DOCTOR OF MEDICINE

Multiparametric MRI and MRI/US fusion guided biopsy in the diagnosis of prostate cancer

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Multiparametric MRI and MRI/US fusion guided biopsy in the diagnosis of prostate cancer

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by

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ABSTRACT

Background

Established diagnostic pathway for detection of PCa, based on non-targeted gland sampling, has many limitations. There is strong evidence that Multiparametric MRI (MP MRI) performed prior to prostatic biopsy reduces unnecessary biopsies and over diagnosis of clinically insignificant disease as well as improves detection of clinically significant (CS) prostate cancer (PCa). At the time of writing of this thesis, pre-biopsy MP MRI has already been incorporated into the recommended diagnostic pathway for urgent suspected PCa as per NICE 2019 guidance. Although there is growing body of research on the subject, there are still areas, which lack high level data from randomised trials and studies, using radical prostatectomy (RP) specimen as a gold standard.

This thesis aimed to investigate the ability of MP MRI to detect foci of CS PCa at per-lesion level, in comparison with RP specimen and to assess the added value of MR guided targeted biopsies, in addition to standard trans rectal (TRUS) biopsies, in confirming the presence of CS disease in a setting of a randomised controlled trial.

Methods

The data were collected during prospective, multicentre parallel-group study with subgroup randomization, which has been granted all the necessary approvals including registration at CLINTrials.gov, NCT02745496.

It comprised of two main parts:

A prospective study on 89 patients suspected of having PCa, with subsequent positive pre-biopsy MP MRI, who underwent RP as a curative treatment option. In this group, diagnostic accuracy of MP MRI in detection of PCa and CS PCa with gold standard of histology of RP specimen on per-lesion and per-patient levels were performed, using customised molds for precise correlation;

Added value of MR guided targeted biopsy was assessed in a setting of a prospective randomized controlled trial of 603 patients, suspected of having PCa and with positive MP MRI (assessed using PIRADS v2 system), who underwent either MRI-

trans rectal US fusion targeted biopsy (FUS-TB) used in conjunction with TRUS biopsies or standard of care TRUS biopsies alone.

Results

A total of 624 biopsy-naïve participants with clinical suspicion of organ-confined PCa were enrolled into the study over a period of 66 months (February 2015-August 2020). 603 participants underwent pre-biopsy MP MRI and those with positive MP MRI result (413/603) were subsequently randomised to undergo either TRUS/FUS-TB biopsies (intervention) or TRUS biopsies (standard of care).

89 participants with positive MP MRI, who opted for RP as a curative treatment option, had their MP MRI compared to RP specimen using customised molds, enabling lesion-level analysis. This revealed high sensitivity of pre-biopsy MP MRI in detection of foci of CS PCa of 72%, with relatively high specificity of 71% and reassuringly balanced PPV and NPV of 78% and 64.1% respectively, when comparing to RP specimen as a gold standard.

91% of all PIRADS 5 lesions, 77% of all PIRADS 4 and 48% of all PIRADS 3 lesions corresponded to CS PCa foci on RP.

Majority of PCa foci missed on MP MRI were non-significant (NS) PCa, the CS PCa missed were in large proportion situated in the anterior half of the gland and smaller than 15 mm in size.

TRUS/FUS-TB pathway detected CS PCa in 130/207 (62.8%) patients, 28/130 (21.5%) by FUS-TB only, 17/130 (13%) by TRUS only and 85/180 (65.3%)by both techniques combined and NS PCa in 21/207 patients (10.1%). The MP MRI positive TRUS alone arm had detected 106/206 CS PCa (51.4%) with 18/206 (8.7%) of NS PCa. The probability of CS cancer detection by TRUS/FUS-TB pathway was statistically significantly higher (p=0.002) than by control TRUS only arm.

The safety profile and reported side effects of the combined biopsy approach was clinically no different than standard TRUS pathway.

Negative MP MRI performed prior to biopsy in biopsy-naïve men, with clinical suspicion of PCa, would have allowed 28% men to avoid biopsy with a risk of missing CS PCa in 5.7% of those patients.

Conclusions

Pre-biopsy MP MRI detected CS PCa with high sensitivity and specificity and avoided over detection of NS PCa (only 4% of NS PCa seen on pathology were detected on MP MRI). The CS PCa missed on MP MRI were in large proportion small and /or situated in the anterior half of the gland.

Combined TRUS/FUS-TB pathway in MP MRI positive patients had significantly higher detection rate of CS PCa than TRUS biopsy alone pathway with a small increase in NS PCa detection as an expense. FUS-TB biopsy alone was non-inferior to TRUS biopsy in diagnosing CS cancer with an added benefit of less cores.

Not performing TRUS in MP MRI negative group would have saved 28% biopsies with a cost of missing CS PCa in 5.7% patients.

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DECLARATIONS

I, Magdalena Joanna Szewczyk-Bieda, hereby certify that this thesis is written by me, my own work and has not been submitted in any other degree qualification except as specified. The study on which the thesis is based is a joint research and my individual contribution is listed in appendix D1

Signature of candidate

Electronically signed by Magdalena Szewczyk-Bieda-14th February 2022

I confirm that Magdalena Szewczyk-Bieda has completed the minimum duration of registration of study at the University of Dundee and has fulfilled the conditions of the University of Dundee, thereby qualifying her to submit this thesis in application for the degree of Doctor Of Medicine

Signature of supervisor

Electronically signed by Ghulam Nabi -14th February 2022

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ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
AE	Adverse events
AS	Active surveillance
AUROC	Area under the receiver operating characteristics curve
BAUS	British association of Urological Surgeons
BP	Bi-parametric
BPH	Benign prostatic hypertrophy
CDR	Cancer detection rate
CI	Chief Investigator
COG-TB	Cognitive targeted biopsy
CRF	Case report form
CS	Clinically significant
CZ	Central zone
DCE	Dynamic contrast Imaging
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
EAU	European association of Urology
ESUR	European Society of Uroradiology
FUS-TB	MRI-trans rectal US fusion targeted biopsy
FGB	Fusion guided biopsy
GCP	Good clinical practice
GG	Gleason grade
GPS	Global positioning system
GS	Gleason score
HIC	Health Informatics Centre
HRA	Health Research Authority
K trans	constant of the contrast agent

L	left
LMW	Low molecular weight
MD	Doctor of Medicine
MP MRI	Multiparametric Magnetic resonance imaging
MRI	Magnetic Resonance Imaging
MR-GB	MR guided biopsies
MRS	MR Spectroscopy
MULTIPROS	Acronym of the research study
NHS	National Health Service
NICE	National Institute for Health and Care excellence
NPV	Negative predictive value
NS Pca	Non-significant Prostate cancer
Pca	Prostate cancer
PIN	Prostatic intraepithelial neoplasia
PIRADS	Prostate Imaging and Reporting Data System
PPV	Positive predictive value
PSA	Prostate specific antigen
PZ	Peripheral zone
RCR	Royal College of Radiologists
REC	Research Ethics Committee
RF	Radiofrequency
R	Right
ROI	Region of interest
RP	Radical prostatectomy
SAE	Significant adverse events
SC	Standard of care
SE	Spin Echo
SPACE	**S**ampling **P**erfection with **A**pplication optimized **C**ontrasts using different flip angle **E**volution

STR	Signal to noise ratio
TCTU	Tayside Clinical Trials Unit
TNM	Tumour, Node and metastasis
TPM	Transperineal mapping biopsy
TRUS	Trans rectal ultrasound guided biopsy
TZ	Transitional zone
UK	United Kingdom
US	Ultrasound
US-GB	Ultrasound guided biopsies
VIBE	Volumetric interpolated breath-hold examination

1. INRODUCTION

The established diagnostic pathway for prostate cancer (PCa) based on prostate gland sampling by trans rectal US-guided (TRUS) biopsy has many limitations, including high incidence of false negative biopsies (21-23%), need for repeated biopsies, under grading of the disease and over diagnosis of clinically insignificant disease leading to overtreatment (1-4).

Over the last 10 years, we have witnessed a beginning of transformation of the PCa diagnostic pathway into a new, tailored triage and accurate risk-assessment. An alternative pathway has emerged, comprising pre-biopsy multiparametric magnetic resonance imaging (MP MRI) and image-guided targeted biopsies, with growing body of evidence to support it. Developments into MP MRI technique, standardization of its acquisition and reporting using standardised Prostate Imaging–Reporting and Data System (PIRADS)(5), validation of the pre-biopsy MP MRI for disease detection and characterization and subsequent evaluation of the MRI directed targeted biopsies in large trials, have shifted the paradigm of PCa diagnosis and treatment planning (6-9).

Subsequent publication of UK consensus meeting recommendations and National Institute for Health and Care Excellence (NICE) guidelines put pressure on the health providers to introduce the new pathways and deliver them to the expected standards (10, 11). There is still a huge variation in the ways, in which health boards across UK, Europe and wider world provide diagnosis for suspected PCa (12). The main challenges to overcome are around the cost, equipment, workforce and training required for new pathways implementation, maintaining standardization and quality of imaging and targeted biopsy and accreditation and training for radiologists.

Prostate Cancer UK, the leading charity for the disease in the UK, has facilitated a Freedom of Information Act research in 2018, which found that only 42% of UK NHS Boards were providing the new diagnostic pathway to the standards outlined in the guidelines. There are also inequities in relation to access to this pathway across

boards, with only 30% of eligible patients being offered the new standard of care (13, 14). The resource gap in trained and accredited radiologist workforce is being addressed by putting training and mentoring schemes, taught training courses, web based learning material in place and through encouragement of self- certification scheme with QA and audit practice (15).

In research, there are still many gaps to fill, especially from prospective studies and blinded randomized controlled trials, representing highest-level of evidence, on topics such as long term data on follow up of negative MP MRI patients and validation of recently published national and international guidelines on management of patients with suspected PCa with stratification into low and intermediate/high risk groups (16).

The proposed safety net for MP MRI negative patients, who will avoid initial biopsy and will be followed up with repeated prostate specific antigen (PSA) levels instead, need further validation (9). More research is required to validate the current version of the structured system for prostate assessment on MP MRI (PIRADS v2.1) and reveal potential limitations leading to development of PIRADS 3 version. The data on cost-effectiveness from the largest prospective studies are yet to be reported on, to assess long term cost effectiveness of the new pathway.

There is also need to develop and validate new screening strategies, based on biomarkers and personal risk assessment calculators (17), which will have an impact on the type and number of patients referred to secondary care with suspicion of PCa.

The use of dynamic contrast enhanced sequence (DCE) and its role in PCa diagnosis has been evolving since publication of PIRADS v1 in 2012 and in the current PIRADS 2.1 version is used as an adjunct sequence for certain problem solving. Many experts are advocating that biparametric MRI (BP MRI) should only be reserved for selected clinical indications, such as stable active surveillance patients and low risk biopsy naïve group (18). MRI image quality audit reported that only 53% of UK centres were routinely performing DCE despite it being recommended by guidelines (18). Further high level research is needed to place the DCE in the suspected PCa pathway.

Although there are many good quality studies looking at the detection accuracy of MP MRI in biopsy naïve group (6, 19, 20), there is still a lack of high level prospective studies directly comparing MP MRI with gold standard RP specimen on lesion to lesion basis. The radiologic/whole mount pathologic correlation is specifically important to establish which foci of PCa can and cannot be detected by MRI, in terms of lesion size, its aggressiveness (Gleason score), lesion position and dependence of the gland size (16).

A good number of prospective data are available on assessment of MR guided biopsy approaches but they relate to patients with prior negative prostate biopsy (7, 8) or place randomization point high in the diagnostic pathway, comparing groups undergoing trans rectal biopsy (TRUS) versus MP MRI and MR guided biopsy (MR GB) (7, 9). To fully validate the use of MR GB in a group of biopsy naïve patients with high suspicion of CS cancer, there is a need to design further randomized controlled studies (21). The randomization point needs to be placed lower in the diagnostic pathway, to perform MP MRI on all the participants prior to biopsy to adequately compare the diagnostic accuracy of both biopsy approaches. As concluded in the recent Cochrane review (22), the MRI pathway with targeted biopsies, omitting TRUS biopsies, misses significant cancers so including TRUS biopsy in both study arms will assess the combined pathway of MR GB biopsies in addition to systematic TRUS biopsies in MP MRI positive group (detection-focused diagnostic pathway) (23).

The research questions posed in this thesis were designed to address crucial research gaps outlined in the above paragraph and the results are aiming to add value to the existing data available.

1.1. Research questions

This thesis was designed to answer the following research questions:

1. How reliable is pre-biopsy MP MRI in identification of foci of clinically significant prostate cancer (CS PCa) in prostate gland and avoidance of over detection of foci of non-significant cancers (NSC)?

2. Will adding MR-guided targeted biopsy to standard TRUS biopsy of prostate gland detect more CS PCa than standard TRUS biopsy alone, with no significant increase of NSC detection and with similar profile of adverse events?

The investigations described in this thesis were undertaken by the author to answer the above research questions. The data were obtained during interventions performed in collaboration with other researchers/clinical teams as a part of the *MULTIPROS study* (24) supported by Prostate Cancer UK (PCUK), registered charity In England and Wales (1005541) and in Scotland (SC039332)

2. BACKGROUND

2.1. Background and diagnosis of prostate cancer

2.1.1. Pathophysiology of PCa

The prostate gland is a part of male reproductive system and is situated below the urinary bladder, surrounding the prostatic portion of the male urethra. In a healthy young male, it weights approximately 20g and is 3cm long. The gland consists of three histologically different major glandular regions, namely peripheral (PZ), transition (TZ) and central zones (CZ) with specific architectural and stromal features. The PZ and TZ originate from endoderm and consist of 70% and 25% of the gland respectively. CZ is ectodermal in origin, makes up 5% of the gland and is less likely associated with carcinogenesis (25).

The prostate has both an endocrine and an exocrine function. The former relates to the metabolism of testosterone into a more effective androgen (dihydrotestosterone). The latter, to production and secretion of prostatic fluid, containing proteins, lipids, enzymes , amines and zinc that have a protective role to the semen, by reducing the acidity of the urethra and enhancing sperm motility (26).

The glandular tissue within the prostate gland contains three main epithelial cell types: luminal, basal and neuroendocrine. The luminal cells produce secretory proteins. One of the proteins secreted is a specific glycoproteine from the family of glandular kallikreins, that is exclusively excreted by the luminal cells, known as a Prostate Specific Antigen (PSA), currently widely used in diagnosis and monitoring of prostate cancer (27). Studies have demonstrated that both luminal cells and basal cells most often serve as the cell of origin for prostate cancer, hence adenocarcinoma is the most common histological type of PCa (28). Most prostate carcinomas are acinar in origin, arising from the cells of the gland's acini and tubules. Non-acinar PCa accounts for only about 5-10% of all carcinomas originating from the prostate, with examples including sarcomatoid, ductal, urothelial and small- cell

carcinomas (29). Malignant transformation of the cells is a multistep process originating as prostatic intraepithelial neoplasia (PIN), followed by localised PCa, progressing to advanced stage and finally to metastatic PCa.

2.1.2. Epidemiology of PCa

PCa is the most commonly diagnosed male cancer in the United Kingdom (30), accounting for 26% of all male cancers, and the second most commonly diagnosed cancer in men worldwide (31), with growing incidence reported in many countries (32). 47,151 new new PCa cases were confirmed in the UK in 2015, giving an average of 129 new diagnoses every day. 1 in 8 men will be diagnosed with PCa in their lifetime. The risk of prostate cancer increases with age, with steep rise from the age of 50-54 and peak in the 75-79 age group with 35% of new cases are diagnosed in males over 75 years of age. Mortality of PCa in the UK was recorded at 10 837 in 2012 with mortality rate of 23 deaths per 100 000 men (33). 6% increase has been noted in the PCa incidence over the last decade. Expected incidence raise is projected to reach 12% between 2014 and 2035 (34).

2.1.3. Definition of Clinically significant PCa

The clinically significant (CS) cancer is a cancer in which the benefit of treatment outweighs the treatment risks.

The PCa aggressiveness is defined by the Gleason grading (GG) system, which is the most widely used system of histological patterns of prostatic adenocarcinoma. It was first described by American pathologist Donald Gleason in 1974 (35) and subsequently redefined, up to its most recent update, by consensus meeting of International Society of Urological Pathology (ISUP) in 2014 (36). It is a 5-piont scale with prognostic stratification, where 3 corresponds to the well differentiated lowest risk disease and 5 to the most aggressive disease. There are many definitions of CS PCa, but the most widely used is the definition from ISUP consensus meeting, as a

presence of GG of 7 disease in any core (ISUP grade 2).

2.1.4. PCa screening

At present, population-based screening test for detection of PCa is not available in the UK, as there is no strong evidence to support it (37). Despite publication of the results of two large cohort trials in Europe and United States on PSA-based screening (38-40), there are many controversies surrounding it, resulting in different recommendations across the globe (41-46). The results of the largest ever cluster randomized trial (CAP Trial), conducted in the UK, on single PSA testing in 419 582 asymptomatic males between the ages of 50-69, published in 2018 (47), show no long-term life-saving benefit on a median follow up of 10 years. Moreover, there is a non-negligible risk of unnecessary biopsies, over diagnosis and unnecessary treatment potentially leading to urine incontinence, erectile dysfunction and bowel problems and risk of detecting non-aggressive disease. To prevent 1 death from prostate cancer, 781 men would need to be tested and 27 of them will receive unnecessary treatment for NS disease (39).

There is a need for a new test or combination of tests, with higher sensitivity to overcome adverse events of over diagnosis and overtreatment. Large prospective population-based Stockholm-3 study, published in 2015, used a predefined risk-based model (STHML-3), including a combination of plasma protein biomarkers, genetic nucleotide polymorphisms and clinical variables to screen men ages between 50-69. The results showed that the STHML-3 model performed significantly better than PSA with higher specificity for detection of CS PCa reducing need for unnecessary biopsies and over diagnosis of NS PCa (17). This is a step towards more personalized, risk-based prostate cancer screening programme. The role of MP MRI in such a programme is not yet fully established but the preliminary results are encouraging (48).

2.1.5. Diagnostic pathways in PCa

The established, standard of care, diagnostic pathway in men suspected to be suffering from PCa comprises digital rectal examination (DRE), measurement of serum PSA level and gland sampling, using TRUS biopsy (49). There are many challenges in this approach. Despite PSA measurement being a widely used tool to diagnose PCa (49), results of a multicentre clinical trial of 6630 men showed moderate sensitivity of 75% and low positive predictive value (PPV) of 35% for PSA > 4 ng/ml in early PCa detection (50). PSA also has limited specificity, especially in early detection of PCa in men with PSA levels between 2-10 ng/ml (51).

The TRUS biopsy technique also has several limitations, including high incidence of false negative biopsies (21-23%) (1, 2), need for repeated biopsies (3), under grading of the disease (4) and the risk of overdiagnosis, with 50% detection rate of clinically unimportant disease, when considering other factors such as grade of the tumour and comorbidities (52). Limited precision of tests contributes to the high morbidity of the biopsy procedure in target disease (53) where no improvement in mortality has been seen despite increased detection rates (38).

Standard MRI using T2- weighted sequences, used primarily for local staging of the disease, has an estimated sensitivity in detection of PCa between 60-96% (54). An alternative diagnostic pathway using pre biopsy MP MRI and image guided targeted biopsy emerged in view of growing body of evidence supporting its noninferiority (6, 7). MP MRI combines standard spin echo T2- weighted sequences with functional sequences, including diffusion weighted imaging (DWI), dynamic contrast imaging (DCE) and optionally MR spectroscopy (MRS) (55). The addition of DCE improves sensitivity in cancer detection (56, 57), whereas DWI (58, 59) and MRS (60) add specificity to characterisation of the lesions.

MP MRI is assessed using standarised scoring systems to enable structured, reproducible reporting. Two most widely used systems include PIRADS and Likert scoring systems.

The improved detection of PCa has potential to reduce the need for initial or repeated biopsies and, when used in conjunction with MRI GB, reduce the incidence of false negative biopsies. The ability to characterise foci of PCa with MP MRI leads

to reduced over-detection of clinically unimportant disease and reduction of overtreatment, through facilitating better individual risk stratification, informed decision making and more tailored treatment, including focal therapy.

2.2. MP MRI in detection of PCa

2.2.1. Definition of MP MRI

The MP MRI comprises functional imaging techniques (diffusion weighted imaging, dynamic contrast enhanced imaging and optionally MR spectroscopy) in addition to conventional high resolution anatomical sequences (small field of view spin echo T2- and T1- weighted sequences (T2WS)). The functional sequences compliment the standard anatomical MRI, by adding molecular information about the prostatic tissue, such as tissue cellularity, vascularity and metabolites concentrations (61).

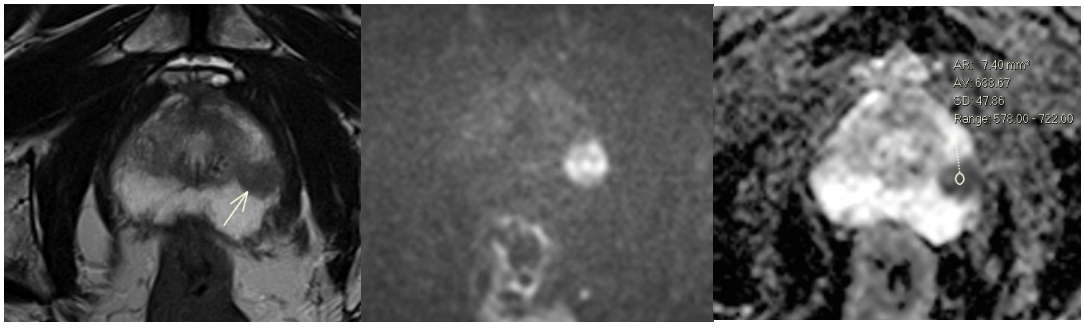
2.2.2. Diffusion weighted imaging (DWI)

The principles of DWI

Molecular diffusion (brownian motion) was first described in 1827 by John Brown and relates to a random, unrestricted, three-dimensional displacement of molecules agitated by thermal energy (62). In a biological tissue, this motion is impended by the presence of cell membranes, tissue compartmnents and intracellular organelles. The technique of DWI enables assessment of cellularity of the tissue and integrity of cell membranes by measuring the differences in motion of water molecules between the cells and displaying it as mathematically calculated apparent diffusion coefficient map (ADC). The DWI sequence was initially described by Stejskal in 1965 as an adaptation of T2 weighted sequence (63). In order to measure the water diffusion and generate a DWI image, two radiofrequency (RF) pulses (a 90°pulse followed by 180° pulse) and two gradients (dephasing and rephrasing) are applied. In the tissues with limited water movement, such as highly cellular tumours, the effect of the first gradient is cancelled out by the second gradient so the T2 signal is maintained

(Figure 1b). In the contrary, in tissues with unimpended water movement, the water molecules travel long distances between both gradient applications, resulting with lack of re-phasing and consequent reduction in overall T2 signal intensity (64). The strength and gradient used to generate the DWI is reflected by a factor called the **b-value**. The higher the b-value, the higher the strenght of the dephasing gradient applied (65). The choice of the b-values depends on the tissue being imaged. In the standard DWI acquisition in the MP MRI prostate imaging protocols, three strenghts of the dephasing gradient (b-vaules) are sequentially applied, including low b value (0-100 sec/mm2), intermediate b-value (400-800 sec/mm2) and so called high b-value (1000-2000 sec/mm2). In the high b-value image (Figure 1b), the high-cellularity tissue will retain their high signal intensity, while the low-cellularity tissues will show a complete signal drop off, resulting in a high contrast resolution between the two tissue types. High b-value image is therefore the most useful in clinical assessement of the prostate and allows differentiating tumour from normal glandular prostatic tissue with intrinsic high signal on DWI, especially in TZ . Due to higher cellularity of glandular tissue in the TZ, the DWI plays supplementary role in its assessment, with T2WI remaining the primary sequence.

To enable quantitative assessement of the DWI image, an apparent diffusion coefficient (ADC) map is automatically calculated by the computer software, using data from acquisitions using different b-values (Figure 1c). ADC is displayed as a graphic representation reflecting the differences in tissue diffusity at different b-values.



A B C

Figure 1 Axial T2 (A), high B-value DWI (B) and ADC map (C) image of prostate. Lesion of high suspicion of being clinically significant cancer (white arrow). The lesion is of low signal on T2 with corresponding high signal on high b-value image and signal drop on the calculated ADC map

Clinical use of DWI

The DWI sequence was initially used in neuroradiology in delineation of ischaemic stroke and differentiation of intracranial tumours (66), but subsequently its applications were broadened to include, among others, the prostate gland. Gibbs et al (67) were the first to obtain DWI of human prostate in vivo, enabling quantification of ADC maps in normal and pathological tissue. Hosseinzadeh et al (68) subsequently demonstrated differences in ADC values between malignant and benign prostatic peripheral zone tissue, which has been further confirmed in multiple studies (59, 69, 70). Currently, DWI is a key component to MP MRI examinations of the prostate and is considered the primary determining sequence in assessment of the PZ, with intrinsically low tissue cellularity, and supplementary sequence in assessment of lesions in TZ, according to widely used PIRADS classification (71) (Table 1).

PIRADS SCORE	**PZ and TZ lesions on DWI**
1	No abnormality on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI; < 1.5cm in greatest dimension
5	Same as 4 but >= 1.5cm in greatest dimension or definite extraprostatic extension/invasive behaviour

Table 1 Appearances and signal characteristics of PZ and TZ lesions on DWI sequence

Role of DWI sequence in detection of CS PCa

Functional imaging with DWI, which assesses restriction of motion of water molecules within a tissue, adds specificity to lesion characterization. PCa has lower ADC values than normal prostatic tissues due to higher tissue cellularity. ADC values were also shown to correlate with tumour aggressiveness (GG). For example, Hambrock et al (72) showed a high discriminatory performance of DWI in differentiation between low-, intermediate- and high- grade cancer, with statistically significant differences of median ADC values between these three groups. Several studies published to date have assessed the relationship between ADC value and GG most which report moderate to strong correlations between them (73-75).

Several studies have been published calculating sensitivity and specificity of DWI in distinguishing between high/intermediate and low GG tumours. The results vary, depending on selected cut-off points for ADC values and b-values, which reflect the strength of the diffusion-sensitizing gradients, used during the sequence acquisition. Among the studies using RP specimens as a gold standard, sensitivity of DWI in differentiating between significant and indolent PCa ranges between 62-84%, with specificities of 66-93% (73, 76-80).

Various factors influence quantitative assessment of the ADC, such as field strength, inter-patient or inter-scanner variability, different models to fit the data. Especially, the choice of b-values influences ADC measurements of the tissue (81), which suggests that unification of b-value selection will be needed before a validated cuff-off value of ADC in distinguishing between CS and NSPCa is established.

2.2.3. Dynamic contrast enhanced imaging (DCE)

The principles of DCE

Angiogenesis is an essential process for growth and spread of cancerous tissue and has important prognostic considerations for overall survival (82). Indirect and non-invasive assessment of tissue vascularity in vivo is possible using MRI technique called dynamic contrast enhanced (DCE) imaging, where a sequential acquisition of gradient echo T1 weighted images during the passage of low molecular weight

(LMW) contrast medium (> 1kDa) through the tissue of interest is performed (61). The LMW gadolinium-based contrast medium has paramagnetic quantities, which shortens the T1 relaxation time resulting in tissue enhancement. The behaviour of the LMW contrast medium in the tissue is determined by three factors: blood perfusion, transport of contrast agent across the walls of the vessel and diffusion of the contrast into the interstitial space. The LMW contrast agent does not cross the cellular membrane.

Assessment of the differences of contrast behaviour in the microcirculations of the benign and malignant tissue aids tumour detection (83, 84). The analysis of the enhancement pattern can be performed using 3 approaches: qualitative (visual), semi-quantitative (graphs) and by calculation of quantitative parameters such as micro- vessel perfusion, permeability and extracellular leakage within the tissue, which was shown to aid differentiation between benign and malignant tissue (85).

Qualitative approach

Qualitative (visual) approach is the most accessible and least standardized method. It is based on the general observed feature of cancers having more leaky vessels and increased vascularity than normal tissue, hence PCa is expected to show early, rapid, high enhancement and relatively fast wash-out after contrast injection (Figure 2). Although this method is subjective, limited by inter-observer variability and an overlap between enhancement patterns in benign and malignant tissue, especially in the TZ, it is used as a supplementary tool as a part of PIRADS v. 2 and v 2.1 assessment of the PZ (Table 2)due to lack of complexity and good reproducibility (71)

score	DCE assessment for Peripheral zone
(-)	No early enhancement or diffuse enhancement not corresponding to a focal finding on T2WI and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WE
(+)	Focal and earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and, corresponds to suspicious finding on T2WE and/or DWI

Table 2 PIRADS v2.0 assessment of lesions on DCE sequence

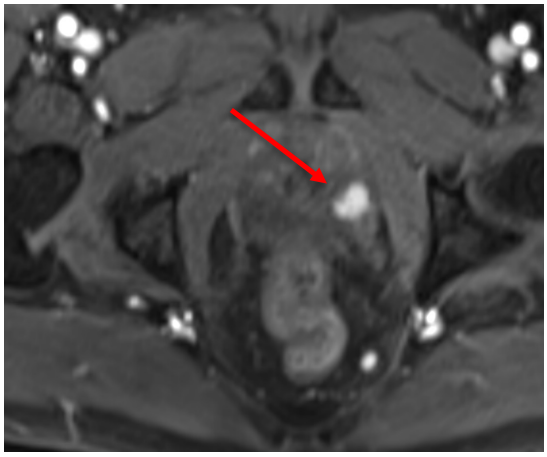


Figure 2 DCE Axial T1 VIBE Acquisition 30s following administration of LMW contrast showing an area of focal and early enhancement (red arrow) corresponding to a suspicious PIRADS 5 lesion

Semi-quantitative assessment

Semi-quantitative analysis of signal intensity changes is performed by generating the T1-weighted kinetic enhancement time-intensity curves. The shape of the time-intensity curve is characterized further, using various parameters, such as: time to peak, maximum slope, peak enhancement, area under the curve (AUC) and wash-in and wash-out curve shape and gradients. There are three common dynamic curve types described (Figure 3): Type 1-persisent increase; Type 2- plateau; Type 3-rapid decline after initial upslope, with the third type being most typical for PCa (86). Relative peak enhancement was reported to be the optimal parameter for discrimination between benign and malignant tissue in the PZ (87).

Although semi-quantitative approach is widely used and was incorporated into PIRADS v.1 classification system (5), its limitations relate to inter-scanner differences in the curve metric, caused by alteration of MR signal intensity due to lack of standardization of the imaging parameters used, and hence it was omitted in PIRADS v 2.0 and 2.1 upgrade.

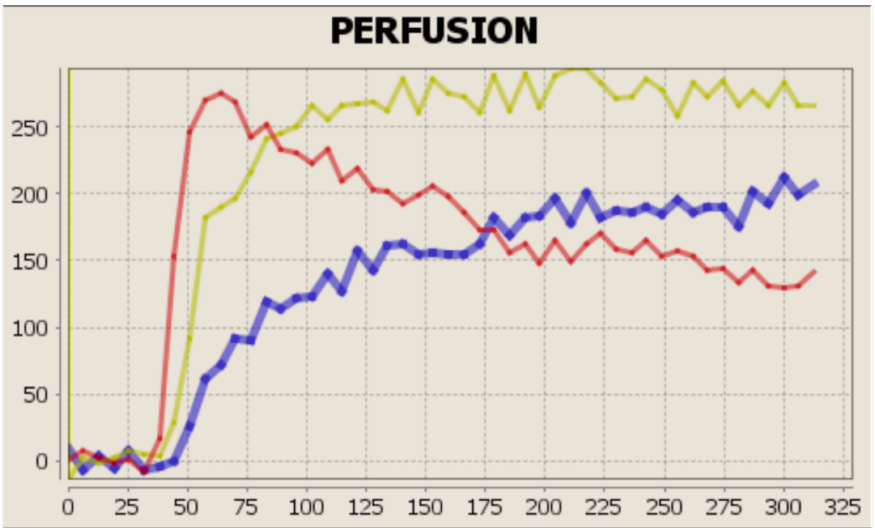


Figure 3 DCE Enhancement curves types.

Type 1 (blue graph) -persistent increase; Type 2 (yellow graph)- plateau; Type 3 (red graph)-rapid decline after initial upslope

Quantitative assessment

Quantification of LWM contrast agent concentration changes in the tissue can be assessed using pharmacokinetic modelling techniques (83). Concentration-time curves are mathematically fitted into one of the recognized mathematical models and various quantitative parameter are derived, such as volume transfer (influx) constant of the contrast agent (K^{-trans}), efflux rate contrast (K_{ep}), leakage space (V_e) (88). Many different models have been described, including basic and more complex second generation models, but the most commonly used models in prostate imaging include the Tofts-Kermode, extended Tofts, Lawrence-Lee and Lawrence-Lee delayed models (89).

Many studies show a clear distinction between a benign and malignant tissue in those parameter values and K^{-trans} is considered the most cogent DCE quantitative parameter (74, 90). A study from my research group has confirmed that the K^{-trans} value derived from the Lawrence-Lee delayed model presents a good performance accuracy in distinguishing low-grade PCa (Gleason score = 3+3) from high-grade PCa (Gleason score ≥ 3+4) (Figure 4) (91)

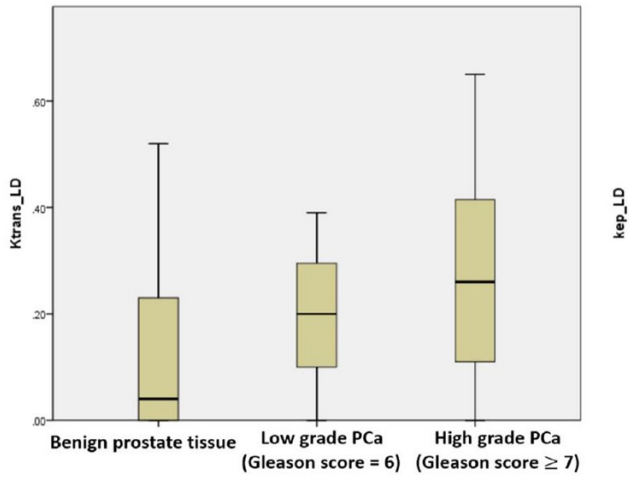


Figure 4 The boxplots of K^{trans} derived using Lawrence-Lee delayed model showing performance in low grade vs. high grade prostate cancer [Wei et al, Oncotarget 2018 Mar 23;9(22):15997-16007] (91).

The clinical use of pharmacokinetic modelling is limited due to its complexity and inherent limitations. Each model makes a lot of assumptions that may not be fit with the tissue or tumour type (modelling error) and the data obtained may not fit the model chosen (83).

Clinical use of DCE

The technique of DCE was established in breast and musculoskeletal tumours imaging (92, 93) but its clinical applications were subsequently broadened to include a variety of organs, including prostate gland (84, 94). The first studies reporting the use of DCE in staging and detection of PCa date back to 1995 (94, 95).

The role of DCE sequence in detection of CS PCa

DCE sequences assess the permeability of the blood vessels within a tissue, adding sensitivity to MRI for PCa detection (96, 97).

Presence of enhancement however is not definitive for CS PCa and lack of early enhancement does not exclude its presence.

DCE, alongside DWI become equally important part of PIRADS v.1 assessment tool but the subsequent update to PIRADS version 2 in 2015 has diminished its role to be

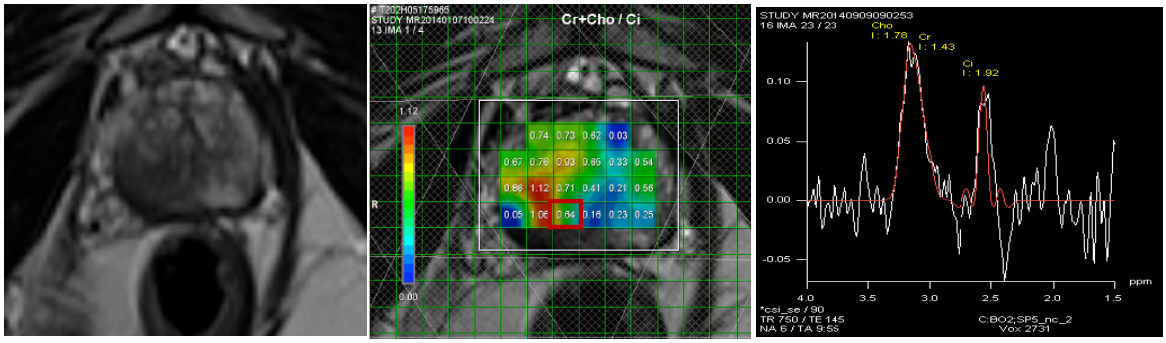
used as a problem solver in equivocal lesions situated in the PZ (71). Semi-quantitative analysis with time-intensity curves, incorporated into PIRADS v.1 has been replaced with qualitative visual assessment of early focal enhancement. Due to the lack of peer reviewed published data the qualitative assessment using kinetic models has not been recommended by the expert consensus for routine clinical use. There is lack of prospective randomized controlled trials comparing the detection rate of CS PCa using PIRADS scoring system with and without DCE but it is recommended in PIRADS v2.0 guidelines that DCE is included in all prostate MP MRI detection protocols and presence of focal early enhancement is scrutinised and compared with DWI and T2WI and to act as a safety net for false negative results and when DWI or T2WI are degraded by artefact and non-diagnostic.

The data on the role of DCE in assessment of PCa aggressiveness at 1.5T are inconsistent. Two semi-quantitative parameters, wash-in and wash-out times and the quantitative parameter, K^{trans} derived at 3T, have been shown to have high discriminatory performance in differentiating between low-, intermediate- and high grade PCa, hence helping to assess aggressiveness of PCa within PZ tumours (98). Oto et al suggest however, that there is no significant correlation between quantitative DCE parameters and GG (99) while the study of Peng et al (74) demonstrated a moderate correlation between the quantitative pharmacokinetic parameter, transfer constant (K^{trans}) and GG and Chen et al reported a significant correlation between one of the semi-quantitative parameters (washout gradient) and tumour aggressiveness (98).

2.2.4. Magnetic Resonance Spectroscopy (MRS)

Spectroscopic imaging is a technique that obtains metabolic information (spectra) of relative concentrations of various metabolites in the cell cytoplasm and the extracellular space (100). In prostate, preliminary data suggested that the MRS improves specificity of MRI in detection of PCa (60).
In 1996, Kurhanewicz et al reported statistically significant differences in metabolite concentrations between normal and cancerous prostatic tissue, with markedly lower

citrate levels and higher choline levels in the latter (Figure 5) (101). Significant correlation between metabolic parameters measured by MRS at 3Tesla field strength (3T) (choline + creatinine/citrate [CCC] and choline/creatinine [CC] ratios) and GG were reported by Kobus et al in two consecutive studies (75, 102). Thormer et al (79) achieved a sensitivity of 72% in distinguishing between aggressive and indolent tumours using CCC ratio threshold of 0.82. A study by Chang et al (103) looked at the performance of MRS in identification of dominant treatable PCa foci and found the volume of spectroscopic abnormality to be the only factor to predict identification of a dominant treatable lesion on the T2 weighted sequence. MRS was incorporated into clinical use in 2012 as a part of PIRADS v.1 assessment of prostate lesions (5). Despite promising primary results and proven cost-effectiveness in a published large meta-analysis, performed by National Institute of Health Research in 2013, it was then subsequently omitted from PIRADS classification system v. 2 due to lack of prospective reliable data (104).



A B C

Figure 5 Example of abnormal MRS spectra **-a**bnormal Choline/Citrate ratio in a suspicious prostate lesion (red area on figure 5b), corresponding abnormal area of low signal on anatomical axial T2WI sequence (Figure 5a)

2.2.5. PIRADS- Prostate Imaging-Reporting and Data System

PIRADS is a scoring system for structured assessment of MP MRI, first introduced by a consensus meeting of prostate cancer experts. The first version was published in European Society of Uroradiology (ESUR) prostate MR guidelines in 2012 (5) with an aim to standardize and simplify the interpretation and terminology in reporting of

MP MRI and establish unified acceptable technical imaging parameters. The concept is similar to the BIRADS scoring system, widely used in breast imaging (105). The PIRADS scoring is based on 5-grade probability scale, assessing the risk of presence of CS PCa in MP MRI from very unlikely to very likely (Table 3).

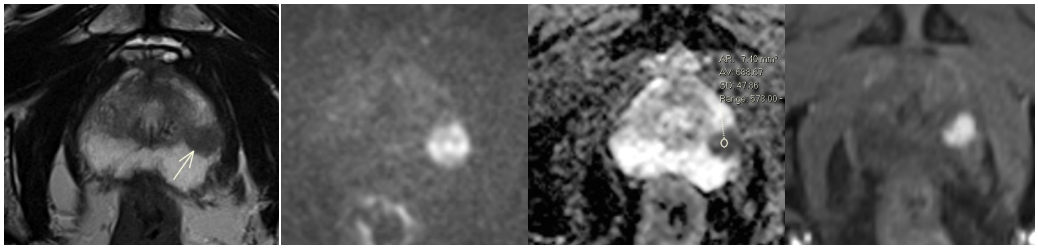
PI-RADS v2 Assessment Categories	
PIRADS 1	Very low likelihood of CS PCa being present
PIRADS 2	Low likelihood of CS PCa being present
PIRADS 3	Intermediate likelihood of CS PCa being present
PIRADS 4	High likelihood of CS PCa being present
PIRADS 5	Very high likelihood of CS PCa being present

Table 3 PIRADS v2 Assessment Categories

The PIRADS score is based purely on appearances from MP MRI and does not consider clinical or laboratory factors such as PSA level, findings from DRE or clinical history.

Individual PIRADS score is assigned to each identified lesion on main sequences (T2WI and DWI), based on presence of specific features (Table 6, page 54) and a final PIRADS score is established for each lesion, considering individual scores from T2WI, DWI, zone of origin and appearances on DCE, where appropriate. Example of a PIRADS 5 lesion in peripheral zone of the prostate with very high likelihood of clinically significant cancer is shown in Figure 6.

Detailed description of PIRADS score application to individual sequences and calculation of the final PIRADS score of each lesion is described in section 3.3.1 of this thesis.



A B C D

Figure 6 Example of PIRADS 5 lesion in PZ (white arrow on A) –Very high likelihood of being a clinically significant cancer. DWI is a dominant sequence in PZ lesions and shows focal marked hyper-intensity on high B-value image (B) with corresponding focal markedly hypo intense lesion on ADC (C) with low signal area on T2WI image (A) and early contrast enhancement on DCE (D)

Since publication, the first version of the system has been validated in clinical and research settings (106). The PIRADS scoring system, when used in conjunction with image-targeted biopsy, has potential to enable reduction of the over diagnosis of clinically non-significant disease (107). Hamoen et al. (106) in his meta-analysis, calculated a pooled sensitivity of 84% and specificity of 75% in detection of clinically significant cancer using PIRADS v1 scoring system.

The experience with version 1 of PIRADS revealed some of its limitations, related to advances in the field. In order to improve it, a steering committee was established between American College of Radiology (ACR), ESUR and ADMedTech foundation, which resulted in development and subsequent publication of PIRADS version 2 in 2015 (71). The main change related to omittment of MRS, relegation of DCE to a role of a problem solver limited to PZ lesions, and establishing a dominant sequence for each prostate zone. Since its introduction in 2015, PIRADS v2 was in clinical use till 2019 and was evaluated in many studies. Mertan et al examined cancer detection rate (CDR) of PIRADS v2 scores 3-5 in 62 consecutive patients (116 lesions) and reported a 78% CDR for PIRADS 5 and 30% CDR for the score of 4, which is lower than expected (108). Vargas et al have retrospectively evaluated the version 2 of the scoring system on a group of 150 patients with confirmed diagnosis of PCa prior to RP. When using score 4 and 5 as positive, PI-RADS v2 correctly identified 94-95 % of PCa foci ≥0.5 mL, but was limited for the assessment of Gleason Score (GS) ≥4+3 tumours ≤0.5 ml. DCE-MRI offered limited added value to T2WI+DW-MRI (109).Inter

observer reproducibility of PIRADS v2 lexicon was examined by Rosenkratz et al and found to be moderate for experienced radiologists, with better agreement in relation to the lesions in the PZ than TZ of the gland (110). In 2019, Padhani et al. evaluated all the relevant studies, systematic reviews, professional guidelines and expert opinions and concluded that the test performance of PIRADS v2 in research and clinical practice has higher diagnostic accuracy over systematic TRUS biopsies in CS PCa diagnosis and decreases the rate of detection of NS PCa (19).

Latest update to PIRADS v2.1 was released in March 2019 including several modifications, addressing the limitations and ambiguities revealed during clinical validation of version 2 (111). The framework was maintained with dominant sequences and combined scores derival and the main change related to assessment of TZ lesions on T2WI and DWI, especially in relation to PIRADS category 2 and 3.

2.2.6. Role of MP MRI in detection of PCa and CS PCa

Variable sensitivity between 60-96% has been reported for standard MRI in the detection of prostate cancer (54), depending on the definition of the significant disease and the method of imaging. Advances in the field of MRI and addition of functional sequences, which provide unique multimodal information regarding tumour biology, lead to improvement of detection accuracy of PCa. Wu et al (112) reported a pooled sensitivity of 76% and specificity of 82% by combining T2WI with DWI versus 72% and 67% respectively for T2WI alone, across 10 studies (627 patients). In the meta-analysis of 526 patients from 7 studies by Rooij et al. (113) a pooled sensitivity of 74% and specificity of 88% for MP MRI combining T2WI with DWI and DCE, in PCa detection, were calculated. A systematic review of 9 studies (297 patients) by Umbehr et al (114) revealed a combined sensitivity and specificity of 68% and 85% respectively, for MP MRI and MRS in the detection of prostate cancer.

One of the factors impairing diagnostic accuracy of MRI in detection and staging of PCa is post-biopsy artefact (115, 116). There is a common opinion amongst experts that performing MP MRI prior to biopsy can increase the CDR (117) with recently published NICE guideline for prostate cancer diagnosis and management (2019) recommendations supporting this approach (11).

There is growing evidence that MP MRI can help differentiate between CS PCa and NS PCa. A meta-analysis by Fütterer et al (20) of 12 studies has reported sensitivity between 44-87% for MP MRI in detection of CS cancer with negative predictive value between 63-98%. Recently published paired validating confirmatory study (PROMIS) by Ahmed et al (6) looked at 740 men with suspicion of PCa and compared diagnostic accuracy of MP MRI and TRUS biopsy against reference standard of template prostate mapping biopsy. The group reported significantly higher sensitivity of MP MRI than TRUS biopsy for CS disease (93% vs 48%) and suggested reduction by 27% in a number of patients requiring a primary biopsy and by 5% in patients with detected NS PCa if MP MRI was performed in pre-biopsy setting and used to guide decision making about the need for subsequent biopsy. A study by Pokorny et al on 223 consecutive biopsy-naïve men with suspicion of PCa who underwent MP MRI and in bore MR GB found 89.4% decrease in diagnosis of low-risk PCa and 17.7% increase of detection of intermediate/high PCa when compared to TRUS biopsy (118).

2.2.7. MP MRI in local staging of PCa

Accurate local staging of PCa in the context of differentiating between organ-confined and locally advanced disease is critical for treatment planning and prognostication. The most widely used classification system is the Tumour/Node/Metastasis (TNM) system developed by American Joint Committee on Cancer, most recently updated in 2018 (119). MP MRI is the examination of choice and is routinely used for local staging of PCa, especially for determining the T stage, defining the presence of extracapsular extension (T3a) or seminal vesicles (SV) invasion (T3b) and for assessment of pelvic nodal and pelvic bony involvement. The

implication of presence of T3 disease is a negative impact on the prognosis due to risk of positive margins at RP and subsequent risk of biochemical recurrence, as well as increased risk of nodal involvement (120, 121).

T2WI remains a cornerstone of local staging and addition of DWI and DCE increases accuracy of MP MRI (122). PIRADS v2 criteria for assessment of T staging have been validated and showed moderate sensitivity and specificity (81 and 78% respectively) as well as inter-reader agreement for prediction of T3a disease (123). Similar results were achieved in relation to assessment of SV invasion (124).

European Association of Urology (EAU) guidelines recommend adding wide field of view axial T1 WI from the level of aortic bifurcation to groin, for assessment of pelvic nodes to pre-biopsy MP MRI performed for detection of PCa (125). The performance of MP MRI for N staging remains however suboptimal due to its poor sensitivity and high false negative rate both for anatomical sequences and after addition of DWI (126, 127).

2.2.8. Image quality in detection of PCa at 1.5T vs 3T field strength

A need to obtain higher quality images has caused an evolution of the clinical MRI systems from 1.5T to 3T field strength. MR imaging at higher magnetic field strength has its advantages and drawbacks. The main gain is improved spatial resolution due to increase in signal to noise ratio (SNR). This phenomenon is due to linear correlation between signal and static magnetic field strength. The disadvantage of using higher field strength is increase in chemical shift and susceptibility artefacts, which degrade image quality (128).The overall image quality of T2 SE anatomical imaging is not expected to improve at higher field strength, as tissue contrast remains constant at 1.5 and 3T. Two studies have revealed comparable T2 SE image quality, gland delineation and similar staging performance between imaging at 1.5T with endo-rectal coil and at 3T with phased-array surface coil (129, 130). Prospective study by Beyersdorff et al examined 24 patients with prostate cancer, using RP specimen as a gold standard and revealed identical staging accuracy of 73% of the 1.5T and 3T systems (129). Shah et al, comparing T2 high-spatial resolution SE MR

images of 83 patients obtained at 1.5T and 3T field strength, achieved no statistically significant differences in diagnostic accuracy for cancer location, extra-capsular extension and seminal vesicles invasion (130). Park et al found imaging at 3T slightly better than at 1.5T for T3 staging accuracy on T2 SE (72 vs 70%) but with no statistically significant differences in overall image quality (131).

The quality of DWI images, which is intrinsically low SNR technique, increases in higher field strength (132). Imaging at 3T allows the use of a higher diffusion gradient strength (scanning with high b-values), which provides better contrast, higher spatial resolution, allows thinner slices and less T2-shine through effect (133). DCE imaging also benefits from increase in the higher field strength, due to increase in relaxation time of the prostate tissue, resulting in larger signal differences between enhancing and non-enhancing tissue. Increased SNR, leading to increase in spatial resolution is also an advantage (134).

To my knowledge, there are no published studies comparing detection of CS PCa between 1.5 and 3T magnets nor studies looking at diagnostic accuracy of PIRADS score in higher versus lower field strength.

2.3. Image guided biopsies in diagnosis of PCa

2.3.1. Ultrasound guided prostate biopsies (US-GB)

In the pre-MRI and systematic TRUS biopsies era, the trans rectal ultrasound was used to detect suspicious foci within the prostate gland, to direct trans rectal biopsies and to locally stage PCa. On standard B-mode US, foci of cancer in the PZ are typically hypoechoic and well defined, when compared to normal echo pattern of the PZ (135). Due to mixed echogenicity of the TZ the trans rectal US was found to be less accurate in detection of TZ tumours. Comparing to the performance of DRE, there was a two-fold increase in the detection rate of PCa after introduction of trans rectal US (136). It also allowed accurate assessment of prostate volume. Subsequent developments in the use of the technique led to a change from US directed trans

rectal biopsies to systematic sextant biopsies, which were proven to be more accurate in PCa detection (137).

Trans rectal US (TRUS) guided biopsy

Principles of the technique

Standardized TRUS biopsy is still a in use as a technique for detection PCa. First described in 1989 by Hodge et al was shown to be more accurate than directed US guided biopsies of hypoechoic lesions seen on ultrasound (137). It is a sampling technique, in which the operator uses ultrasound to direct needle towards the prostate gland and obtains 12 cores according to agreed template (Table 4) 6 from each PZ (138). Previously, Hodge sextant template was used, where 6 cores were obtained from PZ (3 from each side: base, midgland and apex) but a significant sampling error, leading to under detection of clinically significant cancer, resulted in introduction of extended-core model, including additional 6 cores laterally directed taken from each PZ sextant template (139, 140). The sensitivity of extended 12-core approach was calculated at 80% for CS PCa using mathematical models (141) and several studies confirmed its superior diagnostic accuracy over the traditional sextant model (140, 141).

1	R upper lateral	7	L upper lateral
2	R base	8	L base
3	R mid lateral	9	L mid lateral
4	R para midline	10	L para midline
5	R lower lateral	11	L lower lateral
6	R apex	12	L apex

Table 4 Extended 12-core TRUS biopsy pattern –12 cores are taken from peripheral zone

Intuitively, increase in the number of samples taken, especially in the larger volume gland, should improve PCa detection. Several studies have compared standard 12-core extended approach with more aggressive approaches of obtaining >12 cores, up to a so-called saturation biopsy (>24 cores) and reported improved cancer detection rates (142, 143). There is however an inherent risk in this approach, as it will inadvertently increase detection rate of NS PCa and therefore it is advocated, that in the initial biopsy setting, number of cores should be limited to 12, regardless of the prostate volume (144).

Clinical use of the technique

TRUS biopsy has been an integral part of PCa detection pathway for over 30 years. The role of it has evolved from pure PCa detection to assisting clinical management decision making. It is also a critical part in active surveillance (AS) protocols (138). The recommendations for the specific indications for prostate biopsy vary between published guidelines but is predominantly based on the results of PSA level/density and DRE result, with recent addition of the influence of pre-biopsy MP MRI (11, 125, 145).The major limitations of the technique, as described in chapter 1.4 of this thesis, include under sampling of the gland, leading to under detection of CS tumour, over detection of NS PCa and high morbidity of the biopsy procedure (4, 52, 53).

2.3.2. MR guided biopsies (MR-GB)

MRI images are used to aid trans rectal and trans perineal ultrasound- guided biopsy in targeting suspicious areas in prostate gland. MR GB of the prostate gland serves as an alternative to standard TRUS biopsy, especially in a setting of repeated biopsy in patients with high suspicion of PCa and negative TRUS biopsy results (146). Recently published NICE guideline on prostate cancer diagnosis and management recommends introducing MP MRI influenced prostate biopsy as a part of a standard of care in suspected localized PCa pathway (11).

There are three main MR GB approaches: MRI/US guided targeted biopsy, real time in-bore MR targeted biopsy (MR TB) or MR supported transperineal biopsy.

Two MRI/US guided targeted approaches are described: cognitive registration (COG-TB) using visual targeting and real-time software assisted MRI/trans rectal US fusion targeted (FUS-TB). The use of the FUS-TB for biopsy in prostate cancer was first described in the literature in 2002 by Kaplan et al (147).

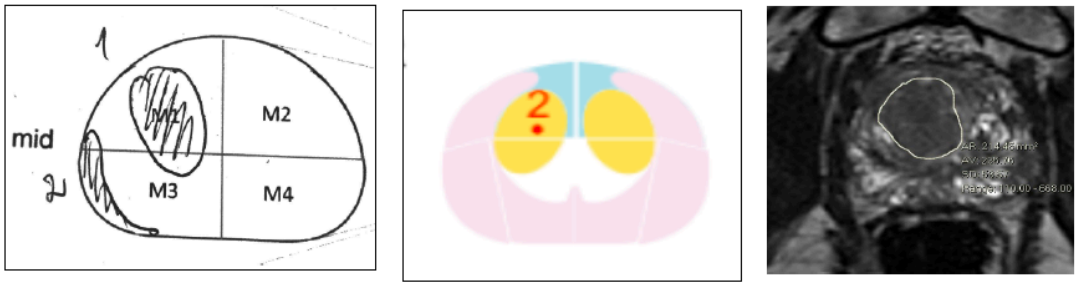
Comparison of performance of the MR GB with TRUS biopsy and the accuracy of the MR GB approaches were reported in metaanalysis by Wegelin et al (148). Analysis of 43 eligible studies showed that MR GB have a higher detection rate of CS PCa, when compared to TRUS biopsy, and lower detection rate of NS PCa. Importantly, in recent FUTURE trial, comparing performance of the three MR GB approaches, all three performed similarly in CS PCa detection (8).
Metaanalysis by Giganti and Moore analysed 11 eligible studies using all three approaches in detection of PCa and concluded that the differences in methodology and study design make comparison of the outcomes unreliable and there is currently no consensus which approach should be used in CS PCa detection (149). The most recent multicentre randomized non-inferiority trial (PRECISION) of 500 men has also compared groups of biopsy naïve men with suspicion of localized PCa undergoing either TRUS biopsy or MP MRI with subsequent MRI TG if the MRI was suggestive of prostate cancer (7). The results on this study have reinforced the body of evidence showing non-inferiority of the MP MRI and targeted biopsy approach versus TRUS biopsy approach and significantly higher detection rates of CS PCa in the former approach.

Cognitive (visual-targeted) MRI assisted US guided biopsy (COG-TB)

Principles of the technique

In this approach, cognitive targeting of suspicious lesions seen on MP MRI is performed by the operator, during a free-hand TRUS biopsy, by reviewing MP MRI images prior to procedure and selecting the most appropriate area for biopsy. This

technique requires the operator (usually Urologist, Urology Nurse Specialist of Radiologist) to be trained in reading MP MRI and relies on using prostatic zonal anatomy and anatomical landmarks (cysts, distinctive BPH nodules) for better in-vivo orientation (150). Mapping of the suspicious areas on hand –drawn, created using customized software templates or on key images by reporting Radiologist may also be used to aid communication of lesion location between the Radiologist and TRUS operator (Figure 7).



A B C

Figure 7 Hand-drawn diagram (A), software-created map (B) and key-image (C) showing position of a suspicious lesion within the prostate gland

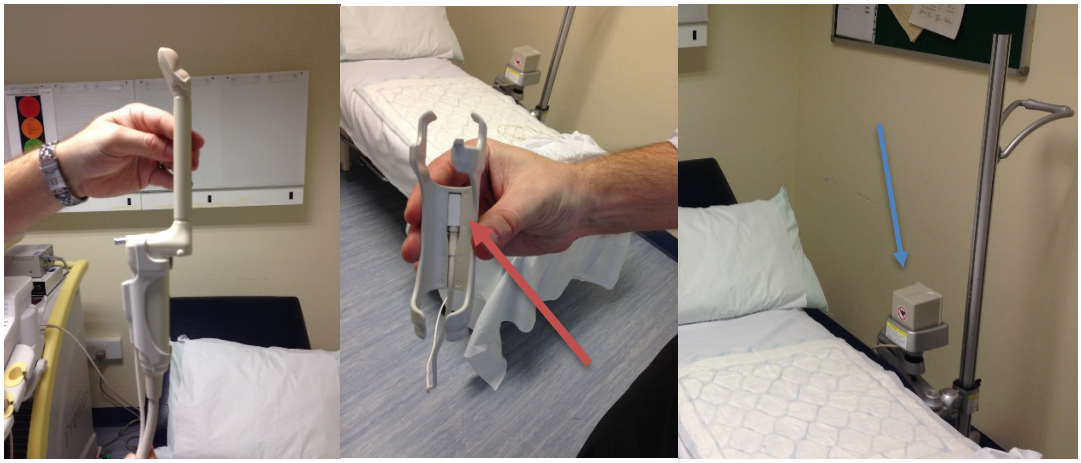
Clinical use of the technique

The COG-TB technique is routinely performed in many centres as is intuitive and does not require use of sophisticated software or hardware. Despite the limitations of a steep learning curve and operator dependence, in trained hands, this approach performs non-inferiorly to other MR GB techniques (150). The pooled sensitivity for CS PCa detection for COG-TB, as calculated by Wegelin, was 86%, which when compared to 89% for FUS-TB and 92% for MR TB resulted in no significant difference between the approaches (148).

Real-time software assisted (MR/US fusion guided) biopsy (FUS-TB)

Principles of the technique

US/MRI fusion targeted biopsy (FUS-TB) is a software co-registered technique of fusion of MRI images with real-life US images on commercially available platforms, to enable targeting suspicious lesions during biopsy. In principle, a conventional US machine with trans rectal transducer is used in conjunction with volume navigation software. Sensor micro coils are attached to the US probe or biopsy needle to enable registration of the probe position within the patient (Figure 8 a, b). Based on the same principles, transperineal approach is also available (151). The coils receive and emit signal from/to electromagnetic signal (RMS) generator positioned at the level of the prostate (Figure 8c), performing a similar function to Global Positioning System (GPS) chips, which allows positioning of the mobile device in the global geometrical region (152). Two types of image fusion platforms are currently available: rigid and non-rigid (flexible). The main limitation of the more commonly used rigid type is that it does not take deformation of the shape and changes in position of the prostate gland, during the biopsy procedure, into account, which may negatively impact on the precision of the targeting. The more advanced flexible systems are equipped with software assisted motion compensation, life-tracking of prostatic contour deformation during the procedure and real-time accurate needle navigation and registration. One of the most advanced flexible system, ARTEMIS® (Eigen, Grass Valley, CA) has been validated on phantoms in 2008 (153) and subsequently used in several clinical studies, proving statistically significant improvement in detection of CS PCa when compared to non-targeted TRUS biopsies (154-156). While initially the FUS-TB were performed under general anaesthesia, via transperineal approach, the more modern systems enable performing FGB under local anaesthesia and using trans rectal probe (157).



A B C

Figure 8 Example of a rectal transducer (A) with attached microcoil (red arrow) (B) and electromagnetic signal genrator (blue arrow) (C)

Clinical use of the technique

The FUS-TB is second most common technique used in targeting of suspicious lesions in the prostate, after cognitive approach. Both techniques have comparable performance reported for CS PCa detection (148). The advantage of using software assisted technique is that it is less operator dependent and the learning curve is less steep, allowing quicker training of independent operators. The technique is used in both in biopsy naïve group and in the setting of repeated biopsy, following negative TRUS results. Phase III clinical trial of FUS-GB of 153 participants with clinical suspicion of PCa and negative primary biopsy revealed a detection rate for FUS-TB of 14.3% for PCa missed by TRUS biopsy, with 86.7% being CS cancers (158). Vourganti et al (159) examining 195 patients with previous negative TRUS biopsy, by using FUS-TB found that 37% had cancer. There is established evidence in the use of FUS-TB as first sampling method in a cohort of patients with suspicion of CS prostate cancer. A systematic review of the literature by Schoots et al (155) identified 16 eligible studies and analysed a cumulative total of 1926 men with positive MRI. The detection of CS PCa by FUS-TB was significantly higher than by TRUS biopsy (sensitivity 0.91 vs 0.76). Among the lesions with intermediate risk of CS cancer being present, sensitivity and specificity FUS-TB was calculated at 85%/73% and 67%/92% respectively (160).

Recent systematic review of literature by Valerio et al (161) assessing accuracy of FUS-TB to detect PCa revealed 2/14 papers reporting on studies conducted in biopsy naïve group (162, 163). Only the first of them, by Mozer et al (162) reported on FUS-TB approach detection rate for CS disease (43.4% vs 36.9% for standard TRUS biopsy). The same review reported on the absolute difference in detection rate of CS PCa between FUS-TB and TRUS biopsy of a median of 6.8% (range: 0.9-41.4%) in favour for the former approach, based on analysis of 14 included studies. Analysis of overall cancer detection, efficiency and utility of the techniques revealed superiority of FUS-TB over standard TRUS biopsy.

Two studies by Panebianco et al and Siddiqui et al add to high-level body of evidence on accuracy of FUS-TB in detection of CS PCa in biopsy naïve cohort (164, 165). In study by Siddiqui et al, 1003 men were recruited prospectively and underwentunderwent MP MRI. If suspicious lesions were found, subsequently underwent FUS- FUS-TB in addition to standard TRUS biopsies. The targeted biopsies diagnosed 30% more high-risk PCa vs TRUS biopsies and 17% less NS PCa.

In the first randomized controlled trial by Panebianco et al, 1140 patients with symptoms highly suggestive of PCa were recruited and randomized into 2 groups; undergoing TRUS biopsy or MP MRI and FUS-TB. The study found higher proportion of men with CS PCa among those randomized to MP MRI and FUS-TB.

2.3.3. Other prostate biopsy techniques

In-bore MR targeted biopsy (MR-TB)

Principles of the technique

In-bore MR targeted biopsy was first proposed in 2000 for clinical use, using transperineal approach (166, 167) in open-bore setting. Since then, the technique evaluated, and is currently most commonly performed within a close-bore system via trans-rectal approach. Results of a first clinical study on 12 patients were published by Beyersdorff et al (168) in 2005.

The procedure is performed using either commercially available MR-compatible devices (ie *DynaTRIM, Invivo, Schwerin, Germany*) or locally developed kits for

needle guidance, under local anaesthesia, in prone position. Non real-time intra-procedural imaging is performed to aid targeting and an average time of biopsy is ranging between 19-68 minutes (169).

Clinical use of the technique

The main indication for the use of in-bore MR –TB is in a setting of a repeated biopsy after a prior negative TRUS biopsy and positive MRI result. While a detection rate for repeated TRUS in this scenario ranges between 7-17%, as reported in metaanalysis by Overduin et al, for MR-TB is significantly improved to median of 42%, depending on the study, with a high proportion (81-93%) being CS cancers (169). The complication rates between both approaches remain comparable.
Of note, the specimens obtained during MR-TB match definite histopathology grade from PR in 88%, which is a significant achievement in reducing under grading of the disease, when compared to TRUS biopsies (170).

Comparison of all 3 MRI targeted approaches reveals statistically significant advantage of using in-bore MR-TB over COG-TB for overall PCa detection, but no statistically significant difference was found in performance of MR-TB over FUS-TB or FUS-TB over COG-TB (148).

Trans perineal template mapping biopsies (TPM)

Principles of the technique

Standardized template-assisted, US-guided, TPM prostate biopsy is performed under general anaesthesia, using a brachytherapy template grid (sampling frame), placed externally on patient's perineum, with patient placed in lithotomy position. Samples are taken every 5mm throughout the gland, with 2 samples taken from the same grid coordinate if the prostate is longer than the length of the biopsy core (171). Many other variations of the technique were described in the literature, with variable number of cores and sampling distances (172).

Clinical use of the technique

This approach is established as a second line investigation in diagnostic pathway, specifically for patients with rising PSA and negative standard biopsies. It has shown to be particularly effective in diagnosing tumours located in the anterior and apical gland, regions frequently under sampled during TRUS biopsies (173, 174). The detection rate of PCa in a naïve gland remains similar for both trans rectal and trans perineal approaches (138). Sheikh et at (175) reported 60% PCa detection rate in a cohort of 200 men with rising PSA and at least 1 previous negative TRUS biopsy. The limitations of the technique include potential over diagnosis of clinically insignificant cancer due to oversampling, need for GA and length of the procedure.

3. MATERIALS AND METHODS

3.1. STUDY DESIGN

The data used to answer the research questions posed in this thesis were acquired prospectively during multicentre study (*MULTIPROS study*) of diagnostic accuracy of pre-biopsy MP MRI with subgroup randomisation to intervention (TRUS and FUS-TB) or control (TRUS-only biopsy). The study protocol has been published in peer–reviewed Trials journal in 2019 (24). The role of the candidate in the study is described in section 3.1.2.

The data were collected in two main study parts:

- A prospective study of 89 patients suspected of having PCa, comparing diagnostic accuracy of their pre-biopsy MP MRI in detection of foci of CS PCa using histology of their RP specimen as a reference standard on lesion-basis

- A prospective randomized controlled trial of 603 patients, suspected of having PCa and with positive MP MRI, undergoing randomisation to either FUS-TB combined with TRUS biopsies or TRUS-only biopsies

There were 3 actively recruiting UK sites (NHS Tayside, NHS Grampian and Royal Free London NHS Foundation Trust). NHS Tayside was the main recruiting site, providing 100% participants for the first part of the study and 98% participants for the second randomised part of the study.

A favourable approval for the study was obtained from the East of Scotland REC 1 (Ref: 14/ES/1070) on 20 November 2014. Appropriate NHS Research and Development office (R&D) Sponsor approval(s) for each participating site were obtained (2013ON23).

The work was supported by Prostate Cancer UK (PCUK), registered charity In England and Wales (1005541) and in Scotland (SC039332), Movember and the Chief Scientist Office through a Prostate Grant (CSO-PG13-005).

The study was also a part of UK Clinical Research Network (UKCRN), the national organization supporting high quality clinical research studies for the benefit of the patients (Trial registration number 18082).

The study has been registered on ClinicalTrials.Gov, web-based resource, managed by US National Library of Medicine (NLM) and National Institutes of Health (NIH) (NCT02745496), to provide public access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions (20th April 2016) and the details can be accessed via this link: https://clinicaltrials.gov/ct2/show/NCT02745496.

3.1.1. Research questions and endpoints

1st research question:

How reliable is pre-biopsy MP MRI in identification of foci of clinically significant prostate cancer (CS PCa) in prostate gland and avoidance of over detection of foci of non-significant cancers (NSC)?

2nd research question:

Will adding MR-guided targeted biopsy to standard TRUS biopsy of prostate gland detect more CS PCa than standard TRUS biopsy alone, with no significant increase of NSC detection and with similar profile of adverse events?

1st research question endpoints:

A. Sensitivity, specificity, positive and negative predictive value of MP MRI in detecting lesions of SC PCa
B. Sensitivity, specificity, positive and negative predictive value of MP MRI in detecting patients with SC PCa
C. Accuracy of Inter-observer agreement on positivity of MP MRI between Uro-radiologists on patient-basis
D. Sensitivity, specificity, positive and negative predictive value of each positive PIRADS scores (3-5) on MP MRI in detecting lesions of SC PCa
E. MP MRI detection of PCa depending of its Gleason Score (measure of aggressiveness)
F. Qualitative analysis of location and size of foci of CS PCa undetected on MP MRI

2nd research question endpoints:

A. Difference in probability of cancer detection between intervention and control groups (TRUS/FUS-TB biopsy versus TRUS biopsy) presented as an odds ratio, representing the odds of each test correctly detecting the presence or absence of the disease
B. Review of the safety outcomes of death, post biopsy side effects such as pain and bleeding and duration of symptoms in each of the two randomized groups
C. Cancer detection rate (CDR) and CS CDR in MP MRI negative group to assess the false negative rate of MP MRI

3.1.2. Intended learning outcomes specified for me in this joined large research study

Due to the nature of this large clinical study, I, the author of this thesis, was a part of a multidisciplinary study group. I was working with the team of researchers and clinicians, including accredited NHS Urologists, Uro-Radiologists, Uro-Pathologists, Urology Specialist nurses, Research nurses, MR expert Physicist, Bioengineer, Study Coordinator (supported by TCTU unit), Study Assistant and with support from statistical team from DEBU unit at University of Dundee.

At the start of my thesis, I performed critical review of the research published in this area, as this was a "hot topic" in uro-radiology. My specified objectives were:

- Critically appraise and discuss published literature in pre-biopsy MRI in men clinically suspected of PCa;
- Refine research questions and prepare protocol (both relevant clinical question and image acquisition) for the study, including obtaining regulatory approvals for the study;
- Contribute to acquisition of quality assured data and using data and information to answer a clinical research question;
- Analyses of data and interpretation to answer pre-specified research questions

Besides providing service as study uro-radiologist (NHS Tayside), my aims were to develop research skills in clinical trials, by working in a multidisciplinary research team, including setting protocols for multi-site acquisition of data and accomplishment of a higher degree.
During this study, I have demonstrated competence in research and the ability to operate independently by learning:

- research design, methodology, ethics and theoretical arguments, and design of data sheets for critical piece of research (data acquisition)
- Gained skills in ultrasound/MRI fusion methods and performed transrectal ultrasound guided biopsies independently
- Acquisition of data and its quality assurance
- Data analyses
- Presentation of data and discussions in multi-disciplinary meetings and professional peer-reviewed meetings
- Write up of dissertation and papers for publications.

Based on this, I presented my work for the award of higher degree.

My individual learning through participation in MULTIPROS project:

1) **Study design**:

- **Grant application**-I joined the study team in January 2014, after the study has been granted support from Prostate cancer UK (October 2013). The grant application has been prepared by the Study Chief Investigator (my thesis supervisor) and senior researchers from the research team. I went through the grant application and prepared study protocol and standard operating procedures for the study to start locally and at national level. This included thorough literature review and interpretation of data, with new large studies published since grant was awarded to the team.
- **REC and R&D application**- I lead those applications and was successfully granted the research ethics committee (REC) and R&D approvals for the study. I gained skills in protocol preparation, writing up data extraction sheets, preparation of ethics application and presentation of research questions to ethics committee.
- **Study protocol** -I developed Multipros Study protocol. I authored the first draft of the protocol and produced the subsequent drafts in collaboration

with the study team (Appendix 5). Although the protocol was based on the Grant application, and while the overall aims remained unchanged, to make the study more translational, feasible to complete in given time and applicable to clinical practice, I have subsequently changed the objectives and hypotheses as well as methodology of the project. This was specifically based on up to-data literature review and incorporation of emerging evidence in this area of research.

I made following main changes, in the time preceding the recruitment period:

1. *Change to PIRADS scoring system*- The scoring system recommended for assessment of prostate gland on MP MRI has been updated in 2015 by ESUR from version 1 to version 2 (71). The analysis of DCE has been simplified from semi-quantitative to qualitative and MRS was removed from analysis. Before the final Study protocol and start of recruitment, I decided to significantly amend methodology and statistical plan of the study to accommodate the change to make the results more applicable to clinical use.

2. *Addition to outcome measures* related to safety of the biopsy types and inclusion of patient-reported outcomes to assess post-biopsy side effects and adverse events to inform second research question outcome measure 3 (Appendix B6)

3. *Addition of outcome measure* related to assessment of the MRI negative group

4. *Amendment of the definitions* of clinically significant cancer on biopsy and in RP specimen as per most up to date recommendations

5. *Inclusion of assessment of inter observe*r variability by introduction of retrospective double reading of a subgroup of MRI scans . There were few modifications required as the study progressed. The study protocol

underwent further amendments to adjust the methodology to fit better into the clinical pathways and to optimise the recruitment (Appendix B7). The main changes included:

6. *Strength of the magnet- initially*, MP MRI scans were to be acquired on high field strength 3T scanners to achieve the highest quality of MR images for optimal assessment of prostate gland (improved signal to noise ratio). This has however resulted in difficulties in finding new recruitment sites, as the NHS sites were predominantly equipped with standard 1.5T scanners. I have decided to allow acquisition of scans at 1.5T to balance the quality and accessibility after I have performed literature search and have not found any data comparing diagnostic accuracy of PCa detection using PIRAD scoring system between both field strengths (described in the following chapter Image quality in detection of PCa at 1.5T vs 3T field strength).

7. *Addition of hip replacement in the exclusion criteria* to ensure optimal MR image quality – Original list of exclusions for suitability of participants to undergo MRI scan oscillated around MRI safety. After the start of recruitment, I have come across participants who had hip replacements, which have significantly degraded image quality of MRI, especially DWI, due to the presence of susceptibility artefact, which is exacerbated in high 3T field strength magnet. To maintain high image quality for detection of foci of PCa, I have decided to include hip replacements in the list of exclusion criteria.

8. *Removal of Magnetic Resonance Spectroscopy (MRS*) sequence from MRI protocol- MRS has been a part of the acquisition protocol for PIRADS v1 assessment of the MP MRI as per ESUR guidance since 2012 (5). Following update to PIRADS v2 in 2015, I amended the study methodology and removed spectroscopy from main analyses. I have however decided, initially, to still acquire spectroscopy data, and analyse them separately. After a period of recruitment however, I had decided to stop acquiring this sequence

as it had negative impact on the length of the scan and decreased tolerance of participants to manage the length of acquisition.

9. *Adjustment of PSA level range in the inclusion criteria*
   This inclusion criterion was initially set with a lower cut off value of 2.5 ng/ml. After the recruitment has started, it became apparent that there are patients who were referred with suspicion of PCa but their PSA level was below this value. Following consultation with Urologists, I decided to amend this inclusion criterion and allow recruitment of participants with PSA value less than 2.5 ng/ml if there was clinical suspicion on CS PCa made on the clinical grounds.

10. *Publication of the study protocol*- I was the first author of the published study protocol (24), I authored the original draft and coordinated the review and editing of the manuscript.

11. *Patient information leaflets (PIL)*- I have drafted PILs for patients at each participating site, with site-specific participant-relevant study information and was available to contact, shall they had any questions related to study participation

12. *Case Report Form* (CRF) - I have authored both paper and electronic versions of the forms for data collection, ensuring all necessary data points were recorded and available for data analysis

13. *Patient post biopsy questionnaire***-** I have designed questionnaire for participants undergoing biopsy procedure to capture and quantify post-procedural side effects and adverse events. Data from the questionnaire informed 3rd outcome measure for the 2nd research question (Appendix B6).

2) **Study management**

The study provided a unique opportunity to act as Principal Investigator (PI) for the main coordinating site (NHS Tayside)- As defined by good clinical practice (GCP) NHIR, I met all the requirements and held qualifications to be appointed in my role as a PI of the main coordinating study site. My main responsibilities and learning included, but were not limited to:

- Understand compliance with GCP and other applicable regulatory requirements
- working with appropriately qualified team members, to change imaging protocols
- Acquisition of skills of leading monthly Trial Management Group meetings, liaising with clinical teams, answering queries from research nurses, study coordinator and study assistant
- Efficient time management by preparing all necessary sponsor, funder and regulatory bodies progress and final reports, in timely manner, during/after duration of the recruitment
- Safety reporting of the serious adverse events to the study sponsor
- Staff recruitment- I have prepared person specification, shortlisted and interviewed candidates for two paid study positions: Study assistant and study coordinator
- Securing new sites –I have actively lead search and activation of new recruitment sites and have visited NHS Grampian and hosted local visits from two potential sites, I was also responsible for mentoring and training of sites Uro- Radiologists

3) Data acquisition

Acquisition of imaging data:

- *MR imaging protocol*- I developed quality assured MP MRI imaging protocol for both 3T and 1.5T scanners in NHS Tayside for prostate cancer imaging, with help from Study Medical Physicist and based on ESUR guidelines

- *Image analysis software*- I performed an extensive search of image analyses software. I have selected and started using the imaging analysis platform (Olea Sphere) for analysis of the MP MRI images at the main study site (98% MP MRI studies were analysed on this software). The software provided reproducible data

- *Imaging data acquisition and analysis*- I prospectively supervised acquisition of imaging data for 490/595 MP MRI examinations providing, in addition to standard clinical report, all additional data required for the research analyses. In addition, I retrospectively reported 55/160 MP MRI examinations for assessment of the inter-observer agreement

Data acquisition for image fusion using MRI-trans rectal US fusion targeted biopsy (FUS-TB)

- I underwent a period of phantom training, with help of Hitachi application specialists, to safely and efficiently plan and assist in targeted biopsies on study participants as this was a new biopsy technique, not previously clinically used in NHS Tayside. The biopsy samples were physically obtained by Urologists/Urology Specialist nurses with direct guidance from myself, at the time of the biopsy, regarding fusion of MRI and US images and targeting of the lesions

- I developed a written training handout, how to assemble and use the biopsy equipment and efficiently plan and perform the procedure and performed face-to-face training of a second fellow Clinical Radiologist involved in the targeted biopsies

- I have personally planned US/MRI fusion of images and assisted in 150/207 of all targeted biopsies procedures during the study. I performed some of the TRUS biopsies independently.

Other data acquisition:

- Past medical history- I contributed to collection of data on the past medical history for each participant, based on the NHS electronic patient record. The data were necessary for statistical analysis (as comorbidity score)

- Adverse events –I cross-referenced post-biopsy patient's questionnaire with clinical letters available on NHS electronic database to establish the number of post-procedural adverse events /serious adverse events for sponsor reporting and to inform one of the study outcomes

4) Data analysis

Main analyses

I started with preparation of basic data analyses to answer my research questions and consulted study statistic team on regular basis. During this period, I learnt various aspects of data analysis including quality assurance and data pruning. Analysis of the randomised arm of the study required more direct input from the DEBU statistical team, due to its complexity, and the logistic regression modelling and AUROC analyses were performed using statistical software (SAS v 9.4). The results are presented in thesis. I have actively participated in drafting the final statistical analysis plan and statistical report and had full access to all the data in the

study, taking responsibility for the integrity of the data and the accuracy of the data analysis.

Additional analyses

I have independently, with indirect support from statistical team, performed multiple additional analyses, as detailed in the methodology and results chapters of the thesis i.e. related to the size, location of the cancer foci and inter observer variability. The correlation of MP MRI vs RP based on RP readings (provided by NHS Pathologist) was performed by me manually, based on data from the CRF and recorded in section M, this was subsequently used in main statistical analyses

5) Dissemination of results

-I was a first author and have drafting the published protocol paper

- I have presented the methodology of the study as an oral presentation at European Congress of Radiology in Vienna in March 2019 in an exclusive Clinical Trials in Radiology category data dissemination via competitive entry

-I am a first author of the results paper currently being prepared for submission

3.2. PARTICIPANTS

3.2.1. Participant selection and enrolment

Prospective recruitment of men referred with suspected clinically localised PCa was carried out in urology clinics in three active recruitment centres in the UK (NHS Tayside and NHS Grampian, Scotland and Royal Free NHS Trust, London, England).

Inclusion criteria

- Males aged 40–75 years at referral
- With at least 10 years' life expectancy at referral

- With clinically localised PCa: PSA ≤ 20 ng/ml and/or with abnormal DRE but < T3 disease
- Ability to give informed consent

Exclusion criteria

- Unable to give informed consent
- Prior prostatic biopsy within the last 12 months
- Contraindications to biopsy
- Poor general health and life expectancy < 10 years
- Previous diagnosis of acute prostatitis within 12 months
- History of PCa
- Prior transurethral prostatectomy
- Contraindications to MRI, including cardiac pacemakers, allergic reaction to gadolinium-based contrast, renal failure, intracranial clips, claustrophobia
- Previous hip replacement

3.2.2. Participants' flow

Eligible participants were recruited and offered pre-biopsy MP MRI scan of the prostate. MP MRI was assessed using PIRADS v 2 system and if result was positive (PIRADS score 3 or above) participants were randomised to undergo intervention (TRUS+FUS-TB biopsy) or standard of care TRUS biopsy. If MP MRI scan was negative (PIRADS score 1-2) participants were offered standard of care TRUS biopsy.
If prostate cancer was confirmed on biopsy, participants were further managed as per NHS standard of care. This included discussion at NHS multidisciplinary clinical meeting and offering treatment options, depending on stage and grade of the disease and general fitness. RP was offered a standard of care option of radical treatment for patients with clinically significant PCa confirmed on biopsy and localised disease confirmed by imaging.

If participant was offered, and has elected for, RP then his prostate gland underwent histopathological analysis using customised mold (detailed description in section 3.3.3) and the results were compared to the MRI findings to answer the first research question.

Figure 9 Trial design

3.3. INTERVENTIONS

3.3.1. Study intervention: MP MRI

All enrolled participants were offered 3.T or, if unavailable, 1.5TMP MRI prior to prostate biopsy.

Protocol and acquisition

Participant preparation

Prior to the MP MRI, all participants were screened for MRI, Gadolinium contrast agent and anti- peristaltic medication safety. Prior to the scan, patients were administered with soft muscle relaxant medication *(Buscopan®)* to minimize artefact from the bowel peristalsis, if not contraindicated.

MP MRI was performed on 3T or 1.5T clinical MRI scanner, equipped with surface phased 16- channel pelvic array, by NHS-accredited Radiographer(s) with relevant qualifications and training.

The scan took approximately 45min. During the scan, participants were administered with Gadolinium-based contrast agent (*Dotarem®)*, which is a medium used routinely for contrast enhanced MRI sequences.

Scanning protocol

The standardized scanning protocol was used, adapted from ESUR 2012 guidelines (5) for detection of ppCa, optimized to individual scanner type. The protocol comprised of anatomical sequences, followed by functional sequences, acquired with uniform slice thickness of 3mm for all key acquisitions on the 192 matrix size (Table 5).

Anatomical sequences:

Small field of view spin echo (SE) sequences of the pelvis

T2 spin echo (SE) high resolution pulse sequences were acquired in sagittal, axial and coronal oblique planes, planned to the long axis of the prostate. These sequences aid lesion detection, local staging and depict prostate zonal anatomy.

T1 SE large field of view pulse sequence of the pelvis, acquired in the axial plane, from the level of aortic bifurcation to groins, served assessment of loco regional lymph nodes.

T2 3D SPACE sequence was acquired for fusion biopsy planning. This single slab 3D turbo spin echo (TSE) isotropic sequence enabled acquisition of high-resolution 3D datasets to allow retrospective reformatting for viewing of multiple orientations of the gland during TRUS/FUS-TB biopsy procedure.

Functional sequences:

Diffusion weighted imaging (DWI)

Echo planar DWI sequences acquired in axial oblique plane, with four b-values (50, 100, 500,1000 s/mm^2) with motion probing gradients applied in three orthogonal directions and adapted to the quality of signal to noise ratio (SNR). The data were used to generate the ADC map. Separate acquired high b-value (2000 s/mm^2 for 3T scanner and 1400 s/mm^2 for 1.5T scanner) image was used for lesion detection as per PIRADS v2 protocol.

Dynamic Contrast Enhanced Imaging (DCE)

DCE sequences are 3D fast gradient-echo T1 sequences acquired in axial oblique plane with temporal resolution of 6 seconds, using 2ml/kg of *Dotarem®,* gadolinium-based contrast agent [Guerbet,France].

Table 5 Example of MP MRI acquisition parameters optimized for Siemens Prisma FIT 3T scanner

	High Res T2W	High Res T2W	High Res T2W	T1W Axial	DWI	DWI High B	3D T2 SPACE	Dyn Gd-MRI	T1W 2DSE
Sequence	2DTSE	2DTSE	2DTSE	2DTSE	2D EPI	2D EPI	3D SPACE	3D VIBE	T1TSE
Turbo Factor	27	23	25	3	144 (EPI)	144 (EPI)	79	---	9
Orientation	Sagittal Obl	Axial Obl	Coronal Obl	Axial Obl	Axial Obl	Axial Obl	Axial Obl	Axial Obl	Axial
TR (ms)	6000	4000	5000	650	3300	3300	2000	4.76	450
TE (ms)	102	100	100	11	95	95	123	2.45	11
Flip Angle (°)	140	150	150	150	---	---	120	10	140
Slice Thick (mm)	3	3	3	3	3	3	1	3	10
Slice Sep (mm)	0.6	0.6	0.6	0.6	0	0	0	0	10
Resolution (pixels)	320	320	320	320	192	192	256	192	384
Phase Res (%)	85	90	90	80	75	75	100	72	70
Phase Part Fourier	OFF	OFF	OFF	OFF	6/8	6/8	ALLOWED	6/8	OFF
Slice Resolution (%)	100	100	100	100	---	---	83	67	---
FOV (mm)	approx 200	approx 200	approx 200	200	280	280	256	280	400
Phase FOV (%)	100	100	100	100	100	100	100	78.1	100
Voxel Size	0.7 x 0.6 x 3.0	0.7 x 0.6 x 3.0	0.7 x 0.6 x 3.0	0.8x0.6x3.0	2.0x1.5x3.0	2.0x1.5x3.0	1.0x1.0x1.0	2.0x1.5x3.0	1.5x1.0x10
No Averages	3	3	2	2	12	9	1.5	1	1
Concatenations	2	2	2	2	1	1	1	1	4
Parallel Imaging	GRAPPAx2	GRAPPAx2	GRAPPAx2	NONE	GRAPPAx2	GRAPPAx2	GRAPPAx2	GRAPPAx2	GRAPPAx2
Phase O/S (%)	35	50	100	50	25	25	75	0	0
Slice O/S (%)	---	---	---	---	---	---	11.1	9.1	---
Est Scan Time (sec)	240-270	240-270	240-270	330	300	240	300	4 (50 meas)	33
B-Values	---	---	---	---	50, 100, 500, 10	2000	---	---	---
Bandwidth (Hz/Pix)	252	203	203	203	1302	1302	651	540	766
Fat Suppression	None	None	None	NONE	FATSAT	FATSAT	NONE	NONE	NONE
Water Suppression	None	None	None	NONE	NONE	NONE	NONE	NONE	NONE
Water Excitation	None	None	None	NONE	NONE	NONE	NONE	NONE	NONE
Filters 1	2D Dist Corr	2D Dist Corr	2D Dist Corr	2D Dist Corr	RAW	RAW	Elliptical	2D Dist Corr	2D Dist Corr
Filters 2	Elliptical	Elliptical	Elliptical	Elliptical	2D Dist Corr	2D Dist Corr	---	Elliptical	Prescan Norm
Filters 3	---	Prescan Norm	Prescan Norm	Prescan Norm	---	---	---	---	Elliptical

MP MRI interpretation

Imaging post-processing

Simultaneous viewing and analysis of multiple MP MRI sequences was performed on commercially available advanced image processing platforms.

Oncological software package, used in the main participating site (NHS Tayside), for the 595/603 participants was Olea *sphere ®* package (*Olea-Medical Solutions ltd, Paris, France)*. The dedicated oncological software package with PCa specific application enabled the use of various functions, such as simultaneous assessment of multiple sequences, localization of suspicious foci within the prostate gland, regions of interest (ROI) co-registration and lesions marking. The functionality also allowed the use of graphical prostate template with 12 segments for lesions allocation, generation of standardized report and semi-quantitative DCE data analysis.

MP MRI reading

The MP MRI data of all participants were read prospectively, prior to randomization and prostate biopsy. Each MP MRI scan was single read by 4 NHS accredited Consultant Clinical Uro-Radiologists [MSB –author of this thesis (81.2% cases read), JS (17.4%), PS (1.17%) and SKR (0.16%)], with previous experience in prostate MRI and MP MRI interpretation. The readers were not blinded to clinical information. The prospective read aimed to identify suspicious areas within the prostate gland and provide nodal staging. For each identified suspicious lesion, the location, size and probability score for the presence of CS PCa (PIRADS v2.0 score) was recorded. The information provided by prospective MP MRI read was used for biopsy allocation and randomization stratification. The standard report was used for clinical decision-making.

Inter-observer agreement

The MP MRI data of the first 89 participants, who underwent RP, were retrospectively read by a different, trained Uro-radiologist, who was blinded to clinical information, primary read and biopsy/prostatectomy result. The reader was given a proportion of control negative scans in addition to the test positive scans

(from RP group) to minimize selection bias (total of 160 MP MRI scans were retrospectively read).

MP MRI reading per study participating sites:

NHS Tayside (Main participating site)

-98,6% (595/603) of all MP MRI were red prospectively and 106/160 (66.25%) of the secondary retrospective reads were performed.2 Consultant Radiologists performed the interpretation:

Uroradiologist 1 (MSB- author of this thesis) has performed 490/603 prospective reads (81.2%) and 55/160 (34.3%) of the retrospective reads.

Uroradiologist 2 (JS)- has performed 105/603 prospective reads (17.4%) and 51/160 (31.8%) of the retrospective reads.

NHS Grampian

Uroradiologist 3 (SKR) has performed 1/603 (0.17%) of the prospective reads and 54/160 (33.75%) of the retrospective reads

Royal Free Hospital, London

Uroradiologist 4 (PS)- has performed 7/603 (1.16%) of the prospective reads

Sequences interpretation-PIRADS SCORING SYSTEM

PIRADS v2 system uses a 5-point scale based on the likelihood that a combination of MP MRI appearances from T2 SE, DWI and DCE sequences correlates with the presence of a CS PCa for each identified lesion in the prostate gland (71). 1 of 5 scores could be assigned, based on imaging appearances. Score of 1 equates to a very low risk for presence of CS PCa and score of 5 to a very high risk of CS PCa presence. The detailed technical description and scientific rationale for PIRADS is described in section 2.2.5 PIRADS- Prostate Imaging-Reporting and Data System of this thesis.

The criteria for application of PIRADS score to each individual lesion differ, depending on the zone of the prostate the lesion is present. The description of

imaging findings for lesions in both PZ and TZ from each sequence and corresponding PIRADS scores is detailed in Table 6.

	Peripheral zone (PZ)		**Transitional zone (TZ)**	
PIRADS score	**T2WE**	**DWI**	**T2WE**	**DWI**
1	Uniform hyperintense signal intensity	No abnormality on ADC or high b-value DWI	Homogenous intermediate signal intensity	Same as for PZ
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity with indistinct margin	Indistinct hypointense on ADC	Circumscribed hypointense or heterogeneous encapsulated nodules BPH	
3	Heterogeneous signal intensity or non-circumscribed, rounded moderate hypointensity + Others that do not qualify as 2,4,5	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high B-value	Heterogeneous signal intensity with obscured margins Includes others that do not qualify as 2,4,5	
4	Circumscribed, homogenous moderate hypointense focus confined to prostate and <1.5cn in greatest dimension	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI; < 1,5cm in greatest dimension	Lenticular or non-circumscribed, homogenous, moderately hypointense and <1.5cm in greatest dimension	
5	Same as 4 but >=1.5cm in greatest dimension or definite extraprostatic extension/invasive behaviour	Same as 4 but > 1.5cm in greatest dimension or definite extraprostatic extension/invasive behaviour	Same as 4 but >= 1.5cm in greatest dimension or definite ECE/invasive behaviour	
score	**DCE assessment for Peripheral zone**			
(-)	No early enhancement or diffuse enhancement not corresponding to a focal finding on T2WI and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WE			
(+)	Focal and earlier than or contemporaneously with enhancement of adjacent normal prostatic tissues, and, corresponds to suspicious finding on T2WE and/or DWI			

Table 6 Assessment of lesions in peripheral and transitional zones on each sequence using PIRADS v 2.0 system (71)

Peripheral zone lesions: for lesions situated in the PZ, DWI is the dominant sequence with DCE playing a problem-solving role in equivocal lesions with PIRADS score of 3 on DWI (Table 7).

PERIPHERAL ZONE LESIONS			
DWI	**T2**	**DCE**	**PIRADS v2**
1	Any	Any	**1**
2	Any	Any	**2**
3	Any	-	**3**
		+	**4**
4	Any	Any	**4**
5	Any	Any	**5**

Table 7 Application of PIRADS score in peripheral zone lesions

Transition zone lesions: for lesions situated in the TZ, T2 WE is playing the major role (dominant sequence) with DWI acting as a problem solver for lesions with score 3 on T2WE (Table 8).

TRANSITIONAL ZONE LESIONS			
T2	**DWI**	**DCE**	**PIRADS**
1	Any	Any	**1**
2	Any	Any	**2**
3	<=4	Any	**3**
	5		
4	Any	Any	**4**
5	Any	Any	**5**

Table 8 Application of PIRADS score in transitional zone lesions

Overall the T2 SE and DWI are the primary sequences determining PIRADS score with DCE playing a secondary role in equivocal lesions with PIRADS score of 3 in PZ or when one of the primary sequences was non-diagnostic.

The literature review and of the PIRADS scoring system is included in chapter 2.3 of this thesis (2.3 PIRADS scoring system).

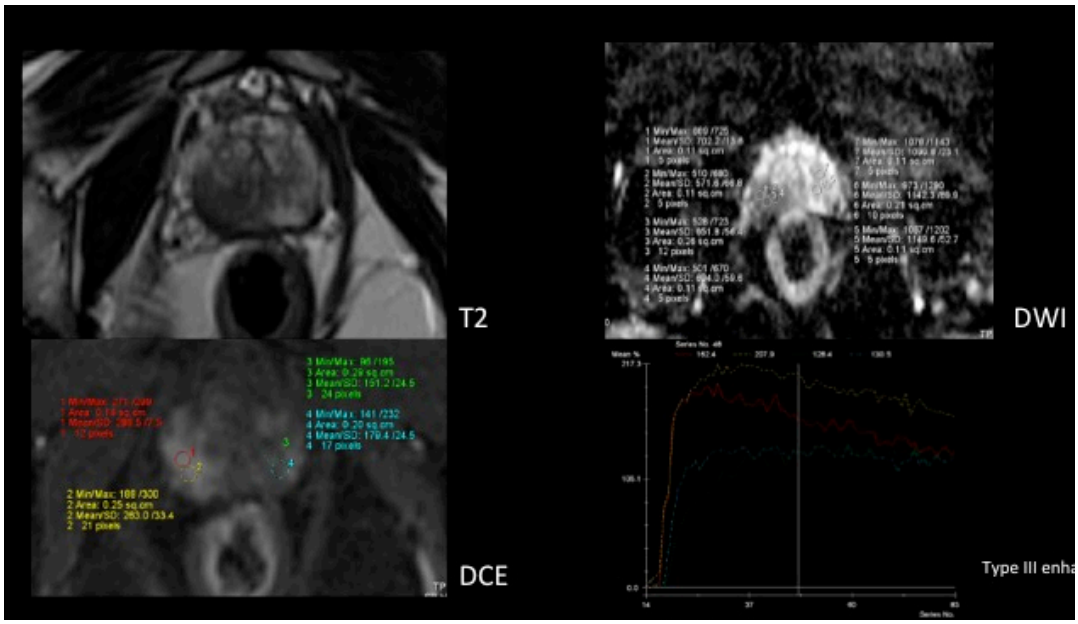


Figure 10 Example of a PIRADS 5 lesion within the right peripheral zone of the prostate on T2 SE, DWI and DCE weighted sequences

3.3.2. Study intervention: Prostate biopsy

All participants with positive MP MRI underwent randomisation to TRUS/FUS-TB biopsy or TRUS biopsy, as described in chapter 6.6.3 of this thesis.
FUS-TB biopsy was performed on a randomised subgroup of patients during the same appointment as TRUS-guided biopsy. A trained and experienced Radiologist with Urologist /Urology Nurse Specialist performed the procedure prior to TRUS-guided biopsy. The persons undertaking the biopsy had prior experience and had received appropriate training from clinical experts and/or the equipment supplier's application specialist(s).

Randomisation

Randomisation was performed via TRUST, a web-based, GCP-compliant randomisation system run by the Health Informatics Centre (HIC) at University of Dundee. Randomisation was implemented with random block sizes stratified by site and minimised by: PIRADS v2 suspicion score (3–5); index lesion size (above and

below 6mm in maximal axial diameter on MRI); age (40–59 years, 60–75 years); and PSA (< 10.1 or PSA ≥ 10.1 to ≤20 ng/ml). The first subgroup underwent TRUS and TRUS/FUS-TB biopsy and the second underwent standard of care TRUS-guide biopsies only.

FUS-TB biopsy technique

The FUS-TB biopsy was performed during the same attendance as the TRUS-guided biopsy. FUS-TB fusion technique is based on co-registration of pre-acquired MRI images with real-time trans rectal ultrasonography. A conventional US machine with trans rectal transducer is used in conjunction with volume navigation software. Sensor micro coils are attached to the US probe or biopsy needle to enable registration of the probe position within the patient. The room set up for TRUS/FUS-TB biopsy is shown on Figure 11. Detailed description of the FUS-TB is included in Real-time software assisted (MR/US fusion guided) biopsy (FUS-TB) chapter of this thesis

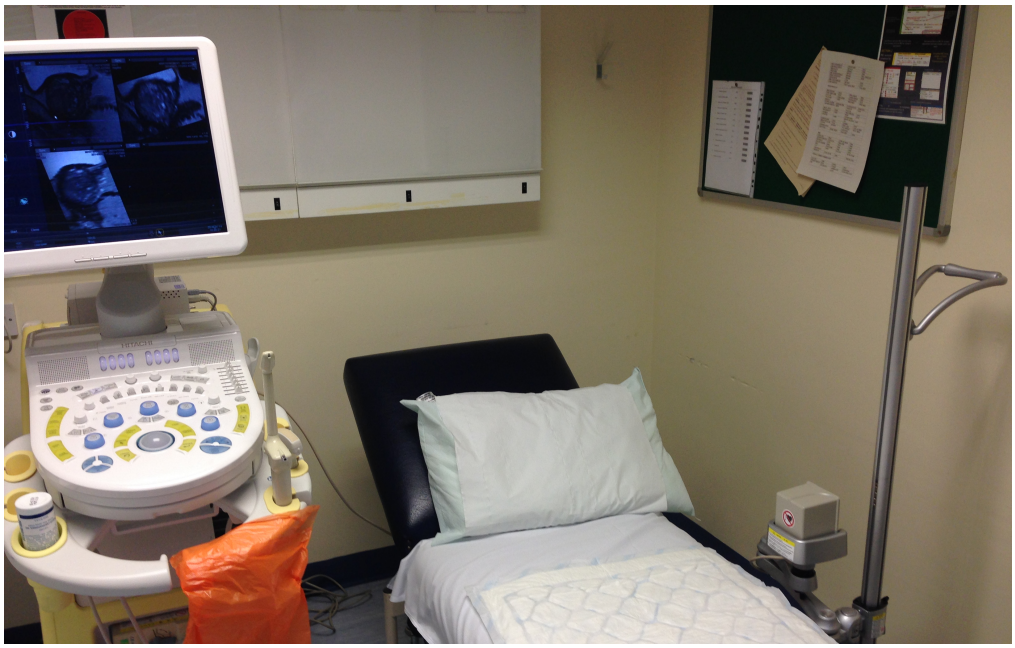


Figure 11 Room set up for FUS-TB biopsy procedure. Electromagnetic signal generator is situated at the level of patient's prostate gland (patient in left lateral position)

Biopsy Planning

T2 3D SPACE sequence acquired as a part of the MP MRI protocol was used for fusion biopsy planning by the study Uro-Radiologist. The MRI data were saved directly into the US machine, equipped with volume navigation software. The T2 SPACE sequence was iso-volumetric, which enabled 3D reformatting without loss of image resolution. Up to two most suspicious lesions, two landmarks (prostate gland apex and bladder neck) and approximate probe position within the rectum were marked on the MRI images by Uro-Radiologist prior to the procedure (Figure 12).

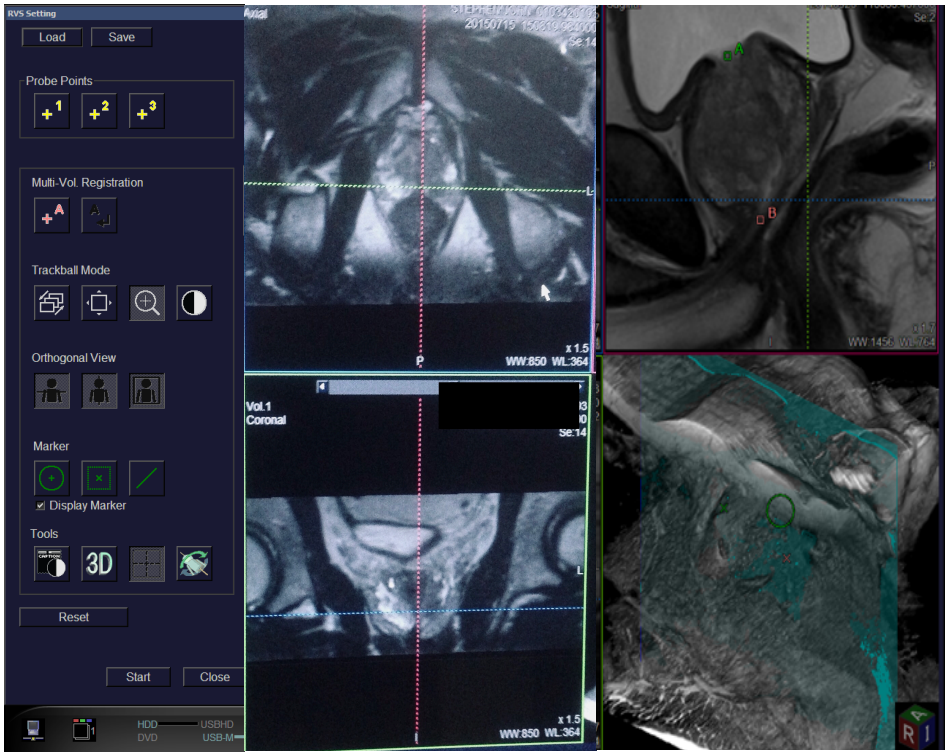


Figure 12 Biopsy planning on T2 SPACE MRI sequence

Patient preparation

The participants were prepared for biopsy as per local standard of care (SC) with oral antibiotics to prevent infection, urine dipstick test (negative for markers of infection) and verbal consent. Endorectal probe was inserted per rectum with a participant in a left lateral position. Local anaesthetic premedication was administered as per SC for TRUS-guided biopsy; no additional premedication was needed. The procedure took approximately 15 -20 min in addition to SC TRUS biopsy time.

Targeting of samples

Data from T2 3D SPACE sequence with marked lesions were reconstructed and displayed in sagittal plane on the left side of a split screen, by Uro-radiologist, during real-time US examination (Figure 13). The real-time US images were displayed on the right of the split screen. The US operator manipulated the probe to visualize the prostate gland in mid-sagittal view to match the MR image. When both images were alike, co-registration function was manually enabled , allowing simultaneous visualization of the gland on both 3D MRI and real time US images. After fusion functionality was enabled, the marked lesions were displayed on matched US images to allow targeted sampling. Needle guide was used to align the needle track with the marked target and biopsies were taken (Figure 13). 2-3 cores were routinely taken from each targeted lesion and stored separately for pathological analysis. 12 standard TRUS cores were obtained immediately after targeted biopsies were taken.

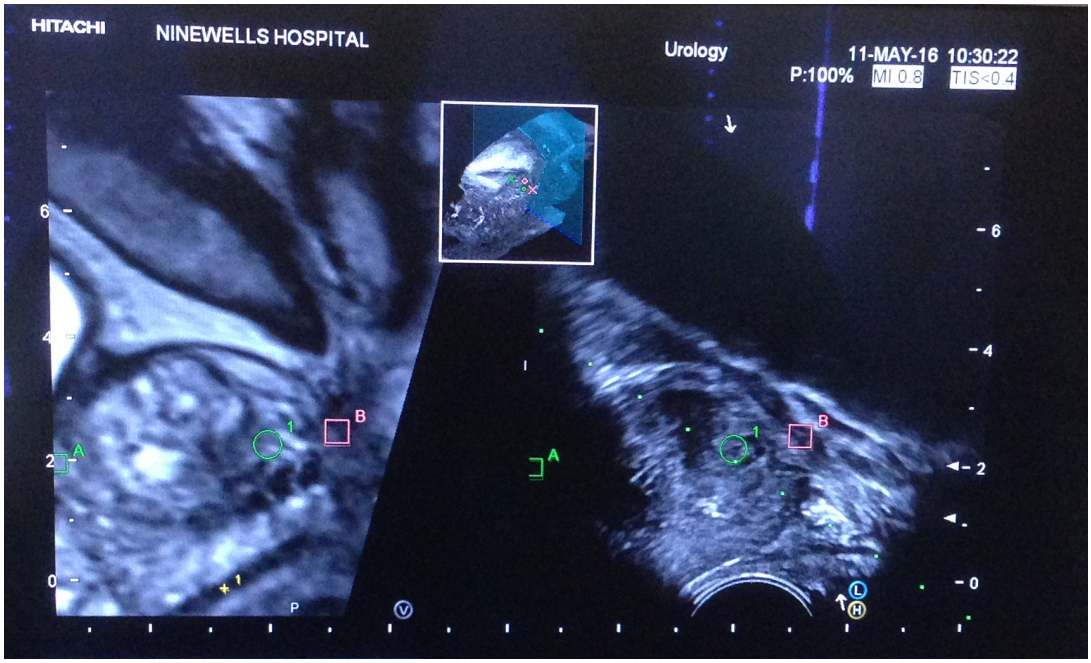


Figure 13 Co-registered MR (left) and US (right) images with marked suspicious lesion (green circle) and needle tract (dotted line) traversing it.

Biopsy specimen

The cores from prostate biopsy were transferred to pathology laboratory and placed in formalin for 48-72 hours at room temperature. Both types of cores (from TRUS and FUS-TB biopsy) were handled as per SC and analysed by NHS accredited, experienced Uro-Pathology Consultant. For each core, the size of the core, the presence and GG of prostate cancer and percentage of core involvement were recorded.

Definition of clinically significant cancer on biopsy

The definition of CS PCa on biopsy specimen was based on the 2014 International Society of Urological Pathology classification system (36) as ISUP grade group 2 or higher tumours (Gleason score 3+4 or above) in any core.

Patient recorded outcomes

Post-biopsy questionnaire

Data collection of post biopsy side effects and their severity was collected using standardised questionnaire (Table 9). All the participants from MR positive group undergoing TRUS and TRUS/FUS-TB biopsy were asked to fill in a post-biopsy questionnaire. The following data were collected: pain at the time of biopsy and after the biopsy, haematuria and bleeding from back passage (all on 4 –point severity and timescale) or others (free text). Adverse events (AE) and Serious adverse events (SAE) were recorded in relation to biopsy procedure and post-biopsy events. Participants were either called or approached at the time of their routine clinic visit approximately 1–2 weeks following the biopsy procedure to record biopsy-related AEs. It was anticipated that pain and bleeding will occur because of biopsy, but they were only recorded as an AE if they continue for more than 4 days post biopsy.

Have you experienced any of the following during/after biopsy?					
	Pain within 24 hours of biopsy	**Pain after 24 hours of biopsy**	**Blood in Urine after biopsy**	**Blood from back passage after biopsy**	**Other, specify** _____
	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	
Severity	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe	☐ Mild ☐ Moderate ☐ Severe
Duration	☐ Only during Biopsy ☐ Up to 1 hour after biopsy ☐ Up to 5 hours ☐ More than 5 hrs but less than 24 hours	☐ More than 24 but less than 48hrs ☐ 2-3 days ☐ 4-7 days ☐ More than 7 days	☐ Less than 24 hrs ☐ 1- 3 days ☐ 4-7 days ☐ More than 7 days	☐ Less than 24 hrs ☐ 1-3 days ☐ 4-7 days y ☐ More than 7 days	☐ Less than 24 hrs ☐ 1-3 days ☐ 4-7 days ☐ More than 7 days

Table 9 Post-biopsy questionnaire

3.3.3. Study intervention: RP specimen evaluation

In a subgroup of patients with confirmed CS PCa on subsequent biopsy, who opted for and underwent RP, the prostatectomy specimen was sectioned by accredited NHS Consultant Uro- pathologist using customised molds (91, 175) allowing for direct slice-to-slice comparison with MP MRI (Figure 14). This was carried out at the main site, NHS Tayside. The technique has been developed by the study biomedical engineer, Dr Wei and published in 2018 (176) and all the molds have been planned and printed by him.

Comparison of MP MRI with a reference standard of RP pathology was performed. This intervention was carried out for the first 89 RP participants, till the primary target was met.

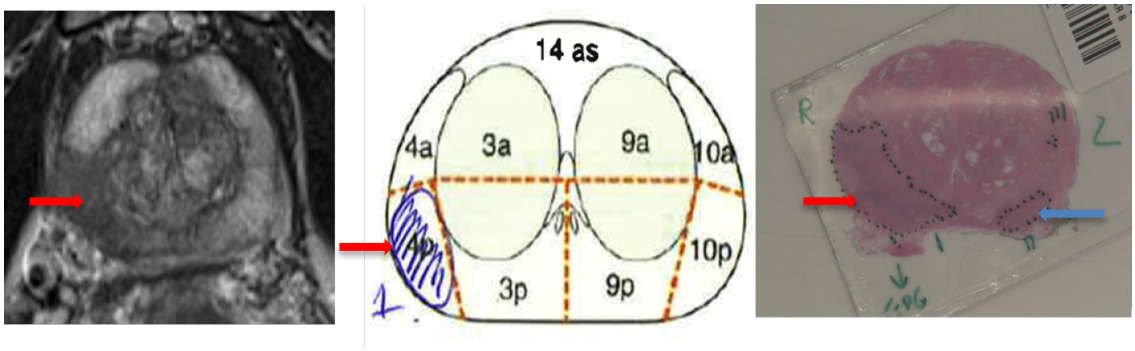


Figure 14- Slice-to-slice comparison between MRI examination and prostatectomy specimen. MRI detected the largest lesion in the right peripheral zone (20mm, GG 3+4 – red arrow) but failed detect another significant lesion in the left peripheral zone (GG 4+3, less than 10mm- blue arrow)

Customized 3-D printed molds for prostate specimen evaluation

The preparation process for the customized molds, for prostate sectioning during histopathology process, is based on anatomical information from MRI (T2WI), comprises of 7 steps (1) -(7), as illustrated in Figure 15.

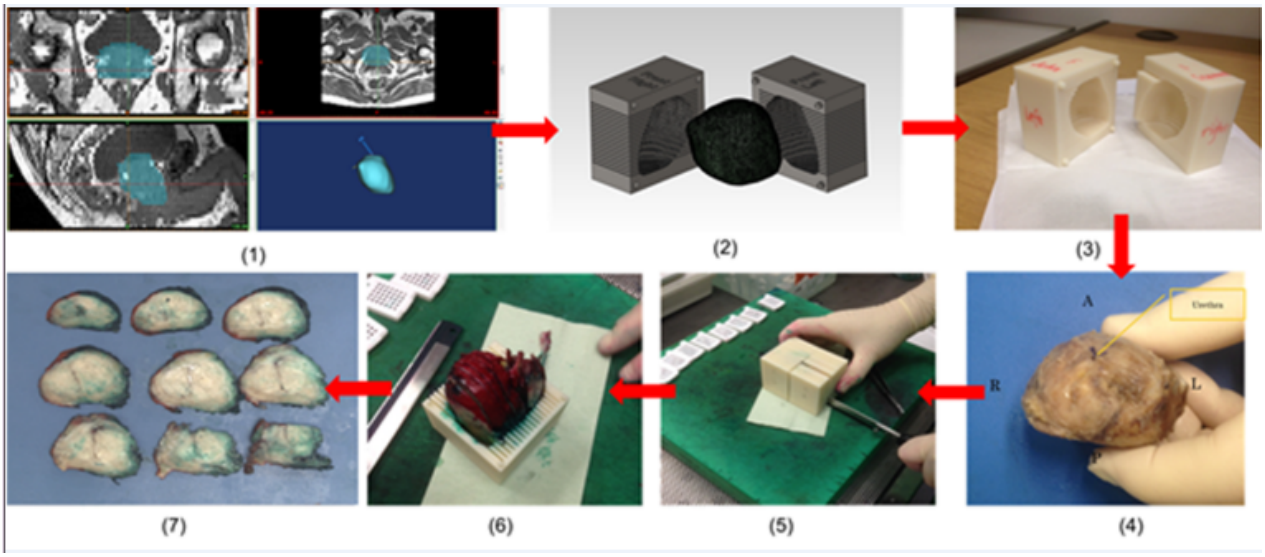


Figure 15 Preparation of 3-D printed customized mold for radical prostatectomy specimen and subsequent specimen sectioning

Step 1 -3D segmentation of prostate contour

T2WI images acquired in three planar views were used to trace the boundary of the prostate capsule, using MIMICS software (Medical Image Segmentation for Engineering on Anatomy). The segmentation of the prostate was done on axial T2WI sequence. Each model was saved as a stereo lithography (STL) file.

Step 2- 3D prostate model generation and modification

3D model was fused and converted into an object, simulated in software MIMICS to represent patient's prostate topography. Before modification, the 3D prostate model was verified and compared with the MRI sequences to ensure matching. The model was subsequently imported to CAD software Meshmixer (2011 Autodesk, Inc.) for smoothing and reducing the difficulty of mold fabrication. The smoothed model was then saved as STL file as a mesh model and transferred back to MIMICS for triangle reduction to reduction of the file size.

Step 3- Mold printing

The triangle-reduced mesh model was imported into SolidWorks (3D CAD design software, analysis software, Dassault Systèmes SolidWorks Corp. USA) as a SolidWorks Part (SLDPRT) model. The solid simulated prostate model was wrapped up by a cubic or rectangular model block and 'subtraction' applied to the two models. As a result, a new model, with an internal cavity for precise holding of patient's prostate, was created. Once the position of prostate in the mold was determined, slots for sectioning the specimens were placed into the mold, with a location of axial direction according to 2D images from axial T2WI MRI sequence. Each slot was 1.2 mm thick to fit single trimming blade with thickness of 0.245mm (Feather Safety Razor Co., LTD. Medical Division) with a 3mm interval, which represents the inter-slice gap between each axial MRI slice. The mold was divided into 2 halves (left and right) using feature 'split' for embedding of prostate specimen. Mold prototyping with fused filament fabrication technology 3D fabrication of each mold was created on a 3D printer (MakerBot Replicator 2X). The 3D printer was equipped with dual print heads, which created two different parts with fused deposition of materials at the same time. Acrylonitrile butadiene styrene (ABS) with

filament diameter of 1.75mm was used. The patients' mold parts were printed layer by layer with the layer height of extruded filament of 100-300 microns. All solid portions of the model parts were automatically printed in the lattice of honeycomb for reduction of materials usage and print time. Printing time ranged from 4 to 7 hours and depended on the size of each mold and the applied layer height.

Step 4-7- RP specimen dyeing and sectioning

Following RP, prostate specimen was transferred to pathology laboratory and placed in formalin for 48-72 hours at room temperature. Before being sliced in the mold, the specimen's edges were painted (left part in green and right part in red). The seminal vesicles were excised. During the sectioning, a single blade was used to cut the prostate within the mold, applied carefully to avoid specimen friction and shifting. After slicing, all histopathology sections were photographed and stored in separated tissue blocks for further analysis. The sliced RP specimen was analyzed under the microscope, slice by slice, by experienced NHS accredited Consultant Uro-Pathologist. The number, location, size and Gleason grade of each prostate cancer focus was recorded.

Definition of clinically significant cancer on RP specimen

The definition of clinically significant disease was based on the pathological assessment of RP and included the presence of the following two prognostic factors:

1. GG ≥ 7 with pattern 4 or/and 5
2. Maximum cancer focus size ≥ 6mm measured in the axial plane

3.4. STATISTICAL ANALYSIS

3.4.1. Sample size calculation

It was calculated that 600 participants were needed to answer the second research question, based on power of 80% and detection difference of at least 11% between randomisation arms. Relevant published study (177) suggested, that 80% of all pre-biopsy MRI will have lesions suspicious of PCa (PIRADS 3 or above). It was therefore estimated that out of 600 participants, 480 (80%) will have a positive MP MRI and each of two randomisation arms will have approximately (n=240) participants.

Local audit information suggested that after a positive diagnosis of localized PCa, around 25% of men will opt for radical surgery as a treatment option.

Based on recruitment of 600 eligible men, the power calculation, based on 80% sensitivity and precision of +/- 9% and an AUROC = 0.9 suggested that at least 80 men with complete datasets from imaging and histopathology of RP were needed to answer the first research question. Dropout rate and incomplete datasets have been taken into consideration.

Initially, the total duration of the recruitment phase was 48 months; however, this was extended to 66 months to achieve target with approval from the funding body (Figure 16).

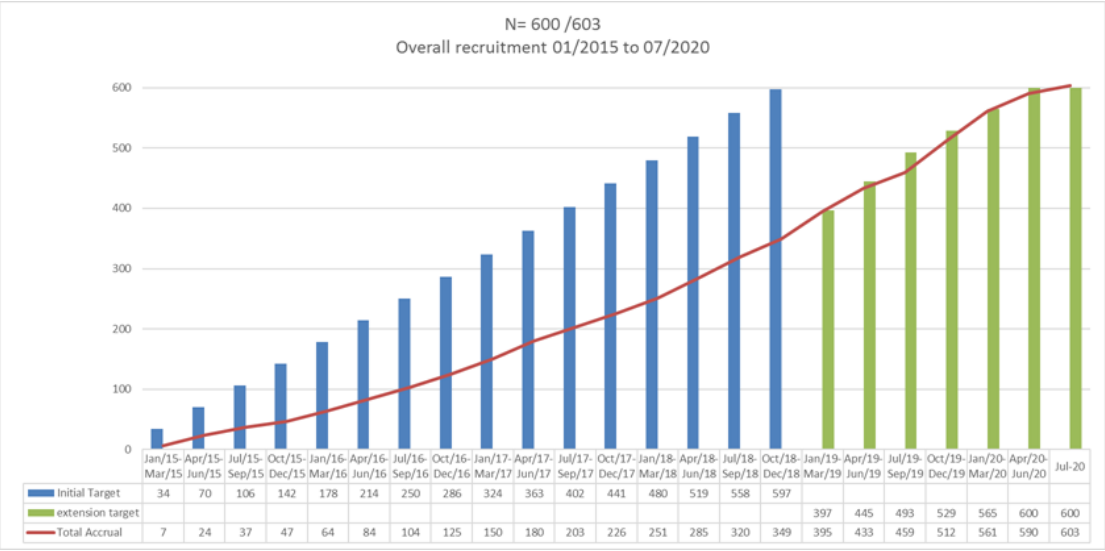


Figure 16 Study Overall Recruitment Graph

3.4.2. Timing of Analyses

The final analysis was performed after all data have been entered and the database has been locked (September 2020).

3.4.3. Cohort demographics

Baseline characteristics for patients were: site, age, PSA, PIRADS score, size of largest lesion and number of lesions.

Medical history was collected as presence/ absence of specific diseases. A composite comorbidity score was created by adding up all entries, which were marked as present. The score went from 0 (no medical history) to 18 (all medical history). The comorbidity score was used as a covariate in the analysis and was categorised as 0, 1-4, 5+ comorbidities if the distribution was skewed.

3.4.4. Efficacy Analyses

Endpoints 1A-B:

Analysis of performance of MP MRI (diagnostic test) against RP histopathology (gold standard) was performed on lesion-level (endpoint 1A) and on patient level (endpoint 1B) on an intention to treat basis, using the receiver operating characteristic curve (ROC) method for binary outcomes (CS PCa present Yes/No) for subjects who underwent RP (n=89). The test data were on the ordinal scale (PIRADS probability scale 1-5) but were dichotomised with a cut-off level (threshold) of 3 (PIRADS 1-2=negative MRI, PIRADAS 3-5 =positive MRI) allowing methods for binary outcomes to be used.

A 2x2 contingency tables containing the counts of the 4 combinations of disease status (true negatives, false negatives, false positives, true positives) were formed (Table 10).

	GS (Radical Prostatectomy)		
Dx (MP MRI)	**Nondiseased (GS=0)**	**Diseased (GS=1)**	**Total**
Negative(Dx=0)	A-true negatives	B-false negatives	A+B=test negatives
Positive(Dx=1)	C-false positives	D-true positives	C+D=test positives
Total	A+C=nondiseased	B+D=diseased	A+B+C+D=total sample size

GS-gold standard DX-diagnostic test Specificity-=true negative rate=A/(A+C)	Sensitivity=true positive rate=D/(B+D) Negative predictive value=A/(A=B) Positive predictive value=D/(C+D)

Table 10 Contingency Table of Counts Based on the Diagnostic Test and Gold Standard

The accuracy of MP MRI was assessed in terms of probability of it correctly classifying diseased subjects as positive (presence of CS PCa)-*sensitivity* and correctly classifying non-diseased subjects as negative (no CS PCa)-*specificity*.

ROC curve was a plot of sensitivity on the Y axis, against 1-specificity on the X axis with a threshold of 3.

Performance of the diagnostic test (MP MRI) was estimated from the area under receiver operating characteristic (AUROC) curve drawn from the estimated probability given by the corresponding logistic regression models.

GEE model was used, which allowed incorporation of clustering of up to 10 lesions per patient.

Accuracy or calibration was assessed by implementing the Hosmer-Lemeshow test for calibration and calibration curves (goodness of fit).

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each variable was calculated with a two-sided p value <0.05.

All ROC analyses were performed using SAS 9.4 version.

Endpoint 1C:

Additional analysis of all the above parameters was performed with an increased threshold of MP MRI positivity to 4 using the same methodology.

Specificity (true negatives/ true negatives + false positives) and positive diagnostic value (true positives/true positives + false positives), on lesion level, was performed separately for individual positive PIRADS scores (1-3).

Endpoint 1D:

Cohen kappa value was used to quantify inter-reader agreement(178). Agreement between the readers was defined as follows: 21-40%-fair, 41-60%-moderate, 61-80%-good, 81-100%-excellent.

Endpoint 1E:

The MP MRI detection rate of PCa depending of its Gleason score was calculated as a number of correctly identified foci of each specific grade of PCa (ordinal scale-Gleason <6,6,7,>7) by MRI in relation to all foci of the same grade detected by RP.

Endpoint 1F:

The foci of CS PCa which were undetected on MR MRI but were present on the RP specimen were qualitatively analysed in relation to their size (7-9mm, >9mm) and location (anterior or posterior half of the gland).

Endpoint IIA:

Analysis for the outcomes of the randomised study was performed on the intention to treat basis. Analysis of the randomised comparison between TRUS and TRUS/FUS-TB biopsy was implemented according to the ICH E9 'Statistical Principles in Clinical Trials'. As most patients will have cancer given the initial positive MRI, the primary outcome was based on differences in CS cancers as this is the key to management. The binary outcome of cancer presence (Yes, No), was analysed using logistic linear regression algorithm with intervention arm as a binary variable in the model. All analyses were stratified by site and all minimisation variables (PIRADS, size, age and PSA) and adjusted for co-morbidity and prostatic volume.
Difference in probability of cancer detection between intervention and control groups (TRUS/FUS-TB biopsy versus TRUS biopsy) were presented as odds ratio representing the odds of each test correctly detecting the presence or absence of the disease (Table 11). Ratios were presented as TRUS/FUS-TB biopsy relative to

TRUS so ratios greater than 1 favour TRUS/FUS-TB biopsy and less than 1 favour TRUS biopsy.

		TRUS/FUS-TB biopsy	
		Positive	**Negative**
TRUS biopsy	**Positive**	A	B
	Negative	C	D

Odd Ratio (OR)= $\frac{\frac{A}{B}}{\frac{C}{D}} = \frac{AD}{BC}$

Upper 95% CI= $e^{[\ln(OR)+1.96\sqrt{(\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}]}$

Lower 95% CI= $e^{[\ln(OR)-1.96\sqrt{(\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}]}$

Table 11 Odds Ratio formula

Endpoint IIB:

Safety analysis of adverse events was performed on all randomised patients. This outcome was assessed by combining all Adverse Events (AE).

AE were coded with MedDRA 20.1. Where more than one diagnosis was present in the AE description, the AE were split with all the descriptors kept the same for all diagnosis. Adverse events were reported by primary System Organ Class (SOC) and Preferred Term (PT).

Subjects were counted only once when calculating the incidence of AEs. An overview table was created counting the number of adverse events by system organ class and preferred term. Descriptors for Adverse events were tabulated separately as described for categorical variables. The total number of AEs was used as basis for tabulation. In a second table, SAE were tabulated as described for AE.

Endpoint IIC:

Detection rate of all cancers and CS PCa in MP MRI negative group was calculated based on results from subsequent TRUS prostate biopsy in a group of patients who underwent it.

3.4.5. Reporting Conventions

P-values ≥0.001 were reported to 3 decimal places; p-values less than 0.001 were reported as "<0.001". The mean, standard deviation, and any other statistics other than quantiles, were reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum used the same number of decimal places as the original data.

3.4.6. Recruitment challenges

The importance of identifying suitable sites to support recruitment of participants underpins the success of all trials. There was active search for recruitment sites in the UK between January 2015 and December 2019. The major challenges for extending recruitment to other centres remained in availability of specialist clinical support, due to NHS staff pressures and shortages, availability of 3T scanner (with subsequent protocol change allowing scanning at 1.5T using optimized imaging protocol to address this issue) as well as the equipment and experienced staff to perform MRI/US guided fusion biopsy. The study required support in three main areas: pre-biopsy MRI, the use of Fusion technology and clinical support (urologists, radiologists, pathologists, urology specialist nurses and research nurses).
A dedicated national database listing hospitals' equipment and infrastructure does not exist in the UK and therefore geographical mapping as a way of displaying support available was used. An online search was the primary means of identifying potential hospitals. A total of 88 contacts were retrieved. An initial contact was made with the local clinicians, R&D offices and networks. The hospital name, MRI and Fusion technology availability, contact details and responses were recorded in an excel spreadsheet. These were then transferred into a geographical mapping tool using Google UK map software (Figure 17), the hospital name was recorded as the primary data. These challenges were:

- The application of the standard of care treatment pathway differs between sites.
- A limited number of sites in the UK have 3TMRI
- A limited number of sites in the UK have Fusion technology

- Some regions have adopted the use of FUSION technology as part of their treatment pathway
- In some sites, the participant pathway requires visits to different hospitals
- MRI scan reporting differs between Boards/Trust
- Staff shortages/research time – due to clinical pressure

Figure 17 Geographical mapping tool using Goggle UK map software depicing approached potential recruitment sites

3.4.7. End of study

The end of study for a participant was the date at which the biopsy procedure was performed plus 30 days. The definition of the end of the study date for the study was database lock.

4. RESULTS

4.1. Research questions

4.1.1. Research question I:

How reliable is pre-biopsy MP MRI in identification of foci of CS PCa and in avoidance of over detection of NS PCa?

Research question I endpoints:

A. Diagnostic accuracy of MP MRI in detecting lesions of SC PCa
B. Diagnostic accuracy of MP MRI in detecting patients with SC PCa
C. Specificity and positive predictive value of each positive PIRADS scores (3-5) on MP MRI in detecting lesions of SC PCa
D. Accuracy of Inter-observer agreement on positivity of MP MRI between Uro-radiologists on patient-basis
E. MP MRI detection rate of PCa depending of its Gleason score (measure of aggressiveness)
F. Qualitative analysis of location and size of foci of CS PCa undetected on MP MRI

4.1.2. Research question II:

Will adding MR-guided targeted cores to standard TRUS biopsy of prostate gland detect more CS PCa than standard TRUS biopsy alone, with no significant increase of NS PCa detection and with similar profile of adverse events?

Research question II endpoints:

A. Difference in probability of cancer detection between intervention and control groups (TRUS/FUS-TB biopsy versus TRUS biopsy) presented as an odds ratio representing the odds of each test correctly detecting the presence or absence of the disease

B. Review of the safety outcomes of death, post biopsy side effects such as pain and bleeding and duration of symptoms in each of the two randomized groups

C. Assessment of false negative rate of MP MRI-number of cancers and CS cancers detected by TRUS biopsy in MP MRI negative group

4.2. Cohort demographics

4.2.1. I research question

A total of 91/413 MRI positive participants (22%) who opted for RP as the treatment option were included to inform the first research question. Of these, 2 participants' prostates were not sectioned in customised molds and were excluded from analysis. The RP specimens of the 89 participants with positive MP MRI were analysed using molds and compared with MP MRI results. The mean patient age was 65.8 ± 5.61 years (range from 51-75); mean PSA was 9.2 (SD 3.66) ng/ml (range from 2.5-19) (Table 12).
Median time between MP MRI and RP was 125 days (IRQ 71-330 days).

	Total(N=89)	
	Mean (SD)	**Median (Range)**
Age (years)	65.8 (5.61)	65 (51, 75)
PSA (ng/ml)	9.2 (3.66)	8.7 (0.0, 19.0)

Table 12 Basic characteristics of MP MRI vs RP study group (N=89)

4.2.2. II Research question

603 eligible and consented participants were recruited to inform the second research question. 21 participants were withdrawn (Figure 18) and 582 had a complete MP MRI examination of the prostate. 413 had a positive MP MRI (presence of at least 1 PIRADS =>3 lesion) and underwent randomisation to intervention (207) and control (206) groups. Basic characteristics of all 603 participants is depicted in Table 13.

Characteristic	Total (n=603)	Intervention group (n=207)	Control group (n=206)	MRI negative arm (n=169)	No MRI results (n=21)
Age at referral					
Mean (SD)	64.8 (6.41)	65.4 (6.34)	65.1 (6.30)	63.8 (6.57)	63.1 (6.01)
Median (IQR)	65.0 (47.0, 75.0)	66.0 (49.0, 75.0)	66.0 (47.0, 75.0)	64.0 (47.0, 75.0)	65.0 (50.0, 74.0)
PSA at referral					
Mean (SD)	9.0 (6.53)	9.3 (6.12)	10.2 (8.62)	7.1 (3.10)	8.4 (2.75)
Median (IQR)	7.7 (1.0, 86.0)	8.2 (1.0, 74.0)	8.6 (1.0, 86.0)	6.7 (1.0, 18.0)	8.1 (4.0, 14.0)

Table 13 Characteristics baseline of all recruited participants (603)

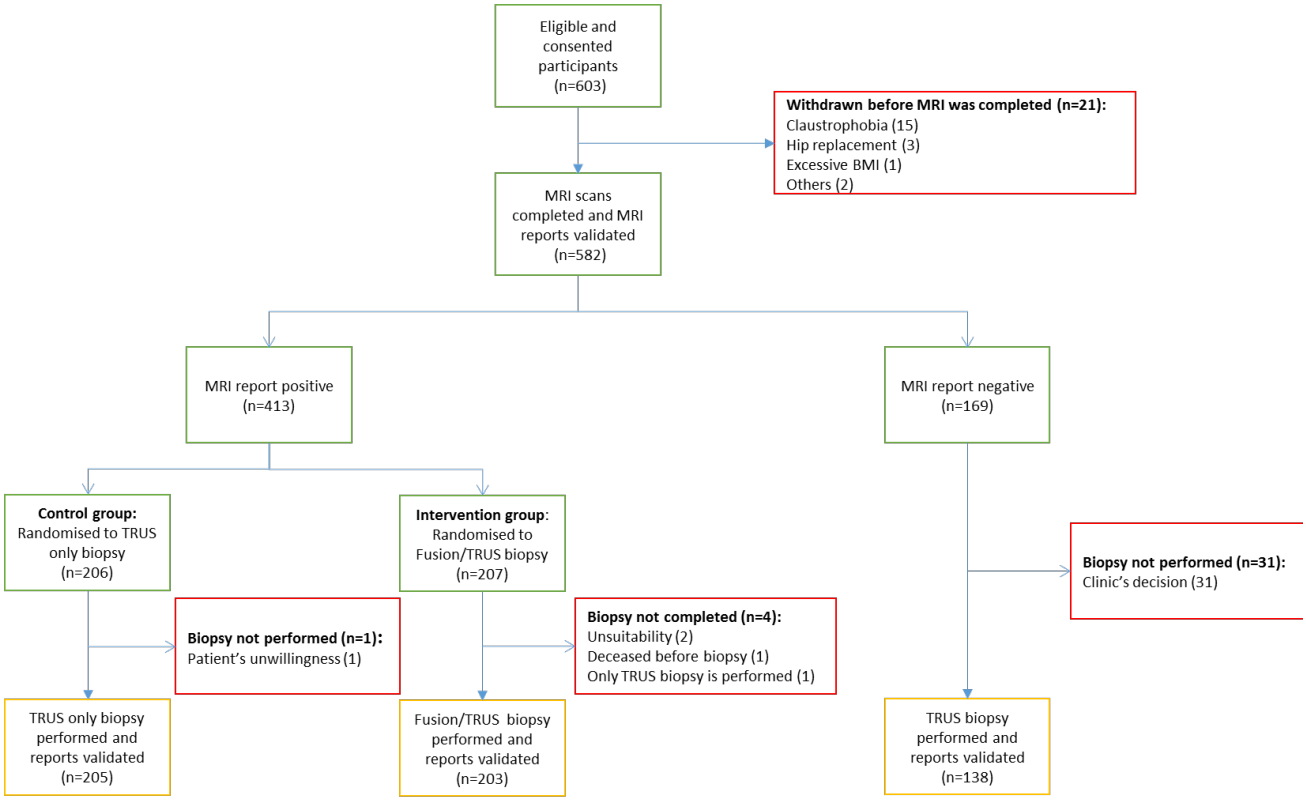


Figure 18 recruitment, randomisation and follow-up of participants

4.3. Endpoints- Research question I

4.3.1. Endpoint IA -Diagnostic accuracy of MP MRI in detecting lesions of SC PCa

In 89 prostate specimens, 182 foci of CS PCa were detected, out of which MP MRI correctly identified 131 (sensitivity: 72.0%, 95% CI 64.9%-78.4%); The specificity, PPV and NPV were 71.1%, 78.0% and 64.1%, respectively (Table 14).

MRI detection analysis for cancer (lesion based)			RP specimen							
			no cancer		Non-sig		sig		total	
MRI (PIRADS)	negative (<3)				91		51		142	
	positive	3	28	11	9	1	131	13	168	25
		4		14		4		48		66
		5		3		4		70		77
	total		28		100		182		310	
Sensitivity			0.72 (95% CI 0.65, 0.78)							
Specificity			0.71 (95% CI 0.62, 0.79)							
PPV			0.78 (95% CI 0.71, 0.84)							
NPV			0.64 (95% CI 0.56, 0.72)							
OR (95% CI)			1.87 (1.33, 2.4); P<0.0001							

Table 14 Significant cancer detection rate for MRI compared with LRP on lesion-basis

4.3.2. Endpoint IB- Diagnostic accuracy of MP MRI in detecting patients with SC PCa

All 89 RP specimens contained foci of PCa (as previously confirmed on biopsy) but 4 RP specimens did not contain foci of CS cancer. The overall patient-level sensitivity of MP MRI for CS PCa was 95.5% (Table 15).

Patient Level		CS PCa detected by LRP
		N (%)
CS Cancer detected by MRI	No	4 (4.49)
	Yes	85 (95.51)
Sensitivity	0.95 (0.89, 0.99)	
Specificity	N/A	
PPV	1.00 (0.96, 1.00)	
NPV	N/A	

Table 15 Significant cancer detection rate for MRI compared with LRP on patient-basis

4.3.3. Endpoint IC - Specificity and positive predictive value of each positive PIRADS scores (3-5) on MP MRI in detecting lesions of SC PCa

A total of 168 lesions of PIRADS 3 or above were identified on MP MRI of 89 participants, consisting of 77 PIRADS 5, 66 PIRADS 4 and 25 PIRADS 3 lesions. PIRADS 5 lesions had the highest percentage of CS cancers (90.9%), followed by PIRADS 4 (69.7%) and PIRADS 3 (52.0%) (Table 16).

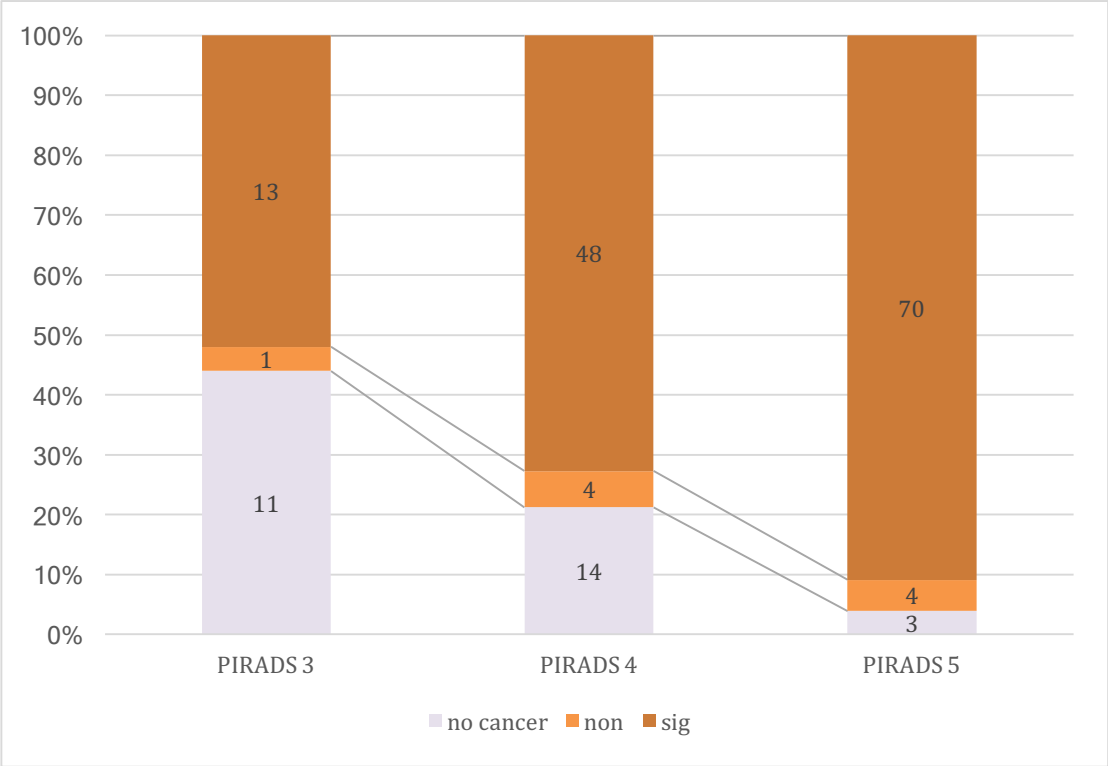


Table 16 Percentage of lesions with CS PCa and non-CS PCa identified according to PIRADS score

70/77 of PIRADS 5 lesions had a matching focus of CS PCa on RP specimen achieving a very high PPV of 91% and specificity of 94.5% to correctly identify focus of CS PCa. 48/66 Of PIRADS 4 had a matching focus of SC cancer (PPV of 72.7%, specificity 13/25 of PIRADS 3 lesions had a matching focus of CS PCa on RP (PPV of 0.48, specificity 90.62%) (Table 17)

A total of 143 lesions were classified as PIRADS 4 or 5 at MP MRI. 25/143 did not have a matching focus of CS PCa on RP specimen, achieving high specificity and PPV in correctly identifying CS PCa of 84.3% and 85.1% respectively. Excluding PIRADS 3 lesions, increases detection rate at the expense of decrease in sensitivity and negative predictive value from 71.9 to 63.1 and 64 to 61.7% respectively.

		CS lesion detected by LRP			
		No (N=128)	Yes (N=182)		
CS Lesion detected by MRI					
PIRADS 5	No	121	112	**Specificity**	0.94 (0.89, 0.98)
	Yes	7	70	**PPV**	0.91 (0.82, 0.96)
PIRADS 4	No	110	134	**Specificity**	0.86 (0.79,0.92
	Yes	18	48	**PPV**	0.73 (0.62, 0.81)
PIRADS 3	No	116	169	**Specificity**	0.91(0.84, 0.95)
	Yes	12	13	**PPV**	0.52 (0.34,0.7)
(PIRADS >=4)	No	103	64	**Sensitivity**	0.63 (0.56, 0.7)
				NPV	0.62 (0.54,0.69)
	Yes	25	118	**Specificity**	0.84 (0.77, 0.9)
				PPV	0.85 (0.78, 0.91)

Table 17 Correlation between PIRADS 3, 4 and 5 lesions from MP MRI and foci of CS PCa on RP specimen

4.3.4. Endpoint ID- Accuracy of Inter-observer agreement on positivity of MP MRI between Uro-radiologists on patient-basis

160 participants' MRI scans (All 89 MRI from the RP group and 71 from the non-RP group to avoid bias) were retrospectively read by a Uro-radiologist, blinded to the first read and clinical information.

The inter-observer agreement accuracy, calculated on the patient-basis (scan positive/negative) was 91.25% (Cohen kappa of 69.73% which corresponds to a

substantial agreement) (Table 18). The MP MRI scans with at least 1 PIRADS lesion 3 or above were considered positive.

Patient based	**First reading**				
Second reading	**Positive**	**Negative**			**Total**
	0.78	0.03	0.81	**Accuracy**	91.25%
	0.06	0.13	0.19	**P1**	71.09%
Total	0.83	0.16	1	**kappa**	69.73%

Table 18 Inter-observer agreement calculations from 160 double-red MP MRI scans

4.3.5. Endpoint IE: M MP MRI detection of PCa depending of its Gleason score (measure of aggressiveness)

When the GS of the detected cancer foci was considered (Table 19), MRI detected 86.7% of GS>7 cancers (26/30), 54.4% of GS 7 cancers (112/206) and only 4.3% of non-significant GS 6 cancers (2/44).

Overall the higher the Gleason score, the more likely it is to be detected by MP MRI and clinically NS GS 6 lesions are extremely unlikely to be observed on MRI (only 4.3% of them visible in our series) (Figure 19).

		Gleason Score				
PIRADS vs Gleason SCORE		<6	6	7	>7	total
PIRADS	<3		44	94	4	142
	3	11	0	13	1	25
	4	14	0	47	5	66
	5	3	2	52	20	77
	total	28	46	206	30	310

Table 19 PIRADS scores from MP MRI vs Gleason scores from RP specimen

Figure 19. MRI detection rate in different group of Gleason Score

4.3.6. Endpoint IF: Qualitative analysis of location and size of foci of CS PCa undetected on MP MRI

282 foci of cancer were identified on RP specimens of the 89 participants out of which 182 were CS PCa. 140/282 matched the suspicious lesions on MP MRI while 142 lesions had no corresponding abnormality on MR (Table 17). However out of 142 lesions with no corresponding MR abnormality, majority - 91 were clinically not significant (GG 6 disease or focus smaller than 6mm) (Table 6). 51 CS cancer foci were missed by MP MRI, with most them (39/51) either small and/or situated in the anterior part of the gland. 15 lesions were less than 10mm in size, 33/51 were situated in the anterior half of the gland (Appendix C3, Table 1)

4.4. Endpoints-Research question II

4.4.1. Endpoint IIA -Difference in probability of cancer detection between intervention and control groups (TRUS/FUS-TB biopsy versus TRUS biopsy)

124 /206 (60.2%) patients had PCa detected on biopsy in the control group (TRUS biopsy). 151/207 (72.9%) patients had PCa detected in the intervention group (TRUS/FUS-TB biopsy) (Table 18). There was statistically significant difference in probability of all cancer detection between intervention and control groups (p=0.00016) both for treatment alone and when adjusted for minimisation variables (OR = 2.16 (1.34, 3.47))

The combined TRUS/FUS-TB pathway detected CS PCa in 130/207 (62.8%) patients, while the TRUS alone arm detected 106/206 (51.5%) CS PCa (Table 18). A significant increase in the detection of CS lesions in the intervention arm compared to systematic alone (OR= 1.79 (1.14, 2.79)) was observed (Table 21).

The combined TRUS/FUS-TB pathway detected NS PCa in 21/207 patients (10.1%) while TRUS alone arm detected 18/206 (8.7%) of NS PCa.

Variable	**TRUS (N=206)**	**TRUS/ FUS-TB (N=207)**
Cancer diagnosed by either TRUS or FUS-TB		
No	82 (39.8)	56 (27.1)
Yes	124 (60.2)	151 (72.9)
Clinically significant cancer diagnosed by either TRUS or FUS-TB		
No	100 (48.5)	77 (37.2)
Yes	106 (51.5)	130 (62.8)

Table 20 Number of all cancers and CS cancers detected in both randomisation arm

	Unadjusted		Adjusted*	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
All Cancers				
	1.90 (1.24, 2.90)	0.0031	2.16 (1.34, 3.47)	0.0016
CS PCa				
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
	1.63 (1.10, 2.42)	0.0163	1.79 (1.14, 2.79)	0.0109

Table 21 Results of logistic regression for trial outcome of all Cancers and Clinically Significant Cancers for Intervention group vs Control group

In the intervention arm, FUS-TB alone biopsy was positive for CS PCa in 114/207 (55%) cases whether TRUS biopsy alone in 103/207 (49%) CS cancers (Table 22).

TRUS/ FUS-B (207)			
	FUS-TB positive	**FUS-TB negative**	**Total**
TRUS +	85	17	**103**
TRUS -	28	77	**100**
	114	**88**	**207**

Table 22 Number of CS cancers detected by each biopsy method in Intervention arm (TRUS/FUS-B)

4.4.2. Endpoint IIB- Review of the safety outcomes of death, post biopsy side effects such as pain and bleeding and duration of symptoms in each of the two randomised groups.

No clinical difference was observed between the randomized groups in relation to duration and type of AE. The higher number of AE in the intervention group (64 vs 48) was mainly due to transient post - procedural symptoms such as haematospermia (6.3% va4.4%), haematuria (19.8% vs 17.05%) and post-procedural

pain (4.8% vs 2.9%) and was thought to be related to a higher number of cores taken during combined biopsy (Appendix C1). The mean and median duration of all AE was similar between both study groups. There was no imbalance in the number of SAE between the study groups with equal number of related SAE between the arms (Only 1 SAE reported from each group related to biopsy procedures) (Table 23).

Characteristic	Control arm	Intervention arm
All participants	206	207
Participants with AEs	48 (23.3%)	64 (30.9%)
Participants with SAEs	1 (0.5%)	2 (1.0%)
Cerebral haemorrhage	0 (0.0%)	1 (0.5%)
Sepsis	0 (0.0%)	1 (0.5%)
Urosepsis	1 (0.5%)	0 (0.0%)

Table 23 AEs and SAEs reported in Control arm and intervention arm

	TRUS (N=206)		TRUS/ FUSION (N=207)	
No of Adverse Events	48		64	
	Mean (SD)	**Median (Range)**	**Mean (SD)**	**Median (Range)**
Duration of AE [days]	7.5 (3.52)	8.0 (1, 23)	8.0 (5.79)	8.0 (1, 46)

Table 24 Comparison of duration of symptoms between both randomisation groups

4.4.3. Endpoint IIC: Assessment of false negative rate of MP MRI-number of cancers and CS cancers detected by TRUS biopsy in MP MRI negative group

169/603 (28%) participants had negative MRI, out of which 138 underwent TRUS biopsy. 31 participants either they opted out or were not offered the biopsy as per clinical decision, as their PSA subsequently normalised. 22/138 (15.3%) had cancer diagnosed on TRUS biopsy, but only 8/138 (5.8%) had significant cancer (GG > 6) confirmed.

5. DISCUSSION

The results of endpoints 1A-C confirm high sensitivity of MP MRI in detection of CS PCa on lesion-level of 72%, with relatively high specificity of 71% and reassuringly balanced PPV and NPV of 78% and 64.1% respectively.

Previous studies assessed the diagnostic accuracy of MP MRI on patient level, reporting variable sensitivity, which in systemic review of the literature by Futterer et al (20) ranged between 44-87% in the included studies, depending on the choice of reference standard, MRI scoring system used and definition of CS PCa. In the same review by Futterer et all, the authors made a comment that the ideal study design to address their research question ("Can CS PCa be detected with MP MRI?") would include MP MRI before prostate biopsy and use definitive pathology for whole-mount sections of RP specimens as a reference standard. Multipros study succeeded in this with the added value of unique and accurate method of spatial correlation on lesion-to-lesion level.

To my knowledge, only 2 previous studies indirectly looked at performance of MP MRI on lesion basis, one by Lin et al, used PIRADS v2.0 and comparing to RP using MRI and RP tumour maps, with a notable limitation of MP MRI performed post-biopsy, small study group and retrospective study design (179). Interestingly, their overall accuracy for detection of SC PCa was 65%, lower but within a similar level as

that in my results. Study by Auer et al, assessed diagnostic accuracy of MP MRI using PIRADS v 2.0, on lesion-basis with RP as a reference standard on a patient group of 50. The study achieved diagnostic accuracy of 90% for all PCa including non-significant disease.

Woo et all, reported on combined sensitivity and specificity of MP MRI on patient-level, using PIRADS v 2.0 system from 21 studies with pooled sensitivity of 89% and specificity of 73% with various choices of reference standards being significant factor affecting heterogeneity of the results (180).

In the PROMIS study, a large paired validating confirmatory study -one of the main pieces of high level evidence that has driven the paradigm shift in diagnostic pathway of PCa and subsequent NICE guidance update (11), sensitivity of MP MRI for CS PCa using transperineal template mapping biopsy as a reference standard, was calculated at 93% (CI 88-96%) with much lower specificity of 41% (6).

Endpoint 1C results regarding ability of each of positive PIRADS scores (3-5) on MP MRI in detecting foci of SC PCa are even more encouraging to other published studies on the subject. 91% of all PIRADS 5 lesions, 77% of all PIRADS 4 and 48% of all PIRADS 3 lesions corresponded to CS PCa foci on RP. PROMIS study results in MRI positive group in relation to PIRADS scores accuracy in detection of CS PCa were much lower (transperineal biopsy as a reference standard) but showed a similar trend (80.7, 58% and 20.8%, respectively).

Endpoint 1E results confirm that the higher the PIRADS score, the more likely it is to detect focus of CS PCa and the higher the GS, the more likely it is to be detected by MP MRI. Study by Auer et al (181), most comparable to these results, as performed on lesion basis, using RP as a reference standard reported 100%, 75% and 18% of PCa detection according to PIRADS 5,4,3 respectively, with the difference that analysis included non-significant PCa.

The problem of over diagnosis of PCa and subsequent overtreatment of indolent disease is well recognised (182) and pre-biopsy MP MRI has been shown in multiple studies to reduce the detection of NS PCa (20).

Lesion-level analysis performed on all 89 RP specimens allowed detailed assessment of each of the 273 foci of PCa present in terms of their visibility on the corresponding

MR image in relation to lesion location, size and aggressiveness. The results confirm, that clinically indolent GS 6 (3+3) lesions are extremely unlikely to be observed on MP MRI (only 4.4% of them were visible). The results unequivocally validate the results of the previous studies examining the ability of MP MRI to assess prostate cancer aggressiveness (210, 211). Results from the PROMIS study show a similar trend, with reduction of diagnosis of clinically insignificant cancers by 5% if MP MRI was used to triage men before the first biopsy (6).

The number of all undetected lesions by MRI, and subsequently found on RP specimen, may seem high, with 142/282 lesions not being seen (52%). Large proportion of them (91/142) were however foci of NS PCa, (G 3+3 and/or < 6mm), detection of which will be a non-desirable.
Out of CS PCA foci, which were missed by MP MRI, majority (39/52) were smaller than 10mm in size and located in the anterior half of the gland. The small size predominance among the missed lesions is explained by the limitation in spatial resolution of MP MRI, impairing their detection, and the anterior gland predominance relates to the presence of TZ in anterior half of the gland, in which the detection of PCa is negatively affected by presence of BPH. The findings are like those found by Sheikh et al, who investigated the results of transperineal biopsies (TPB) in MRI negative patients with clinical suspicion of PCa. In his study, 250/371 lesions missed on MRI were subsequently found on TPB in anterior half of the gland (175).

There was a substantial agreement between the readers (kappa of 69.73%) when assessing MP MRI using PIRADS v2.0 system. This is comparable to the results from a similar study by Purysko et al, who reported a good overall inter-observer agreement while using PIRADS v2.0 (kappa of 63%) with fair agreement in the transitional zone (kappa of 53%) **(183).** Since the start of the study, PIRADS scoring system has been updated from v2.0 to v2.1 to address the limitations discovered in the validating studies (105) and the inter-observer agreement has improved from substantial to exclellent (184).

With further developments of PIRADS grading system, there should be increasing upward trend in MP MRI sensitivity and specificity and further decrease in the over detection of NS PCa. Small cohort retrospective studies published since the update seem to confirm improved diagnostic accuracy of v2.1 system, in relation to both TZ and PZ lesions (185, 186).

The TRUS/FUS-B combined biopsy (endpoint 2A) detected CS PCa in 130/207 (62.8%) patients with NS PCa in 21/207 patients (10.1%) vs 106/206 CS PCa detection rate (51.4%) with 18/206 (8.7%) of NS PCa in the control arm.
The probability of CS cancer detection by TRUS/FUS-B pathway was statistically significantly higher (p=0.002) than by control TRUS arm and both arms have similar profile of adverse events.
Precision study, RTC which influenced paradigm change in PCa diagnosis, looked at a similar patient's cohort of 500 biopsy naïve men with clinical suspicion of PCa and reported lower CS PCa detection rate of 38% (95/252) for MRI-targeted approach alone, but superior to compared 26% in the SC TRUS group (64/248) (7).
In MRI- First study, the detection rate for MR-GB arm was 32% with 6% detection of NCS PCa. In 4M study, the detection rate for MRI+ MR-TB was 39% with 25% of CS PCa and 14% of NS PCa (7, 9, 187).
All studies achieved lower detection rates for CS PCa, predominantly due to differences in methodology, but observed similar trend with higher detection rates for combined biopsy approach when compared to TRUS only pathway.
Table 23 depicts the comparison between the reported study (MULTIPROS) and the other 3 large, level 1 evidence studies with similar design and patient group size. The main difference between this study and the similar published studies is that both arms of the reported study had a positive MP MRI prior to randomisation into TRUS alone vs combined TRUS/FUS-B groups so the detection numbers are not directly comparable.

	MULTIPROS	PRECISION (NEJM 2018)	MRI-First (Lancet Onc 2018)	4M (Eur Urol 2018)
Study design	**RTC (603)**	RTC (500)	Paired validating (251)	Paired validating (626)
MRI	**Majority 3T PIRADS v2.0**	3T +1.5T PIRADS v2.0	1.5T & 3T Likert	3T PIRADS v2.0
Intervention group	**3 cores /target**	MR-GB 4 cores /target	MR-GB 3 cores/ target	MR-GB 3 cores/target
Standard biopsy (SB)	**12 cores**	10-12 cores	12+2 cores	12 cores
Avoid biopsy	**28%**	28%	14%	49%
CS PCa Intervention	**62.8% (TRUS/FUS-B)**	38% (MR-GB)	32% (MR-GB)	25% (MR-GB)
CS PCa Control	**51.4%**	26%	29.9%	23%
NS PCa Intervention	**9.2% (TRUS/FUS-B)**	9%	6%	14%
CS PCa yield in - MP MRI	5.7%	Not reported	11%	4%

Table 25 Comparison of methodology from MULTIPROS study and 3 similar published level 1 studies

In the intervention arm, FUS-B alone biopsy was positive for CS PCa in 114/207 (55%) cases whether TRUS biopsy alone in 103/207 (49%) CS cancers. This proves that FUS-B biopsy alone is non-inferior to TRUS biopsy in diagnosing CS cancer with an added benefit of less cores.

169/603 (28%) patients had negative MP MRI and could have avoided biopsy. Precision study have achieved identical 28% rate of avoidance of biopsy after negative MP MRI, using PIRADS v 2.0 system, yet again confirming rightfulness of the 'no immediate biopsy approach following negative MP MRI'. The yield of missed CS cancers in MR negative group was almost equally low to 4M study at 5.7%. A safety net of PSA monitoring following negative MP MRI, as proposed in 4M study of minimum 12 month follow up in 6-month interval and repeated PSA if PSA increases/remain elevated is advocated.

In Cochrane review by Drost et al, looking at 20 studies with a total of 5219 men, the number of missed CS PCa in every 100 men with negative MP MRI was calculated at 8/100 (8%)(21, 22)

Padhani et al (16), in their literature review, stated that, based on scientific evidence, systemic TRUS biopsy should accompany the MRI-directed cores as many recent studies suggest, that SC PCa foci, which were not detected in targeted cores, are often found on the systemic biopsy cores from adjacent sextants (188, 189).

The estimated added value of TRUS to MRI-directed biopsy is approximately 5% for biopsy naïve group and even higher in men with prior negative biopsy (190). My results support this conclusions with higher CS PCa detection rate in the combined group at the expense of slightly higher rate of detection of non-significant disease.

The equally low number of related significant side effects between study arms in this study is comparable to results from Promis study, which reported a total of 2% SAE of men from TRUS biopsy and from MRI-targeted biopsy. In both arms of the study, the only related SAE was 1 case of urosepsis in each arm, which is a well-recognised complication post trans rectal prostate biopsies (53). The 1 case of non-related SAE in the intervention arm was an intracranial hypertensive haemorrhage 22 days following biopsy, resulting in death, which after consideration had no causative relation with the study intervention.

The less frequent AE in the MRI-targeted biopsy in the Promis series, when compared to TRUS group, reflected fewer biopsy cores obtained during targeted biopsies, which were not accompanied by TRUS biopsy (7). In this study, higher

number of immediate post-biopsy AE is thought to be related to a higher number of cores taken during combined biopsy.

The patient reported outcomes, recorded in the post biopsy questionnaire and collected 14 days following the biopsy assessed the frequency and severity of pain, haematuria, haematospermia and were only considered as AE if lasted more than 4 days. The frequency of haematospermia and haematuria lasting beyond 4 days post biopsy, between study arms (control/intervention), were 54,43% and 14,13% respectively and are less frequent to those observed during 35 day follow up post TRUS biopsy from the Protec study of Rosario et al, who reported as much as 66% patients complaining of haematuria and 90% of hematospermia lasting beyond immediate post-biopsy period.

5.1. Strengths and limitations of the study design

The prospective study design with inter-observer agreement calculation, to ensure reproducibility, and use of pre-biopsy MP MRI and precise lesion-level analysis are the major strengths of the study.

One of the biggest strength of the study was the use of customised patient-specific molds for analysis of RP specimens. The molds design was based on anatomical MRI data and enabled slice-to-slice spatial correlation of RP specimen and the MRI images. This rapid prototyping method was developed by bioengineering team from my research group and first published in 2017 (175). The use of this technique addresses the challenge of MR-histology correlation, which is a recognised factor influencing variability of reported sensitivity and specificity of MP MRI in PCa detection. Various methods have been adapted in previously published studies to allow lesion-level comparison between MRI and RP specimen. For example, Lin et al in their study used tumour maps with anatomical landmarks and tumour laterality, size and location with manual comparison between them (179).

The major strength of the study is also its prospective and randomised controlled trial design, providing level 1a evidence into performance of combined FUS-TB and TRUS approach in biopsy naïve men.

Use of single method of targeted biopsy may be considered both a strength and a limitation. This design makes the results more technique-specific but less comparable to other targeting methods. FUS-TB was performed under local analgesia so was more prone to motion induced miss-registration, potentially resulting in less precise targeting, while being less expensive, time consuming and more available than in bore MR-GB. In my study, one standardised type of targeted biopsy has been used -software assisted MRI/US fusion biopsy in the aim to minimise variability resulting from the use of different approaches. This choice was based on the preliminary evidence, which suggested good registration accuracy of the fusion algorithms and practical advantages such as good patient toleration and fitting into existing clinical workflow (191) as well as better performance than cognitive fusion guidance (150). The largest comparative trial, published after my methodology has been defined, suggests however that all three main targeted biopsy approaches perform similarly in detecting clinically significant disease (8, 192). The Precision study design allowed use of two MRI-targeted biopsy approaches- cognitive fusion (visual registration) as well as software assisted MRI/US fusion and did not test DA of combined TRUS and MR-targeted approach.

A selection bias caused by a choice of RP as a reference standard resulting in patient-level sensitivity rise, with only patients with biopsy-confirmed CS PCa cancer undergoing RP, may be considered as a limitation of the study.
The PIRADS v2.0 was used for assessment of MP MRI during this study, has been replaced by updated version 2.1 during the recruitment phase of study in 2019. Due to statistical considerations, the version used for assessment of MP MRI during the study remained unchanged. The results aren't therefore fully translatable into the currently used version and its performance. It is however expected that with the improvements introduced in the current version, diagnostic accuracy is going to improve further.

6. CONCLUSIONS

The results presented in this thesis provide level 1a evidence into performance of MP MRI and combined TRUS/FUS-TB approach in biopsy naïve men to detect clinically significant prostate cancer. The detection and characterisation of CS PCa by pre-biopsy MP MRI has been thoroughly analysed and the results confirmed that MP MRI can detect majority of significant cancers and avoid over-diagnosis in most of the non-significant disease. MRI guided targeted biopsy in combination with systemic TRUS biopsy performed better than TRUS alone and there were no additional significant AE recognised from addition of the targeted biopsy procedure.

Word Count 21,888

7. Appendixes

Appendix A Approval Letters and Study Protocol

A1 East of Scotland Research Ethics Service Favourable Letter 20Nov2014

A2 R&D Management approval Tayside 10Dec2014

A3 R&D Management approval Grampian

A4 R&D Management Approval Royal Free London 31Aug2018

A5 Published protocol

A6 ECR Clinical Trials in Radiology presentation 2017

Appendix B

B1 CFR

B2 Patient Information Leaflet-Tayside

B3 Patient Information leaflet-Grampian

B4 Patient Information Leaflet –Royal Free London

B5 Multipros Leaflet

B6 Post-biopsy Questionnaire

B7 Study Amendments Log

Appendix C

C1 Summary of all adverse events

C2 Location and size of CS PCa missed by MP MRI

Appendix D

D1 MD Thesis revision-changes tracking document

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