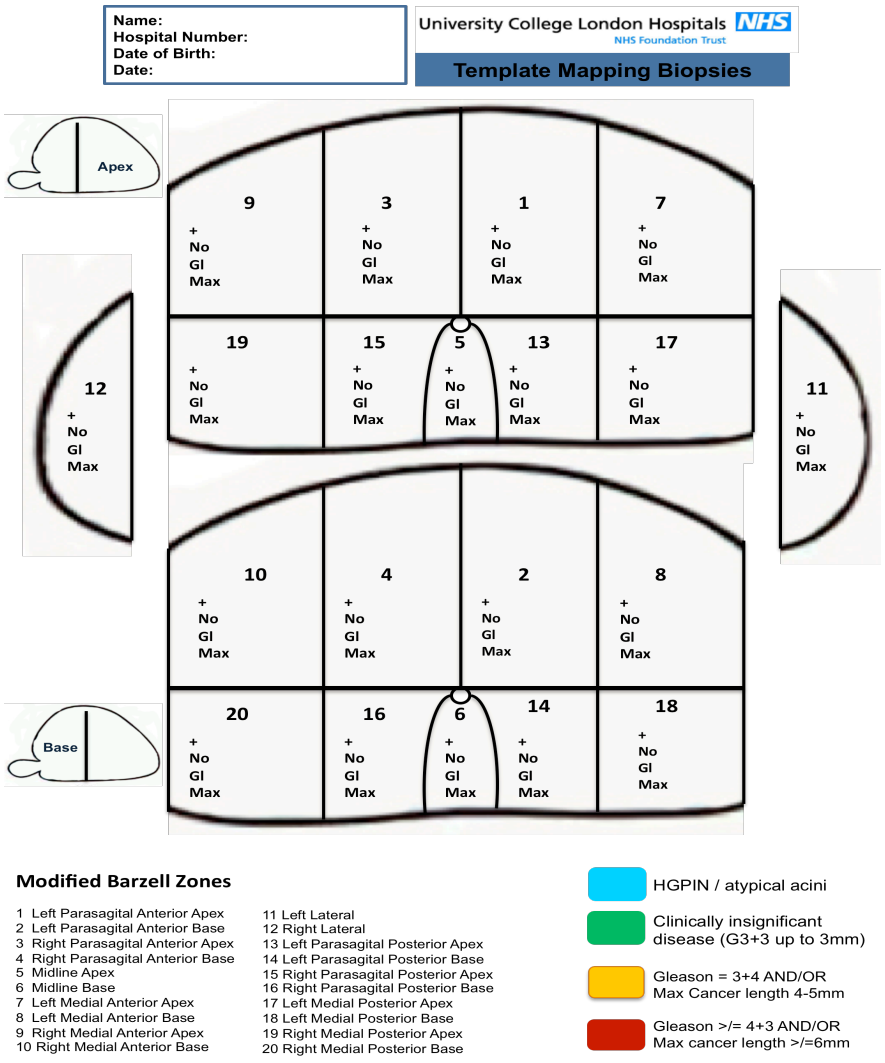



**Figure 3.** Template biopsy report as used by pathologists

# Chapter 3

## Mp-MRI performance in men with no prior prostate biopsy

## Introduction

As previously illustrated, the current prostate cancer diagnostic pathway – serum PSA followed by TRUS-guided biopsy – is associated with a number of errors. Principal amongst these are over-diagnosis and over-treatment but less well recognized are the errors of missed diagnoses and poor risk stratification (157-160). These result, in large part, from the conduct of TRUS-guided biopsy that is blind to the location of disease (161). Currently, the only widely accepted strategy to correct these flaws is to significantly increase the biopsy sampling density (162).

Another strategy, used in all other solid organ cancers, is to identify the location of an area with a high probability of being cancerous, in order to permit targeted sampling. The platform that might have the optimal performance characteristics of a diagnostic test that can both rule-out clinically significant prostate cancer and provide information on location is mp-MRI (40, 57, 69).

A number of groups have used mp-MRI in order to improve the conduct of biopsy in men at risk of prostate cancer (52, 92, 116, 163). Others have used it in men with a persistently elevated PSA but negative TRUS-guided biopsies (80, 164-167). These studies have been compromised at least to some degree by use of TRUS-guided biopsy as a reference test (which is limited in accuracy) or RP (which incorporates selection, work-up and verification biases). TPM biopsy appears to offer the optimal characteristics as a reference test for the evaluation of mp-MRI in men at risk of prostate cancer. The histological outputs of TPM have been recently validated (168). Importantly, it is a test that can be applied to all men at risk, unlike RP that can only be applied to those men testing positive on biopsy and agreeing to surgery.

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 DRE), to what extent can mp-MRI detect and rule out clinically significant prostate cancer using TPM biopsies as the reference standard, in a real practice setting?

## Materials and Methods

129 patients that fulfilled the inclusion criteria were included in this study. These were men that had mp-MRI overall gland score ≥3 (as previously described in chapter 2). Mp-MRI scoring 1-2 was still present at hemi-gland level but not as an overall gland score. This was followed by template biopsy. Exclusion criteria were: a) prior prostate biopsy, b) previous treatment for prostate cancer, c) Men with PSA >20ng/ml (as subjecting such patients to TPM would have been much invasive where systematic TRUS sampling would suffice), d) period of time > 12 months between mp-MRI and TPM and e) patients with limited number of TPM biopsy cores where non-systematic sampling was done.

**Index test (mp-MRI)**

As previously described in chapter 2, mp-MRI was comprised of T2-weighted imaging, DWI and DCE imaging. This was at either 1.5T (n=113) or 3T (n=16). Five radiologists (each one is reporting at least 100 prostate mp-MRIs per year) reported all the mp-MRI images using a score 1-5 as previously described.

A single radiologist reviewed mp-MRI images for each patient. The index test was conducted in a blinded manner to the reference test as all mp-MRI 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 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 mp-MRI 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, mp-MRI 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 mp-MRI was positive in an area proven to harbor clinically insignificant disease, according to the definition used, this area was deemed as false positive.

**Reference Standard (Template prostate mapping (TPM) biopsy)**

All patients underwent TPM biopsy as previously described in chapter 2. Urologists doing TPM biopsies were not blinded to MRI results however all 20 zones of the prostate were systematically biopsied.

**Target conditions**

We classified the output from TPM biopsy into groups of definitions of clinically significant prostate cancer (Table 3) (169, 170), in order to reflect the fact that no universally accepted definition currently exists.

**Table 3.** Definitions of clinical significance used as target conditions in the reference test, template prostate mapping

| Definition of Clinically Significant Prostate cancer | Maximum Cancer Core Length (CCLmax) | Gleason Score |
|---|---|---|
| **•UCL Definition 1** | ≥ 6mm | and / or ≥ 4+3 |
| **UCL Definition 2** | ≥ 4mm | and / or ≥ 3+4 |
| **Gleason ≥ 4+3** | any | ≥ 4+3 |
| **Gleason ≥3+4** | any | ≥ 3+4 |
| ***CCLmax ≥ 6 mm** | ≥ 6mm | any |
| **CCLmax ≥ 4 mm** | ≥ 4mm | any |

•UCL, University College London; *CCLmax, maximum cancer core length

Our target condition definitions were 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 (168). We also tested the performance of mp-MRI for the output of "Any cancer" as a secondary outcome. The cancer core length was reported as the actual amount of cancer seen in each core without counting the intervening areas of benign glands (156).

**Statistical considerations**

Analysis was done at half prostate level (right and left). This was achieved by drawing an imaginary saggital line that passes through the patient's 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), negative predictive value (NPV) and the AUROC were calculated 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.

Our predefined primary objective was to assess the ability of mp-MRI (with a score of ≥3 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 mp-MRI score threshold to ≥4 and b) varying the target histological definition for clinical significance.

## Results

Baseline demographic data are presented in Table 4.
Prostate cancer was found in 92/129 (71%) of patients and in 141/258 (55%) of prostate halves.

MRI score 1-2 was reported in 47/258 (18%) of prostate halves. Out of those 47 prostate halves, 33 (70%) had no cancer, 9 (19%) had clinically insignificant cancer (Gl≤ 3+3 and CCLmax <4mm) and 5 (11%) had clinically significant disease where Gleason score was 6-7 (no dominant pattern 4) and/or CCLmax was ≥4mm.

MRI score 3 was reported in 102/258 (40%) of prostate halves. Out of those 102 prostate halves, 54 (54%) had no cancer, 27 (26%) had clinically insignificant cancer and 20 (20%) had clinically significant cancer.

MRI score 4-5 was reported in 109/258 (42%) of prostate halves. Out of those 109 prostate halves, 30 (27.5%) had no cancer, 26 (24%) had clinically insignificant cancer and 53 (48.5%) had clinically significant cancer.

Figure 4 and Figure 5 show mp-MRI scores for each of the target conditions as well as any cancer at positive and negative TPM biopsy results.

Primary outcome

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

Secondary outcomes

At mp-MRI threshold of 3, sensitivity and NPV were similar when using either Gl ≥4+3 (100% and 100%) or CCLmax ≥6mm (98% and 98%) as a target condition, respectively. Results were also comparable when using either Gl ≥3+4 or CCLmax ≥4mm as the target condition. The performance of the test for different levels of clinical significance on TPM at mp-MRI threshold of ≥3 is shown in Table 5.

When using an mp-MRI score of ≥4 to rule-out UCL definition 2 cancer, we had lower sensitivity (68% [95% CI, 56-78%]) with reduction in NPV (83% [95% CI, 77-89%]). In ruling-in UCL definition 2 cancer at an mp-MRI 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 6.

Table 8 shows the performance of mp-MRI at patient level.

Table 7 and Figure 5 show AUROC curve values and shapes for different definitions of clinically significant disease at mp-MRI scores 1-5.

**Table 4.** Baseline demographics of 129 men undergoing mp-MRI followed by TPM biopsy.

| **Age, years (median, IQ* range)** | **64 (60-68)** |
|---|---|
| **PSA (median, IQ range)** | 5.8 (4.3-8.7) |
| **Prostate volume (median, IQ range)** | 40 (31.2-49) |
| **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, IQ range)** | 41 (31-53) |
| **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%) |

*IQ, interquartile

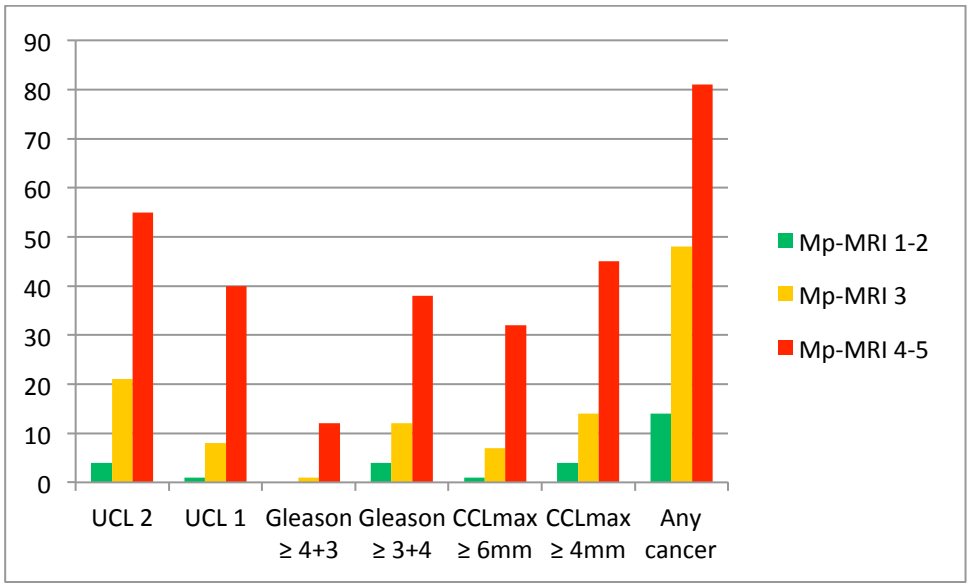



**Figure 4.** Mp-MRI scores in patients with positive TPM biopsy for different target conditions and any cancer

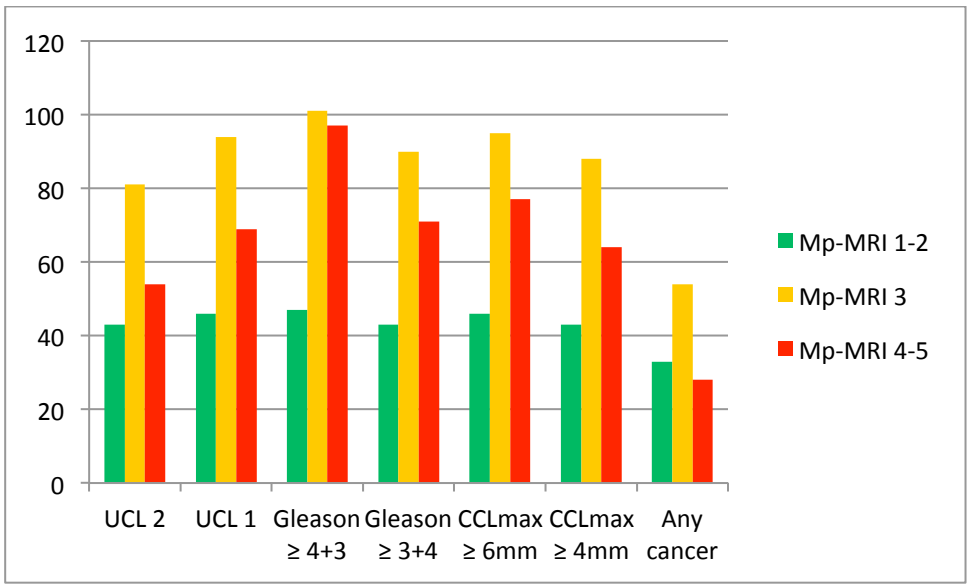



**Figure 5.** Mp-MRI scores in patients with negative TPM biopsy for different target conditions and any cancer

**Table 5.** 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) |

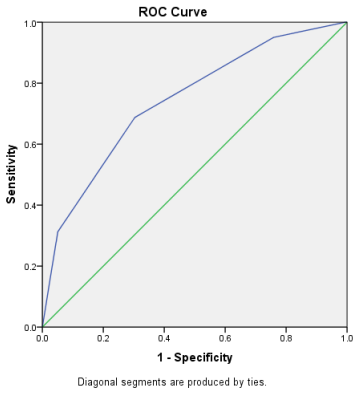
**Table 6.** The performance characteristics of mp-MRI with a radiological score of ≥ 4 to detect and rule-out clinically significant cancer on TPM defined by a number of thresholds at half prostate level (secondary outcomes) (95% confidence intervals in parentheses)

| 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) |

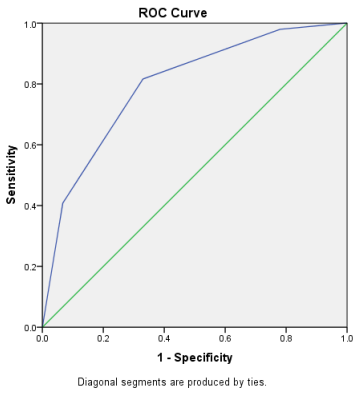
**Table 7.** Area under the receiver operating characteristic curves for different definitions of clinically significant cancer at mp-MRI score 1-5.

| Target condition | AUROC |
|---|---|
| **•UCL2** | **0.74 (0.68, 0.81)** |
| UCL1 | 0.80 (0.73, 0.87) |
| Gleason 4+3 | 0.79 (0.70, 0.89) |
| Gleason 3+4 | 0.71 (0.63, 0.79) |
| *CCLmax ≥ 6 | 0.77 (0.69, 0.85) |
| CCLmax ≥ 4 | 0.73 (0.66, 0.80) |
| Any cancer | 0.71 (0.65, 0.77) |

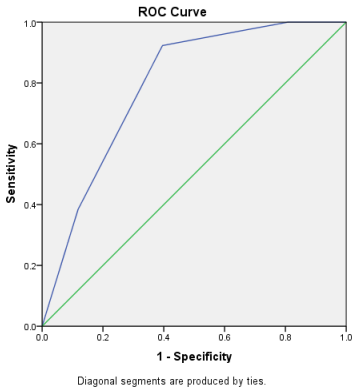
•UCL, University College London; *CCLmax, maximum cancer core length



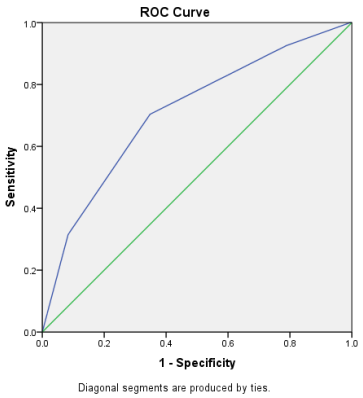

ROC curve for (UCL 2)



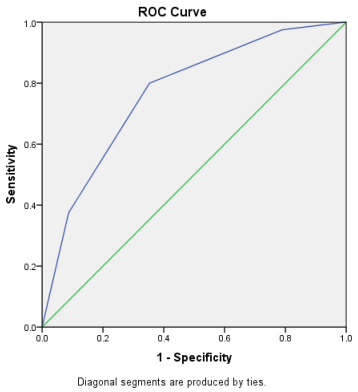

ROC curve for (UCL 1)



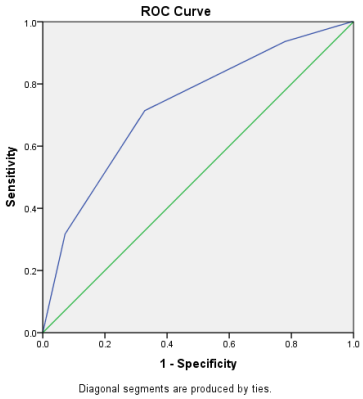

ROC curve for (Gl ≥ 4+3)



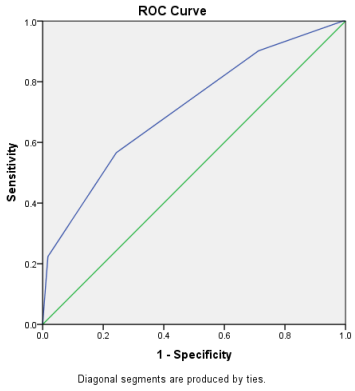

ROC curve for (Gl ≥ 3+4)




ROC curve for (CCLmax ≥ 6mm)




ROC curve for (CCLmax ≥ 4mm)




ROC curve for (Any cancer)

**Figure 6.** ROC curves

**Table 8. 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 <u>patient level</u> (secondary outcomes) (95% confidence intervals in parentheses).**

| Classification | ROI | TP | FN | TN | FP | SEN | SPEC | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| **UCL2** | **129** | **48** | **15** | **34** | **32** | **76 (64-86)** | **52 (39-64)** | **60 (48-71)** | **69 (55-82)** |
| UCL1 | 129 | 35 | 5 | 44 | 45 | 88 (73-96) | 49 (39-60) | 44 (33-55) | 90 (78-97) |
| Gleason 4+3 | 129 | 9 | 1 | 48 | 71 | 90 (55-98) | 40 (31-50) | 11 (5-20) | 98 (89-100) |
| Gleason 3+4 | 129 | 39 | 11 | 38 | 41 | 78 (64-88) | 48 (37-60) | 49 (37-60) | 78 (63-88) |
| CCLmax ≥6 | 129 | 32 | 4 | 45 | 48 | 89 (74-97) | 48 (38-59) | 40 (29-52) | 92 (80-98) |
| CCLmax ≥4 | 129 | 41 | 11 | 38 | 39 | 79 (65-89) | 49 (38-61) | 51 (40-63) | 78 (63-88) |
| Any cancer | 129 | 64 | 28 | 21 | 16 | 70 (59-79) | 57 (39-73) | 80 (70-88) | 43 (29-58) |

## Discussion

### Summary of results

The accuracy of mp-MRI at detecting clinically significant prostate cancer varied with the change of the threshold used to define a positive or negative lesion. 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 only 4 and 5 were used, specificity (61–69%) and PPV (11–48%) improved substantially, while 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 mp-MRI 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 mp-MRI 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 (125). As a result, this method will inevitably lead to an overestimate of false positives: small lesions correctly scored as likely tumours on mp-MRI 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% using T2 and spectroscopy sequences (171). Other studies using whole-mount prostatectomy as reference standard support the proposition that mp-MRI has encouragingly high performance characteristics for detecting and ruling-out clinically significant prostate cancer (172).

Controversy continues on the use of ERC, 3T machines and the relative value of the different components of a 'multi-parametric' scan. However, there is increasing evidence that both DWI and DCE imaging improve the performance of the test (92, 173-175). In our institution at University College London Hospital, we achieved similar results to groups using ERC. As previously discussed, the ESUR guidelines did not recommend routine using of ERC in the detection protocol of mp-MRI (45).

**Clinical implications**

Most studies have used a dichotomous result to declare whether mp-MRI 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 mp-MRI 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 the current 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, 98% chance that the CCLmax would be <6mm and 94% chance that CCLmax would be <4mm. 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.

In contrast, if mp-MRI is attributed a score of 4 or 5 (Figure 7) then the probability of clinically significant disease (using UCL definition 2) being present will be around 50%, (though for any tumour 73%). Accounting for this apparently low figure are many tumours correctly identified on mp-MRI 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 (124, 176, 177).

The indeterminate mp-MRI remains a problem (Figure 8), although it is an under-reported phenomenon (178). We usually see a score of 3 as a positive signal to biopsy, with the mp-MRI 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, co-morbidity and competing mortality risk assessment as well as anxiety.

Overall, if mp-MRI 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 (57). In addition, in the case of a positive diagnosis of tumour, the pre-biopsy mp-MRI is immediately available for staging, and is free of post-biopsy artifact, which can reduce its accuracy.

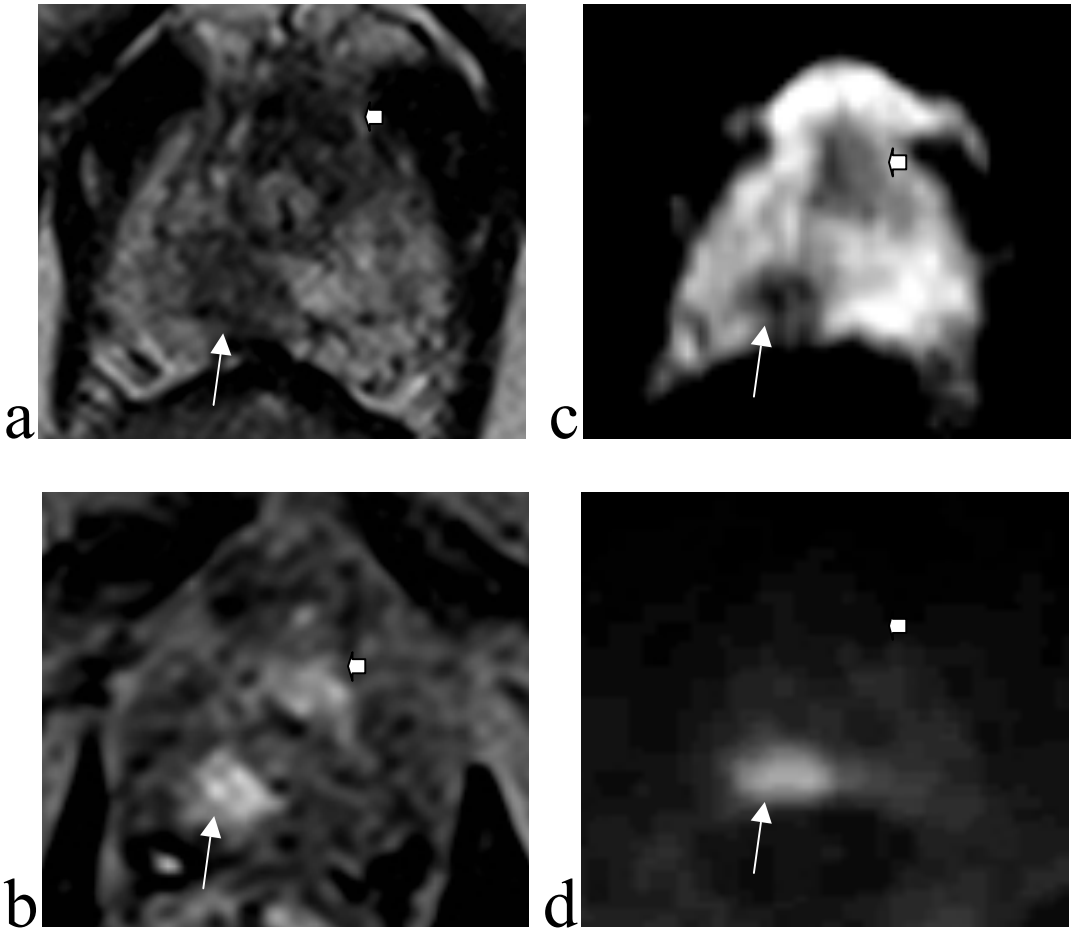



**Figure 7.** Axial images from a positive MRI (scoring 5/5) with a maximum of 5 mm, 50%, of Gleason 3+4 found at template biopsy in the right posterior apical parasagittal zone. The T2 image (a) shows a low signal focus on the right (arrow), the contrast-enhanced image (b) shows corresponding focal 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).

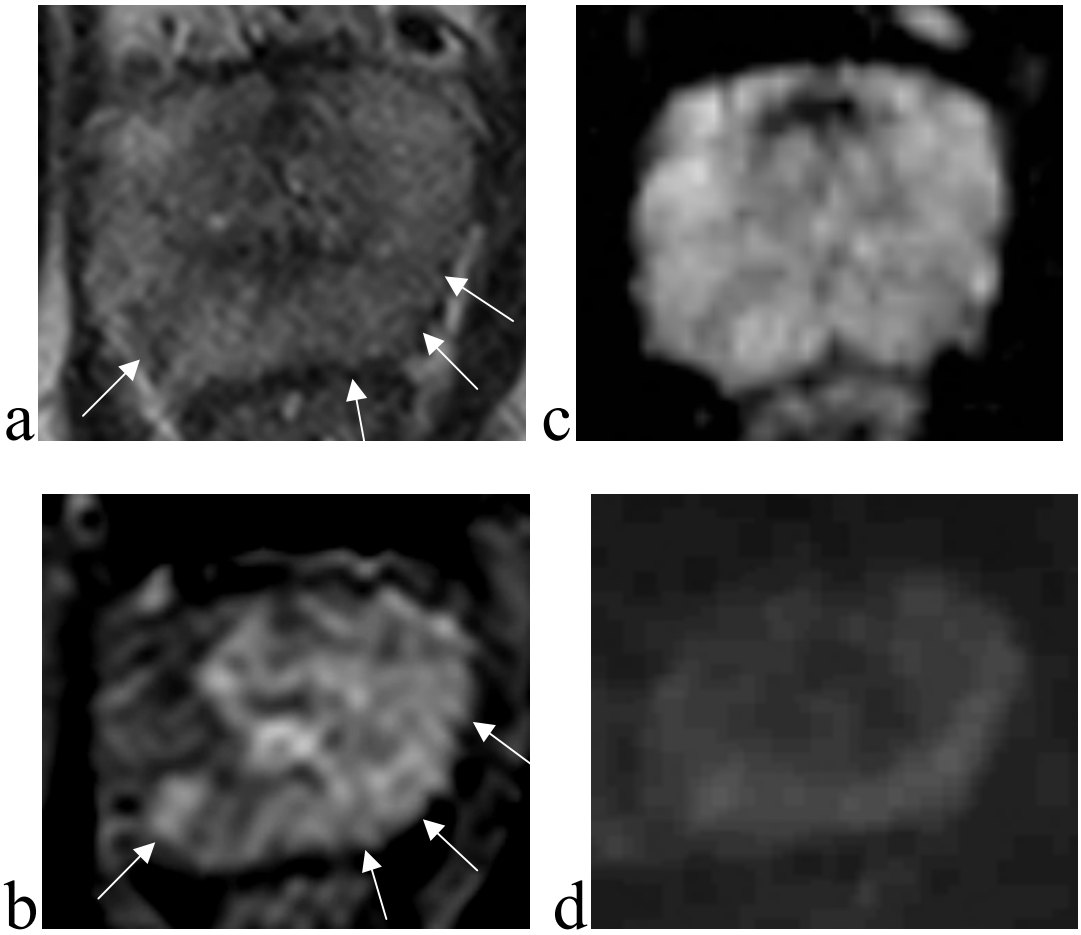



**Figure 8.**Axial images from an indetermnate MRI (scoring 3/5) with no tumour found at biopsy. The T2 image (a) shows diffuse, but slightly heterogenous, moderate reduction in signal in the peripheral zone on each side (arrows). The contrast-enhanced image (b) shows moderate enhancement in a similar distribution (arrows). No significantly restricted diffusion is seen on the ADC map (c) and long b diffusion image (d).

## Summary

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 mp-MRI – was approximately 50%, something which may allow these patients to benefit from targeted biopsy.

Since the sensitivity of mp-MRI in ruling out clinically significant prostate cancer was 93-100% and NPV was 89-100%, we can then reject the null-hypothesis and prove that mp-MRI had good accuracy in detection and localization of prostate cancer in this patient population.

# Chapter 4

## Mp-MRI performance in men with previous negative TRUS-guided prostate biopsy

## Introduction

In men at risk of prostate cancer, it has been found that the first biopsy is negative in 66-71% of cases (179-181). In other words, cancer detection rate ranges from 29-34% on first biopsy. In men with negative initial biopsy, additional rounds of biopsies showed cancer detection rates of 23%, 17.6%, 11.7%, 8.7% and 0% at rounds 1-5, respectively (182, 183). Under-sampled areas, such as the apex and anterior transition zone, are usually missed even in repeat biopsy. The main problem in such patients is missing a window for curative treatment (184) while repeating the same diagnostic pathway using TRUS-guided biopsy.

Several studies have recently documented an incidence of tumours in men with a negative biopsy but persistently elevated PSA. A study using systematic TPM biopsy showed tumour in 57%, with the majority of positive cores lying anteriorly (185). Others have found tumour in 40% (183) and 59% (167) of men when MRI findings are used to target biopsy.

A proposed solution for this could be: using a diagnostic tool that could help identify and rule out prostate cancer in men at risk. It would be of most benefit as well if this tool can help target the suspicious areas within the prostate. Mp-MRI is currently the most recognized imaging tool for significant prostate cancer detection showing reasonable accuracy figures for different prostatic zones (186).

Recent data have suggested that most significant (defined as >0.5cc) tumours are detected on MRI, including those in the anterior part of the gland (116, 187), with DWI especially effective in the latter (183).

Our aim in this chapter was to assess the performance of mp-MRI in men with a continuing suspicion of prostate cancer but negative TRUS-biopsy, by prospective comparison of mp-MRI findings with systematic TPM biopsy. Such mapping biopsy technique has a high sensitivity for detection of significant disease and is the best method we have for confirming absence of disease within the prostate: men without tumour will rarely be subjected to prostatectomy (188).

## Material and Methods

A total of 58 men with at least one negative TRUS-guided prostate biopsy underwent mp-MRI (index test) followed by template prostate mapping (TPM) biopsy (reference standard). Four men were excluded from the study as they received limited template biopsy (less than 20 cores were taken). This gives a total number of 54 patients included in the study.

Patients had between 1-3 prior negative TRUS-guided biopsies (33 had previous one negative set of biopsies, 16 had previous two negative sets of biopsies and 5 had previous three negative sets of biopsies). Most of the patients included in the study were referred from other health care centres to University College London Hospital. Although no record was available for the number of cores taken during each biopsy at the peripheral centres, it is considered standard practice at the referring units to take at least 10-12 core biopsies.

All patients included in the study had either increasing or persistently high PSA.

**Index test (mp-MRI)**

Mp-MRI comprised of T2-weighted imaging, DWI and DCE imaging, as previously described in chapter 2.

Six radiologists, of 3-8 years of experience, reported all the mp-MR images using a score from 1 to 5, as previously described. In 5 cases, the initial report did not contain a numerical score and a single radiologist, based on the report text only, generated one. Mp-MRI was conducted in a blinded manner to the template biopsy as all imaging reports were committed to the electronic medical record prior to the biopsy result becoming available.

**Reference standard (systematic TPM biopsy)**

All patients underwent systematic TPM biopsy using a brachtherapy grid under general anesthesia in the method previously described by Barzel and Melamed (189). Basal and apical cores were obtained routinely, and the minimum number of samples was 20.

For assessment of the performance of MRI we analyzed the prostate in halves (right and left), so that there were 108 sectors (54 patients). To determine the proportion of tumours lying anteriorly on histology we considered anterior cores to lie in front of an imaginary transverse line drawn through the urethra at mid gland level. Biopsy cores taken from the lateral zones of the prostate (according to Barzell's definitions) were considered posterior. Whenever a suspected lesion crossed the midline on MRI, both prostate halves were attributed the same scoring for that lesion.

**Target conditions**

The pathological outputs from the reference test were grouped into a number of definitions of clinical significance as previously described in chapter 3 (Table 3).

**Statistical analysis**

An mp-MRI score of ≥3 was used to designate a positive index test for the purpose of ruling out clinically significant disease. The effect of varying this threshold to ≥4 was also evaluated for predicting clinically significant disease. If the mp-MRI was positive in a sector proven to harbor clinically insignificant disease, according to the definition used, this area was deemed as a false positive, same as the previous chapter. Accuracy figures (sensitivity, specificity, positive and negative predictive values) together with 95% confidence intervals (95% CI) were calculated for the performance of mp-MRI at each definition of significant disease.

Our predefined primary objective was to assess the ability of mp-MRI (with a score of ≥3 considered positive) to detect UCL definition 2 of clinically significant disease, defined as any cancer with Gleason pattern 4 or greater (≥3+4) and/or maximum cancer core length ≥4mm.

Our predefined secondary objectives were to examine the performance of the index test by: a) changing the mp-MRI score threshold to ≥4 and b) varying the target histological definition for clinical significance. We also aimed to determine the distribution of tumours found at template biopsy – in particular, the proportion that lay anterior to the urethra.

## Results

Baseline demographic data are shown in Table 9.

Cancer of any grade or burden was identified in 34/54 (63%) patients, 51/108 (47%) prostate halves.

MRI score 1-2 was reported in 39/108 (36%) of prostate halves. Out of those 39 prostate halves, 26 (67%) had no cancer, 5 (13%) had clinically insignificant cancer (Gl ≤3+3 and CCLmax <4mm) and 8 (20%) had clinically significant disease. Amongst the clinically significant cancers that were missed on mp-MRI, there was no dominant Gleason pattern 4.

MRI score 3 was reported in 35/108 (32%) of prostate halves. Out of those 35 prostate halves, 23 (66%) had no cancer, 9 (26%) had clinically insignificant cancer and 3 (8%) had clinically significant cancer.

MRI score 4-5 was reported in 34/108 (31%) of prostate halves. Out of those 34 prostate halves, 8 (23%) had no cancer, 3 (9%) had clinically insignificant cancer and 23 (68%) had clinically significant cancer.

Figure 9 and Figure 10 show mp-MRI scores for each of the target conditions as well as any cancer at positive and negative TPM biopsy results.

Primary outcome:

In ruling out the presence of any Gleason ≥4 and/or maximum cancer core length ≥4 mm (UCL definition 2), mp-MRI had a sensitivity and NPV of 76% (95% CI, 59-91%) and 79% (95% CI, 66-92%), respectively (Table 10).

Secondary outcomes:

The performance of the test for different levels of clinical significance and at different MRI thresholds is shown in Table 10 and Table 11. At mp-MRI threshold of ≥3, sensitivity and NPV for detection of cancers of Gleason ≥4+3 were 100% (95% CI, 100-100%), while those for Gleason ≥3+4 were 87% (95%CI, 70-100%) and 92% (95%CI, 82-100%), respectively.

Of the 34 patients with a positive biopsy, 16 patients (47%) had an anterior tumour only, 3 (9%) had a posterior tumour only and 15 (44%) had tumour in both anterior and posterior cores.

Table 12 and Figure 11 show different ROC curves' values and shapes for different definitions of clinically significant disease and any cancer.

Table **13** and Table **14** show the performance characteristics of mp-MRI at patient level using thresholds 3 and 4, respectively.

**Table 9.** Baseline demographics of 54 men, with prior negative TRUS-guided biopsy, undergoing mp-MRI followed by template prostate mapping.

| | |
|---|---|
| **Age, years (median, *IQ range)** | **64 (59-66)** |
| **PSA (median, IQ range)** | 10 (6.2-13) |
| **Prostate volume (median, IQ range)** | 53 (38.3-67.5) |
| **Number with no cancer on TPM, N (%)** | 20/54 (37%) |
| **Number with cancer on TPM, N (%)** | 34/54 (63%) |
| **Number of biopsies at TPM (median, IQ range)** | 45 (31-63) |
| **Gleason Score on TPM, N (%)** | |
| **6** | 16/34 (47%) |
| **7 (3+4)** | 13/34 (38%) |
| **7 (4+3)** | 5/34 (15%) |
| **≥ 8** | 0/34 (0%) |

*IQ, Interquartile

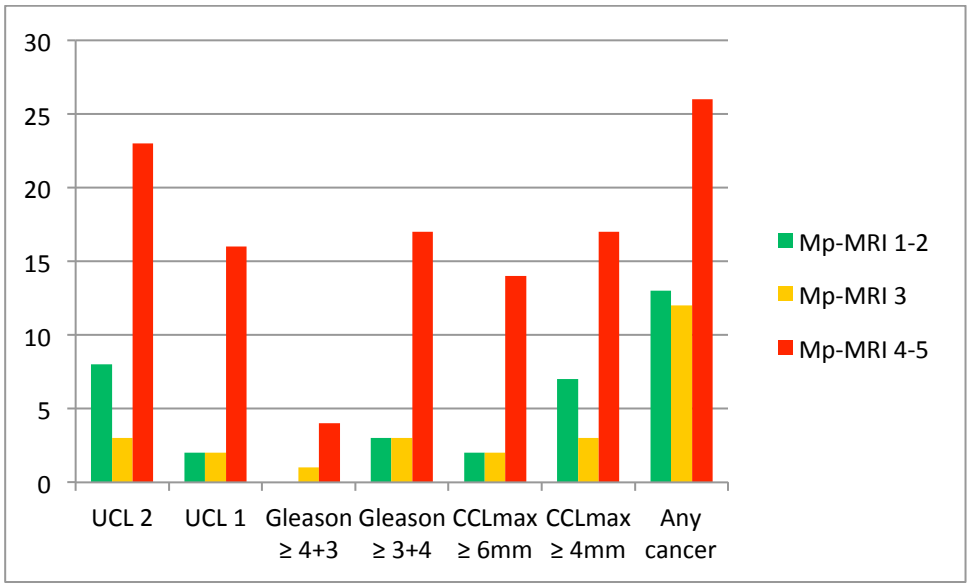



**Figure 9.** Mp-MRI scores in patients with positive TPM biopsy for different target conditions and any cancer

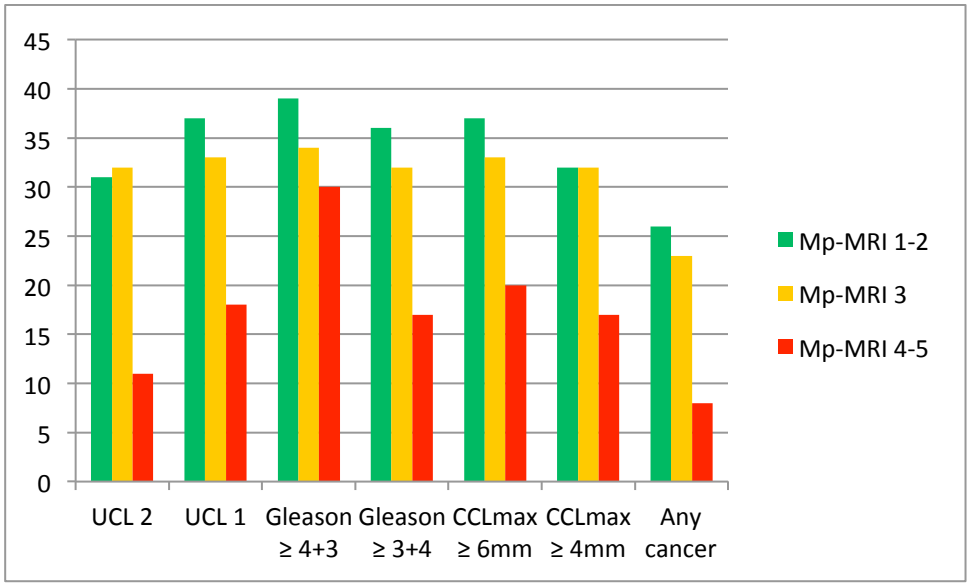



**Figure 10.** Mp-MRI scores in patients with negative TPM biopsy for different target conditions and any cancer

**Table 10.** The performance characteristics of mp-MRI with a radiological score of ≥3 to detect and rule-out clinically significant cancer on TPM at multiple levels of significance (95% confidence intervals in parentheses).

| Classification | ROI | TP | FN | TN | FP | SEN | SPEC | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| **UCL2** | **108** | **26** | **8** | **31** | **43** | **76 (59-91)** | **42 (30-52)** | **38 (25-49)** | **79 (66-92)** |
| UCL1 | 108 | 18 | 2 | 37 | 51 | 90 (74-100) | 42 (30-50) | 26 (16-36) | 95 (86-100) |
| Gleason ≥4+3 | 108 | 5 | 0 | 39 | 64 | 100 (100-100) | 38 (28-47) | 7 (2-14) | 100 (100-100) |
| Gleason ≥3+4 | 108 | 20 | 3 | 36 | 49 | 87 (70-100) | 42 (31-52) | 29 (19-40) | 92 (82-100) |
| CCLmax ≥6 | 108 | 16 | 2 | 37 | 53 | 89 (71-100) | 41 (30-51) | 23 (14-33) | 95 (86-100) |
| CCLmax ≥4 | 108 | 20 | 7 | 32 | 49 | 74 (54-90) | 39 (28-49) | 29 (19-39) | 82 (69-93) |
| Any cancer | 108 | 38 | 13 | 26 | 31 | 74 (61-86) | 45 (31-59) | 55 (43-67) | 66 (51-82) |

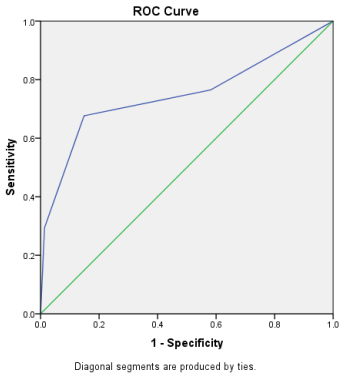
**Table 11.** The performance characteristics of mp-MRI with a radiological score of ≥ 4 to detect and rule-out clinically significant cancer on TPM at multiple levels of significance (95% confidence intervals in parentheses).

| Classification | ROI | TP | FN | TN | FP | SENS | SPEC | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| **UCL2** | **108** | **23** | **11** | **63** | **11** | **67** | **85** | **67** | **85** |
| | | | | | | **(50-83)** | **(76-93)** | **(48-84)** | **(77-93)** |
| UCL1 | 108 | 16 | 4 | 70 | 18 | 80 | 80 | 47 | 94 |
| | | | | | | (60-91) | (71-88) | (31-64) | (89-99) |
| Gleason 4+3 | 108 | 4 | 1 | 73 | 30 | 79 | 71 | 12 | 99 |
| | | | | | | (29-100) | (62-79) | (2-23) | (95-100) |
| Gleason 3+4 | 108 | 17 | 6 | 68 | 17 | 74 | 80 | 50 | 92 |
| | | | | | | (55-90) | (71-89) | (32-69) | (85-97) |
| CCLmax ≥6 | 108 | 14 | 4 | 70 | 20 | 77 | 78 | 41 | 94 |
| | | | | | | (57-95) | (69-86) | (26-59) | (89-99) |
| CCLmax ≥4 | 108 | 17 | 10 | 64 | 17 | 62 | 79 | 49 | 86 |
| | | | | | | (41-80) | (70-88) | (32-68) | (78-93) |
| Any cancer | 108 | 26 | 25 | 49 | 8 | 51 | 86 | 76 | 66 |
| | | | | | | (38-65) | (76-95) | (61-91) | (55-77) |

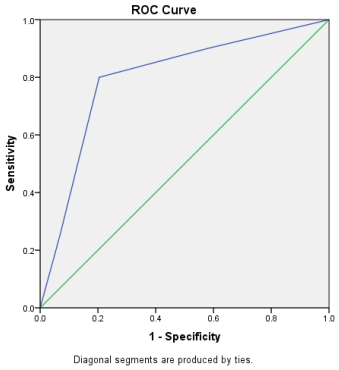
**Table 12.** Area under the receiver operating characteristic curves for different definitions of clinically significant cancer at mp-MRI score 1-5.

| Target condition | AUROC |
|---|---|
| •**UCL2** | **0.75 (0.63-0.86)** |
| UCL1 | 0.80 (0.69-0.91) |
| Gleason 4+3 | 0.75 (0.62-0.88) |
| Gleason 3+4 | 0.79 (0.68-0.91) |
| *CCLmax ≥ 6 | 0.79 (0.66-0.91) |
| CCLmax ≥ 4 | 0.68 (0.56-0.81) |
| Any cancer | 0.70 (0.60-0.80) |

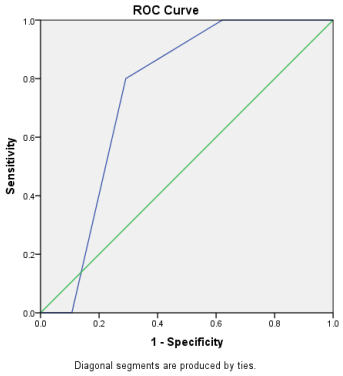
•UCL, University College London; *CCLmax, maximum cancer core length



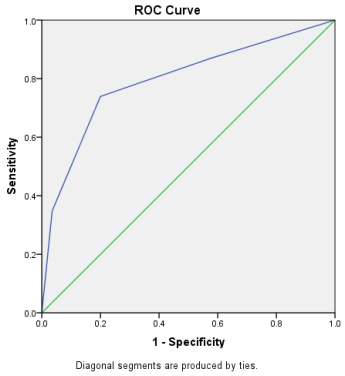

(ROC curve UCL def.2)



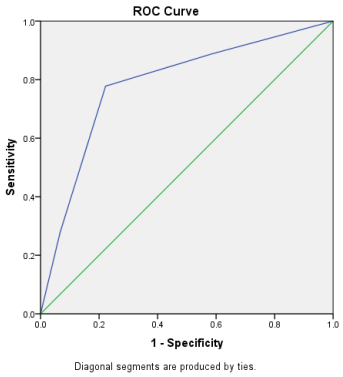

(ROC curve UCL def.1)



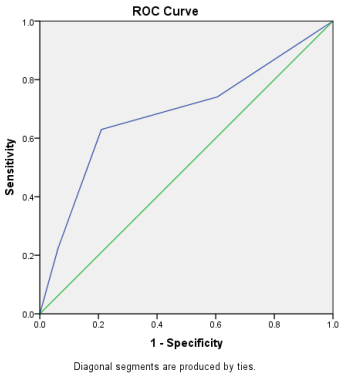

(ROC curve Gl ≥4+3)




(ROC curve Gl ≥3+4)




(ROC curve CCLmax ≥6mm)




(ROC curve CCLmax ≥4mm)

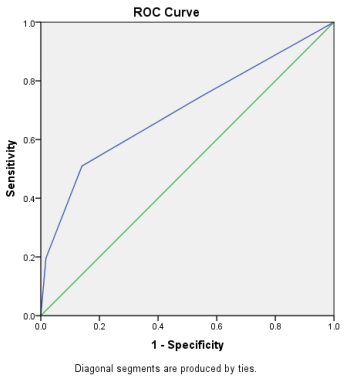



**Figure 11.** ROC curves

(ROC curve Any cancer)

Table 13. The performance characteristics of mp-MRI with a radiological score of ≥ 3 at patient level to detect and rule-out clinically significant cancer on TPM at multiple levels of significance (95% confidence intervals in parentheses).

| Classification | ROI | TP | FN | TN | FP | SENS | SPEC | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| UCL2 | 54 | 20 | 3 | 6 | 25 | 87 (66-97) | 19 (8-37) | 44 (30-60) | 67 (30-92) |
| UCL1 | 54 | 16 | 1 | 8 | 29 | 94 (71-99) | 22 (10-38) | 36 (22-51) | 89 (52-98) |
| Gleason 4+3 | 54 | 4 | 0 | 9 | 41 | 100 (40-100) | 18 (9-31) | 9 (3-21) | 100 (66-100) |
| Gleason 3+4 | 54 | 16 | 2 | 7 | 29 | 89 (65-98) | 19 (8-36) | 36 (22-51) | 78 (40-97) |
| CCLmax ≥6 | 54 | 14 | 1 | 8 | 31 | 93 (68-99) | 21 (9-36) | 31 (18-47) | 89 (52-98) |
| CCLmax ≥4 | 54 | 17 | 3 | 6 | 28 | 85 (62-97) | 18 (7-35) | 38 (24-53) | 67 (30-92) |
| Any cancer | 54 | 27 | 7 | 2 | 18 | 79 (62-91) | 10 (2-32) | 60 (44-74) | 22 (3-60) |

Table 14. The performance characteristics of mp-MRI with a radiological score of ≥ 4 at patient level to detect and rule-out clinically significant cancer on TPM at multiple levels of significance (95% confidence intervals in parentheses).

| Classification | ROI | TP | FN | TN | FP | SENS | SPEC | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| UCL2 | 54 | 18 | 5 | 21 | 10 | 78 (56-92) | 68 (49-83) | 64 (44-81) | 81 (61-93) |
| UCL1 | 54 | 14 | 3 | 23 | 14 | 82 (57-96) | 62 (45-78) | 50 (31-69) | 88 (70-97) |
| Gleason 4+3 | 54 | 3 | 25 | 24 | 25 | 75 (20-96) | 50 (36-64) | 11 (2-28) | 96 (80-99) |
| Gleason 3+4 | 54 | 14 | 4 | 22 | 4 | 78 (52-93) | 61 (43-77) | 50 (31-69) | 85 (65-96) |
| CCLmax ≥6 | 54 | 12 | 3 | 23 | 16 | 80 (52-95) | 59 (42-74) | 43 (24-63) | 88 (70-97) |
| CCLmax ≥4 | 54 | 15 | 5 | 21 | 13 | 75 (51-91) | 62 (44-78) | 54 (34-72) | 81 (61-93) |
| Any cancer | 54 | 20 | 14 | 12 | 8 | 59 (41-75) | 60 (36-81) | 71 (51-87) | 46 (27-67) |

## Discussion

### Summary of results

The use of systematic TPM biopsy for verification enabled us to estimate the sensitivity and negative predictive value of mp-MRI in a group of men with previous negative biopsy - something that has been difficult in most previous studies that have used targeted biopsy.

Our main finding was of a sensitivity of 76% for clinically significant disease (UCL Def 2), based on an analysis at half gland level, with sensitivity of 87% for any Gleason 4 element and 100% for tumors with dominant Gleason 4. Specificity was fairly low (38-42%) at mp-MRI threshold of 3. As we explained in the previous chapter, our low specificity was low as we applied our definitions of clinically significant disease rigidly on histology. It improved when a threshold of 4/5 was used to define positive disease (71-85%). However, using a score of 4/5 ('likely' rather than 'equivocal') as the threshold to define clinically significant disease means that even some tumours with dominant Gleason 4 elements would be missed (sensitivity goes down to 79%).

It is becoming clear that small amounts of low grade tumour are both unlikely to harm the patient (115) and unlikely to be detected on MRI (116). Because the definitions of clinically significant disease vary so much, we analysed the performance of MRI at a number of levels. The appropriate definition of course varies with the patient: in a relatively old man with co-morbidities, exclusion of dominant Gleason 4 disease may be all that is necessary, whereas in a younger man the exclusion of UCL definition 2 (CCLmax <4mm and no Gleason 4) may be more appropriate.

As previously described in chapter 3, we used the half gland for analysis because of a compromise. Overall, in a study with a large number of patients, the most clinically relevant level of analysis is the whole gland: equivalent to the question 'have we missed a significant tumour in this patient'. However we had a smaller number of patients scored negative on MRI (n=9/54, 17%) than one would expect in the group of patients with persistently elevated PSA and a previous negative biopsy. The number of halves scored negative was much higher - 39/108 or 36% (apparent disease on MRI is often unilateral).

**Comparison with other studies**

Two important parameters have been measured in previous studies: the overall detection rate of cancer in men with a previous negative biopsy, and the proportion of tumours lying anteriorly. A targeted biopsy technique, as used in almost all previous papers, precludes the estimation of sensitivity and specificity.

For the question of the prevalence of tumour in this group, our finding of any cancer in 63% and significant in 43% is similar to several previous studies: 40% for any tumour in one group of 43 patients (183), 42% for any tumour in men undergoing template biopsy without MRI (n=102) (190), 48% in a recently published study (100) and 59% for significant tumour in another group of patients with suspicious foci on MRI (167, 183).

Several groups have provided estimates of the proportion of tumours lying anteriorly: one group using targeted biopsies found that missed tumours were in the 'most ventral part of the transition zone' or anterior horns in a total of 68% of patients (167), and another group found (again using targeted cores) that 76% of missed tumours lay in the transition zone (183). Finally, a group using template biopsies but not MRI found that 59% of tumours lay in the transition zone or anterior parts of the peripheral zone (190). Again, these results are in agreement with those obtained using our systematic biopsy technique, where the great majority of diseased patients (31/34, 91%) had some anterior tumour, and 16 out of 34 (47%) had only anterior tumour.

Our finding of a relatively low specificity of MRI if 3/5 is considered positive is consistent with the study by Franiel et al. (181). Fifty-four patients with at least one prior negative prostate biopsy underwent mp-MRI including T2-weighted, DWI, DCE imaging and MR spectroscopy. MRI-guided biopsies were obtained and cancer was found in 21/54 (39%) patients. Out of 178 lesions detected on MRI, 53 were positive on biopsy: a positive predictive value of 30%. We also considered lesions identified on mp-MRI as false positives whenever they do not fulfill the criteria for the target condition.

Arumainayagam et al recently evaluated the performance of mp-MRI in the detection of clinically significant prostate cancer (191). Their cohort comprised of three different patient categories; those with known low risk or low-intermediate risk prostate cancer (n=51), those with previous negative biopsies (n=10) and those with no prior prostate biopsy (n=3). Two thresholds, definitions 1 and 2, were used to describe clinically significant disease. These are

comparable to our UCL definitions 1 and 2, respectively. In ruling out prostate cancer, they had a similar negative predictive value that reached up to 95%.

**Clinical implications**

Although previous studies have shown that mp-MRI can be used to detect prostate cancer in many men with previously negative biopsies, they have been less effective at answering the question 'how reliable is a negative MRI' because of the targeted biopsy technique that is generally employed. Our estimates of sensitivity suggest that MRI can be very useful for excluding tumour in this group, and preventing the need for re-biopsy. This is especially true when the definition of significant disease does not include small tumours or those with a small Gleason 4 component. We had 39/108 (36%) negative prostate halves on mp-MRI (scoring 1-2). The implication of that is similar to the results in previous chapter; none of the tumours with dominant Gleason 4 component were missed, 87% chance of being free from any Gleason pattern 4, 89% chance that CCLmax will be <6mm and 74% chance that CCLmax would be <4mm.

In our results, 35/108 (36%) prostate halves were scored 3/5 on mp-MRI. Out of those 35 prostate halves, 23 (66%) had no cancer, 9 (26%) had clinically insignificant cancer and only 3 (8%) had clinically significant cancer (UCL Def.1, n=2 and UCL Def. 2, n=1). As we discussed in the previous chapter, if both prostate halves showed the same score of 3/5 on mp-MRI, a decision to defer a biopsy may be reasonable. However this, again, depends on other clinical factors such as DRE, patient PSA level (including PSA kinetics), family history of prostate cancer and patient co-morbidities

The low positive predictive value of the test in our study (and in others) implies that MRI cannot be used to reliably infer the presence of disease, but this is not a fundamental drawback if a positive MRI is seen as an indication to biopsy – and though not the subject of this work, as a map for biopsy as well. It is then acting as a triage test: ruling out disease in some, and triggering biopsy in others.

## Summary

Mp-MRI showed good performance at both detection (sensitivity 74-100%) and ruling out (NPV of 79-100%) clinically significant disease, according to the definition used. Therefore, we can reject the null-hypothesis and prove that mp-MRI had good accuracy in detection and localization of prostate cancer in this patient population.

# Chapter 5

## Mp-MRI performance in men with previous positive TRUS-guided prostate biopsy

## Introduction

Accurate characterization of prostate cancer has always been important, but has become particularly so in the era of active surveillance, where a decision on whether to proceed to radical therapies is often based on disease grade and biopsy characteristics (such as cancer core length) that correlate with tumour volume (192).

TRUS-guided biopsy is known to underestimate both the size and grade of tumour in a high proportion of patients when compared to histology at RP (12), and even when a repeat biopsy is performed targeted to the site of the tumour, 27% of patients in one study were found to have higher Gleason grade disease (21). These data suggest that we cannot rely on the diagnosis of low risk tumour on TRUS-guided biopsy – and indeed many of those failing active surveillance may do so because of misclassification rather than true disease progression (193).

Recent studies have suggested that conspicuity of a lesion at mp-MRI predicts the presence of clinically significant disease (194). This has been attributed to the inability of small and/or Gleason 3+3 lesions to be identified on mp-MRI (97, 195).

We assessed the ability of mp-MRI to predict higher grade and burden prostate cancer disease on confirmatory TPM biopsy. As previously discussed, this method of biopsy is accurate (133) compared to TRUS-guided biopsy and in one recent series compared to RP (196). It also has the great virtue of including a higher proportion of patients than just those subjected to RP.

## Material and methods

Two hundred and ten men with cancer on TRUS-guided biopsy underwent re-classification of their prostate cancer disease using mp-MRI followed by TPM biopsy. These patients were often considering enrolment in a research program of focal therapy, but in some cases were referred for active surveillance. Patients who could be enrolled into focal therapy programme (following mp-MRI and template biopsy) included those men with low to intermediate-risk disease with a PSA ≤15 ng/mL and stage ≤T2 with a life expectancy of 5 years or more. Additionally, to be eligible these patients had an index lesion suitable for focal therapy during which either a unilateral ablation could be performed or a bilateral ablation with preservation of at least one neurovascular bundle. Patients with low risk prostate cancer diagnosed with TRUS-guided biopsy and wish to be enrolled into one of the active surveillance programmes, are offered mp-MRI then TPM biopsy for better characterization of their disease.

Sixteen men were excluded for the following reasons:

a) >18 months between initial TRUS-biopsy and TPM biopsy
b) Limited TPM biopsy (< 20 zone biopsy)
c) Prostate cancer treatment started.

**194** men were therefore eligible.

**Index test (mp-MRI)**

Mp-MRI comprised of T2-weighted imaging, DWI and DCE imaging, as previously described in chapter 2. Imaging was performed at either 1.5T (n=184) or 3T (n=10) mp-MRI machines.

Mp-MRI was prospectively reported by five radiologists using a score from 1 to 5, which reflected the ESUR guidelines (45). Each of the five radiologists was a subspecialist reporting at least 100 mp-MRIs per year.

**Reference standard (systematic TPM biopsy)**

All patients underwent TPM biopsy using a brachytherapy grid under general anesthesia in the method previously described by Barzell (129). Basal and apical cores were obtained routinely, and a minimum number of 20 systematic cores samples were obtained.

Four different definitions of low risk cancer were applied to the group of 194 men, to reflect current uncertainties about which criteria to use for categorization of low risk disease on TRUS-guided biopsy:

**Definition1**: patients with Gleason 3+3 disease on their TRUS-guided biopsy, regardless of cancer core length (n= 137).

**Definition2**: patients with CCLmax of <50% on their TRUS-guided biopsy, regardless of Gleason grade (n=62).

**Definition 3**: patients with Gleason 3+3 disease and CCLmax <50% on their TRUS-guided biopsy (n=52).

**Definition 4**: patients with Gleason 3+3, CCLmax <50%, PSA <10 and <50% positive cores (n=28).

Under each definition, we classified patients according to mp-MRI scores into 3 groups; those that had score 4-5, those with an equivocal mp-MRI of score 3 and those with mp-MRI score 1-2. We then correlated mp-MRI scores with TPM histology in order to determine the rate of transition from low-risk on TRUS-guided biopsy to higher risk on TPM biopsy in each group, according to the definition used.

Clinical parameters (Age, PSA, prostate volume and TPM biopsy data) were recorded for all patients and under each definition separately. Binomial logistic regression was run to test for the predictive power of mp-MRI for upgrade of prostate disease at TPM biopsy and odds ratios, with 95% CI, were calculated. P-value of <0.05 was considered significant. All analyses were performed using SPSS v21.0.

## Results

Table 15 summarizes demographics amongst patients in different definitions of low risk disease.

Median PSA was 7ng/ml (IQ range, 5.2-9.3), median time between TRUS-guided biopsy and mp-MRI was 120 days (IQ range, 90-210) and median time between mp-MRI and TPM biopsy was 60 days (IQ range 30-90). Median number of cores at TPM biopsy was 48 cores (IQ range, 37-63).

Figure 12 shows the pattern of disease reclassification among patients under different definitions of low risk disease.

Definition 1 (patients with Gleason 3+3, n=137):

62 out of 137 (45%) patients had disease upgrade to Gleason score of ≥7 on TPM biopsy. Of those upgraded, 4 had Gleason 4+3 or higher (three scored 4 and one scored 5 on mp-MRI) and 58 had Gleason 3+4 (44 scored 4/5 on mp-MRI, 10 scored 3 and 4 scored 1-2). The four patients that were upgraded to Gleason score 3+4 with mp-MRI score 1-2 had CCLmax of 1, 2, 4 and 6mm at TPM biopsy.

An mp-MRI score of 1-2 had a NPV for predicting non-upgrade of prostate cancer, to Gleason grade ≥3+4, of 75%.

Definition 2 (patients with CCLmax <50%, n=62):

32 out of 62 (52%) patients had disease upsize to an CCLmax ≥50% on TPM biopsy. An mp-MRI score of 1-2 had a NPV for predicting non-upsize of prostate cancer, to CCLmax ≥50%, of 100%.

Definition 3 (patients with Gleason 3+3 and CCLmax <50%, n=52):

29 out of 52 (56%) patients had either disease upgrade to Gleason score ≥7 and/or upsize to CCLmax ≥50%. An mp-MRI score of 1-2 had a NPV for predicting non-upgrade/upsize of prostate cancer, either to higher Gleason score and/or CCLmax ≥50%, of 83%.

Definition 4 (patients with Gleason 3+3, CCLmax < 50%, PSA <10 and positive cores <50%, n=28):

13/28 (46%) of patients had either disease upgrade to Gleason score of ≥ 7 and/or upsize to CCLmax of ≥ 50%. An mp-MRI score of 1-2 had a NPV for predicting non-upgrade/upsize of prostate cancer to Gleason score ≥7 and/or CCLmax ≥ 50%, of 100%.

**Table 1.** Demographics amongst patients in different definitions of low-risk disease.

| | Definition 1 | | | Definition 2 | | | Definition 3 | | | Definition 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | MRI 4-5 | MRI 3 | MRI 1-2 | MRI 4-5 | MRI 3 | MRI 1-2 | MRI 4-5 | MRI 3 | MRI 1-2 | MRI 4-5 | MRI 3 | MRI 1-2 |
| Mean ± SD age | 62.7 ± 5.8 | 61.5 ± 5.7 | 59.4 ± 8.2 | 63.7 ± 5.9 | 61 ± 6.5 | 57.8 ± 8.1 | 63.6 ± 5.3 | 60.5 ± 6.5 | 57.8 ± 8.1 | 63.3±4.6 | 59.1±5.1 | 54.5±7.6 |
| Median ng/ml PSA (***IQ** range) | 7 (5.2-9.4) | 8.3 (5.2-9) | 5 (5.2-8.7) | 7.1 (5.3-9.4) | 8 (5.2-9) | 5.7 (6.1-9.2) | 7.7 (5.3-9.4) | 8 (5.2-9) | 5.8 (6.1-9.2) | 7 (4.8-7.5) | 6.5 (2.3-9.9) | 5.75 (5-6.4) |
| Median No. of TRUS-guided biopsy cores (**IQ** range) | 12 (10-12) | 12 (10-12) | 12 (9-12) | 12 (10-12) | 12 (10-12) | 12.5 (10-12) | 12 (10-12) | 12 (10-12) | 12.5 (10-12) | 12 (10-13) | 12 (10-12) | 13.5 (10-12) |
| Mean± SD cc prostate volume | 37 (15-91) | 44 (22-173) | 43 (19-90) | 41 (18-103) | 53 (26-173) | 49 (41-90) | 41.5 (18-91) | 53 (26-173) | 49 (41-90) | 50.6±20.5 | 50.3±22 | 56.2±23 |
| Median No. biopsy on TPM (**IQ** range) | 42 (37-63) | 48.5 (38-64.5) | 54.5 (37-63.5) | 39 (38-63) | 48 (39-64.3) | 57 (37.5-67.3) | 38.5 (38-63) | 48.5 (39-64.3) | 57 (37.5-67.3) | 37 (37.5-63.5) | 46 (38-65.5) | 70 (37-65) |
| Median number of positive cores on TPM (**IQ** range) | 8 (3-12) | 4 (3-12) | 6.5 (3-12) | 7 (3-12) | 4 (3-12.3) | 1.5 (2-9) | 7 (3-12) | 4 (3-12.3) | 1.5 (2-9) | 5 (3-12) | 4 (3-11) | 1.5 (2-8) |

*IQ, interquartile

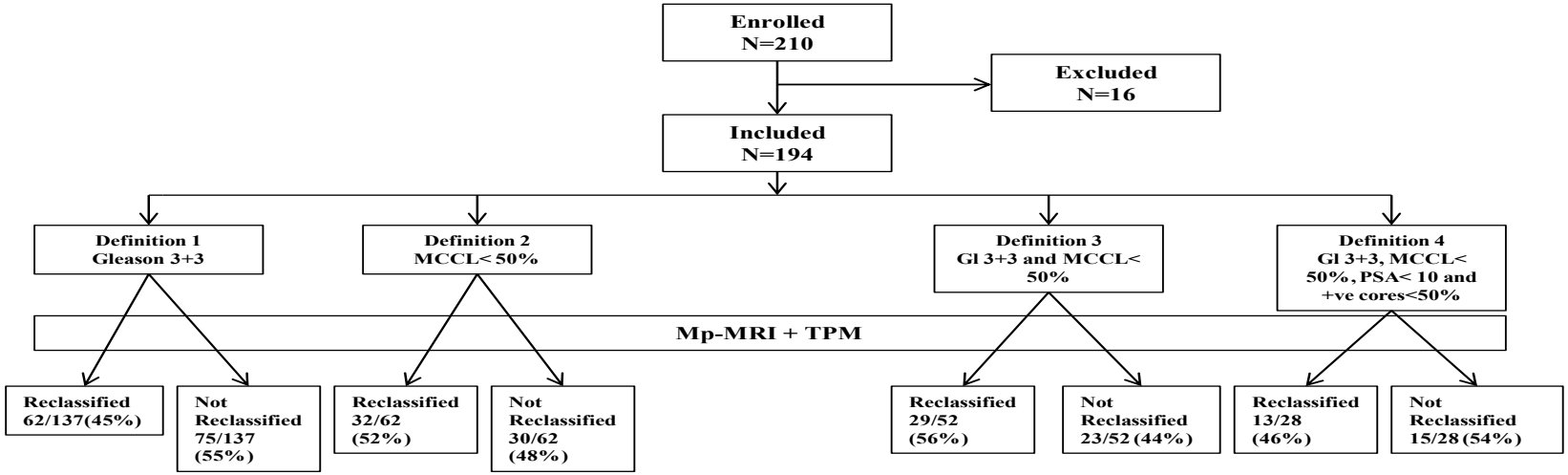



**Figure 1.** Distribution of disease reclassification among patients under different definitions of low-risk disease.

Table 16 and Figure 13 show the rate of prostate cancer disease upgrade for each "Definition" together with Odds ratios for upgrade based on different mp-MRI scores.

**Table 16.** Prediction of upgrade of prostate cancer disease on TPM biopsy from initial TRUS-guided biopsy findings (Definitions 1-4) according to different mp-MRI scores

| | MRI 4-5 | MRI 3 | MRI 1-2 | Patients with upgraded disease | OR (95% CI) | P-value |
|---|---|---|---|---|---|---|
| **Definition 1 (Gleason 3+3, n=137)** | 48/81 (59%) | 10/40 (25%) | 4/16 (25%) | 62/137 (45%) | 2.41 (1.55-3.75) | < 0.001 |
| **Definition 2 (CCLmax <50%, n=62)** | 24/36 (67%) | 8/20 (40%) | 0/6 (0%) | 32/62 (52%) | 2.09 (1.14-3.83) | 0.017 |
| **Definition 3 (Gleason 3+3 and CCLmax <50%, n=52)** | 21/28 (75%) | 7/18 (39%) | 1/6 (17%) | 29/52 (56%) | 2.86 (1.34-6.09) | 0.007 |
| **Definition 4 (Gleason 3+3, CCLmax <50%, PSA <10 and <50% positive cores, n=28)** | 9/15 (60%) | 4/9 (44%) | 0/4 (0%) | 13/28 (46%) | 2.32 (0.97-5.56) | 0.059 |

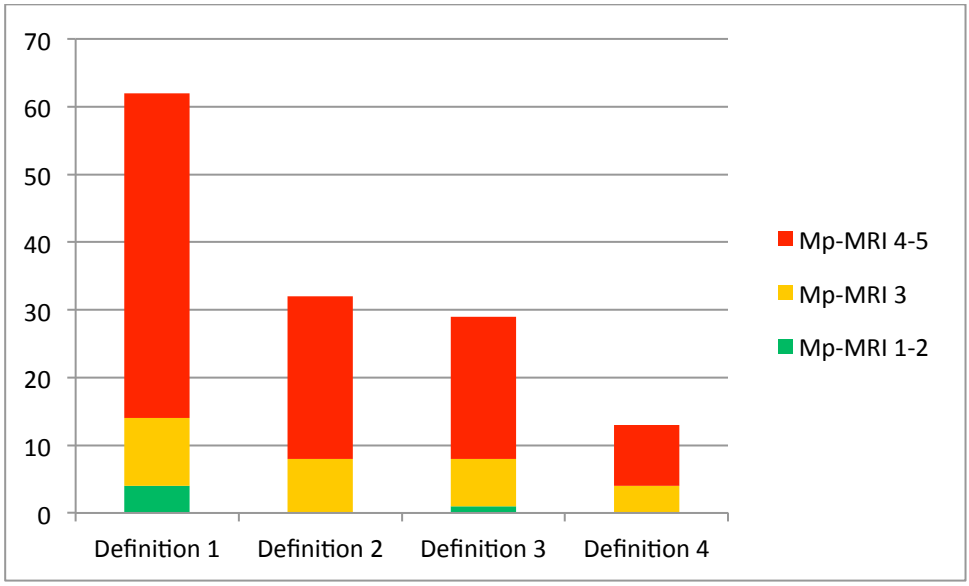



**Figure 13.**Patients that had an upgrade/upsize of prostate cancer disease for each of the four definitions at mp-MRI score 1-5

## Discussion

### Summary of results

Our primary finding was that mp-MRI score (based on a scoring system from 1 to 5) strongly predicted reclassification from low-risk on TRUS-guided biopsy to higher risk on TPM biopsy based on either disease volume or Gleason grade. The effect was strongest in the case of lesion size (Definition 2), where all those cancers, which were upsized, scored at least 3 on MRI. In the case of grade (Definition 1), the effect was not quite as strong: some lesions (n=4) with Gleason 4 elements were not seen (scoring 1-2) on mp-MRI. This is consistent with previous observations that detection of tumours on MRI is strongly related to both size and grade - a small tumour with a minor proportion of Gleason 4 is not usually conspicuous (70, 197, 198). Some type of tumours, the so called sparse tumours where cancer is mixed with intervening normal tissues, were poorly detected on MRI compared to more dense ones (195). On the other hand, the four patients upgraded to dominant Gleason 4 all scored either 4 or 5 on mp-MRI: even a small tumour is likely to be seen if it is predominantly high grade.

### Comparison with other studies

Several previous studies have used 'confirmatory' TRUS-guided biopsy to examine the predictive value of mp-MRI in upgrading low-risk prostate cancer. Before summarizing their findings, we must consider a possible bias due to the TRUS approach. Studies of targeting and saturation biopsies show that the accuracy of estimates of size and grade are highly dependent on sampling density (199, 200). If the confirmatory biopsy includes 'targeted' cores based on MRI findings (as is usually the case) then the sampling density will be higher in areas with MRI lesions. Purely as a function of sampling density (and not necessarily because of the MRI findings) these areas are therefore more likely to show upgrades; the effect is to artifactually increase the power of MRI to predict upgrading (201). To minimize this problem, a high sampling density in areas both with and without MRI lesions is necessary, and was achieved in our study by the use of systematic TPM biopsy.

The study conducted by Barzell et al., over 124 men that were considering active surveillance for favourable risk prostate cancer suggests that template biopsy is an accurate method for determining prostate cancer grade (202). All men underwent combined TRUS-guided biopsy as well as TPM biopsy, and in 13 patients who underwent RP, the final histology agreed with the template biopsy in 12/13 patients, and with the TRUS-guided biopsy in only 5/13.

Vargas et al. used T2-weighted MRI to predict the rate of upgrade of prostate cancer at confirmatory TRUS-guided biopsy, with targeted cores if there was a lesion on DRE, TRUS scanning or MRI (194). The rate of Gleason upgrading (79/388, 20%) on TRUS-guided biopsy was significantly less than that found in Definition 1 (62/137, 45%) of our study based on TPM biopsy, but it is possible that this was because they used TRUS-guided biopsy as a reference standard. Of the 129 patients in this series that underwent RP, 84 (65%) were found to have higher grade prostate cancer at whole-mount processing. Their NPV of 96-100% for MRI score 1/2 is comparable to our findings (75-100%) and a score of 5 strongly (87-98%) predicted upgrading.

Margel et al. recently evaluated mp-MRI in men with low risk prostate cancer (203). A total of 56 patients were included in the study and subsequently divided into 3 groups based on lesion visibility and size on MRI. They found that the finding of a lesion >1cm in diameter on mp-MRI (in 22% of patients) had a positive predictive value of 83% for reclassification into a group not suitable for active surveillance (with criteria involving size and grade) based on TRUS-guided biopsy. When no lesion was seen on mp-MRI, only 3.5% of cases were reclassified. Overall, 18/56 (32.1%) patients were reclassified on confirmatory TRUS-guided biopsy. Again, the lower rate of upgrading compared to our study may in part reflect the sampling method, and the same applies to two previous studies applying a confirmatory TRUS-guided biopsy to patients considering active surveillance, showing upgrading rates of 16% and 18% (21, 204).

More recently, Park et al. retrospectively assessed 298 with a diagnosis of prostate cancer and on active surveillance. All patients underwent mp-MRI (T2-weighted, DWI and DCE imaging) before proceeding to RP. Patients with visible cancer on mp-MRI (n=263, 88.3%) were more likely to have their disease upgraded (49.8 vs 14.3) than patients with non-visible MRI disease (n=35, 11.7%) (205). This work is in agreement with another group that found that a suspicious lesion on mp-MRI is more likely to be associated with disease re-classification among patients on active surveillance (206).

**Clinical implications**

The current attribution of risk based on TRUS biopsy is flawed, and it is likely that many patients ‘failing’ active surveillance have either completely missed or under-sampled tumours, (207), with some lying anteriorly (207, 208). Indeed, upgrade of prostate cancer disease was found in up to one third of patients deemed eligible for active surveillance (186, 209). Is there a role for mp-MRI in this setting? Our finding that a tumour that is not seen well on mp-MRI (ie. mp-MRI score 1-2) rarely appeared markedly larger at more definitive

histology, and that it was upgraded in a minority of cases, may enable the urologist to be confident enough of the diagnosis of low risk disease to recommend active surveillance without a further confirmatory biopsy. In particular, none of the patients having all of the criteria for low risk disease (our Definition 4) were upgraded if the lesion was invisible on mp-MRI.

Conversely, the finding of a visible lesion on MRI suggests that reclassification based on tumor volume or grade is likely, and enables targeting – either 'cognitively' or with the variety of techniques for MRI-guidance or MRI/ultrasound fusion (176). Increasingly the mp-MRI is being performed before first (and targeted) biopsy (210). More speculative also is the use of mp-MRI in ongoing active surveillance, where its role is as yet undefined.

In a recent systematic review over the value of novel tools that could be used in active surveillance for prostate cancer, authors found that mp-MRI showed a very high NPV among various studies published in this respect, something that may obviate the need for repeat biopsy during this management program (211).

## Summary

Using a high density sampling technique for histological confirmation, we have shown that a visible lesion on mp-MRI strongly predicts reclassification of low-risk to higher risk disease based on grade and cancer volume on biopsy. Conversely, in the absence of a visible lesion on mp-MRI the attribution of low risk status is likely to be correct. Mp-MRI may therefore have a role in selecting men who might wish to enter a program of active surveillance.

Mp-MRI showed a positive predictive value for upgrade of low-risk disease at 59-75%. Therefore, we can then reject the null-hypothesis and prove that mp-MRI had good accuracy in characterization of prostate cancer in this patient population.

# Chapter 6

## Mp-MRI performance in men with biochemical failure after radiotherapy

## Introduction

Fifteen percent of low risk and 67% of high-risk patients biochemically relapse (defined as either a prostate specific antigen (PSA) increase of ≥2ng/dl above their nadir or more than 2 consecutive rises of PSA) within 5-years of radiotherapy. Yet biochemical relapse does not always signify disease relapse and false positive rates are reported as high as 32% (212, 213). Moreover, PSA elevation can represent recurrence of local disease or development of metastatic one. Therefore stratification of patients between no therapy, salvage local therapy and systemic therapy remains problematic (214).

Conventional anatomical T2-weighted imaging has been evaluated for detection of local disease in this setting (215). However glandular atrophy and fibrosis induced by radiation therapy severely limit accuracy. Several studies have demonstrated that microstructural and functional MRI techniques such as DWI and DCE imaging, either performed individually (68, 216-219) or as part of multi-parametric examination (174, 191, 220), can improve detection of recurrent disease following radiotherapy. However the robustness of studies that use TRUS-guided biopsy as a reference standard to evaluate MRI (174, 216, 219-221) is limited, given the imperfections in the reference standard itself i.e. rates of false negative findings on TRUS biopsy can be as high as 42% (222).

Alternative and more robust reference standards are often difficult to obtain in the setting of potential radio-recurrent disease. Salvage RP is technically challenging and needs high expertise in special centres; therefore whole gland prostatectomy specimens are not usually the reference standard for direct correlation with MRI in this setting (174, 220, 221, 223-225). Even if they are, it is likely that large selection biases will exist and limit external validity to the biochemical failure group.

TPM biopsy provides an alternative for systematic biopsy of the entire gland, but this has only been reported in a single study of 13 patients in the post-radiotherapy setting (224). Furthermore, there is little described on precisely which MRI sequences are necessary for an optimal examination for detection of radio-recurrent disease (221). In this chapter, we evaluated the performance of mp-MRI and explored the added diagnostic value of functional sequences (DWI and DCE imaging) for detection of radio-recurrent disease using TPM biopsy as the reference standard.

## Materials and Methods

A TPM biopsy database of 509 patients was interrogated to identify patients presenting with biochemical failure (more than 2 consecutive rises of PSA or an increase of 2ng/ml or more above the PSA nadir as in Phoenix recommendations (226)) following radiotherapy and: (a) subsequent standardized mp-MRI (T2-weighted imaging, DWI (high b-value and apparent diffusion coefficient (ADC) map) and DCE imaging); (b) TPM biopsy performed within 10 months following mp-MRI.

Of the 49 patients eligible for inclusion; patients were excluded if there was: (a) history of brachytherapy (n=5); (b) limited TPM biopsy sampling i.e less than 20 cores or non-Barzell zone sampling (n=1); (c) limited (incomplete) mp-MRI due to artifact from hip replacement (n=6).

A total of 12 patients were excluded leaving a final study cohort of **37 men**.

**Index test (mp-MRI)**

As previously described in chapter 2, imaging was performed on two separate platforms, either 1.5 Tesla (Siemens Avanto, n=34) or 3.0 Tesla (Philips Achieva, n=3).

Full sequence parameters for 1.5T and 3.0T scans are given in Table 1 and Table 2.

Image Viewing

Anonymous studies were independently reviewed on an OsiriX workstation (version 3.7.1 32-bit) by two experienced radiologists (with 7and 5 years of mp-MRI prostate experience). Both radiologists were aware of the history of radiotherapy and biochemical relapse; but were unaware of other clinical details, PSA value or histology. Both radiologists performed a locked sequential read in a single session with the following read order:

1. T2-weighted images
2. T2-weighted + high b-value images
3. T2-weighted + high b-value+ ADC images
4. T2-weighted + high b-value+ ADC + DCE images

Mp-MRI images were scored from 1-5, as previously described, based on the likelihood of the presence of cancer (45).

**Reference Standard (Template prostate mapping (TPM) biopsy)**

All patients within the study cohort underwent TPM biopsy as previously described in chapter 2. In all patients the full gland was systematically sampled. The median time from mp-MRI to TPM biopsy was 2 months (IQ, 1-3 months).

**Histopathology and mp-MRI matching**

Pathologists were aware that the patients had previous radiotherapy with or without neoadjuvant/adjuvant hormonal treatment. Only cores with no pronounced radiation/hormone effect were assigned a Gleason score. All patients with positive TPM biopsy included in the study have been given Gleason scores.

Primary and secondary Gleason patterns of a tumour were recorded for each positive core, together with the cancer core length (length of cancer in each core excluding intervening normal areas) (156). Mp-MRI reader scores were matched to histopathology at the hemi-gland level (n=74).

**Statistical analysis**

Sensitivity, specificity, positive and negative predictive values together with positive and negative likelihood ratios ($LR^+$, $LH^-$) were calculated for each reader at each locked sequential read step using positive mp-MRI thresholds scores of 3 and 4 (i.e. equivocal scores (3/5) categorized as positive and negative respectively) via MedCalc v13.0.0.0. AUROC curves analysis was performed for each reader at each locked sequential read step using SPSS v22 and significant changes were statistically assessed as previously described (227) using MedCalc. McNemar's test was used to test for statistical differences of sensitivity and specificity between different mp-MRI datasets.

Inter-observer agreement was evaluated using Cohen's Kappa coefficient statistics. To test agreement, the 1-5 scores were categorised into 3 groups based on clinical interpretation; negative (score 1 and 2); equivocal (score 3) and positive (score 4 and 5) for cancer. Kappa values of 0.00–0.20 were considered as 'slight'; 0.21–0.40, 'fair'; 0.41–0.60, 'moderate'; 0.61–0.80, 'substantial'; and 0.81–1.00, 'almost perfect' agreement (228).

## Results

Table 14 shows baseline demographics of patients included in the study.
Forty-nine out of 74 (66%) prostate halves (33 patients) had prostate cancer on TPM biopsy.

A typical mp-MRI dataset for locked sequential read scores for readers 1 and 2 is presented in Figure 13.
Figure 15 and Figure 16 show the AUROC curves for readers 1 and 2 at different locked sequential read. Table 18 and Table 19 show accuracy figures (sensitivity, specificity, PPV, NPV, $LR^+$ and $LR^-$) for both readers at different locked sequential read. Table 20 shows inter-observer agreement between reader 1 and reader 2 for different mp-MRI sequential read.

First-read: T2-weighted imaging

Using mp-MRI score threshold of ≥3 as positive, sensitivity/specificity and PPV/NPV were 76%/52% and 76%/52%, respectively for reader 1, and 78%/44% and 73%/50% respectively for reader 2.
For a score threshold of ≥4 as positive, sensitivity/specificity and PPV/NPV were 14%/100% and 100%/37% respectively for reader 1, and 24%/100% and 100%/40% respectively for reader 2.
The AUROC, for classification of hemi-gland status, was 0.67 (95%-CI 0.55-0.80) for both readers 1 and 2 (Table 21).
There was a 'fair' inter-observer agreement ($\kappa = 0.39$; 95% CI 0.20-0.58) between the two readers.

Second-read: T2-weighted + high b-value DWI

Using an mp-MRI score threshold of ≥3 as positive, sensitivity/specificity and PPV/NPV were 69%/88% and 92%/59% respectively for reader 1, and 65%/92% and 94%/58% respectively for reader 2.

For a score threshold of ≥4 as positive, sensitivity/specificity and PPV/NPV were 41%/96% and 95%/45% respectively for reader 1, and 47%/100% and 100%/49% respectively for reader 2.

With addition of high b-value DWI, the AUROC improved for both readers to 0.80 (95%-CI 0.70-0.90). This was a statistically significant rise (p value= 0.02 and 0.01 for reader 1 and reader 2, respectively) from the first read, T2-Weighted imaging.

Inter-observer agreement was 'moderate' (κ = 0.51; 95% CI 0.36-0.64) following review of high b-value DWI.

Third-read: T2-weighted + high b-value DWI + ADC maps

Using an mp-MRI score threshold of ≥3 as positive, sensitivity/specificity and PPV/NPV were 63%/88% and 91%/55% respectively for reader 1, and 63%/92% and 94%/56% respectively for reader 2.

For a score threshold of ≥4 as positive, sensitivity/specificity and PPV/NPV were 41%/96% and 95%/45% for reader 1, and 43%/100% and 100%/47% respectively for reader 2. Inter-observer agreement was moderate (κ = 0.48; 95% CI 0.31-0.64).

In comparison to the previous locked read, AUROC showed statistically insignificant drop (p value= 0.08, 0.47 for reader 1 and reader 2) to 0.77 (95%-CI 0.67–0.89) for both readers.

Final-read: T2-weighted + high b-value DWI + ADC maps + DCE imaging

Using an mp-MRI score threshold of ≥3 as positive, sensitivity/specificity and PPV/NPV were 80%/68% and 83%/63% respectively for reader 1, and 76%/72% and 84%/60% respectively for reader 2.

For a score threshold of ≥4 as positive, sensitivity/specificity and PPV/NPV were 63%/92% and 94%/56% respectively for reader 1, and 69%/92% and 94%/61% respectively for reader 2. Inter-observer agreement was 'substantial' (κ=0.65; 95%-CI 0.51-0.79).

AUROC was marginally higher after inclusion of DCE images (0.80, 95%-CI: 0.69-0.91 for reader 1, and 0.84, 95%-CI: 0.76-0.93 for reader 2). However this was not statistically significant, neither from T2+high b-value read (p= 0.90 and 0.27 for reader 1 and reader 2, respectively), nor from T2+high b-value+ ADC read (p= 0.47 and 0.11 for reader 1 and reader 2, respectively).

**Table 17. Patients' demographics**

| | All patients (n = 37) |
|---|---|
| **Age (mean, IQ)** | 69.7 (66-74) |
| **PSA at time of MRI (median, IQ)** | 4.5 (3-7.3) |
| **Time between end of DXT and MRI (months) (median, IQ)** | 66 (54-90) |
| **Time between MRI and biopsy (months) (median, IQ)** | 2 (1-3) |
| **Total biopsy cores/patient (median, IQ)** | 41 (31-52) |
| **Positive cores/patient (%)** | 17 (9-30) |
| **Clinical stage at diagnosis** | |
| **1b** | 1 |
| **1c** | 8 |
| **2a** | 7 |
| **2b** | 1 |
| **2c** | 4 |
| **3a** | 10 |
| **3b** | 6 |
| **Gleason score at diagnosis** | |
| **3+3** | 15 |
| **3+4** | 9 |
| **4+3** | 2 |
| **4+4** | 4 |
| **4+5** | 6 |
| **5+4** | 1 |
| **Hormones before MRI** | |
| **Yes** | 27 |
| **No** | 10 |

**IQ, interquartile range**

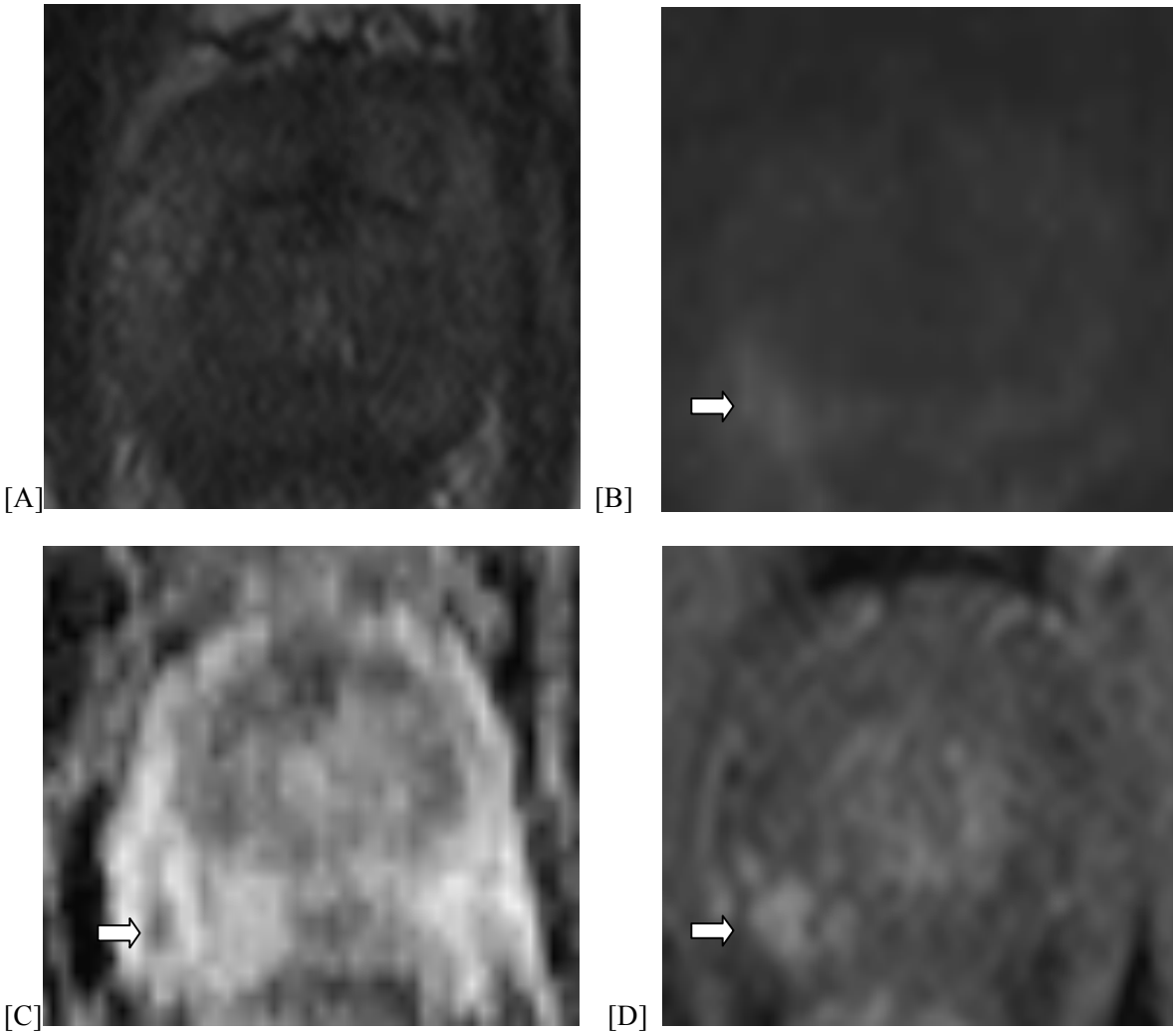



**Figure 14.**

Axial images from a 68 years old patient with positive MRI (scoring 5/5), 9 positive cores with a maximum cancer core length of 6 mm, 50%, Gleason 3+4 were present at TPM biopsy in the right lateral zone. Both readers scored the right hemi gland as: 3/5 on T2-weighted [A], 4/5 on b1400 [B] and on ADC [C] and 5/5 on DCE imaging [D]. The left hemi gland was scored by reader 1 and reader 2as: (3/5 and 3/5 on T2-weighted [A], (2/5 and 2/5 on b1400 [B], (2/5 and 2/5 on ADC[C] and (2/5 and 1/5 on DCE [D]. No cancer was present in the left hemi gland on TPM biopsy.

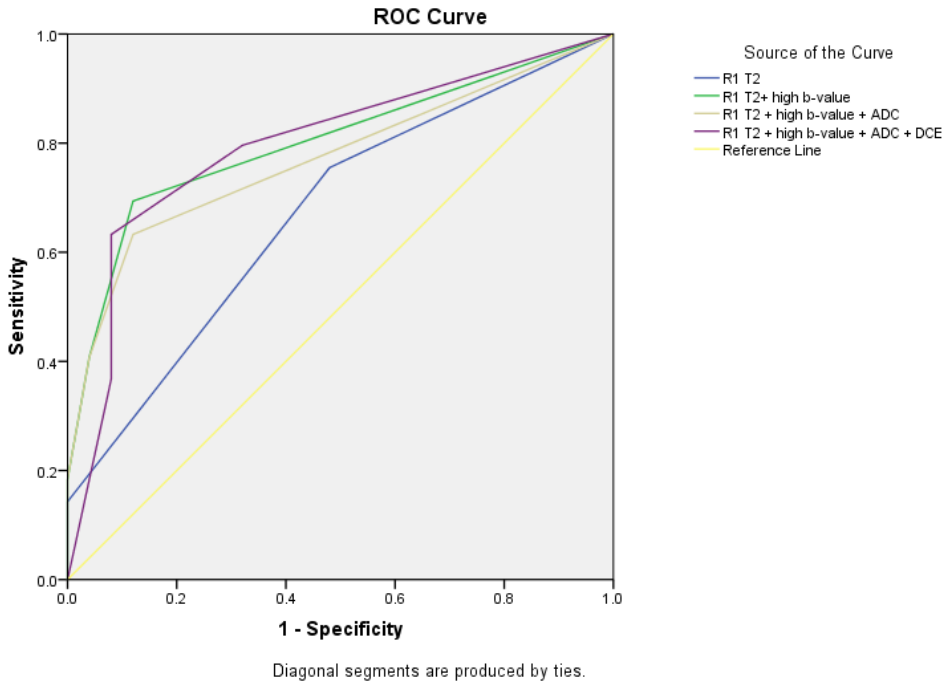



**Figure 15.** Receiver operator characteristic curves of reader 1 for the 4 locked sequential read. AUC of ROC curves for T2, T2+high b-value, T2+high b-value+ADC and T2+high b-value+ADC+DCE were; 0.67, 0.80, 0.77 and 0.80, respectively.

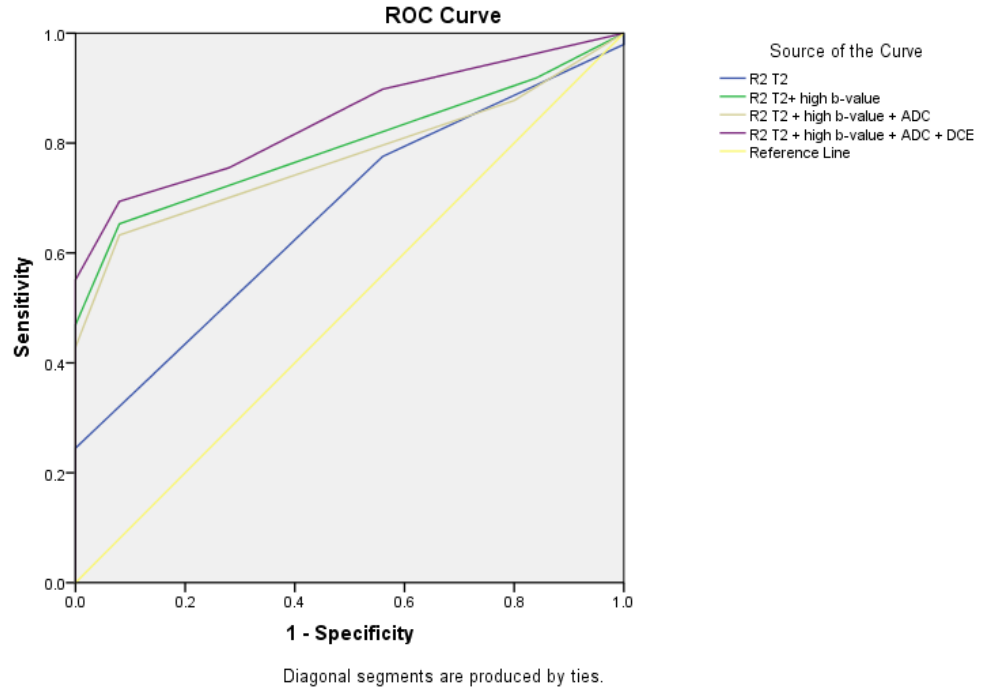



**Figure 16.** Receiver operator characteristic curves of reader 2 for the 4 locked sequential read. AUC of ROC curves for T2, T2+high b-value, T2+high b-value+ADC and T2+high b-value+ADC+DCE were;0.67, 0.80, 0.77 and 0.84, respectively.

**Table 18.** mp-MRI score ≥3

(a) Reader performance at the hemi-gland level with mp-MRI score ≥3 as positive

| | R1 | | | | R2 | | | |
|---|---|---|---|---|---|---|---|---|
| | T2W | T2W +high b-value | T2W +high b-value +ADC | T2W + high b-value + ADC + DCE | **T2W** | **T2W + high b-value** | **T2W +high b-value +ADC** | **T2W + high b-value + ADC + DCE** |
| **Sensitivity** | 76 | 69 | 63 | 80 | **78** | **65** | **63** | **76** |
| **Specificity** | 52 | 88 | 88 | 68 | **44** | **92** | **92** | **72** |
| **PPV** | 76 | 92 | 91 | 83 | **73** | **94** | **94** | **84** |
| **NPV** | 52 | 59 | 55 | 63 | **50** | **58** | **56** | **60** |
| **$LR^+$** | 1.57 | 5.78 | 5.27 | 2.49 | **1.38** | **8.16** | **7.91** | **2.7** |
| **$LR^-$** | 0.47 | 0.35 | 0.42 | 0.3 | **0.51** | **0.38** | **0.4** | **0.34** |

(b) P values between different mp-MRI reads at threshold ≥3 as positive

| | R1 | | R2 | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity |
| **T2** vs **T2+high b-value** | 0.548 | 0.004 | 0.146 | 0.002 |
| **T2** vs **T2+high b-value +ADC** | 0.179 | 0.004 | 0.065 | 0.002 |
| **T2** vs **T2+high b-value +ADC +DCE** | 0.791 | 0.388 | 1.0 | 0.923 |
| **T2+high b-value** vs **T2+high b-value+ ADC+ DCE** | 0.125 | 0.063 | 0.227 | 0.063 |

**Table 19.** mp-MRI score ≥4

(a) Reader performance at the hemi-gland level with mp-MRI score ≥4 as positive

| | R1 | | | | R2 | | | |
|---|---|---|---|---|---|---|---|---|
| | T2W | T2W +high b-value | T2W +high b-value +ADC | T2W + high b-value + ADC + DCE | **T2W** | **T2W +high b-value** | **T2W + high b-value +ADC** | **T2W + high b-value + ADC + DCE** |
| **Sensitivity** | 14 | 41 | 41 | 63 | **24** | **47** | **43** | **69** |
| **Specificity** | 100 | 96 | 96 | 92 | **100** | **100** | **100** | **92** |
| **Positive PV** | 100 | 95 | 95 | 94 | **100** | **100** | **100** | **94** |
| **Negative PV** | 37 | 45 | 45 | 56 | **40** | **49** | **47** | **61** |
| **$LR^+$** | NA | 10.2 | 10.2 | 7.9 | **NA** | **NA** | **NA** | **8.67** |
| **$LR^-$** | 0.86 | 0.62 | 0.62 | 0.4 | **0.76** | **0.53** | **0.57** | **0.33** |

(b) P values between different mp-MRI reads at threshold ≥4 as positive

| | R1 | | R2 | |
|---|---|---|---|---|
| | Sensitivity | Specificity | Sensitivity | Specificity |
| **T2** vs **T2+high b-value** | 0.001 | 1.0 | 0.001 | NA |
| **T2** vs **T2+high b-value +ADC** | 0.001 | 1.0 | 0.004 | NA |
| **T2** vs **T2+high b-value +ADC +DCE** | <0.0001 | 0.5 | <0.0001 | 0.5 |
| **T2+high b-value** vs **T2+high b-value+ ADC+ DCE** | 0.001 | 1.0 | 0.003 | 0.5 |

**Table 20.** Inter-observer agreement between readers of locked sequential mp-MRI reads

| | Inter-observer agreement | | | |
|---|---|---|---|---|
| | T2 W | T2W + high b-value | T2W + high b-value + ADC | T2W + high b-value + ADC + DCE |
| **κ** | 0.392 | 0.512 | 0.475 | 0.648 |
| **SE** | 0.097 | 0.08 | 0.084 | 0.073 |
| **95% CI** | 0.202-0.581 | 0.356-0.699 | 0.309-0.640 | 0.505-0.791 |
| **Wt κ** | 0.468 | 0.632 | 0.596 | 0.722 |
| **Agreement** | Fair | Moderate | Moderate | substantial |

SE – standard error
Wt k – weighted kappa
ADC- Apparent diffusion co-efficient,
DCE- Dynamic contrast enhanced

**Table 21.** Receiver operator characteristic area under curve

(a) Reader 1

| | Area | Std. | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| **T2** | .67 | .065 | .55 | .80 |
| **T2, b1400** | .80 | .051 | .70 | .92 |
| **T2, high b-value, ADC** | .77 | .054 | .67 | .88 |
| **T2, high b-value, ADC, DCE** | .80 | .055 | .69 | .91 |

(b) Reader 2

| | Area | Std. | 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| **T2** | .67 | .063 | .55 | .80 |
| **T2, high b-value** | .80 | .051 | .70 | .90 |
| **T2, high b-value, ADC** | .77 | .053 | .67 | .88 |
| **T2, high b-value, ADC, DCE** | .84 | .044 | .76 | .93 |

ADC- Apparent diffusion co-efficient,
DCE- Dynamic contrast enhanced,
Std. – standard of error

Interpretation of accuracy figures (mp-MRI ≥3) (Table 18 (b)):

Sensitivity was highest for the full mp-MRI dataset read (80% and 76% for reader 1 and reader 2, respectively). However, this did not show statistically significant difference in comparison to T2+high b-value (p value = 0.125 and 0.227 for reader 1 and reader 2, respectively).

Specificity was highest for, T2+high b-value and T2+high b-value + ADC (88% and 92% for reader 1 and reader 2 respectively). This was statistically insignificantly higher than that of the full mp-MRI dataset (p= 0.063 for both readers).

The highest $LR^+$ was 5.78 and 8.16 for reader 1 and reader 2 at locked sequential read of T2+high b-value. This was much higher than the same values for the full mp-MRI dataset (2.49 and 2.70 for reader 1 and reader 2, respectively).

The lowest $LR^-$ was 0.30 and 0.34 for reader 1 and reader 2, respectively, at full mp-MRI dataset. However this was only marginally higher than that at T2+high b-value (0.35 and 0.38 for reader 1 and reader 2, respectively.

Interpretation of accuracy figures (mp-MRI ≥4) (Table 19 (b)):

Sensitivity was highest for the full mp-MRI dataset read (63% and 69% for readers 1 and 2, respectively). There was a statistically significant difference in comparison to T2W and T2W+high b-value (p value = <0.0001 and 0.001 for reader 1 and <0.0001 and 0.003 for reader 2, respectively).

Specificity ranged between 92-100% for the four mp-MRI datasets. There was no statistically significant difference between any of the combination datasets.

Table 22**and**

Table **23** show accuracy figures at the patient level.

Table 22.Accuracy figures for both readers at MRI threshold ≥ 3, Patient level

| | R1 | | | | R2 | | | |
|---|---|---|---|---|---|---|---|---|
| | T2W | T2W + b1400 | T2W + b1400 + ADC | T2W + b1400 + ADC + DCE | T2W | T2W + b1400 | T2W + b1400 + ADC | T2W + b1400 + ADC + DCE |
| **Sensitivity** | 100 | 91 | 81 | 94 | 94 | 84 | 84 | 88 |
| **Specificity** | 29 | 80 | 80 | 60 | 20 | 80 | 100 | 40 |
| **Positive PV** | 86 | 97 | 96 | 94 | 88 | 96 | 100 | 90 |
| **Negative PV** | 100 | 57 | 40 | 60 | 33 | 44 | 55 | 33 |

Table 23. Accuracy figures for both readers at MRI threshold ≥ 4, Patient level

| | R1 | | | | R2 | | | |
|---|---|---|---|---|---|---|---|---|
| | T2W | T2W + b1400 | T2W + b1400 + ADC | T2W + b1400 + ADC + DCE | T2W | T2W + b1400 | T2W + b1400 + ADC | T2W + b1400 + ADC + DCE |
| **Sensitivity** | 22 | 56 | 56 | 78 | 38 | 63 | 56 | 81 |
| **Specificity** | 100 | 100 | 100 | 80 | 100 | 100 | 100 | 80 |
| **Positive PV** | 100 | 100 | 100 | 96 | 100 | 100 | 100 | 96 |
| **Negative PV** | 17 | 26 | 26 | 36 | 20 | 29 | 26 | 40 |

## Discussion

### Summary of results

Whilst evidence is starting to emerge that mp-MRI can aid detection of local disease following radiotherapy, study sizes remain small and what constitutes an optimal mp-MRI dataset remains unknown (221, 224). In this work we explored the incremental value of individual mp-MRI sequences for detection of radio-recurrent prostate cancer validated against a robust TPM biopsy reference. We employed a locked sequential read paradigm using T2-weighted imaging; high-b value DWI; ADC maps and DCE imaging. Our sequence of reading mp-MRI pictures in the current study was; T2-weighted>> high b-value>> ADC maps then DCE imaging). Our cohort was homogenous; all our patients had previous external beam radiotherapy only and we did not include patients with brachytherapy as in other studies (174, 229).

Consistent with the work of others our results show that addition of 'functional' MRI sequences to anatomical T2-weighted imaging improves performance of readers for detection of radio-recurrent prostate cancer (174, 224, 225). The sensitivity/specificity for readers was greatest when mp-MRI scores of ≥3 were considered as positive for cancer and after review of the full mp-MRI examination (80%/68% and 76%/72% for reader 1 and reader 2 respectively). We did not observe a statistically significant increase in AUROC curve of readers between T2-weighted imaging+ high b-value DWI and sequential addition of ADC and DCE MRI.

### Comparison with other studies

Recent work showed that DWI has similar sensitivity and higher specificity than DCE imaging in patients with radio-recurrent prostate cancer (68, 216, 225, 230). A single preliminary study of mp-MRI (validated by TPM biopsy) suggested a good performance for detection of radio-recurrent prostate cancer (224). AUROC curves for two readers were reported as 0.77 and 0.89 for all cancers and 0.86 and 0.93 for cancer core lengths ≥ 3mm (clinically significant). Our results of a larger cohort are in line with that previous study. Moreover, in the current study we looked at the added value of functional MRI sequences to the basic anatomical T2-weighted sequence, something that was not handled in the other study.

Akin et al. have also reported on mp-MRI performance in the radio-recurrent setting (174). Similar to our study they employed two MRI score cutoffs (3 and 4); however their analysis was performed at a patient and prostate sextant level and TRUS-guided biopsy (12-16 cores)

was used as reference standard. They did not perform a locked sequential read for each sequence. However, our results on the overall performance of mp-MRI are in agreement with their work.

There is little data on the incremental value of DCE imaging to other mp-MRI sequences for radio-recurrent disease. Donati et al. showed that DCE imaging did not add significant value in such patients (221). Our results reaffirm only a marginal increase in performance with the addition of DCE imaging (p=0.90 and 0.27 for reader 1 and reader 2 respectively). Our study also compared the utility of high b-value DWI in combination with multi b-value DWI derived ADC maps; an area not covered by the work of Donati et al. We found no significant incremental value of reading ADC after high b-value DWI (p= 0.08 and 0.47 for reader 1 and reader 2, respectively). Haider et al. found better performance of DCE than T2-weighted imaging in localization of prostate cancer. However there was no DWI included in their study (219).

Our inter-reader agreement data also demonstrate that agreement between readers improved with addition of 'functional' imaging ($\kappa$ = 0.65, 95% CI; 0.51-0.79), which is comparable to other studies (174, 224). The lowest agreement was for T2 ($\kappa$ = 0.39, 95% CI; 0.20-0.58), which is also comparable to that in the literature (174).

**Clinical implications**

For the post-radiotherapy setting the greatest benefit of mp-MRI identification of local recurrence is likely to be the enabling targeted salvage therapies (231, 232). As a general benefit mp-MRI enables a reduction in unnecessary biopsy cores and thereby reduces the risk of biopsy associated complications. Establishing an optimal mp-MRI examination will help reduce examination cost, reduce scan time and improve patient comfort. We recommend a minimum examination of T2-weighted imaging plus either a single high b-value DWI acquisition or multi-b derived ADC map, depending on capability of the MRI scanner. Routine use of DCE MRI in the radio-recurrent setting is not supported by our results.

## Summary

Mp-MRI performs well for identifying local recurrence of prostate cancer in patients presenting with biochemical failure following radiotherapy. Our study shows that a minimum examination of T2-weighted imaging plus high b-value DWI acquisition might be all that is necessary for detection of radio-recurrent prostate cancer. Addition of DCE MRI has marginal (if any) performance benefit.

Therefore, we can then reject the null-hypothesis and confirm that mp-MRI had good accuracy in detection and localization of prostate cancer in this patient population.

# Chapter 7

# The clinical value of using PSA density in conjunction with mp-MRI for the prediction of clinically significant prostate cancer.

## Introduction

Prostate cancer screening started in the early 1990s using PSA. A serum level above 4ng/ml was considered as suspicious for the presence for prostate cancer and an indication to proceed for TRUS-guided prostate biopsy. However PSA showed low specificity, as various other reasons could be responsible for its high level. PSA kinetics has been proposed to improve the specificity of PSA such as PSA density (PSAD), PSA velocity, age specific PSA and PSA free/total ratio (233, 234).

PSAD is calculated by dividing the PSA level by the prostate volume. Traditionally, prostate volume is being measured via TRUS using ellipsoid formula, which was found to under-estimate the prostate volume in patients treated with radical prostatectomy (235, 236). Variability in prostate size was found to be in the range of 20% using TRUS, leading to inaccuracies calculating PSAD (237). The use of MRI does not only provide more detailed anatomy of the prostate compared to TRUS, but also provides more accurate volume estimation using the contoured volume method (238).

A PSAD threshold of 0.15 ng/ml was suggested as a cut-off to predict the presence of prostate cancer, where higher levels preclude the presence of the disease (239). However using this cut-off was found to miss nearly half of the diagnosed tumours amongst 5000 men screened for prostate cancer (240).

In this chapter we explored the performance of PSAD for the prediction of the presence of clinically significant prostate cancer. We also examined the performance of combined PSAD and mp-MRI for the same purpose.

## Material and Methods

We included all the patients from chapters 3, 4 and 5 in this study. These were patients that had no previous prostate biopsy (n= 129), patients that had previous negative prostate biopsy (n= 54) and those that had previous positive TRUS-guided prostate biopsy (n=194). In the last group, those with previous positive TRUS-guided biopsy, 30 patients were excluded due to some missing clinical details as PSA level at mp-MRI time and/or gland size on mp-MRI report. This left a number of 346 patients included in this study.

All the 346 patients underwent mp-MRI followed by TPM biopsy. PSAD was calculated by dividing the PSA level by mp-MRI determined prostate volume. Prostate volume was measured on T2-weighted images.

Overall performance of mp-MRI across the 346 patients to predict the presence or absence of prostate cancer was assessed using the previously described target conditions (chapter 3). The addition of PSAD to mp-MRI results was also assessed to see if there was a significant improvement. The use of PSAD was also assessed separately in the group of patients that had mp-MRI score of 3 using two different PSAD cut-off values, 0.15 and 0.085.

**Statistical analysis**

Accuracy figures for the performance of PSAD at the 6 definitions of clinically significant disease were calculated using Medcalc v13.0.0.0. Spearman's correlation coefficient was run to measure the statistical dependence between mp-MRI and PSAD. The performance of both PSAD and mp-MRI was assessed separately and jointly, by measuring the AUC-ROC curve at different target definitions. 95% confidence intervals were generated and p-value was calculated to see if there was any statistical clinical significance between: a) PSAD vs PSAD + mp-MRI and b) mp-MRI vs PSAD + mp-MR. P-value of $<0.05$ was considered as clinically significant.

## Results

Median age was 62 years (IQ range, 58-67). Median PSA level was 6.8ng/ml (IQ range, 4.8-10). Median gland volume was 40ml (IQ range, 31-54). Median PSAD was 0.162 (IQ range, 0.115-0.241). Table 24 show the different levels of PSA and PSAD for patients having clinically significant disease.

Prostate cancer was found in 282/346 (82%) patients. UCL Def.1 and UCL Def.2 were found in 125 (36%) and 202(58%) patients, respectively. Gleason ≥4+3 and Gleason ≥3+4 were found in 27 (8%) and 153 (44%) of patients, respectively. CCLmax ≥6mm and CCLmax ≥4mm were found in 115 (33%) and 178 (51%) patients, respectively.

At cut-off 0.15, PSAD showed sensitivity (65-72%), specificity (51-56%), positive predictive value (43-68%) and negative predictive value (53-95%), (Table **25**).

Spearman's correlation coefficient showed that there was a statistically significant dependence between mp-MRI and PSAD (p=0.003).

The AUC-ROC for using the PSAD only in the prediction of the presence/absence of clinically significant disease ranged from 0.626 to 0.698. The AUC-ROC curve for using the mp-MRI only in the prediction of clinically significant disease ranged from 0.681 to 0.722. The addition of PSAD in the interpretation of mp-MRI improved the overall performance of mp-MRI (AUC-ROC curve ranged between 0.735 to 0.794). However, this was not statistically significant from using the mp-MRI alone through all the definitions of clinically significant disease (

| | | Area | Std. Error[a] | Asymptotic 95% Confidence Interval | | P value PSAD vs PSAD + mp-MRI | P value mp-MRI vs mp-MRI + PSAD |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| UCL Def.1 | PSAD | .698 | .030 | .640 | .757 | 0.017 | 0.07 |
| | mp-MRI | .722 | .028 | .667 | .777 | | |
| | PSAD + mp-MRI | .794 | .025 | .746 | .843 | | |
| UCL Def.2 | PSAD | .671 | .029 | .614 | .727 | 0.018 | 0.09 |
| | mp-MRI | .698 | .028 | .643 | .753 | | |
| | PSAD + mp-MRI | .761 | .026 | .711 | .811 | | |
| Gl ≥4+3 | PSAD | .694 | .060 | .576 | .812 | 0.016 | 0.08 |
| | mp-MRI | .707 | .047 | .616 | .799 | | |
| | PSAD + mp-MRI | .780 | .040 | .702 | .858 | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gl ≥3+4 | PSAD | .626 | .030 | .567 | .685 | 0.007 | 0.37 |
| | mp-MRI | .701 | .028 | .646 | .756 | | |
| | PSAD + mp-MRI | .735 | .027 | .682 | .788 | | |
| CCLmax ≥6mm | PSAD | .690 | .030 | .630 | .750 | 0.03 | 0.11 |
| | mp-MRI | .712 | .029 | .655 | .768 | | |
| | PSAD + mp-MRI | .779 | .026 | .728 | .829 | | |
| CCLmax ≥4mm | PSAD | .671 | .029 | .615 | .727 | 0.06 | 0.1 |
| | mp-MRI | .681 | .029 | .625 | .737 | | |
| | PSAD + mp-MRI | .744 | .026 | .693 | .796 | | |

Table 26).

Mp-MRI was scored as 3/5 in 114 patients, of which 80 (70%) had any cancer. Twenty (18%) and 47 (41%) patients had UCL Def.1 and UCL Def.2 disease, respectively. For UCL Def.1, 15/20 (75%) patients had PSAD >0.15. For UCL Def.2, 28/47 (60%) had PSAD >0.15. Three out of the 114 patients with mp-MRI score 3/5 had Gl ≥4+3, two of which had PSAD of >0.15 and the third had a PSAD of 0.136. Thirty-one out of the 114 patients had Gl ≥3+4 but only 18 of them had PSAD >0.15.

Using the stricter PSAD threshold of 0.085 on patients with indeterminate mp-MRI score (3/5), none would have been missed for UCL Def.1 and only 2/47 (4%) would have been missed for UCL Def.2. Again, none of the patients with Gl ≥4+3 (n=3) and only 2/31 (6%) with Gl ≥3+4 would have been missed.

**Table 24. PSA and PSAD levels for different definitions of clinically significant disease**

| Cancer Definition | Number of pts | PSA Median (IQ range) | PSAD Median (IQ range) |
|---|---|---|---|
| **UCL Def.2** | 202 | 7 (4.9-10) | 0.183 (0.133-0.272) |
| **UCL Def.1** | 125 | 7.2 (5.7-10.8) | 1.03 (0.139-0.292) |
| **Gl ≥4+3** | 27 | 10 (6.25-12.95) | 0.268 (0.140-0.365) |
| **Gl ≥3+4** | 153 | 7 (5.0-10.3) | 0.180 (0.132-0.276) |
| **CCLmax ≥6mm** | 115 | 7.3 (5.61-10.9) | 0.213 (0.140-0.292) |
| **CCLmax ≥4mm** | 178 | 7 (5.0-10.4) | 0.188 (0.135-0.275) |

Table 25. Performance of PSAD at cut-off 0.15 to detect and rule-out clinically significant cancer on TPM at multiple levels of significance (95% confidence intervals in parentheses).

| Classification | ROI | TP | FN | TN | FP | SEN | SPEC | PPV | NPV |
|---|---|---|---|---|---|---|---|---|---|
| UCL2 | 346 | 131 | 71 | 81 | 63 | 65 (58-71) | 56 (48-64) | 68 (60-74) | 53 (45-61) |
| UCL1 | 346 | 89 | 36 | 116 | 105 | 71 (62-79) | 52 (46-59) | 46 (39-53) | 76 (69-83) |
| Gleason ≥4+3 | 346 | 19 | 8 | 144 | 175 | 70 (50-86) | 45 (40-51) | 10 (6-15) | 95 (90-98) |
| Gleason ≥3+4 | 346 | 99 | 54 | 98 | 95 | 65 (57-72) | 51 (41-58) | 51 (44-58) | 64 (56-72) |
| CCLmax ≥6 | 346 | 83 | 32 | 120 | 111 | 72 (63-80) | 52 (45-59) | 43 (36-50) | 79 (72-85) |
| CCLmax ≥4 | 346 | 118 | 60 | 92 | 76 | 66 (59-73) | 55 (47-62) | 61 (54-68) | 61 (52-68) |
| Any cancer | 346 | 165 | 117 | 35 | 29 | 59 (53-64) | 55 (42-67) | 85 (79-90) | 23 (17-31) |

Table 26. Comparison between AUC-ROC curve for PSAD, mp-MRI and PSAD + mp-MRI with 95% confidence intervals at different definitions of clinically significant disease.

| | | Area | Std. Error[a] | Asymptotic 95% Confidence Interval | | P value PSAD vs PSAD + mp-MRI | P value mp-MRI vs mp-MRI + PSAD |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| UCL Def.1 | PSAD | .698 | .030 | .640 | .757 | 0.017 | 0.07 |
| | mp-MRI | .722 | .028 | .667 | .777 | | |
| | PSAD + mp-MRI | .794 | .025 | .746 | .843 | | |
| UCL Def.2 | PSAD | .671 | .029 | .614 | .727 | 0.018 | 0.09 |
| | mp-MRI | .698 | .028 | .643 | .753 | | |
| | PSAD + mp-MRI | .761 | .026 | .711 | .811 | | |
| Gl ≥4+3 | PSAD | .694 | .060 | .576 | .812 | 0.016 | 0.08 |
| | mp-MRI | .707 | .047 | .616 | .799 | | |
| | PSAD + mp-MRI | .780 | .040 | .702 | .858 | | |
| Gl ≥3+4 | PSAD | .626 | .030 | .567 | .685 | 0.007 | 0.37 |
| | mp-MRI | .701 | .028 | .646 | .756 | | |
| | PSAD + mp-MRI | .735 | .027 | .682 | .788 | | |
| CCLmax ≥6mm | PSAD | .690 | .030 | .630 | .750 | 0.03 | 0.11 |
| | mp-MRI | .712 | .029 | .655 | .768 | | |
| | PSAD + mp-MRI | .779 | .026 | .728 | .829 | | |
| CCLmax ≥4mm | PSAD | .671 | .029 | .615 | .727 | 0.06 | 0.1 |
| | mp-MRI | .681 | .029 | .625 | .737 | | |
| | PSAD + mp-MRI | .744 | .026 | .693 | .796 | | |

## Discussion

Our results show statistically significant higher performance of mp-MRI compared to PSAD in predicting the presence or absence of clinically significant disease. Although the AUC-ROC curve increased at mp-MRI + PSAD (0.735-0.794) compared to mp-MRI (0.681-0.722) alone however this was not statistically significant at any of the target conditions detected on TPM biopsy.

The utility of mp-MRI with PSAD has not been handled before in the literature. Kuboto et al. ran a study over 185 patients with no previous prostate biopsy to see if MRI can improve the detection of prostate cancer when used in conjunction with PSAD. Only T2-weighted imaging was used in their study and reference standard was 8-core TRUS-guided biopsy. They found that MRI improved the specificity to 40% while retained sensitivity at 95% for PSAD for the detection of any prostate cancer (241).

In active surveillance protocols, the National Comprehensive Cancer Network (NCCN) suggested PSAD cut-off value of 0.15 whereas Prostate Cancer Research International Active Surveillance (PRIAS) recommended a cut-off value of 0.2 ng/ml (242). Ha et al. found that even with the lower cut-off value of 0.15, >30% of patients on AS experienced upgrading and upstaging of their prostate cancer disease (243). They called for a lower PSAD cut-off value of <0.085 ng/ml.

The use of the PSAD could help in cases where there is an indeterminate result on the mp-MRI images. In our study when PSAD cut-off 0.15 was used, 75% and 60% of patients with indeterminate mp-MRI score of 3/5 were correctly diagnosed with UCL Def.1 and UCL Def.2, respectively. Applying stricter threshold of 0.085 as proposed by Ha et al. (243) meant that none of the patients falling into UCL Def.1 or having Gl ≥4+3 would have been missed. Also, only 2/47 (4%) and 2/31 (6%) from patients falling into UCL Def.2 or having Gl ≥3+4 would have been missed, respectively. This could help the clinician to take a decision to proceed with prostate biopsy in such patient population.

## Summary

PSAD did not significantly improve the overall performance of mp-MRI in the prediction of clinically significant disease. It may have a value in patients with indeterminate result on mp-MRI to decide whether or not to proceed for prostate biopsy.

# Chapter 8

## Further discussion

## Summary of results and clinical implications

In an era of over-diagnosis and over-treatment of prostate cancer with a lot of conflict on which is the best diagnostic pathway, it was important to run our study. In most of diagnostic pathways, an imaging study is used before attempting to perform organ biopsy. This is used to rule in/out as well as target visible lesion on imaging with biopsy. Prostate cancer is one of the few diseases, if not the only one, where prostate biopsy is performed before imaging. Therefore, it was important for us to try to see whether mp-MRI could have a role in changing this diagnostic pathway.

We hypothesized that mp-MRI has an accurate performance in the diagnostic pathway of prostate cancer. In order to pursue this hypothesis, we tested the performance of mp-MRI at detection (confirm or rule out), localization (registration against an anatomical reference, TPM) and characterization (predicting tumour grade and volume) of prostate cancer over four different patient populations. This is including patients with no prior prostate biopsy, patients that had previous negative TRUS-guided biopsy, patients that had prior positive TRUS-guided biopsy then went for re-classification of their prostate cancer disease and finally patients that had biochemical failure after treatment with radiotherapy. We chose to use MRI in its multiparametric form based on recommendations from more than one consensus group (40, 45).

Our way of dividing patient population into four homogenous groups of patients gave us the chance to explore the performance of mp-MRI among different patient populations separately without having any contamination by including heterogenous groups of patients. Inside each group (chapters 3-5), we stratified target conditions based either on the Gleason grade, the maximum cancer core length or both combined.

As we discussed before, both TRUS-guided biopsy and RP have some drawbacks as a reference standard because of the inherent random and systematic errors of the former and the selection bias of the latter. Twenty five percent of cancers are being missed with the initial TRUS-guided biopsy (180), and detection rate becomes lower with repeat biopsies (244, 245). Concordance between TRUS-guided biopsy detected Gleason score and RP was only found in 30-58% (246, 247). Theoretically, RP would have been the best reference standard if it can be applied to all patients in a study however, clearly, this is not possible as some patients would opt for other modalities of treatment and some will not even have a positive biopsy to justify treatment. We chose a test that can systematically sample the prostate, including areas that are usually missed by TRUS sampling, and can be applied to all men in a study- that is TPM biopsy.

In the first two studies, six different definitions of clinically significant disease were used as target conditions. We tested mp-MRI performance against combined disease grade and volume (UCL definitions 1 and 2) then individually against either grade (Gl ≥4+3 and Gl ≥3+4) or volume (CCLmax ≥6mm and CClmax ≥4mm). We also ran the test for "Any cancer" detected at TPM biopsy. In the third study, we used different definitions (definitions 1-4) of low risk disease on TRUS-guided biopsy. These were derived from criteria being used in different active surveillance programs. In our last study, our target condition was "Any cancer" as there is no consensus on the clinical significance of locally radio-recurrent prostate cancer. This is due to the difficulty to assess the Gleason grade of cancer on biopsy secondary to the radiotherapy effect.

It was essential to start with patients that had no prior prostate biopsy or treatment. Imaging of such patients does not show the possible artifact from previous biopsy or prostate cancer treatment and so the performance of a diagnostic test, as mp-MRI, is expected to be ideal. We demonstrated that mp-MRI has a NPV of 89-100% and a sensitivity of 93-100% for ruling out clinically significant disease, with negative MRI defined as score 1 or 2/5). In this group, none of the tumours with Gleason score 4 were missed and chances to be free from Gleason score 4, CCLmax <6mm and CCLmax <4mm were 93%, 98% and 94%, respectively. This, in effect, could lead mp-MRI be used as a triage test where deferring a biopsy would be a safe choice for the patient. AUROC for different definitions of clinically significant disease at mp-MRI score 1-5 ranged from 0.71-0.80. Our near 50% positive predictive value in this population means that mp-MRI could be used to target specific lesions within the prostate.

It was then important to explore the performance of mp-MRI in patients with previous negative TRUS-guided biopsy as they represent a real challenge to urologists. We tried to see whether mp-MRI would be able to solve this puzzle and either confirm the absence of clinically significant cancer or perhaps discovering one in an area that was missed on the previous TRUS-guided biopsy. In our population, anterior tumour only was found in nearly half of patients with positive biopsy (47%), whereas combined anterior and posterior tumours and posterior tumours only were found in 44% and 9%, respectively. Sensitivity and NPV for clinically significant disease were 74-100% and 79-100%, respectively. AUROC for different definitions of clinically significant disease at mp-MRI score 1-5 ranged from 0.68-0.80. These results are comparable to our previous results in patients with no prior prostate biopsy. None of the tumours, again, with dominant Gleason 4 component were missed on mp-MRI and chances to be free from Gleason score 4, CCLmax <6mm and CCLmax <4mm were 87%, 89% and 74%, respectively. These results also are similar to those of the previous study. They all confirm that mp-MRI can be used as a triage test to rule

out the presence of clinically significant disease with accurate detection and localization of prostate cancer.

It is clear that detection of prostate cancer via mp-MRI relies not only on Gleason score (248-250) but also on the cancer size (85, 248, 249). Tumours of small size (<0.2cc) are difficult to detect whereas those of larger size (>0.5cc) are easily detected. Likewise, tumours of Gleason 3+3 are less likely to be detected in comparison to those of predominant Gleason 4 component.

Accurate localization of prostate cancer on mp-MRI may help better targeting of suspicious lesions at biopsy (124, 251-255). It also helps planning for focal therapy of the index lesion, the most aggressive one.

Prostate cancer is known to be a slowly progressive disease where patients usually die with, rather than from, it. This has made active surveillance a viable option in patients with low-intermediate risk disease (23). Accurate characterization of this cancer is of utmost importance before advising the patients to choose this treatment pathway. Failure was found to be mainly due to improper disease characterization rather than true progression (207). We tried to explore whether mp-MRI could have a role in this setting. In a population with previous positive TRUS-guided biopsy (n=194), we tried to see how far mp-MRI can confirm the presence of low-risk or predict upgrading of prostate cancer disease. We used 4 different definitions to define low-risk disease, using characteristics from various active surveillance programs. All lesions with predominant Gleason 4 component were detected on Mp-MRI. Out of the 58 patients with upgraded disease to Gl 3+4, 54 had an mp-MRI score of ≥3. Mp-MRI showed a NPV for non-upgrade/upsize of prostate cancer disease between 75-100% amongst the 4 definitions we used to define low-risk disease. Lesions not detected on mp-MRI and scored 1-2/5 (n=6) were not upsized to >50% of cancer core length at TPM biopsy and were upgraded in only a small number of patients. Also, when we used several criteria for low-risk disease (definition 4), none of the patients scored 1-2/5 (n=4) on mp-MRI were upgraded/upsized.

We extended our research around the role of mp-MRI in prostate cancer diagnosis to patients that developed biochemical failure after radiotherapy. Most of the studies published in this context either used heterogeneous patient population with previous EBRT+BT (174, 221) or used TRUS-guided biopsy/RP as a reference standard. We also had a chance to explore the added benefit of functional mp-MRI sequences to standard T2-weighted imaging in ruling in/ruling out prostate cancer. Our results show that the addition of functional MRI sequences to the basic T2-weighted imaging improved the performance of readers for the detection of radio-recurrent prostate cancer. However, we could not find any significant change of

performance after adding ADC to T2-weighted imaging + high b-value. Adding DCE imaging to T2-weighted imaging + DWI increased the sensitivity of mp-MRI however this increase was not statistically significant from T2-weighted imaging + high b-value. This has a great implication on time and cost as T2-weighted imaging + high b-value might be all that is necessary to scan this group of patients. However larger studies are needed before this can be adequately validated.

We finally explored the potential value of interpreting the PSAD with the result of mp-MRI to predict the presence or absence of clinically significant disease (chapter 7). We found no statistical significant difference between the combination of the two versus the mp-MRI alone. However PSAD could serve as a good positive test in patients with indeterminate results on mp-MRI.

## Limitations and future recommendations

The main limitation of our study is the retrospective design. The four studies show the real life experience of reporting mp-MRI for patients with either a suspicion, based on clinical data, or a diagnosis, based on previous positive TRUS-guided biopsy, of prostate cancer. Several radiologists reported studies in chapters 3, 4 and 5. We did this, as one of the major critiques of mp-MRI 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. Prospective study would have been more ideal. However, retrospective analysis allowed us to explore the performance of mp-MRI in different groups of patients; patients with no prior biopsy, prior negative biopsy, prior positive TRUS-guided biopsy and those with biochemical failure after radiotherapy. It also enabled us to include more patients within our study away from the strict rigid protocols of prospective studies. On the other hand, in our last group of patients (those with biochemical failure after radiotherapy, chapter 6), only two radiologists prospectively reported the mp-MRI images.

Our cohorts may have encountered workup bias. Although some patients with mp-MRI score 1-2/5 throughout the prostate might still have proceeded to TPM biopsy due to the continued high clinical suspicion, others might have opted out from further diagnostic testing or chose to have TRUS-guided biopsy. As a result, more patients with mp-MRI score 3-5/5 were included. This led to a high prevalence of disease among our patient populations, especially with using TPM biopsy as a reference standard with higher cancer detection rate than TRUS-guided biopsy. Since prevalence was high, one would expect to see a low NPV within our results. However our NPV was consistently high for different definitions of clinically significant disease and also for any cancer (patients with biochemical failure after radiotherapy). In order to mitigate this un-avoidable bias in our studies, we ran our analysis

at the prostate half level. This gave us a balanced ratio between the positively and negatively mp-MRI scored prostate halves. Although high prevalence is known to affect positive and negative predictive values, our NPV was consistently high among the four different groups of patients.

Despite the fact that template biopsies perform well for the detection of significant disease (both in theoretical studies and in practice (256), with figures of up to 87% for the detection of significant tumour), they are arguably less accurate than radical (or salvage) prostatectomy, and we used a core biopsy technique to estimate tumour significance. Although the technique for doing so has been validated (168), it introduces another potential source of error. Although it is known that no biopsy is free from sampling error (201), we used TPM to address as much of the systematic error that is inherent to TRUS-guided biopsy (134). Ideally, radical (or salvage) prostatectomy specimen would have been more accurate and informative if available, however, as discussed before, it cannot be applied to all men under the study. Also in our last group of patients with radio-recurrent prostate cancer, salvage prostatectomy is known to be a technically difficult operation.

We did not evaluate the data from targeted biopsy separately, as this was beyond the scope of our studies. Our studies were designed to ensure that the two tests – the index test under evaluation (mpMRI) and the reference test (TPM biopsy) – were conducted independent of each other so as to minimize incorporation bias. We therefore excluded patients that did not have systematic TPM biopsy from the previously described 20 Barzel zones (129). For validating cohort studies evaluating the clinical accuracy of a diagnostic test, it must meet the highest standards as laid down by the STARD guidelines (9). These criteria aim to minimize the numerous biases that can make diagnostic studies questionable. Therefore, we chose a reference test that was independent of the index test – in line with STARD recommendations – that offered the most reliable sampling of the prostate that can be applied to all men at risk. This by general consensus is template prostate mapping using a 5mm sampling frame.

We combined results from mp-MRI of different field strengths (1.5T and 3T). This is an area of discussion at present and the technological advances that are occurring are certainly rapid. The increased field strength on our magnets is an incremental one; smaller changes occur in hardware and software in many medical devices. Studies find it difficult to incorporate separate cohorts for each change, as the results of each iteration would be out-of-date by the time they report. We decided to be pragmatic in embracing the heterogeneity of the technology provided the minimal standards of quality were maintained in both conduct and reporting. Pragmatic studies aim to reflect real practice and generally have greater external

validity. The strength of the magnet will be dependent upon local provision. Therefore, whilst we agree that some see this as a legitimate weakness and limitation, we would argue that this is a potential strength as our work is then about mp-MRI not of mp-MRI of a given field strength. Interestingly, and perhaps reassuringly, our NPV is in line with earlier studies that were undertaken on a 1.5T MRI (116).

Although it is widely recognized that not all prostate cancer requires treatment (121), 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 (12, 257).

In chapter 5 (patients with previous positive TRUS-guided biopsy), we examined the effect of mp-MRI on the presence of several adverse pathological components: grade and size, individually and combined, as well as a combination of clinical and pathological criteria. To some extent this complicates the analysis, but it reflects significant uncertainty about what factors are most important in the attribution of insignificant disease. In particular, there is growing evidence that a Gleason 4 component is a more adverse finding than a volume >0.5cc (258).

In chapters 3, 4 and 6 we based our analysis on half gland level whilst others have based their analysis on quadrants (224), sextants (174, 221) or even octants (225). We believe that increasing the number of prostatic divisions has fundamental drawbacks: First, 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 (248). Second, the clinical question is usually at the level of the prostate, or half gland – 'does this patient have disease' or 'do I only need to treat half the gland'. We analyzed the prostate in halves rather than wholes because of the high prevalence of disease in some of these cohorts, but did not divide further into sectors, and the results are therefore directly relevant to some important clinical questions (259). 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 (260).

In evaluating the performance of mp-MRI in the radio-recurrent disease setting, we did not implement separate locked sequential reads of T2-weighted + DCE or DWI + DCE as we opted to order the sequences based on potential time/financial cost associated with each additional sequence. Specifically high-b-value DWI can be performed faster than acquisition of data for a full ADC map and performance of DCE involves additional time and financial cost of the contrast agent.

*Overall*: MRI performed on standard clinical machines has the potential to fundamentally alter the clinical pathway for many men suspected of having, or who have been diagnosed with, prostate cancer.

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# Appendix

## Publications and Presentations

## Publications

A) **Publications from the thesis**:

**Abd-Alazeez M**, Kirkham A, Ahmed HU, Arya M, Anastasiadis E, Charman SC, et al. Performance of multiparametric MRI in men at risk of prostate cancer before the first biopsy: a paired validating cohort study using template prostate mapping biopsies as the reference standard. Prostate cancer and prostatic diseases. 2014 Mar;17(1):40-6. PubMed PMID: 24126797. Pubmed Central PMCID: 3954968.

**Abd-Alazeez M**, Ahmed HU, Arya M, Charman SC, Anastasiadis E, Freeman A, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level--can it rule out clinically significant prostate cancer? Urol Oncol. 2014 Jan;32(1):45 e17-22. PubMed PMID: 24055430.

**Abd-Alazeez** M, Ahmed HU, Arya M, Allen C, Dikaios N, Freeman A *et al*. Can multiparametric magnetic resonance imaging predict upgrading of transrectal ultrasound biopsy results at more definitive histology? *Urol Oncol* 2014; **32**(6)**:** 741-747.

B) **Publications related to the thesis**:

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 Mar;189(3):860-6. PubMed PMID: 23063807.

Dikaios N, Alkalbani J, Sidhu HS, Fujiwara T, **Abd-Alazeez M**, Kirkham A *et al*. Logistic regression model for diagnosis of transition zone prostate cancer on multi-parametric MRI. *Eur Radiol* 2014.

## Presentations

1. Abstract accepted and I presented at **AUA 2014**: Title: "Multi-parametric MRI for detection of radio-recurrent prostate cancer: what constitutes an optimal dataset? The Journal of Urology, Volume 191, Issue 4, Supplement, April 2014, Pages e589-e590. Authors: **Mohamed Abd-Alazeez**, Navin Ramachandran, Nikolaos Dikaios, Hashim Ahmed, Mark Emberton, Alex Kirkham, Manit Arya, Alex Freeman, Shonit Punwani.
2. Abstract accepted and I presented at the **British institute of Radiology (BIR) Feb 2014** and **AUA 2013**: Title: "Can MRI predict upgrading of TRUS biopsy results at more definitive histology?" The Journal of Urology, Volume 189, Issue 4, Supplement, April 2013, Pages e602-e603. Authors: Mohamed Abd-Alazeez, Hashim Ahmed, Manit Arya, Clare Allen, Alex Freeman, Mark Emberton, Alex Kirkham.
3. Abstract accepted and I presented at **IPEM 2012** "Advancements in Body MRI: clinical applications and new techniques" in London: Title: "Derivation of a quantitative multi-parametric MRI diagnostic model for determination of peripheral zone prostate cancer".
4. Abstract accepted and I presented at "**BAUS 2012**": Title: "Can Multi-parametric MRI prior to first TRUS biopsy rule out clinically important prostate cancer? A validating cohort study using template prostate mapping as a reference test".
5. Abstract accepted and presented at **Focal Therapy and Imaging in Prostate and Kidney Cancer** conference in **Durham/USA 2012**. Title: "Can multiparametric MRI accurately detect local prostate cancer recurrence in patients treated with radiotherapy, before focal salvage therapy?"
6. Abstract accepted and I presented at **AUA 2012**: Title: "The role of multiparametric MRI in men with negative biopsy and elevated PSA - can it rule out clinically significant disease?" The Journal of Urology, Volume 187, Issue 4, Supplement, April 2012, Page e585. Authors: **Mohamed Abd Alazeez**, Hashim U. Ahmed, Caroline Moore, Alex Freeman, Clare Allen, Alex Kirkham, Mark Emberton.
7. Abstract accepted and I presented at the "**SIU**" in **October 2011**: Title: "Can targeted transperineal biopsy, based on lesions seen on pre-biopsy multiparametric MRI, be used to detect significant prostate cancer?"
8. Abstract accepted and I presented at **BUG meeting** in **September 2011**: Title: "The Role of Mp-MRI in the Detection of Prostate Cancer". This was one of the best three abstracts accepted for oral and poster presentation. Clinical Oncology, Volume 24,

Issue 2, March 2012, Page 154. Authors: **M. Abd Alazeez**, H. Ahmed, C. Moore, A. Kirkham, A. Freeman, M. Emberton.

9. Abstract accepted and I presented at **Focal Therapy and Imaging in Prostate and Kidney Cancer** Conference in **Amsterdam May 2011**: Title: "Can pre-biopsy mp-MRI be used to preferentially detect significant prostate cancer?" Urology, Volume 78, Issue 3, Supplement, September 2011, Page S42. Authors: **M. Abd Alazeez**, C. Moore, H.U. Ahmed, M. Arya, A. Freeman, A. Kirkham, C. Allen, M. Emberton.
10. Association of level of suspicion of prostate cancer on multi-parametric MRI with detection rate of prostate cancer. European Urology Supplements, Volume 12, Issue 1, March 2013, Pages e218-e219. Authors: V. Kasivisvanathan, R. Dufour, C.M. Moore, H.U. Ahmed, **M.A. Abd-Alazeez**, S. Charman, A. Freeman, A. Kirkham, C. Allen, J. Van Der Meulen, M. Emberton.