MULTI-PARAMETRIC MAGNETIC RESONANCE IMAGING IN THE DIAGNOSIS OF PROSTATE CANCER

MD (Res) Thesis

University College London (UCL)

Nimalan Arumainayagam

DECLARATION

“I, Nimalan Arumainayagam, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.”

Signature:

Nimalan Arumainayagam

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Thanks must also go to Anjaly Mirchandani for her help and patience in allowing me time to write up my thesis.

I would like to dedicate this work to my Father whose own battle with prostate cancer continues.

PEER REVIEWED PUBLICATIONS RESULTING FROM WORK IN THIS THESIS (see appendix)

Multi-parametric MR Imaging for detection of clinically significant prostate cancer: a validation cohort study with transperineal template prostate mapping as the reference standard. Arumainayagam N, Ahmed HU, Moore CM, Freeman A, Allen C, Sohaib A, Kirkham A, Emberton M. Radiology September 2013

Accuracy of multiparametric MRI in detecting recurrent prostate cancer after radiotherapy. Arumainayagam N, Kumaar S, Ahmed HU, Kirkham A, Allen C, Emberton M. BJU International October 2010.

ABSTRACT

Introduction

Multi-parametric magnetic resonance imaging (mp-MRI) has shown promise in the detection of prostate cancer. The purpose of this thesis was to evaluate the diagnostic performance of mp-MRI for prostate cancer detection by using transperineal prostate mapping (TPM) biopsies as the reference standard in men who had previous external beam radiotherapy and men who had not had any previous treatment.

Methods

Mp-MRI was performed on 13 men with previous external beam radiotherapy treatment for localised prostate cancer and 64 men who had not had any previous treatment. Mp-MRI included T2-weighted, dynamic contrast enhanced and diffusion weighted imaging sequences, using a 1.5T magnet and a pelvic phased-array coil. All men in these studies then underwent TPM biopsies. Two radiologists reported on the 13 mp-MRI scans in the previous radiotherapy treated population, using 4 sectors (quadrant) analysis, and an additional radiologist (total of three) reported on the 64 mp-MRI scans in the previously untreated group.

Mp-MRI reports used a Likert scoring system to quantify the degree of suspicion of cancer being present in a given quadrant. The diagnostic accuracy of mp-MRI was evaluated at varying thresholds of cancer for both groups.

Results

In the post-radiotherapy group overall accuracy was 0.77 – 0.89 for all cancer and 0.86 – 0.93 when only cancer with ≥ 3mm biopsy core length was considered significant.

In the treatment naïve group for the primary endpoint definition of clinically significant cancer (Gleason ≥ 3+4 and / or any cancer core length ≥ 4mm) accuracy values were 58-73% (sensitivity), 71-84% (specificity), 49-63% (positive predictive value), 84-89% (negative predictive value), 2.0 - 3.44 (positive likelihood

ratio) and 0.3 - 0.5 (negative likelihood ratio). Overall accuracy values (area under receiver operator characteristic curves) were 0.73 – 0.84.

Conclusions

Mp-MRI can help identify and rule out clinically significant prostate cancer both in treatment naïve and post-radiotherapy prostate glands.

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ADC	apparent diffusion co-efficient
AUC	area under curve
CAD	computer assisted diagnosis
CCL	cancer core length
DCE	dynamic contrast enhanced
DRE	digital rectal examination
DWI	diffusion weighted imaging
EBRT	external beam radiotherapy
ESUR	European Society of Urogenital Radiology
ERSPC	European Randomized Study for Screening for Prostate Cancer
FN	false negatives
FP	false positives
HIFU	high intensity focussed ultrasound
HTA	Health Technology Assessment
LR	likelihood ratio
MCCL	maximum cancer core length
Mp-MRI	multi-parametric magnetic resonance imaging
MRI	magnetic resonance imaging

MRSI	magnetic resonance spectroscopic imaging
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
Pi-RADS	Prostate Imaging Reporting and Data System
PIVOT	Prostate Cancer Intervention versus Observation Trial
PPV	positive predictive value
PSA	prostate specific antigen
ROC	receiver operator characteristic
ROI	region of interest
SEER	Surveillance Epidemiology and End Results
SI	signal intensity
STARD	Standards for Reporting of Diagnostic Accuracy
1.5T	1.5 tesla
T2 TSE	T2 weighted turbo spin echo
T2W	T2 weighted
TE	echo time
TN	true negatives
TP	true positives
TPM	transperineal template prostate mapping biopsies
TR	repetition time

TRUS	transrectal ultrasound
TURP	transurethral resection of prostate
VIBE fat sat	volumetric interpolated breath-hold examination with fat saturation.

CHAPTER 1

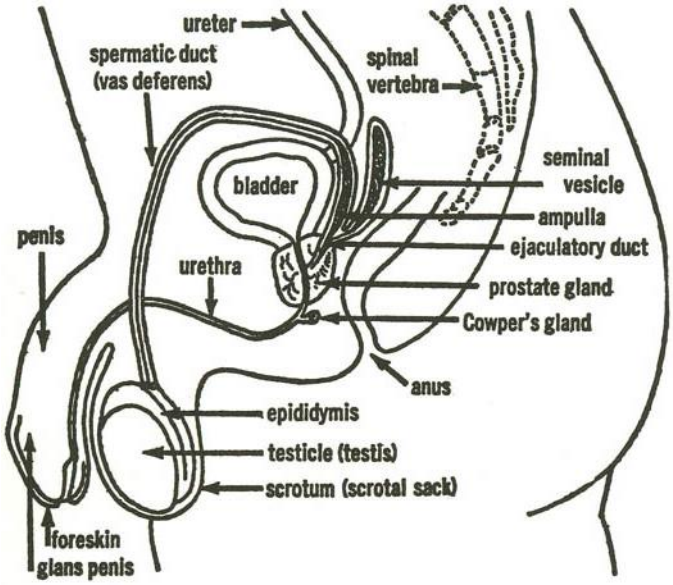
INTRODUCTION: PROSTATE CANCER OVERVIEW AND DIAGNOSIS

1.1 The Prostate – Anatomy and Function

The prostate is a male organ surrounding the urethra, lying between the neck of the bladder above and the urogenital diaphragm below. It is a fibro- muscular glandular structure measuring approximately 3 cm long.

The prostate is conical in shape and has a base superiorly against the bladder neck and an apex towards the urogenital diaphragm inferiorly. There are two ejaculatory ducts, which open into the prostatic urethra (see figure below).

Figure 1 – Diagram of the male reproductive system showing location of the prostate.



The prostate can be divided into five lobes (see figure): anterior (in front of the urethra), median (in between the urethra and ejaculatory ducts), posterior lobe (behind the urethra and below the ejaculatory ducts) and the right and left lateral lobes (on either side of the urethra separated from each other by a shallow vertical groove on the posterior surface of the prostate).

Prostatic glands are embedded in smooth muscle and connective tissue, with ducts from the glands opening into the prostatic urethra. All lobes of the prostate outlined above except for the anterior lobe, contain glandular tissue.

The arterial blood supply of the prostate is from branches of the inferior vesical and middle rectal arteries, with venous drainage into the prostatic venous plexus (between the capsule of the prostate and outer fibrous sheath). The nerve supply is from the inferior hypogastric plexuses, with sympathetic nerve mediated stimulation of the smooth muscle cells of the prostate during ejaculation.

McNeal (1) defined three separate zones of the prostate: the central zone, peripheral zone and transition zone, which differed histologically and biologically. He observed that the central zone was resistant to carcinoma and other disease, and that the transitional zone was the main site of prostatic hyperplasia. However, as will be discussed later this observation no longer appears to hold true, and tumour can be found within all parts of the gland.

The function of the prostate is to produce a thin fluid containing citric acid and acid phosphatase, which is added to seminal fluid during ejaculation. Prostatic fluid is alkaline, thus helping to neutralize acidity in the vagina.

1.2 Prostate Cancer

1.2.1 Epidemiology

Prostate cancer is the most commonly diagnosed malignancy affecting men accounting for 25% of all new cancer cases in males (2), with 40,975 new cases diagnosed in 2010 (a crude incidence rate of 133.7 cases per 100 000 males in the UK) and a life-time risk of developing the disease of 1 in 8.

Prostate cancer is strongly related to age with 75% of cases being diagnosed in men over 65 years and only 1% diagnosed in the under 50 year old age group (2). Age-specific incidence rates of prostate cancer reach a peak in the 75-79 year old age group (794 per 100 000, compared with 163 per 100 000 in the 55-59 year old group and 551 in 100 000 in the 65-69 year old group). There is a slight drop in incidence rates above 79 years of age, which may reflect less use of PSA testing.

Over time the incidence of prostate cancer has been rising worldwide. This was initially attributed to incidental detection of prostate cancer following transurethral resection of the prostate (TURP) and then to the widespread use of prostate specific antigen (PSA) testing. The role of PSA testing will be discussed later in this section.

In the UK there were 10 721 deaths from prostate cancer in 2010, with 93% of prostate cancer deaths between 2008-10 being in men 65 years or older (2). European age-standardised mortality rates were fairly stable at around 20 deaths per 100,000 men during the 1970s, but increased throughout the 1980s to reach a peak of 30 per 100,000 in the early 1990s; since then, mortality rates have fallen by around a fifth to an average of 24 deaths per 100,000 men in 2008-2010. This reduction in prostate cancer deaths may in part be related to PSA testing (and hence earlier detection of the disease) as well as advances in treatment.

Within the European Union there were 69,069 deaths from prostate cancer in 2009 and the number of deaths predicted for 2013 is 70,347 (3). Worldwide prostate

cancer is the 6th most common cause of cancer death in men and was estimated to be a cause for 258,000 deaths in 2008 (2).

1.2.2 Pathology

The most common prostatic malignancy is adenocarcinoma (>95%), arising from the acinar or ductal epithelium. There is an absent basal cell layer, with the basement membrane being breached by malignant cells invading into the fibromuscular stroma. Macroscopically such tumours appear hard and white.

Alternatively transitional cell carcinoma of the bladder may invade the prostatic urethra, ducts or stroma. Prostatic sarcomas can rarely occur in childhood and metastatic deposits from other sites are also rare.

For the purposes of this thesis the term prostate cancer will be referring to adenocarcinoma of the prostate only, given that this is the overwhelmingly predominant tumour type seen within the gland.

Most adenocarcinomas are seen within the peripheral zone (70%), with approximately 24% arising in the transition zone and 8% in the central zone (4). This distribution of cancers within the prostate has helped shape the current trans-rectal approach when biopsying the prostate in order to detect cancer.

1.2.3 Grading and Staging

Prostate cancer is graded using the Gleason system (5). Gleason was a pathologist who drew the different glandular patterns of prostate cancer, with five levels of increasing aggressiveness (grading) based on the extent to which tumour cells are arranged into recognizably glandular structures (glandular differentiation) at relatively low magnification:

Grade 1 – small uniform glands with minimal nuclear changes

Grade 2 – medium sized acini still separated by stromal tissue but more closely arranged

Grade 3 – these tumours show marked variation in glandular size and organization with infiltration of stromal tissue

Grade 4 – marked cytological atypia with extensive infiltration

Grade 5 – sheets of undifferentiated cancer cells.

Cytological features play no part in this grading system. As most prostate cancers are multifocal and heterogeneous, allowance is made by adding the two most widely represented grades to produce a composite Gleason score (e.g. 3+4). Occasionally more than two grades are observed, the least common being known as the tertiary grade.

Thus, the higher the Gleason score, the more aggressive the tumour. This is reflected by the correlation between Gleason score and the chance of dying from prostate cancer within 15 years of diagnosis being 4-7% for those tumours of Gleason score 2-4 and 60-87% for those with scores of 8-10 (6). Of note Gleason score 2-4 is now no longer commonly used for prostate biopsy grading.

Prostate cancer is staged using the TNM classification, developed and maintained by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) 7th edition in 2010 (7), as outlined below.

Primary tumour assessment (T):

TX - Primary tumour cannot be assessed

T0 - No evidence of primary tumour

T1 - Clinically in apparent tumour neither palpable nor visible by imaging

T1a - Tumour incidental histologic finding in 5% or less of tissue resected during transurethral resection of prostate (TURP).

T1b - Tumour incidental histologic finding in more than 5% of tissue resected during TURP.

T1c - Tumour identified by needle biopsy (for example, because of elevated PSA)

T2 - Tumour confined within prostate

T2a - Tumour involves one-half of one lobe or less

T2b - Tumour involves more than one-half of one lobe but not both lobes

T2c - Tumour involves both lobes

T3 - Tumour extends through the prostate capsule

T3a – Extra-capsular extension (unilateral or bilateral) or microscopic invasion of bladder neck

T3b - Tumour invades seminal vesicle(s)

T4 - Tumour is fixed or invades adjacent structures other than seminal vesicles, such as external sphincter, rectum, bladder, levator muscles and/or pelvic wall.

Regional lymph node involvement (N):

NX - Regional lymph nodes were not assessed

N0 - No regional lymph node metastasis

N1 - Metastasis in regional

Distant Metastasis (M):

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s) with or without bone disease

1.3 Diagnosis of Prostate Cancer – current practice

1.3.1 – Digital rectal examination (DRE)

Previously men with prostate cancer tended to present with symptoms of locally advanced or metastatic disease. However since the introduction of PSA testing the disease is being diagnosed in younger asymptomatic men and also as an incidental finding in some men following TURP.

The earlier presentation of prostate cancer in the PSA testing era therefore poses difficult dilemmas for patients and clinicians, with regards to accurate diagnosis and risk stratification initially to help guide appropriate management of the disease.

Digital rectal examination (DRE) is an important part of the assessment of a patient suspected of having prostate cancer. Since most prostate cancers arise in the peripheral zone (4) (i.e. the posterior part of the prostate), larger or advanced lesions can be palpable on DRE. An abnormal DRE may be defined by asymmetry, a palpable nodule or fixed craggy mass. An abnormal DRE initial assessment is highly predictive for high grade prostate cancer (odds ratio 6:1) and estimating prostate size also improves diagnostic accuracy when combined with PSA (8). Previous work by Epstein et al (9) had already highlighted the importance of assessing the estimated prostate volume in conjunction with the patient's PSA reading, finding that a PSA density of less than 0.1 ng/ml per gram was predictive of no adverse pathological findings on needle biopsy and a PSA density of 0.1 - 0.15 ng/ml per gram indicative of low or intermediate grade cancer smaller than 3mm in one needle core biopsy specimen.

Thus, DRE still plays an important role in the diagnostic evaluation of men suspected of having prostate cancer, although the positive predictive value of DRE in primary care remains extremely variable (10).

1.3.2 PSA testing

PSA is a glycoprotein enzyme responsible for liquefaction of semen thus enabling fertilisation. It is produced by columnar acinar and ductal prostatic epithelial cells, being present in both benign and malignant cells. PSA is mainly secreted into the semen with small quantities found in the urine and blood. Normally there are significant tissue barriers (basal cell layer, basement membrane, stromal layer and the capillary wall itself), between prostatic cells and capillaries. In prostate cancer these barriers are compromised and thus PSA leaks into circulating capillaries and hence serum PSA values rise.

Within the circulating blood 75% of PSA is bound to plasma proteins and metabolised in the liver, whilst the other 25% of serum PSA is free and is excreted in urine. Complex PSA (i.e. bound PSA) is stable. It is bound to alpha-1 antichymotrypsin and alpha-2 macroglobulin. Free PSA is unstable and consists of 2 types: pro-PSA, a peripheral zone precursor (elevated in prostate cancer) and BPSA, the transition zone precursor (elevated in benign prostatic hyperplasia.

Stamey et al (11) first published results of 699 patients who underwent both PSA testing and prostatic acid phosphatase (PAP) testing (this was the only serum marker for prostate cancer prior to PSA), concluding that PSA was more sensitive than PAP in detecting prostate cancer.

The half-life of PSA is 2.2 days (11). The original work on PSA thresholds conducted by Catalona et al in the early 1990s (12) suggested a PSA cut-off value of 4ng/ml when guiding whether to perform prostate biopsy in absence of any positive examination findings. They found that prostate cancer was detected in 26% of men with a PSA in the range 4-10ng/ml and in 53% of men with PSA > 10 ng/ml. Oesterling et al (13) conducted work which concluded that age-specific PSA thresholds were more useful.

They suggested the following cut-off points to determine a raised PSA based on age:

Age (years)	PSA (ng/ml
40 - 50	2.5
50 – 60	3.5
60 - 70	4.5
70 - 80	6.5

Table 1 – Age specific PSA values

Catalona et al (14), compared the ability of DRE, transrectal ultrasound (TRUS) and PSA to diagnose prostate cancer. In this study of 1653 men, those with PSA readings > 10ng/ml automatically had a sextant TRUS biopsy even if DRE and TRUS findings were normal. Men with PSA readings <4ng/ml on consecutive testing did not have any further examinations or tests (1516 men). Men with PSA 4-10 ng/ml (107 men) only had biopsies if DRE or TRUS imaging was also abnormal, and in this group 85 underwent biopsy with 22% subsequently found to have cancer. The results revealed that PSA had better positive predictive value (PPV) (40%) and overall accuracy (64%) than TRUS or DRE. However, the authors also stated that a combination of DRE, PSA, TRUS and needle biopsy was the best approach to detect prostate cancer than any method alone. This is essentially the rationale used in the current practice of diagnosing prostate cancer, although the PSA thresholds have been changed to represent age-specific values.

Until the development of commercial serum PSA tests in the late 1980s most men diagnosed with prostate cancer had advanced incurable disease. However, numerous longitudinal studies have observed a downward pathologic stage migration at radical prostatectomy since the onset of PSA testing, with the implication that PSA testing has allowed for earlier detection of smaller volume disease especially when lower thresholds of PSA (2.6ng/ml rather than 4ng/ml) are used (15).

This ability to detect prostate cancer at an earlier stage has had obvious implications for treatment, with only 14% of men diagnosed with prostate cancer in a study by Gleason and Mellinger (16) undergoing radical prostatectomy in the pre-

PSA era. As a result of introducing PSA testing the population of men with potential organ confined disease amenable to surgical intervention increased, with an increase in the proportion of men diagnosed with prostate cancer undergoing radical prostatectomy from 15% in 1984 to around 43% in 1991, with resultant decrease in mortality from prostate cancer in the United States of 6.3% (17).

However, despite the usefulness of PSA testing, it is far from reliable as it is prostate specific and not prostate cancer specific. Even using a cut-off value of 4ng/ml Catalona et al (18) found that 22% of men with a PSA of 2.6 – 4.0ng/ml have prostate cancer, and the Prostate Cancer Prevention Trial (PCPT) showed that at least 15% of men with a PSA under 4ng/ml and normal DRE had prostate cancer, with a quarter of these tumours having a Gleason score of 7 or more (19).

Thus, PSA alone is not a robust diagnostic test for prostate cancer and DRE is also not an accurate predictor of whether a patient has underlying prostatic malignancy. A combination of PSA, DRE and TRUS offers a more reliable method for detecting or ruling out prostate cancer in men at risk of the disease.

1.3.3 Transrectal Ultrasound Guided Prostate Biopsy

The current standard of care for patients with suspected prostate cancer by virtue of either a raised PSA or abnormal feeling prostate on digital rectal examination is to obtain tissue for histological analysis to either confirm or exclude cancer.

Previously, 'blind' finger guided biopsies were taken of suspicious areas in the prostate on DRE. Transrectal ultrasound (TRUS) was first developed by Japanese researchers in the 1970s, with further evolution of technology allowing for smaller probes, better grey-scale real time imaging and also the introduction of biopsy guides to be fitted to the probe.

Systematic TRUS biopsies of the prostate was first introduced by Hodge et al (20) in 1989. They proposed a sextant systematic biopsy scheme (i.e. 3 biopsy cores taken from the mid-lobar region on each side of the gland), rather than echography directed sampling. In 1995 Stamey (21) suggested directing the needle more laterally when biopsying the prostate to better target the peripheral zone where most tumours arise from. Subsequent studies have suggested that laterally directed biopsies aimed at sampling the lateral horn of the prostate results in 25% increased prostate cancer detection (22).

A computer simulation modelling study by Crawford et al in 1998 highlighted that sextant transrectal prostate biopsy missed 42-48% of clinically significant cancers, the majority of which had a focus in the peripheral zone. They therefore suggested that more extensive sampling of the peripheral zone was required. The value of far lateral biopsies improving the cancer detection rate has since also been verified in further studies (23), (24). Singh et al (23) suggested that a peripheral zone tumour would only be detected at a later stage once the tumour had grown medially into the sextant template biopsy region, and that these tumours may be larger with increased risk of extra-prostatic extension. They hypothesised that a systematic 12 core biopsy approach, which sampled the lateral peripheral zones more adequately, would detect a greater number of surgically curable, clinically significant tumours than the sextant protocol. In their study of 176 men their results confirmed their suggestion with 26 more tumours with Gleason grade <7, 13 extra tumours with Gleason grade 7, and 3 additional tumours with Gleason grade 8-10

detected with the 12 core biopsy protocol, which would not have been detected with the standard sextant protocol. The 12 core method also significantly detected more organ confined tumours when compared with the sextant approach.

Presti et al (24) analysed the use of the 12 core biopsy strategy in 2299 patients by 167 community based urologists. They concluded that standard sextant biopsies missed 20-30% of cancers, and that overall detection rates improved with additional cores taken, with a detection rate of 92% with an 8 core protocol and 93-97% with a 10 core technique. They found that the laterally directed biopsies as well as the apical biopsies were the most important additional factors in increasing the detection rate. Midline biopsies have been shown to have the lowest probability of being positive (22).

Despite the detection rate of the 12 core biopsies, some studies have suggested the use of even more biopsies in order to report even higher cancer detection rates and specific targeting of the transition zone in the biopsy strategy, such as the 21 core protocol advocated by De La Taille et al (25). They observed an increased diagnostic yield from 22.7% with the sextant approach to 31.3% with the 21-core strategy, with no difference in risk of complications.

However, the additional benefit from increasing the number of biopsy cores taken beyond 12-cores, should be taken with caution. A systematic review of the literature (26), with pooled data from 68 studies comparing a total of 94 extended biopsy schemes with the standard sextant scheme, has suggested that there is no significant gain in taking more than 12 cores, with strategies needing more than 18 cores potentially having a greater risk of side effects. They also suggested that as mentioned previously laterally directed biopsies increased cancer detection rates significantly and centrally directed cores did not.

It is also known that the size of the prostate is a factor in determining the likelihood of detecting cancer on an initial set of biopsies, with an inverse relationship between cancer detection and prostate volume (27) and that the number of biopsies should therefore be tailored accordingly.

Thus, whilst TRUS biopsy is the current ‘gold-standard’ method for obtaining tissue from the prostate for histological analysis it is far from perfect. There are issues of over-diagnosis (i.e. detecting small volume, low grade cancer which is unlikely to cause the patient harm during their lifetime) and also under-sampling of the prostate especially if significant tumours are present anteriorly, given up to 30% of tumours may lie anterior to the peripheral zone (4). The issues of clinical significance will be discussed later within this thesis, as any imaging technology used to either detect or rule out of prostate cancer should ideally only highlight areas of suspicion which are likely to be clinically significant disease, hence avoiding the issue of over- diagnosis brought about by systematic biopsy regimes.

Over-diagnosis relating to extended biopsy schemes has shown that greater number of biopsies taken to obtain a diagnosis correlates with smaller tumour volumes at radical prostatectomy (28). Thus, not only has PSA testing resulted in a downward stage migration and associated detection of clinically insignificant cancers, but the use of extended biopsy schemes also results in potential over-detection of insignificant cancers. In this study (28) of 56 patients who underwent radical prostatectomy between 1998-2004 for ‘insignificant cancer’ based on their TRUS biopsy histology, the authors commented that 30-55% of patients with biopsy insignificant prostate cancer will indeed have insignificant tumour at the histopathological evaluation of their radical prostatectomy specimen. Another important message from this and similar studies was also the issue of upgrading of tumours (i.e. due to still relative under-sampling). They found that up to 70% of patients deemed to have clinically insignificant disease on TRUS biopsy went on to have ‘significant disease’ (i.e. Gleason score of 7 or more, or tumour volume >0.5ml) at evaluation of their radical prostatectomy specimen.

Hence, systematic TRUS biopsy schemes are inherently flawed due to both the potential for under-sampling as well as the potential for over detection of insignificant disease with extended biopsy or saturation biopsy schemes (especially if used as a repeat biopsy strategy in those men with a first set of negative biopsies). When considering this, TRUS biopsy is thus an unreliable reference test when trying to evaluate the diagnostic accuracy of any prostate cancer imaging modality.

Given that TRUS biopsy may miss anterior tumours and also under-sample the prostate, attention has turned to the role of transperineal template mapping prostate biopsies as a means for reliably detecting or excluding significant prostate cancer.

1.3.4 Transperineal Prostate Biopsies

Initial studies evaluating the role of the transperineal route to biopsy the prostate reported conflicting results. These studies used free-hand transperineal biopsies with ultrasound guidance. In a study of 20 men undergoing radical prostatectomy by Shingal and Terris, patients underwent sextant transperineal biopsy undertaken with transperineal ultrasound guidance, followed by TRUS sextant biopsy (29) just before proceeding to radical prostatectomy in the same anaesthetic. Results of both biopsy strategies were compared to the final prostatectomy specimen. They reported that sextant transperineal biopsies had a sensitivity of only 10% compared with 65% sensitivity with the TRUS sextant biopsies.

A year later a similar study using sextant transperineal and sextant TRUS biopsies, by Vis et al concluded that the two techniques did not differ with detection rates of 82.5% (transperineal) versus 72.5% (transrectal). These biopsies were however taken on radical prostatectomy specimens just after surgical removal, with an ultrasound probe placed on the dorsal aspect of the prostate in an attempt to simulate a real clinical setting. Thus, these results should be taken with caution. Also the transperineal biopsies were directed along the plane of the peripheral zone, thus directly comparing the ability of each technique to accurately assess the peripheral zone for cancer, rather than the whole gland including the anterior prostate.

After these initial conflicting studies in 2003 Emiliozzi et al (30) performed the first ‘in vivo’ study comparing the two sextant techniques in 107 patients. They used a ‘fan-shaped transperineal biopsy pattern to comprehensively cover the peripheral zone including the lateral horns, without sampling the transitional zone. Their results showed superior detection rate for transperineal sextant biopsies of 38%

versus 32% with sextant transrectal sampling. Of the 43 diagnosed cancers 95% were found with the transperineal method and 79% transrectally. This was found to be statistically significant. Hence they concluded that their results when compared with those of Shingal and Terris reflected the fact that they used TRUS guidance when performing transperineal biopsies, which gives a better image of the prostate when compared with the transperineal ultrasound imaging guidance used by Shingal and Terris for their transperineal sampling. They also suggested that because transrectal biopsies traverse the peripheral zone and distally the needle enters the transition zone, the transperineal approach was actually better for sampling the peripheral zone as each needle sample traverses entirely along the peripheral zone throughout its length. Transperineal biopsies may also have been better at sampling the apex.

1.3.5 Transperineal Template Mapping Prostate Biopsies (TPM)

The above studies investigating both transrectal and transperineal prostate biopsies involve ‘free-hand’ systematic sampling of the gland. This can still lead to a sampling error.

In 2001 Igel et al described a technique aimed at providing a more systematic and reproducible approach to biopsying the prostate transperineally (31). They reported on 88 men who already had previous negative TRUS biopsies (13 had one previous negative biopsy and 75 men had two previous negative biopsies) between 1997 and 1999 at the Cleveland Clinic Jacksonville. The authors identified the use of the template grid placed (see below for their diagram of the grid pattern) on the perineum to aid accurate placement of brachytherapy seeds. Under general anaesthetic this grid was placed flush to the perineum on a brachytherapy stepper with transrectal ultrasound guidance to visualise biopsy needle deployment. The biopsy strategy they used involved taking biopsies from 4 coronal planes anterior to posterior with at least 4 cores in a line from each of these coronal planes (see below):

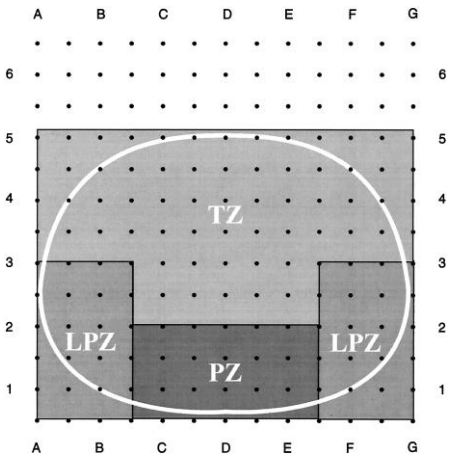


Figure 2 - Figure from Igel et al 2001, showing grid co-ordinates on the template grid and how this would cover a typical prostate in axial view.

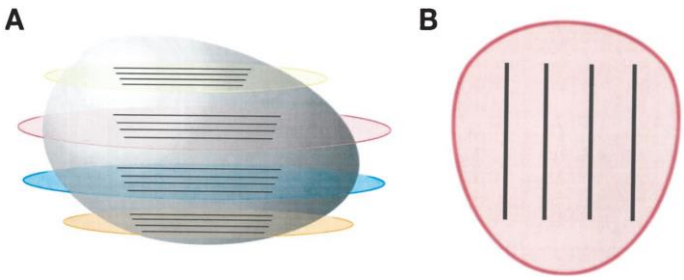


Figure 3 - Figure taken from Igel et al 2001 - (31) to highlight the way in which the template grid helped cover distinct coronal planes within the prostate.

Patients with prostate volumes greater than 45cc had an additional two cores taken more distally in two coronal planes with two cores in each row of that plane (see below **Figure 4)**:

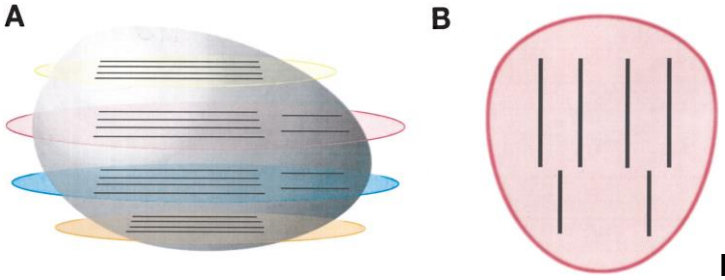


Figure 4 from Igel et al (31)

The number of cores taken ranged from 12 (in a 35cc prostate) to 29 in a prostate with a volume of 103cc.

The authors of this study found that the cancer detection rate using this technique was high (43%) despite the fact that many (85%) of these patients previously had two or more sets of negative TRUS biopsies. Of the patients who had cancer detected, 39% had tumour in the transition zone, highlighting the advantage of the technique in sampling these anterior tumours.

Following this Barzell and Whitmore (32) in 2003, described a modification to this technique to enable saturation prostate biopsies to be undertaken using the template transperineal method. They described sampling the prostate at 5mm intervals using each hole on the grid overlying the prostate, and grouping cores into zones when sending them for histopathological analysis. This technique will be described in more detail in our methodology section as it is the strategy used in the studies in this thesis for TPM. The authors however, stated that in their opinion,

transperineal template mapping biopsies should only be undertaken after at least 3 sets of negative transrectal biopsies using a 10-12 core technique.

Crawford et al (33) undertook a study a few years later in 2005 evaluating TPM using 3D-computer modelling of 86 autopsy prostate specimens and 20 stage T1c radical prostatectomy specimens. They compared the detection rate when using 5mm versus 10mm spaced sampling, and also evaluated the number of clinically threatening / significant cancers (defined as tumours with volumes ≥ 0.5ml or Gleason sum ≥ 7) in these computer model reconstructed specimens. Detection rates in the autopsy prostates were 76% using the 5mm sampling method and 45% with the 10mm sampling method. They found that 5mm sampling detected significantly more clinically significant autopsy cancers (95%) and clinically non-significant cancers (70%) than 10mm sampling (78% - clinically significant, 34% non-significant detection rate). They also calculated a sensitivity of 95% in detecting clinically significant cancer in autopsy prostates with a negative predictive value of 95%. Thus, 5mm sampling appeared to confer the best certainty when attempting to either rule-in or rule-out significant cancer within this population. However, this study was based on computer simulation modelling and was not 'in-vivo', and the autopsy population whilst having a mean age of 67 years also had a wide range of 36-87 years and may therefore not be representative of the target population of men who were likely to be investigated with TPM.

Another study in the same year (34), evaluated the use of a 22-core TPM technique in 128 patients with previous negative transrectal biopsies. Their 22-core protocol involved taking 4 biopsies anterior to posterior from each of four coronal planes in the mid-gland region with a further 3 biopsies in each of 2 coronal planes in the apical region (see below).

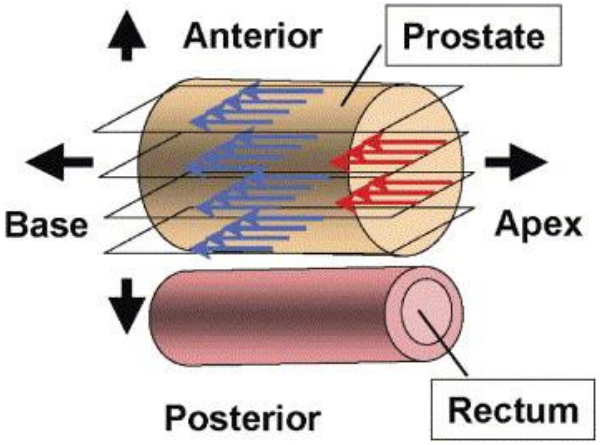


Figure 5 taken from Satoh et al 2005 (34).

This technique yielded a prostate cancer detection rate of 22.7% in this cohort of men with previous negative transrectal biopsies (highlighting once again the significant false negative rate associated with transrectal biopsy), and importantly identified that these men had a significantly higher cancer-core rate in the anterior gland (6.1%) when compared to the posterior gland (3.4%). They also cited a low complication rate of 3.9%, with five patients having an adverse event. The most serious complication was prostatitis in one patient, with two men developing urinary retention and another two patients experiencing difficulty urinating after biopsy.

This detection rate when using TPM in men with previous negative transrectal biopsies was mirrored in a study by Furuno et al (35), who found that in 27 men with previous negative sextant transrectal biopsies, the cancer detection rate using TPM was 26%. Their study also included men with no previous biopsy and in this group the cancer detection rate was 49% (population of 86 men with PSA ranging from 4.02 – 9.79) – thus a much higher detection rate than compared with the transrectal biopsy approach. Overall cancer was detected in 49/113 men (43%) – exactly the same as that reported by Ingel et al (31) previously. In their biopsy protocol, the biopsy needle was inserted in template grid channels to evenly cover the whole prostate in an axial view 1cm proximal from the apex. In the repeat biopsy group they again found the cancer core rate in the anterior region to be significantly higher than the posterior region.

Further evidence from a large prospective study of 303 biopsy naive men, by Li et al in 2007 showed a cancer detection rate of 37.6% (114/303) using a scheme where the prostate was biopsied in 11-regions with 1-4 cores taken in each region, with higher detection rates in smaller volume prostates (68% in glands ≤ 20cc and 23.1% in those ≥60cc). Interestingly the majority of men (290/303) in this study had TPM biopsies performed under local anaesthesia, with only 13 having general anaesthesia for the procedure. They reported no serious complications.

Bott et al prospectively studied an extensive transperineal template biopsy scheme to investigate 60 men who had undergone at least 2 previous sets of negative octant biopsies with 2 subsequent consecutive PSA rises or repeat biopsies containing HGPIN or ASAP within a 12 month period. Their technique divided the prostate into right and left halves and then equally divided each of these halves into anterior, middle and posterior areas. The prostate was further subdivided in the longitudinal axis if a needle biopsy placed at the apex did not also cover the base of the gland.

They reported a 38% (23/60) cancer detection rate and importantly highlighted the finding that cancer was found only in the anterior third of the gland in 12 of these men (60%). They reported 2 patients developing acute urinary retention, 1 patient requiring hospitalisation for haematuria and no sepsis or general anaesthetic related complications.

The Mayo Clinic Jacksonville group followed up their original description of the TPM technique (31) outlined previously, with an update of their experience in 210 men over a three year period from 1999 – 2003 (36). Again all men had undergone at least one set of transrectal biopsies and their detection rate was 37%, with a significant post-procedure complication of urinary retention in 11% of patients. Of those cases where cancer was detected 46% had tumours located only in the transition zone, once more highlighting the need to be sure that this area of the prostate is covered adequately with any biopsy strategy.

Table 2 (below) summarises the detection rates in the studies using TPM as a biopsy strategy in patients with previously negative transrectal biopsies:

Study	Detection rate using TPM after one or more previous negative biopsy
Igel et al 2001	43%
Furuno et al 2004	26%
Satoh et al 2005	23%
Pinkstaff et al 2005	37%
Bott et al 2006	38%

Table 3 (below) summarises the cancer detection rate using various TPM strategies in patients who had never previously had a biopsy:

Study	Detection rate of TPM in biopsy naïve patients
Furuno et al 2004	49%
Crawford et al 2005 (5mm sampling)	76%
Crawford et al 2005 (10mm sampling)	45%
Li et al 2007	37.6%

In a review of their experience in 80 men from 2001 to 2006 having TPM, Barzell and Melamed (37) found that concordance between initial TRUS biopsy and subsequent TPM showed that 16% of these men had their Gleason score upgraded. This cohort contained men who had whole gland TPM for active surveillance / expectant management purposes, but did also contain 28 men who were being considered for focal (hemi gland) cryotherapy. In these 28 men only the side deemed to be cancer-free on the basis of previous TRUS biopsy was subjected to TPM simply to exclude cancer in this side. Thus, not all patients had whole gland TPM and this may have a bearing on the proportion of patients upgraded.

Onik et al (38) reviewed the results of 180 men with proven prostate cancer in only one half of the gland as per previous TRUS biopsy, considering conservative management who then underwent TPM with 5mm spaced sampling for better risk stratification. Of these 180 men with presumed unilateral disease on the basis of

TRUS biopsy, 61% actually had bilateral cancer on TPM. In 22.7% of the 180 men there was an upgrading of Gleason score to ≥ 7. In this study the complication rate following TPM included 14 (7.7%) patients who required a short-term urethral catheter for urinary retention and 2 patients with haematuria.

More recently Crawford et al (39) evaluated TPM in 25 men who subsequently had radical prostatectomy. They then used computer 3D models of the radical prostatectomy specimens to compare how TPM compared against the gold standard prostatectomy specimen. There were 64 lesions in total in this group of men. The authors defined criteria for significant disease on whole mount radical prostatectomy as any tumour volume ≥0.5cc or any tumour with Gleason score ≥ 7. Of the 64 lesions, 25 were deemed to be clinically significant. TPM failed to identify 18/64 lesions, but only one was deemed to be clinically significant (Gleason score 8 volume 0.02cc) in a patient with 2 other significant lesions which were detected by TPM. The authors also looked at 22 men who had a prior diagnosis of cancer on TRUS biopsy before having TPM and then radical prostatectomy. They found that there was a 52% upgrading from TRUS biopsy to prostatectomy. This was much higher when compared with the 8% upgrading seen with TPM to radical prostatectomy. They also observed a 56% concordance in Gleason score between TPM and prostatectomy, with 36% being downgraded. Thus, they concluded TPM with 5mm sampling was able to provide accurate grading and presence or non-presence of significant cancer and therefore reliably guide physicians and patients in deciding management.

Merrick et al (40) reported the effects of TPM on urinary, bowel and sexual function in 129 men from 2005 – 2006. After TPM, 39.4% of their patients needed a urinary catheter on the day of the procedure, with a 7.1% catheter dependency rate at 3 days post-procedure and 1.6% at 6 days post-procedure. No patients needed a catheter more than 12 days following TPM. There was no significant change in sexual function as deemed by International Index of Erectile Dysfunction-6 (IIEF-6) questionnaires pre- and post-TPM and no significant worsening of lower urinary tract symptoms as measured by pre- and post-TPM International Prostate Symptom Score (IPSS) - mean 10.4 pre-TPM, 4.6 at 7 days and 3.8 at 30 days. One patient required overnight hospitalisation for haematuria. Rectal function

(measured using Rectal Function Assessment Score – R-FAS) showed no significant change and there was no change in post-void residual volume when measured at baseline and 30 days after TPM.

The authors concluded that whilst the incidence of temporary urinary retention was significant when compared with TRUS biopsy, there appeared to be no other significant risks.

In summary TPM appears to be safe and confer better accuracy than TRUS biopsy in the detection of prostate cancer, with good correlation when compared with gold standard radical prostatectomy or autopsy prostate specimens. It may therefore serve as a good alternative way of obtaining accurate histological verification or absence of cancer (as a reference test), when evaluating whether an imaging modality (index test) can accurately detect cancer within the prostate.

It also has the advantage over radical prostatectomy as a reference standard because it can be applied to all men suspected of having prostate cancer, whereas radical prostatectomy specimens only represent a proportion of men diagnosed with prostate cancer and does not include those men who choose other treatment modalities or active surveillance. It may therefore be argued that men choosing radical prostatectomy are more likely to have higher volume and / or higher grade disease, and that any imaging modality is more likely to detect such disease. The use of radical prostatectomy specimens as a reference standard may therefore positively bias the accuracy rates observed when testing the usefulness of an imaging modality in prostate cancer. Based on current evidence TPM is a reliable test, which can be applied to all men suspected of having prostate cancer, and therefore is a good candidate for use as a reference standard in studies evaluating accuracy of imaging modalities in detecting or ruling out prostate cancer.

1.4 Significant and Non-significant Prostate cancer

1.4.1 How do we define significant prostate cancer?

The notion of ‘non-life threatening’ prostate cancer was recognised as far back as 1954 by Franks (41) based on autopsy studies identifying undiagnosed tumours in men who had died from other causes.

Stamey et al (42) analysed volumes of prostate cancers found incidentally in men undergoing radical cystoprostatectomy for bladder cancer. They used the Surveillance Epidemiology and End Results (SEER) program database to ascertain the probability of a man being diagnosed with prostate cancer in his life to be 8% and went on to combine this percentage with tumour volumes found on cystoprostatectomy to propose that the potential for a prostate tumour to progress or metastasise was largely dependent on tumour size. They suggested that prostate cancers ≥ 0.5 ml corresponded to the 8% of men likely to be diagnosed with clinically significant prostate cancer, and that 80% of tumours < 0.5 ml were unlikely to reach a significant size.

A year later Epstein et al (9) identified insignificant prostate cancers as those with volume < 0.2ml and Gleason score < 7 in men who underwent radical prostatectomy for clinical T1c disease. Based on this, their model identified that having only one positive core on biopsy with cancer core length smaller than 3mm, along with the use of PSA density and pathological grading of tumour on biopsy resulted in a 95% positive predictive value for predicting clinically insignificant disease.

More recently Wolters et al (43) used data from the European Randomized Study for Screening for Prostate Cancer (ERSPC) trial to confirm that tumours < 0.5ml are insignificant but to also suggest that this threshold may be increased to < 1.3ml.

More recent reports of large radical prostatectomy series again confirm the notion that Gleason 6 disease is ‘latent’ and very unlikely to metastasise. In a study of 12000 men with only Gleason 6 cancer in the prostatectomy specimen, prostate

cancer mortality was 0.2% (44). This is supported by the work of Ross et al (45) who reviewed the pathology specimen results for 14123 men with Gleason ≤ 6 disease who underwent radical prostatectomy and pelvic lymph node dissection between 1975 - 2010 in 4 large academic urological centres. Of these patients 22 had lymph node metastasis, but on re-review of the pathology and using the updated International Society of Urological pathology (ISUP - 2005) grading system, all patients with lymph node metastasis actually harboured higher Gleason patterns >6 within the prostate. They found that none of the patients with true Gleason 6 cancer had lymph node metastasis.

Hence initial studies based on prostatectomy specimens have allowed us to entertain the notion that significance of prostate cancer can be based on tumour volume thresholds as well as the absence of higher grade (Gleason grade ≥ 7) disease. Such cancer is also unlikely to metastasise.

The recently published PIVOT study (46) highlights the concept of over-treatment. This prospective study enrolled and randomised 731 men to either radical prostatectomy (364 men) or observation (367 men) from 1995 – 2002 and then followed them up until January 2010. It was observed that radical prostatectomy did not significantly reduce all-cause or cancer-specific mortality over 12 years follow-up, with an absolute difference of 2.9% between all-cause death (47% radical prostatectomy versus 49.9% observation), and 2.6% absolute difference of prostate cancer specific death (5.8% treated by radical prostatectomy versus 8.4% who were assigned observation). Interestingly they also reported that men with low-risk prostate cancer had a statistically non-significant 15% increase in mortality when assigned to radical prostatectomy when compared with those who were assigned to observation. The absolute difference at 12 years was 5.4% (37.2% for surgery and 31.8% for observation). Among those men with a PSA > 10 ng/ml, radical prostatectomy reduced all-cause mortality by 13.2%.

The authors also reported that 21.4% of men had complications within 30 days of surgery, with a significantly higher rate of urinary incontinence (17.1% in surgery group versus 6.3% in observation group, $p < 0.001$), and also significantly higher

rates of erectile dysfunction in the surgery group when compared with observation alone (81.1% versus 41.1%, $p < 0.001$).

D'Amico et al (47) suggested a method of risk stratifying men diagnosed with prostate cancer based on their PSA, clinical stage and Gleason score on TRUS biopsy. Men with T1c-T2a, Gleason score of 6 or presenting PSA < 10 ng/mL were deemed low risk. Men with clinical stage T2b, Gleason score 7 or PSA 10.1 - 20ng/mL were classified as intermediate risk, and those men with clinical stage T2c or more, PSA > 20ng/mL or Gleason score 8-10 were defined as high risk. The low risk group had an 85%, the intermediate risk 60% and high risk group 40% 5 year PSA failure-free survival rate.

In a subsequent study of 427 low risk patients, the same research group (48) identified a 29% upgrading from Gleason score 6 at biopsy in these low risk men to prostatectomy Gleason score ≥ 7. Logistic regression multivariable analysis was used to determine that the only significant factor for predicting such upgrading was the presence of ≥ 50% positive biopsy cores.

The ability to accurately identify men with organ confined prostate cancer that is of low-risk with respect to disease progression allows us to question whether these men should be treated at all or simply observed.

Given the potential morbidity associated with the standard treatment options of radical prostatectomy or radiotherapy, with subsequent negative effects on quality of life, there is a strong ethical argument to simply closely observe men classified with low risk disease. This is an even more compelling argument with the outcomes of the PIVOT study where it appears that men with low-risk disease do not gain a significant survival advantage by having treatment. The evidence summarised above therefore provides the basis for active surveillance of men with low risk prostate cancer.

1.4.2 Active Surveillance for prostate cancer

Active surveillance, whereby men with low-risk disease are placed on regular follow-up involving PSA monitoring, re-examination of the prostate and repeat biopsy, has therefore developed as a way of managing low-risk patients and is gaining increasing popularity with clinicians and patients. In such active surveillance protocols any finding indicative of disease progression during follow-up would trigger the option of treatment.

Choo et al (49) first proposed the notion of active surveillance in the literature in 2001, and followed this up with a feasibility report in 2002 (50), based on 206 men recruited from 1995 with a mean follow-up of 29 months (range 2 – 66 months). Only men with disease staged T1b - T2bN0M0, Gleason score ≤ 7 and PSA ≤ 15ng/ml were deemed suitable for active surveillance. Their protocol involved 3 monthly follow-up for the first 2 years and then 6 monthly follow-up thereafter for the duration of the study. Each patient had transrectal ultrasound every 6 months and underwent TRUS biopsy again at 12 – 18 months. Bone scan was performed every 12 months for the first two years and then every 24 months for the duration that the patient remained in the study. They used change in DRE findings, PSA doubling time of < 2 years or upgrading on repeat biopsy to ≥ Gleason score 8. In this initial report 36 patients showed evidence of disease progression as defined by one of the criteria above, of which 29 had treatment (25 received radical radiotherapy and 4 underwent radical prostatectomy), 5 had transurethral resection of prostate for lower urinary tract symptoms, one patient was treated with hormones alone and another remained untreated due to a concurrent haematological malignancy managed with a palliative approach. Interestingly 23 men asked to stop active surveillance, with 9 of these having deteriorating health preventing them from maintaining follow-up, 10 patients choosing radiotherapy treatment, 3 patients having radical prostatectomy and one patient given hormonal treatment only (i.e. 14 men actually came off active surveillance to have treatment without any evidence of disease progression).

The authors calculated the probability of being progression-free as 81% at 2 years and 67% at 4 years post-initiation into the active surveillance program.

The 14 men who had treatment despite no evidence of cancer progression reflected an inevitable anxiety associated with an observational approach. Such patient anxiety relating to 'missing the window of opportunity for curative treatment' should their cancer progress is understandable.

The Royal Marsden Hospital, London, UK recently published their experience of a cohort of men who subscribed to an active surveillance protocol (51). In their protocol men aged 50 – 80 years old, with T1/2 stage disease, PSA < 15ng/ml, Gleason score 6 or Gleason ≤ 3 + 4 if aged > 65 years and percentage positive biopsy cores ≤ 50% were deemed eligible. Patients in this active surveillance regime were seen 3 monthly in the first year, 4 monthly in the second year and 6 monthly thereafter with DRE and PSA measurement. TRUS biopsy of the prostate was repeated at 18-24 months after commencement of active surveillance and every 2 years thereafter. Disease progression in this protocol was defined as PSA velocity > 1ng/ml per year, detection of Gleason ≥ 4+3 disease or > 50% percentage positive cores on repeat biopsy. This study reported a 70% freedom from treatment at 5 years, with 85% of men having deferred treatment showing no evidence of biochemical recurrence. Also of note this study incorporated mainly patients who had 8-core TRUS biopsy, which was standard at the time. Interestingly 42 out of the 54 patients who showed evidence of disease progression did so within first biopsy at 18-24 months (22 patients) or 2nd biopsy at 48 months (20 patients). Given that evidence regarding TRUS biopsy reviewed earlier in this thesis suggests that TRUS biopsy under-samples the gland (especially anteriorly) and has a false negative rate approaching 30%, the patients who showed early 'progression' may have not been properly risk stratified at the outset.

This beckons the question as to whether patients who progress on active surveillance actually harbour higher risk disease to begin with, which is not identified with TRUS guided biopsy. The possibility of initial misclassification of true risk, rather than the possibility of actual tumour biological progression also contributes towards some clinicians and patients' anxiety regarding remaining on active surveillance as observed by the Toronto active surveillance cohort (50).

One possible solution to this is to sample the prostate more intensively at the outset using TPM, given the high detection rate of cancer and high sensitivity outlined earlier. However, as seen in TPM series, there are risks of urinary retention and haematuria as well as the need for general anaesthesia in most series. TPM is also very invasive for patients.

Thus, with respect to prostate cancer diagnosis there is an issue of over-detection of clinically insignificant disease due to systematic rather than targeted biopsy with the possibility for over-treatment, hence the evolution of active surveillance protocols for such men. At the same time the current diagnostic pathway using TRUS biopsy does not provide a sufficient degree of certainty with respect to risk stratification of these men, with subsequent early attrition rates to treatment within a few years of enrolment into active surveillance either due to patient anxiety or clinical re-classification to higher risk disease.

What is therefore lacking is a non-invasive imaging modality capable of detecting only clinically significant disease to guide targeted biopsy rather than systematic biopsy.

Such an imaging modality would ideally be able reliably to exclude significant cancer (with a degree of certainty acceptable to both patients and clinicians) to avoid subjecting regions of the prostate deemed normal to biopsy. At the same time any imaging modality should reliably detect regions of the gland harbouring significant prostate cancer in order to inform targeted biopsy to confirm the diagnosis and guide treatment.

Magnetic resonance imaging (MRI) has shown promise in fulfilling this role as an imaging tool to reliably exclude and detect clinically significant prostate cancer. In the next section we will review the current evidence for proposing the use of MRI in the prostate cancer diagnostic pathway.

CHAPTER 2

INTRODUCTION: MAGNETIC RESONANCE IMAGING FOR PROSTATE CANCER

2.1. Brief overview of the history of MRI

Raymond Damadian, physicist and Professor at State University of New York, created the world's first MRI machine in 1972. Damadian had reported a year earlier the idea that nuclear magnetic resonance could be used to distinguish between cancerous and normal tissue (52) in rat animal models. The first MR image of a human body part was performed by physicist Sir Peter Mansfield at the University of Nottingham in 1977, when he presented and published MR images of his research student's finger (53) after having developed MR techniques allowing scans to take seconds rather than hours and with clearer images. This was followed by MR body scans of a human subject in July 1977, by Damadian et al (54).

In 1980 Paul Bottomley left the University of Nottingham MRI research group to join the GE research centre in New York, to help build the first MRI whole body scanner using the highest field strength magnet then available (1.5 tesla), which formed the basis for the commercial production of the 1.5T MRI scanner.

In 1983 Hricak et al (55) published their findings of MR imaging, using a 0.35T machine, of the male pelvis in 25 subjects (5 normal volunteers, 6 with bladder cancer, 9 with benign prostatic hyperplasia of which 5 had concurrent bladder tumours, 9 with prostate cancer and 1 patient with lymphocele after radical prostatectomy). The authors suggested that this new imaging modality showed promise in detecting pathology within the bladder and prostate and could also give information regarding extension of malignancy into surrounding structures and tissues. Thus the possibility for the use of MR imaging for detecting and staging prostate cancer was born.

Further studies using 1.5T magnetic field strength scanner in 81 patients, concluded that prostate malignancy was characterised by low T2 signal intensity, which replaced the normal high T2 signal intensity in the peripheral zone (56). The authors noticed that haemorrhage within the gland caused a problem with tumour detection and volume measurement, but reported sensitivity of 72%, specificity 84% and overall accuracy of 84% in differentiating between organ-confined and

non-organ confined disease, with 88% accuracy in MRI detection of lymph node metastasis.

2.2 Basic principles of Magnetic Resonance Imaging (MRI)

MRI is based upon the spinning motion of specific nuclei within atoms present in biological tissues. Each nucleus contains protons and neutrons, with pairs of subatomic particles spinning in opposite direction but at the same rate as their partners. In nuclei with an even mass number (same number of protons and neutrons) half spin in one direction and the other half in the opposite direction with resultant no net spin. However, in nuclei with odd mass numbers, where the number of protons and neutrons are not equal, the overall spin directions of these subatomic particles is not equal and opposite and therefore the nucleus overall has a net spin or angular momentum. Such nuclei are known as MR active, and are characterized by their tendency to align their axis of rotation to an applied magnetic field.

In clinical MRI the hydrogen nucleus is used as the MR active nucleus as it is very abundant in the human body. It contains a single proton, which gives it a large magnetic moment (i.e. net charge and spin with its own magnetic field induced around it). When a patient is placed within the MRI machine, the magnetic moments of the protons within hydrogen atoms become aligned with the direction of the field of the MR magnet. A varying electromagnetic field is then created using a radiofrequency current (radiofrequency pulse), and this has just the right frequency (resonance frequency) to be absorbed and flip the spin of the protons' magnetic moments within the magnetic field. The MR signal is produced by the protons flipping their magnetic moment spin due to the electromagnetic field, and thus changing their net magnetisation vector to a flipped angle which cuts across a receiver coil, thereby inducing an electrical voltage in the receiver coil. This voltage produces the MR signal.

After the electromagnetic field is turned off the protons magnetic moments realign with the static magnetic field of the machine, and during this relaxation phase, hydrogen nuclei lose energy given to them by the radiofrequency pulse. Protons in different tissues have different relaxation rates, and this factor along with other tissue variables are used to construct images.

Thus when the radiofrequency pulse is turned off, the amount of magnetisation in the longitudinal plane, (in line with the magnetic field induced by the bore of the magnet in the scanner, gradually increases (called T1 recovery), whilst at the same time the amount of magnetisation in the transverse plane gradually decreases (called T2 decay).

During an MRI scan a combination of repeated radiofrequency pulses and intervening periods of recovery are used to generate MR signals in each slice. A pulse sequence consists of a 'repetition time' or 'TR', which is the time from the application of one radiofrequency pulse to the next one for each slice. This TR time (measured in milliseconds) determines the amount of relaxation in the protons (and hence the amount of T1 recovery allowed in tissues) when the MR signal is generated. The 'echo time' or 'TE' is the time from the application of the radiofrequency pulse to the peak of the signal induced in the receiver coil. Hence, the echo time (TE) influences the amount of T2 decay (i.e. decay in transverse magnetisation) that has occurred when the MR signal is generated.

2.2.1 T1 and T2 weighted images

The T1 recovery time is much quicker in fat than in water and T2 decay is also much faster in fat than in water. Therefore, when the radiofrequency pulse is momentarily turned on and then off, fat molecules realign much faster with the longitudinal field of the MR magnet when compared with water (i.e. shorter T1 recovery time in fat). After the radiofrequency pulse is turned off, the loss of transverse magnetisation in water is slower than in fat (i.e. longer T2 decay in water than in fat).

T1 contrast is brought about by using a repetition time (TR) that is shorter than the total relaxation times of the tissues (i.e. the next radiofrequency pulse is applied before the tissues are allowed to relax). Fat as discussed above has a shorter T1 time than water, and therefore realigns with the longitudinal field faster, with a resultant larger longitudinal component of magnetisation when compared with water. When the next radiofrequency pulse is applied before complete relaxation,

the longitudinal components of both fat and water are flipped into the transverse plane, and as fat has more longitudinal magnetisation before the radiofrequency pulse, there is more transverse magnetisation in fat after the pulse is applied. Thus, fat generates a high signal and appears bright on a T1 contrast image. Water has less longitudinal magnetisation before the repeat radiofrequency pulse and therefore less transverse magnetisation after the pulse is applied, and therefore generates low signal and appears dark on T1 contrast imaging.

Thus, in T1 weighted images (where the contrast depends mainly on the differences in fat and water), the repetition time (TR) between each radiofrequency pulse must be short enough to prevent both fat and water from recovering their longitudinal magnetisation. TR therefore controls the amount of T1 weighting and must be short in duration.

T2 contrast is dependent on allowing sufficient time for decay of transverse magnetisation to occur before the signal is read by the receiver coil (i.e. echo time or TE should be sufficiently long). The T2 decay time of fat is shorter than that of water so that the transverse magnetisation of fat decays faster, leaving a greater transverse magnetisation in water, which therefore generates a high signal and appears bright on T2 weighted imaging, with fat which has a small transverse magnetisation giving low signal. Thus in T2 weighted images the TE should be long enough to give fat and water both enough time to decay. If TE is too short then there is not enough time for either fat or water to decay and therefore the differences in their T2 times are not seen.

In summary therefore in T1 weighted imaging the TR (repetition time between radiofrequency pulses) should be short, along with a short TE (echo time). In T2 weighted imaging the TR is long and the TE is also long.

2.2.2 Proton Density Weighted Images

Different tissues contain different relative number of protons per unit volume, and this can be used to create proton density weighted images, where this difference is the main factor in determining image contrast. Tissues with high proton density,

such as brain, have a large transverse component of magnetisation and thus high signal on proton density weighted imaging. In order to achieve proton density weighted images, the effects of T1 and T2 contrast need to be minimised. This is done by using a long TR to allow fat and water to fully recover longitudinal magnetisation as well as a short TE to not allow sufficient time for fat or water to decay, and thereby minimising T2 weighting.

2.2.3 Functional MR Imaging Techniques

Diffusion Weighted MR Imaging

Diffusion weighted MRI measures the diffusion of water in tissues, with the net displacement of molecules termed the 'apparent diffusion coefficient' (ADC). A sequence can be sensitized to diffusion by applying two gradients on either side of the radiofrequency pulse. In diffusion images normal tissue has lower signal intensity than abnormal tissue, as molecules within normal tissue are relatively free to move, whereas in tissue with pathology diffusion of molecules is restricted.

The magnitude of the signal depends on the ADC of the tissue and strength of the gradients, the amplitude of which are controlled by the 'b-value'. Increasing this b-value causes more diffusion weighting.

There are 2 types of diffusion weighted imaging. Diffusion images are where damaged tissue with restricted diffusion (and hence low ADC) is brighter than normal tissue (which has free diffusion and high ADC), because magnetic spins of protons in restricted tissue are refocused as they stay in the same place during excitation and refocusing. However in normal tissue with random diffusion, refocusing is not complete and signal is lost in that area. Thus, abnormal tissue is bright and normal tissue dark.

ADC maps are acquired by calculating the ADC of each voxel of tissue and allocating signal intensity according to this ADC value. In ADC maps restricted tissue (i.e. with pathology) has a low ADC and appears darker (low signal) than normal freely diffusion areas which have high ADC.

Perfusion MR Imaging

This measures the regional blood flow in tissues and is therefore a measure of the quality of vascular supply to a tissue. Tumours have increased microvasculature and the vessels within tumours are more permeable because of weak integrity of the tumour vessel walls. MRI can be used to measure perfusion by tagging the water in arterial blood by using a bolus injection of a contrast agent such as gadolinium. The difference between tagged and untagged areas is very small and therefore ultrafast imaging methods are used to reduce artefact. Perfusion images are acquired with fast (hence the use of the term ‘dynamic’), scanning acquisitions before, during and after bolus injection of intravenous contrast. Dynamic contrast enhanced (DCE) MRI is based on the fact that malignant lesions show earlier and faster enhancement and earlier contrast agent washout, compared with normal prostate tissue.

Gadolinium shortens T1 recovery, and thus tissues with high perfusion appear bright on T1 weighted images. Another way of assessing perfusion, involves bolus injection of gadolinium during fast T2 acquisitions. Gadolinium causes decrease in T2 decay in and around the microvasculature perfused with the contrast. A signal decay curve (time intensity curve) can then be used to measure perfusion.

Magnetic Resonance Spectroscopic Imaging (MRSI)

MRSI gives metabolic information about prostate tissue by displaying the relative concentrations of chemicals within small volumes of interest (voxels). Normal prostate tissue contains high levels of citrate (higher in the peripheral zone when compared with central or transition zone levels). In prostate cancer the cells change from having a citrate producing to a citrate oxidising metabolism, and therefore the citrate levels in prostate cancer cells are reduced or undetectable. In conjunction with this, choline levels are elevated due to a high phospholipid cell membrane turnover in the proliferating malignant tissue. MRSI hence detects tumours based on an increased choline to citrate ratio. However in practice the

creatine peak on MRSI is very close to the choline peak in the spectral reading, and therefore as the two peaks are inseparable, the choline + creatine / citrate ratio is used for the spectral MRSI analysis in the clinical setting. Voxels are considered suspicious for cancer if choline + creatine / citrate ratio is ≥ 2 standard deviations above the average ratio for normal prostate tissue.

2.3 Current use of MRI - Prostate Cancer Staging

As mentioned earlier in section 2.1 the use of MRI in prostate cancer was first investigated in 1983 (55). Since then MRI has come to be used as the imaging modality of choice when assessing the local staging of prostate cancer within the pelvis. The role of MRI in differentiating between organ-confined and non-organ confined cancer was proposed by Phillips et al in 1987 (57), when they retrospectively reviewed MR images of 31 men they observed that using long TR and TE imaging (i.e. T2 weighted), patients with known extra-capsular prostate cancer had peripheral zone defect with low signal measuring ≥ 1cm in diameter with ill-defined borders, which correlated with the site of clinic-pathological involvement. They quoted 100% sensitivity and 54% specificity for such imaging findings as a sign of extra-capsular spread of prostate cancer, with good inter-observer agreement. This was obviously a limited early study given the small number of men and the observational retrospective nature of the study. However, it did pave the way for further evaluation of MRI in predicting localised staging of prostate cancer. Further small studies around that time also suggested that 1.5T MRI could have a role in accurately predicting local staging of prostate cancer (58), (59). Bezzi et al (56) in a study of 81 patients in 1988 published results suggesting that 1.5T MRI had a sensitivity of 72%, specificity of 84% and overall accuracy of 78% in differentiating between prostate confined cancer and non-prostate confined cancer. Their study observed that seminal vesicle invasion was easier to detect than extra-capsular spread. They also evaluated the ability of MRI to detect lymph node metastasis, with sensitivity of 69%, specificity of 95% and overall accuracy of 88% in detecting lymph node involvement in the pelvis. They did also comment that post-biopsy haemorrhage in the peripheral zone caused problems with tumour detection and accurate tumour volume measurement, which is an issue to be discussed later in this thesis.

Given the promise 1.5T MRI had showed in small early single centre studies, in 1987 a 5 centre (Cleveland Clinic, Johns Hopkins, Thomas Jefferson University Hospital, University of Michigan and University of California) study aimed at comparing MRI and trans-rectal ultrasound in early staging of prostate cancer was

undertaken, with 230 patients enrolled over 15 months. In 1990 the New England Journal of Medicine published the results of this multi-institutional co-operative trial (60). The findings of the authors led them to conclude that MRI was not as accurate in localised staging of prostate cancer, as previous studies had suggested. They found no statistically significant difference between ultrasound and MRI in staging prostate cancer. They found an overall accuracy of 58% for ultrasound and 69% for MRI, with both modalities showing greater accuracy when identifying patients with advanced disease, (63% for TRUS and 71% for MRI), when compared with accuracy in identifying patients with organ confined disease (49% for TRUS and 64% for MRI). However, their results showed that the performance of MRI was consistently better than TRUS for all sizes of lesions, despite the finding of no statistical difference between MRI and TRUS for local staging of prostate cancer.

Since then further studies in the 1990s helped to further evaluate the role of MRI in prostate cancer local staging. Chelsky et al (61) analysed 111 patients who underwent MRI for pre-treatment staging, of which 47 underwent radical prostatectomy to enable correlation between MR imaging and pathological outcome. Of these 47 patients overall staging accuracy was 68% with MR staging of advanced disease showing 74% accuracy and 91% accuracy for detection of seminal vesicle involvement. Research groups also began to evaluate various aspects of MR technology to see if improvements could be made. Hricak et al (62) reported their results of comparing the use of pelvic phased array receiver coils or integrated endorectal coils, with observed better staging accuracy (77%) when using endorectal coils as opposed to 68% accuracy when using pelvic phased array coils, although this difference was not statistically significant. In 1996 D'Amico et al (63) evaluated endorectal coil MRI / pathology correlation for extra-capsular extension and seminal vesical invasion, in 445 patients who had radical prostatectomy between 1989 and 1995. They looked at the additive value of MRI when combined with pre-operative PSA, clinical DRE findings, biopsy Gleason score in predicting extra-capsular extension, seminal vesicle invasion, positive surgical margins and post-operative PSA failure. Interestingly they found that MRI was not of use in the high risk patients (by virtue of PSA, Gleason score and DRE

alone), as it did not add any weighting to the likelihood of non-organ confined disease, and MRI generated false negatives due to its inability to detect microscopic extra-capsular extension. However, in the intermediate risk patients MRI was able to add important information regarding extra-prostatic disease and thus help to reclassify these men into either low or high risk of non-organ confined cancer with resultant positive surgical margins and post-op PSA failure. Multivariable analysis was used in their study to determine that a pre-operative finding of extra-capsular extension on MRI was the most significant predictor of positive surgical margins. They found an overall accuracy in this intermediate risk group of 70% for extra-capsular extension and 94% for seminal vesicle invasion.

Further meta-analyses highlight the wide variation between studies evaluating the accuracy of MRI in determining localised staging. Sonnad et al (64) conducted a meta-analysis of 27 studies and used sub-group analyses to evaluate the strength of magnetic field strength and use of endorectal coil on accuracy of MRI in predicting organ-confined disease. Interestingly in reviewing these early studies prior to 2001, they found that use of higher field strength or endorectal coil seemed to confer less accuracy. Engelbrecht et al (65), from the Nijmegan research group in The Netherlands conducted a wider meta-analysis a year later in 2002 consisting of 71 articles and 5 abstracts, which in total contained 146 studies. In this meta-analysis the authors analysed MR imaging protocol characteristics used. They found that accuracy of determining T3 disease was significantly better when more imaging planes were used, endorectal coils were used and with the use of contrast agents. Magnetic field strength did not appear to have a significant effect on staging performance of MRI. An overall maximum sensitivity and specificity of 71% respectively in distinguishing between T2 and T3 disease was calculated in their meta-analysis.

However, despite the findings of the above studies that higher field strength does not improve accuracy of MRI staging of prostate cancer, more recent publications using 3T MR systems have shown sensitivities and specificities of 80-88% and 96-100% respectively (66, 67). Heijmink et al (67) compared 3T MRI accuracy when using a body array coil compared with using an endorectal coil. They observed that in their study of 46 patients, motion artefact was significantly greater in endorectal

coil imaging, but that overall accuracy values were better for all 4 radiologists in their study when an endorectal coil was used.

The use of dynamic contrast enhanced (DCE) MRI may improve accuracy in staging prostate cancer as observed by Futterer et al (68). They found that using DCE images improved accuracy, (using area under receiver operator curve - from 66% using T2-weighted imaging alone, to 82% when DCE images were also used), in local staging for less experienced radiologists but did not significantly improve results for experienced radiologists. Bloch et al (69) 2 years later also published their experience relating to the additive effect of DCE imaging techniques to MRI accuracy in locally staging prostate cancer. They used 1.5T field strength with both surface and endorectal coils, and used two experienced radiologists to interpret images. They yielded results that showed improved diagnostic accuracy in staging with the combination of DCE and T2-wieghted imaging (95 and 96% for each radiologist respectively), compared with T2-weighted MRI alone (84 and 86%).

More recently Hole et al (70) published their series of 209 men having MRI pre-operative staging (using T2-weighted imaging and DW-weighted sequences) prior to having radical robotic prostatectomy. Pathological locally advanced disease was present in 139/209 men. The authors evaluated the additive benefit of MRI in predicting T3 disease, and reported that DRE and TRUS alone detected 25.9% of cases with pathological locally advanced disease. The use of pre-operative T2-weighted and DW-weighted MRI increased the detection of T3 disease by 30.4% to 56.3%.

In summary, studies evaluating the ability of T2-weighted MRI alone to accurately determine whether prostate cancer is organ confined or not report widely variable results. More recent studies incorporating either contrast enhanced or diffusion weighted imaging in addition to T2 weighted sequences have shown that this may confer additional accuracy in MR local staging of prostate cancer.

Thus, historical data sets using only T2 weighted imaging for staging formed the basis of the 2008 National Institute for Health and Care Excellence (NICE) guidelines on the use of MRI in prostate cancer (71), in which the role of MRI is for staging purposes only after a positive biopsy. These guidelines stated that MR

imaging was not routinely recommended in those men in whom no radical treatment is intended and that MRI was indicated in those men with high risk clinically localised or locally advanced disease being considered for radical treatment.

Thus, current clinical practice is to use MR imaging to help accurately stage patients when deciding on treatment options and planning. However, there has also been research in the last decade to evaluate the ability of MRI to accurately detect and localise cancer within the prostate. The development of diffusion weighting and contrast enhanced imaging has also generated interest in the role that these additional parameters may have in improving MRI localisation of cancer within the prostate. The next section will review what is known on this area to date.

2.4 The Potential role of MRI in Detecting and Ruling Out Clinically Significant Prostate Cancer

Having established the role of MRI in staging of prostate cancer, research has shifted towards the ability of MRI to accurately detect and rule-out prostate cancer. This has been further galvanised by the use of multi-parametric sequences, such as contrast enhanced and diffusion-weighted imaging, as a way of improving quality of MRI accuracy.

The search for an imaging modality which can accurately identify regions harbouring cancer and also reliably rule-out cancer within the prostate is largely due to the poor performance of systematic TRUS guided prostate biopsies as outlined earlier. TRUS biopsy does not give accurate risk stratification by virtue of under-sampling (especially of the anterior gland) and also results in over-detection of clinically insignificant tumours and subsequent over-treatment, as highlighted by the PIVOT trial (46). The prostate is also the only organ whereby cancer is detected by systematic biopsy. In other organs the standard of care is to use an imaging modality to identify potential cancerous lesions, and then to obtain histological verification that these lesions are indeed cancer by using targeted biopsy. Recent research has shown that MRI may provide the imaging platform needed to change the current diagnostic paradigm and allow clinicians to perform targeted biopsy of suspicious MR lesions within the prostate.

2.4.1 Use of T2-weighted MRI alone to detect prostate cancer

In 1998 Ikonen et al (72) were one of the first groups to evaluate MRI localisation of cancer alongside staging publishing their results of MRI cancer detection in 51 consecutive men with biopsy proven prostate cancer. They used two radiologists to retrospectively review MR images and draw tumour location on schematic prostate maps whereby the prostate was divided, and compared them to final histopathology findings at radical prostatectomy. They used T2-weighted imaging with a 1.5T magnet and endorectal coil. Their results indicated overall accuracy for localising tumour of 61%, sensitivity of 60% and specificity of 63%, with moderate

inter-observer agreement rates. They commented that their results might have been limited, as there was no T1 protocol to detect post-biopsy haemorrhage and thereby reduce false-positive findings. They also observed that sensitivity for detection of cancer was better in the peripheral zone (77%) when compared to the anterior prostate (55%). All foci of tumour regardless of size or grade were deemed to be significant cancer and this may have compromised the overall sensitivity of MRI (60%), especially given the finding that only 5% of tumour foci <5mm and 89% of foci >10mm, were detected by MRI in this study. The authors concluded that MRI may be useful for locating cancer foci in patients with raised PSA values but repeated negative biopsy findings. The same Helsinki based group used the same MRI parameters to analyse results in 63 consecutive patients, and found that detection rate of cancer significantly improved with higher Gleason scores (73).

2.4.2 Use of contrast enhanced (DCE) MR Imaging

Hara et al (74) in 2005 suggested in conclusion to their study that dynamic contrast enhanced (DCE) MRI could be used to perform biopsies selectively in those patients with 'equivocal imaging outcomes or incompatible clinical manifestations despite negative imaging studies'. Their study of 90 men (of which 82 had organ confined disease and thus were used for analysis), compared accuracy of DCE-MRI with 14-core TRUS guided biopsies as the histological reference standard. The authors divided the prostate into 42 regions (each of the 14 cores was divided into anterior, central and posterior segments to give this 42 region histological map). They also deemed any cancer with < 2mm cancer in a single core and no Gleason pattern 4 or 5 disease to be insignificant, when assessing DCE-MRI accuracy. Their results showed that DCE-MRI identified 26/28 cases of clinically significant cancer (92.9%) and had a specificity of 96.3%.

These results with DCE-MRI were followed a year later in 2006 by Villers et al (75) in Lille, France. In this study a pelvic phased array coil rather than endorectal coil was used, and the reference standard was radical prostatectomy rather than TRUS biopsy. They had 24 patients who underwent pre-biopsy DCE-MRI who went on to have radical prostatectomy. Radiologists used a 1 – 5 point scoring system (5

being indicative of cancer), for lesions identified on DCE-MRI. These mapped areas of suspicion on MRI were correlated with histopathology maps from prostatectomy for each patient. For lesions > 0.2cc, they found sensitivity, specificity, positive and negative predictive values of 77%, 91%, 86% and 85%. For lesions > 0.5cc the corresponding values were 90%, 88%, 77%, and 95%.

The Lille based group updated their series in 2009 (76) with a total of 83 patients having pre-biopsy DCE-MRI before then undergoing radical prostatectomy. Each prostate was divided into octants for analysis and MRI scoring based on the 1 to 5 point Likert system, using a visual assessment only without the use of any semi-quantitative or quantitative outputs. When a score of ≥ 3 was taken to mean radiological suspicion of cancer, sensitivity was 32% and specificity 95% for any histological cancer. For detection of tumour lesions ≥ 0.5cc sensitivity and specificity values were 86% and 94% respectively. For lesions ≥ 0.2cc a sensitivity of 66% and specificity of 95% was observed.

Cheikh et al (77) reported using T2-weighted and DCE-MRI to localise prostate cancer lesions before repeat transrectal biopsies in 93 patients with previous negative biopsy. Of these 93 patients 23 had cancer on repeat biopsy. At a patient (whole gland) level analysis sensitivity, specificity, positive and negative predictive values were 48%, 44%, 20% and 80% respectively when using T2-weighted imaging alone, and 83%, 20%, 24% and 93% when DCE-MRI was used. In the same year Lemaitre et al (78) reported on the value of DCE-MRI in giving good localisation, morphological description, and volume assessment of anterior prostate tumours in 27 patients having pre-biopsy DCE-MRI and subsequent whole-mount radical prostatectomy.

More recently semi-quantitative interpretation of prostate DCE-MRI has been evaluated (79). This study had 53 consecutive patients who had 1.5T DCE-MRI using a phased-array body coil and spinal coil (without use of an endorectal coil), prior to radical prostatectomy. In this study speed of contrast uptake was found to be a good discriminator between cancer and benign tissue (area under receiver operator characteristic curve or AUC 0.82). Using a combination of speed on

contrast uptake and clearance rate of contrast agent gave even better accuracy in discriminating between cancerous and non-cancerous tissue (AUC 0.87).

However, semi-quantitative or quantitative values or outputs are not needed to accurately detect and localise tumours within the prostate as shown by studies using visual analysis only of DCE images (76, 80, 81).

2.4.3 Use of DW-MRI to detect prostate cancer

Early work investigating the use of diffusion-weighted imaging using a pelvic phased array coil in evaluating prostate tissue and cancerous lesions within it was initially undertaken and published just over 10 years ago (82, 83), tumours in the peripheral zone had lower ADC values than normal peripheral zone, and central gland with benign prostatic hyperplasia had lower ADC values than normal peripheral zone in healthy volunteers. These findings were repeated in a study of 10 patients with prostate cancer, using endorectal coil rather than pelvic phased array coil diffusion-weighted imaging (84). Further research has helped to highlight the valuable contribution of diffusion weighted sequencing to MR imaging of prostate cancer.

Shimofusa et al in 2005 (85) published one of the first studies evaluating the benefit of DW-MRI in addition to conventional T2-weighted MRI in the detection of prostate cancer. This study evaluated 60 patients of whom 37 had a histological diagnosis of prostate cancer (18 had undergone radical prostatectomy and 19 had TRUS biopsy verification only). As only 18 patients had undergone surgical excision of the prostate accuracy in the transition zone could only be evaluated properly in these patients. A 1.5T MR-imaging system was used with a pelvic phased-array coil and 3 radiologists independently reviewed images, scoring suspicious lesions on a Likert scale from 1 to 5. Analysis in this study defined radiological scores of ≥ 4 as cancer, with scores of 1-3 being defined as no cancer. Although this study was limited by the use of two different reference histology standards, it did reveal important results. Overall accuracy for detection of tumour within the prostate was significantly improved with T2+DW-MRI (93%) as

compared to T2-weighted MRI alone (87%). Overall mean negative predictive values were better with combined T2+DW-MRI (79%) than with T2-weighted imaging only (69%). Of the 18 radical prostatectomy cases, 8 had transition zone tumours. DW-MRI clearly highlighted transition zone tumour in 5 out of these 8 patients (63%), whereas T2-weighted MRI only picked up 1 (13%) of these transition zone lesions. This early study highlighted that using DW-MRI in conjunction with T2-weighted MRI improved the ability to detect and rule-out cancer.

A retrospective study of 37 patients who had pre-operative T2- and DW-MRI before radical prostatectomy, highlighted significantly improved sensitivity of 71% for detecting prostate cancer with a combined approach versus 51% using T2-weighted MRI alone (86). Specificity in this study was not improved (61% using T2- and DW-MRI versus 60% using only T2-weighted MRI). Lesions highlighted by radiologists on MR imaging were correlated with radical prostatectomy maps and the prostate divided into sextants for purposes of analysis. A drawback of this study was that it was retrospective and thus radiologists knew that all patients had undergone radical prostatectomy. Nevertheless it still highlighted the improved sensitivity seen with T2+DW-MRI. The authors also conducted analysis, which showed better detection of transition zone lesions using ADC maps. They also looked at quantitative ADC values in relation to Gleason score of lesions detected and found statistically significantly lower ADC values when comparing well and poorly differentiated tumours. However, there was no significant difference when comparing ADC values of well and moderately differentiated tumours and again no significant difference in ADC values when comparing moderate and poorly differentiated tumours.

Van As et al (87) reported their experience of using 1.5T DW-MRI (with endorectal coil) in 86 men diagnosed with prostate cancer on the Royal Marsden Hospital UK active surveillance program between 2002 and 2006. They found that tumour ADC value was a significant predictor of adverse histology on repeat biopsy and also a significant predictor of time to radical treatment. Thus, they postulated that DW-MRI ADC values may be a useful marker of prostate cancer behaviour with potential to improve patient selection for active surveillance and to offer a non-

invasive technique for monitoring the disease. More recently Verma et al (88) in 2011 published their results of using DW-MRI in 110 patients with prostate cancer, using a 1.5T MR machine with body, pelvic phased-array and endorectal coils. In this study ADC values were found to be significantly negatively correlated with Gleason grade in peripheral zone tumours (i.e. low ADC values associated with higher Gleason grade tumour). However, the authors did not find a correlation when analysing transition zone tumours.

2.4.4 Combining MRI Sequences

Kozloski et al (89) evaluated the effect of combining diffusion weighting and DCE techniques on MRI accuracy in 14 patients. They used an endorectal coil and a 1.5T scanner. The study actually analysed quantitative outputs from the DW images (apparent diffusion coefficient or ADC values) and DCE images (contrast enhancement curves), rather than radiologists interpretation of images. This study was limited due to small numbers but also because the histological reference standard used was not consistent – correlation with histology was based on octant TRUS guided biopsy in 6 patients with 8 patients having radical prostatectomy, which was then used as the reference standard. Taking these limitations into account the authors found that sensitivity improved from 54% for ADC outputs and 59% for DCE data, to 87% by combining DW and DCE imaging. Specificity was 100% for ADC data and 74% for DCE data, and this was found to decrease slightly to 74% when both techniques were combined. They therefore found that using both DW and DCE-MRI techniques conferred better sensitivity for detection of prostate cancer.

Chen et al (76) conducted a study of 42 patients who underwent 1.5T MRI with body and spine coils, and had T2-weighted, DW imaging and MR spectroscopy (MRS). The reference standard used was sextant TRUS guided prostate biopsies. Two radiologists evaluated the MR images and scored each of the sextant regions of the prostate using a Likert scale from 1 to 5 (1 being definitely negative and 5 definitely positive). The authors found that accuracy of detection of cancer

increased through a combination of the techniques, again adding weight to the idea that multi-sequence MRI offered a better way of imaging prostate cancer.

2.4.5 Potential for MRI to assess prostate cancer aggressiveness

In addition to the DW-MRI papers mentioned earlier, which indicate the potential role of ADC values in assessing prostate tumour Gleason score, there is also other evidence to support the use of MRI in the assessment of tumour aggressiveness.

Wang et al (90) in 2008 published their data on 74 men who underwent 1.5T MRI using both pelvic phased array and endorectal coils. They evaluated signal intensity ratios on T2-weighted images of tumours, non-tumour prostatic tissue and internal obturator muscle tissue, and found that higher Gleason grade lesions were associated with lower tumour-muscle signal intensity ratios, and thereby suggested that MRI may be used to assess prostate cancer aggressiveness. Bittencourt et al (91) assessed DW-weighted 1.5T MRI using a pelvic phased array coil. In 24 men with biopsy-proven prostate cancer who underwent radical prostatectomy in this study the correlation between ADC values of suspicious lesions on DW-weighted imaging and subsequent radical prostatectomy Gleason score was assessed. This was compared to the correlation between TRUS biopsy Gleason score and radical prostatectomy Gleason score. The authors found that DW images gave better correlation with prostate cancer aggressiveness than TRUS guided prostate biopsies, which under-estimated prostate cancer aggressiveness.

2.4.6 Issues of Post-Biopsy Haemorrhage affecting MRI accuracy

Prostate biopsy causes bleeding within the gland and this can in turn affect the quality of MR images obtained and accuracy in evaluating these images. White et al (92) reported their experience of MR T1 and T2-weighted imaging using and endorectal coil and 1.5T scanner. Of the 73 patients in their series 26 had imaging < 21 days after transrectal biopsies, and 47 had MRI > 21 days after biopsy. Post-biopsy haemorrhage was detected in 81% of patients who underwent imaging < 21

days after biopsy, and in 49% of those who were imaged > 21 days after biopsy. They observed that post-biopsy changes persisted for up to 4.5 months. They also found that tumour staging accuracy < 21 days post-biopsy was 46% compared with 83% > 21 days after biopsy. Post-biopsy haemorrhage was observed to result in over-estimating tumour presence and extra-capsular extension.

A recent publication of a consensus meeting of UK radiologists (93) suggested that ideally MRI should be delayed at least 10 weeks after biopsy but if possible after 20 weeks. The group advised that in cases where an MRI scan was needed less than 10 weeks after biopsy, that DCE sequence images were likely to be very degraded, and that therefore sequences should be limited to using T1-, T2- and diffusion-weighted only.

2.4.7 The issue of whether to use an endorectal or pelvic phased-array coil

The authors of the recent UK consensus group (93) stated that although performance of detection and staging of prostate tumours can be improved by using an endorectal coil, the benefits of pre-biopsy MRI can be achieved with a multi-channel pelvic-phased array coil only. Endorectal coil use also comes with additional cost, extra time for placement of coil, patient discomfort and some field inhomogeneity. In the UK consensus group the majority of radiologists did not use an endorectal coil.

Recent European Society of Urogenital Radiology (ESUR) guidelines (94) in 2012 have also stated that an endorectal coil is not necessary for a detection protocol MRI, but a pelvic phased array coil, ideally with a minimum of 16 channels is required. The ESUR guidelines did state that in the MRI protocol for staging rather than detection alone, that preferably staging MRI should be performed with an endorectal coil.

Thus, current practice and recommendation in the UK and Europe is to only use a pelvic phased array coil for detection mp-MRI scans. The above guidelines from UK and European consensus also state that 1.5T MR imaging is the standard field strength in widespread current practice.

2.5 The potential role for MRI in detecting and ruling out recurrent prostate cancer after external beam radiotherapy

Surveillance following organ preserving treatment of prostate cancer, such as external beam radiotherapy (EBRT) is an area for potential use of MRI. This becomes important in evaluating for objective imaging based evidence of disease recurrence in the presence of biochemical recurrence after treatment. It may also help distinguish from truly localised versus metastatic recurrent disease.

Such MR detection of recurrent disease can help to inform need for re-biopsy and also to inform salvage treatment options, such as salvage prostatectomy or brachytherapy. Ablative technologies such as cryotherapy or high-intensity focussed ultrasound (HIFU) may be used to focally treat areas of localised recurrence within the prostate in a focal manner, to reduce risks of toxicity in a previously irradiated prostate. In the focal therapy setting, accurate localisation with imaging would allow for informed treatment and also post-procedure imaging.

Early evidence suggested that MRI may be limited by radiotherapy changes within the prostate (including prostate shrinkage, diffuse low T2 signal intensity in the gland and loss of normal zonal anatomy). However subsequent research has showed that the use of multi-parametric sequences such as MRSI and DCE can improve MRI accuracy rates in detecting recurrent cancer post-EBRT. Coakley et al (95) reported their experience of using conventional T1 and T2-weighted 1.5T MRI using a pelvic phased array coil and an endorectal coil in 21 men with recurrent prostate cancer after external beam radiotherapy. They also used MRSI and evaluated this modality as well. They used TRUS guided sextant prostate biopsy as the reference standard (performed at least within one year of MRI). Given the known limitations of tumour localisation and registration with sextant biopsy, the authors used a hemi-prostate (i.e. divided the prostate into left and right halves) level of analysis. Two radiologists used a 1 to 5 point Likert scoring system to evaluate MR images for evidence of recurrent cancer, with area under receiver operator characteristic (AUC) curves giving accuracy values of 0.49 and 0.51 for

each radiologist using T1 and T2 weighted imaging only. AUC values were much higher (0.81) for MRSI imaging, but it should also be noted that MRSI images were reported by a third different radiologist and thus these results cannot be directly compared to the T1/T2 imaging results in this study. Nevertheless it did indicate that additional sequences may help to localise recurrent cancer better.

Haider et al (96) compared the ability of T2-weighted MRI and DCE-MRI to accurately detect recurrent prostate cancer after external beam radiotherapy in 33 patients. All MR imaging was reviewed by one radiologist in this study and the reference standard used was TRUS guided sextant prostate biopsy. Again given the limitations of transrectal biopsies as a reference standard (as outlined previously), the authors only conducted analysis in the peripheral zone, dividing the peripheral zone into an apical, mid-gland and basal region on each side to give six zones for analysis. Their scoring system was also different to other studies (0 – no cancer, 1 – probably no cancer, 2 – possibly no cancer, 3 – definite cancer). Any cancer was considered significant. At this sextant peripheral zone only level of analysis T2-weighted imaging had sensitivity, specificity, positive predictive value and negative predictive value of 38%, 80%, 24% and 88%. The same values using DCE-MRI were 72%, 85%, 46% and 95% respectively. They suggested that DCE may have better performance in previously irradiated prostates because radiotherapy induces fibrosis (97), which would therefore enhance less and washout slower than normal prostate tissue, which may help to accentuate the difference between cancer and background prostate to a greater degree.

In a small study of 9 patients, Pucar et al (98) reported a sensitivity of 68% and 77% for T1/ T2 weighted MRI and MRSI respectively, with specificities of 96% (T1 and T2-weighted MRI) and 78% (MRSI). This limited study used salvage radical prostatectomy specimens as the reference standard.

A subsequent larger series of 45 consecutive patients, who had T1 and T2-weighted 1.5T MRI (using pelvic-phased array and endorectal coils), prior to salvage radical prostatectomy for recurrent cancer after EBRT was published by Sala et al (99) the following year. They reported MR scans using a 1 to 5 point Likert scoring system for degree of suspicion of cancer. Using whole mount

salvage prostatectomy as the histological reference test, the accuracy of T1- and T2-weighted MRI was better in this study than those previously reported, with AUC overall accuracy values of 0.75 and 0.61 respectively for each of the radiologists in the study.

2.6 Aims of Thesis

The use of MRI in prostate cancer has slowly been expanding in the last decade, from initial use for staging purposes only to now having a potential role in the accurate detection and localisation of tumour foci within the prostate. Such imaging techniques have been greatly improved through the addition of 'multi-functional' or 'multi-parametric' sequences such as DCE- and DW-MRI to improve accuracy.

The evidence reviewed so far has been limited by the type of histological reference standard used. Studies using TRUS guided biopsies as a reference standard are immediately limited by the poor sampling of the anterior prostate in assessing for accurate tumour detection by MRI in this region of the prostate. There is also an issue of relative under-sampling of the peripheral zone itself.

Most prostate cancer localisation MRI studies use whole-mount radical prostatectomy specimens as the histological reference standard. Whilst this gives absolute confirmation regarding position of tumours within the gland to allow meaningful evaluation of MRI accuracy, these studies are limited by a positive selection bias, in that men undergoing radical prostatectomy are more likely to have larger volume and more aggressive disease. Many men with either no cancer or small volume / clinically insignificant disease are therefore not included in such series. Cancer in radical prostatectomy specimens will likely be easier to detect on MRI and thus the use of radical prostatectomy specimens will result in more favourable results when analysing MRI accuracy.

As outlined earlier in this introduction TPM has been shown to have excellent overall accuracy for the detection of cancer. It provides a good accurate way of sampling the entire prostate including the anterior gland. TPM therefore provides an excellent histological reference standard, which does not have the issues of under-sampling associated with TRUS guided biopsies, whilst allowing histological evaluation of all men 'at risk of having prostate cancer' by virtue of a raised PSA or DRE finding. It therefore does not have any of the positive selection bias associated with radical prostatectomy patients.

The aim of this thesis is therefore to evaluate the potential role for multi-parametric (mp)-MRI (T1, T2, DCE- and DW-MRI) in detecting and ruling-out significant cancer, using TPM as the reference standard. I will evaluate this in patients who have had no previous treatment. I will also test the ability of mp-MRI to detect and rule-out recurrent cancer in patients treated with external beam radiotherapy.

CHAPTER 3

MATERIALS USED FOR EXPERIMENTAL STUDIES

3.1 Diagnostic Methodology Standards

The studies conducted in this thesis used the Standards for Reporting of Diagnostic Accuracy (STARD) guidelines as a framework for ensuring quality of diagnostic methodology, results reporting and analysis (100). The STARD document consists of 25 separate criteria, which should ideally be included in any diagnostic study to allow assessment of potential bias in a study and also to evaluate a study's generalizability.

The 25 STARD criteria are listed below:

1. Identify the article as a study of diagnostic accuracy

2. State the research questions or aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.

Methods (Participants):

3. Describe the study population: the inclusion and exclusion criteria and the settings and locations where the data were collected.

4. Describe participant recruitment: was this based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?

5. Describe participant sampling: was this a consecutive series of participants defined by selection criteria in items 3 and 4? If not, specify how participants were further selected.

6. Describe data collection: was data collection planned before the index tests and reference standard were performed (prospective study) or after (retrospective study)?

Methods (Test Methods):

7. Describe the reference standard and its rationale.

8. Describe technical specifications of material and methods involved, including how and when measurements were taken, or cite references for index tests or reference standard, or both.

9. Describe definition of and rationale for the units, cut-off points, or categories of the results of the index tests and the reference standard.

10. Describe the number, training, and expertise of the persons executing and reading the index tests and the reference standard.

11. Were the readers of the index tests and the reference standard blind (masked) to the results of the other test? Describe any other clinical information available to the readers.

Methods (Statistical Methods):

12. Describe methods for calculating or comparing measures of diagnostic accuracy and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).

13. Describe methods for calculating test reproducibility, if done.

Results (Participants):

14. Report when study was done, including beginning and ending dates of recruitment.

15. Report clinical and demographic characteristics (e.g. age, sex, spectrum of presenting symptoms, comorbidity, current treatments, and recruitment centre).

16. Report how many participants satisfying the criteria for inclusion did or did not undergo the index tests or the reference standard, or both; describe why participants failed to receive either test (a flow diagram is strongly recommended)

Results (Test results):

17. Report time interval from index tests to reference standard, and any treatment administered between.

18. Report distribution of severity of disease (define criteria) in those with the target condition and other diagnoses in participants without the target condition.

19. Report a cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, report the distribution of the test results by the results of the reference standard.

20. Report any adverse events from performing the index test or the reference standard.

Results (Estimates):

21. Report estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).

22. Report how indeterminate results, missing responses, and outliers of index tests were handled.

23. Report estimates of variability of diagnostic accuracy between readers, centres, or subgroups of participants, if done.

24. Report estimates of test reproducibility, if done.

Discussion:

25. Discuss the clinical applicability of the study findings.

Study design was therefore undertaken with the above criteria in mind. Institutional review board exemption was given by the local research ethics committee for the studies undertaken.

3.2 Study Populations

Patients in both studies were men referred to the Urology department at University College Hospital London, UK from December 2006 to October 2008, with standardised blinded radiology reporting of these mp-MRI images undertaken between June 2009 and April 2011 for each study.

Chapter 4 Experimental Study:

Inclusion criteria:

(a) Patients with confirmed biochemical recurrence after external beam radiotherapy for previously diagnosed prostate cancer having mp-MRI prior to TPM (13 patients).

Exclusion criteria:

(a) Patients who had not had previous external beam radiotherapy to treat prostate cancer

Again all men underwent both mp-MRI (index test) followed by TPM (reference test). The time interval from biochemical relapse following external beam radiotherapy to mp-MRI imaging was not pre-determined, nor was the time between mp-MRI and TPM.

Chapter 5 and 6 Experimental Studies:

Inclusion criteria:

(a) Men who had low-risk or low-intermediate risk prostate cancer at TRUS guided prostate biopsy seeking reassurance about risk classification (51 patients).

(b) Men who had prior negative TRUS guided prostate biopsy findings with persistently elevated PSA levels (10 patients).

(c) Men who were referred for prostate biopsy for the first time and wanted to prevent the known sepsis risk of TRUS guided prostate biopsy (3 patients).

Exclusion criteria:

(a) Patients who had received any previous treatment that may compromise the performance of either the index test or reference test

- previous external beam radiotherapy (13 patients)

- previous brachytherapy (4 patients)

- androgen suppression or exposure to 5 alpha-reductase inhibitors (5 patients)

Other than the above criteria, no other exclusion criteria were set in order to allow a fairly heterogeneous population to be included in this study and thereby limit spectrum bias.

In addition reporter bias would hopefully be limited as both men with previously diagnosed cancer and those without a diagnosis of cancer were included.

All men underwent both mp-MRI (index test) followed by TPM (reference test). The time interval between mp-MRI and TPM was not fixed.

3.3 Index Test: mp-MRI Protocol

Mp-MRI imaging was performed (after verbal consent) with a 1.5T scanner (Magnetom Symphony or Avanto; Siemens Medical Solutions, Erlangen, Germany) and a pelvic phased-array coil.

Although it is acknowledged that performance for detection of tumour may have been improved by using an endorectal coil as well, the benefit was not felt to outweigh the costs, patient discomfort, extra time for placement and field inhomogeneity, with a recent consensus meeting of UK radiologists revealing that the majority did not routinely use endorectal coils (93). Thus our methodology of using a pelvic phased array coil was designed to reflect standard UK practice and also allow the index test (mp-MRI) to be acceptable to the patient.

The protocol included axial and coronal T2-weighted imaging and pre- and post-intravenous gadolinium chelate (dotarem gadoteric acid) dynamic contrast enhanced sequences.

The protocols for each sequence are outlined in the table 4 below.

Table 4 –mp-MRI sequence protocol

Parameter	TR (ms)	TE (ms)	Flip angle (degrees)	Plane	Slice Thickness (gap)	Matrix size	Field of view (mm)	Time for scan
T2 TSE	5170	92	180	Axial, coronal	3mm (10% gap)	256x256	180x180	3m 54s (axial) 4m 18s (coronal)
VIBE Fat sat	5.61	2.52	15	Axial	3mm (20% gap)	192x192	260x260	9m 59s (35 x17s acquisitions)
Diffusion (b values: 0, 150, 500, 1000) (s/mm2)	220	Min (<98)		Axial	5mm	172x172	260x260	5m 44s (16 averages)

TE – echo time, TR – repetition time, T2 TSE – T2 weighted turbo spin echo, VIBE fat sat – volumetric interpolated breath-hold examination with fat saturation.

3.4 Index Test: Reporting of mp-MRI

Scans were reviewed independently by two uro-radiologists (CA and AK) in the experimental study in chapter 4, and three uro-radiologists (CA, AK and SAS) in the studies outlined in chapters 5 and 6.

The prostate MR imaging experience of each uro-radiologist was as follows:

R1 - SAS 3 years

R2 - CA 10 years

R3 - AK 6 years

of being dedicated consultant uro-radiologists within their respective tertiary centre institutions.

For each study the radiologists were given the following information for each patient:

- Age

- DRE findings

- PSA level

Radiologists did not have access to any previous TRUS guided prostate biopsy results or TPM outcomes.

For purposes of analysis the prostate was divided into 4 sectors by using the urethra as the dividing point (i.e. left and right anterior, left and right posterior). This generated 256 sectors of analysis in studies in chapters 5 & 6 (64 patients) and 52 sectors of analysis in the study in chapter 4 (13 patients).

Each region was given a score of 1 to 5 by using a standardised scoring system based on the Likert scale that was reported on in a recent consensus meeting (101).

The recent ESUR prostate MR guidelines (94) recommended the use of the above Likert 1 – 5 scoring system as already used successfully by breast radiologists.

For all patients T2-weighted images were scored first, then quadrants were re-scored after a second sequence was viewed (either DWI or DCE) and a final score for each quadrant was given after all three sequences had been reviewed. See standard operating procedure (SOP) and reporting proforma in appendix.

The criteria used for scoring outlined below were similar to those described in recent ESUR guidelines (94) for T2-weighted and diffusion weighted imaging:

T2 images (peripheral zone):

If there was uniform high signal intensity then a score of 1 was attributed to that quadrant. Areas of lower signal intensity not well demarcated were scored at 2, with intermediate appearances scored 3. Quadrants containing areas of discrete homogenous low signal intensity were scored as 4 or 5 depending on degree of suspicion.

T2 images (transition zone / TZ):

A score of 1 was given to appearances of TZ adenoma with well-defined margins. A score of 2 indicated an area(s) of more homogenous low signal intensity, which was well marginated and arising from the TZ. The intermediate score was again 3, with areas of more homogenous low signal intensity which appeared more ill-defined (the 'erased charcoal sign') given a score of 4. A transition zone lesion, which appeared similar to one with a score of 4, had its score increased if the anterior fibromuscular stroma or the anterior horn of the peripheral zone was involved.

Diffusion weighted images:

Scores were attributed according to the following criteria:

1 - If there was no reduction in ADC compared with normal glandular tissue and no increase in signal intensity on any high b-value image (≥b800).

2 – Diffuse hyper signal intensity on ≥b800 imaging with corresponding low ADC, but no focal features

3 – Intermediate appearances not in categories above or below

4 – Focal area of reduced ADC but iso-intense signal intensity on high b-value images (≥b800)

5 – Focal area of hyper signal intensity on the high b-value images (≥b800) with reduced ADC

Radiologists used in the experimental studies in this thesis when evaluating DCE images, used no quantitative measures (unlike the ESUR PI-RADS system for scoring). Thus the degree of enhancement seen in a given region / lesion within the prostate was subjectively judged and scored using the Likert 1- 5 scale.

Combining T2-weighted images with DWI and DCE imaging to give overall score for quadrants:

As mentioned above no absolute enhancement curve parameters or ADC values were used when interpreting images. When generating the overall score for each quadrant all sequences were used. For example an overall score of 2 indicated a low-signal area on T2 weighted images with no abnormality on the other sequences. A score of 3 would indicate patchy enhancement on DCE in the same area of T2-weighted low signal. A score of 4 indicated more intense homogenous enhancement on DCE or on DW imaging the presence of a high signal area on high b-value images with reduced ADC. A score of 5 for a quadrant indicated that all 3 sequences met the visual criteria for suspicion of cancer.

3.5 Reference Test: Transperineal Template Mapping (TPM) Biopsy Technique

After informed consent TPM was performed under general anaesthesia by using a 5mm brachytherapy template grid mounted onto a stepper (see diagram below).

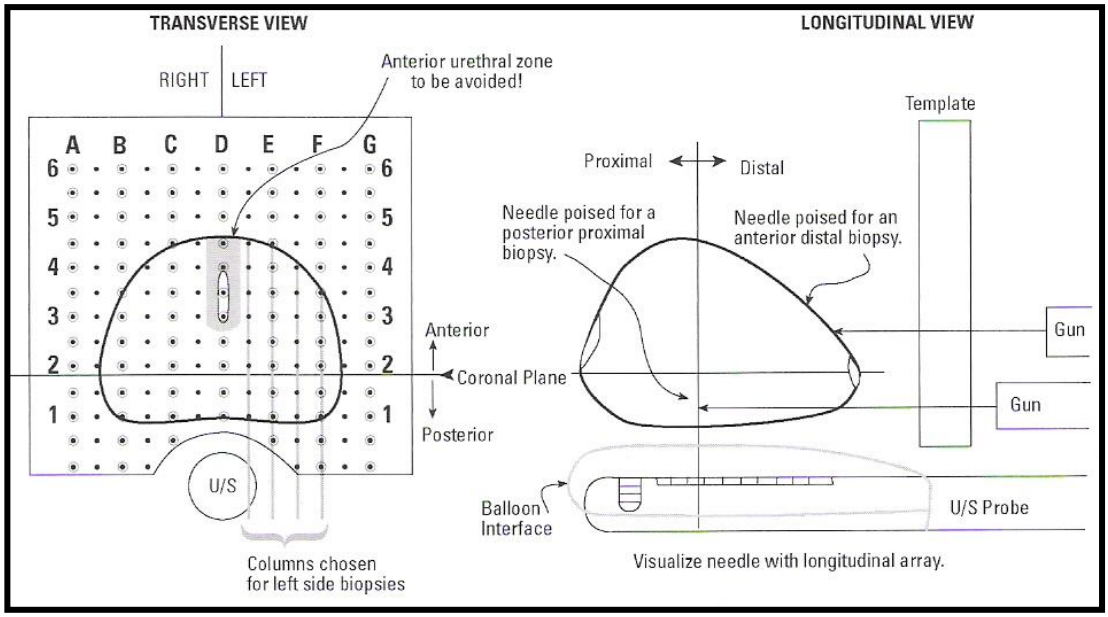


Figure 6 – Schematic representation of TPM.

Biopsy samples were obtained at every 5mm grid point on the prostate and the operator was blinded to imaging results. If the prostate apex – base length was greater than the core length, two biopsy samples were obtained at the same grid co-ordinate to cover the whole length of the prostate at that point.

Biopsy cores were analysed and reported by a dedicated uro-pathologist with 8 years of experience, blinded to the imaging reports. Biopsy results were grouped into 4 quadrants per prostate in the same way that the prostate was divided for mp-MRI reporting. For TPM, biopsies were grouped into quadrants by using the midline to determine left and right, with any biopsy cores taken on or anterior to the grid level of row 2.0 being assigned to anterior quadrants, and those below row 2 assigned to posterior quadrants. If a lesion spanned two or more regions it was allocated to the sector that was predominantly involved, independent of mp-MRI reports.

3.6 Performance of mp-MRI with Changing Definitions of 'Clinically Significant Cancer'

Two target definitions were used to define clinically significant recurrent disease post-radiotherapy:

1. All Cancer (on the basis that all recurrent cancer post radical treatment should be viewed as significant)

2. Only cancer ≥ 3mm cancer core length on TPM (to assess the ability of mp-MRI to detect larger volume recurrent cancer).

To define clinically significant prostate cancer in patients who had not had any previous treatment a primary target definition was used (see Definition 2 below) as well as a higher threshold (see Definition1 below).:

The primary target definition (Definition 2) for clinically significant disease on TPM was set at a Gleason score ≥ 3+4 and / or with cancer core length involvement of ≥ 4mm. This relates to an area of cancer on TPM biopsies that has high-grade components (non-dominant Gleason score of ≥ 4) and / or is approximately equal to a lesion volume ≥ 0.2ml (102). This primary target definition for 'clinically significant cancer' was chosen on the basis that few would disagree that any man who had this level of cancer would require treatment.

A higher threshold for clinically significant cancer (Definition 1): cancer core involvement ≥ 6mm and / or Gleason score ≥ 4+3 was also used.

It is also recognised that there is legitimate professional disagreement on what constitutes clinically significant prostate cancer and hence other target definitions of clinically significant disease were also used to define the target condition on the reference test (TPM). Other definitions were also used, and the TPM thresholds of 'clinically significant cancer' listed in ascending order of cancer burden are outlined below:

(a) All cancer: cancer core length ≥ 1mm and any Gleason score

(b) Goto et al (103): cancer core length ≥ 2mm and / or Gleason score ≥ 3+4

(c) Epstein et al (9): cancer core length ≥ 3mm and / or Gleason score ≥ 3+4

(d) Gleason score 7: cancer core length ≥ 1mm and ≥ Gleason 3+4

(e) Definition 2: cancer core length ≥ 4mm and / or ≥ Gleason 3+4

(f) Definition 1: cancer core length ≥ 6mm and / or ≥ Gleason 4+3

3.7 Statistical Analysis

Two-by-two tables were constructed at the quadrant level for primary analyses. Subsequent validation of mp-MRI imaging for all target conditions of clinical significance was performed by using two sectors of analysis per prostate (left and right lobes) and also by analysis per prostate at a whole gland level.

Sensitivity, specificity, positive predictive values and negative predictive values were calculated as were measures of overall accuracy, such as overall fraction correct and area under the receiver operating characteristic (ROC) curves. Positive and negative likelihood ratios (LRs) were also calculated to demonstrate changes in pre-test probability that resulted from the outcomes of mp-MRI. A LR > 1 would indicate a post-test probability that was higher than the pre-test probability, and a LR < 1 indicates a post-test probability that was lower than the pre-test probability. Binomial 95% confidence intervals were calculated.

Inter-rater reliability analysis using the kappa statistic was performed to determine consistency among radiologists. A weighted kappa calculation was used given that the categories were ordered, and more specifically a quadratic weighted kappa was used given that we were using an mp-MRI threshold score of ≥ 3 to represent a positive mp-MRI, thus meaning that the weighting of the mp-MRI score 1 – 5 was not a linear relationship.

Kappa values were interpreted as follows: 0 – 0.20 slight agreement, 0.21 – 0.40 fair agreement, 0.41 – 0.60 moderate agreement, 0.61 – 0.80 substantial agreement, and values > 0.81 indicating almost perfect agreement.

All statistical analysis used was performed with statistical software (SPSS v17.0 SPSS Chicago III and MedCalc version 13).

CHAPTER 4

EXPERIMENTAL STUDY:

MP-MRI IN DETECTION OF PROSTATE CANCER RECURRENCE POST-RADIOTHERAPY

4.1 Introduction

External beam radiotherapy (EBRT) is used to treat men with organ confined prostate cancer, with the potential however for biochemical recurrence in 20-41% of men at 5 years and up to 47% at 8 years following treatment (104). Many of these men have locally recurrent prostate cancer although up to half may have metastatic disease. Localised radio-recurrent disease can be amenable to salvage treatment including radical prostatectomy (RP), cryotherapy, brachytherapy or high-intensity focused ultrasound ablation. If salvage therapy is not undertaken early, then the median time to development of distant metastases is approximately 3 years (105). However, determining the presence of localised recurrence can be difficult as other imaging methods (e.g. TRUS or CT) have poor sensitivity and specificity for intra-prostatic cancer (106).

As discussed earlier in this thesis mp-MRI has shown promise as an imaging modality in this situation. Early research showed that the use of MRI to detect recurrent prostate cancer after EBRT might be hampered by radiotherapy changes, including prostate shrinkage, diffuse low T2 signal intensity within the gland, as well as loss of normal zonal anatomy (107).

The current evidence for using MRI to detect recurrent prostate cancer after EBRT is hampered by verification bias. Previous studies have used either salvage radical prostatectomy specimens or TRUS-guided biopsies as the reference standard. Salvage prostatectomy introduces a selection bias, as this group might not be representative of the entire group of patients who have biochemical failure. In fact they may over-represent more favourable radio-recurrent cancer amongst the population with biochemical failure after EBRT. TRUS biopsies as outlined earlier are inherently inaccurate, with both random and systematic error, the latter resulting from over-sampling of the peripheral zone and under-sampling of anterior / transition, apical and midline regions of the prostate.

TPM provides an alternative reference test, which avoids the deficiencies of both radical prostatectomy and TRUS biopsies as reference standards. It can be applied

to all men who have biochemical failure before any treatment, sampling the whole prostate at 5mm intervals (as outlined in the materials section of this thesis), and provides Cartesian coordinates enabling registration with imaging easier.

To my knowledge the following study is the first to evaluate the role of mp-MRI (using T2-weighted, DCE-MRI and DW-MRI) in detection of locally recurrent prostate cancer after EBRT, using TPM as the reference standard.

4.2 Methods

Institutional review board exemption was granted by the local research ethics committee.

Patient Population:

Patients in this study were men referred to the Urology department at University College Hospital London, UK. All men in this study had confirmed biochemical recurrence after EBRT and underwent mp-MRI followed by TPM at one centre over a two year period.

Inclusion criteria:

(a) Patients with confirmed biochemical recurrence after external beam radiotherapy for previously diagnosed prostate cancer having mp-MRI prior to TPM (13 patients).

Exclusion criteria:

(a) Patients who had not had previous external beam radiotherapy to treat prostate cancer

Again all men underwent both mp-MRI (index test) followed by TPM (reference test). The time interval from biochemical relapse following external beam radiotherapy to mp-MRI imaging was not pre-determined, nor was the time between mp-MRI and TPM.

Mp-MRI:

All mp-MRI scans were taken using a 1.5T scanner (Symphony or Avanto, Siemens AG, Munich, Germany) using a pelvic phased-array coil. The protocol included T2W, DW (TR 2200, TE 98, b-values 0, 150, 500, 1000, field of view 260 x 260mm), and pre- and dynamic (15s acquisition frame) sequences after IV

gadolinium contrast. The detailed mp-MRI parameters are outlined in the materials section earlier.

Radiologists:

Mp-MRI scans were reviewed independently by two uro-radiologists:

R1 CA – 10 years' consultant uro-radiology experience

R2 AK – 6 years' consultant uro-radiology experience

Each prostate was divided into 4 regions of interest (ROIs): left and right anterior, left and right posterior, using the urethra as the anatomical dividing point. This generated 52 paired datasets. Each region was scored 1 to 5 using a standardized scoring grid (see appendix), with 1 = no radiological evidence of cancer, 2 = low suspicion, 3 = possible cancer, 4 = suspicion, 5 = highly suspicious.

No quantitative variables were used when determining suspicion of cancer, in an attempt to reflect everyday clinical practice.

TPM:

Transperineal template biopsies were taken under general anaesthesia using a 5-mm brachytherapy grid mounted on a stepper, with TRUS guidance. The technique was described previously. In summary, biopsies were taken at every 5 mm point on the prostate. If the prostate apex-base length was greater than the core length, two biopsies were taken at the same grid coordinate and labelled separately. Biopsy cores were analysed and reported by a dedicated expert uro-pathologist with 8 years of consultant experience. Biopsy results were grouped into four ROIs per prostate, reflecting the mp-MRI reporting

Definitions of significant cancer on TPM:

Two target definitions were used to define clinically significant recurrent disease post-radiotherapy:

1. All Cancer (on the basis that all recurrent cancer post radical treatment should be viewed as significant)

2. Only cancer ≥ 3mm cancer core length on TPM (to assess the ability of mp-MRI to detect larger volume recurrent cancer).

Analysis:

To assess accuracy 2 x 2 tables were constructed and two analyses were used based on the target definitions above. Sensitivity, specificity, positive and negative predictive values were determined, together with construction of receiver-operator (ROC) characteristic curves.

4.3 Results

4.3.1 Patient demographics

Table 5 (a - d) shows a summary of the patient group characteristics pre- and post-radiotherapy.

The mean age of the 13 men was 65.5 years (range 55 - 70). Mean PSA prior to radiotherapy was 36.6ng/ml (4.5 - 150), with four men having stage T2, and three men stage T3 disease prior to radiotherapy. There was no record of pre-radiotherapy stage for six patients. Gleason scores prior to radiotherapy varied from 4 to 8ng/ml. The mean time from radiotherapy to biochemical relapse was 5.7 years (range 3 – 10 years), with mean PSA at relapse prior to MRI and template biopsy being 7.1 ng/ml (0.83 - 27.9).

None of the patients had evidence of bony metastases on MRI and one patient only had a solitary pelvic lymph node which was suspicious. Local staging of recurrent disease based on multi-functional MRI was ≤T2 in seven patients and ≥T3 in six patients with mean gland size on MRI of 35 cc (7 – 153 cc). The mean interval between MRI and template biopsy was 5 months, but this extended to 13 months for two patients (range 0 - 13). A mean number of 32 cores were taken at template prostate mapping biopsy (range 14–60), with a mean of 4.4 cores being positive (0–12) and mean 4.7mm maximal cancer core length (1–10). Of the eleven patients with positive biopsy findings, ten had Gleason score 7 disease (seven with 3+4 and three with 4+3 pattern) with one patient having radiotherapy effects preventing accurate grading.

The information relating to the original radiotherapy treatment was limited as most (ten) patients were referred from other centres for consideration of salvage high intensity focused ultrasound ablative therapy. Where information was available 4 patients had 64 Gy in 32 fractions, and another patient had conformal high dose rate radiotherapy. On histology, tumour was present in at least one quadrant in 11/13 patients. 3/11 had cancer in only a single quadrant, 4/11 had cancer in two quadrants, with 4/11 having tumour in three quadrants. No patient had tumour in all four quadrants.

Of note three men had commenced bicalutamide and two were already on LHRH analogues prior to referral to our centre. A further two commenced bicalutamide after imaging, but before having prostate mapping.

4.3.2 MRI Accuracy

Table 6 shows the accuracy values for various threshold scores of defining a positive MRI zone on the 5-point system. For the initial analysis, any cancer detected on biopsy was deemed significant.

Figure 7 shows the receiver-operator characteristic curves for each observer, **when all cancer detected on biopsy was deemed significant**. Accuracy expressed as area under the curve (AUC) was 0.77 (95% confidence intervals 0.63, 0.90) for observer 1, and 0.89 (95% confidence intervals 0.80, 0.99) for observer 2.

Table 7 shows the accuracy values for various threshold scores of defining a positive MRI zone on the 5-point system. For this analysis, only cancer core length involvement ≥ 3mm in any one core was deemed significant. Figure 8 shows the ROC curves **when only cancer core length involvement ≥ 3mm was deemed as showing significant cancer recurrence**. Accuracy as calculated by AUC was 0.86 (95% confidence intervals 0.74, 0.98) for observer 1, and 0.94 (95% confidence intervals 0.87, 1.00) for observer 2.

An example of a perfect correlation of MRI and histology is seen in figure 9 and 10 (showing T2 weighted, dynamic gadolinium contrast enhanced and diffusion sequences, with subsequent histology). This shows a tumour in the right hemi-gland (scored by both radiologists as 5 – definite cancer, and confirmed to be cancer on histology – maximum cancer core length 10mm and Gleason 4+3 disease). Of note the T2 weighted sequence did not reveal any abnormality and the radiological suspicion was based on the contrast enhanced and diffusion weighted sequences

Inter-observer agreement was statistically evaluated by using weighted kappa values. As already described in the literature, kappa values were interpreted as follows: 0 – 0.20 slight agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; ≥0.81 almost perfect agreement. When a radiological score of ≥3 to define cancer on mp-MRI was used for both radiologists, the inter-observer agreement was 0.42 (indicating moderate agreement) for all cancer on

histology. For analysis of all histological cancer being included, overall inter-observer agreement using a weighted kappa calculation was 0.26 (indicating fair agreement), across all mp-MRI thresholds. The inter-observer agreement was even better (0.65 indicating substantial agreement), when only biopsy cores with cancer ≥ 3mm were included.

4.3.3 Tables and graphs of Results

Table 5 – Summary of Patient Characteristics (pre- and post-radiotherapy)

(A)		**RANGE**
Mean age of patients (at time of template biopsy)	65.5	55 - 70
Mean PSA prior to radiotherapy	36.6	4.5 - 150
Mean PSA prior to MRI and template prostate mapping	7.1	0.83 - 27.9
Mean time from radiotherapy to biochemical relapse (years)	5.7	3 – 10
Mean interval between MRI and Template biopsy (months)	5	0 - 13

(B) OVERVIEW OF DISEASE PRE-RADIOTHERAPY		
Stage at radiotherapy	T2	4
	T3	3
	No record	6
Gleason score **prior** to radiotherapy	4	1
	5	1
	6	3
	7	4
	8	2
	Unknown	2

(C) MRI STAGING AT RECURRENCE		
MRI Stage at recurrence prior to template prostate mapping	≤ T2	7
	≥ T3	6

(D) OVERVIEW OF DISEASE AT RADIO-RECURRENCE			RANGE
Number of patients with no cancer on template biopsy		2	
Number of patients with cancer on template biopsy		11	
Patients with radio-recurrent cancer on template mapping	No. patients with Gleason score 7	10	
	Radiotherapy effect preventing grade	1	
Mean Number cores taken		32	14 - 60
Mean number positive cores		4.4	0 - 12
Mean MCCL (mm)		4.7	1 - 10

Table 6 – Radiology score results for all cancer on histology being significant

All cancer on Histology Significant								
Observer 1								
Cancer definition MRI Score	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
≥1	23	29	0	0	100	0	44	0
≥2	24	28	0	0	100	0	46	0
≥3	18	11	18	5	78	62	62	78
≥4	12	2	27	11	52	93	86	71
≥5	3	0	29	20	13	100	100	59
Observer 2								
Cancer definition MRI Score	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
≥1	23	29	0	0	100	0	44	0
≥2	23	29	0	0	100	0	44	0
≥3	20	4	24	4	83	86	83	86
≥4	17	2	27	6	74	93	89	82
≥5	13	1	28	10	57	97	93	74

Figure 7 – ROC curves when all cancer deemed significant

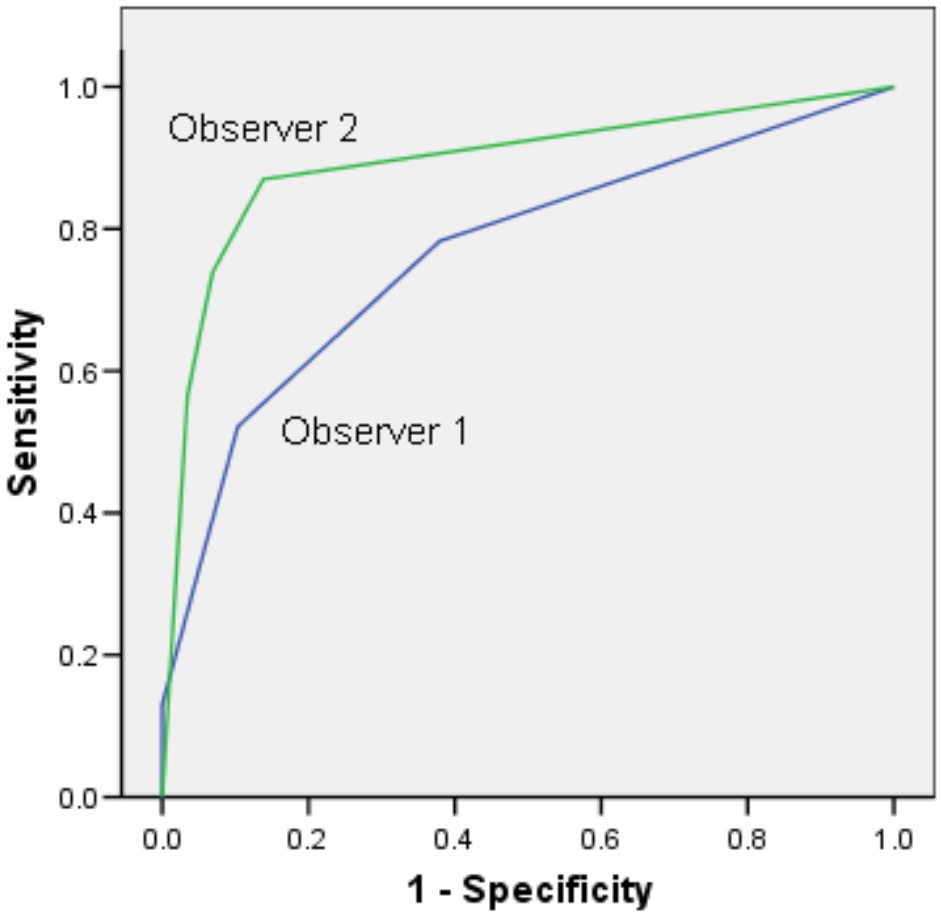


Table 7 – Radiology score results when only cores ≥ 3mm cancer considered significant

Cancer on histology defined as cores with ≥ 3mm cancer length								
Observer 1								
Cancer definition MRI Score	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
≥1	14	38	0	0	100	0	27	0
≥2	14	38	0	0	100	0	27	0
≥3	13	16	22	1	93	58	45	96
≥4	10	6	33	3	77	85	63	92
≥5	3	0	38	11	21	100	100	78
Observer 2								
Cancer definition MRI Score	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
≥1	14	38	0	0	100	0	27	0
≥2	14	38	0	0	100	0	27	0
≥3	14	10	28	0	100	74	58	100
≥4	13	6	32	1	93	84	68	92
≥5	11	3	35	3	79	92	79	92

Figure 8 – ROC curves when only ≥ 3mm cancer core length used as definition of presence of cancer

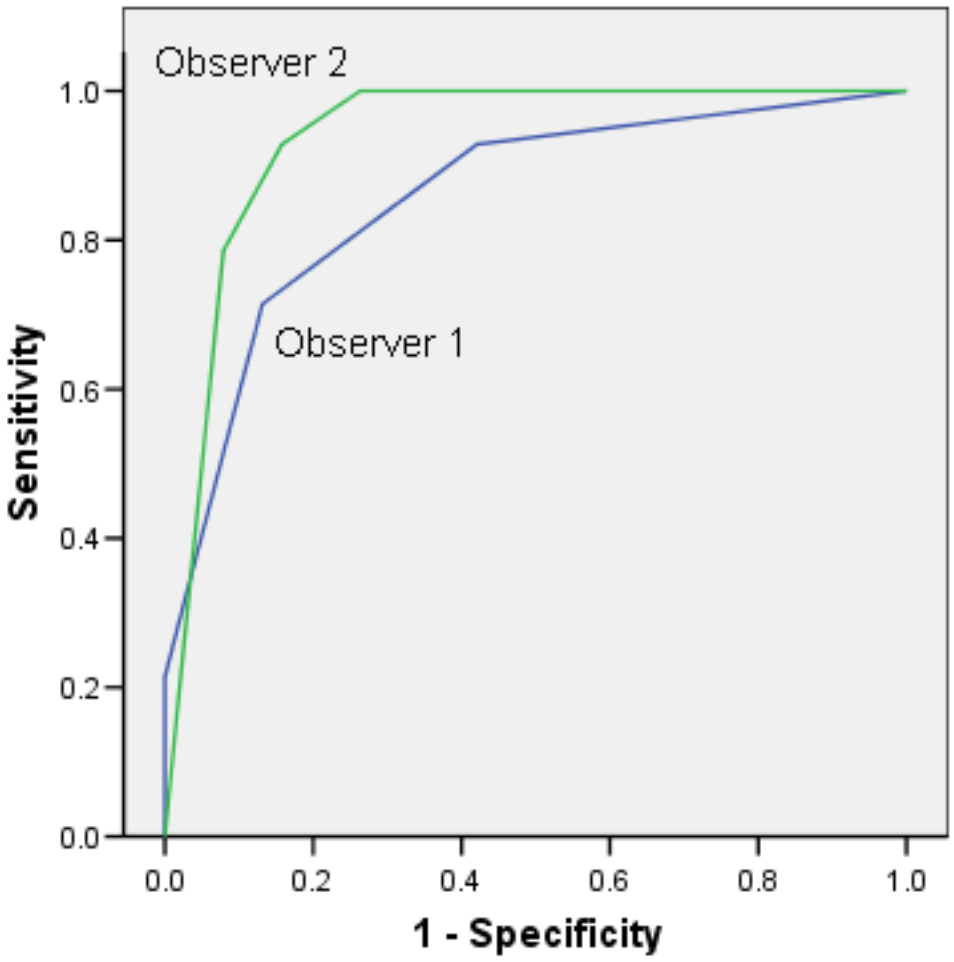


Figure 9 – T2 weighted, dynamic contrast enhanced and diffusion weighted sequences showing region highly suspicious of cancer in right side of prostate (both observers scored Right Anterior and Right Posterior quadrants as 5/5).

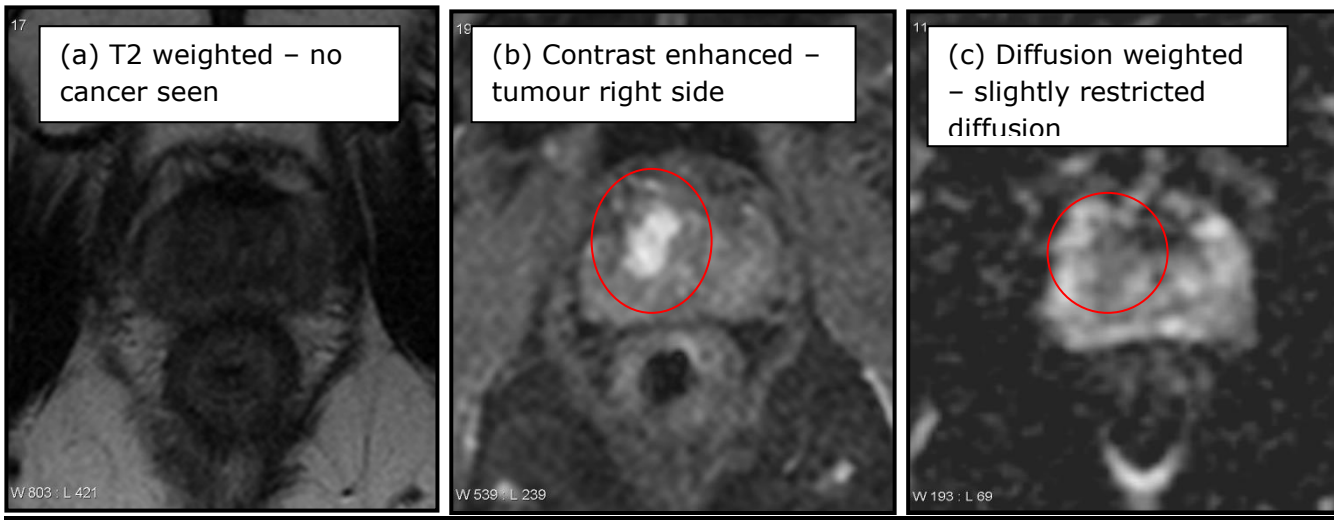
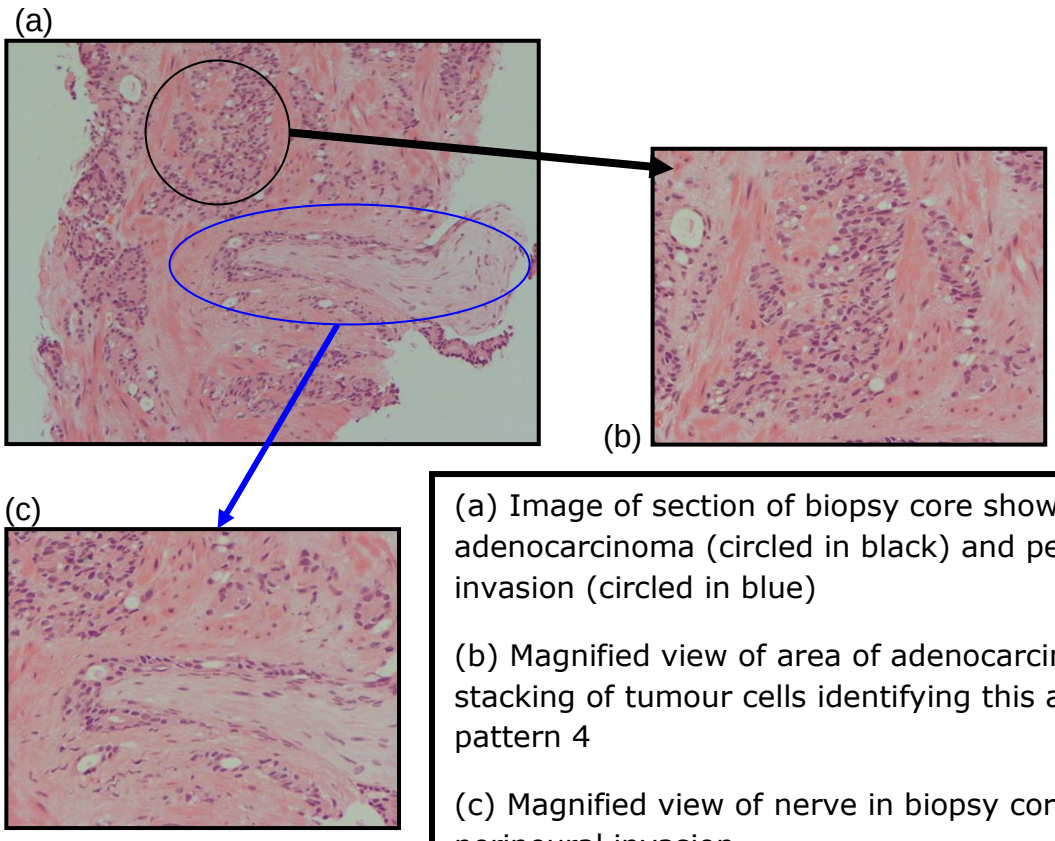


Figure 10 – Low Power Microscope view histology of template biopsy core taken from above region



(a) Image of section of biopsy core showing adenocarcinoma (circled in black) and perineural invasion (circled in blue)

(b) Magnified view of area of adenocarcinoma shows stacking of tumour cells identifying this as Gleason pattern 4

(c) Magnified view of nerve in biopsy core showing perineural invasion

4.4 Conclusion

The results of this study highlight the ability of mp-MRI to potentially detect and rule out recurrent prostate cancer within a previously irradiated gland, with a NPV of 78 – 86% (when a radiological score ≥ 3 is taken as cancer) for all recurrent cancer. When only recurrent cancer on TPM with a core length ≥ 3mm is deemed significant, the performance of mp-MRI to rule-out this larger volume recurrent cancer only, improves with a calculated NPV of 96 – 100%.

Thus, mp-MRI can serve as a triage test for men with evidence of biochemical recurrence following previous external beam radiotherapy for prostate cancer. It may also serve as a means of selectively sampling areas with suspicious findings on imaging only and not sampling negative areas on mp-MRI. Thus, the number of biopsies needed could be reduced and the associated risk of toxicity associated with systematic needle sampling of a previously irradiated prostate may be minimised.

This is obviously a small study with limitations and such results would need to be replicated in a prospective manner with greater numbers of patients and more radiologists with varying levels of expertise, but highlights an important proof of principle. Such will be elaborated on further in the discussion chapter 7 later in this thesis.

CHAPTER 5

EXPERIMENTAL STUDY: MP-MRI ACCURACY IN NEW PROSTATE CANCER DIAGNOSIS

5.1 Introduction

Men deemed to be at risk for prostate cancer because of either a raised serum PSA or abnormal DRE finding, usually undergo TRUS guided biopsy of the prostate. Such a strategy may miss clinically significant cancers due to sampling error (as outlined earlier), with many men also being diagnosed with clinically insignificant disease. Currently approximately one in two men diagnosed with localised prostate cancer has clinically insignificant prostate cancer when verified by more detailed histological analysis (38, 108).

As described earlier consequences of the current diagnostic pathway include poor risk stratification, repeat biopsy in those who test negative and potential over-diagnosis of insignificant cancer with resultant over-treatment.

Recent work described in chapter 2 of this thesis, highlights that mp-MRI shows promise in detecting and helping to rule-out clinically significant prostate cancer when whole mount radical prostatectomy has been used as a reference standard (109). However, these studies only evaluated men who underwent surgery and therefore have a positive bias, as such patients are more likely to harbour more aggressive and / or larger volume disease, thus favouring the performance of mp-MRI. There may have also been reporter bias in such studies as radiologists would have been aware that the subjects had already been diagnosed with cancer.

TPM as described previously, has a number of attributes making it a good reference test for validation of prostate imaging. It does not have the random and systematic sampling error of TRUS guided biopsies. It allows good representative sampling of the entire prostate including the anterior and apical parts of the prostate that are prone to under-sampling by TRUS biopsy. TPM can be applied to all men who undergo mp-MRI without the positive selection bias associated with men who then only have radical prostatectomy.

TPM was therefore once again used as the reference test, with mp-MRI (index test) being assessed against this using a number of differing target conditions to define clinically significant cancer. This allowed incorporation of wide-ranging views

as to what is regarded as clinically significant and non-significant prostate cancer, and to determine the accuracy of mp-MRI across these definitions.

The aim of this study was to evaluate the diagnostic performance of mp-MRI in prostate cancer (in men who have not had previous treatment) using TPM as the reference standard.

5.2 Methods

Patient Population:

All patients were men referred to the Urology department at University College London Hospital for suspected prostate cancer or previous diagnosis of prostate cancer on TRUS biopsy over a 2 year period.

Inclusion criteria:

(a) Men who had low-risk or low-intermediate risk prostate cancer at TRUS guided prostate biopsy, seeking reassurance about risk classification (51 patients).

(b) Men who had prior negative TRUS guided prostate biopsy findings with persistently elevated PSA levels (10 patients).

(c) Men who were referred for prostate biopsy for the first time and wanted to prevent the known sepsis risk of TRUS guided prostate biopsy (3 patients).

Exclusion criteria:

(a) Patients who had received any previous treatment that may compromise the performance of either the index test or reference test

- previous external beam radiotherapy (13 patients)

- previous brachytherapy (4 patients)

- androgen suppression or exposure to 5 alpha-reductase inhibitors (5 patients)

Other than the above criteria, no other exclusion criteria were set in order to allow a fairly heterogeneous population to be included in this study and thereby limit spectrum bias.

In addition reporter bias would hopefully be limited as both men with previously diagnosed cancer and those without a diagnosis of cancer were included.

All men underwent both mp-MRI (index test) followed by TPM (reference test). The time interval between mp-MRI and TPM was not fixed.

Mp-MRI:

All mp-MRI scans were taken using a 1.5T scanner (Symphony or Avanto, Siemens AG, Munich, Germany) using a pelvic phased-array coil. The protocol included T2W, DW (TR 2200, TE 98, b-values 0, 150, 500, 1000, field of view 260 x 260mm), and pre- and dynamic (15s acquisition frame) sequences after IV gadolinium contrast. The detailed mp-MRI parameters are outlined in the materials section earlier.

Radiology Reporting:

Mp-MRI scans were reported by three uro-radiologists with varying experience:

R1 - SAS 3 years

R2 - CA 10 years

R3 - AK 6 years

For each study the radiologists were given the following information for each patient:

- Age

- DRE findings

- PSA level

Radiologists did not have access to any previous TRUS guided prostate biopsy results or TPM outcomes.

For primary endpoint analysis purposes, the prostate was divided into 4 sectors by using the urethra as the dividing point (i.e. left and right anterior, left and right posterior). This generated 256 sectors of analysis from 64 patients.

Each region was given a score of 1 to 5 by using a standardised scoring system based on the Likert scale that was reported on in a recent consensus meeting (101). The score given for each region was based on an overall impression when accounting for T2, DCE and DW weighted imaging as described in chapter 3 previously. Table 9 in the results section of this chapter outlines the scoring system used.

TPM:

Transperineal template biopsies were taken under general anaesthesia using a 5-mm brachytherapy grid mounted on a stepper, with TRUS guidance as already previously described in this thesis. Biopsy cores were analysed and reported by the same dedicated uro-pathologist with 8 years of experience, as in the study outlined in chapter 4. Biopsy results were grouped into four ROIs per prostate, reflecting the mp-MRI reporting, and allowing for direct correlation of histopathology and mp-MRI scores for a given quadrant.

Definitions of clinically significant cancer on TPM:

The primary target definition (Definition 2) for clinically significant disease on TPM was set at a Gleason score ≥ 3+4 and / or with cancer core length involvement of ≥ 4mm. This relates to an area of cancer on TPM biopsies that has high-grade components (non-dominant Gleason score of ≥ 4) and / or is approximately equal to a lesion volume ≥ 0.2ml (102). This primary target definition for ‘clinically significant cancer’ was chosen on the basis that few would disagree that any man who had this level of cancer would require treatment.

A higher threshold for clinically significant cancer (Definition 1): cancer core involvement ≥ 6mm and / or Gleason score ≥ 4+3 was also used.

Other variations of ‘clinically significant’ cancer definitions were also used in analysis and these are outlined in table 10.

Analysis:

To assess accuracy 2 x 2 tables were constructed and two analyses were used based on the target definitions above. Sensitivity, specificity, positive and negative predictive values were determined, together with construction of receiver-operator (ROC) characteristic curves.

5.3 Results

Sixty-four consecutive men undergoing both index and reference tests (256 sectors of analysis) were included. Fifty-one had cancer on prior transrectal ultrasound guided biopsy. Fifty-four had cancer on TTPM; between 53% (34/64) and 75% (48/64) were clinically significant according to a number of definitions.

The performance characteristics obtained when a score of ≥ 3 was used as a cut-off for a positive mp-MRI sector are summarised in the tables.

(A) Different levels of analysis were performed to determine mp-MRI accuracy in detecting and ruling out prostate cancer:

1. Quadrant Analysis
2. Hemi-gland (Left/Right) Analysis
3. Whole Gland Analysis

(b) A further study analysis was undertaken to evaluate the accuracy of mp-MRI in detecting and ruling-out cancer within different anatomical parts of the gland by comparing accuracy within the anterior gland (mainly transition zone) versus the posterior gland (mainly peripheral zone).

The results of each analysis are summarised in each sub-section with accompanied tables of results and receiver-operator characteristic (ROC) curves. The details of the MRI sequences used, the MRI reporting scale and the thresholds of cancer burden defining a positive outcome on the reference test (template prostate mapping), and characteristics of the study population are summarised in the following tables.

Table 8 - MRI Sequences used in the Index Test (Siemens Avanto 1.5 T, pelvic phased array coil)

	TR (ms)	TE (ms)	Flip angle/ degrees	Plane	Slice thickness (gap)	Matrix size	Field of view /mm	Time for scan
T2 TSE	5170	92	180	Axial, coronal	3mm (10% gap)	256x256	180x180	3m 54s (ax), 4m18s (cor)
VIBE fat sat	5.61	2.52	15	axial	3mm (20% gap)	192x192	260x260	9m 59s (35 17s acquisitions)
Diffusion (b values: 0, 150, 500, 1000) (s/mm2)	2200	Min (<98)		axial	5mm	172x172	260x260	5m 44s (16 averages)

Table 9: Multi-parametric MRI reporting scale

Mp-MRI score	Suspicion of clinically significant cancer
1	Highly unlikely to be clinically significant cancer
2	Unlikely to be clinically significant cancer
3	Equivocal
4	Likely to be clinically significant cancer
5	Highly likely to be clinically significant cancer

Table 10: Thresholds of Cancer Burden defining a positive Outcome on the Reference Test (Template Prostate Mapping)

Listed in ascending order of increasing cancer burden)

Definition	Number Biopsies positive	Cancer Core Length (mm)	Gleason Grade
All Cancer	>/=1	>/=1	Any
Goto	>/=1	>/=2	>/=3+4
Epstein	>/=1	>/=3	>/=3+4
Gleason 7	>/=1	>/=1	>/=3+4
Definition 2	>/=1	Maximum CCL >/=4mm AND/OR Total CCL >/=6mm*	Gleason >/= 3+4
Definition 1	>/=1	Maximum CCL >/=6mm AND/OR Total CCL >/=6mm*	>/= 4+3

CCL – cancer core length

* measured per lesion

Table 11: Characteristics of Study Population

Characteristic	Value
PSA, ng/ml #	6.7 (5.3 – 10.3)
Age, years #	62 (58 – 67)
Number with previous TRUS biopsy	61/64 (95%)
Prostate volume, ml #	37 (28.8 – 55.3)
Previous TRUS biopsy cancer diagnosis (n=51/64, 80%) - Total cores # - Positive cores, n # - Maximum cancer core length, mm # - Maximum cancer core length, % # - Gleason score ~	 9.0 (8.0 – 12.0) 1.0 (1.0 – 2.0) 3.0 (1.0 – 5.0) 15.0% (5.0% - 35.0%) 6, 6-7
Time interval between tests, days * - From TRUS biopsy to mp-MRI ^ - From mp-MRI to TPM @	 343 (+/-359) 106 (+/-95)
TPM outcomes - Total cores (n) # - Positive cores (n) # - Maximum cancer core length (mm) # - Maximum cancer core length (%) # Overall TPM Gleason grade (N) - No cancer - Too small to grade - 3+3 - 3+4 - 4+3	 34.0 (29.0 – 40.8) 5.0 (2.0 – 8.8) 6.0 (3.0 – 8.3) 50% (28.8% - 70.0%) 10 1 18 35 0

median (interquartile range)

* mean (+/-SD)

~ median (range)

^ n= 59

@ n=64

5.3.1 – Quadrant / Four Sector Analysis

mp-MRI to rule-out clinically significant prostate cancer:
For the primary endpoint definition (definition 2: >/=4mm AND/OR Gleason >/=3+4), sensitivity, negative predictive value, and negative likelihood ratio, were 58-73% (41/71 – 49/67), 84-89% (154/184 – 152/170), and 0.3-0.5, respectively (Table 12).

For Definition 1 (maximum cancer core length or total cancer core length >/=6mm and/or any Gleason >/=4+3 disease), sensitivity, negative predictive value and negative likelihood ratio, were 64-81% (29/45 – 35/43), 91-95% (168/184 – 162/170) and 0.2-0.5 respectively.

Detection of prostate cancer:
For definition 2, specificity, positive predictive value, and positive likelihood ratio, were 71-84% (132/185 – 152/181), 49-63% (51/104 – 49/78), and 2.5-4.6, respectively (Table 12).
For Definition 1, specificity, positive predictive value and positive likelihood ratio, were 68-80% (143/211 – 168/211), 35-45% (36/104 – 35/78), and 2.5-3.9 respectively.

Overall accuracy:
For definition 2, AUC values were 0.73-0.84 and for definition 1 AUC values were 0.72-0.82 (Table 12).

Inter-observer Agreement measured by weighted (quadrantic) Kappa calculation:
The inter-rater agreement for radiologists R1 and R2 was found to be Kappa = 0.55 (95% CI 0.44-0.66). The inter-rater reliability for radiologists R1 and R3 was Kappa = 0.39 (95% CI 0.28-0.50). Kappa was 0.50 (95% CI 0.39-0.61) for R2 and R3. Inter-rater reliability was therefore between fair and moderate.

Table 12 - Performance characteristics of mp-MRI in detecting and ruling-out cancer for Definitions 1 & 2 (Quadrant / Four Sector Analysis)

Disease Threshold	Reporter~	TP	FP	FN	TN	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive Likelihood Ratio (+LR)	Negative Likelihood Ratio (-LR)	Overall accuracy	ROC AUC	Asymptotic significance of AUC (null hypothesis AUC=0.5)
Definition 1 (Prevalence 17%)	**R1**	29	43	16	168	64 (50.5-76.6)	80 (76.6-82.2)	40 (31.6-47.9)	91 (87.9-94.3)	3.2 (2.16-4.30)	0.5 (0.29-0.64)	77 (72.1-81.2)	0.72 (0.643-0.796)	<0.001
	R2	35	43	8	162	81 (67.7-90.8)	79 (76.2-81.0)	45 (37.3-50.0)	95 (91.8-97.7)	3.9 (2.84-4.77)	0.2 (0.11-0.42)	79 (74.7-82.7)	0.82 (0.746-0.884)	<0.001
	R3	36	68	9	143	80 (66.3-89.6)	68 (64.9-69.8)	35 (28.7-38.8)	94 (90.0-96.9)	2.5 (1.89-2.97)	0.3 (0.15-0.52)	70 (65.1-73.3)	0.77 (0.697-0.840)	<0.001
Definition 2 (Prevalence 27%)	**R1**	41	31	30	154	58 (47.8-66.8)	83 (79.4-86.7)	57 (47.2-65.8)	84 (79.9-87.2)	3.4 (2.33-5.02)	0.5 (0.38-0.66)	76 (70.7-81.2)	0.73 (0.633-0.818)	< 0.000
	R2	49	29	18	152	73 (63.1-81.5)	84 (80.3-87.1)	63 (54.2-70.0)	89 (85.5-92.7)	4.6 (3.20-6.30)	0.3 (0.21-0.46)	81 (75.6-85.6)	0.84 (0.762-0.913)	< 0.000
	R3	51	53	20	132	72 (61.6-80.6)	71 (67.4-74.7)	49 (42.1-55.0)	87 (82.1-90.9)	2.5 (1.89-3.18)	0.4 (0.26-0.57)	72 (65.8-76.3)	0.80 (0.725-0.876)	< 0.000

~There were four missing values for reporter 2 and these were excluded from analyses.

Table 13 - Performance characteristics of mp-MRI in detecting and ruling-out cancer for other disease definitions (Quadrant / Four Sector Analysis)

Disease Threshold	Reporter	TP	FP	FN	TN	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive Likelihood Ratio (+LR)	Negative Likelihood Ratio (-LR)	Overall accuracy	ROC AUC	Asymptotic significance of AUC (null hypothesis AUC=0.5)
All cancer (Prevalence 49%)	**R1**	51	21	76	108	40 (34.3-45.2)	84 (78.0-88.7)	71 (60.5-79.8)	59 (54.7-62.2)	2.5 (1.56-4.00)	0.7 (0.62-0.84)	62 (56.3-67.1)	0.64 (0.570-0.707)	<0.001
	R2	64	14	56	114	53 (47.5-57.8)	89 (83.6-93.3)	82 (73.0-89.0)	67 (62.9-70.2)	4.9 (2.89-8.62)	0.5 (0.45-0.63)	72 (66.1-76.1)	0.73 (0.664-0.793)	<0.001
	R3	74	30	53	99	58 (52.0-63.9)	77 (70.6-82.3)	71 (63.5-78.0)	65 (59.9-69.8)	2.5 (1.77-3.60)	0.5 (0.44-0.68)	68 (61.4-73.2)	0.70 (0.631-0.764)	<0.001
Goto (Prevalence 37%)	**R1**	43	29	54	130	44 (36.7-51.4)	82 (77.1-86.1)	60 (49.4-69.3)	71 (66.6-74.4)	2.4 (1.60-3.70)	0.7 (0.56-0.82)	68 (61.8-73.0)	0.66 (0.585-0.728)	<0.001
	R2	56	22	36	134	61 (53.1-67.6)	86 (81.3-89.8)	72 (62.6-79.7)	79 (74.6-82.4)	4.3 (2.84-6.66)	0.5 (0.36-0.58)	77 (70.8-81.6)	0.76 (0.687-0.823)	<0.001
	R3	61	43	36	116	63 (54.8-70.3)	73 (68.0-77.5)	59 (51.1-65.6)	76 (71.1-81.1)	2.3 (1.71-3.12)	0.5 (0.38-0.67)	69 (63.0-74.8)	0.72 (0.650-0.788)	<0.001
Epstein (Prevalence 30%)	**R1**	41	31	36	148	53 (43.9-61.8)	83 (78.7-86.4)	57 (47.0-66.1)	80 (76.5-84.0)	3.1 (2.06-4.54)	0.57 (0.44-0.71)	74 (68.2-79.0)	0.70 (0.626-0.775)	<0.001
	R2	51	27	22	148	70 (60.4-77.9)	85 (80.6-87.9)	65 (56.5-72.9)	87 (83.0-90.5)	4.5 (3.12-6.45)	0.36 (0.25-0.49)	80 (74.7-85.0)	0.80 (0.727-0.865)	<0.001
	R3	53	51	24	128	69 (59.1-77.4)	72 (67.3-75.2)	51 (43.8-57.3)	84 (79.3-88.5)	2.4 (1.81-3.12)	0.44 (0.30-0.61)	71 (64.9-75.8)	0.75 (0.677-0.820)	<0.001
Gleason >/=7 (Prevalence 17%)	**R1**	26	46	18	166	59 (44.9-72.0)	78 (75.4-81.0)	36 (27.5-44.0)	90 (86.8-93.3)	2.7 (1.83-3.79)	0.5 (0.35-0.73)	75 (70.1-79.4)	0.71 (0.622-0.803)	<0.001
	R2	32	46	11	159	74 (60.3-85.4)	78 (74.6-79.9)	41 (33.2-47.1)	94 (89.9-96.3)	3.3 (2.37-4.24)	0.3 (0.18-0.53)	77 (72.1-80.8)	0.79 (0.710-0.878)	<0.001
	R3	36	68	8	144	82 (68.1-91.1)	68 (65.1-69.8)	35 (28.8-38.5)	95 (90.8-97.4)	2.6 (1.95-3.02)	0.3 (0.13-0.49)	70 (65.6-73.5)	0.80 (0.715-0.876)	<0.001

Figure 11– Receiver Operator Characteristic (ROC) curves for Quadrant / Four Sector Analysis

All Cancer

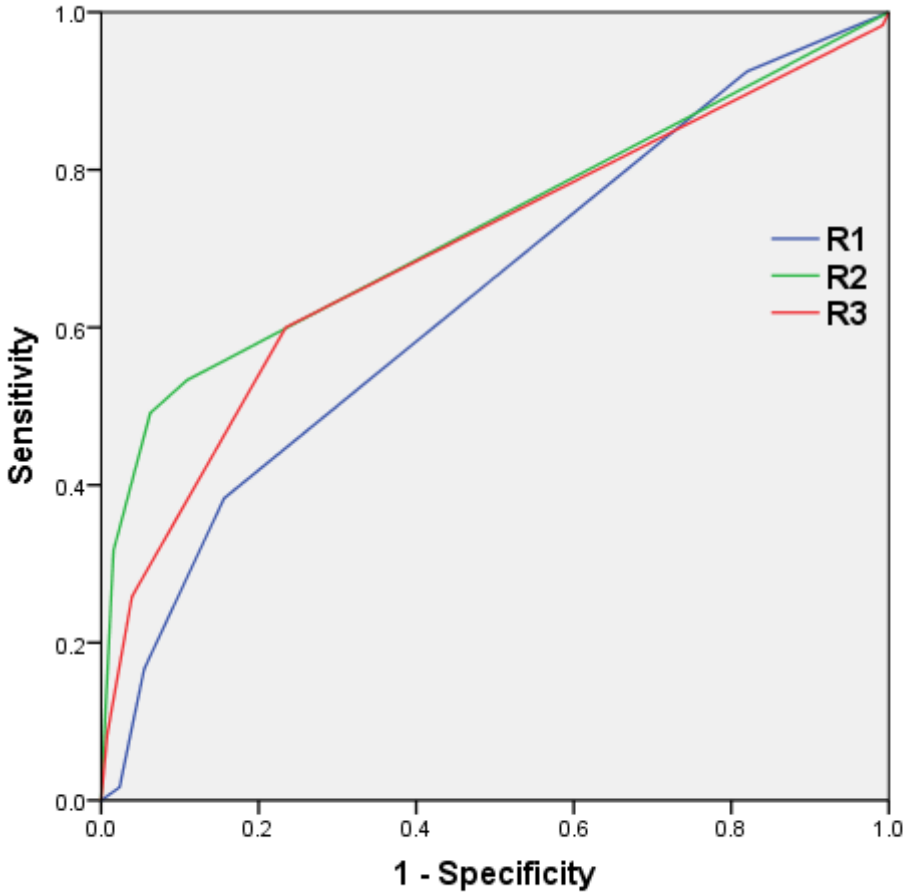


Figure 12 – Receiver Operator Characteristic (ROC) curves for Quadrant / Four Sector Analysis

Definition 1

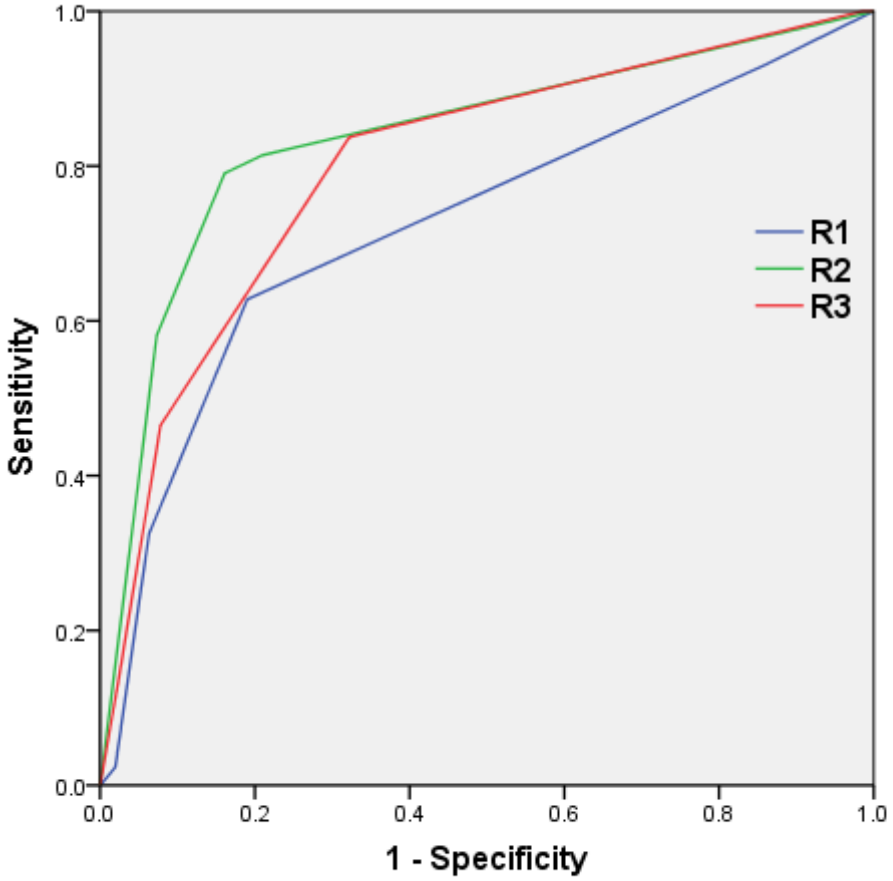
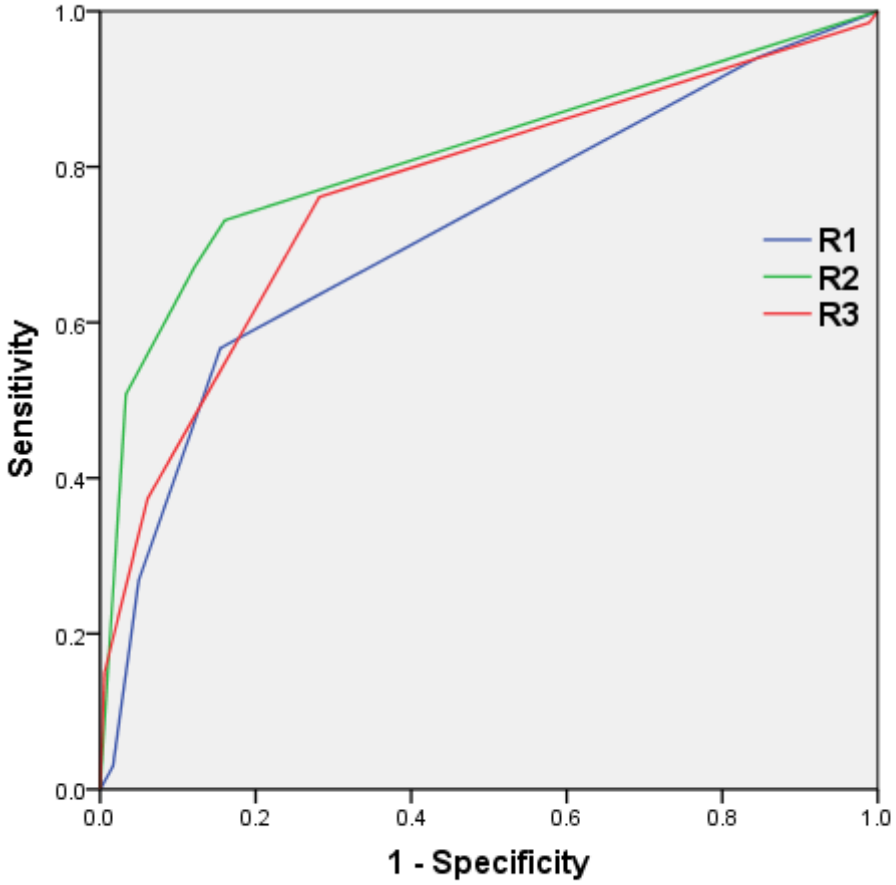


Figure 13 – Receiver Operator Characteristic (ROC) curves for Quadrant / Four Sector Analysis

Definition 2



5.3.2 – Hemi-gland (Right and Left lobe) Analysis

Mp-MRI to rule-out clinically significant prostate cancer:
For the primary endpoint definition (definition 2: >/=4mm AND/OR Gleason >/=3+4), sensitivity, negative predictive value, and negative likelihood ratio, were 67-76%, 76-85% and 0.2-0.4, respectively (Table 14).

For Definition 1 (maximum cancer core length or total cancer core length >/=6mm and/or any Gleason >/=4+3 disease), sensitivity, negative predictive value and negative likelihood ratio, were 82-90%, 89-91% and 0.2-0.3 respectively.

Detection of prostate cancer:
For definition 2, SP, PPV, and +LR were 46-69%, 56-67% and 1.5 – 2.5, respectively (Table 14).
For Definition 1, specificity, positive predictive value and positive likelihood ratio, were 43-62%, 41-49%, and 1.6-2.2 respectively.

Overall accuracy:
For definition 2, AUC values were 0.74-0.83 and for definition 1 AUC values were 0.73-0.79 (Table 14).

Inter-observer Agreement measured by weighted Kappa calculation:
The inter-rater agreement for radiologists R1 and R2 was found to be Kappa = 0.48 (95% CI 0.38-0.58). The inter-rater reliability for radiologists R1 and R3 was Kappa = 0.49 (95% CI 0.37-0.61). Kappa was 0.56 (95% CI 0.44-0.67) for R2 and R3. Inter-rater reliability was therefore moderate.

Table 14 - Performance characteristics of mp-MRI in detecting and ruling-out cancer using different definitions for clinically significant disease on the reference test with two sectors of analysis per prostate (right and left lobes)

Disease Threshold (Prevalence)	Reporter	TP	FP	FN	TN	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive Likelihood Ratio (+LR)	Negative Likelihood Ratio (-LR)	Overall accuracy	ROC AUC	Asymptotic significance of AUC (null hypothesis AUC=0.5)
All cancer (71%)	**R1**	55	11	36	26	60 (54.4-65.4)	70 (55.4-65.4)	83 (75.0-90.2)	42 (33.1-49.2)	2.0 (1.22-3.74)	0.6 (0.42-0.82)	63 (54.7-70.4)	0.70 (0.603-0.797)	<0.001
	R2	61	10	26	27	70 (63.9-75.0)	73 (58.4-84.6)	86 (78.3-91.9)	51 (40.8-59.0)	2.6 (1.54-4.86)	0.4 (0.30-0.62)	71 (62.3-77.9)	0.77 (0.690-0.855)	<0.001
	R3	70	16	21	21	77 (71.1-82.2)	57 (42.3-69.8)	81 (75.2-87.0)	50 (37.3-61.5)	1.8 (1.23-2.73)	0.4 (0.25-0.68)	71 (62.8-78.7)	0.73 (0.632-0.820)	<0.001
Goto (57%)	**R1**	48	18	25	37	66 (57.6-72.9)	67 (56.5-76.8)	73 (63.7-80.7)	60 (50.1-68.1)	2.0 (1.32-3.14)	0.5 (0.35-0.75)	66 (57.1-74.6)	0.71 (0.617-0.800)	<0.001
	R2	53	18	17	36	66 (57.6-72.9)	67 (56.6-76.8)	73 (63.7-80.7)	60 (50.1-68.1)	2.0 (1.32-3.14)	0.5 (0.35-0.75	66 (57.1-74.6)	0.78 (0.703-0.864)	<0.001
	R3	58	28	15	27	80 (71.7-86.3)	49 (38.8-58.2)	67 (60.9-73.2)	64 (50.8-76.2)	1.6 (1.17-2.06)	0.4 (0.24-0.73)	66 (57.6-74.2)	0.73 (0.640-0.817)	<0.001
Epstein (48%)	**R1**	45	21	17	45	73 (63.1-80.7)	68 (59.2-75.8)	68 (59.3-75.8)	73 (63.1-80.7)	2.3 (1.55-3.34)	0.4 (0.25-0.62)	70 (61.1-78.2)	0.74 (0.651-0.826)	<0.001
	R2	49	22	10	43	83 (73.6-90.3)	66 (57.6-72.7)	69 (61.2-75.0)	81 (70.6-89.2)	2.5 (1.74-3.31)	0.3 (0.13-0.46)	74 (65.2-81.1)	0.81 (0.727-0.885)	<0.001
	R3	51	35	11	31	82 (73.2-89.6)	47 (38.4-53.9)	59 (52.8-64.6)	74 (60.4-84.6)	1.6 (1.19-1.84)	0.4 (0.19-0.70)	64 (55.3-71.2)	0.73 (0.645-0.821)	<0.001

Disease Threshold (Prevalence)	Reporter	TP	FP	FN	TN	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive Likelihood Ratio (+LR)	Negative Likelihood Ratio (-LR)	Overall accuracy	ROC AUC	Asymptotic significance of AUC (null hypothesis AUC=0.5)
Gleason >/=7 (30%)	**R1**	34	32	4	58	90 (76.4-96.5)	64 (58.9-67.4)	52 (44.0-55.5)	94 (85.5-97.8)	2.5 (1.86-2.96)	0.2 (0.05-0.40)	72 (64.1-76.0)	0.81 (0.731-0.889)	<0.001
	R2	34	37	3	50	92 (78.9-97.8)	58 (52.0-60.0)	48 (41.1-51.0)	94 (85.3-98.5)	2.2 (1.64-2.45)	0.1 (0.04-0.41)	68 (60.0-71.3)	0.84 (0.759-0.915)	<0.001
	R3	37	49	1	41	97 (86.0-99.9)	46 (40.8-46.6)	43 (38.0-44.1)	98 (87.4-99.9)	1.8 (1.45-1.87)	0.06 (0.00-0.34)	61 (54.2-62.4)	0.85 (0.776-0.914)	<0.001
Definition 2 (45%)	**R1**	44	22	14	48	76 (65.8-84.2)	69 (60.3-75.4)	67 (57.9-74.0)	77 (68.1-85.2)	2.4 (1.66-3.43)	0.4 (0.21-0.57)	72 (62.8-79.4)	0.75 (0.658-0.834)	<0.001
	R2	47	24	8	45	86 (75.6-92.5)	65 (57.3-70.9)	66 (58.5-71.7)	85 (74.7-92.3)	2.5 (1.77-3.18)	0.2 (0.11-0.43)	74 (65.4-80.5)	0.83 (0.749-0.902)	<0.001
	R3	48	38	10	32	83 (73.1-90.3)	46 (37.7-52.0)	56 (49.3-60.9)	76 (62.9-86.6)	1.5 (1.17-1.88)	0.4 (0.19-0.71)	63 (53.8-69.4)	0.74 (0.656-0.831)	<0.001
Definition 1 (30%)	**R1**	32	34	7	55	82 (68.4-91.5)	62 (55.8-65.9)	49 (40.4-54.1)	89 (80.1-94.6)	2.2 (1.55-2.69)	0.3 (0.13-0.57)	68 (59.6-73.7)	0.73 (0.639-0.829)	<0.001
	R2	32	39	5	48	87 (72.7-94.7)	55 (49.3-58.7)	45 (37.9-49.4)	91 (81.0-96.3)	2.0 (1.44-2.29)	0.2 (0.09-0.55)	65 (56.3-69.4)	0.79 (0.704-88.2)	<0.001
	R3	35	51	4	38	90 (77.0-96.6)	43 (37.1-45.7)	41 (34.9-43.8)	91 (78.8-96.8)	1.6 (1.23-1.78)	0.2 (0.08-0.62)	57 (49.3-61.2)	0.77 (0.681-0.861)	<0.001

Performance characteristics of mp-MRI in detecting and ruling-out cancer using a number of different definitions for clinically significant disease on the reference test with two sectors of analysis per prostate (right and left lobes) – results table continued from previous page ~There were four missing values for reporter 2 and these were excluded from analyses.

Figure 14– Receiver Operator Characteristic (ROC) curves for Left / Right Hemigland Analysis

All Cancer

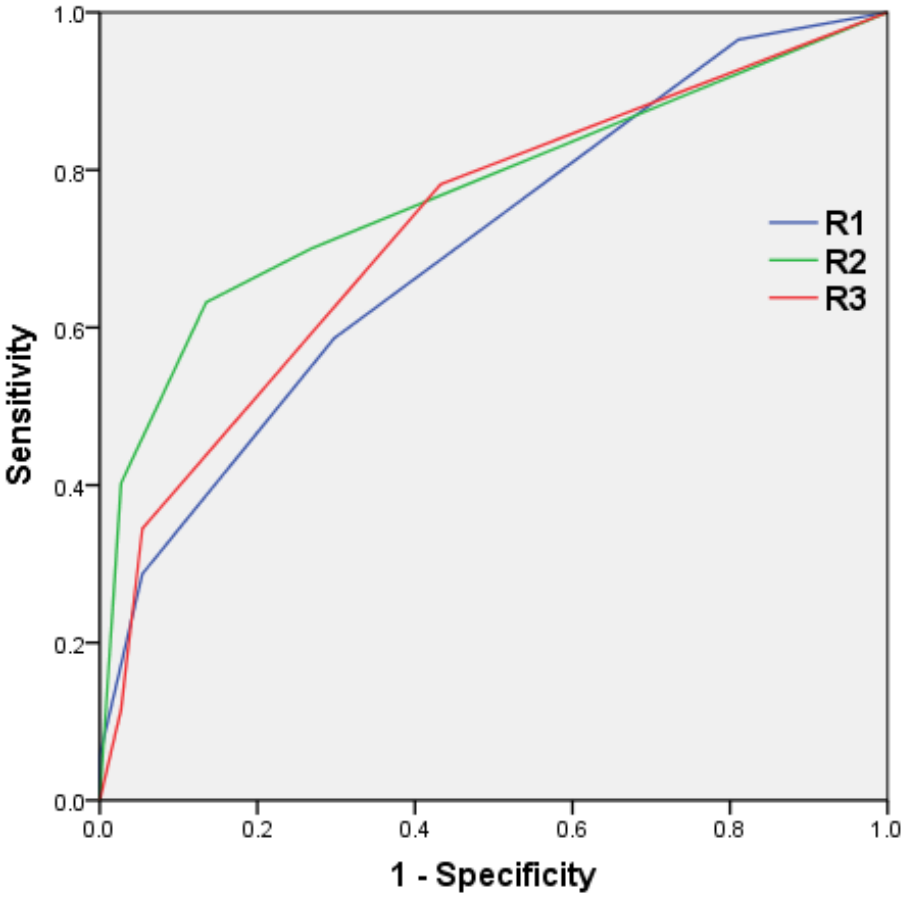


Figure 15 – Receiver Operator Characteristic (ROC) curves for Left / Right Hemigland Analysis

Definition 1

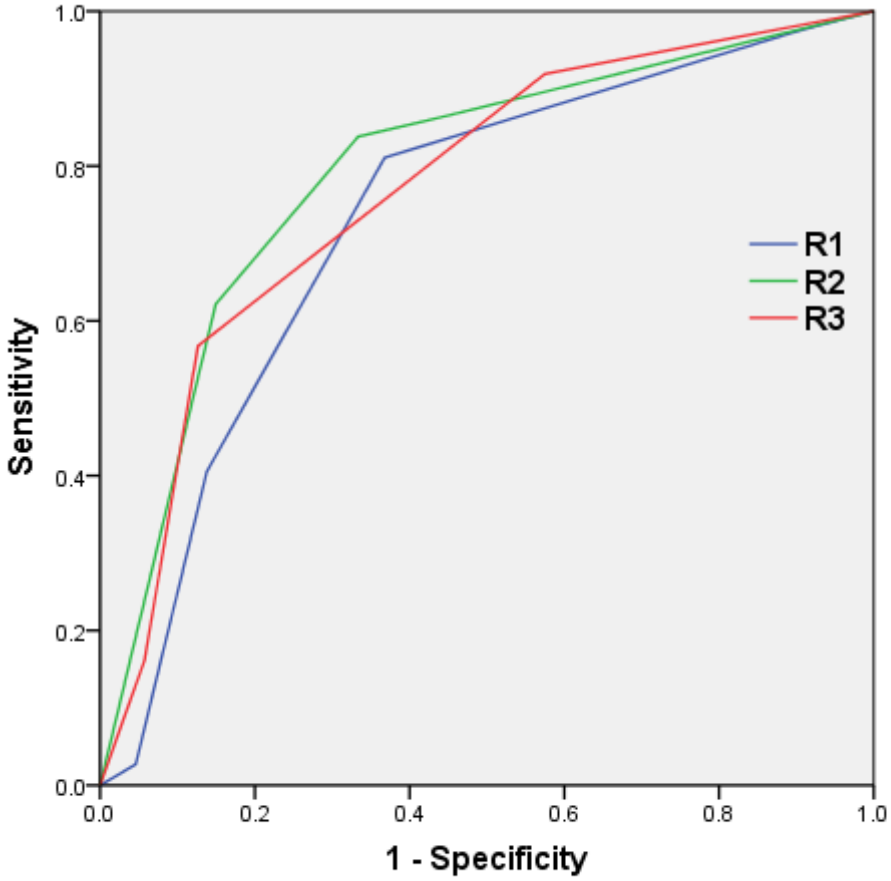
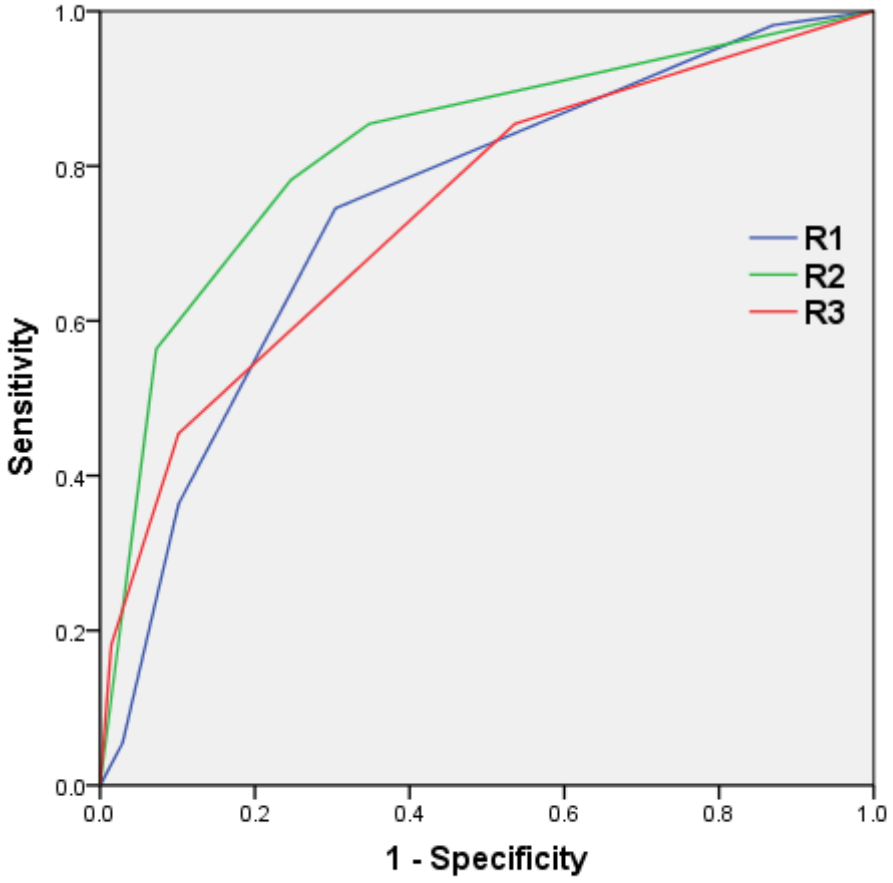


Figure 16 – Receiver Operator Characteristic (ROC) curves for Left / Right Hemigland Analysis

Definition 2



5.3.3 – Whole Prostate Analysis

Mp-MRI to rule-out clinically significant prostate cancer:
For the primary endpoint definition (definition 2: >/=4mm AND/OR Gleason >/=3+4), sensitivity, negative predictive value, and negative likelihood ratio, were 88-95%, 67-78% and 0.2-0.3, respectively (Table 15).

For Definition 1 (maximum cancer core length or total cancer core length >/=6mm and/or any Gleason >/=4+3 disease), sensitivity, negative predictive value and negative likelihood ratio, were 88 -94%, 73 - 78% and 0.30 - 0.32 respectively.

Detection of prostate cancer:
For definition 2, SP, PPV, and +LR were 30-48%, 71-75% and 1.4 – 1.7, respectively (Table 15).
For Definition 1, specificity, positive predictive value and positive likelihood ratio, were 23-38%, 58-62% and 1.2-1.4 respectively.

Overall accuracy:
For definition 2, AUC values were 0.74-0.84 and for definition 1 AUC values were 0.65-0.73 (Table 15).

Inter-observer Agreement measured by weighted Kappa calculation:
The inter-rater agreement for radiologists R1 and R2 was found to be Kappa = 0.44 (95% CI 0.30-0.59). The inter-rater reliability for radiologists R1 and R3 was Kappa = 0.56 (95% CI 0.42-0.71). Kappa was 0.53 (95% CI 0.38-0.62) for R2 and R3. Inter-rater reliability was therefore moderate.

Table 15 - Performance characteristics of mp-MRI in detecting and ruling-out cancer using different definitions for clinically significant disease on the reference test with one sector of analysis per prostate (whole prostate)

Disease Threshold (Prevalence)	**Reporter**	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**Specificity**	**Positive Predictive Value (PPV)**	**Negative Predictive Value (NPV)**	**Positive Likelihood Ratio (+LR)**	**Negative Likelihood Ratio (-LR)**	**Overall accuracy**	**ROC AUC**	**Asymptotic significance of AUC (null hypothesis AUC=0.5)**
All cancer (84%)	**R1**	42	7	12	3	78 (73.8-83.6)	30 (8.4-61.3)	86 (81.3-92.1)	20 (5.6-40.9)	1.1 (0.81-2.16)	0.7 (0.27-3.12)	70 (63.6-80.1)	0.65 (0.491-0.811)	0.13
	R2	42	5	10	5	81 (75.3-86.1)	50 (21.5-77.8)	89 (83.3-95.3)	33 (14.3-51.9)	1.6 (0.96-3.88)	0.4 (0.18-1.15)	76 (66.6-84.8)	0.82 (0.709-0.923)	0.002
	R3	50	5	4	5	93 (87.5-96.9)	50 (22.3-73.4)	91 (85.9-95.2)	56 (24.8-81.6)	1.9 (1.13-3.65)	0.1 (0.04-0.56)	86 (77.3-93.3)	0.81 (0.670-0.949)	0.002
Goto (75%)	**R1**	40	9	8	7	83 (76.3-90.1)	44 (22.8-64.1)	82 (74.8-88.3)	47 (24.3-68.4)	1.5 (0.99-2.51)	0.4 (0.15-1.04)	73 (62.9-83.6)	0.76 (0.627-0.882)	0.03
	R2	40	7	6	9	87 (79.2-93.2)	56 (34.0-74.3)	85 (77.5-91.3)	60 (36.3-79.3)	2.0 (1.20-3.63)	0.2 (0.09-0.61)	79 (67.6-88.4)	0.87 (0.781-0.954)	<0.001
	R3	45	10	3	6	94 (87.4-98.2)	38 (18.6-50.9)	82 (76.3-85.7)	67 (33.1-90.4)	1.5 (1.07-2.00)	0.2 (0.04-0.68)	80 (70.2-86.4)	0.76 (0.634-0.895)	0.002
Epstein (72%)	**R1**	39	10	7	8	85 (77.1-91.8)	44 (24.9-62.3)	80 (72.4-86.1)	53 (29.9-74.7)	1.5 (1.03-2.43)	0.3 (0.13-0.92)	73 (62.4-83.5)	0.77 (0.649-0.889)	0.01
	R2	39	8	5	10	89 (80.3-94.9)	56 (35.3-71.0)	83 (75.2-88.9)	67 (42.3-85.2)	2.0 (1.24-3.27)	0.2 (0.07-0.56)	79 (67.3-88.0)	0.85 (0.749-0.953)	<0.001
	R3	43	12	3	6	94 (86.9-98.1)	33 (16.4-45.3)	78 (72.7-82.1)	67 (32.9-90.5)	1.4 (1.04-1.79)	0.2 (0.04-0.80)	77 (67.1-83.3)	0.74 (0.614-0.873)	0.003

Disease Threshold (Prevalence)	**Reporter**	**TP**	**FP**	**FN**	**TN**	**Sensitivity**	**Specificity**	**Positive Predictive Value (PPV)**	**Negative Predictive Value (NPV)**	**Positive Likelihood Ratio (+LR)**	**Negative Likelihood Ratio (-LR)**	**Overall accuracy**	**ROC AUC**	**Asymptotic significance of AUC (null hypothesis AUC=0.5)**
Gleason >/ =7 (52%)	**R1**	33	16	0	15	100 (89.8-100)	48 (37.5-48.4)	67 (60.5-67.3)	100 (77.6-100)	1.9 (1.44-1.94)	0.00 (0.00-0.27)	75 (64.5-75.0)	0.84 (0.742-0.938)	<0.001
	R2	31	16	1	14	97 (85.6-99.8)	47 (34.7-49.8)	66 (58.3-68.0)	93 (69.4-99.6)	1.8 (1.31-1.99)	0.07 (0.00-0.41)	73 (61.0-75.6)	0.85 (0.744-0.947)	<0.001
	R3	33	22	0	9	100 (90.6-100)	29 (19.0-29.0)	60 (54.3-60.0)	100 (65.5-100)	1.4 (1.12-1.42)	0.0 (0.00-0.50)	66 (55.9-65.6)	0.81 (0.707-0.914)	<0.001
Definition 2 (64%)	**R1**	36	13	5	10	88 (78.7-94.8)	44 (27.2-56.0)	74 (65.8-79.4)	67 (41.7-85.9)	1.6 (1.08-21.6)	0.3 (0.09-0.78)	72 (60.2-80.9)	0.78 (0.659-0.891)	<0.001
	R2	35	12	4	11	90 (80.1-96.3)	48 (31.5-59.0)	75 (66.5-79.9)	73 (48.3-90.4)	1.7 (1.17-2.35)	0.2 (0.06-0.63)	74 (62.1-82.5)	0.84 (0.734-0.943)	<0.001
	R3	39	16	2	7	95 (87.4-99.1)	30 (16.6-37.6)	71 (65.1-73.9)	78 (42.4-96.0)	1.4 (1.05-1.59)	0.2 (0.02-0.76)	72 (61.9-77.0)	0.74 (0.618-0.865)	0.002
Definition 1 (53%)	**R1**	30	19	4	11	88 (77.0-95.9)	37 (23.9-45.3)	61 (53.4-66.5)	73 (47.9-90.6)	1.4 (1.01-1.75)	0.32 (0.09-0.96)	64 (52.1-72.2)	0.65 (0.511-0.794)	0.039
	R2	29	18	4	11	88 (76.4-95.7)	38 (24.8-46.9)	62 (53.6-67.2)	73 (48.0-90.6)	1.4 (1.02-1.80)	0.3 (0.09-0.95)	65 (52.3-72.9)	0.73 (0.596-0.855)	0.002
	R3	32	23	2	7	94 (84.7-98.9)	23 (12.7-28.8)	58 (52.4-61.2)	78 (42.3-96.0)	1.2 (0.97-1.39)	0.3 (0.04-1.21)	61 (50.9-66.1)	0.68 (0.547-0.820)	0.013

Performance characteristics of mp-MRI in detecting and ruling-out cancer using a number of different definitions for clinically significant disease on the reference test with one sector of analysis per prostate (whole prostate) – results table continued from previous page

~There were four missing values for reporter 2 and these were excluded from analyses.

Figure 17 – Receiver Operator Characteristic (ROC) curves for Whole Gland Analysis

All Cancer

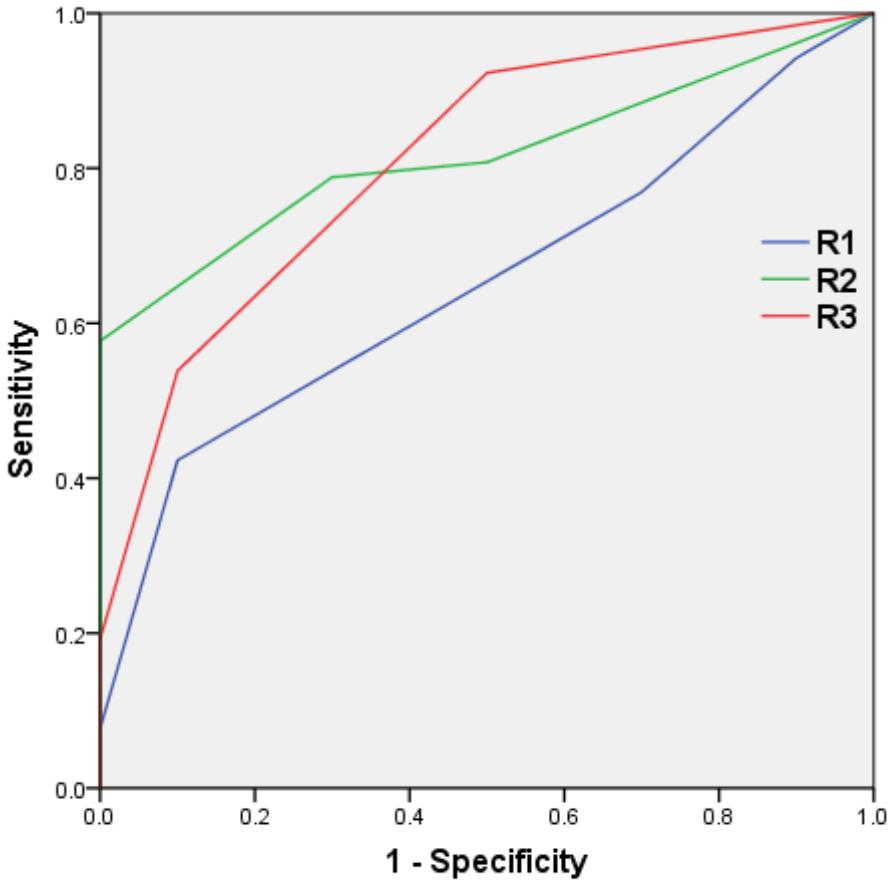


Figure 18 – Receiver Operator Characteristic (ROC) curves for Whole Gland Analysis

Definition 1

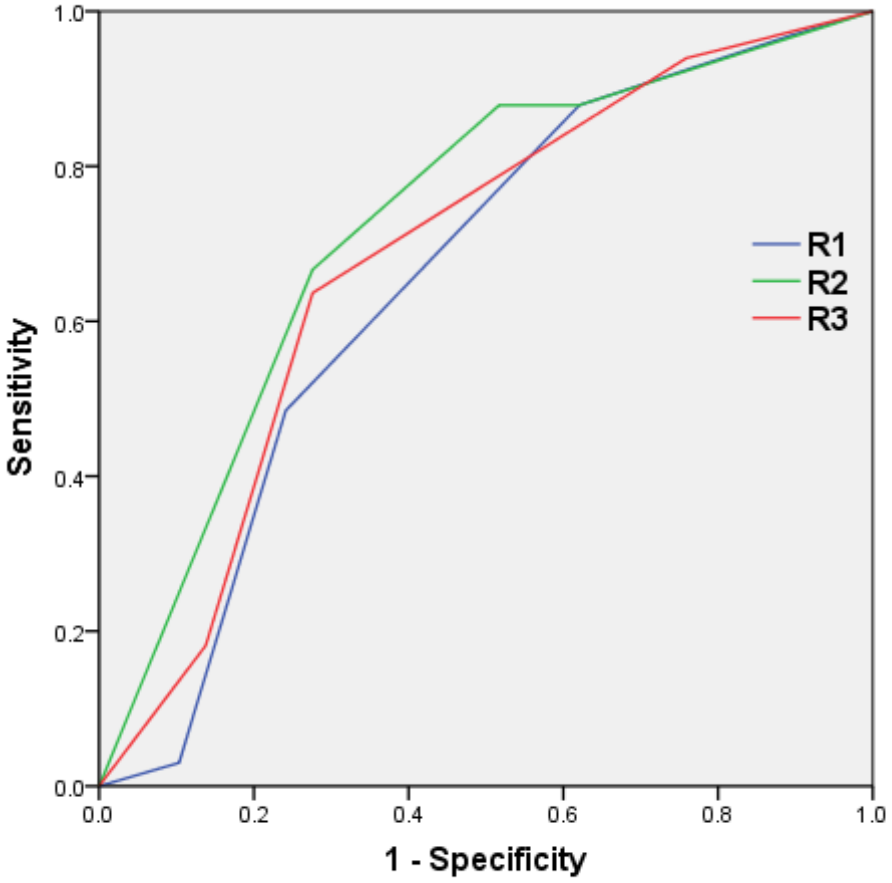
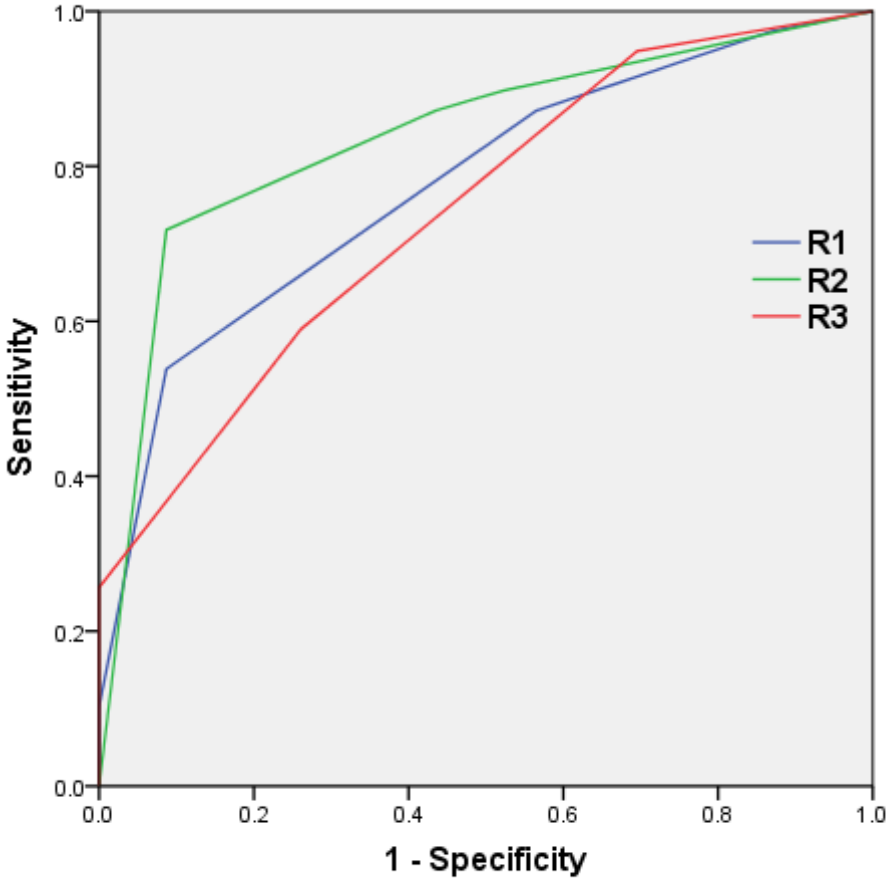


Figure 19 – Receiver Operator Characteristic (ROC) curves for Whole Gland Analysis

Definition 2



5.4 Conclusion

This study demonstrates that mp-MRI has an acceptable range of accuracy values over a broad range of definitions of what is defined as clinically significant cancer, at a quadrant, hemi-gland and whole gland analysis.

Importantly the results in this study (n = 64 patients, with quadrant analysis n = 256 sectors) demonstrate that mp-MRI in conjunction with experienced uro-radiology interpretation confers a good negative predictive value of up to 95% (95% CI 92 - 98) for Definition 1, and 89% (95% CI 86 – 93) for Definition 2. There were good negative likelihood ratios of 0.2 (95% CI 0.1 – 0.4) for Definition 1, and 0.3 (95% CI 0.2 – 0.5) for Definition 2, for clinically significant prostate cancers. This would indicate that mp-MRI when interpreted by an experienced uro-radiologist may be useful in ruling-out clinically significant prostate cancer.

Further evaluation of the methodological limitations and hence limitations of the results of this study will be critiqued in the discussion chapter 7 of this thesis, along with a comparison with similar previous studies. The data from this study went on to form part of the successful grant application for the prospective PROMIS trial (MRC PR11), which is a multi-centre trial recruiting men to have pre-biopsy mp-MRI followed by both TRUS biopsy and TPM (with the surgeon and histopathologist blinded to the mp-MRI result). Prospective studies such as PROMIS will hopefully provide verification of the results found in this study.

CHAPTER 6

EXPERIMENTAL STUDY:

COMPARISON OF MP-MRI ACCURACY BETWEEN ANTERIOR AND POSTERIOR PROSTATE GLAND

6.1 Introduction

As outlined earlier in the introduction section to this thesis, the prostate consists of distinctly separate anatomical zones, which have differing cellular architecture. These corresponding anatomical differences may potentially therefore result in variation in the accuracy of mp-MRI in detecting and ruling-out prostate cancer depending on which region of the prostate cancerous lesions are located.

Given that although most tumours arise in the peripheral zone, but that a significant proportion of tumours may arise in the transition zone, it is important to establish whether there are any differences in the performance characteristics of mp-MRI accuracy when comparing these two zones of the prostate. If mp-MRI had significantly worse accuracy rates in the transition zone this may limit its additional value to the current diagnostic paradigm, given that the ability to reliably detect anterior tumours, which may not be reached during transrectal biopsy, is one of the important potential benefits of using mp-MRI prior to deciding on biopsy strategy.

Previous studies have not shown a distinct difference in the ability of radiologists to detect tumours within one zone over another (110, 111) even when multi-parametric technology is used. It therefore seemed reasonable to test the hypothesis that there is no significant difference in accuracy for detection and ruling-out of clinically significant prostate cancer when comparing the transition zone and peripheral zone.

This experimental study set out to test the null hypothesis outlined above.

6.2 Methods

The patient population, inclusion and exclusion criteria were the same as those for study 2 previously.

Patient Population:

All patients were men referred to the Urology department at University College London Hospital for suspected prostate cancer or previous diagnosis of prostate cancer on TRUS biopsy over a 2 year period.

Inclusion criteria:

(a) Men who had low-risk or low-intermediate risk prostate cancer at TRUS guided prostate biopsy, who were seeking reassurance about risk classification (51 patients).

(b) Men who had prior negative TRUS guided prostate biopsy findings with persistently elevated PSA levels (10 patients).

(c) Men who were referred for prostate biopsy for the first time and wanted to prevent the known sepsis risk of TRUS guided prostate biopsy (3 patients).

Exclusion criteria:

(a) Patients who had received any previous treatment that may compromise the performance of either the index test or reference test

- previous external beam radiotherapy (13 patients)

- previous brachytherapy (4 patients)

- androgen suppression or exposure to 5 alpha-reductase inhibitors (5 patients)

Other than the above criteria, no other exclusion criteria were set in order to allow a fairly heterogeneous population to be included in this study and thereby limit spectrum bias.

In addition reporter bias would hopefully be limited as both men with previously diagnosed cancer and those without a diagnosis of cancer were included.

All men underwent both mp-MRI (index test) followed by TPM (reference test). The time interval between mp-MRI and TPM was not fixed.

Mp-MRI:

All mp-MRI scans were taken using a 1.5T scanner (Symphony or Avanto, Siemens AG, Munich, Germany) using a pelvic phased-array coil. The protocol included T2W, DW (TR 2200, TE 98, b-values 0, 150, 500, 1000, field of view 260 x 260mm), and pre- and dynamic (15s acquisition frame) sequences after IV gadolinium contrast. The detailed mp-MRI parameters are outlined in the materials section earlier.

Radiology Reporting:

Mp-MRI scans were reported by the three uro-radiologists with varying experience, as in study 2:

R1 - SAS 3 years

R2 - CA 10 years

R3 - AK 6 years

Again the radiologists were given the following information for each patient:

- Age

- DRE findings

- PSA level

Radiologists did not have access to any previous TRUS guided prostate biopsy results or TPM outcomes.

For primary endpoint analysis purposes, the prostate was divided into 4 sectors by using the urethra as the dividing point (i.e. left and right anterior, left and right posterior).

Each region was given a score of 1 to 5 by using a standardized scoring system based on the Likert scale that was reported on in a recent consensus meeting (101). The score given for each region was based on an overall impression when accounting for T2, DCE and DW weighted imaging as described in chapter 3 previously. See table 9 previously for a summary of the scoring system used (same as page 120).

Scores for anterior ROIs were grouped together and compared with mp-MRI scores for posterior ROIs giving 128 anterior (transition zone) ROIs versus 128 posterior (peripheral zone) ROIs.

TPM:

As previously described, transperineal template biopsies were taken under general anaesthesia using a 5-mm brachytherapy grid mounted on a stepper, with TRUS guidance. Biopsy cores were analysed and reported by the same dedicated uro-pathologist with 8 years of experience, who participated in all the previous studies. Biopsy results were grouped into four ROIs per prostate, allowing for direct correlation of histopathology and mp-MRI scores for given anterior and posterior quadrants. This allowed accuracy values to be calculated separately for the anterior gland and posterior gland respectively.

Definitions of clinically significant cancer on TPM:

The definitions for clinically significant cancer were the same as those used in the previous study:

The primary target definition (Definition 2) for clinically significant disease on TPM was set at a Gleason score ≥ 3+4 and / or with cancer core length involvement of ≥ 4mm. This relates to an area of cancer on TPM biopsies that has high-grade components (non-dominant Gleason score of ≥ 4) and / or is approximately equal to a lesion volume ≥ 0.2ml (102). This primary target definition for ‘clinically significant cancer’ was chosen on the basis that few

would disagree that any man who had this level of cancer would require treatment.

A higher threshold for clinically significant cancer (Definition 1): cancer core involvement ≥ 6mm and / or Gleason score ≥ 4+3 was also used.

6.3 Results

Statistical comparison of ROC curves for each radiologist was undertaken for each threshold of cancer:

6.3.1 Description of results

All Cancer

R1:
Anterior gland area under ROC curve was 0.68 (95% CI 0.59-0.77), with a posterior gland area under ROC curve of 0.67 (95% CI 0.57-0.76).There was no significant difference (p = 0.88) between these two curves.

R2:
Anterior gland area under ROC curve was 0.64 (95% CI 0.54-0.74). Posterior gland area under ROC curve was 0.71 (95% CI 0.62-0.80). There was no significant difference between these two curves (p=0.30).

R3:

Anterior gland area under ROC curve was 0.62 (95% CI 0.52-0.71). Posterior gland area under ROC curve was 0.73 (95% CI 0.64 – 0.82). There was no statistically significant difference (p=0.10).

Definition 2

R1:

Anterior gland area under ROC curve was 0.71 (95% CI 0.59–0.83), with a posterior gland area under ROC curve of 0.72 (95% CI 0.62-0.82). There was no significant difference (p=0.80) between these curves.

R2:

Anterior gland area under ROC curve was 0.74 (95% CI 0.61-0.87) with posterior gland area under ROC curve being 0.85 (95% CI 0.77-0.93). There was no significant difference (p=0.16) between the two.

R3:

Anterior gland area under ROC curve was 0.68 (95% CI 0.55 – 0.80). Posterior gland area under ROC curve was 0.81 (95% CI 0.72 – 0.90). There was no statistical significant difference (p=0.17) again between these two curves.

Definition 1

R1:

Anterior gland area under ROC curve was 0.69 (95% CI 0.54-0.84). Posterior gland area under ROC curve was 0.74 (95% CI 0.61-0.87). There was no significant difference between these curves (p=0.56).

R2:

Anterior gland area under ROC curve was 0.81 (95% CI 0.66 – 0.95). Posterior gland area under ROC curve was 0.86 (95% CI 0.76 – 0.95). There was no statistical significant difference (p=0.57).

R3:

Anterior gland area under ROC curve was 0.77 (95% CI 0.64 – 0.90). Posterior area under ROC curve was 0.86 (95% CI 0.78 – 0.95). There was no statistical significant difference (p=0.25).

6.3.2 Tables of results

Table 16 - Performance characteristics of mp-MRI in detecting and ruling-out cancer Anterior vs Posterior Gland Analysis for All Cancer, Definition 1 & Definition 2

Anterior Gland Analysis

Disease Threshold	Reporter	TP	FP	FN	TN	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive Likelihood Ratio (+LR)	Negative Likelihood Ratio (-LR)	Overall accuracy	ROC AUC	Asymptotic significance of AUC (null hypothesis AUC=0.5)
All Cancer	**R1**	22	5	40	63	35 (23.8-48.7)	93 (83.7-97.5)	81 (61.9-93.6)	61 (51.1-70.6)	4.83 (1.95-11.97)	0.70 (0.57-0.85)	65 (57.9-70.1)	0.68 (0.59 – 0.77)	< 0.001
	R2	20	1	40	67	35 (23.8-48.7)	99 (92.1-99.8)	96 (78.0-99.3)	63 (52.7-71.8)	24.13 (3.35-173.8)	0.65 (0.54-0.79)	69 (62.1-69.9)	0.64 (0.54 – 0.74)	0.07
	R3	24	11	38	57	39 (26.6-51.9)	84 (72.9-91.6)	69 (50.7-83.1)	60 (49.4-69.9)	2.39 (1.28-4.47)	0.73 (0.58-0.91)	62 (53.9-69.3)	0.62 (0.52 – 0.71)	0.024
Definition 1 (Prevalence 17%)	**R1**	10	17	8	95	56 (30.8-78.4)	85 (76.8-90.9)	37 (19.4-57.6)	92 (85.3-96.6)	3.66 (2.00-6.68)	0.52 (0.31-0.88)	81 (74.6-86.4)	0.69 (0.54 – 0.84)	0.01
	R2	13	8	4	103	78 (52.3-93.5)	92 (85.3-96.3)	61 (38.6-80.3)	96 (90.7-99.0)	9.68 (4.94-18.98)	0.24 (0.10-0.57)	90 (83.8-93.9)	0.81 (0.66 – 0.95)	< 0.001
	R3	13	22	5	90	72 (46.5-90.2)	80 (71.8-87.3)	37 (21.5-55.1)	94 (88.1-98.3)	3.68 (2.29-5.89)	0.35 (0.16-0.73)	79 (72.7-83.8)	0.77 (0.64 – 0.90)	< 0.001
Definition 2 (Prevalence 27%)	**R1**	15	12	14	89	52 (32.5-70.5)	88 (80.2-93.7)	56 (35.3-74.5)	86 (78.2-92.4)	4.35 (2.30-8.23)	0.55 (0.37-0.80)	80 (72.8-86.4)	0.71 (0.59 – 0.83)	0.01
	R2	19	4	10	95	66 (45.7-82.0)	96 (90.2-98.9)	83 (61.2-94.9)	91 (83.5-95.4)	16.54 (6.11-44.79)	0.36 (0.22-0.59)	89 (82.7-93.2)	0.74 (0.61 – 0.87)	< 0.001
	R3	16	19	13	82	55 (35.7-73.5)	81 (72.2-88.3)	46 (28.8-63.4)	86 (77.7-92.5)	2.93 (1.74-4.94)	0.55 (0.36-0.84)	75 (67.9-82.2)	0.68 (0.55 – 0.80)	0.004

~There were two missing values for reporter 2 and these were excluded from analyses

Table 17 - Performance characteristics of mp-MRI in detecting and ruling-out cancer Anterior vs Posterior Gland Analysis for All Cancer, Definition 1 & Definition 2

Posterior Gland Analysis

Disease Threshold	Reporter	TP	FP	FN	TN	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive Likelihood Ratio (+LR)	Negative Likelihood Ratio (-LR)	Overall accuracy	ROC AUC	Asymptotic significance of AUC (null hypothesis AUC=0.5)
All Cancer	**R1**	33	13	35	49	49 (36.2-61.0)	79 (66.8-88.3)	72 (56.5-84.0)	58 (47.1-69.0)	2.31 (1.35-3.98)	0.65 (0.50-0.85)	63 (54.2-70.6)	0.67 (0.57 – 0.76)	0.001
	R2	41	16	25	46	63 (50.7-74.6)	74 (61.5-84.5)	73 (59.7-83.6)	65 (52.5-75.8)	2.45 (1.55-3.88)	0.50 (0.35-0.70)	69 (59.3-76.3)	0.71 (0.62 – 0.80)	< 0.001
	R3	50	22	18	40	0.74 (61.4-83.5)	65 (51.3-76.3)	0.69 (57.5-79.8)	0.69 (55.5-80.5)	2.07 (1.44-2.98)	0.41 (0.27-0.64)	69 (60.1-77.2)	0.73 (0.64 – 0.82)	< 0.001
Definition 1 (Prevalence 17%)	**R1**	14	32	6	78	0.70 (45.7-88.0)	71 (61.5-79.2)	30 (17.8-45.8)	93 (85.1-97.3)	2.41 (1.60-3.62)	0.42 (0.21-0.84)	71 (63.9-75.9)	0.74 (0.61 – 0.87)	0.01
	R2	18	39	2	69	90 (68.3-98.5)	63 (53.0-71.8)	31 (19.2-43.9)	97 (90.2-99.6)	2.41 (1.82-3.20)	0.16 (0.04-0.60)	67 (60.3-69.5)	0.86 (0.76 – 0.95)	< 0.001
	R3	19	53	1	57	95 (75.1-99.2)	52 (42.1-61.5)	26 (16.7-38.1)	98 (90.7-99.7)	1.97 (1.58-2.45)	0.10 (0.01-0.66)	59 (52.2-59.9)	0.86 (0.78 – 0.95)	< 0.001
Definition 2 (Prevalence 27%)	**R1**	25	21	15	69	63 (45.8-77.3)	77 (66.6-84.9)	54 (39.0-69.1)	82 (72.3-89.6)	2.68 (1.72-4.18)	0.49 (0.32-0.74)	72 (63.8-79.7)	0.72 (0.62 – 0.82)	< 0.001
	R2	33	24	7	64	83 (67.2-92.6)	71 (60.6-80.2)	56 (42.4-68.8)	90 (80.7-95.9)	2.86 (2.00-4.07)	0.25 (0.12-0.49)	75 (66.5-80.2)	0.85 (0.77 – 0.93)	< 0.001
	R3	39	89	1	1	98 (86.8-99.6)	1 (0.19-6.06)	30 (22.7-39.2)	50 (8.17-91.8)	0.99 (0.93-1.04)	2.25 (0.14-35.08)	31 (29.3-32.2)	0.81 (0.72 – 0.90)	<0.001

~There were two missing values for reporter 2 and these were excluded from analyses

6.3.3 ROC Curves of Results

Figure 20 – Receiver Operator Characteristic (ROC) curves for Anterior Gland Analysis

All Cancer

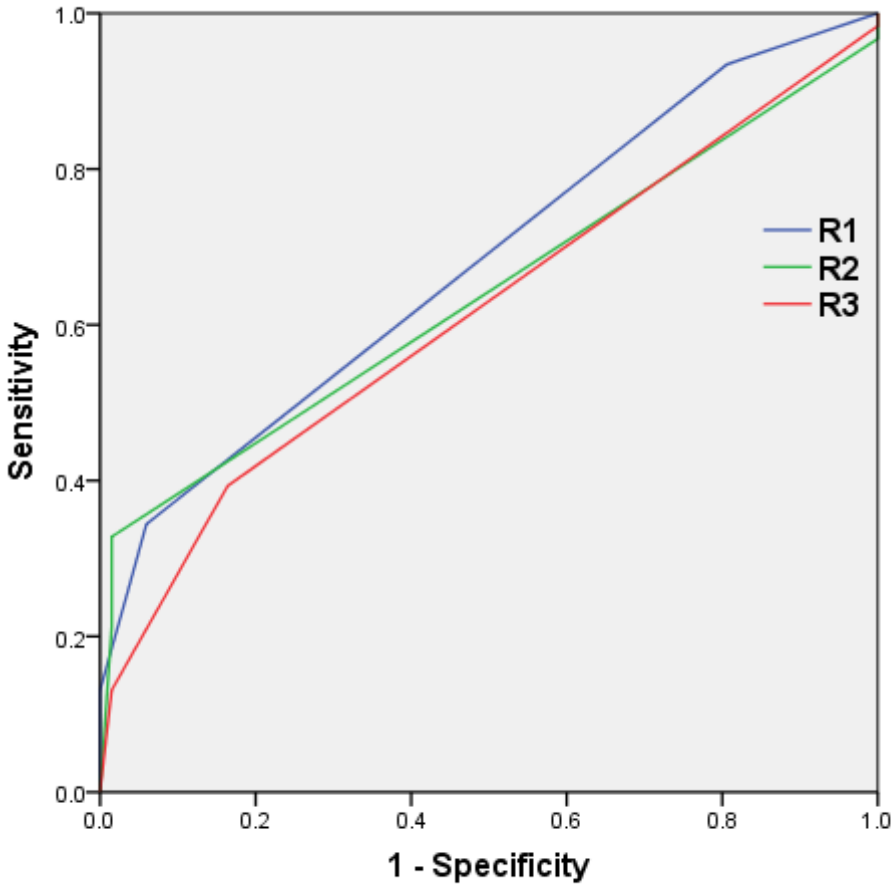


Figure 21 – Receiver Operator Characteristic (ROC) curves for Posterior Gland Analysis

All Cancer

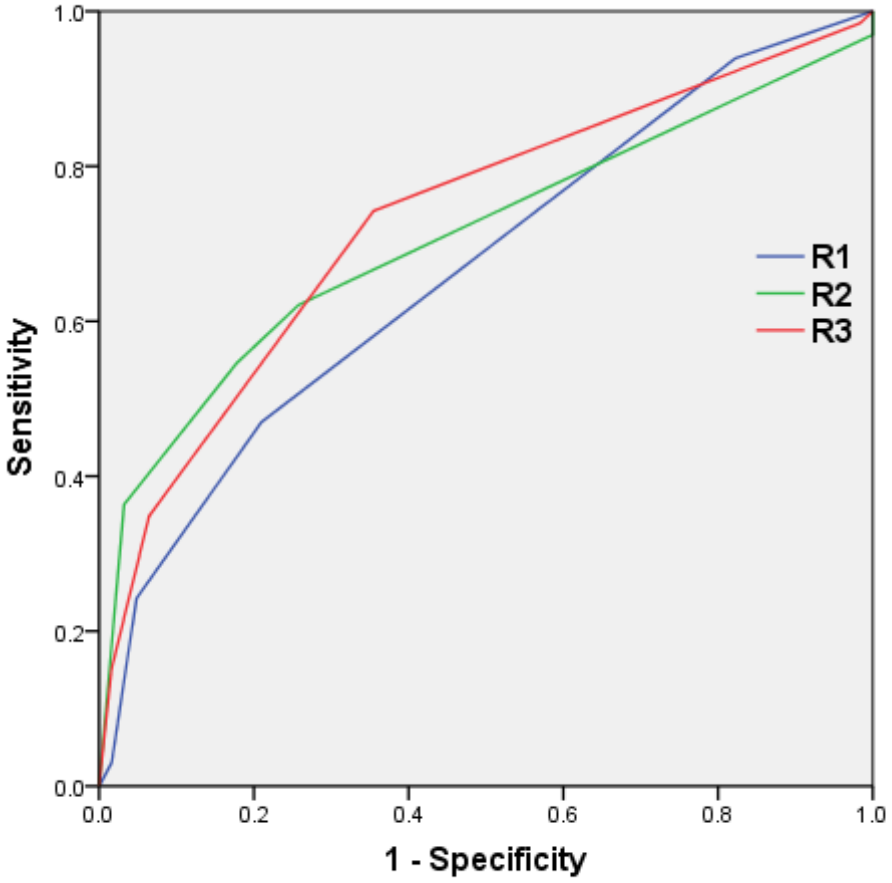


Figure 22 – Receiver Operator Characteristic (ROC) curves for Anterior Gland Analysis

Definition 1

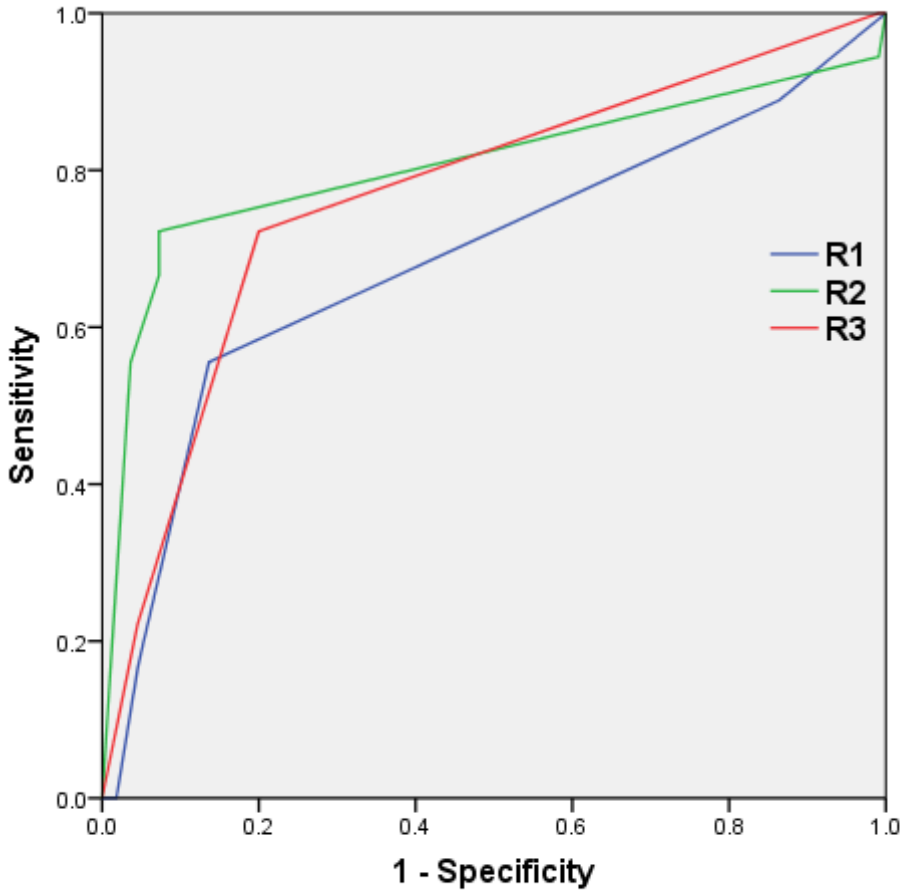


Figure 23 – Receiver Operator Characteristic (ROC) curves for Posterior Gland Analysis

Definition 1

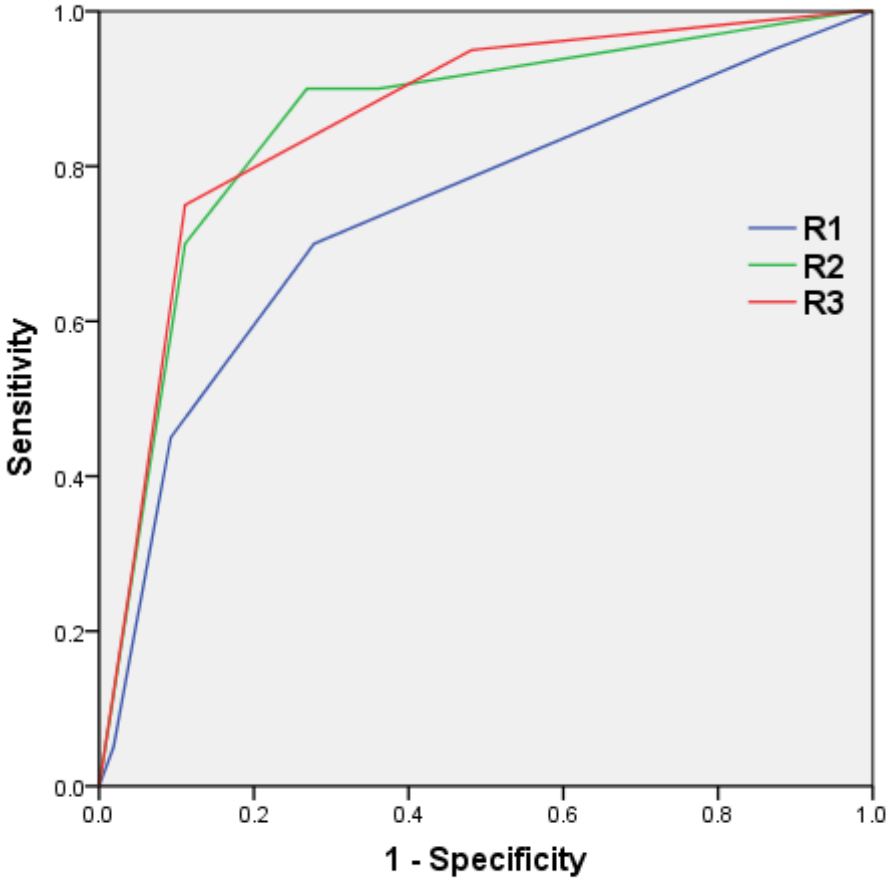


Figure 24 – Receiver Operator Characteristic (ROC) curves for Anterior Gland Analysis

Definition 2

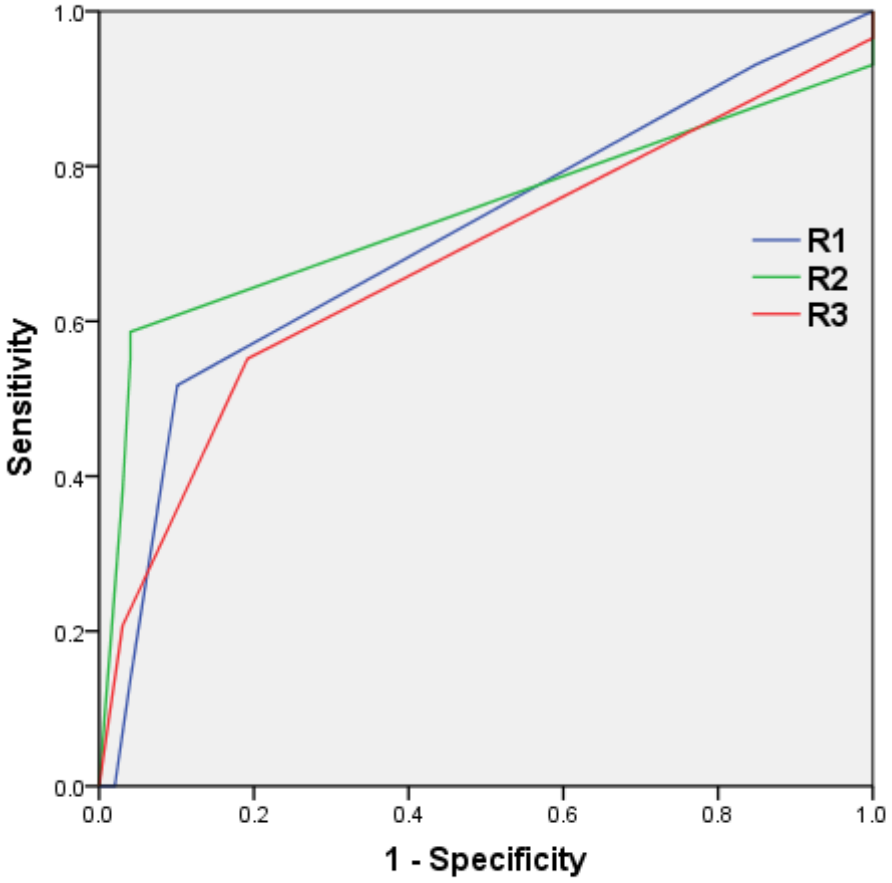
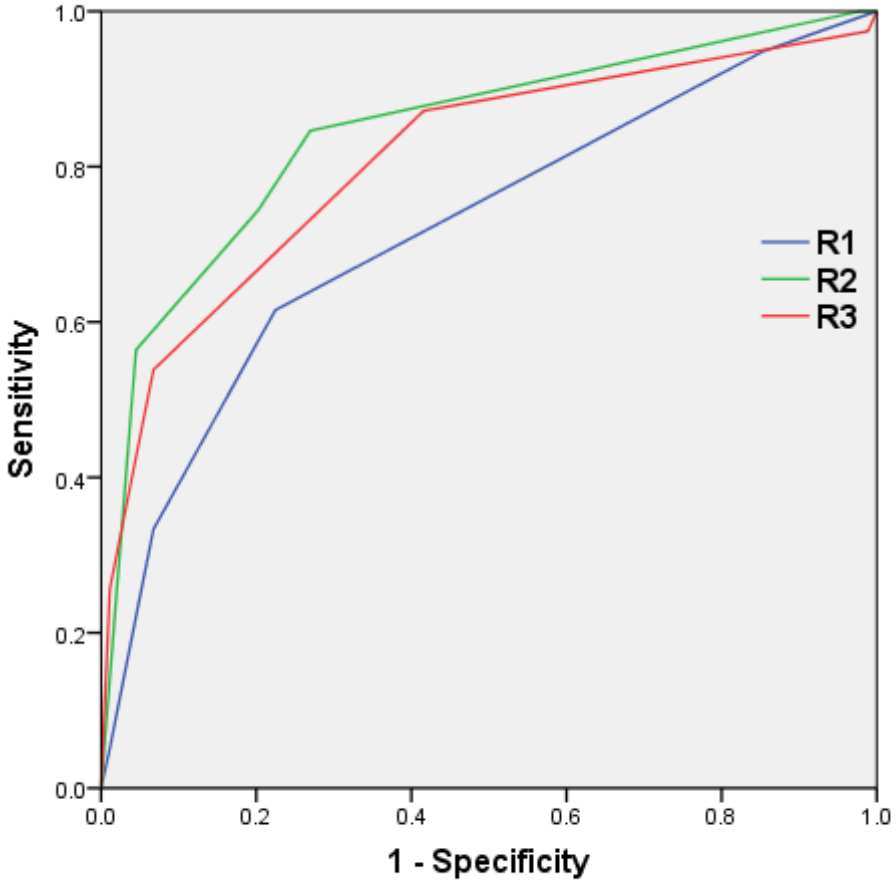


Figure 25 – Receiver Operator Characteristic (ROC) curves for Posterior Gland Analysis

Definition 2



6.4 Conclusion

The results from this experimental study suggest that radiologists did not show a statistically significant difference in terms of accuracy values between anterior and posterior parts of the prostate across the three definitions of clinically significant cancer. The trend observed was that all radiologists had better accuracy values for prostate mp-MRI interpretation in the posterior half of the gland when compared to the anterior gland.

When considering the primary endpoint definition 2 as the threshold for clinically significant cancer there were noticeable differences in overall accuracy between the anterior prostate and posterior prostate for R2 with AUC values of 0.74 (95% CI 0.59 – 0.83) and 0.85 (95% CI 0.77 – 0.93), and R3 with AUC values of 0.68 (95% CI 0.55 – 0.80) and 0.81 (95% CI 0.72 – 0.90), even though these were not statistically significant.

Thus, the findings of the experimental analysis does not show a convincing trend regarding whether prostate cancer is more accurately detected in the anterior or posterior parts of the gland. Comparison with previous studies and further evaluation of these results will be undertaken in the next discussion chapter of this thesis.

CHAPTER 7
DISCUSSION OF RESULTS

7.1 – The Role of mp-MRI in detecting prostate cancer recurrence post-radiotherapy

Summary of Results

Results from this study (n = 52 ROIs), demonstrate that mp-MRI interpreted by two independent readers confers an overall accuracy, as expressed by the area under a constructed receiver-operator curve, of between 0.77 and 0.89 for all cancer, and of between 0.86 and 0.93 for those cancers with at least ≥ 3mm cancer core length.

Methodological Limitations

Prior to addressing the clinical and policy implications of these results it is important to explore some of the methodological limitations of the study that may, as a result, impact adversely on the internal and external validity of these findings.

First, the patient numbers in our study are small, but comparable with previously reported series. However, as all men had a clinical diagnosis of biochemical recurrence it was reasonable to analyse the data on 52 paired datasets using methods well recognised in the literature to produce more meaningful results.

Second, information regarding initial radiation doses given to patients was incomplete owing to the fact that nearly all of the patients were referred from other centres. Some patients were also treated with hormonal manipulation at the time of referral to the centre where the study was conducted. Such factors may have influenced MRI interpretation and histological reporting.

Third, although the mean interval between mp-MRI and transperineal template prostate mapping biopsies was 5 months, the range was variable, with 5 patients having biopsies at more than five months after imaging. It may be argued that in such patients it is impossible to know whether there has been any disease progression from time of index test to reference standard. Such an interval between imaging and verification by biopsy is a methodological issue. Ideally, all patients would have had mp-MRI and subsequent biopsy within a more immediate timeframe.

Fourth, the regions of interest generated by dividing the prostate (in this case into quadrants) are not all truly independent from each other. Presence of tumour in one quadrant will likely confer an increased probability of tumour being in adjacent quadrants. This clustering effect may have a positive bias on the observed results. The score given to each quadrant by the radiologists in this study represented an overall impression once all sequences had been reviewed. It would have been useful to determine the relative contribution of each functional parameter (T2W, diffusion, DCE-MRI) in determining scores. The above limitations of this series are acknowledged, and I would suggest that a future prospective study would be designed to account for such methodological issues.

Fifth, as would be expected, accuracy was improved when only considering cancer likely to be of greater volume (based on a histological 3mm cancer core length). The notion of clinically important disease versus indolent disease is widely accepted in radiation naïve prostate cancer, but not one that has really been explored in this setting. It may well be that in the radiation recurrence setting, any recurrence whatever the size is significant. This will require ongoing study. What we can say is that assuming a sphere, a 3mm diameter maximum cancer core length when sampled on a 5mm sampling frame is likely to represent a cancer focus of 0.2cc or less volume 90% of the time.

Sixth, in order to account for the biases associated with TRUS guided biopsy, many studies have limited their cancer detection by MRI to the peripheral zone alone (96, 98). The study in this thesis included all prostate zones as evaluable, making comparison with peripheral zone limited studies problematic.

Seventh, relates to the clinometric scoring system used by our radiologists to predict the presence of cancer from non-cancer. There existed no accepted scoring system and therefore all those that are used are open to valid criticism. The minimum MRI score attributed to any quadrant was 2 in this series. Our results indicate that defining cancer as a score of 3 or more confers the best balance of sensitivity, specificity, positive and negative predictive values, based on all recurrent cancer being significant. Inter-observer agreement was also very good when this

cut-point was used to define radiological cancer. The inter-observer agreement in our study compares favourably with previous studies using two radiologists. Coakley et al (95) found only slight inter-observer agreement (weighted kappa value of 0.20, with 95% confidence intervals of 0.02 – 0.36), when analysing at the hemi-prostate level.

Despite these methodological issues these results are of possible clinical interest for the following reasons:
(i) This study is, to our knowledge, the first assessment of the role for multi-parametric MRI in recurrent prostate cancer after previous radiotherapy.
(ii) It is the first study to explore the use of transperineal template mapping prostate biopsies as the verification test. The results presented compare favourably with existing reports in the literature and warrant further scrutiny.

Comparison with other studies

These results compare favourably with values seen when using MRSI alone.
In a study by Coakley and colleagues (n = 21 patients), MRSI had accuracy rates of 81% (ROC curves), compared 50% from conventional T2-weighted scans (95). This study, similar to the one in this thesis, used two independent readers but used the more traditional sextant transrectal ultrasound guided biopsy as the reference standard. In contrast to my approach, any cancer detected at biopsy was deemed as significant. In line with methodology in this thesis, the reporters scored hemi-glands from 1 – 5. However the conventional T2-weighted scans used an endorectal coil and the MRSI accuracy analysis used varying cut-points depending on the number of suspicious voxels (≥1, ≥2, ≥3, ≥4) in each hemi-prostate. For both MR modalities ROC curves were used to calculate accuracy values. Hence, although MR imaging was used to assess the whole gland, the reference test - transrectal sextant biopsy – systematically sampled only the peripheral zone. The potential for under-sampling was recognised by the authors and confirmed by the observation that all 5 patients who had ≥ 3 suspicious voxels in a biopsy negative hemi-prostate had other evidence of disease recurrence; three required hormonal therapy for continued increasing PSA and two had positive biopsies in the contralateral hemi-prostate. It is feasible that had these investigators used trans-

perineal prostate mapping that their index / reference test concordance would have increased.

Other studies have also supported the use of MRSI over traditional T1 / T2 weighted MR imaging, due to its detection of abnormal metabolism rather than abnormal anatomy. This seems to confer an advantage in the previously irradiated gland (112). Pickett et al (112) aimed to characterize the metabolic response in the prostate on MRSI (n = 55 patients), and to correlate MRSI with biopsy findings and PSA kinetics after external beam radiotherapy. They again used an extended sextant transrectal ultrasound guided prostate biopsy regimen as their verification test, with areas deemed suspicious on MRSI targeted as additional biopsies. Although 55 patients had MRSI before and at varying times after external beam radiotherapy, only 11 proceeded to biopsy based on a positive MRSI or significantly rising PSA. Four patients positive on biopsy also had positive MRSI, with seven patients negative on biopsy also having negative MRSI results. The authors concluded that MRSI and biopsy findings correlated with each other, but PSA did not have the same relationship. The use of targeted biopsies and the presupposition that positive imaging indicated disease recurrence introduces a selection and incorporation bias to this study, as well as the aforementioned problems with the reference test.

Pucar et al (98) confirmed the superiority of MRSI, by showing a significantly higher sensitivity of 77% for recurrent cancer when compared to a 68% sensitivity using T1/T2 weighted imaging (with pelvic phased-array and endorectal coil) using one reporting radiologist, in nine patients (n = 9), with each prostate divided into 6 ROIs (sextants) (yielding 54 paired datasets for analysis). All nine patients underwent salvage radical prostatectomy, and this was used as the reference standard. In this study although the authors divided tumours into significant (≥ 0.22cc) and insignificant (≤0.22cc) they counted all lesions in subsequent sensitivity/specificity analysis. Overall accuracy of 88% for MRSI was derived from area under ROC curve calculation. Although radical prostatectomy specimens were used to verify MRSI accuracy, the study limited analysis to the peripheral zone alone. Thus ability of MRSI to detect radio-recurrent disease in the transition zone was not evaluated.

DCE-MRI has been shown to perform better than T2 weighted imaging in the detection and localisation of prostate cancer in the peripheral zone after external beam radiotherapy (96), suggesting that use of contrast may define the burden and position of recurrent intra-prostatic lesions. Radiotherapy induces fibrosis of the prostate (97), which therefore would be expected to enhance less and have slower contrast 'washout' than normal prostatic tissue (113). This may help to accentuate the difference between cancer and background prostate to a greater degree than in non-irradiated glands. Haider et al (96), when assessing the use of dynamic contrast enhanced imaging, used transrectal ultrasound guided prostate biopsy (minimum 6 cores taken in each case) as the reference standard. This study again used a single radiologist to report 33 scans (the peripheral zone in each patient divided into sextants to give 198 paired data sets). During DCE imaging cancer has higher, earlier peak and a longer washout slope than normal prostate tissue. The authors in this study used an analytical method, whereby voxels on DCE imaging having signal intensities at 46 seconds after contrast injection that were greater than the mean intensity of the prostate 10 minutes after injection, were considered malignant. The scoring system used (0 = no cancer, 1 = probably no cancer, 2 = possible cancer, 3 = definite cancer), differed to that in our study and that used by Coakley et al (95). Due to the fact that DCE images were almost exclusively scored as 3 or 0, ROC curves could not be constructed. When analysed at a sextant level DCE MRI was found to confer an accuracy of 83% and did not change when analysed at a patient level (82%). Any cancer on biopsy was regarded as significant in this study.

Potential Clinical and policy implications

It is acknowledged that more studies using both the novel Index and Reference test need to be done in a prospective and formal manner it seems likely that mp-MRI imaging of the prostate will become a standard part of the assessment of a man with a rising PSA following radiotherapy. The lack of requirement of an endorectal coil and the wide availability of 1.5T MRI platforms would mean that this method of evaluation could become widely available.

The differences in ROC curves between the two independent observers in this study do show, as have others before (95, 99), that there exists a range of

competencies in the extent to which MRI signals are interpreted by human observers. A number of things may mitigate these apparent differences in the future. Quantitative outputs may reduce some of the subjective nature of reporting. Knowledge of the relative contribution of each sequence to the probability of prostate cancer being present or absent may inform training. Computer Assisted Diagnosis (CAD), so helpful in mammography may have a role in this common male cancer as well. These issues will be reviewed later in the discussion.

The one contribution that could be adopted by the wider research and clinical community is the use of the transperineal template biopsy to map the prostate, especially in the post-radiotherapy population of patients. Not only does this avoid the rectum in a man who has been previously irradiated, it overcomes the 20% false negative rate that is inherent with the use of TRUS guided biopsies when applied to this population (114). The 5mm sampling interval used in the reference standard has a sampling frame similar to whole mount step sectioning but has the benefit of being verifiable in all patients at risk or exposed to imaging. It has been shown to be highly accurate in detection of significant cancers in treatment-naive prostates as outlined in the introduction section in this thesis (33, 115).

If mp-MRI proves to be as accurate as we describe, then it is possible that it could be relied upon to provide a target of ‘measurable disease’ so that treatment could be planned and administered. Focal treatment for prostate cancer aims to treat just disease and leave non-diseased tissue untreated (116). It is possible that such an approach, if feasible, could be associated with a substantial reduction in treatment related toxicity and provide a salvage treatment option in patients with recurrent localised cancer after radiotherapy.

Further work should involve the use of multi-functional MRI using DCE-MRI, diffusion and MRSI in various combinations with prospective blinded reporting to assess their relative contribution to accuracy.

A consensus needs to be reached with respect to a scoring system that is both reliable and valid and this will be discussed in more detail later.

Finally, for all the reasons outlined above we feel that studies such as these can only contribute to the knowledge base if a good reference standard is applied that is free of the selection bias associated with salvage prostatectomy and minimises the random and systematic error associated with TRUS guided biopsy.

7.2 – The Role of mp-MRI in detecting prostate cancer

The combination of an observed negative predictive value of up to 95% (Definition 1) or up to 89% (Definition 2), for clinically significant prostate cancers and a negative likelihood ratio as low as 0.2 (Definition 1) or 0.3 (definition 2), indicates that mp-MRI may be useful in ruling-out clinically significant prostate cancer. Biopsies could be avoided in areas that are negative on mp-MRI. Further, this study is hypothesis generating as to whether mp-MRI could serve as a useful triage test to help men at risk, decide whether or not they should proceed to a prostate biopsy.

The performance characteristics of mp-MRI varied considerably with changing the target definition on reference standard and using different numbers of sectors of analysis. The ability of mp-MRI to rule-out disease (sensitivity and NPV) improved with higher thresholds for the definitions of clinically insignificant cancer. On the other hand, specificity and PPV deteriorated with higher thresholds for definitions of clinically significant cancer; this is likely to be due to classifying a positive sector on mp-MRI which has cancer on TPM in the same sector as a false positive because it just missed the threshold for the target condition for that particular analysis. As expected, changing the sectors of analysis changed the prevalence of each target condition and therefore impacted little on sensitivity and specificity but tended to improve PPV and show deterioration in the NPV.

Early studies investigating the role of MRI in prostate cancer used reduced signal intensity on T2-weighted imaging alone to detect disease and therefore produced very variable sensitivities and specificities. This wide variation is partly explained by differing lesion size inclusion criteria (all cancer for some studies or only lesions ≥0.5ml in other studies) as well as areas of the prostate used for analysis (peripheral zone only, transitional zone only or whole gland) (117).

The introduction of novel MR techniques (DW, DCE and MR-spectroscopy) in the last two decades has allowed for functional characterization of the prostate based on cellular density, microvasculature and metabolic changes in cancer (118). Further research therefore incorporated such techniques when evaluating MRI accuracy.

It was shown that the use of T2-weighted combined with DW imaging improves sensitivity in detection of significant prostate cancer (0.81 vs 0.54) and negative predictive value (0.88 vs 0.77), when compared to T2 imaging alone (119). Our study did not allow for investigation of the effect of individual sequences on accuracy.

Kozlowski et al (89), showed that combining T2, DW and DCE-MRI resulted in improved sensitivity (when compared with T2+DW or T2+DCE only) of 0.87, with a slight decrease in specificity to 0.74. In this pilot study they used only 14 patients of whom 4 did not have cancer on TRUS biopsy. Of the remaining 10 patients, 8 had radical prostatectomy. Thus, the reference standard used in this study varied (TRUS biopsy in 6 and radical prostatectomy in 8), within this small group of patients.

When DCE pelvic phased array MRI in combination with T2-weighted imaging was evaluated in 24 patients (75), an NPV of 0.85 for 0.2cc lesions and 0.95 for 0.5cc lesions was found. Again, this used radical whole-mount specimens as the reference standard, but our results are comparable with similar NPVs for similar thresholds of disease significance.

More recently Delongchamps et al (111) evaluated mp-MRI in 57 patients using radical prostatectomy as the reference standard and dividing each prostate into octants for analysis. They gave accuracy values (expressed as Area under ROC curve) in their results analyzing peripheral and transition zone separately. They found sensitivity of 80% and specificity of 97% in the peripheral zone, and sensitivity of 53% and specificity of 83% in the transition zone. They concluded that adding DWI and DCE to T2W imaging significantly increased MR performance for cancer detection in the peripheral zone. However, this multi-parametric model failed to improve performance in the transition zone. Gleason score significantly influenced cancer detection in the PZ but not in the TZ. This

study used quantitative outputs and a different scoring system to other studies and the one used in this thesis.

This study has limitations. Firstly, the study had verification bias as it included only men who could be sampled using the reference test, TPM.
The population comprised a range of men, although lacking patients with higher Gleason grade disease and this may have resulted in underperformance of mp-MRI.
Despite this I feel that the study population is suitably heterogeneous enough to overcome spectrum effect and reporter bias. Further, I have used recognised methods of analyses, where possible, such as likelihood ratios and ROC curves in order to address for such heterogeneity (120).

An endorectal coil was not used when performing mp-MRI, and it may be argued that this may have affected the diagnostic performance of mp-MRI in this study.

Second, the thresholds used for clinically significant disease are open to debate as no universally accepted definition exists. It is widely accepted that some prostate cancer lesions are clinically significant and others are not (121, 122). Volume thresholds of 0.5ml and 1.3ml for low grade cancer have been supported by recent data from the European Prostate Cancer Screening trial (43).

Third, TPM may not be as accurate as whole-mount prostatectomy, but a number of studies point to its accuracy being sufficiently high to use as a reference test. Indeed, for men with no cancer diagnosis or for those not choosing surgery, it may be the best available reference standard (33, 37, 115, 123). However, TPM is superior to TRUS biopsy of the prostate, on average showing upgrading in about one third and change from unilateral disease to bilateral disease identified in over half (115, 123).

In summary, sensitivities and specificities of between 70%-90% and 61%-89%, respectively, have been reported with negative predictive values of between

85%-95% for clinically significant cancer (124-128). The results in this thesis compare favorably with these previously reported results. However the major methodological difference is that these previous studies used radical whole-mount prostatectomy specimens; to our knowledge, this thesis is the first study to validate mp-MRI using TTPM as the reference test using a number of definitions of clinical significance on the reference test.

The high NPV of mp-MRI for clinically significant prostate cancer could be used in clinical practice to justify reducing the number of biopsies in some parts of the prostate that are reported as negative on imaging, and this will be discussed later.

The NPV of mp-MRI could also be exploited within focal therapeutic protocols in which clinically significant lesions are ablated rather than the entire prostate, in order to reduce the treatment-related harms currently seen with radical therapies (116, 129).

7.3 Differences in ability of mp-MRI to detect prostate cancer within the anterior and posterior gland

The results in this thesis did not show any statistically significant difference in the ability of mp-MRI to detect cancer within the posterior (i.e. peripheral zone) versus the anterior (transition zone) parts of the prostate. This was observed across all radiologists.

The radiologists in this thesis had good observed accuracy for detection of significant cancer in the anterior and posterior gland, with some observed differences:

Definition 1: For any Gleason ≥ 4+3 cancer or any lesion ≥ 0.5cc sensitivity, specificity, PPV and NPV were:

R1: 56%, 85%, 37% and 92% in the anterior prostate; 70%, 71%, 30% and 93% in the posterior prostate. (AUC was 0.69 anterior vs 0.74 posterior)

R2: 78%, 92%, 61%, 96% in the anterior gland; 90%, 63%, 31% and 97% in the posterior gland. (AUC was 0.81 anterior vs 0.86 posterior)

R3: 72%, 80%, 37% and 94% in the anterior prostate; 95%, 52%, 26% and 98% in the posterior prostate. (AUC was 0.79 anterior vs 0.86 posterior)

Definition 2: For any Gleason ≥ 3+4 cancer or any lesion ≥ 0.2cc sensitivity, specificity, PPV and NPV were:

R1: 52%, 88%, 56% and 86% in the anterior gland; 63%, 77%, 54% and 82% respectively for the posterior gland. (AUC was 0.71 anterior prostate vs 0.72 posterior prostate)

R2: 66%, 96%, 83% and 91% in the anterior prostate; with corresponding results of 83%, 71%, 56% and 90% in the posterior gland. (AUC was 0.74 anterior prostate vs 0.85 in anterior prostate)

R3: 55%, 81%, 46% and 86% in the anterior gland; 98%, 100%, 30% and 50% in the posterior gland. (AUC was 0.68 anterior vs 0.81 posterior prostate).

Thus, AUC accuracy values were higher in the posterior prostate when compared with the anterior prostate for all radiologists for both definitions of clinically significant disease. The most notable difference in AUC values when comparing accuracy between anterior and posterior prostate tissue was seen for R3 when definition 2 was used as the threshold for clinically significant cancer. All other differences were modest and would suggest that there was no real difference in the ability of the three radiologists in this study to evaluate anterior (predominantly transition zone) and posterior (predominantly peripheral zone) prostate tissue for cancer.

T2-weighted MR imaging alone is thought to be inadequate when evaluating transition zone tumours because of the heterogeneous T2 signal intensity in normal transition zone and the presence of benign prostatic hyperplasia nodules.

Despite this Wang et al (90) investigating the relationship of signal intensity on T2W imaging, found that Gleason grade 3 tumour lesions in the transition zone had a statistically significantly lower signal intensity than grade 3 tumours in the peripheral zone. Suggesting therefore that use of signal intensity may help detect transition zone tumours more reliably.

Yoshizako et al (130) conducted a study of 35 patients who had mp-MRI and subsequent radical prostatectomy and concluded that the addition of DW-MRI to fat suppressed T2 MR imaging resulted in the best overall accuracy (AUC 0.83 vs 0.64 for T2 weighted imaging alone). They also observed only no real improvement with the addition of DCE-MRI to T2-MRI in transition zone accuracy (AUC 0.69 for DCE+ T2-MRI). The use of all 3 sequences resulted in much better specificity (94%) and PPV (95%) when compared with the other protocols: specificity 69% for T2 alone, 88% for T2 + DW-MRI and 69% for T2 + DCE-MRI) and PPV 76% for T2 alone, 91% for T2 + DW-MRI and 78% for T2 + DCE-MRI. Thus, this small study suggested that DW-MRI may be the most important additional component in accurately evaluating the transition zone for cancer.

Akin et al (131) previously in 2006 evaluated the ability of two junior radiologists to detect transition zone tumours on T2W MRI in patients subsequently

undergoing radical prostatectomy (used as the reference test). They had 148 patients with at least one transition zone lesion and 46 patients without transition zone tumours as a control group. Sensitivity and specificity for transition zone tumours were 75% and 87% for radiologist 1, and 80% and 78% respectively for radiologist 2. Overall accuracy values were 0.75 and 0.73 for the two radiologists, in detecting transition zone tumours. They also noted unsurprisingly that radiologists' ability to detect transition zone cancer on T2W MRI significantly improved as the lesion volume increased ($p = 0.01$, when comparing tumours ≤ 0.77cc and those ≥ 0.77cc).

Akin et al (110) later also reported transition zone versus peripheral zone reader accuracy again using T2W MRI in 11 radiology residents before and after specific training in prostate MRI interpretation. Although overall accuracy improved in detecting transition zone tumours after specific training in T2W MRI interpretation, there appeared to be no obvious difference between transition zone and peripheral zone tumour accuracy, both before and after training, with AUC values of 0.49 in transition zone and 0.52 in the peripheral zone before training and 0.68 and 0.66 respectively after training.

The historical perspective on T1/T2 weighted MRI accuracy, when detecting transition zone prostate cancer was that it underperformed in this region of the prostate when compared with the peripheral zone lesions (132, 133), due to difficulty distinguishing malignant lesions from benign prostatic hyperplasia (BPH), given that both demonstrate low T2 signal on MR imaging. However, differences such as homogenous low T2 signal intensity, ill-defined margins and lack of capsule can be used to distinguish a malignant lesion in the transition zone. BPH nodules tend to have mixed high and low signal intensity on T2 weighted imaging due to mixed stromal and glandular components within the tissue architecture. They also tend to have well defined margins, tend to be round in shape and may displace but do not invade the fibromuscular stroma of the prostate, unlike transition zone cancer which tends to be lenticular in shape and can invade the fibromuscular stroma. Such differences have been incorporated into the ESUR guidelines when scoring transition zone ROIs for likelihood of clinically significant cancer using T2W MR imagines only (94):

T2WI for the transition zone (TZ)

1 Heterogeneous TZ adenoma with well-defined margins: “organised chaos”

2 Areas of more homogeneous low SI, however well marginated, originating from the TZ/BPH

3 Intermediate appearances not in categories 1/2 or 4/5

4 Areas of more homogeneous low SI, ill defined: “erased charcoal sign”

5 Same as 4, but involving the anterior fibromuscular stroma or the anterior horn of the PZ, usually lenticular or water-drop shaped

Tumours which exclusively develop in the transition zone have the potential to evade the current approach to investigating men suspected of having prostate cancer, as they can be difficult to detect on digital rectal examination, and can potentially evade TRUS biopsy given their anterior position. It is important for mp-MRI to be able to detect transition zone tumours with accuracy if it is to improve the diagnostic pathway. Our results suggest that mp-MRI does not significantly under-perform in detection of tumour when compared with peripheral zone detection of tumours. Other studies using only T2W imaging, also suggest this, whilst some research points towards DWI sequences improving tumour detection in the transition zone. Thus, although recent ESUR guidelines place emphasis on T2W sequences in evaluation for transition zone tumours, mp-MRI may provide valuable additional information in the transition zone.

Transition zone tumours tend to have higher tumour volumes than patients with peripheral zone cancers (134), although this does not necessarily translate to easier detection by MRI or mp-MRI given the heterogeneous nature of this part of the prostate as outlined earlier.

Mp-MRI in a study by Delongchamps et al (111) as outlined earlier, failed to significantly improve tumour detection in the transition zone when compared to the peripheral zone. Notably DCE-MRI imaging appeared to decrease accuracy in the transition zone, with DWI-MRI adding accuracy when compared with T2W

imaging alone, but this difference was not statistically significant. Thus, the authors concluded that morphological criteria (as outlined above) described on T2 imaging should still be the gold standard criteria for the detection of transition zone cancer.

A recent study by Rosenkrantz et al (135) evaluated inter-rater reproducibility with the PI-RADS scoring system and a Likert scale scoring system, in the transition zone and peripheral zone separately using a group of ‘experienced’ and ‘less experienced radiologists. The study incorporated 55 patients and used 3T mp-MRI (T2w, DCE and DWI). They found that agreement between experienced readers was strong in the peripheral zone using PI-RADS and the Likert scale, but in the transition zone agreement was moderate using the Likert scale and poor using the PI-RADS system. Agreement between experienced and less experienced readers was moderate in the peripheral zone for PIRADS and Likert scales, minimal to poor in the transition zone for PI-RADS and poor in the transition zone for the Likert scale. The study highlights the better agreement between radiologists for peripheral zone evaluation of tumours and the relatively poorer agreement for transition zone tumour detection, with either scoring tool / system. Thus, MRI evaluation of the transition zone continues to be challenging even in the 3T and multi-parametric era.

Simpkin et al (136) evaluated T2 relaxation and ADC values in normal prostate and tumour. They concluded that the correlation between T2 and ADC that exists in normal prostate is absent in tumour. They also found that peripheral zone compression by an enlarged transition zone did not alter peripheral zone T2 relaxation or ADC, and thus did not affect contrast between tumour and normal peripheral zone tissue. Compression of the peripheral zone by BPH should not therefore affect the ability of mp-MRI to detect cancer in the peripheral zone.

CHAPTER 8

DISCUSSION:

IMPLICATIONS FOR RADIOLOGY REPORTING OF PROSTATE MP-MRI

8.1 Implications for radiology reporting of prostate mp-MRI

8.1.1 – Radiologist Experience

It should be noted that all of the radiologists participating in this study were uro-radiologists and therefore undertook large volume reporting of prostate mp-MRIs in their daily clinical practice. The encouraging results observed in this thesis should therefore be tempered by this, and cannot be extrapolated to all radiologists. Even with sub-specialist prostate mp-MRI interpretation skills, years of experience seem to allow for better interpretation. Across all studies the more experienced radiologist outperformed less experienced radiologists in interpreting mp-MRI imaging to give better accuracy results.

This is not surprising, but does therefore limit the generalisability of these results, and it may not be possible to reproduce equivalent accuracy results with radiologists who were not specifically trained and experienced in prostate mp-MRI reporting.

The need for such training is highlighted by Akin et al (110), who assessed the accuracy of prostate T2W MRI interpretation by 11 radiology fellows before and after an initial set of 5 didactic lectures, and then after an interactive dedicated training curriculum over 20 weeks (reporting 10 prostate MRIs each week with interactive feedback on performance using whole mount radical prostatectomy specimens as the reference standard). Interestingly the accuracy for detection (as measured by area under ROC curves) improved significantly after the 5 didactic lectures, from 0.52 to 0.66 ($p < 0.0001$) in the peripheral zone, and 0.49 to 0.64 ($p < 0.001$) in the transition zone. The ability of residents to detect extra-capsular extension improved significantly following the 5 lectures, from 0.50 to 0.67 ($p = 0.003$). The further 20 week interactive training period resulted in little difference in performance, with accuracy remaining at 0.66 in the peripheral zone and improving slightly to 0.68 in the transition zone. However, ability to detect extra-capsular extension improved significantly further after the 20 week training period to 0.81 ($p< 0.0001$)

Thus, although long-term improvements in prostate MRI reporting accuracy may be served by sub-specialty fellowship training, the results of Akin et al would suggest that a shorter period of training can have a significant impact on radiologist reporting accuracy. Such training may have a greater effect when using mp-MRI as opposed to just T2W MRI as per Akin's study.

The resources to provide structured regular training modules with lectures and face-to-face interaction as described above require considerable resources and time. Another feasible solution to addressing the issue of radiologist experience is to create a national online databank of mp-MRI prostate images and case studies. Such an online educational tool would allow radiologists to acquire the skills needed in prostate mp-MRI interpretation rapidly and would provide a large volume of images / cases to facilitate this learning curve. Thus, experience would be gauged not by years of experience but by number of mp-MRI images reported (both via online training and in real clinical practice). This would allow for remote teaching across multiple centres with a shorter timeframe to gain competency. Such an online resource may also improve standardisation in reporting by the use of online testing and data acquisition of radiologists scoring trends, with accompanying feedback as to how a given radiologists scores compared with the scoring trend nationally of other radiologists. Thus, a given uro-radiologist can see how their allocation of scores for given ROIs compares with the scores of his / her colleagues nationally during the online training modules. Such real-time feedback would allow for a degree of plasticity and moulding of how radiologists allocate scores, and would hopefully result in better inter-reporter agreement and standardisation between radiologists at the end of such an online training scheme.

The issue of variability of experience may also be offset by using more quantitative output information from mp-MRI imaging such as DCE contrast curves in regions of interest and ADC values on DW imaging, when reporting images. Thus a combination of quantitative outputs from all sequences of the mp-MRI scan may improve radiologist reporting accuracy, and help reduce variability in reporting accuracy.

The methodology and timeframes involved in the studies in this thesis did not allow for testing of intra-observer variability, to validate the consistency of each reporting radiologist. This is a consideration for design of future studies.

8.1.2 – Scoring systems in mp-MRI reporting

The use of a standardised radiology scoring system no doubt helps the urologist identify a clear threshold for considering what constitutes possible disease on mp-MRI and what is deemed low suspicion of cancer. This provides a better method of reporting to inform clinical decision making regarding biopsy strategy rather than continuous prose reporting which cannot be standardised. The Likert scale 1 – 5 used in this thesis also allows the urologist to more objectively observe varying trends amongst radiologists (thus, one radiologist's '3' may consistently be another radiologist's '4') for similar lesions seen on mp-MRI. Putting the score into the context of the reporting radiologist may thus allow for better decision making with regards to prostate biopsy. Such scoring systems also allow for meaningful research results.

Other previous studies have used similar scales but differing thresholds of what is deemed a 'positive' mp-MRI result. In this thesis a score of ≥ 3 out of 5 was deemed to be cancer on mp-MRI and scores 1- 2 were deemed not to be cancer. A score of 3 from the radiologist perspective is 'indeterminate'. The reason for choosing the 'cut-point' of ≥ 3 was based on the threshold for performing biopsy in a given region of the prostate and I would suggest that radiologists in this study when attributing a score ≤ 2, are confident that there is no significant cancer in that particular region of interest. An indeterminate score of 3 should therefore also warrant a biopsy along with more confident radiological scores of 4 and 5 for disease being present. This would appear to be the safest approach from a patient perspective, in terms of not missing cancer, whist reducing biopsy burden by selectively only sampling regions scored ≥ 3.

The definitions of the mp-MRI reporting scores used in this thesis are included in the comparison with other previous studies using a 1 – 5 Likert scale in table 18 below:

Score	Thesis Definition (mp-MRI)	Nogueira et al 2010 (T2W only)	Mueller-Lisse et al 2005 (T2W only)
1	Highly unlikely to be clinically significant cancer	Definitely no cancer	No cancer
2	Unlikely to be clinically significant cancer	Probably no cancer	Probably no cancer
3	Equivocal	Indeterminate	Indeterminate
4	Likely to be clinically significant cancer	Probably cancer	Probably cancer
5	Highly likely to be clinically significant cancer	Definitely cancer	Definitely cancer

Table 18 – Comparison of mp-MRI reporting score definitions with previous studies

However, other studies whilst using a 5 point system have used slightly different terminology and 'cut-points'. Nogueira et al (137) and Mueller-Lisse et al (138) in previous studies evaluating T2W MRI detection of prostate cancer, both used the 1 – 5 ordinal scale but defined scores of 1 – 3 as benign radiological findings and 4 – 5 as malignant MRI findings. The definitions in my thesis used the terminology 'clinically significant cancer', whereas in other studies mp-MRI suspicion of 'any cancer' was being measured. Hence there are differences between previous studies even when the same ordinal scale is used. Standardisation of such a scale and the defined 'cut-point' of what is deemed radiological cancer across the mp-MRI reporting community need to be adopted to allow for meaningful comparison between future studies. The recent European consensus meeting (101) and subsequent ESUR guidelines (94) will hopefully provide the platform for this. Of note the terminology advised from the consensus meeting and ESUR guidelines both suggested the 1 – 5 ordinal scale for reporting with the same definitions relating to likelihood of clinically significant cancer as used in this thesis.

8.1.3 Regions of Interest (ROIs) in mp-MRI reporting

Creating regions of interest within the prostate in studies evaluating accuracy of mp-MRI allows for more meaningful analysis as described earlier in this thesis. However, the way in which the prostate has been divided varies in the literature. The reason for using quadrants in this thesis, was due to the limits of the resolution of the reference test. During TPM apical and basal cores are taken for each 5mm grid position. Thus trying to divide the prostate into sextants would have been impossible due to not being able to attribute the mid-gland sextant histology accurately. Studies using whole-mount radical prostatectomy specimens as a reference standard are able to do this.

From a statistical viewpoint it should also be remembered that in such studies each ROI within a gland is not truly independent, as regions which are negative will likely have neighbouring regions that are negative, and those regions adjacent to positive regions are more likely to be positive themselves. Thus, statistically when more ROIs are created within an organ for diagnostic accuracy evaluation, more negative ROIs are created and this leads to a positive bias in the NPV. Therefore, although other studies investigating MRI and mp-MRI accuracy have divided the prostate into more ROIs, I feel that the methodology in only dividing the prostate into quadrants for the studies in this thesis will hopefully limit the bias towards a better NPV.

Quadrant analysis also still allows for meaningful results to be derived and provides a good limit of resolution in terms of clinical applicability. Thus, these results may allow clinicians to do away with sampling quadrants with a low suspicion for significant cancer during transrectal ultrasound guided biopsy, and any ROI scored ≥ 3 could be sampled in a more targeted manner.

8.1.4 Use of Quantitative Outputs in mp-MRI reporting

The radiologists in the studies within this thesis when scoring ROIs did not use any quantitative analysis. The ESUR guidelines do not include quantitative parameters when advising how to attribute scores to a given ROI. The issues of variability in experience and inter-observer agreement, could potentially be

improved by the use of quantitative outputs from mp-MRI. A radiologist would still need to define a potential lesion or suspicious ROI and the point in time when the quantitative data is sampled from the sequences used. The relative weighting placed on each quantitative parameter is also a matter for debate, given that there is no consensus in the literature regarding whether any sequence in mp-MRI should carry more weight than other sequences in deciding on scoring ROIs.

Thus, such reporting, whilst using more objective parameters, effectively translates to a combination of cognitive and quantitative information in order to produce scores for ROIs.

Quantitative outputs from T2W imaging may be used to potentially ascertain biological aggressiveness of prostate cancer detected on MRI. Wang et al (90) as mentioned earlier, investigated the signal intensity (SI) on T2W MRI (1.5 T scanner with pelvic phased array and endorectal coil) of 91 tumour lesions in 74 patients. They found a statistically significantly lower signal intensity on T2W MRI for tumour lesions compared with normal prostate tissue, and suggested that T2W SI values could help to provide a non-invasive method for assessing prostate cancer aggressiveness, thus helping in the stratification of patients for suitable treatment.

Tumour micro-vessel density in prostate cancer has been shown to correlate with Gleason score (139). Given that DCE MRI provides a surrogate marker for micro-vessel density, it might be expected that quantitative outputs from DCE MRI may therefore provide estimation of micro-vessel density and hence grade. Early on, Jager et al (140) showed that poorly differentiated prostate cancer had earlier onset and faster rate of enhancement on DCE-MRI, compared to other histological grades. This was a limited observation in 5 patients and no formal correlation with histological grade or tumour stage could be made. Conversely Yoshizako et al (141) reported that poorly differentiated tumours showed less overall enhancement compared to moderately differentiated tumours. Padhani et al (142) did not demonstrate a correlation between any enhancement parameters and histological grade in 48 consecutive patients having 1.5T DCE-MRI. However, the authors did highlight the lack of patients with either well or

poorly differentiated tumours, with the majority (38 patients) having tumours with Gleason score 5 – 7. This lack of heterogeneity in their study population may have contributed to a lack of correlation being observed.

There has been research into the use of DW imaging quantitative outputs as a potential biomarker to predict tumour aggressiveness in localised prostate cancer. De Souza et al (143) found significant differences in both fast and slow diffusion ADC values when comparing low risk prostate cancer patients and intermediate / high risk patients. They also found that greater tumour volume identified on T2 weighted imaging was associated with intermediate or high risk cancer.

Given the potential for ADC values to distinguish between low and intermediate / high risk prostate cancer, it has been investigated as a tool to monitor patients on active surveillance protocols (144, 145). In a pilot study of 50 consecutive patients on an active surveillance protocol, Morgan et al (145) evaluated the differences in ADC outputs in those patients who progressed to treatment (17 men) versus those that did not (33 men). They analysed their results according to the b-values: (i) all b-values (0 – 800), (ii) fast diffusion components (low b-values 0 – 300) and (iii) slow diffusion components (high b- values 300 – 800). They found that a 10% reduction in ADC (all b-values) indicated progression with 93% sensitivity and 40% specificity, with AUC accuracy of 68%. They also found that percentage reductions in whole prostate ADC values (for all b-values, fast diffusion and slow diffusion components) were statistically significantly greater in men who progressed when compared to those men who did not progress. This was a small study with a small number of patients who actually progressed to radical prostatectomy, but it does highlight the potential for quantitative outputs from mp-MRI (in this case DW imaging), to be used not only as a diagnostic tool but also as a biomarker for disease progression.

Thus, the quantitative parameters from mp-MRI imaging may provide a way to increase diagnostic accuracy, but also provide information to allow mp-MRI to be used as a non-invasive biomarker to estimate prostate cancer aggressiveness. Given the quantitative information available the question arises as to how much weighting to place on each of these parameters (in the same

way as visual inspection of these sequences need to be allocated weighting in the decision making process for the radiologist). Langer et al (146) used step-wise logistic-regression modelling to evaluate the relative performance of ADC values, K-trans values from DCE and T2 weighted imaging values in combination. They found that using all 3 sequence quantitative outputs improved accuracy in the peripheral zone (AUC 0.71), whilst also observing that ADC was the best performing single parameter (AUC values were 0.69 for ADC, 0.67 for T2 and 0.59 for K-trans). This may suggest that ADC values may need to have greater weighting compared to DCE outputs in tumour evaluation in the peripheral zone. The limitations of this study were the small number of patients (25 men) and the limitation of the conclusions to the peripheral zone only.

8.1.5 – The Potential Role of Computer Aided Diagnosis (CAD)

There is clearly inter-reporter variability relating in part to the differing experience of radiologists. The potential role for using quantitative parameters from T2W, DCE and DW imaging to better inform decisions on scoring ROIs within the prostate as outlined above, may provide a means to improve reliability in radiology reporting. This could be taken further by removing the human element to interpretation of such quantitative outputs, by using computer –aided diagnostic (CAD) systems.

Early work by Chan et al (147) described a CAD system that produced a summary statistical map of the peripheral zone of the prostate by combining information from three different magnetic resonance (MR) methodologies: T2-weighted, T2-mapping, and line scan diffusion imaging (LSDI) using multi-channel classifiers, with an overall accuracy AUC value of 0.84.

Vos et al (148) in 2008 published a feasibility study describing a CAD system that calculated the malignancy likelihood of a given suspicious area in the peripheral zone of the prostate using T1W DCE-MRI. This CAD system had an overall diagnostic accuracy of 0.83 (0.75 – 0.92). Two years later the same research group published results describing a CAD system using T2W imaging as an additional MR modality to differentiate between cancer and normal tissue

within the prostate peripheral zone (149). This CAD system was used on a retrospective cohort of 34 men with biopsy proven prostate cancer undergoing 1.5T DCE-MRI prior to radical prostatectomy. They compared the additional value of adding T2W outputs to the T1W DCE-MRI based CAD system. CAD using the T2 values alone yielded a diagnostic accuracy of 0.85 (0.77 – 0.92) and showed improved accuracy when combined with T1W DCE-MRI of 0.89 (0.81 – 0.95).

Hence, CAD may provide a role in the future reporting of mp-MRI to improve reproducibility and inter-observer agreement.

8.2 Mp-MRI performance across varying thresholds of 'clinically significant cancer'

This thesis demonstrates clearly that the performance of mp-MRI to detect and rule-out prostate cancer varies according to the disease burden. The issues of over-diagnosis and over-treatment have been highlighted and discussed in the introduction section of this thesis. These issues partly relate to the lack of confidence in the diagnostic standard of care (i.e. TRUS guided prostate biopsies), with worries about under-sampling and incorrect disease risk stratification.

The results in the studies conducted show that mp-MRI performs worse when all cancer is considered clinically significant, both in post-radiotherapy prostates and treatment naïve glands. This is reflected in the sensitivity of 78 - 83%, specificity of 62 – 86%, PPV of 62 – 83% and NPV of 78 – 86% if all cancer is considered significant in post-radiotherapy treated prostates, compared with values of 93 – 100% (sensitivity), 58 – 74% (specificity), 45 – 58% (PPV) and 96 – 100% (NPV) when only cancer cores ≥ 3mm were considered significant in the post-radiotherapy setting.

A similar picture is seen in the treatment naïve setting, where when all cancer is considered significant: sensitivity 40% - 58%, specificity 77-84%, PPV 71 – 82%, NPV 59 – 65% and AUC accuracy (64 – 73%). With an increase in threshold of what constitutes significant cancer to any Gleason 3+4 disease or any cancer core length ≥ 4mm (Definition 2), values were: sensitivity 58 – 73%, specificity 71 – 84%, PPV 49 – 63%, NPV 84 – 89% and AUC accuracy 73 – 84%. With a further increase in the threshold to any Gleason ≥ 4+3 or any cancer core length ≥ 6mm (Definition 1) values were: sensitivity 64 – 81%, specificity 68 – 80%, PPV 35 – 45%, NPV 91 – 95% and AUC accuracy 0.72 – 0.82).

Thus, as the threshold for clinically significant cancer rises, the sensitivity and NPV improve, with loss of PPV.

By using an imaging triage tool such as mp-MRI it may be possible to avert the need for a biopsy in men with a negative mp-MRI. However, in order for this to

be adopted a prospective study with larger numbers of men would need to be performed to allow meaningful analysis at a whole gland level. If such a study showed a comparable NPV then it may be argued that in the presence of a negative mp-MRI men could opt not to have a biopsy.

One of the potential advantages of using mp-MRI especially in the diagnostic setting before biopsy involves the possibility of not diagnosing men with non-life threatening prostate cancer (i.e. low risk low volume disease), as reflected by the lower sensitivity for detecting all cancer. This may in turn reduce diagnosis of clinically insignificant cancer and results in reduced over-treatment. Such a reduction in over-treatment could save patients from potential complications relating to impotence and incontinence as well as reduce the burden on healthcare systems (by reducing both the number of men being diagnosed and treated and also reducing the resources needed to manage after-effects of treatment).

8.3 Implications of Increasing mp-MRI use in the prostate cancer diagnostic pathway

8.3.1 Cost and Resource Implications

One of the main concerns regarding the implementation of mp-MRI into the prostate cancer diagnostic pathway is that of cost.

In the UK, diagnostic MRI imaging of the prostate using T2-MRI, DW-MRI and MRS are all coded as HRG RA01Z (MRI of one area without contrast) with a national average reference cost of £174, and MRI using DCE is coded as RA03Z (MRI one area pre- and post-contrast) with a national average NHS reference cost of £229 (150).

This recent Health Technology Assessment (HTA) in 2013 also gave an indication of relative staff and equipment costs per patient for a variety of combined sequences to give an idea of the differential costs:

(a) T2-MRI alone (Total cost per patient £106.29):

- Staff cost per patient (2 radiographers and 1 consultant radiologist) = £53.38 and equipment cost per patient = £46.90

(b) T2-MRI + DW-MRI (Total cost per patient £141.30)

- Staff cost per patient (2 radiographers and 1 consultant radiologist) = £74.75 and equipment cost per patient = £60.65

(c) T2-MRI + DCE-MRI (Total cost per patient £189.71)

- Staff cost per patient (2 radiographers and 1 consultant radiologist) = £83.81 and equipment cost per patient = £71.21

(d) T2-MRI + DW-MRI + DCE-MRI (Total cost per patient £239.06)

- Staff cost per patient (2 radiographers and 1 consultant) = £116.02 and equipment cost per patient = £88.42

The 2013 HTA analysed the potential cost-benefit (using Markov modelling), of using MRI prior to repeat prostate biopsy in men who have already had one set

of negative biopsies. This estimated that there are around 41000 repeat biopsies per year in the UK and the additional cost to the NHS if all of these men had mp-MRI prior to repeat biopsy would equate to roughly £8 million. In men who have had negative prostate biopsies who require re-biopsy (assuming a disease prevalence of 24%), the HTA economic modelling suggested that T2W MRI prior to repeat biopsy may be cost-effective in comparison to systematic TRUS guided extended-core biopsies, and suggested that it could negate the need for 55% of men without cancer having to undergo repeat biopsy. Magnetic resonance spectroscopy imaging (MRSI) did not prove to be cost-effective in the modelling, but did calculate to be potentially cost-effective if the cost of TRUS biopsies was increased to £298 or if MRSI was modelled to detect all moderate and high risk cancer (only missing low risk disease) – in keeping with studies showing correlation between MRSI positivity and tumour Gleason scores. They were not able to provide accurate modelling of DW-MRI, but given its lower cost compared to MRSI the authors suggested that DW-MRI could represent a cost-effective approach if it had similar sensitivity to MRSI (92%) and specificity similar to T2 weighted imaging (55%).

In the UK, MRI is widely used to evaluate the stage of prostate cancer, with most centres having 1.5T scanners and some teaching hospitals having 3T scanners, with endorectal coil usage not normally used, and very few centres in the UK with MR spectroscopy experience. Thus, this recent HTA assessment would seem to suggest that at least T2W-MRI should be considered prior to repeat biopsy in men who have already had one set of negative biopsies.

Recently De Rooj et al (151) conducted a cost-effectiveness model comparing MRI-guided prostate biopsy with conventional TRUS guided biopsy, using a decision tree and Markov model for men with an elevated serum PSA (> 4 ng/ml). They found that the MRI strategy was cost effective in diagnosing prostate cancer compared with the TRUS guided biopsy strategy, assuming a sensitivity of ≥ 20% with MRI guided biopsy. The authors did not include costs of treatment or biopsy complications in their model and thus the cost-effectiveness found was likely to be a conservative estimate. Furthermore, this model used mp-MRI prior to further MR imaging at the time of biopsy to guide the needle. One would assume that if mp-MRI were used merely to guide the

biopsy strategy (i.e. the clinician directing the biopsy needle using the previous mp-MRI imaging to regions of suspicion, and not sampling regions with low suspicion) at the time of TRUS biopsy, the cost-benefit would be greater still.

Thus, although the idea of routinely performing mp-MRI prior to prostate biopsy may be met with resistance by those who commission and pay for healthcare, there is certainly evidence from an initial HTA assessment that it may well be beneficial in the patient population who have already had one negative prostate biopsy.

Further evidence suggests that real-time mp-MRI guided prostate biopsies may be more cost effective than conventional TRUS biopsies in a 'biopsy-naïve' setting. Given that targeted TRUS biopsy of mp-MRI positive regions would be cheaper than a real-time MRI-guided strategy, it would seem reasonable to hypothesise that this would also prove to be cost-effective. Further health-economic modelling is required in future studies to evaluate this diagnostic pathway to confirm this, and ideally such an evaluation would investigate the cost-effectiveness of each mp-MRI sequence combination (e.g. T2-MRI alone, T2 + DCE, T2 + DWI, T2 +DCE + DWI), to assess whether costs could be kept low by using a minimum combination of sequences. One would also assume and hope that as technology develops, mp-MRI will hopefully become cheaper to acquire and run (e.g. as 3T MRI scanners become more common, 'older' 1.5T machines will become cheaper to purchase).

8.3.2 Implications for biopsy strategy (initial and repeat biopsy setting)

The studies evaluating the use of mp-MRI in detecting and ruling-out prostate cancer in this thesis, suggest that mp-MRI may be used as an initial triage test to help direct biopsy strategy. Given that a significant proportion of tumours within the prostate may lie anteriorly and therefore evade adequate sampling, it seems reasonable to have an initial imaging test to identify those men who may have identifiable disease anteriorly that may be better sampled with up front transperineal biopsy, rather than conventional transrectal biopsy. The negative predictive value of mp-MRI (based on a quadrant analysis), for ruling out

significant cancer, would suggest that a selective biopsy strategy may also be possible by not sampling regions of interest with low suspicion (score ≤ 2) on mp-MRI. This will in turn reduce pathology processing burden, reduce patient discomfort during TRUS biopsy (the procedure will be shorter with fewer needle punctures of the prostate), and may reduce the risk of biopsy related infection.

Mp-MRI guided targeted prostate biopsy may be offered as a real-time procedure in some research units, although this has substantial financial and time costs, and this is not a realistic practical option currently. An achievable change in the diagnostic pathway is to use ‘cognitive’ targeting of suspicious regions in the prostate on TRUS biopsy after examining the mp-MRI. Such visual cognitive registration of mp-MRI suspicious regions to the equivalent region in the prostate is possible now with some additional training. In the future computerised registration software (taking into account prostate gland deformity and change in shape caused by the TRUS probe) may automatically be able to superimpose mp-MRI images to corresponding TRUS imaging, to accurately target lesions. Such mp-MRI / TRUS fusion imaging has been recently reported by Rastinehad et al (152).

It would also seem reasonable to offer men who have had previous negative prostate biopsies with persistently elevated or rising PSA, mp-MRI prior to repeat biopsy. The results in this thesis and the recent HTA assessment would seem to suggest that this practice should be routinely adopted in all units with access to MRI. Such a stance is advocated by the recently updated NICE guidelines (153), which actually advise the use of T2-weighted and DW-MRI (i.e. without DCE MRI), in assessing men with previously negative prostate biopsies: NICE advises that clinicians should consider mp-MRI (using T2- and diffusion-weighted imaging) for men with a negative transrectal ultrasound 10–12 core biopsy to determine whether another biopsy is needed. Another biopsy should not be offered if the mp-MRI (using T2- and diffusion-weighted imaging) is negative, unless there are any other associated risk factors.

Within the previously irradiated prostate, the results in this thesis show that mp-MRI can be used to detect suspicious lesions within the prostate, and reliably rule-out areas of significant volume disease. Again, in this population of men

with potential rectal post-radiotherapy changes, it would seem reasonable to try and reduce the number of transrectal needle punctures to investigate possible localised recurrence, by performing targeted limited biopsy (based on prior mp-MRI imaging).

Introduction of mp-MRI into the diagnostic pathway is not without additional initial cost to individual departments (as discussed in earlier), but would appear to potentially have a cost-benefit to healthcare systems.

8.3.3 Active Surveillance monitoring of measurable disease

Mp-MRI prior to initial biopsy would allow a baseline assessment of the prostate at diagnosis. Men who choose to go onto an active surveillance pathway will therefore have the benefit of having serial mp-MRI imaging to track any changes in volume of measurable disease / discrete lesions as well as the emergence of any new lesions on imaging. As discussed earlier the use of quantitative parameters (such as ADC values) could also allow potential disease progression to be tracked. Mp-MRI may therefore serve as a non-invasive imaging biomarker in conjunction with PSA dynamics to closely and reliably detect men for prostate cancer disease progression if they initially choose active surveillance. Again the recently updated NICE guidelines on prostate cancer have advised the use of mp-MRI at enrolment into active surveillance and that patients should be re-assessed with repeat mp-MRI and / or biopsy if there is concern about clinical or PSA changes at any time during active surveillance (153).

8.3.4 Treatment implications

The development and use of ablative technologies, such as high intensity focussed ultrasound (HIFU), cryotherapy and photodynamic therapy have allowed the concept of focal therapy to be performed in trial settings. Such focal ablation of areas of the prostate with cancer, whilst leaving regions without cancer untreated, results in reduced impotence rates and incontinence rates when compared with the current standard treatments of radical prostatectomy and external beam radiotherapy.

Such focal treatments require a good imaging modality to help guide treatments in conjunction with TPM biopsies. Mp-MRI with its potential ability to identify clinically significant tumour lesions and exclude significant cancer from other areas of the prostate provides a good imaging platform to help guide focal therapy. Mp-MRI is also needed in follow-up of such patients, in order to be able to visually demonstrate destruction or necrosis and then subsequent fibrosis in the treated cancerous areas of the prostate. Localised recurrence may then

also be detected with mp-MRI, much in the same way as localised recurrence in the post-radiotherapy setting, as demonstrated in this thesis.

8.4 Conclusion

The results in this thesis suggest that mp-MRI should play a role in the diagnostic evaluation of men suspected of having prostate cancer prior to having prostate biopsy. Mp-MRI also has the potential to detect and rule-out localised prostate cancer recurrence with good accuracy and with the emergence of 3T scanners, the performance of mp-MRI is set to improve further.

Mp-MRI can aid the clinician towards a more targeted and selective biopsy strategy, and may have a role as a triage test to prevent biopsy at all in some men, although further studies are required to evaluate this. Mp-MRI will also help in directing focal ablative prostate cancer treatments and to monitor post-focal ablation follow-up.

The potential role of mp-MRI in the prostate cancer diagnostic pathway has been highlighted by the results in this thesis, but would need to be evaluated in a prospective manner in future studies. Such a trial is currently underway: PROMIS Prostate MRI Imaging Study (MRC PR11) – “Evaluation of Multi-Parametric Magnetic Resonance Imaging in the Diagnosis and Characterisation of Prostate Cancer”, aiming to recruit 714 men across 6 – 9 centres with all men having mp-MRI prior to then having TPM biopsy (reference test) and standard TRUS guided biopsy (standard test) at the same time under general anaesthesia. This will also allow a direct comparison of mp-MRI and TRUS biopsy. This study will also evaluate the cost-effectiveness of an mp-MRI based diagnostic pathway.

Research into prostate mp-MRI has advanced substantially in the last 10 years, and the future of this area is exciting.

Future research should concentrate on harnessing quantitative information from mp-MRI to create computer assisted diagnostic software, to help radiologists in reporting mp-MRI. Such technology in combination with sub-specialist training in prostate mp-MRI may help to improve inter-reporter variability and hence consistency in reporting. Quantitative information may also enable mp-MRI to be used to predict aggressiveness of potential tumour lesions identified, and

thus also have a role in the active surveillance population. The evolution of mp-MRI / TRUS fusion technology will also improve the initial diagnostic assessment of patients.

Further evaluation of the sequence components of mp-MRI should be undertaken in order to assess whether DCE-MRI is needed, with the aim to reduce scanning time (and hence increase capacity), prevent the need for IV administration of gadolinium contrast (with the rare risk of nephrogenic systemic fibrosis in patients with renal impairment) and reduce costs, by using only T2 and DW imaging.

Thus, consistent prospective randomized trial data from a variety of institutions is required to verify the results found in this thesis. Such studies may involve randomizing men with raised PSA to alternative diagnostic protocols (standard systematic TRUS biopsy vs mp-MRI followed by targeted biopsy) to assess differences in cancer detection rates. Such a study was conducted recently by Panebianco et al (154). Such randomization may also allow longer term follow-up of men with negative initial TRUS biopsy vs men with negative initial mp-MRI (who therefore did not go on to have biopsy), to compare the re-investigation rate and incidence of significant prostate cancer found on subsequent re-investigation. Such prospectively gathered trial data will be important when advocating the role of a negative mp-MRI in avoiding biopsy in men with raised PSA.

CHAPTER 9

REFERENCES & APPENDIX

9.1 REFERENCES

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9.2 APPENDIX

RADIOLOGIST MP-MRI REPORTING PROFORMA FOR TREATMENT NAÏVE STUDIES

RADIOLOGIST REPORTING PROFORMA FOR POST-RADIOTHERAPY MP-MRI STUDY

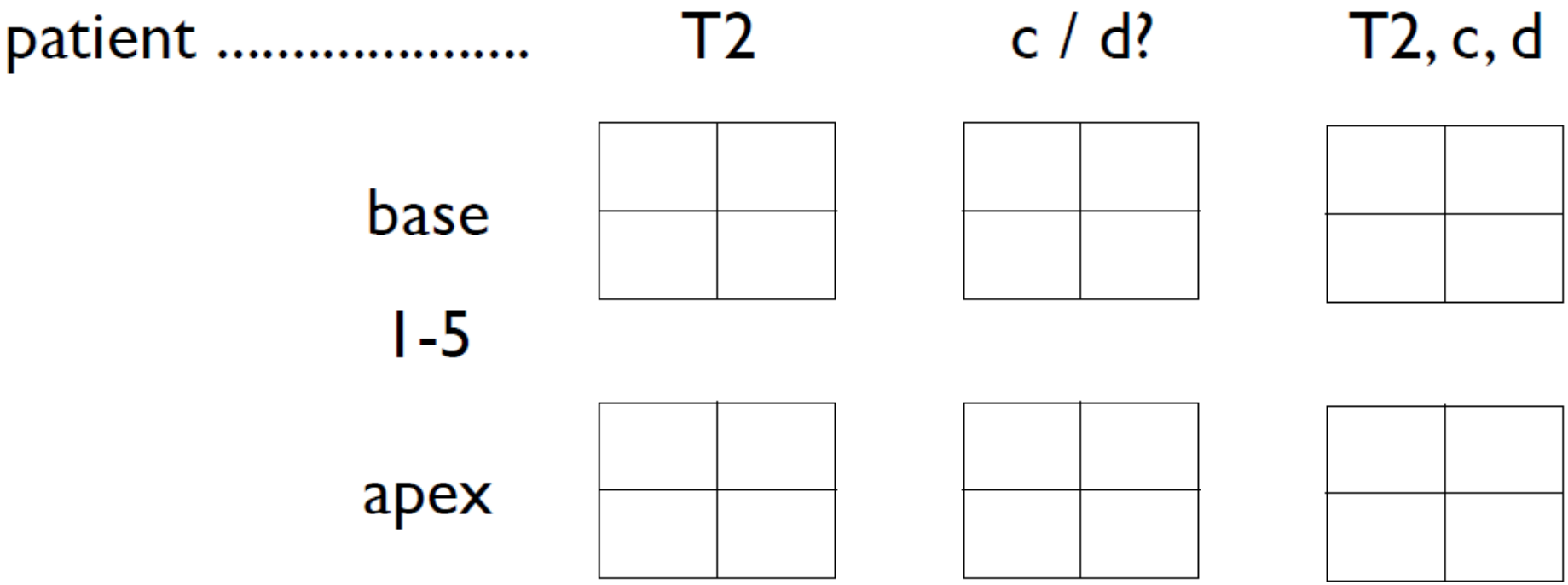
GRID POINT HISTOLOGY RECORDING PROFORMA

BARZELL HISTOLOGY RECORDING PROFORMA

ETHICS LETTER

PUBLICATIONS FROM THESIS WORK

RADIOLOGIST MP-MRI REPORTING PROFORMA FOR TREATMENT NAÏVE STUDIES



RADIOLOGIST REPORTING PROFORMA FOR POST-RADIOTHERAPY MP-MRI STUDY

Patient Number:

Score 1 – 5

	Right	**Left**
Anterior		
Posterior		

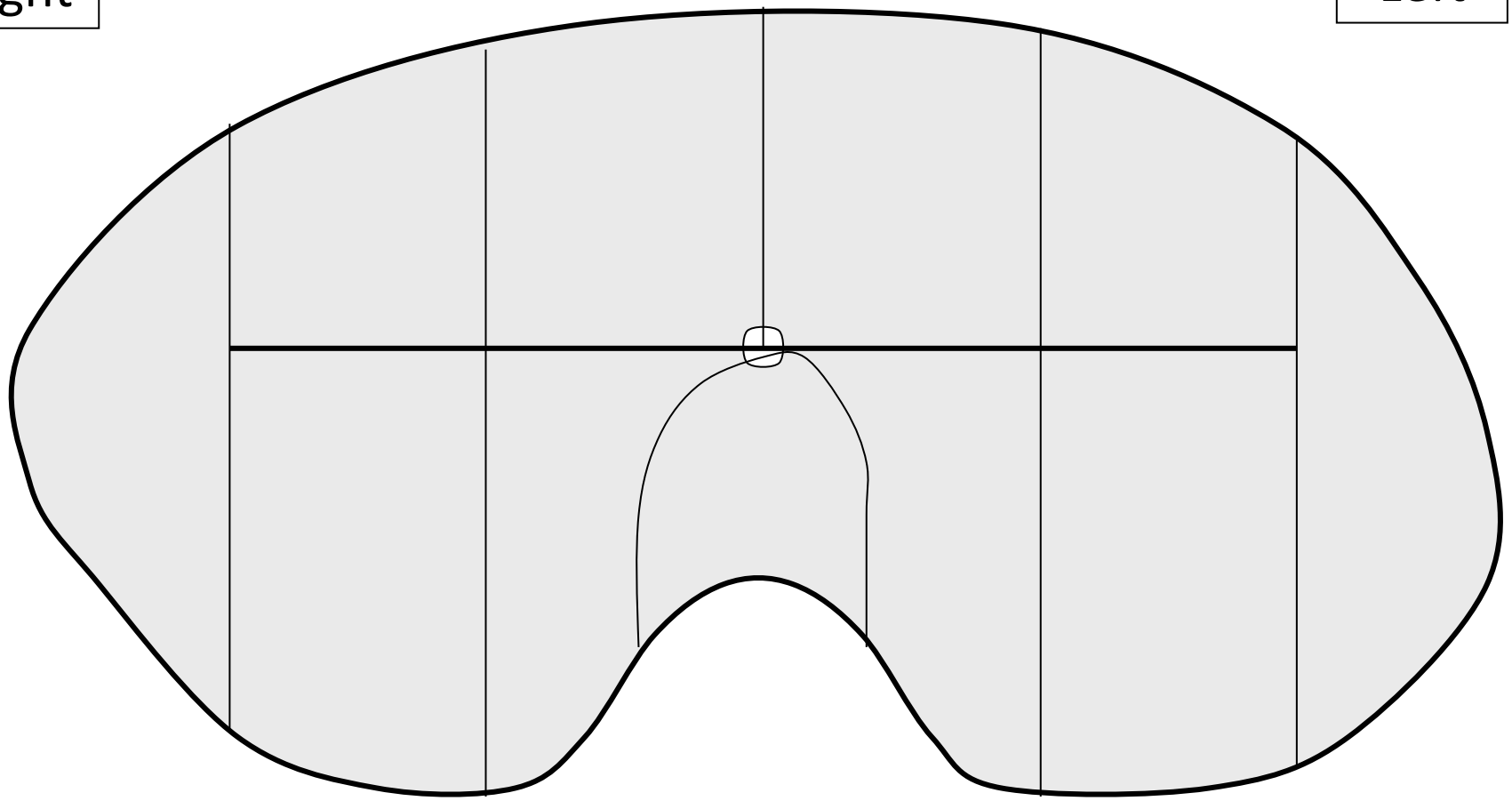
Grid Point Histology Recording Proforma

5.5												
5												
4.5												
4												
3.5												
3												
2.5												
2												
1.5												
1												
	A	**a**	**B**	**b**	**C**	**c**	**D**	**d**	**E**	**e**	**F**	**f**

Barzell Zone Histology Recording Proforma

Right

Left



DETAILS

Hosp No: