MONASH University

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

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MBBS (hons), Grad. Dip Anatomy.

A thesis submitted for the degree of *Doctor of Philosophy* at

Monash University in 2020.

Faculty of Medicine, Nursing and Health Sciences.

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Abstract

There is evidence that multiparametric prostate MRI (mpMRI) is superior to the incumbent prostate cancer detection paradigm of prostate specific antigen (PSA) tests triaging random ultrasound (US) guided biopsies. MpMRI diagnoses greater numbers of clinically significant disease, with fewer false positives and is non-invasive. These advantages are anticipated to be reflected in widespread demand for mpMRI in the future. In this context, the false negative rates of mpMRI must be clearly understood. Using three separate comparator tests, the false negative rate was calculated at 7.5% (radical prostatectomy), 18% (transperineal template biopsy) and 19.5% (hemigland analysis) respectively. Tthe causes and histopathological characteristics of these missed tumours were analysed. Our studies broadly agree with the wider literature that multiple factors (such as scan artefacts and tumour characteristics) contribute to wide variations in reporting accuracy. However this thesis established that the most significant factor in reporting accuracy is the prior experience of the reporting radiologist. This was assessed using a novel online case-bank that isolated the radiologist's prior experience as the only variable of interest. Radiologist accuracy was found to vary widely and correlated with their degree of prior experience. This finding may partially explain the wide variation in mpMRI accuracy described in literature and additionally implies a prerequisite level of experience is required for satisfactory mpMRI accuracy in clinical practice. The possibility of removing the contrast series component of mpMRI was examined (termed biparametric MRI); and our retrospective analysis suggested that removing the contrast study did not result in any statistically significant differences in tumour detection.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature:

Print Name:
Dr. Rowan James Sinclair Miller

Date:
4/10/2020

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes (*4)* submitted publications. The core theme of the thesis regards establishing and improving the accuracy of Multiparametric Prostate MRI in detecting clinically significant disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the (*Faculty of Medicine, Nursing and Health Sciences*) under the supervision of (*a/Prof Jeremy Grummet* and Prof. Mark Frydenberg).

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of *chapters 1, 2 3, and 4,* my contribution to the work involved the following (over-page):

	Publication Title	Status	Student contribution	Co-authors	Co-author(s), Monash student
1	**Sensitivity and Negative Predictive Value of Multiparametric Prostate MRI Against Whole Mount Radical Prostatectomy Specimens by Performing Hemigland Analysis**	*Submitted to the American Journal of Radiology*	*85%. Concept, data collection and writing first draft*	*1) a/Prof Jeremy Grummet, input into manuscript 4%* *2) Prof Mark Frydenberg, input into manuscript 3%* *3) Dr. Richard O'Sullivan, input into manuscript 3%* *4) a/Prof Andrew Whan, input into manuscript 3%* *5) Dr. Andrew Ryan, data analysis 2%*	*No*
2	**An MRI-Histopathology Correlated Analysis of Missed Prostate Cancers Amongst Expert Radiologists.**	*Submitted to the American Journal of Radiology*	*85%. Concept, data collection and writing first draft*	*1) a/Prof Jeremy Grummet, input into manuscript 4%* *2) Prof Mark Frydenberg, input into manuscript 3%* *3) Dr. Richard O'Sullivan, input into manuscript 3%* *4) a/Prof Andrew Whan, input into manuscript 3%* *5) Dr. Andrew Ryan, data analysis 2%*	*No*
3	**A Radpath Correlated Evaluation of the Prostate MRI Learning Curve amongst 50 Radiologists: How Does Experience Affect Reporting Accuracy?**	*Submitted to the American Journal of Radiology*	*85%. Concept, data collection and writing first draft*	*1) a/Prof Jeremy Grummet, input into manuscript 4%* *2) Prof Mark Frydenberg, input into manuscript 3%* *3) Dr. Richard O'Sullivan, input into manuscript 3%* *4) a/Prof Andrew Whan, input into manuscript 3%* *5) Dr. Andrew Ryan, data analysis 2%*	*No*

4	**Retrospective Comparison of Biparametric vs Multiparametric MRI: what is the marginal benefit of contrast in prostate cancer detection amongst biopsy naive men?**	*Submitted to the American Journal of Radiology*	*85%. Concept, data collection and writing first draft*	*1) a/Prof Jeremy Grummet, input into manuscript 4%* *2) Prof Mark Frydenberg, input into manuscript 3%* *3) Dr. Richard O'Sullivan, input into manuscript 3%* *4) a/Prof Andrew Whan, input into manuscript 3%* *5) Dr. Andrew Ryan, data analysis 2%*	*No*

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis. Specifically, individual reference lists were merged into a single reference list, presented at the end of the thesis.

Student name: Dr. Rowan James Sinclair Miller

Student signature: **Date:** 4/10/2020

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Mr. Jeremy Grummet

Main Supervisor signature: **Date:** 27.10.20

Acknowledgements

This research was supported by a research scholarship from the Barwon Health Foundation, to whom I am genuinely grateful. I hope that the findings of this thesis underscore tangible, real-world improvements in prostate cancer care; closely aligned to the Foundation's goal of improving the Health of the Community.

The prior work of Dr. Sean Huang must be acknowledged, who created the research database this thesis heavily relied upon, without which this thesis could not have been undertaken, thankyou;

The support of a/Prof. Andrew Whan at Barwon Medical Imaging must be acknowledged - your support in promptly reviewing publications was very much appreciated and always insightful, thankyou;

The guidance of a/Prof Richard O'Sullivan, in tirelessly reviewing publications, resulted in step-change improvements to each successive draft, thankyou;

Finally to a/Prof Jeremy Grummet and Prof Mark Frydenberg - for keeping me on track (as best as possible), endlessly sound-boarding, and setting aside time for their supervisory duties, amidst an abundance of other commitments; i am very appreciative and extremely grateful for your supervision, thankyou.

List of Abbreviations

ADC Apparent Diffusion Coefficient

bpMRI Biparametric Magnetic Resonance Imaging

BPH Benign Prostatic Hypertrophy

CZ Central zone

DWI Diffusion Weighted Imaging

EAU European Association of Urology

GG International Society of Urogenital Pathology Grade Group

ISUP international Society of Urogenital Pathology

MCCL Maximum Cancer Core Length

mpMRI Multiparametric Magnetic Resonance Imaging

MRI Magnetic Resonance Imaging

PI-RADS Prostate Imaging-Reporting and Data System

PZ Peripheral Zone

T2 T2 Weighted Imaging

US Ultrasound

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CHAPTER 1:

Literature Review

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

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CHAPTER 1: LITERATURE REVIEW

Clinically Relevant Prostate Anatomy

Situated at the base of the bladder, the prostate is a roughly almond sized bilobed gland of the male reproductive system. It serves to produce secretions that support the liquefaction semen and support sperm motility. As such, the gland is histologically composed of secretory acini supported within a fibromuscular matrix [1]. The gland is contained by a pseudocapsule: an outer layer of collagen and inner layer of smooth muscle [2]. Acini secrete into larger ductules which originate centrally and then radiate to the periphery of the gland, running parallel to the hemigland capsule: this morphology means the secretory units and glands are distributed mostly in the periphery and explains why adenocarcinoma has a predominance for the peripheral gland[1].

The prostate is divided into 4 zones: the central zone, transition zone, peripheral zone and anterior fibromuscular stroma [3]. Whilst the names of each zone imply that their division is on an anatomical basis (i.e their location within the gland), they also have differing embryological origins, unique histology, spectra of pathology [4] and differing appearances on multiparametric MRI.

The Central Zone

The central zone (CZ) is located in the superioposterior sagittal quadrant of the gland. It wraps around the ejaculatory duct of the seminal vesicles; with both the vesicles and central zone being embryological derivatives of the wolffian duct [5]. In men without benign prostatic hypertrophy, it contains around 25% of the glandular tissue, but only around 5-7% of prostatic adenocarcinoma originates here [1] [5]. As the degree of benign prostatic hypertrophy increases, the central gland then comprises a smaller fraction of the total glandular tissue. BPH will increase gland size by around 0.4cc per year [6]. Hence by 60 and 80 years of age respectively, the central gland comprises closer to 18% and 15% of total glandular tissue respectively. Stroma is densest in the central zone, which has implications for the ease of tumour discovery and explains its low signal appearance on T2 weighted imaging.

The Peripheral Zone

As the largest zone - extending from base to apex - in non BPH affected glands, the peripheral zone contains approximately 70% of the glandular tissue and gives rise to around 70% of prostatic adenocarcinoma [7]. However by 60 and 80 years of age, the impact of BPH means the peripheral

zone comprises closer to 52% and 42% of total glandular tissue respectively, although there is wide variation in men due to the variable degree of benign prostatic hypertrophy. The peripheral zone extends from the base to the apex along the posterior surface, surrounding the distal urethra inferiorly. This zone is palpated during a digital rectal exam. It consists of loose fibromuscular stromal architecture, widely spaced smooth muscle bundles and high glandularity [8]. These histological features create a high signal on T2 weighted imaging.

The Transition Zone

The transition zone of the prostate is located within the superior half of the gland, anterior to the prostatic urethra. It contains approximately 5% of the glandular tissue but approximately 25% of prostatic adenocarcinoma originate from this location. In addition to this glandular tissue the transition zone consists of moderately compact fascicles of smooth muscle and relatively dense stroma (in between peripheral and central zone density)[8]. TZ tumours are typically lower grade: however higher grade tumours of the transition zone are more likely than peripheral tumours to have positive anterior and bladder neck margins at radical histoprostatectomy [9]. Benign prostatic hypertrophy almost exclusively originates in the transition zone,where hypertrophy of stromal or muscular tissue can both occur, creating nodules and compressing the adjacent urethra to cause urinary symptoms [10].

The Anterior Fibromuscular Stroma

The anterior fibromuscular stroma curves along the anterior aspect of the prostate. It's stroma interdigitates with muscular slips from the levator ani and bladder base [11] and peripherally the anterior fibromuscular stroma thins to continue as the prostatic pseudocapsule. There is no glandular content within the anterior fibromuscular stroma [1], and therefore no prostatic adenocarcinoma originates from within the anterior fibromuscular stroma itself. However adenocarcinoma may extend into the anterior fibromuscular stroma when it originates at its border, as the anterior fibromuscular stroma can be more conducive to tumour spread than the denser transition zone in which it originated [12].

Background: Prostate Cancer Overview, Histology and Epidemiology

With the exclusion of non-melanotic skin cancers, prostate cancer is the most prevalent malignancy affecting men in western countries [13]. In 2017, the 5 year Australian prevalence of prostate cancer was estimated at 94,114 males, with an approximate incidence of 16,665 new cases per year. On an age and population standardised basis, this reflects an incidence of 115 per 100,000 men and a mortality rate of 26 deaths per 100,000 men. In first world countries prostate cancer is the third leading cause of death [14] and on a global scale, prostate cancer is the fifth leading cause of cancer related deaths [15]. These statistics underscore the importance of effective *screening,* defined by the World Health Organisation as "the presumptive identification of unrecognized disease in an apparently healthy, asymptomatic population". Yet, at the commencement of this thesis, the paradigm of prostate cancer screening had remained unchanged since the introduction of prostate specific antigen (PSA) testing in the 1970's, despite advances in screening methods of the other burdensome visceral malignancies of lung, breast, cervical and colon cancer.

Throughout this thesis, prostate cancer refers specifically to prostate adenocarcinoma, the histopathological subtype responsible for 99% of prostatic malignancies. Like other adenocarcinomas, prostate adenocarcinoma arises from glandular tissue. Grading of prostate adenocarcinoma is traditionally based on the Gleason score, which categorises tumours based on their degree of glandular architectural disruption. The degree of architectural disruption is classified on a 1-5 scale, where (1) represents normal and (5) represents complete architectural disruption. The two most common patterns of architectural disruption within the gland are then summed for the overall score. The Gleason score correlates with the likelihood of metastasis, extraprostatic spread and overall cancer mortality, but multiple updates to the original system developed some 30 years ago - particularly the upgrading of "Cribriform" pattern 3 disease to pattern 4 - have replaced the Gleason system with a classification devised by the International Society of Urogenital Pathology (ISUP) termed "grade grouping", referred to hence forth as "grade" or the acronym 'GG' [16]. Grade Group increases with Gleason score - for example GG1, GG4 and GG5 correlate to Gleason 6, 8 and ≥ 9 disease respectively. However Grade Group additionally distinguishes between Gleason 3+4 disease (GG2) and Gleason 4+3 disease (GG3), because of differences in clinical outcomes (such as rate of metastases and disease specific mortality).

Clinically, the most important distinction is whether the disease is indolent. These two groups have entirely different prognoses, management and natural history. Cadaveric studies of men demonstrate a prostate cancer prevalence of 5% (95% CI: 3–8%) even before the age of 30 and approaching 60% (up to 59%) in men over 80 [17]. Yet the lifetime risk of clinically apparent disease is only 17%: an observation only explained by the hypothesis that there is a subgroup of

prostate cancer that displays extremely indolent characteristics [17]. This indolent prostate cancer subgroup corresponded histologically to Gleason 3+3 (6) disease (ISUP Grade Group 1). Before 2005, Gleason 6 cancers, whilst overwhelmingly considered benign, could not be treated as clinically insignificant due to persistent albeit, low rates of metastasis and death from these cancers. In 2005 ISUP made modifications to the Gleason scoring. These changes concerned some previously described pattern 3 disease being re-classified as pattern 4. This resulted in cases of lymph node metastases previously attributed to pattern 3 disease being reassigned to pattern 4. After this update, no cases of metastasis, nor seminal vesicle invasion from true pattern 3 disease have been demonstrated (Table 1). Thus, although Gleason 3 disease has the ability to erode locally through the prostatic capsule [18] and has a genetic signature of cancer, there is robust evidence it lacks metastatic potential. The ability of prostate Magnetic Resonance Imaging (MRI) to "appropriately ignore" Gleason 6 cancers is further discussed in 'Screening tests'.

Table 1: Summary of Clinical Outcomes in Large Scale Trials that evaluated for Seminal Vesicle Invasion or Metastases in Radical Prostatectomy confirmed Gleason 6 Prostate Cancer: The Results demonstrate that no cases of metastases nor Seminal Vesicle invasion were recorded.

Ref	Number of Radical Prostatectomy Cases of Histopathologically Confirmed Gleason 6 Disease Evaluated in Each Study	Reported Clinical Study Outcome Result	Percentage of Gleason 6 Patient's with that Clinical Outcome
[19]	2502	seminal vesicle invasion	0%
[20]	451	lymph node metastases	0%
[21]	14,123	lymph node metastases: 0 Gleason 6	0%

Prostate Cancer: Defining Clinically Significant Disease

The literature review has identified that various authors and research groups define 'Clinically Significant Disease' differently. Not only does this introduce a source of heterogeneity (Table 2) in meta-analyses, but the various definitions require this PhD thesis to select a definition of clinically significant disease.

Table 2: Definitions of Clinically Significant Prostate Cancer within landmark prostate MRI papers. Landmark papers have been cited in the "Study" column, and their definition of Clinically Significant Disease is summarised in the second column. Tumour Volume was calculated from radical prostatectomy specimens, unless specifically stated.

Study	**Clinically Significant Prostate Cancer Definition**
Wolters et al 2011 [22]	Any Grade Group 4 or 5, largest tumour volume > 1.3 cm^3
Stamey et al 1993 [23]	Organ-confined tumours of >0.5 cm^3 Gleason 3+3
PROMIS Trial 2017 [24]	Gleason ≥4 + 3 or more, or a maximum cancer core length (MCCL) involvement of 6 mm or more in any location
Precision Trial [25] 2018	At least a single biopsy core indicating disease of Gleason score 3+4 or higher.
PI-RADS Working Committee 2012,2015 [26]	Gleason score ≥7 (including 3+4 with prominent but not predominant Gleason 4 component), and/or volume ≥0.5cc, and/or extraprostatic extension (EPE)

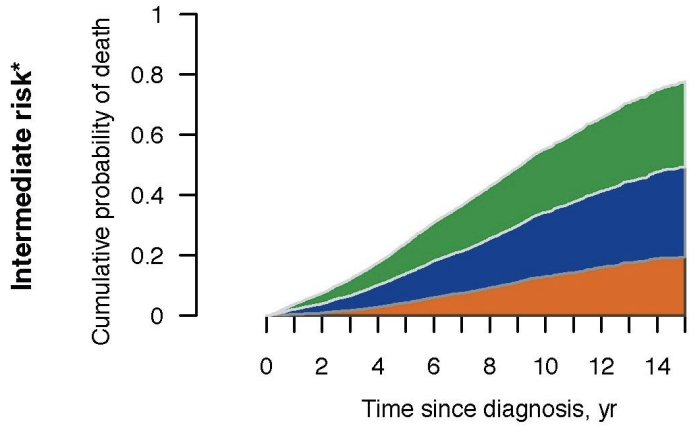
As the table above demonstrates, the definition of clinically significant disease requires two key considerations. Firstly, should tumours have a minimum volume, such as the Stamey et al definition (requiring 0.5 cm^3), the Wolters et al definition (at least 1.3cm^3) or the PI-RADS Working committee definition (volume of ≥0.5cc). Secondly, should the minimum grade of clinically significant cancer be defined by Gleason 3+3=6 disease (Stamey et al), Gleason 3+4 = 7 disease (PI-RADS Working Committee) or even Gleason 4+3 = 7 disease (PROMIS Trial).

Regarding the latter question, there is ample evidence from large scale studies that Gleason 3+4 disease has a material mortality rate.To exclude Gleason pattern 3+4 disease would be to exclude a large number of patient's, some of whom certainly demonstrate a disease related burden;

A retrospective analysis of 2,323 patients with localized GS 3+4 prostate cancer who underwent a radical prostatectomy between 2005 and 2013 from 6 academic centres found that 46% of patients with biopsy GS 3+4 cancer had unfavourable disease at final pathology [27].

In a large scale, 20 year follow up of 76,437 patients in the Swedish prostate cancer registry, when managed with non-curative intent, intermediate-risk PCa, defined as Gleason score of 7 (either 3+4 or 4+3), is associated with 10-year and 15-year prostate-cancer-specific mortality rates of 13 and 19.6%. [28]

FIGURE 1: Graph from "Long-term Outcomes Among Non-curatively Treated Men According to Prostate Cancer Risk Category in a Nationwide, Population-based Study.



Area under the curve represents the cumulative probability of death from prostate cancer (orange), cardiovascular event (blue) and all other causes (green). Patients in this study were sub-grouped into "low", "intermediate" and "high" risk cancer groups, where biopsy confirmed Gleason Grade 7 disease was intermediate risk (Ref: [28]**).**

Research indicates that Gleason pattern 4 disease is predictive of survival time [29]. However, men with a low percentage of pattern 4 disease on biopsy nonetheless have a material risk of prostate cancer morbidity and mortality, especially on long-term follow-up. In a 20 year follow-up of patients in the Physicians' Health Study, Gleason grade 3+4 disease was associated with a mortality rate of 2.1 per 1000 person years vs. 6.3 per 1000 person years for Gleason grade 4+3.

This has been emphasized by the 2014 ISUP guidelines which differentiate Gleason score 7 prostate cancer into either Grade Group 2 for 3+4 disease or Grade Group 3 for 4+3 disease to crystallize the clinically significant outcomes between these two groups [30].

As Grade Group 3 has been conclusively demonstrated to lack metastatic potential (Table 1), this thesis defines any amount (by volume, cc) of Gleason 3+3=6, or ISUP 1 tumours as *clinically insignificant.* However, as Gleason 4 disease has definite metastatic potential - regardless of tumour size - any amount of Gleason 4 tumour within either biopsy specimen or prostatectomy has been considered *clinically significant* disease within the results presented in this thesis. No other surrogate markers of disease - such as PSA, PSA Density (PSAD) or apparent diffusion coefficient (ADC) values were considered in the definition of clinically significant disease (csPCa), which is defined exclusively by histopathological grading.

Overview of Incumbent Diagnostic Pathway

PSA Testing

Antigens specific to the prostate were first characterised in the 1960's before the development of the first reproducible prostate specific antigen assays in the 1980s ([21]. PSA assays are organ, but not disease specific [31]. The positive predictive value of a PSA test is heavily dependent on the length of follow up, threshold cutoff and population prevalence of prostate cancer. Most positive predictive values are in the range of 19.9 - 37% (FIGURE 2) [32]. Elevated PSA levels are further investigated by transrectal ultrasound guided biopsies (TRUS-Bx). A 2013 Cochrane review and meta-analysis of the 5 largest population based studies of this prostate cancer screening pathway demonstrated this had zero reduction in likelihood of prostate cancer specific mortality. However the same meta-analysis demonstrates clear proof of harm: For every 1000 men screened, 160 experienced an unnecessary biopsy (with an associated risk of urosepsis) and 20 received unnecessary treatment. In 2014, the prostate was the only organ in the body where the diagnosis of cancer was still made by blind biopsies [33] .

FIGURE 2: Schematic Distribution of PSA scores in Clinically Significant Prostate Cancer vs Normal Controls.

This graph illustrates the distribution of PSA in csPCA and normal controls. Two data sources evaluated the Positive Predictive Value (PPV) and false negative rate of a 4.0mg/ml threshold. 7.8% of patients in the prostate cancer prevention trial had csPCa despite a PSA level within the normal range. Of 1693 men within our local database, 15.7% had a positive biopsy result despite a PSA in the normal range (unpublished result). The PPV for csPCa was 21% in the Prostate Cancer Prevention Trial and 37% from our own local database.

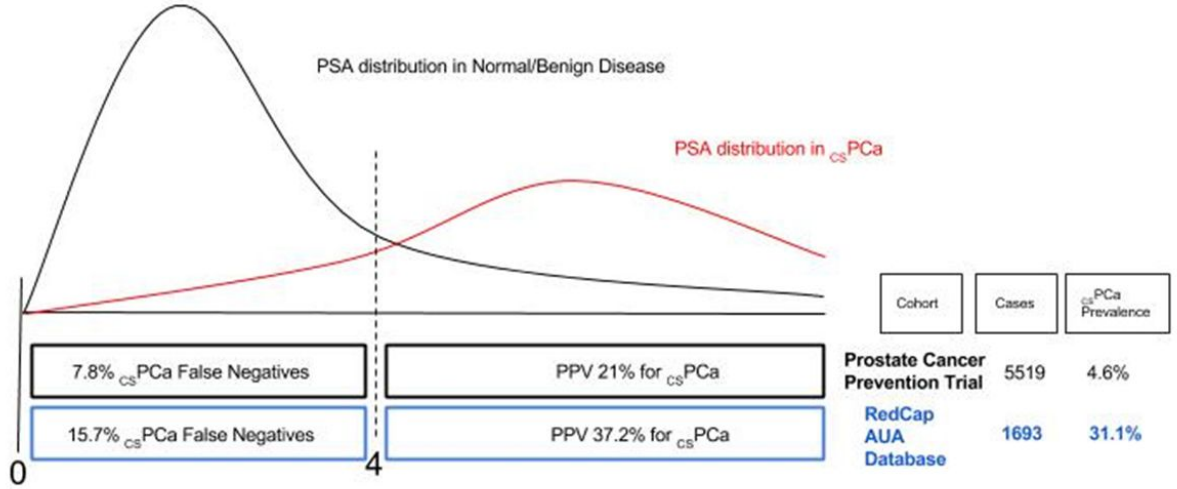


Table 2: Summary of United States Preventive Services Task Force Recommendations on PSA screening.

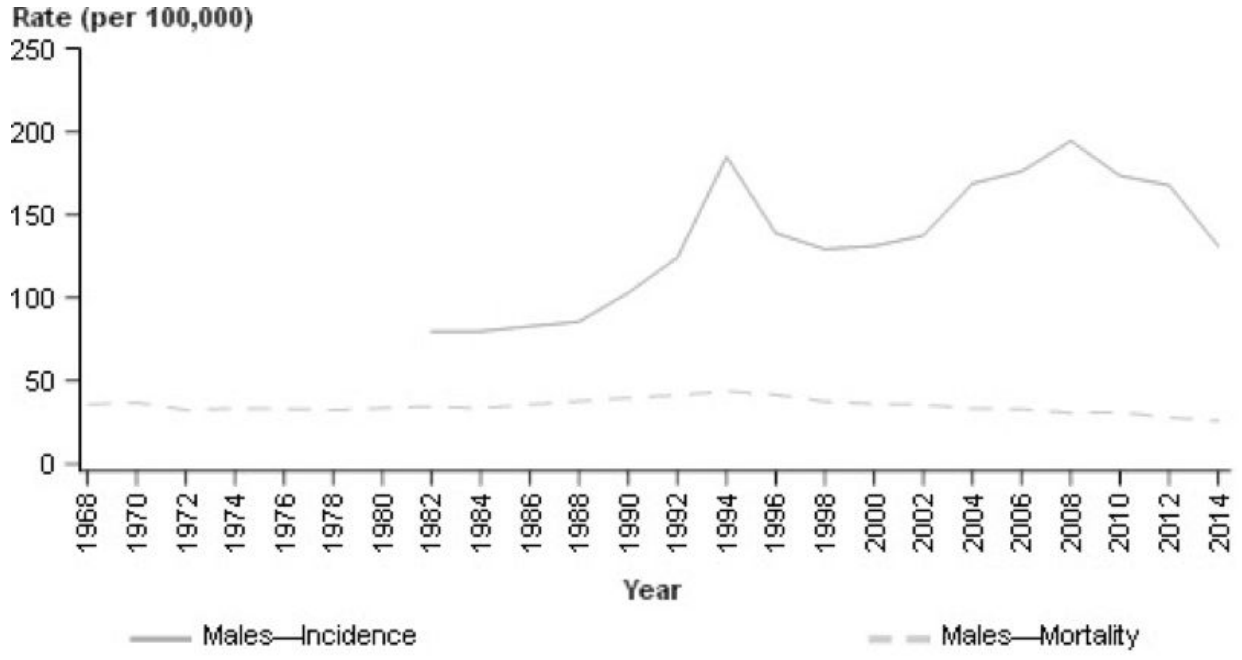
Year	United States Preventive Services Task Force Recommendation	Comments
2012-2017 [34]	Category D – Recommend Against	1. Overdiagnoses of insignificant disease. 2. Overexposes patients to biopsy risk. 3. Has at best "minimal" mortality benefit.
2017 [35]	Category C - Selectively Offer	1. Possible mortality benefit in younger men requires personalised approach.

TRUS Biopsy

The 2013 European Association of Urology (EAU) guidelines on prostate cancer screening describe transrectal ultrasound guided biopsy (TRUS-Bx) as one of the "main tools to diagnose PCa"[36]. In this method an ultrasound probe is introduced into the rectum and under imaging 10-12 core biopsies are taken in a systematic fashion.Trus-Bx demonstrably lacks in both sensitivity and specificity [37], as some tumours are simply not seen on ultrasound [38]. In a meta-analysis of more than 14,000 patients, 67% had either low or moderate cancer on biopsy despite having high grade cancer confirmed in their prostatectomy specimen ([39] In addition to low sensitivity, TRUS has high false-negative rates, 20-30%[40,41] and risk of urosepsis. The PSA - TRUS Biopsy pathway has not improved prostate cancer mortality (FIGURE 3)

FIGURE 3: Rates of prostate cancer Incidence (filled line) and mortality (dashed line) per 100,000 men.

The graph demonstrates that the introduction of PSA testing in the 1990's produced no change in mortality despite a large incidence increase. [42]



Background: Magnetic Resonance Imaging

Overview

Magnetic resonance imaging (MRI) produces images by exploiting a quantum physics property known as spin. Spin refers to an intrinsic and persistent angular momentum found in subatomic particles, which causes certain nuclei to have a small magnetic field, termed a magnetic or dipole moment [43]. Nuclei with odd atomic masses such as hydrogen have an overall charge, and the constant spinning of the charged particle creates an electrical current and an associated magnetic field [44][45]. Although a spinning top (in the real world) may possess angular momentum of a numerical quantity, quantum spin angular momentum must take discrete values, or spin states. The lower energy state is known as spin up, and a higher energy state known as spin down. Although there are several elements in the body such as ^{23}Na and ^{13}C that possess spin, ^{1}H, makes up around two thirds of all the atoms in our body and this abundance conveys the most sensitivity in clinical imaging [45][46][47]. The abundance of hydrogen atoms found mostly in water and fat is also the reason that MRI is considered an excellent soft tissue imaging modality, but produces no signal from pure cortical bone (as calcium lacks spin).

In the presence of an external magnetic field nuclei with spin undergo two processes. Firstly, the axis of the spins align with the axis of the external magnetic field[43]. In an MRI machine, the external magnetic field is created by a powerful magnet - typically 1.5 or 3 Tesla, which surrounds the bore in which patients are positioned. The spins can either be orientated along the axis in a low energy state “North-South”, termed spin up that aligns with the field, or a higher energy configuration, “South-North” (spin down) that aligns against the field [48]. The Boltzmann statistics

Formula One $N^-/N^+ = e^{-\Delta E/kT}$

$\Delta E = \gamma * B0 * h$

$N^+/N^- = e^{-(\gamma * B0 * h / kT)}$

(at 1 Tesla for H1 atoms at human body temperature)

$N^+/N^- \approx 1.0000066$ (Ref [49]))

[1] ΔE - the energy difference between the spin states;
k - Boltzmann's constant, 1.3805×10^{-23} J/Kelvin;
T - temperature in Kelvin, calculated at 310K (36.7 degrees Celsius, close to human body temp).
N^+ - number of spins in the lower energy level
N^- - number of spins in the upper level.
h - Plank’s constant, $h = 6.626 \times 10^{-34}$ J s
y - gyromagnetic ratio, For Hydrogen = 42.57 MHz (at 1 Tesla)
B_0 - 1 Tesla in this example

demonstrate that the number of spins in the lower level marginally outweighs the number of spins in the higher energy configuration: of 1 million hydrogen atoms at 1Tesla, there is only around 6 additional lower energy level nuclei [49] [45]. As a result of this slight spin state population difference, there is nonetheless an overall magnetic vector of the tissue, which at equilibrium is in the direction of the magnetic field [48]. The Boltzmann statistics can be used to describe that net magnetic vector for the tissue - as determined by the ratio of n-/n+ [50]. This is clinically significant because MRI signal strength is proportional to this ratio n-/n+, not the absolute number of spins. [48]. Nuclei undergo a second event under the influence of an external magnetic field - precession. This quantum phenomenon parallels that of a spinning top when it starts to wobble, with the nuclei precessing around the main magnetic axis of the external magnetic field. Nuclei precess at a frequency known as the larmour frequency, and this precession speed is defined by the larmour ratio.

Formula Two $f = \gamma B$

Hence precession frequency is seen to vary both amongst atomic species - due to their differing gyromagnetic ratios (γ) - and in proportion to B_o, the strength of the magnetic field[48,51]. Hydrogen for example has a gyromagnetic ratio of 42.58 MHz / T, and at a field strength of 1 Tesla (≈20,000 times larger than the earth's surface magnetic field), the proton Larmor frequency is 42.57 Mhz. Doubling the magnetic field to 2 T will increase the Larmor frequency to 85.14 MHZ [43]. At the magnetic field strengths of 1.5 T and 3 T (typically used in medical imaging), the Larmor frequency is 63.8 Mhz and 127.71 Mhz.

The basis of MRI is in imparting energy into hydrogen atoms that are aligned against an external magnetic field such that the spin state of some atoms flip, and then recording the emission of that energy amongst various tissues over time. In order to actually flip the spin state of hydrogen atoms , a radiofrequency pulse at the larmour frequency is required. Non-Larmor frequency radiowaves will change the precession speed, but will not flip the spin state[51].The spin states are only flipped when the hydrogen atoms absorb energy at their Larmor frequency, *or resonance* frequency, hence the '*resonance'* term in 'magnetic *resonance* imaging'. When the radiofrequency pulses stop, flipped hydrogen atoms fall back into the lower energy spin state, emitting energy in the process. This energy is recorded via the radiofrequency coils of the MRI machine.

The Accuracy of Prostate MRI in Diagnosing Prostate Cancer

In order to standardise the various scan parameters, scan sequences and moreover reporting methods that separate groups employed when performing Prostate MRI, in 2012 the PI-RADS (Prostate Imaging Reporting and Data System) standard was created. Essentially all Prostate MRI performed presently is based upon the PI-RADS scan protocol, which is defined as a combination of high-resolution T2-weighted images (T2WI), and at least two functional MRI techniques, Dynamic Contrast Enhancement (DCE) and Diffusion Weighted Imaging (DWI) +/- spectroscopy [26]. The PI-RADS system also created an objective framework for radiologists to report Prostate MRI studies, and its goal was to "diminish variation" in interpretation [26].

PI-RADS Version 2 was introduced in December of 2014 to allow a more standardised approach to prostate MRI reporting. Where PI-RADS Version 1 gave equal weighting to each imaging parameter. PI-RADS Version 2 defined dominant parameters for the transition (T2) and peripheral (DWI) zones. PI-RADS Version 2 also removed the equal weighting of the contrast assessment, and lessens its role to that of equivocation of PI-RADS 3 lesions on DWI for the peripheral zone [52] The authors noted that "the added value DCE is not firmly established, and most published data show that the added value of DCE over and above the combination of T2W and DWI is modest" [52]. Moreover PI-RADS Version 2 was based on expert consensus, and the authors noted that "PI-RADS Version 2 needs to be tested and validated for specific research and clinical applications".

In this context, a literature search was performed using Medline, Embase, Pubmed, the Cochrane Library and Google Scholar with the aim of evaluating the accuracy of prostate cancer detection according to PI-RADS Version 1 and PI-RADS Version 2, respectively.

Search Structure
(mri (title) OR mpmri (title) OR magnetic resonance (title)**)** AND (prostate(title) OR prostatic(title) OR PI-RADS) AND (meta-analysis).

Search Dates: 1990 - February 2019.

A consistent theme across all studies and meta-analyses was the statistically significant relationship between the PI-RADS grade and likelihood of clinically significant prostate

cancer[53],46,47,48,49,50,51,52), as evidenced by Mehralivand et al, where the cancer detection rate for PI-RADS , version 2 was 0%, 9.6%, 12%, 22.1% and 72.4% for clinically significant prostate cancer, respectively [[54].

In 2015, the year that PI-RADS v2 was released, meta-analysis of 14 studies and 1785 patients demonstrated sensitivity of 0.84 (95% CI 0.76–0.89) and specificity of 0.75 (95% CI 0.66–0.83) for detection of clinically significant prostate cancer based on the PI-RADS Version 1 reporting system [53]. Clinically significant cancer was defined as any pattern 4 disease with the samples. A second meta-analysis released just prior demonstrated sensitivity and specificity in a similar range (0.78 and 0.79 respectively)[55]. In evaluating these meta-analyses (and hence in forming an assessment of the diagnostic accuracy of PI-RADS Version1 against PI-RADS Version 2, at least 2 pertinent considerations exist: firstly that all radiologists had less clinical experience with mpMRI in these earlier studies than with the later PI-RADS Version 2 tests, and that these meta-analyses were published before the importance of high b-value images were established and hence a higher b value image was not consistently used.
A meta-analysis of PI-RADS Version 2 performance by Zhang et al reviewed literature up to August 2016. This found PI-RADS Version 2 had a sensitivity of 0.89 (0.83 - 0.93) and specificity 0.73 (0.57-0.85)[56]. A second meta-analysis in 2017 of 3857 patients demonstrated pooled sensitivity was 0.89 (95% [CI] 0.86–0.92) with specificity of 0.73 (95% CI 0.60–0.83) [57]. These meta-analyses suggest that PI-RADS Version 2 has a higher sensitivity but lower specificity than PI-RADS Version 1.

Since these meta-analyses several studies have directly compared version 1 and 2 in the same patient populations. An initial 2016 study found essentially similar results with AUCs of 0.91 and 0.92 respectively [58]. A 2017 study by Auer found overall Area Under the Curve values of 0.96 for PI-RADS Version 1 to have better overall accuracy than PI-RADS Version 2 (AUC 0.90) [59], a similar conclusion to that drawn by Polanec et al [60]. Conversely, 2016 findings by Kasel suggested better AUCs for PI-RADS Version 2 (0.91) over PI-RADS Version 1(0.88).

One apparent cause for these discrepancies is tumour location: in a 2017 comparative study that performed sub-analysis on low grade peripheral zone cancers, it was found that whilst the overall accuracy rates were similar, Version 1 detected more low grade peripheral zone cancers, concluding that “Given that a minority of prostate cancers will not be apparent on DWI, the importance of T2-weighted imaging requires reconsideration” and that “DCE-MRI also detected a minority of PZ cancers that were otherwise underestimated using PI-RADS Version 2”.

Conversely, in directly comparing PI-RADS Version 1 and PI-RADS Version 2 for assessment of the transition zone,there is some evidence that PI-RADS Version 2 has greater sensitivity [61]. In a study by Wang et al, PI-RADS Version 2 exhibited a comparatively higher sensitivity (79.2 vs. 70.8%) but lower specificity (83.1 vs. 88.1%), with a slightly higher AUC V1 (0.86 vs. 0.85). This study suggests that the higher sensitivity of PI-RADS Version 2 is directly attributable to the lower discriminatory power of DWI and DCE in distinguishing between PCa and BPH nodules which were given equal weighting in the transition zone assessment in PI-RADS Version 1.This finding was not supported in a 2018 study focusing specifically on anterior prostate cancers, that found “there was no difference in accuracy when using PI-RADS Version 1 or PI-RADS Version 2 to predict clinically significant cancer”[62].

Overall there is no clear consensus of whether PI-RADS Version 2 is superior to PI-RADS Version 1. This heterogeneity may reflect differing proportions of anterior and peripheral zone tumours within the respective studies.
The above studies, subsequent to the PI-RADS Version 2 release, generally concur with the steering committee's remarks that the effect of Dynamic Contrast Enhancement is “modest” [52]. The focus of more recent literature is whether any modest incremental gain from contrast enhancement justifies the extra 20 minutes, requirement for intravenous access and extra cost that this component of the mpMRI study requires [63].

Kang et al and Woo et al conducted meta-analyses (published 3 months apart, in the same journal) evaluating whether biparametric MRI was non-inferior to multiparametric MRI, demonstrating similar results with sensitivity of 0.74 vs 0.76 (mpMRI), specificity 0.90 vs 0.89 (mpMRI) [64] and sensitivity of 0.79 vs 0.79, specificity 0.88 vs 0.89 (mpMRI) [65].

Role of Diffusion weighted Imaging in Prostate Cancer

On a molecular level, cellularity and cell membranes influence the impedance of water molecule diffusion [66]. For example, the luminal space in benign human prostate tissue has been reported to average several hundreds of microns wide; whereas, in prostate cancer, water molecules diffuse over tens of microns[67,68]. Tumour, abscess, fibrosis and cytotoxic oedema cause impairment to diffusion [66]. Conceptually, diffusion weighted images are created by two successive T2 weighted scans that are designed as mirror images of one another. These “dephase” and then “rephase” the water molecules so that any ultimate difference in signal intensity has occured due to the incompete rephasing of water molecules because of their movement. Water molecules that have moved the furthest have rephased the least and thus demonstrate the lowest signal intensity [66].

The strength of the electromagnetic gradient and hence the phasing/dephasing of the water molecules and the time difference before recapturing the signal are collectively summarised as the *b-value* of the study [66]. In essence by varying these factors, the b-value ultimately adjusts the sensitivity to diffusion; with higher sensitivity demonstrating larger differences between the impedance of diffusion between different tissues[69].

Multiple studies have attempted to pinpoint the perfect b-value for prostate cancer discrimination from background tissue. According to Syer et al “Theoretically increasing the maximum b-value results in a better contrast-to-noise ratio (CNR) because there is greater suppression of normal prostate tissue signal, so resulting tumors are more apparent”[70]. In their 2018 meta-analysis, their research group found a significant increase in both sensitivity and specificity with high b-values > 1000 s/mm2: sensitivity increased from 0.60 (.56-0.64) to 0.78 (0.76-0.79) and specificity from 0.80 (0.78-0.83) to 0.83 (0.82-0.84).

The initial component of DWI signal decay is caused by flowing blood (i.e vascularity) and the second component is due to the movement of water in the intra- and extracellular space [66]**.** Therefore at low b value levels both molecular diffusion and microvascular perfusion contribute to the calculation of the signal intensity, particularly microvascular perfusion due to the relatively high vascularity of the prostate. Using a low b-value greater than zero may more accurately reflect tumour cellularity by mitigating the effects of perfusion [71].

As the diffusion weighted images are derived from T2 weighted images, parameters other than diffusion (T1 and T2 relaxation times) affect the diffusion weighted image [72]. The most well

known of these is T2 shine-through, whereby high water content structures increase the signal intensity in diffusion weighted images [66].

Diffusion weighted images potentially introduce some interobserver variability into prostate MRI reporting: As Rosenkrantz et al points out, there is inherent subjectivity in distinguishing “mild-to-moderate” versus “marked” signal abnormality on high-b-value DWI [73] A subsequent 2017 study found that DWI score ≥4 had 11.8% inter-reader disagreement [74]. This study then attempted to standardise marked diffusion restriction by using ADC ratios. The ADC value of the region of interest was measured and divided against the ADC value within a region of normal tissue. Using ADC ratios of >1.3 yielded 100% (reader 1, 54/54; reader 2, 51/51) positive predictive value for clinically significant cancer [74].

Role of ADC maps in multiparametric prostate MRI

ADC maps avoid the problem of T2 shine-through and attempt to isolate diffusion characteristics [75].These are generally created by plotting the relative (apparent) log function of signal intensity for various b values and then measuring the slope of the resultant line (FIGURE 4). This can be calculated using several similar but slightly different methods. For example, ADC values can be calculated by drawing a straight line between two b values (slope) or by a least squares regression analysis; a study comparing 4 different methods of calculating ADC across multiple cancer types found differences of up to 7% based on the calculation method [76]. However the larger issue is in choosing the actual b-values for computing the ADC as these create larger differences in ADC values [77].

FIGURE 4: Diagram of the ADC Calculation Method:

This diagram illustrates that the ADC value represents the change in relative signal intensity between Diffusion Weighted Images of different b values. As a result, ADC values are immune from the T2 shine-through phenomenon seen in Diffusion Weighted Imaging. Ref:[75]

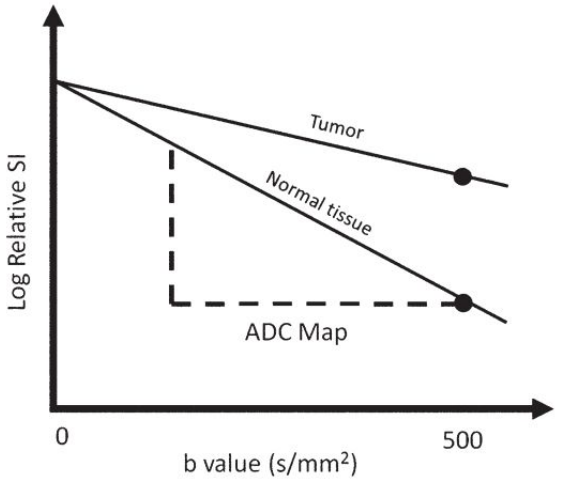
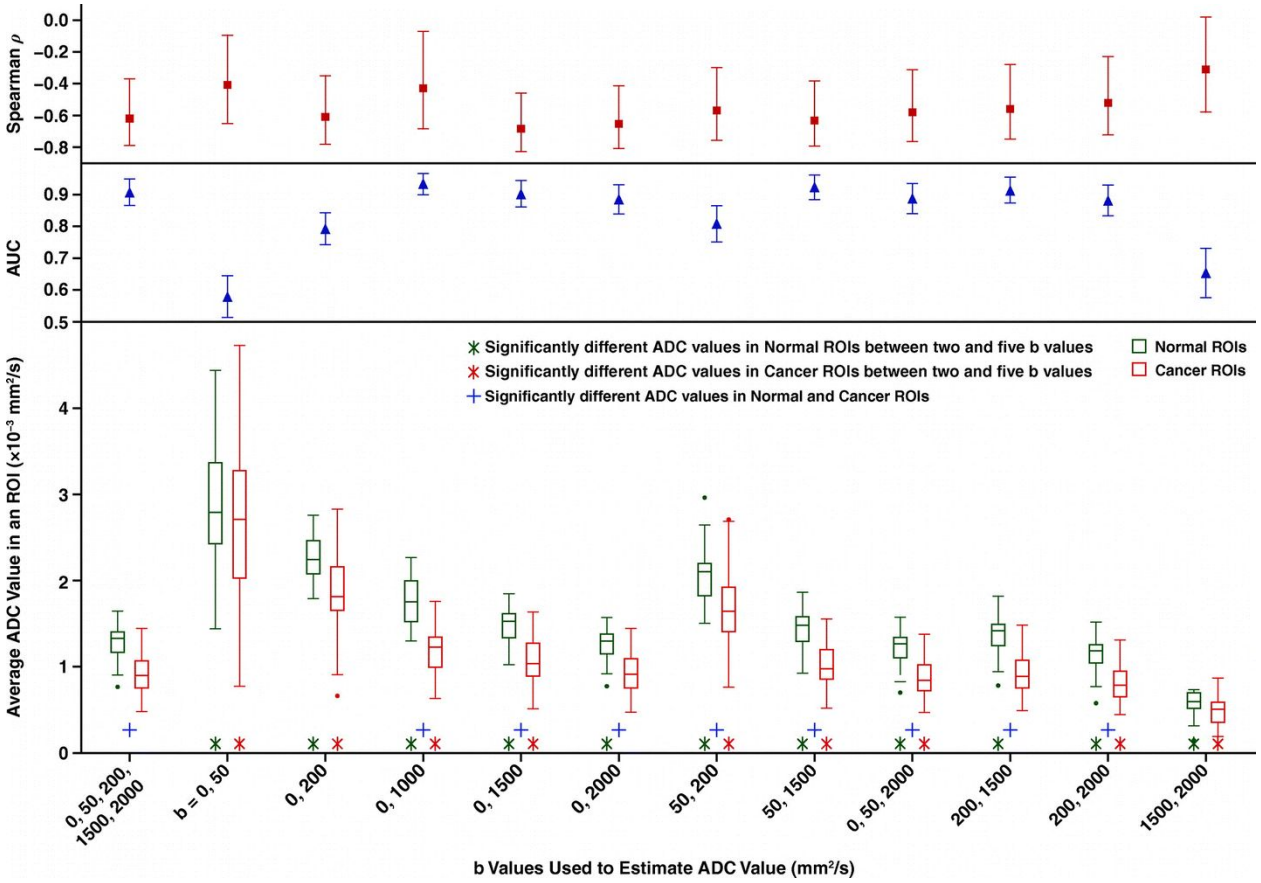


FIGURE 5: Calculated ADC values for Cancer and Normal tissue with Various b values. This study experimented with multiple b values when creating ADC maps. It demonstrates that higher b value produces the greatest ADC differences between normal regions of interest against cancer regions of Interest.



- from reference [77]

The differences in ADC values caused by using different underlying b values can result in clinically significant ramifications, as tumour and non-tumour ADC values may be distinct or demonstrate almost identical overlap, depending on the b value used [77] (Figure 5). The study in Figure 5 demonstrates that ADC maps should be calculated using a lower b value between 0-200s/mm and high b value greater than 1000s/mm. ADC maps derived from b values between 0 and 200s/mm did not demonstrate discriminative ability between normal prostate and cancerous tissue, and this

is presumably because within this range the ADC is more representative of vascularity than it is of cellular diffusion [71]. Similarly, ADC values appear most likely to discriminate between prostate cancer when the lower number in the calculation is 50 or 200 mm2/s as this appears to yield ADC values that neglect vascularity and are more representative of cellular diffusion[77]. When both b values were greater than 1000s/mm ADC becomes less discriminative likely because of a greater degree of noise introduced into the measurement[77].

ADC values are typically calculated assuming that the signal decay is a monoexponential decay function [78]. However as higher b values (>1000s/mm) started being used, the decay function has been found to be better modeled by a biexponential function that breaks down the decay function into fast and slow components. Multiple studies suggest that bi-exponential ADC modelling may provide additional, unique tissue characterization for both normal and cancerous prostate tissue [78–80], however there is no evidence that this has improved clinical outcomes.

ADC values have been shown to correlate with cellularity across multiple different cancers, however the degree of correlation varies between mild to strong depending on the malignancy in question [81]. ADC values also appear to correlate with degrees of tumor necrosis and microvessel density in high-grade prostate cancer. The significance of ADC values therefore, lies in their possible discriminative ability to separate low risk (Gleason 6/Grade Group 1) prostate cancer from higher risk disease that necessitates further investigation and treatment. In a recent subgroup meta-analysis, the addition of ADC maps to diffusion weighted images increased the diagnostic odds ratio [70]. Indeed, ADC clearly demarcates other common prostate pathology: in one study prostatitis showed restricted diffusion with ADC ≥ 900 mm2/s in 100% of cases[82]

PI-RADS Version 1 notes that DWI/ADC adds specificity to lesion characterisation[26]. ADC also correlates with the degree of cancer aggression: a feature that was well established by 5 individual supporting studies in the first iteration of the ESUR PI-RADS documentation and has continued to be so. Each of these studies demonstrated a statistically significant inverse relationship between Apparent Diffusion Coefficient values and Gleason Score [83–87]. The study by Itou et al 2012 clarified that whilst a relationship between the cancer aggressiveness and ADC is statistically significant, there was “considerable overlap” between Gleason 6 and Gleason 7 disease, and that no arbitrary ADC cut-off values would accurately characterise a lesion based on its Gleason score due to “considerable intrasubject heterogeneity” [85].

A 2019 meta-analysis by Surov et al assessed the correlation between ADC values and Gleason scores in 39 studies [88]. The predominant comparator was radical prostatectomy, and hence

undersampling by biopsy was unlikely to influence the meta-analysis. This study only found a mild overall correlation between ADC and Gleason score: −0.45 [−0.50; −0.40]. This correlation was entirely based upon the moderate correlation in the peripheral zone subgroup −0.48 (95% CI = [−0.54; −0.42]) whereas in the transition zone subgroup, the pooled correlation coefficient was weak (−0.22) and indeed the 95% confidence interval was statistically insignificant = [−0.47; 0.03]).

In 2016, Fuetterer extolled the potential of ADC cutoffs in discriminating between low,medium and high risk patients, but cautioned that further research was required because of significant overlap between those groups[89]. Subsequent studies suggested ADC cutoffs could discriminate [90]

In a December 2018 study, Polanec addressed whether false positive rates from PI-RADS could be avoided through the use of quantitative ADC values. They found that using cutoff thresholds for minimum ADC value (which correlates with the greatest degree of tissue diffusion) [91] would have prevented unnecessary biopsy in 16 of 49 men with a single positive lesion in mpMRI.

What is the value of dynamic contrast enhancement?

A literature review was conducted utilising Ovid Medline,the Cochrane Library, Embase and Google Scholar. Existing meta-analyses and systematic reviews were evaluated [64,65,92,93] before more recent studies of relevance were considered.

Study Parameters:
(mri (title) OR mpmri (title) OR magnetic resonance (title)**)** AND (prostate(title) OR prostatic(title)) AND (contrast(title) OR DCE(title) OR Biparametric (title))
Date:
1990 - February 2019
Inclusion Criteria
Human Studies

The basis for dynamic contrast enhanced imaging is that tumours demonstrate increased angiogenesis, vessel density and increased vessel permeability [94] [95] [96] compared with normal prostate tissue.

Dynamic Contrast Enhancement is an umbrella term that refers to multiple possibilities: most commonly qualitative features such as peak enhancement, early contrast enhancement, washout

or quantitative features such as pharmacokinetics[97]. These introduce significant heterogeneity to meta-analyses [92], and subgroup analysis suggest that k-trans values offer slight improvement to sensitivity over other alternatives [92]

Peripheral Zone Tumours

In meta-analyses DCE (by qualitative or quantitative means) offers sensitivity of 0.70 (95% CI 0.46 to 0.86), and specificity of 0.88 (95% CI 0.76 to 0.94) within the peripheral zone[92]. In a study published just after the above meta-analysis, positive DCE scans were twice as likely to reflect clinically significant cancer in the peripheral zone, irrespective of the DWI findings [98] and across PI-RADS 2,3 and 4 lesions. In a 2018 study, 45 of 271 men had PI-RADS 3 lesions that required further discrimination with DCE; When compared with final pathology, DCE was correct in increasing the assessment category in 68.9% of cases[99].

No studies were identified during the literature review that assessed the utility of characterising PI-RADS 3 lesions based on means other than DCE, such as ADC cutoffs or PSA Density.

Central Zone Tumours

The presence of benign prostatic hypertrophy in the central zone limits the usefulness of DCE in detecting central zone tumours. Benign prostatic hypertrophy nodules can have similar patterns of uptake to prostate carcinoma [100]. DCE therefore appears of value in peripheral zone but not central zone tumours [101,102]

There are significant differences between mean k-trans values in glandular hypertrophy and adenocarcinomas in the central zone, but not between stromal hypertrophy and carcinoma [103]. Furthermore DCE does not provide extra-discriminatory power over ADC alone for central lesions [103]. Assessment with DCE in the Transition Zone for prostate cancer detection does not appear to be of additional benefit [59,104]

What does research currently reveal about the Negative Predictive Value of mpMRI, is it good enough to omit biopsy? The significance of false negative results

The European Association of Urology (EAU) working group formulated this very question when addressing the increasingly important role of mpMRI in the initial diagnosis of prostate cancer.

The EAU working group subsequently performed their own systematic review and meta-analysis on the negative predictive value (NPV) of mpMRI [105]. Of 8 studies that met their criteria, “Only one study selected for meta-analysis reported results for Gleason ≥7 cancers”, yielding a NPV of 87.9%. Significant heterogeneity, particularly due to the clinically significant disease, rendered the EAU’s results insubstantial; “The NPV of mpMRI varied greatly”. However, the working group concluded that “it *should* be possible to use an MRI scan to avoid biopsy”, when “risk stratification ... (defines) those in whom biopsy may be omitted when the mpMRI is negative”.

Subsequent to this meta-analysis, a study of 134 patients, of whom 43.4% had clinically significant cancer, underwent mpMRI matched to biopsy, which demonstrated a negative predictive value of 98.4%.[106]. Patients in this study had on average 16 biopsy cores each. There were 23 instances of clinically significant cancer in biopsy specimens where the corresponding region in the MRI was reported as normal, these came from 17 patients. 15 of these patients had positive overall mpMRI, only 2 patients had invisible lesions [106]. In evaluating this negative predictive value, the per-lesion approach may have artificially increased the true negative results, giving an unusually high negative predictive value. Apart from study design, the reference test had a large effect on negative predictive value; this was well illustrated in a study that used two separate comparator tests for mpMRI; in men with no suspicious MRI target, there was a 3% chance of detecting clinically significant prostate cancer with TRUS biopsy but systematic biopsies revealed csCaP in 16% of men [107].

In a landmark paper, “Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study” [24], Ahmed et al found that mpMRI was far superior to transrectal ultrasound guided biopsy in cancer detection. In their final cohort of 576 men who underwent MRI, TRUS biopsy and saturation transperineal template biopsy, 158 men recorded a negative mpMRI result. Amongst this subgroup, sixteen Gleason 3+4 cancers greater than 6mm were missed on mpMRI that were subsequently detected on transperineal biopsy, yielding a negative predictive value of 89%. Importantly, no Gleason 4+3 disease was missed on mpMRI. When the clinical definition of cancer was 3+4 disease greater than 4mm in any core, a negative predictive value of 76% was found [24]. By comparison, TRUS Biopsy recorded 112 false negative mpMRI results, of which 13 were Gleason 4+3 disease [24].

Overall, published studies since the initial EAU meta-analysis have not galvanized a particular viewpoint. Research remains too heterogeneous, leading to conflicting results; with conflicting implications for the need to perform systematic biopsy after negative mpMRI.

PSA Density

PSA Density has been shown to be an independent predictor for suggesting clinically significant prostate cancer and its aggressiveness [108]

There is additional strong evidence that PSA Density, when used in combination with mpMRI improves negative predictive values of mpMRI: In a study of 141 men, a PI-RADS v2 score of ≤3 and PSA Density of <0.15 ng/mL/mL yielded no clinically significant prostate cancer in any of the 35 men in this category and no additional detection of prostate cancer on further biopsies[109]. In a non-academic setting, PSA Density increased the ROC curve for PI-RADS Version 2 up to 0.76 (95% CI 0.69–0.82), statistically higher (P=<0.001) than PI-RADS alone: 0.69 (95% CI 0.63–0.76) The negative predictive value of 236 PI-RADS 1–2 MRIs in combination with PSAD of <0.1 ng/mL/mL for Gleason score 7–10 was 0.91[110].

In a 2017 study of 451 patients assessing the negative predictive value of mpMRI (scores of 2 or less) for clinically significant cancer defined as any pattern 4 disease, negative predictive value increased from 79% up to 89% when prostate specific antigen density was 0.15 ng/ml/ml or less[111]

Effect of Radiologist Experience on mpMRI Accuracy

Several studies have demonstrated that experienced radiologists produce better results:
In a non-academic setting, an AUC of 0.69 (95% CI 0.63–0.76) was established in a study of 170 men**,** lower than those in typical more experienced academic centres[112]. The inference in this paper was that radiologists in non-academic centres are less experienced (or at least have a lower caseload) and therefore that the difference in accuracy rates was explained by intrinsic differences in prior experience. Inter-reader agreement has also been demonstrated to be higher between more experienced readers, with the most experienced groups achieving the highest cancer detection rate (0.73 for csPCa using category ≥4) [113]. This study commented that “readers' experience influenced inter-reader agreement and cancer detection rate.” [113]
Whilst these studies unsurprisingly show that more experienced radiologists have greater accuracy rates than less; there is no literature regarding an evidenced-based argument for the threshold at which a radiologist is experienced enough for satisfactory reporting. This remains a deficiency in the existing literature that can be further examined.

Literature Gaps and Avenues for Future Research

1. Evidence on the negative predictive value of MRI is conflicting. The literature presents a large range of negative predictive values due to study heterogeneity: clinically significant cancer thresholds, per-lesion or per-patient analysis and comparator studies are amongst the largest (but not sole) introducers of study discrepancy. An accurate understanding of negative predictive value is a priority for mass screening stakeholders. This should be performed on a per-patient (not per-lesion) basis to clinically contextualise results. Negative Predictive Values derived locally may reduce heterogeneity introduced from different scanners, image acquisitions, b values, methods of creating ADC maps, and ultimately experience of the reporting radiologist. In this context, this PhD thesis utilises a local database of prospectively acquired data from men who underwent Prostate MRI scans. The database was created in February of 2017. It collects data from men attending a private urology clinic in Melbourne, from seven high-volume urologists. These men attend having been referred by their General Practice Doctor; they are not able to self-refer. Typical referral indications would be lower urinary tract symptoms, an increased PSA test or other concern of prostate cancer such as family history. The specific inclusion criteria for the database is that the patient subsequently has prostate MRI scan, the vast majority of which are multiparametric studies. The database contained 1693 patients at the commencement of the thesis, and currently contains 2315 men. The size of the database reflects its creation early in the course of mpMRIs clinical utilisation, as well as the significant number of patients that are referred to this high volume centre. As such, the patient numbers within the following studies have been constantly within the largest reported cohort sizes in the field, if not the largest. Given that our database is significantly larger than the patient cohorts of individual studies reporting negative predictive value elsewhere, clarifying the negative predictive value of mpMRI in our study cohort would influence this literature globally. Also, as the first country with government-rebated prostate mpMRI, Australian clinicians need to have the most reproducible, locally applicable data available as they determine how to act on their patients' mpMRI results. This literature gap translates into an addressable research question.

   Additionally, literature combining PSA Density cut-off values with negative mpMRI is consistently demonstrated in literature to improve the negative predictive value of multiparametric MRI. In addressing the diagnostic accuracy of mpMRI, PSA Density values can additionally be incorporated.

2. A consistent motif throughout development of the PI-RADS score has been the decreasing importance of contrast enhanced scans. Initially weighted equally with the other series in PI-RADS Version 1, contrast enhancement is only employed rarely in PI-RADS Version 2, and now research focuses on its removal altogether. As DCE influences PI-RADS scoring infrequently in PI-RADS Version 2, it would seem reasonable to shorten overall scan times by 20 minutes and omit this phase. However, there are some pockets of research suggesting that contrast uniquely improved the sensitivity and negative predictive value of peripheral zone lesions in PIRADS 1. In the prevailing clinical zeitgeist of using multiparametric MRI to obviate biopsy, and predicting a move from multiparametric MRI (with contrast) to biparametric (without) in the future, any trade off in accuracy needs to be clearly articulated. Especially given that the PI-RADS working group themselves suggest that "the added value of DCE is not firmly established", high quality studies that attempt to isolate the marginal benefit of DCE are required.

   As an extension to this, if contrast imaging is removed, then a new method of arbitrating between PI-RADS 3 lesions is required. Any high quality study that compared bpMRI (without contrast) to mpMRI (with contrast) could additionally propose a method of replacing the current discriminatory role of DCE in PI-RADS 3 lesions. For example, the literature review demonstrated that ADC values are known to have a statistically significant correlation to Gleason score [83–87]. These may offer a substitute for DCE in PI-RADS 3 lesions. The literature review also demonstrated that PSAD is also a known independent predictor of clinically significant disease - suggesting it may have the potential to replace DCE in arbitrating PI-RADS 3 lesions.

3. Multiple studies demonstrate improvements in accuracy and decreased inter-reader variability with scans read by experienced radiologists. But literature neglects the obvious question: what threshold defines experience? Though conceptually simple, this literature gap has real clinical significance. That is, that readers without an appropriate amount of training may have suboptimal accuracy in their prostate MRI reporting.

Research Questions

This thesis was undertaken to improve MRI-based prostate cancer detection, and does so by addressing several distinct but interlinking topics described below. The overarching narrative regards first establishing the accuracy of mpMRI, specifically sensitivity and negative predictive values given their importance in disease detection and lack of consensus described in the prior literature review. Once the accuracy is established, the thesis then examines reasons for inaccuracy, in particular false negative scans; both generally via a root-cause analysis and then with specific regard to radiologist experience. The purpose for doing so is pragmatic; as understanding the reasons for false negative scans provides an avenue for improvements. Finally, the thesis examines one other factor in prostate MRI accuracy; that of Dynamic Contrast Enhancement (DCE). Its marginal benefit is not established in the existing literature. Yet the need to cannulate patients, longer scan times, extra expenses and requirement of in-hours scanning, all of which DCE imposes, are established adverse factors. Removing DCE would make prostate MRI far more efficient. In this overarching context the following research questions were investigated:

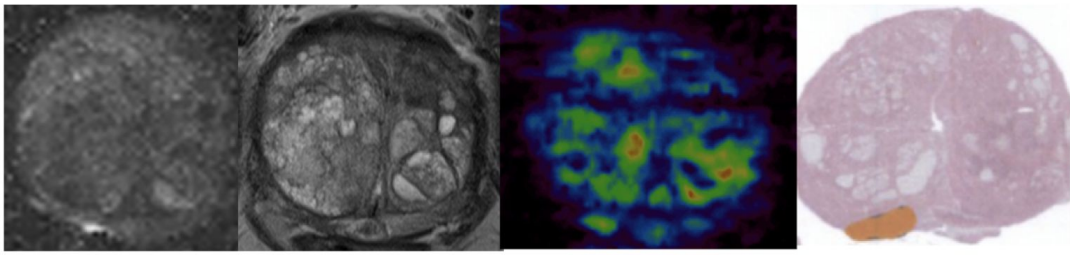
CHAPTER 1: Evaluating the Sensitivity and False Negative Rate of Prostate MRI Scans and Their Clinical Significance

Establishing widespread use of mpMRI mandates an accurate understanding of its limitations. False negative tests are a common characteristic of almost all diagnostic tests; and their frequency and clinical significance - serious or otherwise - must be clearly understood before extensive adoption. Evidence on the negative predictive value of MRI is conflicting, as literature presents a large range when trying to define the negative predictive values. There are multiple known sources of heterogeneity [114]. The definition of clinically significant cancer, per-lesion or per-patient analysis and type of reference standard introduce heterogeneity at the study design level. But even different scanners, image acquisitions, b-values, contrast imaging parameters and experience of the reporting radiologist have the ability to influence these results [53,105,114]. Our local database contained significantly higher patient numbers than the individual studies pooled in meta-analyses at the commencement of the thesis. Furthermore, with the 2018 Australian Government announcement of a Medicare rebate for prostate cancer, false negative rates of overseas institutions with different population based rates of prostate cancer prevalence and different levels of radiologist experience, are less relevant than the same results calculated locally. This Chapter evaluates the sensitivity of mpMRI by performing two separate analyses; using first transperineal template biopsy as comparator, and then a novel whole-mount hemi-gland analysis.

This study sought to understand the causes of false negative mpMRI scans. Radical prostatectomy proven false negative scans were evaluated. Known causes of errors from the literature before commencing the study were errors from artefact and small volume tumours. Additionally, quantifying any systematic errors, or blind spots that may exist as a result of the PI-RADS system which radiologists used to evaluate Prostate MRI was a further research aim. Moreover, the study alternatively sought to identify if there was any commonality amongst false negative cases, which could be corrected by introducing new systematic review techniques. Such analysis was possible because of the validation method: In prostate MRI tissue-based feedback occurs through transrectal ultrasound-guided biopsy, transperineal ultrasound-guided template biopsy or radical prostatectomy specimen. Wholemount sectioned radical prostatectomy specimens are considered the gold standard due to their evaluation of the entire gland, compared to biopsy specimens which sample approximately 2% by volume. This study was undertaken using wholemount radical prostatectomy specimens, analyzed by a pathologist in a manner which was unique at time: That was by inking with orange dye (see FIGURE 6), the most significant tumour foci in the specimen for explicit visualisation. This allowed the regions of histopathological interest to be exactly correlated with the area of concern on mpMRI. The original MRI scans could be re-analysed with a confident understanding of their tumour burden and location.

FIGURE 6: Dataset Example:

A dataset of multiparametric prostate MRI images - from Left to Right, Diffusion Weighted, T2-Weighted, and Dynamic Contrast Enhanced, were juxtaposed against the equivalent wholemount sectioned radical prostatectomy specimen, which had index tumours marked in orange by a pathologist.



CHAPTER 3: The Role of Radiologist Experience in Multiparametric Prostate MRI Accuracy

Whereas Chapter 2 sought to understand any systematic errors in radiologist interpretation, Chapter 3 seeks to understand individual errors arising from inexperience; the impact that the number of cases previously performed has on accuracy rates. If prostate MRI utilization rates continue at their current trajectory, large numbers of radiologists will be required to interpret these scans, despite variable levels of training. However this situation may increase the inaccuracy of prostate MRI due to the abundance of inexperienced readers. This chapter seeks to understand the impact of prior experience on accuracy (or inter-reader variability). Radiologists will be grouped into cohorts based on their self-reported level of prior prostate MRI experience, based on the number of cases they have performed. The cohort's accuracy will be plotted against other cohorts. All radiologists will interpret the same dataset. This may allow evidence-based suggestions for when radiologists should be allowed to report prostate MRI as a single reader, or when dual reporting should be mandated.

CHAPTER 4: Does Dynamic Contrast Enhancement have a marginal benefit in prostate cancer detection amongst biopsy naive men?

Multiparametric prostate MRI comprises three core sequences; T2 weighted imaging, diffusion weighted imaging and dynamic contrast enhancement. In the initial version of the PI-RADS scoring system, all three were weighted equally in the overall assessment of the gland. However in the 2014 update (Version 2) the scoring system was changed to reflect a "dominant sequence" paradigm. Specifically, the peripheral zone is scored predominantly according to its appearance on diffusion weighted imaging; the transition zone is scored according to its appearance on T2 weighted imaging. This update, in effect, served to reduce the importance of dynamic contrast enhancement in the overall scoring. In PI-RADS Version 2 the role of dynamic contrast enhancement is only to upgrade PI-RADS 3 lesions that are equivocal (score of 3) on the diffusion weighted imaging, for lesions in the peripheral zone. The contrast sequence (if positive) has the ability to upstage these equivalent lesions to an overall PI-RADS 4 score. Therefore, the overall scoring of the gland is not affected at all if there is a) no suspicious lesion, b) a suspicious lesion in the transition zone, or c) a clearly suspicious lesion in the peripheral zone. This section of the thesis thus examines what impact removing the dynamic contrast enhancement series entirely would have on the accuracy of the scans. It may be reasonable to entirely remove the dynamic contrast enhancement series all together if it is shown to be of no benefit. The reasons favouring removal regard the extra cost, extra time (approximately 15-20 minutes) and added inconvenience of requiring intravenous access for the contrast, which additionally requires a nurse / doctor to

perform the intravenous cannulation. Furthermore, the requirement for a doctor to supervise the contrast administration limits the hours during which patients can be scanned. Additionally there is some concern regarding the long-term effects of contrast itself, with polycyclic gadolinium-based contrast agents being shown to deposit at the blood-brain barrier (presently of unknown clinical significance)[115] - although this has not been demonstrated with Gadovist contrast (Bayer, Switzerland) which is routinely used in Australia. This chapter therefore examines what increase in accuracy (if any) results from the inclusion of dynamic contrast enhancement.

CHAPTER 2:

Evaluating the Sensitivity and False Negative Rate of Prostate MRI Scans and Their Clinical Significance

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

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MBBS (hons), Grad. Dip Anatomy.

CHAPTER 2 INTRODUCTION

The PROMIS trial was the first to robustly demonstrate superiority of multiparametric MRI to random transrectal ultrasound-guided biopsies in detecting clinically significant prostate cancer [24]. This finding has been reinforced by multiple studies highlighted in a Cochrane Review, and the comparative advantages of prostate MRI over the incumbent diagnostic workup are well articulated in literature[116]. Given the clinical demand for prostate MRI resulting from these advantages, an understanding of its pitfalls and limitations must be equally available to the medical community. Specifically, the number and significance of false negative and false positive test results must be clearly articulated. Although false positive tests, which result in unnecessary biopsies, should be reduced as much as possible, the overlapping appearances of significant prostate cancer, insignificant prostate cancer, benign prostatic hyperplasia and prostatitis imposes a natural limitation on optimising false positive results based on imaging [117]. Prior to composing this chapter, literature regarding the weaknesses of prostate MRI was methodologically suboptimal but consistent: most studies demonstrate that prostate MRI is imperfect in detecting clinically significant prostate cancer. The quality of these studies was lacking in two primary respects, deficiencies which are addressed in the research within this chapter.

1. *Reference test*

In order of least to most accurate reference test, the validation methodology of prostate MRI studies are transrectal ultrasound guided biopsy (TRUS-Bx), transperineal ultrasound guided biopsy, or whole-mount radical prostatectomy, which represents the gold-standard [118]. TRUS-Bx, although a common office based procedure, is the least preferred method for two reasons. Firstly, by passing the biopsy through the rectum it may result in prostatitis or bacteraemia, which has prompted some authors to advocate for its cessation entirely[119]. In addition, as the biopsies are introduced into the gland posteriorly, some research suggests that TRUS-Bx risks systematically undersampling the anterior gland. Alternatively, transperineal biopsy has at least equivalent or superior detection rates, with a far smaller risk of sepsis[120]. Two other variables also affect the strength of the biopsy comparator tests; the number of core samples performed, and targeting [121]. Lower numbers of core samples are more likely to undersample the extent and grade of prostate cancer. Targeting refers to the ability of prostate MRI to offer a region of interest which is suspicious for cancer of which biopsy is specifically performed. Targeting may be performed by both transrectal or transperineal biopsy. Targeting may be cognitive (the urologist manually analyses the prior MRI scan and attempts to co-locate the biopsy in the same region of the prostate with ultrasound in real time) or employ software that fuses the real-time ultrasound with

the prior MRI (“fusion”). Targeting can also be robotic, in which the urologist uses software to establish the region of interest within the prostate, with the biopsy performed by a robotic arm. Whilst there is evidence for the superiority of targeted biopsy sampling over non-targeted in terms of csPCa detection [110], no particular method of targeting has proven superior. In addition, targeted biopsy appears to be comparable to "saturation" biopsy, which refers to biopsies in which a large number of non-target systemic core samples are performed [122].

Although radical prostatectomy is frequently used as the comparator test in cohorts of patients with biopsy proven disease, it is impossible to use radical prostatectomy as the comparator group in cohorts of prostate MRI scored as normal. This is due to the practical limitation that patients with a low likelihood of disease do not routinely progress to radical prostatectomy. Attempting to ascertain the false negative rate of mpMRI based on transperineal template biopsy is therefore conventionally the best alternative; and such studies are relatively common within literature [122–126]. However even transperineal saturation biopsy has been shown to miss approximately 7% of clinically significant disease subsequently detected on wholemount radical prostatectomy [127]. The following study sought to solve this impasse of assessing normal prostate MRI scans against radical prostatectomy specimens. This was done by using a hemigland analysis methodology. Scans that had previously been scored positive by an experienced uroradiologist were included in the study group. As the radiologist specifically labelled, on a triplanar diagram, the exact region/s of suspicion for which they had designated the scan positive, those prostate MRI scans could be described as positive or negative for both the right and left hemiglands respectively. These scans proceeded to biopsy and then those with biopsy confirmation of clinically significant disease proceeded to surgery. Hence for scans in which the lesion was confined to only one hemigland, the other hemigland had been reviewed and prospectively described as normal and had gold-standard histopathology available for comparison.

2. *Histopathological Characteristics of Missed Tumours*

Dichotomising prostate MRI results into true positive or false negative fails to accurately characterize the clinical significance of missed tumours. Four histopathological characteristics are known to impact the natural history of the disease. Firstly the overall tumour grading described in literature by either ISUP grade group (International Society of Urogenital Pathology) or Gleason score[30]. Secondly, the volume (if radical prostatectomy) or greatest core length (if biopsy) of cancer[128]. Thirdly, the proportion of Gleason pattern 4 vs Gleason pattern 3 disease within the sample for low grade cancers[129]. Finally, the tumour location[130,131]. In both the biopsy and wholemount radical prostatectomy comparators (for the hemigland analysis), the above

characteristics were described so that the clinical significance of missed disease could be determined.

FIGURE 7: Example of the localisation sheet used by the radiologist to convey lesion location.

Radiologists had access to a triplanar diagram such as this, and would shade the area of concern as demonstrated below.

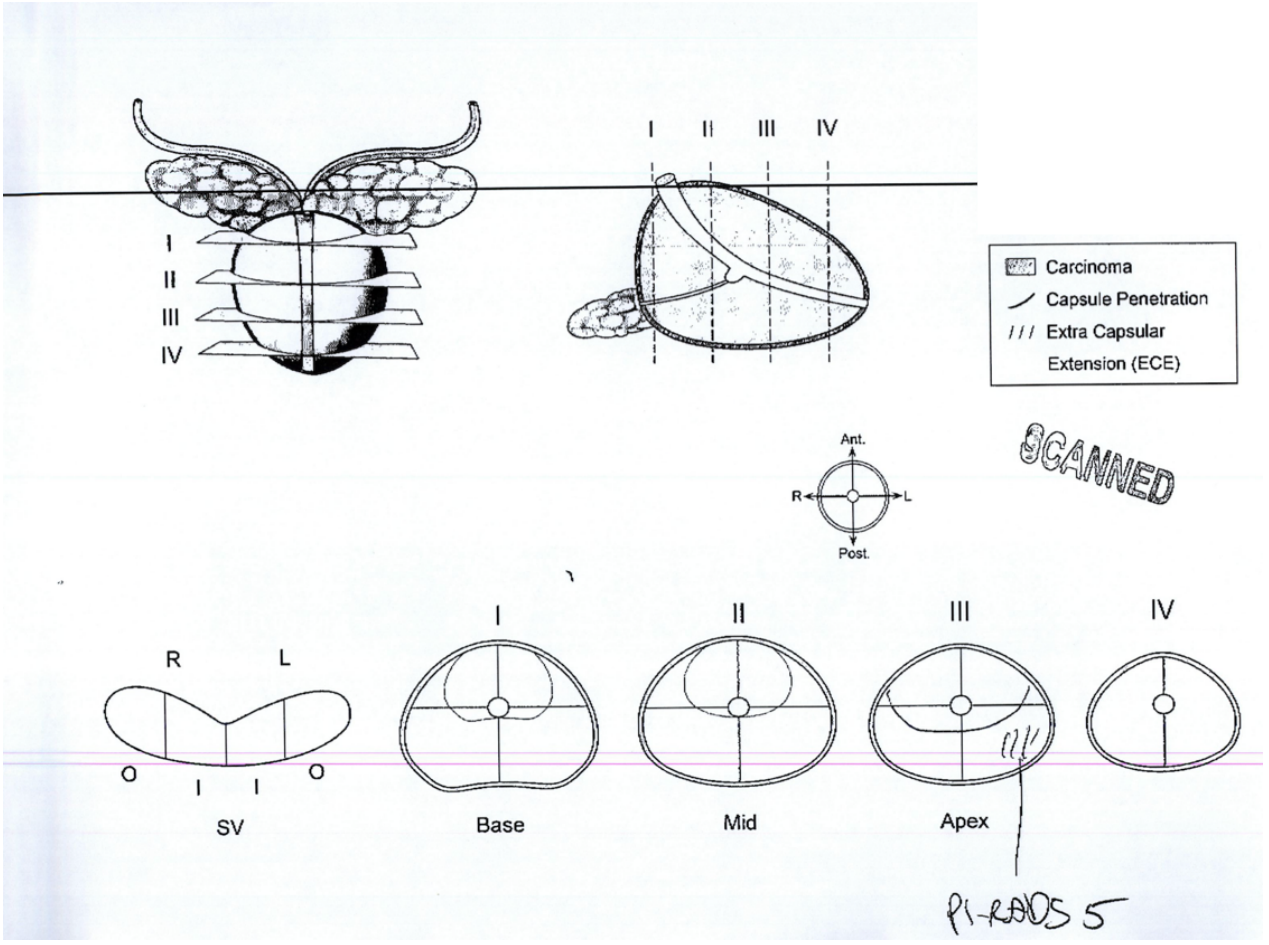
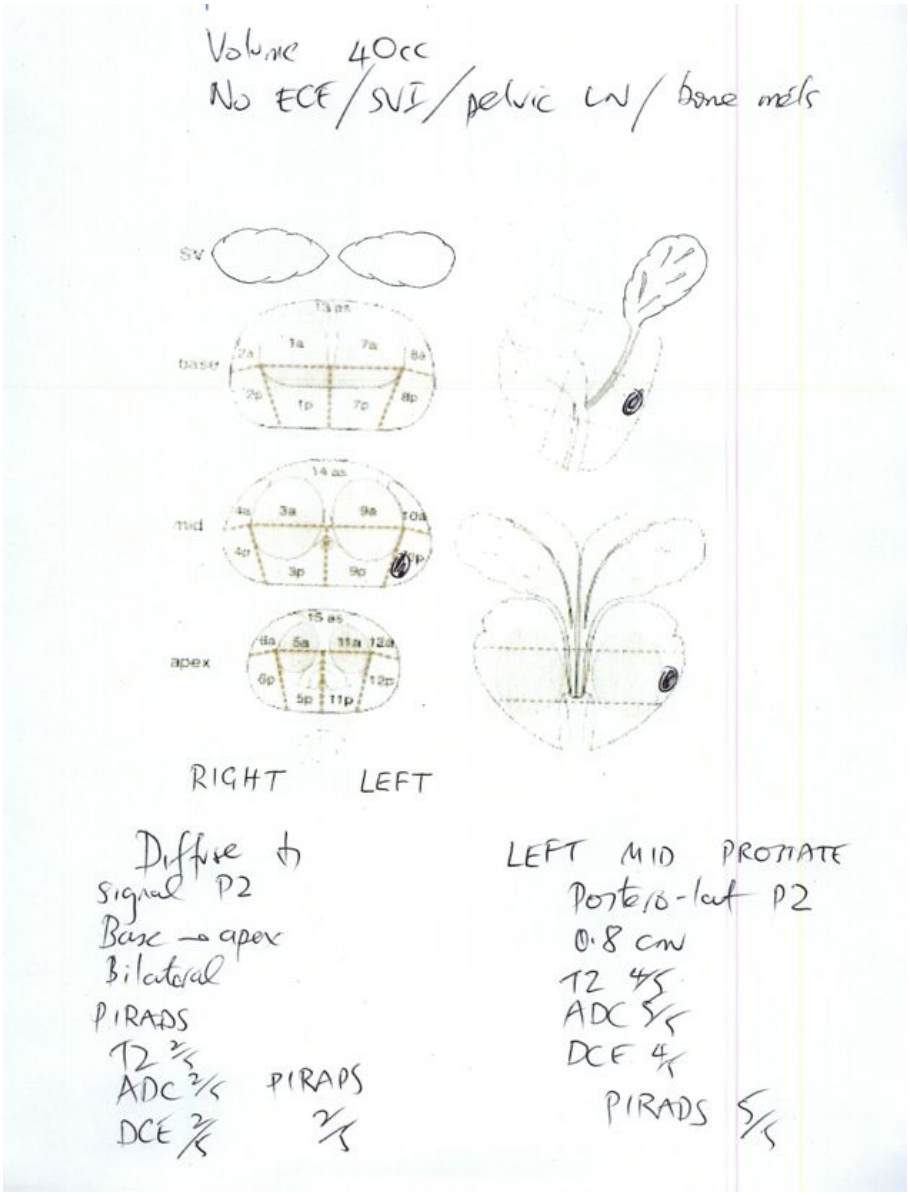


FIGURE 8: Second example of the localisation datasheet provided by the radiologist.

Second example of the triplanar diaphragms that radiologists were provided, with the area of concern shaded as demonstrated below.



Sensitivity and Negative Predictive Value of Multiparametric Prostate MRI Against Whole Mount Radical Prostatectomy Specimens by Performing Hemigland Analysis

Introduction

With mounting evidence and guideline incorporation multiparametric MRI scans of the prostate (mpMRI) are increasingly used in the diagnostic workup for clinically significant prostate cancer[36]. In this context, an understanding of mpMRI false negative rates is paramount. However these are impacted by the choice of reference standard, with known upgrade rates between biopsy and prostatectomy. Patients with negative MRI scans do not customarily proceed to radical prostatectomy, precluding their radiology-pathology correlation. However, retrospectively analysing known cancer cases on a hemigland basis allows correlation between normal hemiglands and their wholemount radical prostatectomy results, which this paper performed and compared to their biopsy equivalents. The histopathological correlation of hemiglands which were reportedly normal were analysed in this paper in an attempt to inform clinicians of the prevalence and clinical significance of false negative MRI scans using wholemount sectioned radical prostatectomy specimens.

Table 1: Study Characteristics
*Other acquisition parameters are consistent with PIRADS 2.0 specifications, and technical MRI parameters are available in the appendix.

Patients	2166 men had mpMRI 1093 had correlative biopsy 126 had Radical Prostatectomy analysed according to hemigland analysis
Enrolment:	Prospective Data Collection
Age:	Mean 66.7, 95% CI [56,77]
PSA:	Median 6.3, IQR (4.1, 8.8)
Number of Prior Biopsies	Median 2, IQR (1, 2)
Scanner	3.0 Tesla Siemens. No phased array/endorectal coils 1400 s/mm^2 high B value*
Reference Standard	1. Saturation Transperineal Biopsy with additional targeted biopsy in 45% of patients. 2. Radical Prostatectomy
mpMRI scoring	PIRADS 2.0
MRI criteria for Biopsy	Lesion greater than PIRADS 3, or clinician preference.
Clinically Significant Disease Definition:	Any (>0cc) Gleason Pattern 4 Disease - ISUP Grade Group 2 or greater.

Methods

Participant Recruitment

Data from a private group practice of 7 urologists was prospectively collected, stored in a HREC approved cloud-based REDCap database and retrospectively analysed. Database entries for 2166 men who underwent MRI, due to clinical concern for prostate cancer between (1/1/13 - 1/10/2019) were reviewed. Study characteristics are described in Table 1.

MpMRI Acquisition and Reporting

These men underwent 3.0 Tesla mpMRI almost entirely on a single Siemens Magnetom Skyra Scanner (without endorectal coils). Scans were acquired according to PI-RADS Version 2.0 specifications, with the exact acquisition parameters described in Appendix B. A uroradiologist (>5 years of conducting multiparametric prostate MRI multidisciplinary meetings) reported the scans. They have a caseload of more than 500 mpMRI scans per year. MpMRI scoring was initially performed according to PI-RADS Version 1 before changing to PI-RADS Version 2.0 when it was published. A standardized 27-region/sector MRI prostate reporting schema was used by the radiologist to convey the location of suspicious lesions.

Reference Standard

1093 men went on to transperineal biopsy performed within 6 months of the initial mpMRI. The decision to biopsy was based on the clinical decision of the urologist, normally due to a concerning prostate MRI result, or otherwise a negative scan result with persistent clinical suspicion (strong family history, lower urinary tract symptoms, elevated PSA Density). For each biopsy core, location, core length, length of cancer involvement and Gleason grade were recorded.

303 of the patients from the initial cohort went on to radical prostatectomy, as a result of clinically significant disease on the transperineal biopsy specimen, of which 119 had wholemount volumetric maps available for hemigland comparison.

Data Analysis

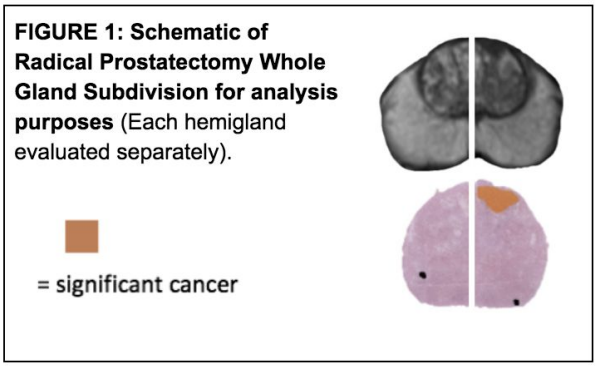


FIGURE 1: Schematic of Radical Prostatectomy Whole Gland Subdivision for analysis purposes (Each hemigland evaluated separately).

Biopsy included 127 PI-RADS 3 results which were excluded from binary analysis leaving 966 scans for inclusion. PI-RADS scores of 1 and 2 results were considered negative, PI-RADS 4 and 5 positive. Biopsy results were analysed for the presence of csPCa (Gleason pattern 4 disease) of any tumour volume. Biopsy results were analysed on a per-patient (whole-gland) basis. In order to evaluate the significance of normal (negative) multiparametric prostate MRI results against radical prostatectomy, the prostate MRI and tissue specimens were sagittally bisected and the suspicion (MRI) and presence of (wholemount hemigland) clinically

significant cancer were analysed for each half of the prostate separately (per hemigland analysis). A specialist uropathology service (Tissupath) marked the index tumour orange, and non-index tumour (second highest grade) black (See FIGURE 1). As exemplified in Fig. 1, the left and right hemiglands in this case recorded true positive and true negative results respectively (the small black focus marked by the pathologist in the right hemigland was only Gleason 6 disease). The case series of false negative hemiglands were re-reviewed noting their initial MRI and histopathology.

Results

There were 966 men in the biopsy analysis and 119 of these were included in the hemigland analysis, for a total of (119*2=) 238 hemiglands. The prevalence of csPCa within the cohorts was 56% (biopsy) and 68% (hemiglands) respectively.

MpMRI had a sensitivity of 90.5 (95% CI 87.94% to 92.74%) based on transperineal biopsy and a wholemount sensitivity of 85.90% (95% CI 79.70% to 90.90%) as 23 glands with csPCa out of 141 were called normal. However six of these 23 false negative hemiglands were scored so due to subtle midline extension from correctly identified contralateral tumours in otherwise normal hemiglands. Clinically each of these lesions were correctly documented and biopsied. By the strict definition of our analysis, these remain false negatives, however if these were reclassified as true negatives, the sensitivity rose to 89.2% (95% CI 83.3%, 93.6%) and false negative rate improved to 17 in 87 cases (19.5%), resulting in a negative predictive value of 79.2% (95% CI 70.79%, 85.80%), at a disease prevalence of 0.68.

PI-RADS scores were tabulated against biopsy results (TABLE 2). These demonstrated a strong association between increasing PI-RADS scores and grade groups, with Grade Group 5 lesions occurring in 3%, and 15% of PI-RADS 4 and 5 scored MRIs respectively. There were 335 patients who had transperineal biopsies after PI-RADS 1 or 2 studies, in whom 58 had GG2 disease or higher, a false negative rate of 17.3%.

The histopathology of the remaining 17 false negative hemiglands is described in TABLE 2. Missed lesions were predominantly Grade Group 2 disease (13/17) and 8/17 were less than 0.5cc.

Table 1: Accuracy of multiparametric prostate MRI according to transperineal saturation biopsy and hemigland radical prostatectomy specimens (WM) as reference standards. Prevalence of csPCa within the cohort.

	Biopsy N=966		**Wholemount**N=238 hemiglands	
	CaP = 56%	95% CI (p=.05)	WM CaP=68%	95% CI (p=.05)
Positive Predictive Value	73.20%	[70.41,76.00]	93.10%	[88.33, 96.02]
Negative Predictive Value	82.60%	[80.21,85.00]	74.37%	[66.28, 81.08]
Sensitivity	90.50%	[87.94% to 92.74%]	85.90%	[79.70, 90.90]
Specificity	57.70%	[54.58, 60.81]	86.50%	[76.50, 93.32]

TABLE 2: Correlation between PI-RADS scores and transperineal template biopsy histopathology results (rows sum to 100%)

(GG = Grade Group, B = Benign, N = number enrolled).

N=	**B**	**GG1**	**GG2**	**GG3**	**GG4**	**GG5**
12	9/12 (75%)	2/12 (17%)	1/12 (8%)	0/12 (0%)	0/12 (0%)	0/12 (0%)
323	174/323 (54%)	90/323 (28%)	48/323 (15%)	6/323 (2%)	3/323 (1%)	0/323 (0%)
127	43/127 (34%)	32/127 (25%)	42/127 (33%)	8/127 (6%)	1/127 (1%)	1/127 (1%)
325	42/325 (13%)	55/325 (17%)	143/325 (44%)	65/325 (20%)	13/325 (4%)	10/325 (3%)
306	9/306 (3%)	21/306 (7%)	110/306 (36%)	95/306 (31%)	24/306 (8%)	46/306 (15%)

TABLE 3: Histopathological Characteristics of False Negative Hemiglands.	
ISUP Grade Group Number of Cases (N=17)	
ISUP2: <10% Pattern Four	5
ISUP2: >10% Pattern Four	8
ISUP3 or higher	4
Lesion Volume Number of Cases (N=17)	
<0.5cc	8
0.5-1cc	5
>1cc	4

Discussion

Hemigland analyses have previously been performed against TRUS [132] [121] and transperineal mapping biopsy [133] but this study appears to be the first to assess mpMRI false negative rates using hemiglands correlated to radical prostatectomy specimens. Meta-analysis by the EAU prostate cancer guidelines panel, as well as separate meta-analyses by Zhang et al and Stabile et al., have described the Negative predictive Value of Prostate MRI as “var(ying) greatly” and listed several sources of heterogeneity affecting prostate MRI accuracy, particularly reference standard and cohort cancer prevalence [105,114] [56,134,135]. Indeed, upgrading of pathology results from biopsy to radical prostatectomy has been consistently demonstrated in literature [39] [136] [137]. Even compared against the optimal biopsy method of transperineal saturation, Calio et al. still demonstrated upgrading in 7% of cases [127] compared to subsequent wholemount radical prostatectomy. For this reason, comparison to definitive wholemount radical prostatectomy, in the form of hemigland analysis, was felt important so as to understand the true incidence and histopathological significance of missed cancers on mpMRI. The primary findings of this study were that mpMRI has a sensitivity of 90.5% (based on per-patient transperineal template biopsy comparison) and 89.2% (based on hemigland sectioned radical prostatectomy comparison) in the detection of clinically significant disease (ISUP GG>2 of any size) when reported by expert radiologists using PI-RADS Version 2.0 at 3 Tesla.

The results of our study are similar to those of other authors. The landmark PROMIS trial reported headline sensitivity and negative predictive values of 93% and 89% respectively, although this was for cancers with Gleason score >4+3 or more than 6mm in biopsy length. When the equivalent definition as in our study of ISUP Grade group 2 or higher for any size was employed in PROMIS, sensitivity was 88% and NPV 76%; similar to our own results of 89.6%-90.5% and NPV of 74.3-79.2%. The prevalence of cancer within their study of 57% for ISUP GG2 or greater matched our own biopsy prevalence (56%), whilst our hemigland prevalence was higher (68%). Thompson et al determined a sensitivity of 93-96% although their csPCa prevalence was 30-41% [138]. Hansen et al, used the same definition as our study and had the same prevalence of csPCa as our hemigland cohort. Their finding of a negative predictive value of 80% [110] was within the range reported by our own results.

Missed tumours in our study were typically smaller and low grade lesions. 76% of missed lesions were Grade Group 2 and 29% of missed lesions contained <10% pattern 4. This is consistent with results of other authors who have demonstrated that more conspicuous lesions contain higher percentages of Gleason pattern 4 disease [139]. In a study by Mohammadian Bajgiran, 75.7% of clinically significant missed lesions were ISUP Grade Group 2 [56,134,135] by size alone, 47% of missed tumours in our study were less than 0.5cc and only 23% were greater than 1cc. This is similar to results of Branger et al, who found that 35.3% of missed lesions were below 0.5cc, and only 5.9% were above 2cc.[140] . Rather than just the prevalence of csPCa within study cohorts, the prevalence of low volume/low Gleason pattern 4 disease within the cohort may also represent a cause of heterogeneity due to its predisposition for inconspicuity.

Understanding the natural history of mpMRI missed lesions is of vital importance in both disease detection and clinical management. Chu et al recently demonstrated that mpMRI alone should not replace biopsy in determining disease upgrading in an active surveillance cohort, as 14.9% of Grade Group 2 disease was missed on subsequent biopsy in their active surveillance cohort using mpMRI alone [141]. Whilst our sensitivity values were slightly higher, our results also demonstrate that there is a proportion of men in whom csPCa is missed. Our results add caution to the growing trend of focal ablation, as our results demonstrate inconspicuous disease in the contralateral hemigland may render some patients undertreated. However, missed lesions in our study were predominantly low volume low percentage Gleason pattern 4, which a growing body of literature suggests can be appropriately surveilled. In 219 men with untreated Grade Group 2 disease

followed over a median of 3.1 years at Memorial Sloan Kettering, 64 went on to treatment (mainly due to patient preference) but none developed distant metastasis and two patients developed local nodal disease [142]. Focal therapy may therefore be entirely appropriate in some patients, as long as they undergo close surveillance. Similarly, patients in whom a low volume Grade Group 2 lesion is missed on initial mpMRI, but are followed up with subsequent mpmRI testing over a 1 or 2 year period, appear unlikely based on these active surveillance cohorts to develop incurable disease in the interim. To this end, multiple studies demonstrate an additional benefit of combining negative mpMRI with serum markers in order to correctly risk-stratify patients [143]. There is also a growing body of literature that PSAD < 0.15 ng/ml/cm, combined with negative mpMRI, improves sensitivity and negative predictive values [110–112,122,141,144,145]. Our study was unable to assess the added benefit of PSA Density in negative tests due to the index lesions in the positive hemiglands.

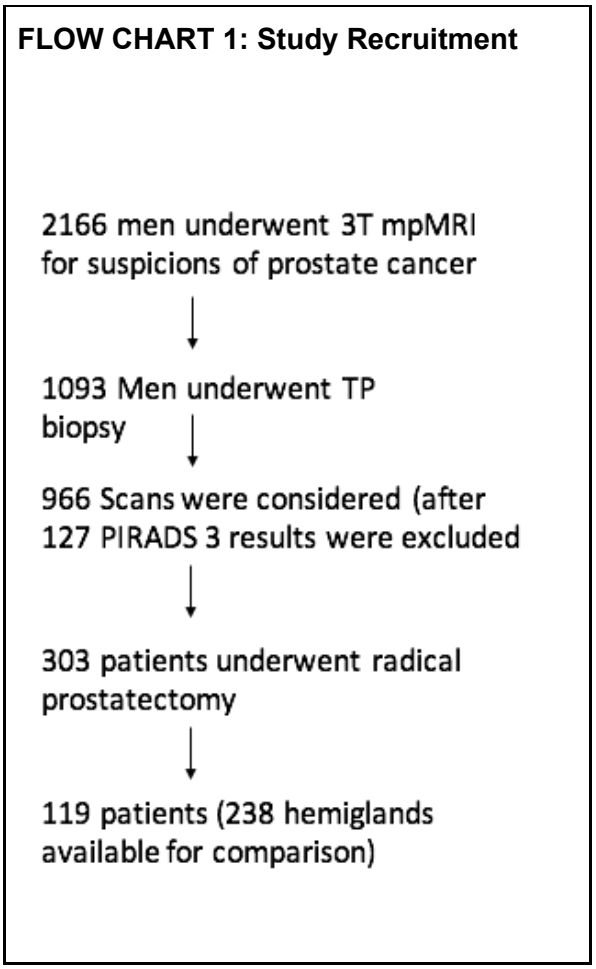
There are several limitations of our analysis. A single 3T MRI machine was used amongst all patients, so any heterogeneity in scanner types is not considered. The reporting radiologist in our study has more than 5 years experience in prostate MRI, and therefore less experienced radiologists may not be able to reproduce our results, given the demonstrated link between radiologist experience and reporting accuracy. The study did not consider the effect of clinical parameters such as PSA Density, which combined with Prostate MRI may help avoid biopsy [146], although this was clinically evident. Furthermore, not all patients from our original cohort went on to biopsy. Of 2166 men, only 1093 proceeded to biopsy. This is because based on a reassuring PI-RADS score, and low clinical suspicion (for example, a low PSA Density), the patient's urologist would choose to avoid biopsy. Therefore, our study design includes (an unavoidable) selection bias, as it does not consider the missed cancers in patients who did not proceed to radical prostatectomy, such as active surveillance patients, or those PI-RADS 2 cases where biopsy was omitted. Overall however, if (hypothetically) all PI-RADS 1 and 2 scored patients had been mandated to have a subsequent biopsy, this would be expected to further improve the negative predictive value of our study results, as this cohort would provide far more true negative than false negative results, just based on risk stratification alone. Despite these limitations, the study ultimately adds to the strong discriminative ability of prostate MRI in prostate cancer detection.

CONCLUSION

A novel hemigland analysis was performed to correlate negative MRIs against wholemount histopathology. The false negative rate of mpMRI for the detection of any volume of ISUP Grade Group 2 cancer or higher, was 17.3% on transperineal biopsy and 19.5% on hemigland analysis. Clinicians should be aware that mpMRI can miss clinically significant disease, but that the majority of these missed lesions are small and low percentage Gleason pattern 4. Histopathologically 76% of missed lesions were Grade Group 2 and 29% of missed lesions contained <10% Gleason pattern 4, with 47% of missed tumours less than 0.5cc in volume and only 23% greater than 1cc.

APPENDIX A

FLOW CHART 1: Study Recruitment



APPENDIX B

3.0 Tesla mpMRI protocol. Abbreviations: TR = Repetition Time, TE = Echo Time, FOV = Field of View, DWI = Diffusion Weighted Imaging, DCE = Dynamic contrast enhancement.

Parameter	
T1 TR ms/ TE ms	510/11
T1 section thickness (mm)	1.5
T1 FOV (mm)	350
T2 TR ms/ TE ms	4000-6000/101
T2 section thickness (mm)	3
T2 FOV (mm)	150
DWI TR ms/ TE ms	3800/71
DWI b-values	50,400,800, Calculated 1400
DWI Section thickness (mm)	4
DWI FOV (mm)	170 (Sag + Ax)
DCE TR ms/ TE ms	4.83/1.87
DCE section thickness (mm)	3.5
DCE FOV (mm)	260

Contrast Agent: Intravenous Gadovist (0.1 mmol/kg body weight)

CHAPTER 2 DISCUSSION

Hemigland analysis results were consistent with those reported by transperineal template biopsy comparator studies[122]. Although prior studies have described up to 7% of transperineal template saturation biopsy results (gold-standard biopsy) upgraded on subsequent radical prostatectomy[127], discrepancy between transperineal template and wholemount radical prostatectomy disease detection rates were equivalent in our study: sensitivity was 90.5% on transperineal biopsy and only slightly lower (89.6%) on hemigland analysis. A limitation of this study is that the transperineal and hemigland cohorts were not perfectly matched, as some patients were excluded because both hemiglands were suspicious, based on the original MRI. For example, of all 303 patients who had undergone radical prostatectomy at the time of data collection, only 119 patients had hemiglands that could be included in the analysis. This is a natural limitation of any hemigland analysis and would be a limitation for other authors performing the same methodology. However, one additional consideration within these patients is that their likelihood of harbouring clinically significant disease is arguably much higher than that of any population-based cohort. As the patients within this analysis were known to have clinically significant prostate cancer, and given that prostate cancer pathogenesis frequently involves a "field change" theory [147] of an index lesion within small multifocal tumorlets dispersed throughout the gland, the likelihood of clinically significant prostate cancer is higher within our hemigland cohort than within hemiglands of patients not known to have established contralateral disease. Thus the increased likelihood of clinically significant disease within the hemigland cohort strengthens the validity of these results should the sensitivity and false negative results from this study be extrapolated to a population of men undergoing screening without prior biopsy due to raised PSA/PSAD (baseline prostate cancer risk).

There are several implications for these results in clinical practice. Firstly, these results need to be contextualised by the findings of other studies which demonstrate that risk stratifying patients for biopsy based on their MRI result alone results in inferior risk stratification compared to combining prostate MRI with additional information such as PSA Density [111,122].

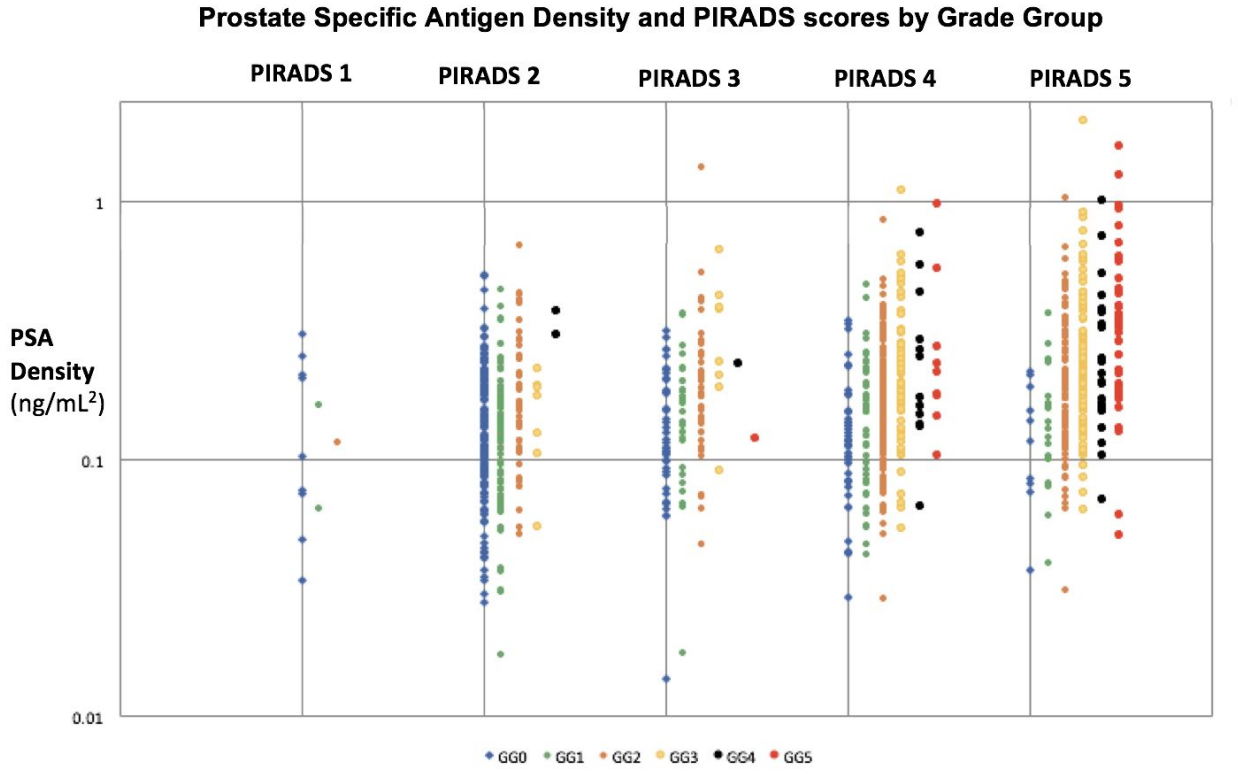
Consideration one: do these results mandate biopsy in all PI-RADS 1 or 2 scans?

The first clinical consideration is whether these results mandate subsequent biopsy in all men subject to prostate MRI regardless of their result. Regis et al argued in a 2019 publication that PI-RADS 1 or 2 results should not be considered 'normal' and that routine biopsies can not be omitted [148]. This was based upon a 20% false negative rate of mpMRI. Based on the results of our own study, mpMRI can be used to 'selectively omit' biopsy - as part of a combined risk assessment including, in particular, PSA Density. Other authors support this view[105]. Although

approximately 10% of clinically significant cancers on hemi-glands in our own study were missed, these were predominantly low-grade and small-volume. However at the same time, 4 of the 17 cases that proceeded to radical prostatectomy harboured at least ISUP Grade Group 3 disease. When transperineal template biopsy with targeting was used as the comparator, for which there were 996 men within the cohort, 17% of PI-RADS 2 scores harboured clinically significant disease. That is, 15% of PI-RADS 2 scores contained Grade Group 2 disease, and 3% of PI-RADS 2 scores contained Grade group 3 or 4 disease. These mpMRI results were combined with PSA Density scores (unpublished data, graph below) to ascertain whether there is any PSA Density threshold above which PI-RADS 2 MRIs should be routinely biopsied (in order to isolate these false negative mpMRI patients). Unfortunately, the Grade Group 2 tumours had PSA Density results that perfectly overlapped the benign biopsy results. However, the most likely cause for this is that the volume of Gleason pattern 4 disease within the Grade Group 2 tumours was not enough to drive a significant increase in the overall PSA Density; in other words, they are likely to reflect low-volume Gleason pattern 4 disease - as was suggested by the volume of clinically significant disease within the false negative results of the cases that proceeded to radical prostatectomy (TABLE 3 within the study). This is further supported by the fact that mpMRI commonly misses cancers less than 0.5cc, as demonstrated in CHAPTER 2 and by other authors[135]. Therefore, the Grade Group 2 tumours within this analysis were both macroscopically and biochemically inconspicuous. This suggests a low volume of Gleason pattern 4 disease which confers a lower morbidity/mortality burden [129].

In contradistinction, of the two Grade Group (GG) 4 biopsy results within the transperineal template matched prostate MRI cohort, both had PSA Density results above 0.30mg/ml; one case had PSA Density of 0.30mg/ml and the other of 0.373mg/ml respectively. If negative mpMRI cases are biopsied when their PSA Density is equal to or greater than 0.3mg/ml, two biopsies returned GG3, seven returned GG2 disease and 10 returned GG1/benign results. Whereas several studies have evaluated PSA Density cut-offs below which patients with reassuring prostate MRI results need not be biopsied[105], the implication here is the corollary. These findings suggest that despite a PI-RADS 2 MRI result, a small subgroup of those patients - with a PSA Density > 0.30 mg/ml - should be considered for biopsy as they have an almost 50% chance (9 of 19 patients) of harbouring clinically significant disease. This result is consistent with other studies demonstrating that the negative predictive value of PI-RADS 2 scores mpMRIs decreases as the patient's PSA Density levels rise[146]. One benefit of the full mpMRI protocol (including contrast) is that the scan (in particular the DCE series) may illustrate whether a raised PSA Density results from prostatitis. As an alternative cause of raised PSA Density, this could be used to dismiss the raised PSAD[82] .

In patients with a PSA Density greater than 0.30 mg/ml and without MRI evidence of prostatitis, these results suggest subsequent biopsy is worthwhile.



Consideration two: the role of ongoing follow-up

The options for ongoing management after an mpMRI have immediate and complete discharge from clinical care at one extreme, and mandated biopsy at the other. The most appropriate option for follow-up post negative mpMRI is determined by diagnostic accuracy, of which sensitivity and negative predictive value are the key metrics to consider because patients have a low pre-test probability [149]. Whereas sensitivity describes the proportion of patients with the disease who were accurately characterised, negative predictive value describes the percentage of normal tests that were correct in predicting the absence of disease. Our study was suboptimal in its evaluation of the negative predictive value of mpMRI. The reason for this is that predominantly only suspicious (PI-RADS >=3) mpMRI results proceeded to biopsy. Whilst subjecting all patients to biopsy, regardless of mpMRI result, would be a superior study methodology, our study was only able to analyse biopsy results in those patients who underwent biopsy based on the clinical suspicion of the patient's urologist. This is a common phenomenon in literature. For example, in a literature review of the Negative Predictive Value of mpMRI, only 10 studies were identified in which biopsy results were available for all patients who had undergone mpMRI. The literature review excluded

17 studies that predominantly biopsied only positive mpMRI results, as ours did [150]. That 17 out of 27 studies routinely omitted biopsy in patients with PI-RADS 1/2 scans demonstrates that the practice of omitting biopsy based on negative scan is quite widespread. However this results in recruitment bias within any subsequent study, falsely elevating the baseline cancer prevalence and decreasing the negative predictive value [151]. A Cochrane Review from June 2019 (published after the literature review) removed some of the heterogeneity identified by the 2017 European Association of Urology systematic review on Negative Predictive Values. This Cochrane Review analysed the diagnostic accuracy of mpMRI against saturation biopsy as gold standard [116]. This identified 12 studies with 3091 pooled patients in which mpMRI was assessed for its ability to detect ISUP Grade Group 2 disease (of any volume), the prevalence of which within the pooled analysis was 34%. The pooled percentage of mpMRI initially scored PI-RADS 1 or 2 was 29% and their negative predictive value was 0.91 (0.86–0.94). In our own study, which alone evaluated 996 men for ISUP Grade Group 2 disease, the cohort prevalence of csPCa was far higher at 56%. The percentage of biopsy-correlated mpMRIs which were scored PI-RADS 1 or 2 was similar at 33%. However in our cohort there were an additional 1073 men who had mpMRI but did not proceed to biopsy (based on the decision of the treating urologist), having recorded a PI-RADS 1 or 2 result. Had these men been included, the prevalence of csPCa within the study would have been far lower. The average PSA Density of the cohort that did not proceed to biopsy was 0.125mg/cc (SD 0.008mg/cc). PSA Density is known to incrementally improve the negative predictive value of mpMRI, particular at a threshold lower than 0.15mg/cc [122], where the likelihood of harbouring csPCa is approximately 8% (+/- 4%) [122]]. This is very likely one of the factors that reassured the urologists against the need for biopsy. These results suggest that, similar to breast, colon and lung cancer screening guidelines[152], very few patients with an initial negative prostate MRI can be indefinitely discharged, given the low, but non-zero percentage of clinically significant cancer within the PI-RADS 1 and 2 cohorts found on subsequent biopsy. These results represent those of optimal image acquisition quality with subspecialist uroradiologist scan interpretation. These are both factors known to affect the accuracy of multiparametric prostate MRI. Therefore any suggestion of ongoing follow-up needs to also account for the possibility of suboptimal interpretation or acquisition. There is preliminary evidence regarding the timeframe for repeat scanning - with a 2018 study by Steinkohl et al suggesting that evaluation of indeterminate lesions (PI-RADS 3) at one year is an appropriate follow-up period [153]. However, in patients with a normal PSA Density and mpMRI, there is neither chemical (PSA Density) or macroscopic (MRI-based) evidence of significant tumour burden. This suggests any disease, if present, is low volume. Patients with negative mpMRI could be followed with ongoing PSA monitoring. This is the conclusion of several studies and results of a recent Cochrane Review [116]. Ongoing follow-up

with yearly PSA, with knowledge of the prior PSA Density - with a significant increase triggering repeat imaging - may represent a reasonable course of action. Ultimately, further research is required to assess the prospective outcomes of such a follow-up plan for PI-RADS 1 and 2 patients. An additional consideration that could be the subject of further research, is whether those men who have already had a negative multiparametric MRI scan could be considered for repeat imaging by biparametric study only (without contrast) given that they have already been risk stratified by the initial mpMRI.

In conclusion, this chapter demonstrates that multiparametric MRI acquired at 3 Tesla with high b value imaging and post processed contrast maps, read by expert radiologists, provides low rates of missed clinically significant disease when compared to gold standard histopathology. Predominantly, missed clinically significant disease is low volume and low grade. This subsequently suggests that negative prostate MRI results can omit the need for biopsy in some men but not all, and that ongoing management should be weighed against other factors involved in risk stratification such as family history and PSA Density stratification. Men with a PSA Density greater than 0.30mg/cc should be considered for biopsy despite negative mpMRI, in agreement with other studies demonstrating that patients with elevated PSA Densities and negative mpMRI results are still statistically more likely to harbour csPCa [146,154]. This chapter broadly agrees with other studies that suggest that MpMRI should be used in combination with clinical risk assessment tools and PSA Density to stratify men with negative initial mpMRIs into those who should nonetheless undergo biopsy, those who can omit biopsy with subsequent mpMRI in the future, and those who only require further periodic monitoring with biochemical markers such as PSA.

CHAPTER 3:

A Root Cause of Analysis of False Negative prostate MRIs Identified on Radical Prostatectomy

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

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CHAPTER 3 INTRODUCTION

The prostate imaging-reporting and data system (PI-RADS) is the predominant reporting system for prostate MRI scans. Its creation from the consensus opinion of subject matter experts has subsequently standardised and increased the reproducibility of mpMRI. Despite these significant improvements, its creators describe it as a "living document", that may be altered by the results of high quality studies as they arise. In this context, at the commencement of this chapter several studies existed that validated the PI-RADS scoring system, particularly the PI-RADS Version 2 update which had been recently introduced. Many of these studies simply confirm the excellent overall discriminative ability of the scoring system rather than critically appraise it with a view to improvement.

Overall accuracy of PI-RADS Version 2.0 has been described as “widely” varied in accuracy by meta-analyses[105]. The factors that account for this can be categorised on the basis of patient-related, tumour-related, scan acquisition-related, or interpretation-related. Patient-related factors are artefact from hip prosthesis or incomplete rectal emptying. Tumour-related factors refer to the heterogeneity of tumours themselves with respect to size and overall conspicuity. Examples of acquisition-related factors are the use of post processing on dynamic contrast enhancement maps, high b value images and scanner type (1.5 or 3 Tesla machine). Interpretation-related factors are principally the experience of the reporting radiologist (described further in CHAPTER 3) and the PI-RADS scoring system itself.

In the following retrospective review of false negative MRI scans each false negative case was analysed to understand the reason for the incorrect scoring. Each scan was acquired according to optimal acquisition methods according to the current PI-RADS system (high b value imaging, 3 Tesla machine). The reporting radiologist is amongst the highest volume prostate MRI readers (globally), described within the literature. The reference test, in wholemount radical prostatectomy specimens, provided a granular understanding of the false negative tumour characteristics (tumour grade group and tumour volume).

The overarching aim of the study was to perform a “root cause analysis” of missed prostate cancers. In particular, if a lesion was visible in retrospect, the location of the tumour would be noted in order to assess for the presence of any “blind spots”. Furthermore any interpretive errors by a highly experienced uroradiologist would be very instructional to the large number of low-volume prostate MRI readers. At the same time, the study provided the opportunity to assess whether there were any non-PI-RADS findings that consistently occurred in false negative cases.

An MRI-Histopathology Correlated Analysis of Missed Prostate Cancers Amongst Expert Radiologists.

Introduction

The utilization of prostate MRI continues to increase, steadily driven by research publications, incorporation into clinical guidelines and more widespread reimbursement [155]. This demand must be met by upskilling radiologists in reading prostate MRI [156]. Prostate MRI interpretation is difficult due to mimickers of prostate adenocarcinoma such as stromal hyperplasia and prostatitis [157,158]. Although the PI-RADS scoring system greatly improved prostate MRI interpretation through the standardization of reporting and acquisition [52], large numbers of cases, with feedback, are nonetheless required to reduce inter-reader variability [159]. Multidisciplinary meetings are one of the most common and effective means of achieving tissue correlated feedback for improving interpretive accuracy [160–162]. This paper explores the results of one such tissue-based feedback process amongst experienced uro-radiologists (defined as at least 5 years of attending uroradiology MDT meetings for prostate MRI), for whom radical prostatectomy wholemount sectioned histopathology was available for retrospective comparison with their initial scan interpretation. These results quantify the zonal distribution of missed lesions on prostate MRI. This subsequently enabled the formulation of systematic techniques that radiologists may employ to reduce blind spots and false negative rates in prostate MRI interpretation.

Methods

Patient data were prospectively stored in a REDCap database approved by our local ethics review board. Between 7/23/2013 and 8/1/2020 2,324 patients were referred to a private urology practice and underwent at least one multiparametric prostate MRI scan. These were performed on a single 3T Siemens machine and acquired in accordance with the PI-RADS Version 2.0 stipulations. Scans were read in accordance with ESUR/PI-RADS Version 2.0 guidelines and technical details can be viewed in Appendix B. Of these 2,324 patients, 464 underwent radical prostatectomy; and of these 464 patients, 34 were false negatives in that their initial prostate MRI was scored as PI-RADS 1 or 2. The inclusion criteria were: time between MRI and surgery of less than 6 months,

and index tumours of any size, comprising Gleason 3+4 =7 or greater (the equivalent of ISUP Grade Group 2 or higher).

The 34 false negative MRIs were retrospectively reviewed by a second clinician (radiology trainee-RM) against their corresponding wholemount pathology images (open simultaneously, see Picture 1). The initial scan result was conveyed by the radiologist drawing the location of any lesion on a diagrammatic representation of the prostate in 3 planes. As the cases in Appendix 1 and Picture 1 demonstrate, the wholemount specimens were photographed with their index lesion highlighted in orange and non-index lesions in black. The entire gland underwent wholemount sectioning, selected images are just single axial slices from the gland which were available for review. This enabled the reviewer to correlate any index lesion identified by the reporting radiologist with the index lesion of the pathologist. If the index lesion was not observed by the original radiologist, the reviewer would note if the lesion was visible on any sequence in retrospect, or if there was any other explanation for the lesion's inconspicuousness; specifically lesion size, location, image artefact, prostate appearance or distracting pathology.

In patients who had multifocal disease, this study examined only the index lesion – defined as the highest grade lesion or largest lesion in multifocal disease of the same grade. False negative carcinomas were categorized using their wholemount specimen location according to the zonal divisions of the prostate and lesions crossing zonal divisions were defined by the primary bulk of the tumour.

Results

Overview

There were 34 false negative studies (mean age 63 +/- 6 years) of which 15 lesions were totally invisible despite knowing their exact location from the histopathology. The 34 false negatives were distributed with the majority (14) within the peripheral zone; with the transition zone (7); anterior fibromuscular stroma (5) and prostate apex (8) roughly sharing the remainder (TABLE 1). Despite having the greatest number of false negatives, the peripheral zone actually had the *lowest* number of lesions - just 3 - that could possibly be identified in retrospect; missed lesions in the peripheral zone were essentially MRI invisible, even with knowledge of the tumour location available whilst retrospectively reviewing the MRI.

transition Zone (TZ)

Seven lesions within the transition zone were identified on radical prostatectomy, of which 5 were visible in retrospect. But 4 of these 5 lesions, which were scored correctly according to PI-RADS Version 2.0 at the time of reporting, would have been up-graded to PI-RADS 3 if reported again under the current PI-RADS Version 2.1 conventions due to increased diffusion restriction relative to the surrounding central gland (see cases labelled TZ 1-4 in Appendix 1). A further lesion was only partially visible due to hip prosthesis artefact. Two lesions were not visible in retrospect, and although histologically they were similar to the identified tumours, no cause was identified for their inconspicuity.

Anterior Fibromuscular Stroma (AFMS)

There were 5 false negative anterior fibromuscular stroma lesions *(Cases Labelled AFMS 1-4).* They each displayed crescentic restriction on axial diffusion weighted imaging to differing degrees. With their exact location known whilst reviewing the scans, these lesions were missed due to varying conspicuity - perceptible signal strength - of the diffusion studies. In retrospect, these tumours were visible on coloured early contrast enhancement DCE series maps in three of the four cases in which contrast was administered. Histologically, two of these five lesions were Gleason 4+3=7 (ISUP GG3), the rest being 3+4=7 (ISUP GG2).

Prostate Apex (PA)

There were 8 tumours at the inferior most prostate apex, of which 6 were identifiable in retrospect. These lesions demonstrated either isolated focal diffusion restriction (consistent with a PI-RADS Version 2.1 score of 4), or weak diffusion restriction with focal early contrast enhancement. In 5 of 6 cases (see Apex Cases 1-4 in the appendix), early contrast enhancement on DCE colour maps was more conspicuous than on diffusion weighted imaging. There were two apical tumours which were invisible in retrospect, presumably due to their histopathological characteristics; One was only 5% Gleason pattern 4 (predominantly pattern 3 disease) and the other only 0.5cc of predominant Gleason pattern 4.

Peripheral Zone (PZ)

There were 14 peripheral zone lesions of which 11 tumours were invisible on MRI imaging despite wholemount review (Table 2). 2 possibly identifiable tumours were small midline lesions. They demonstrated rounded foci of hypointensity on T2 weighted imaging, but only minor linear morphology DWI signal (PZ cases 2 and 3) consistent with a PI-RADS 2 score. A third carcinoma identifiable in retrospect was located within the posterolateral peripheral zone. This demonstrated wedge shaped T2 hypointensity with no diffusion restriction nor contrast enhancement. The area of interest was identified at the time of reporting, but the MRI appearance was characteristic of a PI-RADS 2 score. This lesion was 0.8cc of 4(70%)+3=7.

Low grade (low percentage Gleason pattern 4) or low volume tumours made up the majority (6/11) of invisible peripheral zone lesions (Table 3). These were typically smaller than 0.5cc, or contained 5-10% Gleason pattern 4 disease amongst a predominant Gleason pattern 3. Four lesions were neither low grade nor small, but were still invisible. These occurred in the presence of atrophy or prostatitis (PZ case 1).

Discussion

In our study, 7.5% of clinically significant index lesions in patients who went on to undergo radical prostatectomy were not identified on initial MRI. This is similar to other wholemount matched study results of 5% [134] and 16% [163] respectively. 44% (15/34) of false negative index lesions were invisible on the initial MRI even retrospectively with wholemount review; in agreement with Park et al [135] who found 7 of 14 (50%) Gleason 7 or greater lesions to be truly invisible. The clinical significance of these truly invisible lesions remains unknown – most contained 5-10% Gleason pattern four amongst predominant Gleason pattern 3 disease or were less than 1cc in tumour volume, so may represent lower risk lesions.

The peripheral zone contained 3 false negatives visible in retrospect, all of which were scored PI-RADS 2 due to benign DWI appearances. Although 70-80% of prostate cancer occurs in the peripheral zone [130,131], these results suggest that prostate MRI read by experts is extremely accurate in the detection of peripheral zone cancers. The majority of invisible peripheral zone lesions were small/low percentage Gleason pattern 4 (6 cases), consistent with prior studies suggesting “size and grade” [164] predict lesion conspicuity. Other researchers suggest that higher

Gleason pattern 4 disease of 20-30% predicts MRI visibility of Gleason 7 disease [139] and our results suggest the corollary that invisible Gleason 7 lesions typically contain lower Gleason pattern 4 disease (5-10%).

In our study the distal apex and anterior fibromuscular stroma harbored the greatest relative number of false negatives which could be seen in retrospect (12 of 18). Prior work [163],[165] describes these areas as potential pitfalls, and our results suggest that these are specifically the two most significant locations for radiologists to be wary of.

There was a common MRI appearance to the 4 prostates that harboured invisible yet larger/higher grade peripheral zone lesions, the highest grade of which was 4+3=7, tumour volume 1.3cc. On T2 weighted imaging these prostates demonstrated peripheral zones with lower signal that were essentially isointense to the transition zone; so that the two were indistinct. Radiologists are familiar with the concepts of “T2 shine-through” and “T2 blackout”. These concepts exist because of the relationship between T2 weighted signal intensity and diffusion restriction signal intensity. In 4 cases, prostates with isointense peripheral zones (relative to the transition zone) on T2 weighted imaging harbored significant peripheral zone carcinoma but had negligible diffusion restriction on the diffusion weighted sequences. Suspicious foci of diffusion restriction may be less conspicuous in these low T2 signal peripheral zone prostates, increasing the false negative rates for peripheral zone cancers amongst prostates with this specific ‘indistinct peripheral zone’ appearance. In this subgroup, the DCE series may therefore have a correspondingly higher utility in the detection of clinically significant cancers. Further research is required to investigate this.

Within the anterior fibromuscular stroma five out of five lesions had some degree of diffusion restriction that may have been visible in retrospect and 3 out of 4 missed lesions demonstrated early contrast enhancement on DCE. This region should be specifically scrutinized. The DCE series may provide a useful backstop if isolated focal anterior gland uptake alerts the clinician to scrutinize the DWI images extremely carefully, as the focal early contrast enhancement was more conspicuous than DWI. Whilst DCE is generally considered insensitive for the detection of prostate carcinoma [166], fibrous content renders the AFMS relatively avascular and thus potentially increases the usefulness of DCE in this zone [12] (AFMS Case 1-4). Within our study, we specifically used post-processed quantitative maps reflecting early contrast enhancement (such as K_{trans}) in our evaluation of early contrast enhancement. The raw temporal T1-weighted axial slices were not routinely reviewed. One benefit of reviewing the post-processes images was that they succinctly standardised the time-series data. However, the authors acknowledge that this will be a

limitation to radiologists who do not routinely use post-processes early contrast enahncement maps.

The prostate apex is known to be an area of increased false negatives [167]. In our study the prostate apex contained 6 of the 18 total lesions potentially identifiable in retrospect. In our study the commonality amongst these missed lesions was poor conspicuity on T2 weighted imaging with only faint DWI signal (B value of 1400). Early contrast enhancement on DCE maps greatly improved lesion conspicuity due to the flash of colour from their colour-system overlay (See Appendix Apex cases 1-4). The PI-RADS flowchart evaluates such lesions first with diffusion imaging. However, in missed cases, the diffusion restriction was relatively subtle. An alternative checklist method of evaluating the prostate apex specifically is to interrogate this area for early contrast enhancement on DCE. Radiologists could then correlate these regions of interest with the diffusion weighted study, which may help avoid overlooking apical tumours which demonstrate only subtle diffusion restriction. Compared to the transition zone, these regions contain less competing BPH pathology that might otherwise reduce the positive predictive value of DCE.

Limitations to this study include its single-institution setting and bias introduced by its retrospective nature. Our study did not incorporate genomic data, and therefore is unable to address recent studies reporting a genetic basis for false negatives such as cribriform adenocarcinoma subtype [168]. Probably the largest limitation in this study is that it did not explore the extent to which any of these checklist methods introduced false positive results. This was not possible in this study, due to the study design which started with the radical prostatectomy results and then reviewed the prior false negative mpMRIs. Thus, a further avenue for research regards evaluating the false positive rates of any of these techniques. At the same time, the study highlights the distribution of cancers missed by experts at PI-RADS 2.0, which should serve as a useful evidence base for constructing a search pattern “checklist” for prostate MRI reporting.

Summary

7.5% of Radical Prostatectomy patients had MRIs negative for significant prostate cancer with initial PI-RADS Version 2.0 scores of 1 or 2. 44% of these index lesions were MRI invisible in retrospect (3.3% of radical prostatectomy specimens). Most (11) invisible lesions occurred in the

peripheral zone where the cause was small size/low grade (Gleason 3+4(5%)=7 or <0.5cc) in 6 cases. Our retrospective radiology-histopathology review suggested four “checklist” methods for improving lesion detection, two each for the transition zone and peripheral zone respectively. For the transition zone, PI-RADS Version 2.1 rescoring (where focal restricted diffusion in a BPH nodule upgrades to a PI-RADS 3 lesion) effectively captured almost all missed tumours. Secondly the anterior fibromuscular stroma should be a dedicated check area, and lesion visibility was improved through dedicated assessment of this region for early contrast enhancement on DCE. In the peripheral zone, restricted diffusion at the prostate apex may be extremely subtle, which may be overcome by screening this area specifically for early contrast enhancement on DCE series. Finally, indistinct peripheral zones - where the peripheral zone and transition zone are isointense to one another on T2 weighted imaging - may represent a specific subsection of cases wherein diffusion weighted imaging is less sensitive for peripheral zone cancer detection. Being wary of these cases and assessing the peripheral zone specifically with DCE to assess for focal enhancement may make subtle lesions more conspicuous.

TABLE 1: Location of False Negatives	**Number of False Negative Scans**	**Number of Index Lesions visible in Retrospect**	**Number of Index Lesions Invisible in retrospect**
Transition Zone	7 (21%)	5* (26%)	**2 (13%)**
Anterior Fibromuscular Stroma	5 (15%)	5 (26%)	**0 (0%)**
Prostate Apex	8 (24%)	6 (32%)	**2 (13%)**
Peripheral Zone	14 (41%)	3 (16%)	**11(73%)**

TABLE 2: PZ Carcinomas not identified in retrospect	**11**
DWI unreliable due to rectal gas artefact	1
Carcinomas that were 0.5cc or smaller (up to pattern 4+3)	3
Carcinomas that were low grade (either 5% or 10% pattern 4 Gleason 7’s) all less than 2cc	3
Carcinoma obscured by other pathology	4

TABLE 3: Histopathology of lesions not visible in retrospect	**Grade**	**Volume**
1	3+4(30%)=7	0.4 cc
2	4+3	0.5cc
3	4(80%)+3=7	0.5cc
4	3+4(10%)=7	0.9 cc
5	3+4(5%)=7	1.8 cc
6	3+4(10%)=7	.2cc

FIGURE 1: Example of the Dataset

A dataset of multiparametric prostate MRI images was juxtaposed against the equivalent wholemount sectioned radical prostatectomy specimen, which had index tumours marked in orange by a pathologist.

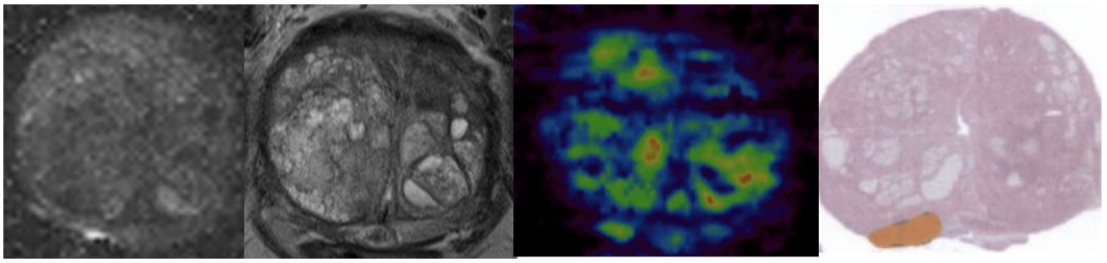
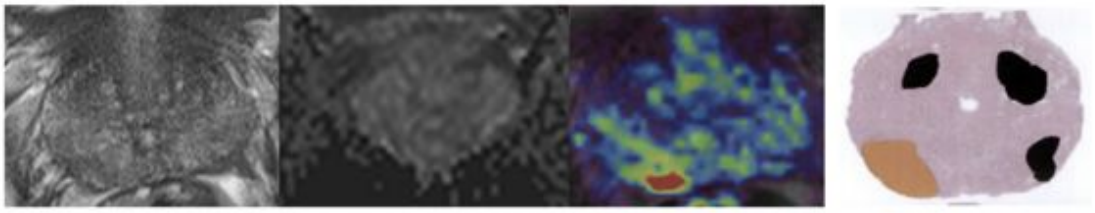
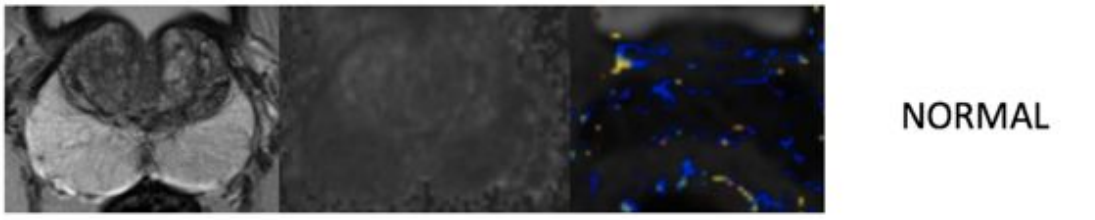


FIGURE 2: Example of the isointense Peripheral Zone/Transition Zone concept.
T2 weighted, Diffusion weighted, DCE images and Histopathology (in that order) are presented. Isointensity between the peripheral and transitional zone in the first column are evident, and the associated cancer was inconspicuous on both T2 and DWI imaging.

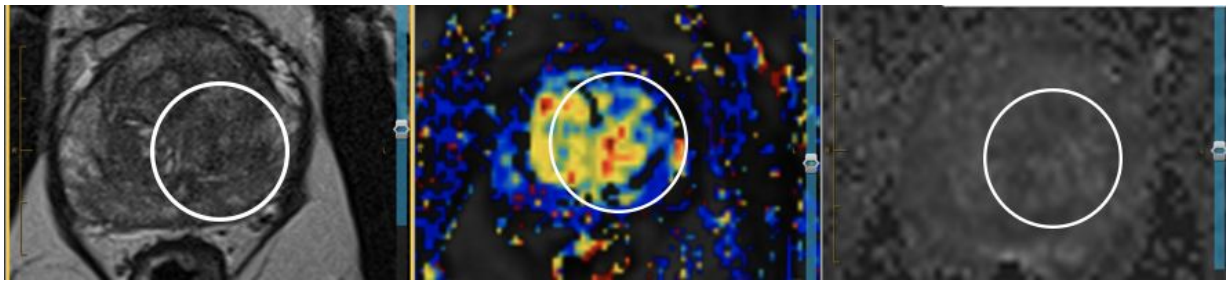
Isointense PZ/TZ	
Normal	

FLOWCHART 1: STUDY ENROLLMENT

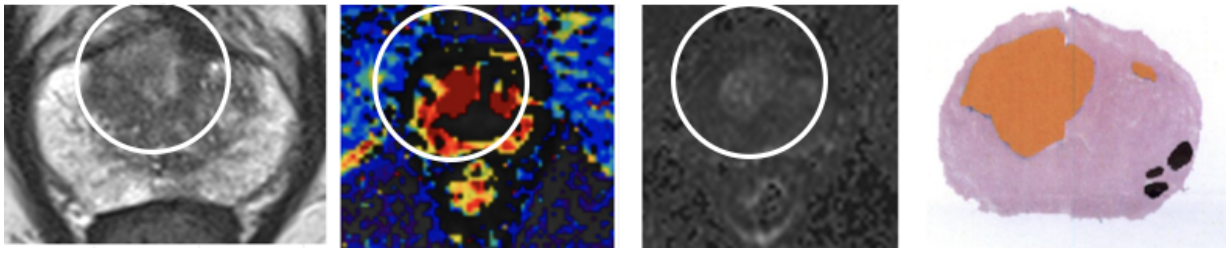
2,324 patients had mpMRI between 7/23/2013 and 8/1/2020
464 of these underwent radical prostatectomy based on positive biopsy result.
34 of these patients had initial prostate MRI results scored as PI-RADS 1 or 2. The inclusion criteria were: time between MRI and surgery of less than 6 months, and index tumours of any size, comprising Gleason 3+4 =7 or greater (the equivalent of ISUP Grade Group 2 or higher).

Appendix A Transition Zone

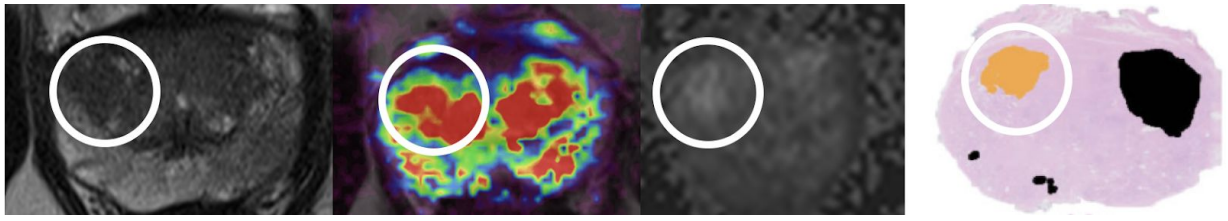
TZ Case 1 – False negative upgraded to PI-RADS 3 due to the relative hyperintensity of the DWI. 3+4 =7



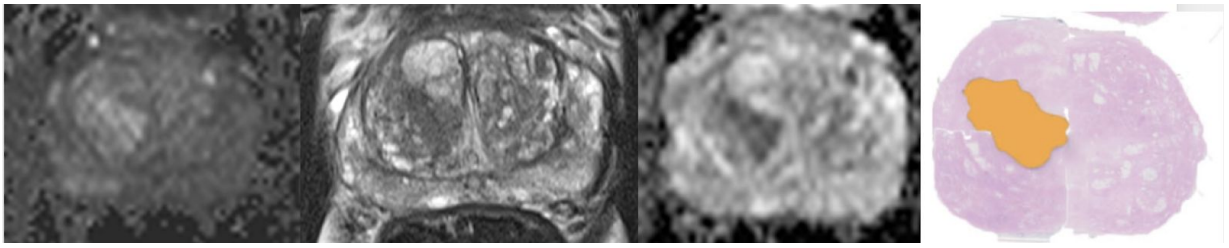
TZ Case 2 - False negative upgraded to PI-RADS 3 due to the relative hyperintensity of the diffusion weighted sequence, which demonstrated a nodular morphology. 3+4 =7



TZ Case 3 – Faint diffusion restriction. DCE interpretation is difficult due to diffuse transition zone enhancement. 3 + 4(20%) = 7

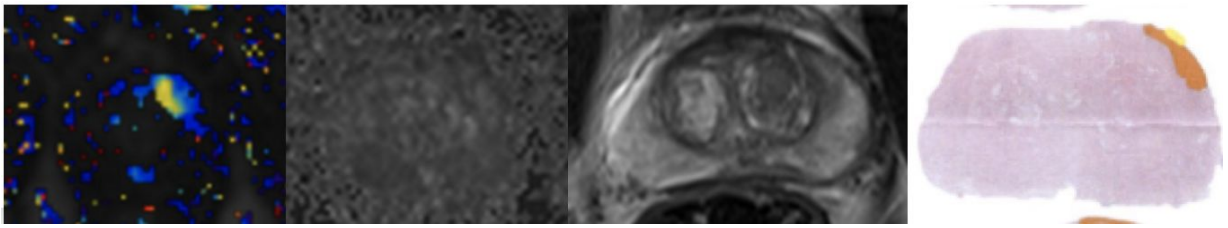


TZ Case 4 - The radiologists commented specifically on the ill-defined BPH nodule in the transition zone - the new PI-RADS v2.1 scoring would have upgraded this to PI-RADS 3. 3+4 =7.

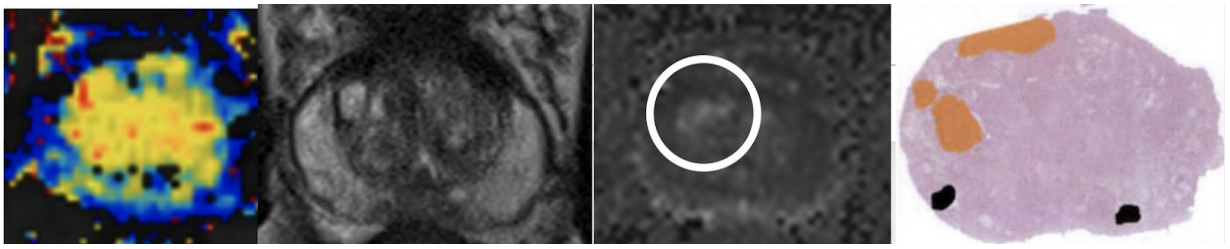


Anterior Fibromuscular Stroma

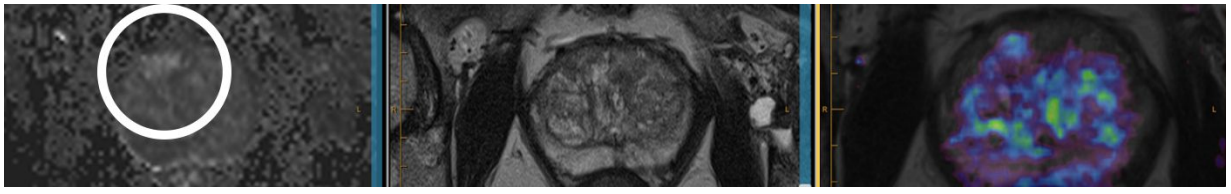
AFMS Case 1: DCE more conspicuous than DWI in this anterior lesion. 4+3(30%)=7



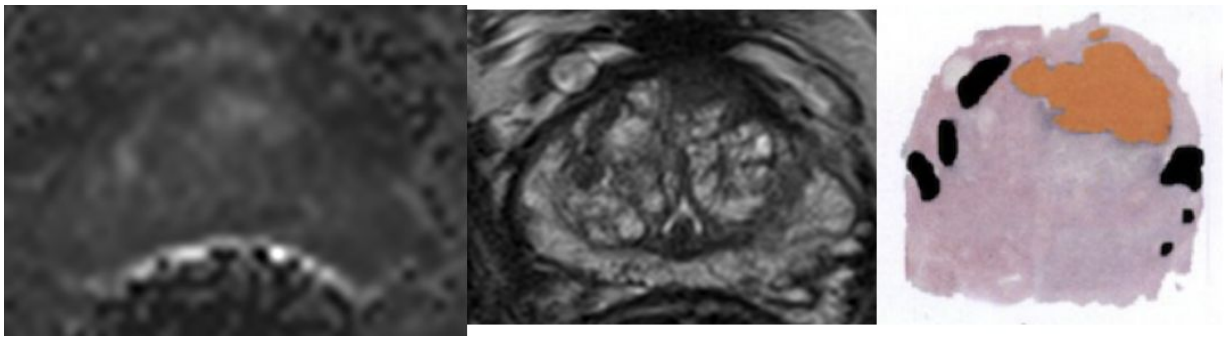
AFMS Case 2: Increased diffusion restriction in DWI correlating to the index lesion. 4(90%)+3=7 2.2cc



AFMS Case 3: Positive DCE and DWI. 3+4(10%)=7

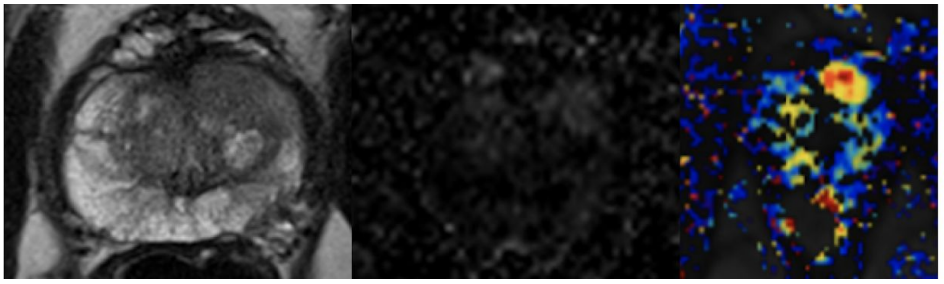


AFMS Case 4: Weakly positive DWI and T2. 3+4=7



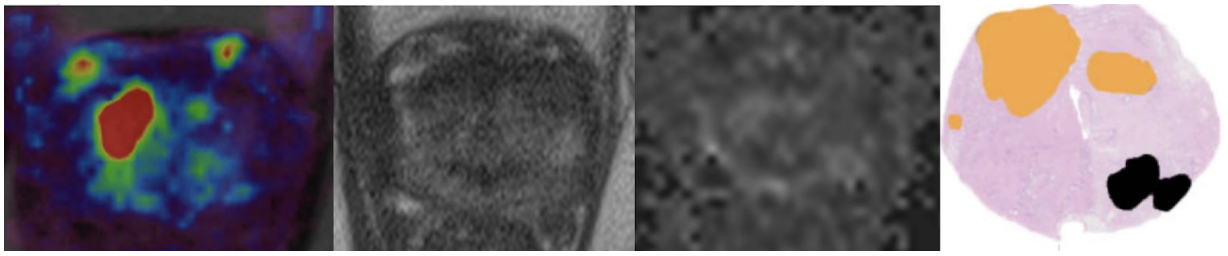
Apex

Case 1: The focal hyperintensity on the DCE was the most conspicuous sign of the apical tumour.

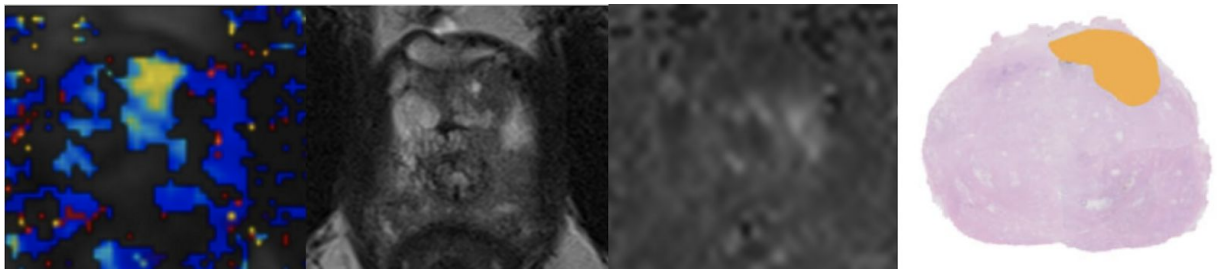


Bilateral, multifocal prostatic adenocarcinoma; index tumour bilateral (L>R) anterior apex and mid, Gleason score 4+4=8;

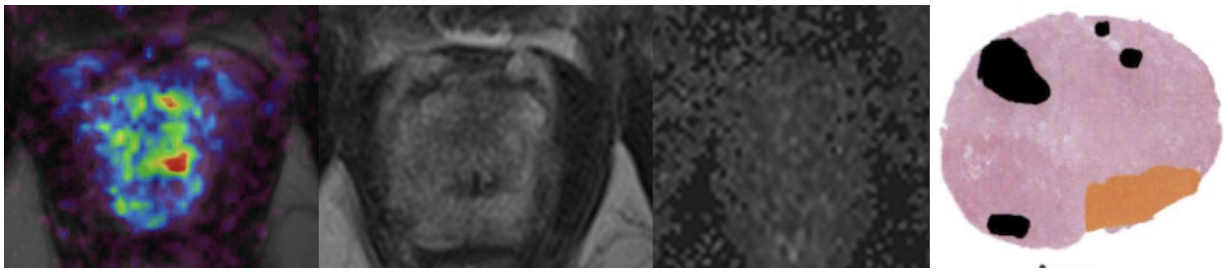
Case 2: Focal hyperintensity on the DCE was the most conspicuous sign of the apical tumour. This case was challenging because axial slices superiorly had symmetrical BPH DCE enhancement in the mid zone. 3+4(30%)=7 3.1cc



Case 3: Focal hyperintensity on the DCE was also the most conspicuous sign of the apical tumour. 4(80%)+3=7

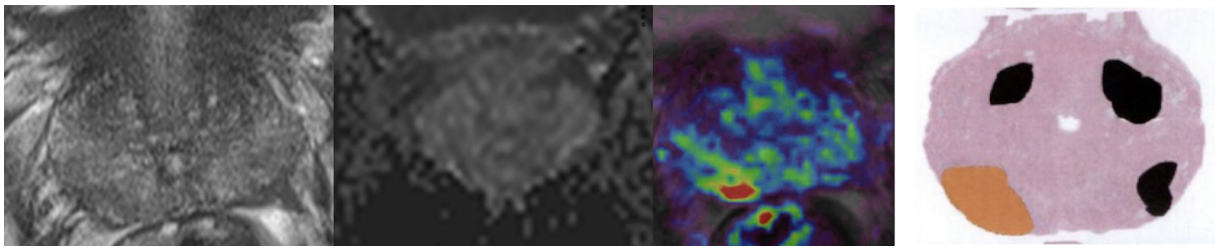


Case 4: Apical lesion essentially invisible on DWI and T2 imaging, small ROI on DCE. 3+4(10%)=7

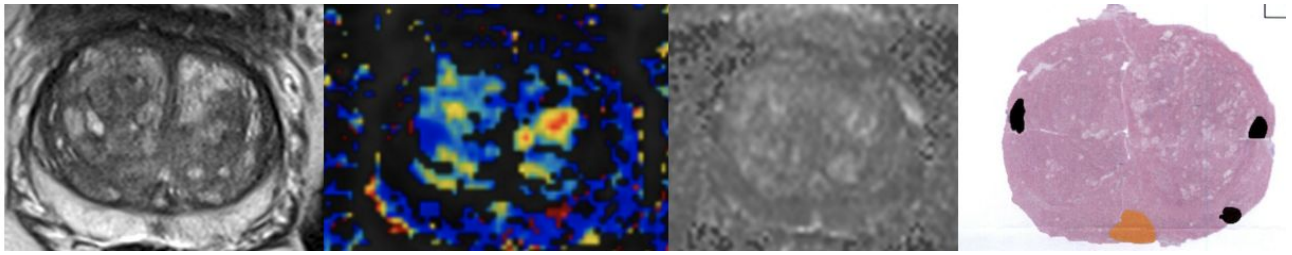


Peripheral Zone

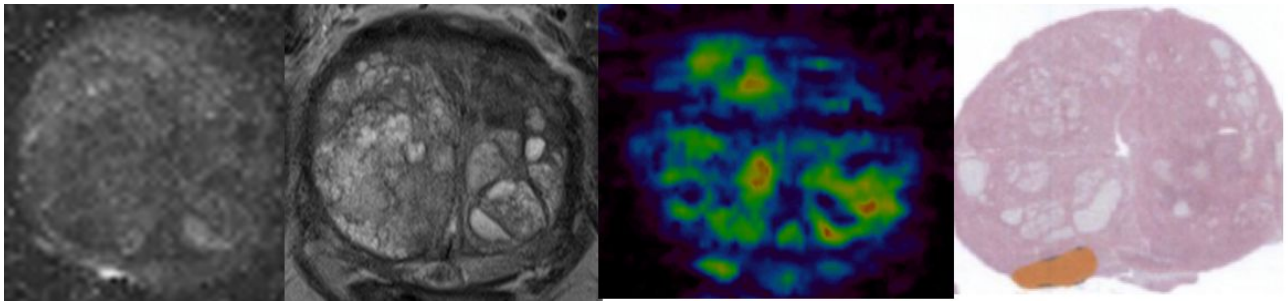
Case 1: The peripheral zone cannot be visibly identified separately from the transition zone. Only DCE appears positive: correlating to a 3+4(20%)=7 tumour.



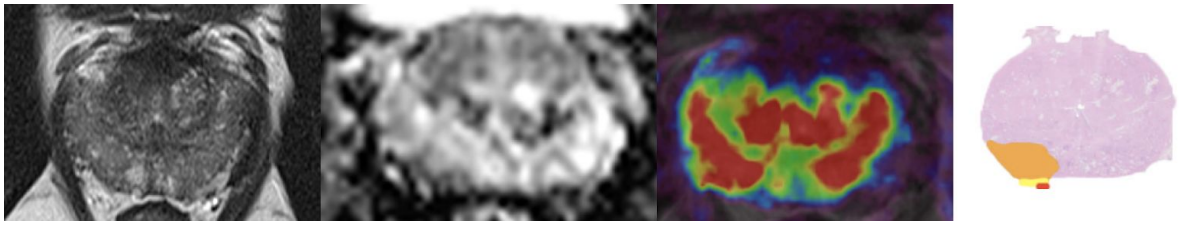
Case 2: Missed peripheral zone lesions: Small midline lesions correlating to 3+4(20%)=7, 0.3cc



Case 3: Small midline lesion - 3+4(40%)=7, 0.4cc.



Case 4: the peripheral zone is indistinct to the transition zone on T2 weighted imaging. Diffusely positive DCE Right PZPL 4+3=7, 1.3cc tumour.



APPENDIX B

3.0 Tesla mpMRI protocol. Abbreviations: TR = Repetition Time, TE = Echo Time, FOV = Field of View, DWI = Diffusion Weighted Imaging, DCE = Dynamic contrast enhancement.

Parameter	
T1 TR ms/ TE ms	510/11
T1 section thickness (mm)	1.5
T1 FOV (mm)	350
T2 TR ms/ TE ms	4000-6000/101
T2 section thickness (mm)	3
T2 FOV (mm)	150
DWI TR ms/ TE ms	3800/71
DWI b-values	50,400,800, Calculated 1400
DWI Section thickness (mm)	4
DWI FOV (mm)	170 (Sag + Ax)
DCE TR ms/ TE ms	4.83/1.87
DCE section thickness (mm)	3.5
DCE FOV (mm)	260

CHAPTER 3 DISCUSSION

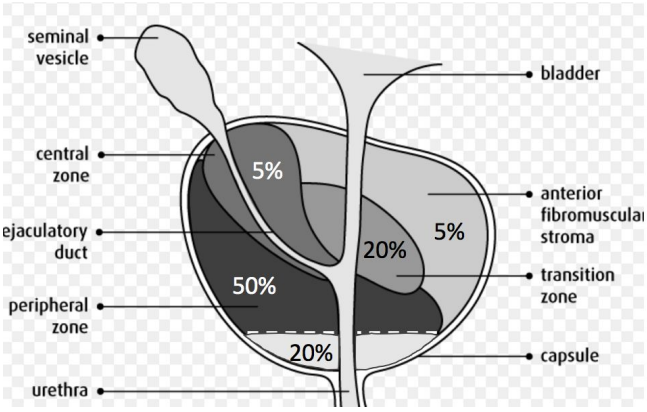
Of the 7.5% of patients who proceeded to radical prostatectomy, 34 patients had initial mpMRI scans reported as normal. Despite a pathologist having clearly stained the exact location of the tumour within the wholemount specimens, in almost half of cases (44%), there was no corresponding abnormality on the MRI. These predominantly occurred within the peripheral zone, and their histopathological characteristics were of either low grade (low percentage Gleason pattern 4), low volume (less than/equal to 0.5cc), or both. Such lesions accounted for 8 of 15 cases. There were 5 cases where image quality likely affected interpretation. One of these was a clear example of artefact from hip prosthesis. The other 4 cases represent a specific phenomenon not previously described; non-existent diffusion restriction in peripheral zone histopathology-proven tumours. Each of these 4 cases was notable for the appearance of the peripheral zone on T2 weighted imaging. The peripheral zone was diffusely low signal, such that it was iso-intense to the transition zone. The underlying cause of this broadly reduced peripheral zone T2 signal was unclear. Peripheral zone T2 hyperintensity stems from its glandular architecture and subsequent high water content[3]. The described appearance may reflect diffuse prostatic atrophy, dehydrating the tissue[10]. Regardless of the etiology, the finding was empirically notable for potentially flagging situations in which DWI may be unreliable. In these cases, early contrast enhancement of the dynamic contrast enhancement best reflected the tumour's location. This finding is particularly relevant to biparametric MRI, in which the contract series is not routinely performed. In such a situation, the presence of peripheral zone/transition zone T2 isointensity may mandate the patient be recalled for an additional contrast series. There were 3 tumours within the peripheral zone which were visualised prospectively, but correctly described as PI-RADS 2. When these glands were subsequently re-reviewed the original PI-RADS score was still correct. Such lesions represent a known limitation of prostate MRI reporting.

The zonal distribution of missed tumours identifiable in retrospect revealed their distribution was not uniform. Anterior fibromuscular stroma and apical tumours were over-represented (FIGURE 9) compared to their baseline zonal prevalence.

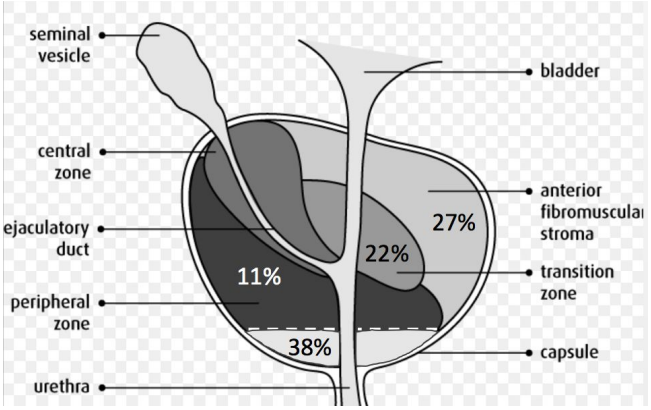
FIGURE 9: Zonal Distribution of Clinically Significant Disease Compared to the Zonal Distribution of Missed Tumours Seen in Retrospect.

The two juxtaposed diagrams demonstrate that the distribution between the two are slightly dissimilar. For example, the anterior fibromuscular stroma makes up only 5% of normal csPCA, but of missed tumours that could be seen in retrospect this area accounted for 27% of cases. This difference suggests that tumours in the anterior fibromuscular stroma may be overlooked, and that this area should be a dedicated checklist item.

Zonal Distribution of Clinically Significant Disease



Distribution of Missed Tumours



The anterior fibromuscular and apical tumours comprised 11 of the 34 false negative scans in total. Although 19 lesions were visible in retrospect, 5 were transition zone based and would likely have been accounted for under the new PI-RADS Version 2.1 scoring. The remaining 3 peripheral zone lesions, whilst identified, were correctly scored PI-RADS 2 according to their lack of diffusion restriction of linear morphology. Therefore these 11 lesions within the prostate apex or anterior fibromuscular stroma comprise (100%) of the lesions that may have been detected.

The prostate apex, as the inferior most component of the peripheral zone, is scored according to its appearance on diffusion weighted imaging as the predominant peripheral zone series. The reason these 5 tumours were missed was because of their subtlety on diffusion restriction. Although there was faint diffusion restriction present with heavy windowing, it was arguable whether their diffusion restriction signal was actually any greater than background. The value of contrast enhancement in these lesions was noteworthy, and is explored separately within the DISCUSSION CHAPTER of this thesis.

CHAPTER 4:

The Role of Radiologist Experience in Multiparametric Prostate MRI Accuracy

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

Rowan James Sinclair Miller

MBBS (hons), Grad. Dip Anatomy.

CHAPTER 4 INTRODUCTION

Despite the standardisation that has occurred in prostate MRI since the introduction of the PI-RADS reporting system[169], the variation in accuracy remains an ongoing criticism of this modality[170]. Multiple studies and meta-analyses have addressed the causes for this[114,171]. The experience of the reporting radiologist is a consistent theme amongst them[117,156,159]. Although studies have concluded that prior experience is a significant determinant of interpretive accuracy, to date literature has not adequately described the extent to which this is true. However, the topic mandates a robust examination of the learning curve, because as Sonn et al suggested, the entire benefit of prostate mpMRI in improved clinically significant disease detection may be threatened or lost if accuracy rates are compromised by inexperienced radiologists[159]. The aim of learning curve studies should not be to point out that a learning curve exists[172], but to produce a high quality study that provides an evidence base for the amount of experience required such that a radiologist can report prostate MRI (as a single reader) without compromising reporting accuracy. As a corollary to this, the same study would suggest when a radiologist should be required to dual read (cross-report) scans with a second radiologist, because of a high likelihood of inaccuracy empirically associated with their skill level.

This is a pressing issue in Australia, precipitated by the recently introduced Government rebate that provides a huge demand boost for prostate MRI. According to the Medicare rebate announcement, government reimbursement is provided for 26,000 prostate MRI studies per year[173]. Whilst some radiologists must invariably upskill to meet the supply shortfall, there needs to be an evidence base for the safest method of doing so. The following study provides robust data that helps in analysing this issue.

As the original literature review noted, this has traditionally been a difficult question to answer, because the nature of any study that assesses differences in interpretative accuracy amongst radiologists, based on prior experience, intrinsically means a small sample size. Indeed, all prior studies on this topic were based on observations made from a handful of local radiologists[117,156,159]. Furthermore, in some studies, radiologists' accuracy was measured according to different sets of patients [112]. Without the same data set available for review amongst radiologists of differing experience, any study would be biased by all other factors known to account for heterogeneity.The following study was in a unique position to answer this question. By presenting a single DICOM data set online, all other causes of heterogeneity relating to image acquisition and the study population were controlled for. The only variable in the study was the

prior experience of the reporting radiologist. These radiologists came from 1 of 4 training jurisdictions (America/Europe/UK/Australia). Although registration in one of these colleges does not provide registration in another, the training required amongst these different jurisdictions was equivalent enough to allow members of any of those colleges (or trainees) to enrol in the study.

A Radpath Correlated Evaluation of the Prostate MRI Learning Curve amongst 50 Radiologists: How Does Experience Affect Reporting Accuracy?

Having risen from obscurity ten years ago, the use of Multiparametric Prostate MRI is increasing sharply and is now utilised in more than 15% of prostate cancer cases[174,175]. Around the world, recently announced government funded rebates for testing[173] and guideline incorporation[176] will continue to reinforce this trend. As such more radiologists will be required to train in prostate MRI interpretation[156], known for its steep learning curve[177]. Though evidence supports the effectiveness of various training methods (didactic and self-directed[172]), there is a crucial literature gap regarding the amount of actual training radiologists require in order to interpret prostate MRI accurately. This has been variably quantified in terms of years of prior experience or number of prostate multidisciplinary meetings attended. Our study defined this learning curve by the number of prior cases read, which we consider the most reproducible unit of measurement. We plot the accuracy rates of 50 board-certified radiologists of varying levels of experience using a novel prostate MRI training tool. MRI PRO (www.mripro.io) has an online DICOM viewer of 300 prostate MRI cases, each paired with histopathology in wholemount radical prostatectomy sections (positive cases) or template transperineal biopsy results (negative cases) . This paper defines the prostate MRI learning curve by analysing the accuracy rates of 50 radiologists who have collectively read 2,500 cases via the platform.

Methods

Data Collection and Inclusion Criteria

On sign-up to MRI PRO, users self-report their level of prior experience and training jurisdiction (table 1). They then review images in a standard DICOM viewer, which displays 3T mpMRI scans acquired using PI-RADS Version 2.0 technical guidelines. Clinical information (PSA level, DRE status, prior biopsies) is not supplied to the radiologist. Radiologists record their answer via a pro forma questionnaire (FIGURE 1); submission of answers is required before revealing the matched histopathology. The de-identified radiologists' answers were stored in a secure cloud-based MySQL database, which has answer data from May 2017 - June 2020.

Table 1: Characteristics of the Radiologists undertaking Prostate MRI Training

Number of Prior Cases Read	American College of Radiology	Royal Australian and New Zealand College of Radiologists	Royal College of Radiologists	Other (Europe)	Total
> 1000 cases	1	3	0	0	4
300-1000 cases	3	1	1	1	6
100-300	0	4	1	3	8
51-100	5	6	2	2	15
21-50	3	4	0	2	9
0-20	4	3	0	1	8

Image Acquisition

All cases were acquired on the same Siemens 3T machine, with the details of the sequences described in APPENDIX 1. These were in keeping with the PI-RADS Version 2.0 acquisition guidelines. No endorectal coil was utilized. The high b value was 1400 and early contrast enhancement colour maps were additionally supplied.

Statistical Analysis

For true PI-RADS 4 and 5 cases, a correct score was awarded if 3 components of the pro forma questionnaire were met: the correct PI-RADS score, the correct number of lesions and the correct location of those lesions. Lesion location was recorded by selecting a single section on a prostate diagram (FIGURE 1). For PI-RADS 1 or 2 cases, only the correct PI-RADS score was required for the case to be marked as correct. Users could only perform each case once. The PI-RADS scores for each case were based on their prospective PI-RADS Version 2.0 reports. This was originally done by a single radiologist with over 3000 tissue-verified prostate MRI cases of experience (ROS). Subsequently JG/RM reviewed each case to ensure inter-observer agreement. Disagreement between the PI-RADS score and histopathology was resolved by case review (JG/RM). Even if a case differed from the histopathology result, the original PI-RADS score was kept if the PI-RADS score was correct despite the histopathology.

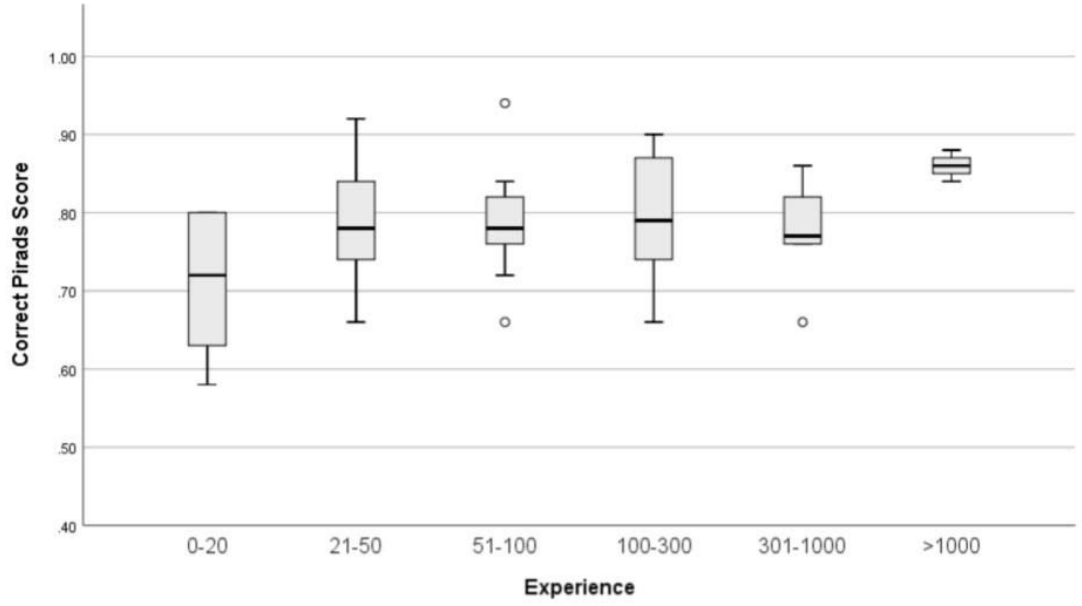
The 50 radiologists were grouped into cohorts according to their self-reported level of prior experience (TABLE 1). For the primary analysis, only the first 50 cases performed by each user were evaluated. 17 of these cases contained clinically significant disease, defined as Gleason 7 disease or greater (ISUP Grade group 2 or greater). The other 33 cases did not contain any cancer, and were assigned PI-RADS scores of 2. For these 50 cases, each user's overall sensitivity, specificity and PI-RADS accuracy were calculated, which was defined as the total number of correct PI-RADS scores assigned by the user out of all 50 cases. A separate analysis of transition zone lesion sensitivity was performed. This was calculated over all transition zone lesions that a radiologist had reviewed. These were spread through the dataset, through which some radiologists had progressed further than others, but the average number of transition zone lesions reviewed was 15. The results of the first 50 cases were graphed for each cohort. For each of the variables of interest, Independent Student t-tests were performed to assess for the statistical significance of differences amongst neighbouring cohorts. SPSS was used to perform statistical analysis.

Results

Overall PI-RADS Score

The minimum (maximum) PI-RADS accuracy over 50 cases was 58.0% (94.0%) , with a mean of 77.9%. There was a moderate correlation (Spearman Rho = 0.33, $p<0.05$) between PI-RADS

accuracy and experience. As demonstrated in Graph 1, PI-RADS accuracy improves significantly over the first 50 cases (one tailed, p = 0.0275), from 71% [95% CI: 63.31%, 78.69%] in novices (0-20 prior cases) to 78% [95% CI: 75.4%, 82.2%] in the 51-100 prior cases cohort. Thereafter overall PI-RADS accuray plateaued across the 51-100 cohort (78.80%), 101-300 cohort (79.50%) and 301-1000 cohorts (77.33%). However, experts - who had an average accuracy of 86.0% (95% CI 83.40, 86.60]) demonstrated statistical superiority over the other cohorts (one tailed, p <0.05).

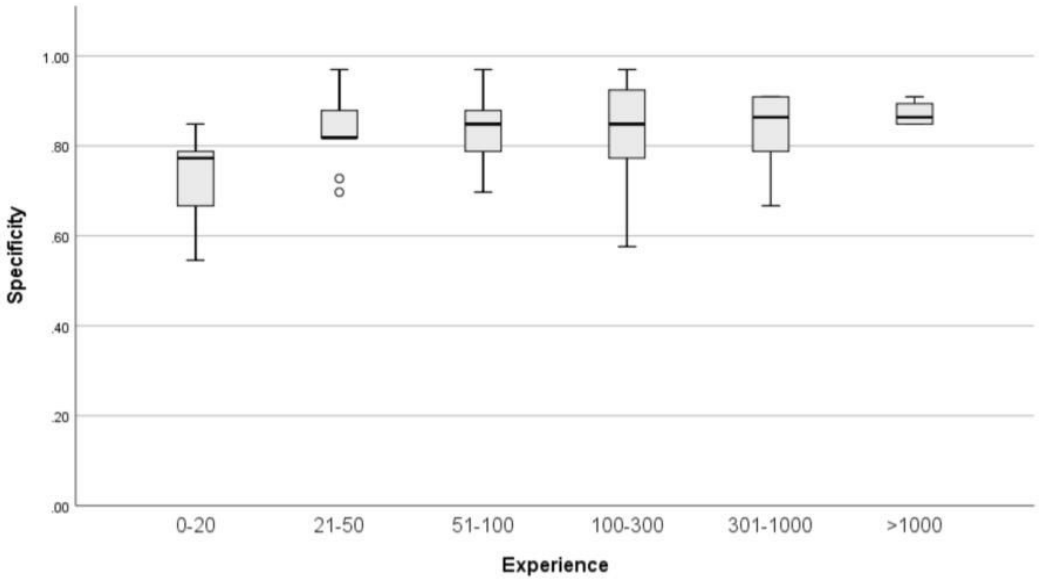


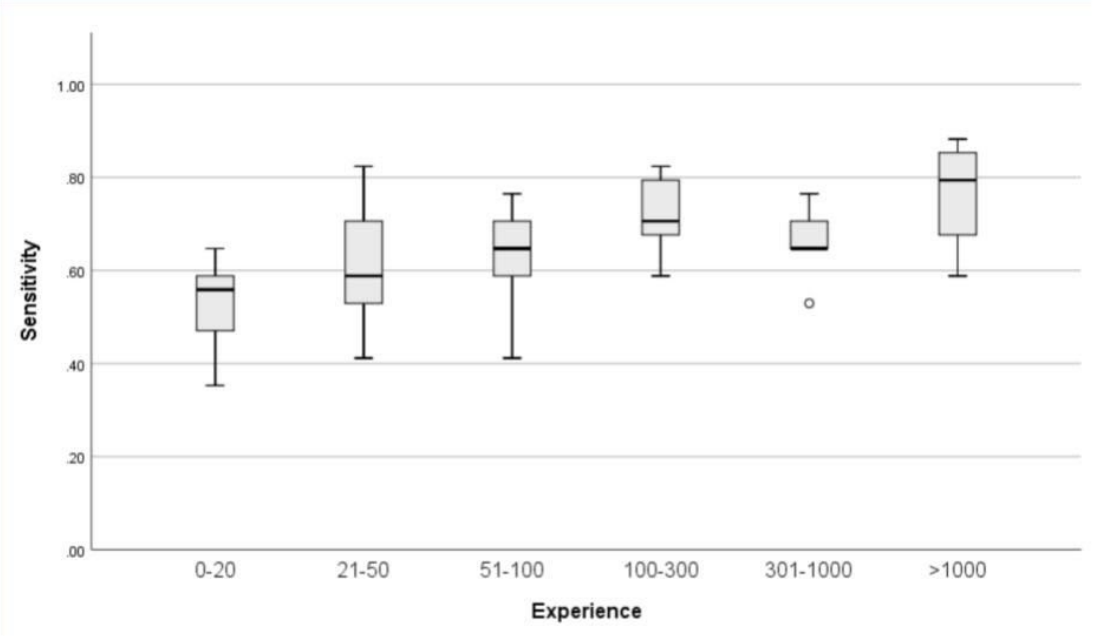
Sensitivity and Specificity

The minimum (maximum) specificity of users' answers was 54% (97%) with an average of 81.7%. Specificity demonstrated a mild correlation (Spearman coefficient = 0.259, p <0.05) with experience. Graph 2 demonstrates that although novices (73.1%) were statistically inferior to the other cohorts (one tailed, p = 029), specificity was otherwise statistically similar (p>0.05) across the remaining cohorts; 83.16% (21-50) , 82.82% (51-100), 82.95% (101-300) , 83.33% (301-1000) and 87.12% (>1000).

The minimum (maximum) sensitivity was 35% (88%) with an average of 64.12%. Sensitivity showed a moderate correlation (Spearman coefficient = 0.491, p <0.05) with experience. Independent T-tests revealed a significant jump in sensitivity after 20 cases (two sided p = 0.033), with sensitivity increasing from 52.9% to 63.1%. There was a similar jump at the 100 cases mark (two sided p =0.04) from 63.14% (51-100 cohort) to 72.06% (101-300). Although experts demonstrated the highest sensitivity (76.4%), sensitivity was not significantly improved between

300-1000 and >1000 prior cases (p=0.131).

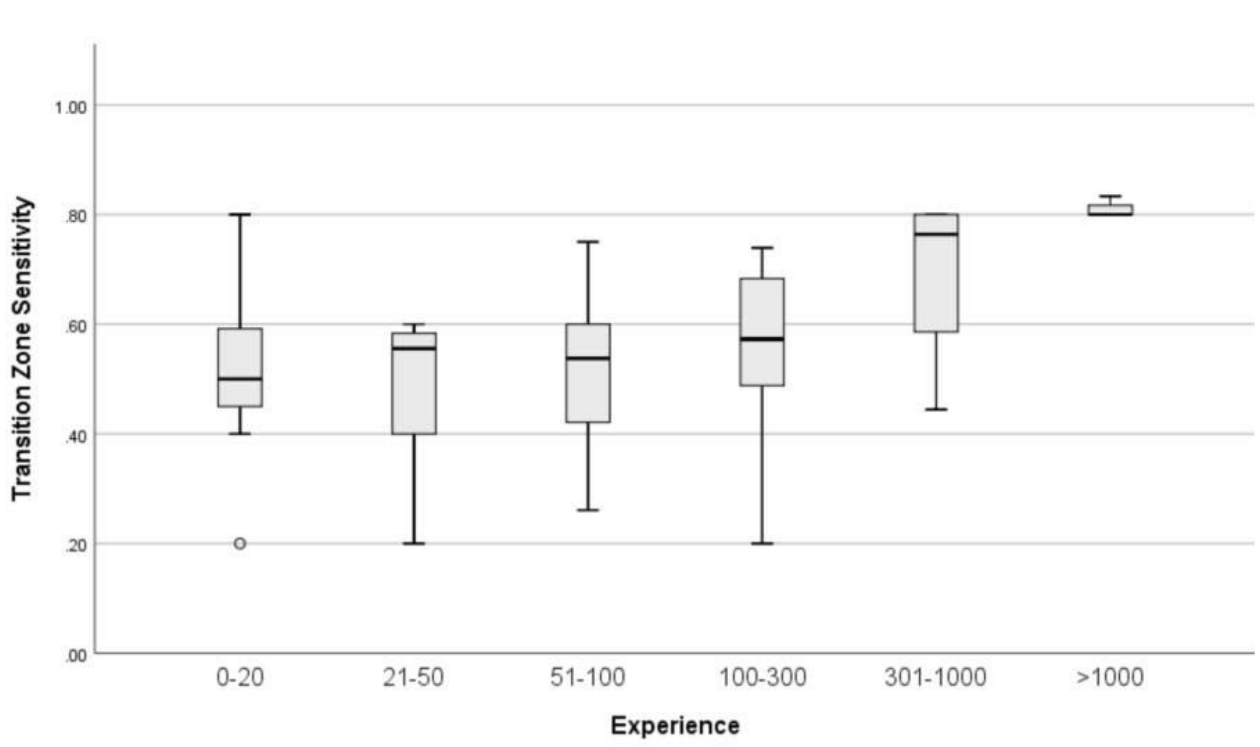




Transition Zone Sensitivity

The minimum (maximum) transition zone sensitivity was 20% (83%) with an average of 55.4%. There was a moderately strong association with experience (Spearman's rho = 0.446) The 4 least experienced cohorts produced similar transition zone cancer detection rates, averaging 51.6%, 46.4%, 52.1% and 55% respectively. The expert group (average of 80.8%) was statistically superior to them (p=0.004), but not to its neighbouring 301-1000 cohort (P=0.266). Similarly the

301-1000 cohort were statistically superior to the 51-100 group but not their neighbouring 100-300 group.



Discussion

This study assessed the relationship between prostate MRI accuracy and radiologist experience. Important aspects of this study were that this online approach allowed evaluation of a large number of radiologists (n=50) and cases were validated against radical prostatectomy in positive MRIs and systematic template transperineal biopsy in negative MRIs. The key finding of this study is a description of the prostate MRI learning curve, and of the relationships between reporting accuracy and case experience.

We described prostate MRI accuracy in terms of sensitivity, specificity, overall PI-RADS accuracy and transition zone lesion sensitivity. Specificity increased significantly after just twenty cases (71% to 83%) and then effectively plateaued; indeed having performed >1000 prior cases recorded only a marginally higher specificity (87%). This suggests users quickly gain an appreciation for the appearance of most normal prostate MRI studies. Sensitivity is moderately correlated with experience. 20 and 100 cases are thresholds either side of which demonstrate statistically

significant differences in sensitivity amongst readers. The overall PI-RADS score is moderately correlated with experience. There is a sharp learning curve over 50 cases before a relative plateau. This confirms the earlier findings of Rosenkrantz [172] who demonstrated a sharp initial increase in skill over approximately the first 40 cases, before a relative plateau. However our study additionally demonstrated that users who have performed greater than 1000 prior cases were statistically superior to those who had not. Transition zone lesion detection, interestingly, only started to improve after 100 cases of experience. Both 300 and 1000 prior cases acted as threshold levels for statistically significant improvement in transition zone sensitivity. This suggests that transition zone lesion detection is the most difficult prostate MRI skill to acquire.

In expert hands, the sensitivity and specificity of Prostate MRI may represent a paradigm shift in prostate cancer detection [178]. However the present study is important because it highlights that such results are predicated on significant radiologist reporting experience in prostate MRI. Whilst meta-analyses conclude that clinically significant disease detection rates for prostate MRI reach 89% [57], they also flag that substantial heterogeneity is introduced by study designs, patient populations, image acquisition, scanner types and radiologist interpretation. All radiologists in our study reviewed the same dataset acquired with the same machine and protocol to control for these other variables. By controlling for these variables, our study suggests that radiologist experience is at least partially accountable for the variation in prostate MRI accuracy rates described in literature.

To date the accuracy of prostate MRI described in literature largely reflects subspecialist radiologists in tertiary centres. But with increased utilization, greater numbers of scans will be performed in community practice and read by radiologists with less prostate MRI experience. This is a significant development, as ours is one of several studies that links greater rates of inaccuracy to less experienced readers[159,179],[114,180] For example, when assessing novice readers as part of a learning intervention, Rosenkrantz et al calculated an initial sensitivity of 57.8%, similar to our own result of 52.9%. Conversely amongst subspecialists Greer et al, demonstrated an average sensitivity for Gleason score 7 or greater lesions, validated against radical prostatectomy, above 91%[171]. In our own study, the average sensitivity of the expert cohort was 76.4%, and the highest individual users' sensitivity was 97%. We believe the difference is due to the exacting method by which we made users identify lesions (described in the next paragraph). Although we did not record the practice type (community or tertiary) of the radiologists involved in our study, three studies have specifically evaluated the performance of Prostate MRI in a community practice setting; Koshani et al established a sensitivity of 54–66% for tumour detection in community practice, although their study included Gleason 6 tumours in their analysis which may have comparatively decreased their sensitivity. Rosenzweig et al demonstrated that these inter-observer

differences between community and tertiary level PI-RADS scores are of clinical significance, as 50% of initial community scores were significantly downgraded, and 12% of PI-RADS scores significantly upgraded in their study[181]. It is easy to concur with their findings, as the absolute difference in sensitivity between novice and expert cohorts in our study was 23.4% (52.9% to 76.4%). Luzzago et al, found secondary reads at a tertiary centre changed clinical management in 48% of cases referred from peripheral sites [182]. In this wider context, our study results should in no uncertain terms caution against radiologists individually reporting prostate MRI with less than 20 cases experience, as their results are demonstrably inferior to the wider cohort of prostate MRI readers, a finding consistent with the recommendation of at least two other studies[159,172]. Furthermore our results suggest that radiologists' interpretative accuracy may be suboptimal until at least 300 cases. The Luzzago et al study demonstrated a significant improvement in negative predictive value - (89% vs. 72%; p=0.04) - and positive predictive value (43% vs. 20%; 288 p=0.02) for second reading of mpMRI studies, and employing this practice for readers of less than 300 prior studies should be considered based on our data.

One limitation of our study is that our definition of lesion detection - i.e true positive/sensitivity - was arguably over-exacting. Whereas essentially all other studies record a 'true positive' result when tissue matched a PI-RADS 4 or 5 result, our users had to take the additional step of selecting the lesion on a 36 segment diagram of the prostate and state the number of lesions. The purpose of doing so was to ensure a correct answer could not be guessed. However this meant a user could enter the correct PI-RADS score, which would ensure the correct clinician management, but receive an incorrect score for that case due to subjectivity in sizing or biopsy location. The difference between these two methodologies - having to select a correct segment and not - is demonstrated in GRAPH 5 in the APPENDIX. The authors of the study accept that the sensitivity described in the results under-reports the sensitivity as conventionally constructed by somewhere between 0-15%, with higher levels of sensitivity affected to a greater degree.

A second limitation of our study is that the "number of cases read" questionnaire given to users when starting the program is open to interpretation, and could be better standardised between users. For example, the number of cases read could refer to cases that had correlated histopathology results (or not), as well as whether the case was read alone (or dual read, or read at a workshop). Furthermore, the questionnaire did not specify whether these cases were read during residency, fellowships or post-fellowship. Additionally, the questions were answered in a training (i.e non-clinical setting). It is unclear if the reporting accuracy directly translates between this online

training and real-world setting. It would be understandable for novice radiologists to be more cautious in real clinical practice than within a training environment.

This study is important because it attempts to delineate the relationship between prostate MRI accuracy according to case-based feedback, at a time when many radiologists are in various stages of training to meet the demands of a burgeoning new imaging procedure. It is important that radiologists are aware of the size of the prostate MRI learning curve, so that the excellent results described in academic journals are reproduced in clinical practice. Amongst institutions, second-reader studies at tertiary institutions of community read scans result in significant differences in progression to biopsy or not [125][181]. This is particularly important, as incrementally higher numbers of prostate MRI will be performed not in the tertiary centres that originally established the evidence base around prostate MRI accuracy, but in community radiology practices who nonetheless must strive for the same accuracy rates[159]. Furthermore, in non-tertiary settings, the process of establishing histopathology based feedback systems is challenging [183]. This underscores the importance of both delivering adequate training and building an evidence base around the amount of training required.

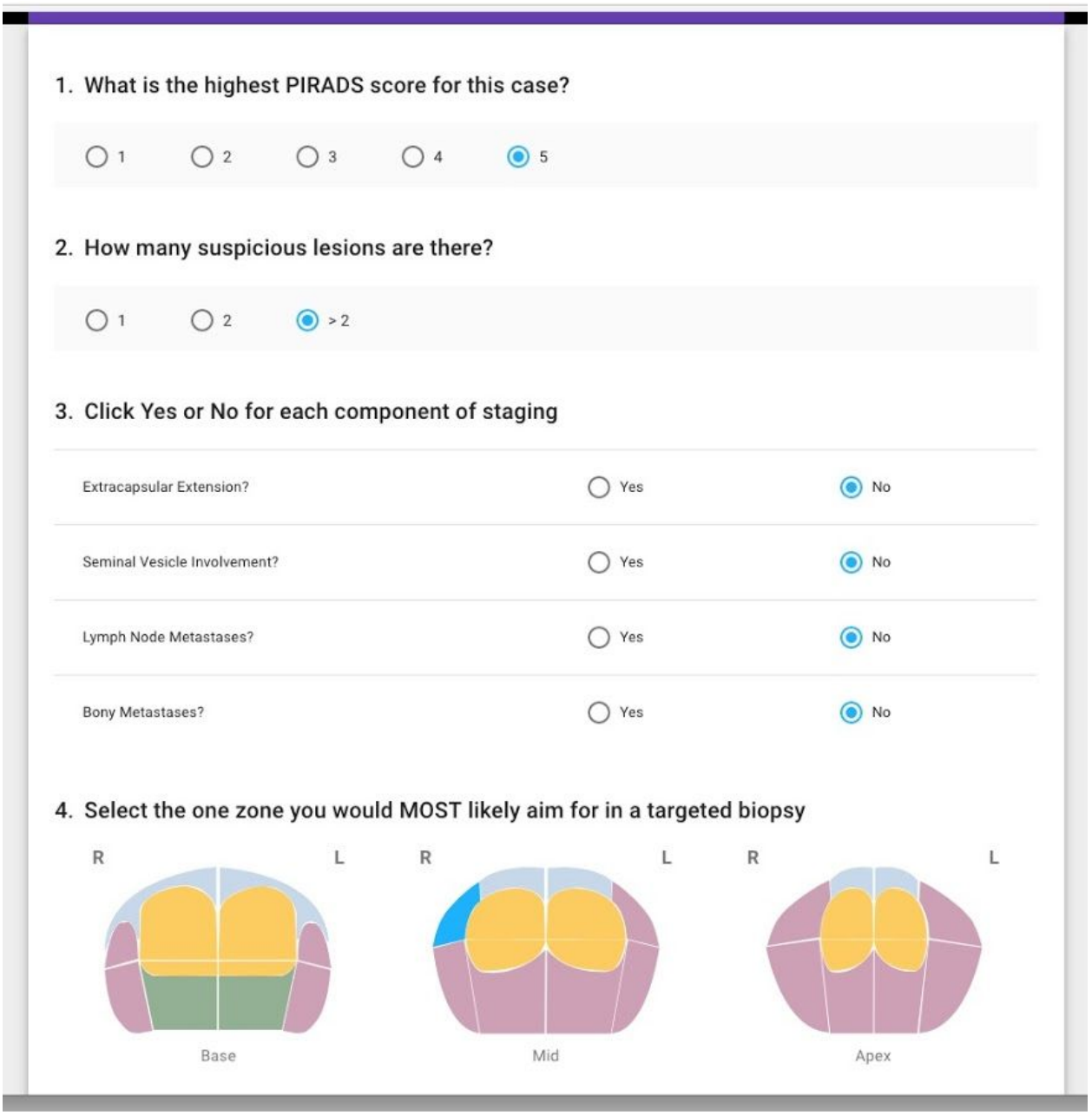
Conclusion

The learning curve of prostate MRI was evaluated by analysing the overall sensitivity, transition zone sensitivity, specificity and percentage of correct PI-RADS scores amongst 50 radiologists who evaluated 50 wholemount correlated cases using an online prostate MRI training platform. We found that PI-RADS accuracy is significantly lower amongst radiologists with less than 50 cases of self-reported prior experience, but accuracy levels then plateaued across cohorts who had previously reported 50 to 300 cases. The cohort of users who had performed more than 1000 cases however, demonstrated statistically greater accuracy during the 50 cases. True negative detection (specificity) increased sharply between users without any prior experience and those with 20 cases of prior experience. However, that negligible improvement was seen amongst more experienced cohorts suggests that this skill is amongst the earliest acquired in the learning curve of prostate MRI. Sensitivity by comparison, continued to improve gradually with experience, as sensitivity rates were positively correlated with experience and continued to improve even between the neighbouring cohorts of 300 prior cases and 1000 prior cases of self reported experience. This was a gradual overall trend upwards, as demonstrated by the Spearman rho. Based on the transition zone lesion detection rates, which only showed significant improvement in cohorts of

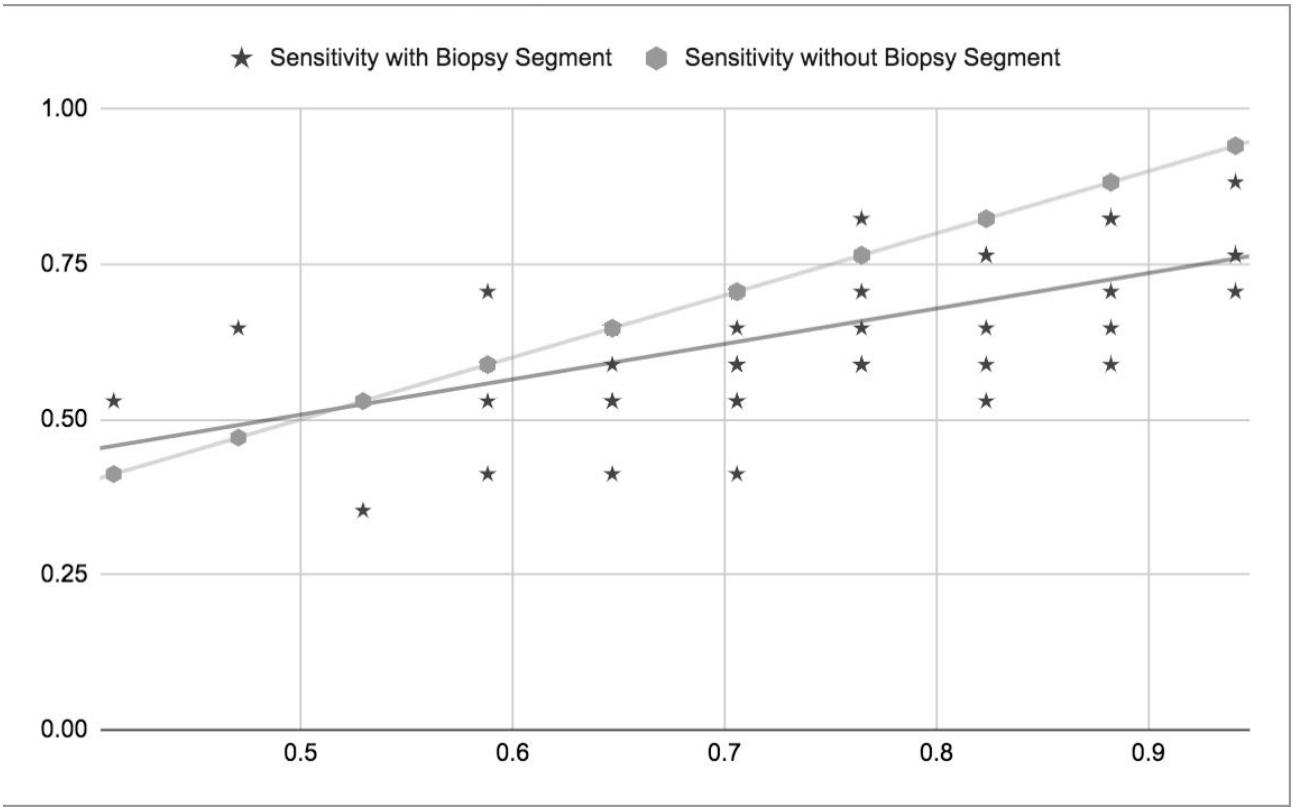
users who had 300 and 1000 cases of prior experience, transition zone lesion detection takes the greatest length of time to acquire.

APPENDIX A:

FIGURE 1: Example of the Scoring Sheet



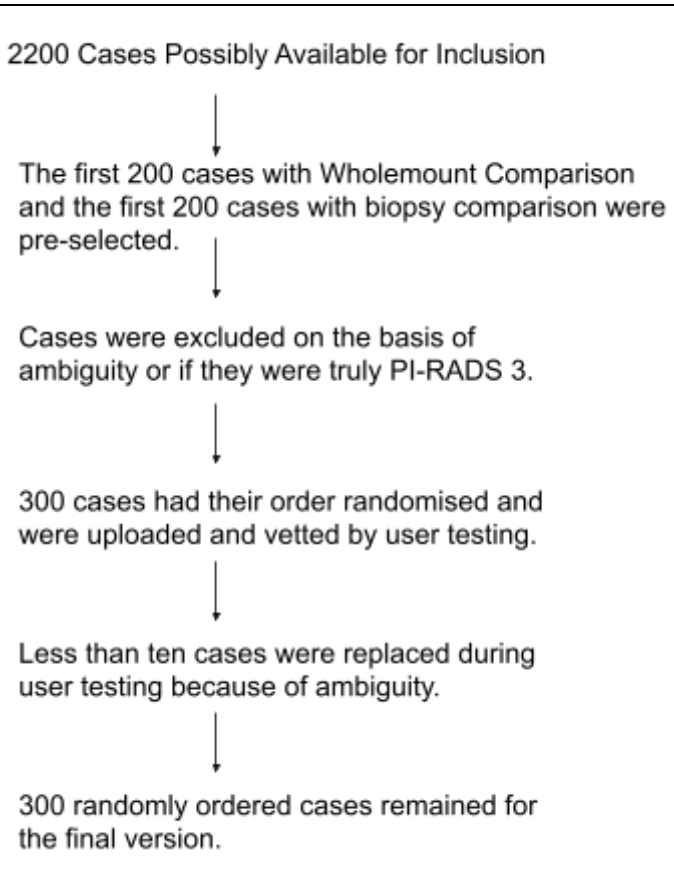
Graph 1: Lines of Best fit comparing Users Sensitivity when required to select the correct biopsy Segment vs Not required to Select the correct Biopsy Segment.



APPENDIX B: Cases Selection

	PI-RADS	NUMBER
TABLE 2: Distribution of PI-RADS Scores within the Training Data. Cases were chosen based on achieving a balance between high yield learning content and a low number of true PI-RADS 3 cases.	1	0
	2	142
	3	6
	4	62
	5	54
	4 or 5	36

FIGURE 2:
Flow Chart of Case Selection: The flow chart adjacent describes the method by which cases were sorted/eliminated from the initial database through to the end product that users interacted with.



CHAPTER 4 DISCUSSION

Prior publications on the prostate MRI learning curve have small sample sizes, typically up to 5 or 6 users [124,172,177]. The present study is not only the first to address the prostate MRI learning curve from novice to expert, its 50 users represent a ten-fold increase in typical cohort size over the studies described above. Furthermore, this is the first study to analyse various components of the learning curve; specifically the domains of overall correct PI-RADS score, specificity, overall sensitivity and transition zone sensitivity.

An additional implication of this study is the ability to quantify user experience; specifically, is there a threshold level of experience at which radiologists should be allowed to report prostate mpMRI, and at which those underneath should not? “Prior number of cases performed” was chosen as the unit of measurement for comparing prostate mpMRI experience. Conceivably, other metrics, such as years of prior experience, number of workshops attended, prostate MRI CME points achieved, number of histopathology matched feedback sessions performed could also have been used. However, each of these are inferior in their degree of reproducibility. Two different users who each describe “one year” of prostate MRI reporting may have had entirely different caseloads; for example one in private practice and the other in a subspeciality uro-oncology fellowship. Workshops were an impractical measurement tool as the majority of users had not attended one, and therefore the cohort largely would have fallen into a dichotomy of those who had and had not attended a workshop which removed any granularity from the data. Prostate MRI CME was also not feasible, given that the study was international, and therefore CME points were not directly equivalent amongst institutions; and more to the point many users had not claimed prior prostate MRI CME points despite their prior experience. Therefore, the number of cases previously performed (recorded on a self assessed basis of statistical bins between approximately 50-100 cases) became the baseline unit of measurement for defining the study subgroups.

Consistent with prior literature, the most experienced cohort of users was most accurate. Their overall percentage of correct PI-RADS scores, sensitivity and specificity were highest. Additionally, their ability to detect transition zone cancers were statistically higher than all other cohorts. However allowing only these users to self report is impractical, given their relatively small number (4 out of 50 users in our study), and the large increase in MRIs that less experienced radiologists will be required to read [156]. An alternative method of dissecting this issue is therefore to assess the point along the learning curve when the marginal improvement per scan begins to taper. There is no doubt that more experienced radiologists have greater accuracy; the question is rather at what point does the incremental benefit per case reported begin to significantly diminish? The

results show that there are statistically significant differences in the specificity and sensitivity of complete novice users vs those who have performed more than 50 cases. There is evidence of a rapid learning curve between 0 and 50 cases, which supports the findings of other authors[172]. In our study of up to 100 cases the learning curve (in terms of sensitivity and overall PI-RADS accuracy) improved significantly, and thereafter, the rate of improvement was lower. After 50 cases, specificity did not improve any further throughout the study; there was no statistically significant difference in specificity of cohorts who had performed as little as 50 cases even compared to those who had performed more than 1000 cases previously. This suggests that identifying a perfectly normal prostate is a relatively easy skill to learn. Conversely however, the curve of sensitivity only gradually trends upward the more cases a user has performed, as demonstrated by its positive correlation (Spearman coefficient = 0.491, $p<0.05$). However, Student t-tests often failed to show statistically significant differences between immediately adjacent cohorts, but did demonstrate differences amongst those cohorts once removed (2nd degree neighbours). The most difficult skill to learn, and one which demonstrated a statistically significant difference between even the most experienced (more than 1000 prior cases) and second most experienced (more than 300 prior cases experience) cohorts was in the detection of transition zone tumours. This was the skill that most clearly demonstrated expertise. This suggests that transition zone tumour detection is the hardest skill to acquire in mpMRI reporting (or at least, takes the most time).

Given that transition zone tumour detection is unaffected by DCE, those particular results are equally applicable to biparametric MRI. Indeed a study by our working group that specifically evaluated the role of experience for 20 radiologists and 40 urologists (Poster Presentation at EAU Copenhagen, 2018) demonstrated similar results for biparametric MRI [184], with positive and negative predictive values equally correlating with experience.

Several other studies have recently validated the need for adequate training. A recently published multicentre study of radiology imaging departments that are members of the Society of Abdominal Radiology Prostate Cancer Disease Focus Panel again demonstrated the significant variability in prostate MRI accuracy first described in the EAU review article of 2017[105]. Amongst 27 centres, the positive predictive value of mpMRI validated against systematic biopsy ranged from 20% to 70% [170]. Variation in prostate MRI accuracy has recently led the American College of Radiology to implement quality control standards that cover prostate MRI acquisition and reporting[185]. One of their specific requirements regards radiologist experience, which is that radiologists have reviewed 150 prior cases in order for the department to be accredited[185]). That target is supported by the results of this study, in that the greatest degree of improvement occurred within

the first 100 cases. However users who had performed 150 prior cases of experience did not achieve equivalent accuracy rates to those with true expertise; in our study those who had performed 150 prior cases were still statistically inferior to those who had performed more than 1000 cases across most domains; Overall PI-RADS accuracy 79.5% vs 86.0% (one tailed, $p < 0.05$), overall sensitivity 72.06% vs 76.4% and transition zone sensitivity (55% vs. 80.8%).

In concluding, this chapter demonstrates the significant impact of radiologist expertise on mpMRI reporting. There is a wide variability in skill with scores varying from 58.0% to 94.0% across all users. Academically, it is important for studies to articulate the number of prior cases their radiologist has read, as radiologist experience may account for a large amount of variability in accuracy studies. Clinically, it is pleasing to see that some jurisdictions are lobbying for tissue-based case feedback and minimum case numbers as part of quality assurance policies[185]. Our data demonstrate that there is indeed a steep learning curve for prostate MRI, with an inflection point around 100 cases. However after this number of cases there were still small increases in overall accuracy. The most experienced users were also the most accurate. They demonstrate significantly higher detection rates of transition zone cancer, presumed to be the hardest skill in prostate MRI to acquire. Different jurisdictions could use these results as an evidence base around policies mandating dual reading for novice radiologists. For example, pairing radiologists who have reported less than 100 cases with those who have reported more than 1000 cases appears an appropriate strategy. This would allow inexperienced readers to gain experience without degrading the overall mpMRI accuracy rate.

CHAPTER 5:

Does Dynamic Contrast Enhancement have a Marginal Benefit in Prostate Cancer Detection Amongst Biopsy Naive Men?

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

Rowan James Sinclair Miller

MBBS (hons), Grad. Dip Anatomy.

CHAPTER 5 INTRODUCTION

Removing the DCE series and associated need to cannulate patients (so-called biparametric MRI), would make prostate MRI scans faster, cheaper and less invasive - and remove the associated risks of gadolinium-based contrast [186]. These are clear benefits from a patient perspective, but increasingly also from the perspective of health systems burdened by burgeoning demand for prostate MRI access. However, proponents of DCE argue that it provides incremental value in prostate cancer detection[64].

The current role of DCE, according to the current PI-RADS scoring paradigm is, however, minor, suggesting only a very small role in prostate cancer detection. As described in the literature review at the start of this thesis, in the initial version of the PI-RADS reporting system, each of the three sequences (DWI, T2 and DCE) were all weighted equally to provide an overall score indicating the likelihood of prostate cancer for a given scan. However in 2014 when PI-RADS was updated, the role of DCE was relegated to having zero impact on the scoring of the transition zone, and to being the secondary scoring sequence for the peripheral zone, to be used only when the primary scoring sequence for the peripheral zone - DWI - had an indeterminate (PI-RADS 3) appearance.

In order to analyse the utility of DCE in PI-RADS scoring and any marginal benefit it may provide over biparametric imaging alone, we performed a retrospective, single centre, per-patient study of mpMRI patients who underwent subsequent transperineal biopsy. We evaluated the frequency with which DCE was required according to the overall PI-RADS Version 2.0 schema, and subsequently compared the accuracy of mpMRI to the same scans retrospectively scored in a biparametric fashion.

Additionally, given that the role of the DCE series is in discriminating peripheral zone PI-RADS 3 lesions, this chapter evaluates alternative measures that could replace contrast in indeterminate lesions.

Retrospective Comparison of Biparametric vs Multiparametric MRI: what is the marginal benefit of contrast in prostate cancer detection amongst biopsy-naive men?

INTRODUCTION

In standardising prostate MRI acquisition and reporting, the PI-RADS scoring system has facilitated a robust evidence base for the role of MRI in prostate cancer detection. Whilst PI-RADS Version 1 ascribed equal weighting to its constituent series - Diffusion Weighted (DWI), T2 and Dynamic Contrast Enhancement (DCE) - PI-RADS Version 2 employs a dominant sequence scoring paradigm, that inherently diminishes the role of DCE. This, combined with uncertainty regarding the marginal benefits of the DCE series, call into question whether DCE should be routinely omitted from prostate MRI acquisition - so called biparametric MRI (bpMRI).

Removing the DCE series (bpMRI) is faster, cheaper and omits intravenous cannulation of patients and the risk of contrast-related adverse effects[186]. These are clear benefits from a patient perspective, but increasingly also from the perspective of health systems burdened by burgeoning demand for prostate MRI access. However, proponents of DCE argue that it provides incremental value in prostate cancer detection[64]. In order to analyse the utility of DCE in PI-RADS scoring and any marginal benefit it may provide over biparametric imaging alone, we performed a retrospective, single centre, per-patient study of mpMRI patients who underwent subsequent transperineal biopsy. We evaluate the frequency with which DCE was required according to the overall PI-RADS Version 2.0 schema, and subsequently compare the accuracy of mpMRI to the same scans retrospectively scored in a biparametric fashion. Given that the role of DCE in PI-RADS Version 2.0 and 2.1 is to upgrade some peripheral zone lesions that receive a score of 3 with the predominant DWI sequence (DWIPZ3), we additionally compared its discriminative ability for that purpose to a simple biochemical adjunct of PSA Density (PSAD), using a PSAD of greater than or less than 0.15ng/ml as an alternative means of risk stratifying peripheral zone PI-RADS 3 scans.

MATERIALS AND METHODS

Study Design

From February 2013 a prospective database was maintained (ethics approval - Epworth Human Research and Ethics Committee LR191-14) that recorded patients who underwent mpMRI imaging. Of 2749 patients captured between September 2013 and October 2019, retrospective review identified 1898 patients who were biops-naive. Of these, 988 patients underwent biopsy within 6 months (Flow Chart 1). All patients were referred based on clinical suspicion of prostate cancer derived from either elevated PSA levels or abnormal findings on DRE (Table 1).

Flowchart 1: Participant enrolment

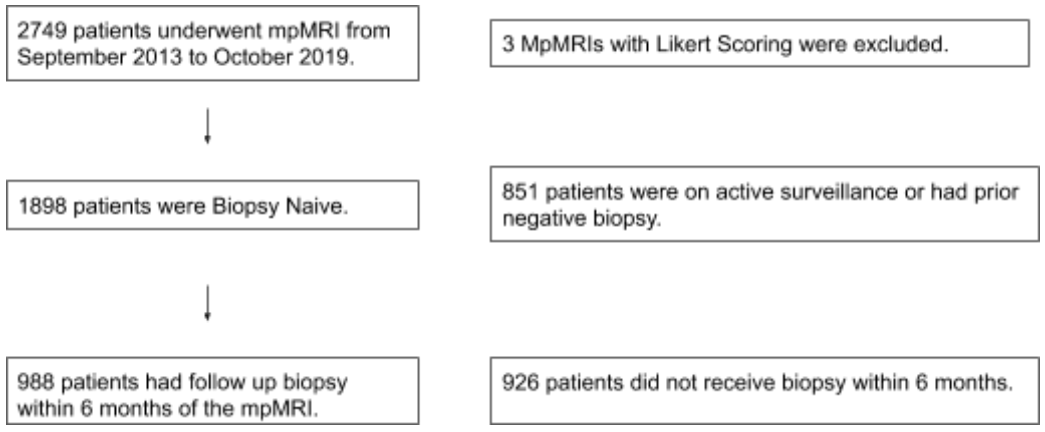


Table 1: Patient Demographics

	Mean	**St. Dev.**
Age	65.98	7.98

PSA	7.32	6.21
PSA Density	0.22	0.176
Indication	**Abnormal DRE**	**Elevated PSA**
	5.70%	94.30%

MRI Acquisition

Patients were scanned on a single Siemens Magnetom Skyra 3T scanner without endorectal coils. Scans were acquired as full mpMRI scans according to the PI-RADS guidelines, with administration of intravenous Gadovist (0.1 mmol/kg of body weight; Gadovist, Bayer HealthCare). Calculated High b value images were 1400mm/Sec (before 2016) and 2000mm/sec (after 2016). ADC maps were derived from b values of 0, 200, 400 and 800mm/sec. Full protocol details are available in Appendix 1.

MRI reporting

75% of scans were reported by a single expert uroradiologist (R.O'S.). Their prior experience is approximately 3000 prostate MRI cases, with an active yearly caseload of more than 500 prostate MRIs as well as monthly prostate MDM participation where continuous tissue-based feedback is provided. The remaining cases were reported by radiologists from the same provider with an annual caseload of 200 prostate MRIs and 3 years of experience. No specific reader training sessions were conducted.

All individual components of PI-RADS scoring (DCE/T2/DWI) were recorded prospectively, as well as the overall PI-RADS score according to the PI-RADS version at the time. The location of up to three lesions per MRI was marked on a triplanar diagram by the reporting radiologist (prospectively). Their specific scoring of T2, DWI and DCE combined with zonal localisation of any lesions is what allowed us to retrospectively analyse peripheral zone PI-RADS 3 scans. In all but 5 cases, the radiologist also provided a calculation of Prostate Volume from which PSA Density was derived.

Comparator Method

The comparator method was transperineal template biopsy under general anaesthesia in 970 patients and TRUS biopsy in 26. An average of 25 core (SD 5.6 cores) samples per patient were performed, including targeted cores in 59% (590 patients). Targeting was by cognitive registration in 454 patients, with BioJet (DK Technologies, Herlev, Denmark) in 61 patients and with Biobot Mona Lisa (Biobot Surgical, Singapore) in 75 patients. 89.8% of target cores were positive for cancer. A pathology service (TissuPath, Melbourne, Australia) reported the biopsy results based on the International Society of Urological Pathology (ISUP) grading system. They additionally quantified the percentage of Gleason pattern 4 disease (5,10 or 20%) in Grade Group 2 tumours and longest core length.

Statistical Analysis

When the contrast series was excluded, biparametric scans were scored according to the dominant sequence only, similar to Junker et al [187]; for example, a peripheral zone lesion with DWI score of 3 was ascribed an overall bpMRI PI-RADS score of 3 (irrespective of the T2 scoring). The prevalence of clinically significant disease was assessed in the DCE positive and DCE negative peripheral zone PI-RADS 3 cases. This was compared to the prevalence of clinically significant disease in the same cases once divided into groups by a PSA Density cutoff of 0.15ng/ml. Rather than optimise a specific cutoff value retrospectively, we arbitrarily chose this cutoff before analysis due to its prevalence in literature. To test for differences between PSA Density discriminatory ability and contrast, Fisher's Exact test was used, where two-sided values of $p < 0.05$ were considered statistically significant.

Empirical receiver operating curves (ROC) were calculated using the Johns Hopkins Medicine online calculator (http://www.rad.jhmi.edu/jeng/javarad/roc). PI-RADS 3, 4 or 5 results were test positive, PI-RADS 1 or 2 were deemed test negative for both mpMRI and bpMRI ROC curves. A third ROC curve for bpMRI with PSA Density incorporation was created (table 2). In this curve, peripheral zone PI-RADS 3 lesions with a PSA Density above (see below) 0.15mg/ml were considered PI-RADS 4 (PI-RADS 3).

Table 2

Strategy	Test Positive	Peripheral Zone PI-RADS 3
MpMRI	MpMRI 3, 4 or 5	DCE +ve upgrades.
BpMRI	BpMRI 3,4 or 5	Nil upgrades.
BpMRI +PSAD	BpMRI 3, 4 or 5	PSA Density > 0.15ng/ml upgrades.

A pathologic diagnosis of adenocarcinoma of the prostate, ISUP Grade Group 2 or higher of any volume from the transperineal biopsy results was accepted as validation-positive; any other histology was validation-negative.

Area under the receiver operating characteristic curve was used to assess the comparative accuracy of these strategies, with Delong's test used to assess significance.

RESULTS

One hundred and eighteen of 988 patients recorded DWI scores of 3 (DWI 3). Of these, 55 and 63 were within the transition and peripheral zones respectively. Therefore, contrast was required in 6.4% of cases, but redundant in 93.6% of the 988 patients. DWIPZ3 scans contained clinically significant cancer in 46.0% of cases.The histopathology of the clinically significant disease identified in DWIPZ3 lesions was Gleason 3+4 (72%), Gleason 4+3 (17.2%) and Gleason 4+4 (11.8%).

Of PI-RADS 3 peripheral zone lesions, there were 13 DCE positive and 50 DCE negative cases. 53% of DCE positive cases and 44% of DCE negative cases contained clinically significant disease, yielding a Fisher Exact test statistic value of 0.5499 (an insignificant result at $p < 0.05$). When the same cohort was separated based on 0.15ng/ml PSA Density cutoff, 32 cases were PSAD Positive and 31 negative (Table 2), containing 59% and 32% clinically significant disease respectively, yielding a Fisher Exact test statistic value of 0.0437, significant at $p < 0.05$.

The overall sensitivity, specificity, positive and negative predictive values of biparametric mRI were 92.1%, 52.1%, 75.4% and 80.4% respectively. There was no difference in AUC values of the receiver operating curves between biparametric, multiparametric or combined biparametric/PSA Density.

Table 3: Comparison of Contrast and PSA Density (Cutoff 0.15ng/mL) for upgrading peripheral zone PI-RADS 3 Lesions

Contrast Discrimination				PSAD Discrimination			
		Pos	**Neg**			**Pos**	**Neg**
Biopsy	**Pos**	7	22	Biopsy	**Pos**	19	10
	Neg	6	28		**Neg**	13	21

Table 4: RoC Curves including AUC values. DeLong test did not reveal a significant difference between Multiparametric nor Biparametric (with or without additional PSA stratification)

MpMRI	BpMRI	BpMRI + PSA Density

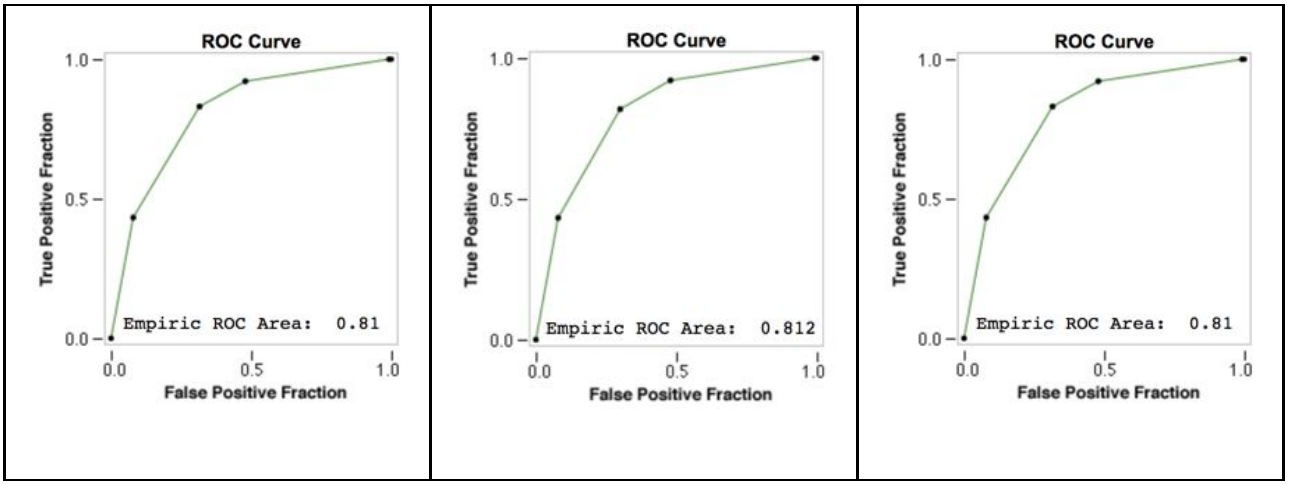


Table 5: Accuracy of BpMRI

		BpMRI				
		Pos	**Neg**	Specificity	**52.11%**	46.95% - 57.23%
Biopsy	**Pos**	560	48	PPV	**75.47%**	73.43% - 77.41%
	Neg	182	198	NPV	**80.49%**	75.56% - 84.62%
				Accuracy	**76.72%**	73.96% - 79.32%

DISCUSSION

According to two recent literature reviews[188,189], this is the second largest cohort of biparametric MRI results within the published literature analysing 988 biopsy-naive men. Additionally, this study is notable for using transperineal biopsy, with a high percentage of

targeting, and large number of cores; collectively demonstrating a superior reference test to TRUS biopsy which frequently undersamples pathology and is predominant in literature.

Our results demonstrate that contrast was redundant in the overall PI-RADS v.2.0 score of 93% of cases. Furthermore, the actual discriminative ability of DCE for upgrading peripheral zone PI-RADS 3 lesions was not statistically significant, and indeed performed worse than simply applying a widely used PSA Density threshold.

Other authors have also assessed the ability of DCE to upgrade peripheral zone DWI score 3 lesions. Our results stand in contradistinction to Bosaily et al who used data from the PROMIS trial [190]. Where our study of 63 lesions considered either positive or negative outcomes for contrast enhancement, their study of 158 lesions had 3 possible outcomes; reassuring (9% clinically significant disease), equivalent and suspicious (48% clinically suspicious disease). However their definition of clinically significant disease used the PROMIS definition (Gleason score ≥4 + 3 or ≥6 mm maximum cancer length) rather than any volume of Gleason 3+4 disease as we did. This is likely to explain the discrepancy in our results, given that almost three quarters of our clinically significant disease comprised Gleason 3+4 disease which were uncaptured in their results. Of two studies that shared our definition Mussi et al concluded that “contrast-enhanced sequences provide minimal or no increased value” [191,192], whereas De Viscshere et al found 22 of 30 DCE positive PI-RADS 3 cases to contain cancer vs 5 of 17 negative DCE cases [192]. These results are inconsistent, and 5 years after the PI-RADS working group first observed that “the added value of DCE is not firmly established,” there remains no consensus regarding its ability to risk stratify DWI score 3 peripheral zone lesions.

Our study compared DCE to PSA Density as an alternative method of risk stratifying peripheral zone PI-RADS 3 lesions. Literature already demonstrates that PSA Density is an independent predictor of clinically significant prostate cancer[193]. A cutoff value of 0.15ng/ml was employed based on the original work by Epstein et al [194] and current recommendation of that value in NCCN guidelines[195]. In our study the discriminative ability of PSA Density for risk stratifying peripheral zone DWI score 3 lesions was significant and superior to DCE. Our results are consistent with prior studies that describe additional value of PSA Density in improving biopsy stratification in either mpMRI or bpMRI scanned patients [109,122][111,196]. Our results agree with those of Brizmohun Appayya et al who specifically used PSA Density to discriminate PI-RADS 3 lesions, and found a statistically significant difference between PI-RADS 3 peripheral zone lesions with clinically significant disease and without [123]. However they advocated for a cut-off of >0.10ng/ml as that threshold would yield 90% sensitivity [95% CI (70–99)], and 89% NPV [95% CI

(67–99)][123] when combined with bpMRI results. Collectively the results suggest that PSA Density could be considered a candidate for replacing the role of DCE imaging in risk stratifying DWIP3 lesions if bpMRI is widely adopted.

In our study, there was no difference between biparametric/multiparametric accuracy based on AUC analysis.This echoes earlier studies demonstrating that the AUC of a biparametric protocol is non-inferior[197] [198]. This was an expected finding given that at most 7% of scores were impacted by the addition/removal of contrast. As DCE is required for DWIPZ3 lesions, the proportion of cases where DCE is redundant equals the number of peripheral zone DWI score 3 lesions. Our result of 7% of cases is similar to Junker et al of 9.75% of cases [187]. However our finding is materially lower than pooled meta-analyses. Westphalen et al recently analysed the PI-RADS scores of 5082 lesions from 3449 patients collected from 26 member institutions of the Society of Abdominal Radiology. They recorded PI-RADS 3 (both transition and peripheral zone) lesions in 29.3% of cases[170]; the proportion of transition zone to peripheral zone lesions was not described, but if 75% of PI-RADS 3 lesions were peripheral zone (as suggested empirically by prostate cancer distribution) [130]), then contrast was required in 21.9% case to calculate the PI-RADS V.2 score. At least two factors explain the discrepancy between the meta-analysis and our own results. Our analysis was per-patient rather than per-lesion. Per-lesion analysis increases the number of PI-RADS 3 scores, arguably unnecessarily as the highest PI-RADS score lesion in the same patient is what ultimately drives treatment decisions and would be correctly captured biparametrically. Moreover variation in PI-RADS 3 scoring simply reflects the larger issue of variation in overall PI-RADS scoring. This is highlighted in that meta-analysis, which principally assessed the positive predictive value of PI-RADS scores, where there was “wide variation” between individual centres, with positive predictive values of individual centres ranging between 20% and 70%.

Whilst the PI-RADS working group recently published that bpMRI represents “a potential solution for meeting the increased demand of MRI in the prostate cancer diagnostic workup” they simultaneously cautioned that “greater evidence is needed to precisely define which patient groups benefit from contrast enhancement and who can safely avoid it”. In our study, the preference of the treating physicians was to biopsy the majority of PI-RADS 3 lesions, as 118 of 169 (69.8%) PI-RADS 3 lesions were biopsied. As other authors have noted [192] the threshold for biopsy generally lies between PI-RADS 2 and 3; making the distinction between PI-RADS 3 and 4 irrelevant with respect to the dichotomised outcome of biopsy or not.

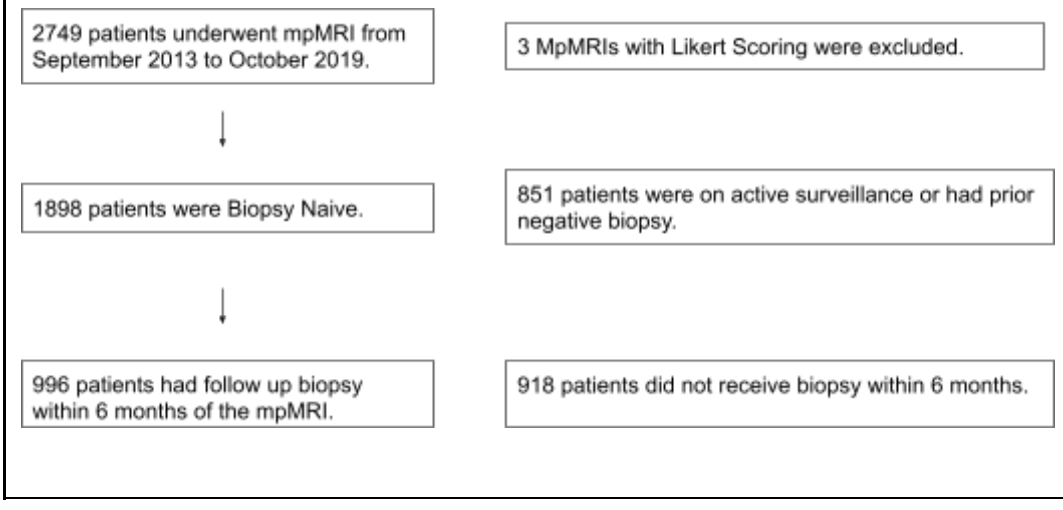
One limitation of our study is its retrospective nature. This meant that the radiologist was aware of the contrast results at the time of reviewing the diffusion weighted imaging in our study, which could bias their interpretation of the diffusion weighted sequences. Other studies used truly prospective designs to address this bias. Stanzione et al performed a prospective study in 82 patients of biparametric MRI first, followed by full mpMRI after an interval between 20 and 30 days. BpMRI was correct in 76/82 cases; mpMRI in 77/82 cases [199]. Zawaideh et al had a similar methodology and found that bpMRI discovered 87 tumours with 27 false positives compared to mpMRI that discovered 88 tumours and 15 false positives [200]. Further prospective trials are required to establish whether the apparent slight improvement with DCE persists. Differences between retrospective and prospective studies (if proven) may reflect the ability of DCE to flag lesions for further scrutiny with other series where DCE isn't required in the overall PI-RADS calculation. Another limitation of our study is that scans were predominantly read according to PI-RADS Version 2.0 whilst PI-RADS Version 2.1 is now in use. However the PI-RADS Version 2.1 update regards changes to transition zone scoring, and therefore we consider our results applicable given peripheral zone interpretation is unchanged. A recent study comparing biparametric and multiparametric MRI using PI-RADS Version 2.1 demonstrates similar results to our own. Further, our study cohort is notable in that PI-RADS 1 and 2 results are under-represented.This is not uncommon in literature, consistent with Junker et al, who note that PI-RADS 1 and 2 "'usually neither received a histologic work up nor follow-up MRI"[187]

One source of heterogeneity of our study resides in the exact method of biparametric reporting. In our study biparametric peripheral zone PI-RADS 3 lesions were scored only according to the dominant sequence (DWI), similar to the methodology of Junker et al [187]. However other authors such as Zawaideh et al assessed the peripheral zone incorporating T2-weighted images as the secondary sequence[200]. As biparametric MRI becomes more commonplace, it will be important to standardise its reporting. If the impetus for removing contrast was faster, more convenient scans which are non-inferior in cancer detection, a future direction of research is whether additional sequences may be removed. These protocols, described in literature as 'abbreviated' or 'fast' bpMRI demonstrate preliminary results of non-inferiority with scan times reduced to as little as 9 minutes.

CONCLUSION

DCE was required in the overall PI-RADS Version 2.0 calculation for 6.7% of this cohort of 988 biopsy-naive men. The discriminative ability of DCE to upgrade peripheral zone DWI lesions was not proven. Using a PSA Density threshold of 0.15ng/ml instead produced a clinically significant increase in likelihood of clinically significant disease. The added cost, timeliness and invasiveness incurred with DCE was not justified by superior accuracy based on AUC curves in this study.

Flowchart 1: Participant enrolment



CHAPTER 5 DISCUSSION

Contrast was not required to determine the PI-RADS Version 2.0 score in 93% of cases. Furthermore, the actual discriminative ability of contrast for upgrading peripheral zone PI-RADS 3 lesions was not statistically significant. These findings suggest contrast is not required under the PI-RADS Version 2.0 and PI-RADS Version 2.1 scoring systems. Two additional studies identified after completing the paper further support this view [201,202].

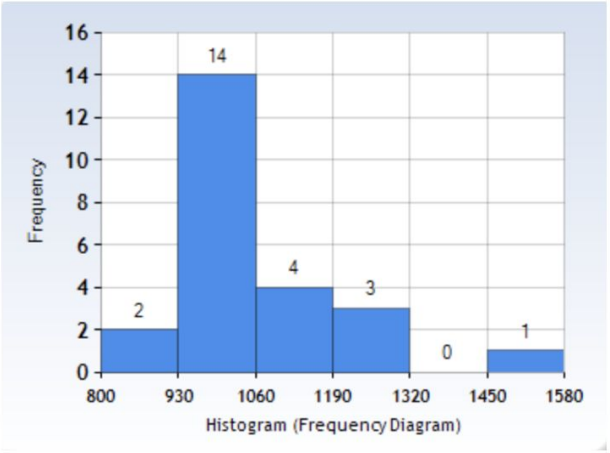
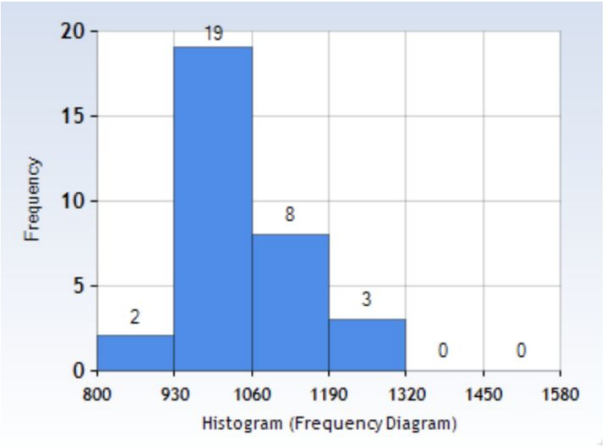
Removing the contrast series suggests that a replacement is required to evaluate indeterminate PI-RADS lesions. Several strategies have been proposed by other authors. Junker et al simply scored these lesions according to the dominant sequence, as our analysis did[187]**.** Zawaideh et al evaluated indeterminate lesions using the secondary sequence, T2 weighted imaging, to upgrade ambivalent T2 weighted scans. Many authors have already demonstrated the role of PSA Density in improving prostate cancer risk stratification and of improving true negative rates in PI-RADS 2 lesions using PSA-Density cut-offs[122]. Our study and the results of Brizmohun Appayya et al suggest that PSA Density can be used to discriminate PI-RADS 3 lesions [123]. Especially given that PSA-Density results are known to be valuable in risk-stratifying PI-RADS 2, it stands to reason that indeterminant PI-RADS 3 lesions also benefit from risk-stratification with PSA-Density.

Other authors suggest that imaging parameters may be useful in arbitrating PI-RADS 3 lesions. Specifically, multiple authors suggest (as described in the literature review) that ADC values may be useful. For example, Jyoti et al found that “tumour foci in both TZ and PZ show reduction of ADC values compared to the normal prostate”[90]. De Cobelli et al found that “the ADC value of lesions suspicious for prostate cancer is significantly lower than the ADC values of the normal prostatic tissue” [203]. Gaur et al found that “ADC and normalized ADC inversely correlate with PI-RADS Version 2 and ISUP categories and can serve as quantitative metrics to assist with assigning PI-RADS Version 2 DWI category 4 or 5” [204]. However, in each of these studies, analyses were performed across all prostate cancer specimens, rather than restricting the analysis to only PI-RADS 3 peripheral zone lesions. In our own dataset, there was far too great an overlap for absolute ADC values to be of any use in discriminating PI-RADS 3 lesions.

A further avenue of research in this area is that pursued by Hansen et al. Their working group did not identify PI-RADS 3 peripheral zone lesions as a homogenous sub-group. Instead, they attempted to categorise PI-RADS 3 peripheral zone lesions according to border, shape and ADC in an attempt to further risk-stratify them [205].

FIGURE 10: Comparison of ADC Values in Peripheral Zone PI-RADS 3 Lesions - Biopsy Proven GG0/1 Lesions vs Biopsy Proven GG2+ Lesions.

These graphs reflect unpublished data from the PI-RADS 3 cases in our dataset. The results demonstrate that there is a significant degree of overlap between the raw ADC values of biopsy proven csPCa and benign controls. For this reason we reject the notion that a threshold ADC value may help distinguish between benign and malignant lesions.

ADC Values of PI-RADS 3 Peripheral Zone Lesions with Biopsy Proven GG2+	ADV Values of PI-RADS 3 Peripheral Zone Lesions with Biopsy Proven GG0/1
	

CHAPTER 6: DISCUSSION

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

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In order to further establish *Prostate MRI as a Standard of Care in Early Prostate Cancer Detection,* this thesis sought firstly to accurately characterise the false negative rate of mpMRI, and then to analyse reasons for its wide variability in literature. If factors influencing prostate MRI accuracy could be described and understood, then they may represent avenues for further improvement.

CHAPTERS 3 to 5 demonstrated that amongst these factors the experience of the reporting radiologist had the largest demonstrable impact on prostate MRI accuracy. CHAPTER 3 found that accuracy amongst radiologists varied widely. Amongst 50 radiologists of varying experience who were assessed on exactly the same cases, accuracy ranged between 58-94%. Radiologists who had previously performed more than 1000 cases demonstrated higher degrees of accuracy than less experienced radiologists, with statistically significant differences in sensitivity, specificity and PI-RADS concordance. When radiologist expertise was maximised, in CHAPTER 3, tumour and scan characteristics - such as low volume/low grade disease, scans affected by artefact, or inconspicuous anterior/apical lesions - were found to result in false negative scans in 7.5% of cases that proceeded to radical prostatectomy. Based on the variability in accuracy when all other factors were accounted for - by providing all radiologists with the same dataset of cases - this thesis suggests that amongst scans which are acquired according to the PI-RADS/ESUR guidelines, the experience of the reader, over any other cause of heterogeneity, is the greatest factor in the wide variability in accuracy rates described in the literature. Future studies should specifically report the experience of the reporting radiologist, quantified according to the number of prior cases reported. It is pleasing that recently introduced quality assurance initiatives, such as the North American “Prostate MRI designation”, require that the designated departments’ radiologist/s have read a minimum of 150 prostate MRI scans previously [185]. Our results support this implementation based on the increased accuracy rate of radiologists who had passed this threshold of experience.

This thesis also demonstrates that even when prostate mpMRI is reported by expert radiologists with optimal scan acquisition, there is a non-zero number of false negative scans - though smaller than the incumbent testing paradigm. The exact percentage of false negative scans varied according to the method of evaluation, with false negative rates of 7.5%, 18% and 19.5% established in this thesis based on radical prostatectomy, transperineal template biopsy and hemigland comparators respectively (CHAPTERS 1 and 2). Given the possibility of rolling out prostate MRI for mass screening, the false negative rate of mpMRI needs to be further optimised. Especially given that these results reflect optimal scan parameters and expert reporting, it is possible that these results reflect amongst the highest accuracy rates. The replicability of these

results is felt unlikely if prostate MRI scales into a screening test, for example with less experienced reporting radiologists.

However, the histopathological characteristics of these false negatives were predominantly low volume low grade disease, with 76% of missed lesions in CHAPTER 1 comprising ISUP Grade Group 2 disease. This is corroborated by the findings of CHAPTER 3 that almost half of missed tumours proceeding to radical prostatectomy are inconspicuous in retrospect because of low volume/grade group features. Within CHAPTER 3, 11 of 19 missed lesions that may have been identifiable were located within the anterior fibromuscular stroma or prostate apex. Other authors have also identified the prostate apex as an area of increased false negatives [167].

Despite this, 3% of patients with normal mpMRI scans harboured ISUP Grade Group 3 disease (CHAPTER 2). How that risk is managed is ultimately a decision for the individual urologist and their patient. However, additional risk stratification, by either PSA Density alone [112] or other proven risk stratification techniques, could be useful in guiding the need for repeat imaging or subsequent biopsy. Multiple studies have demonstrated that the negative predictive value of mpMRI rises in combination with a PSA Density of less than 0.15mg/cc [122,141,143]. Our results suggest that in men with a negative mpMRI and low PSA Density, a biopsy can be reasonably omitted. A future direction of research is whether these men with initial PI-RADS 1 or 2 mpMRI results could undergo a more convenient biparametric study at follow up (if required) given their prior imaging for comparison.

At first glance, the results of CHAPTER 5 and CHAPTER 3 appear conflicting. On the one hand, CHAPTER 5 argues that the provision of intravenous contrast and DCE imaging is unnecessary due to its largely redundant role in the PI-RADS scoring system and moreover weak ($p>0.05$) discriminative ability when actually required for evaluating peripheral zone PI-RADS 3 lesions. On the other hand, CHAPTER 3 demonstrates that contrast was possibly useful in identifying anterior fibromuscular stroma and apical tumours even when these tumours were invisible on other sequences. These are not contradictory but parallel narratives and the difference is explained by sampling bias and study design. Where CHAPTER 3 retrospectively analysed only false negative scans that proceeded to radical prostatectomy (cancer prevalence 100%), CHAPTER 5 retrospectively analysed all patients who underwent transperineal biopsy (cancer prevalence of 60%)

Other retrospective studies of biparametric MRI found similar results to the retrospective study of CHAPTER 3 [197] [198]. However, the two prospective studies on the value of contrast both described marginally - although non-statistically significant - increases in clinically significant

cancer detection when contrast was employed. Specifically, one additional csPCa was detected in 82 men with contrast in a study by Stanzione et al, and one additional csPCa was detected in 264 men in a study by Zawaideh et al through the use of contrast [199,200]. The reason has been described as the "Safety Net" phenomenon [199]. By this the authors mean that tumours are significantly conspicuous on dynamic contrast enhanced imaging, even though the dynamic contrast enhancement series may not be used in calculating that lesions overall PI-RADS score (according to the PI-RADS Version 2.0 criteria). None of these safety net effects are demonstrated in retrospective biparametric studies, because the retrospective nature of the study design intrinsically includes safety net captured lesions. However by retrospectively analysing wholemount confirmed false negatives and their conspiciuity on *any MRI sequence* - i.e not just those specified by the PI-RADS criteria - as was done in CHAPTER 2, the possible value of contrast as a safety net for those lesions can be appreciated (FIGURES 9-13 below).

FIGURE 9: Dataset case of (left to right) axial DCE, axial T2, axial DWI and axially sliced wholemount radical prostatectomy with index tumour inked orange. The left anterior peripheral zone tumour is subtle on T2 and DWI. There is early contrast enhancement on the DCE map.

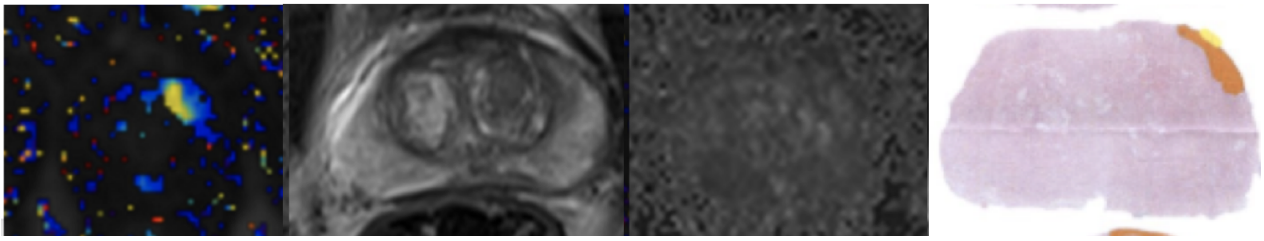


FIGURE 10: Dataset case of (left to right) axial DCE, axial T2, axial DWI and axially sliced wholemount radical prostatectomy with index tumour inked orange. The right prostate apex tumour is subtle on T2 and DWI. There is early contrast enhancement on the DCE map.

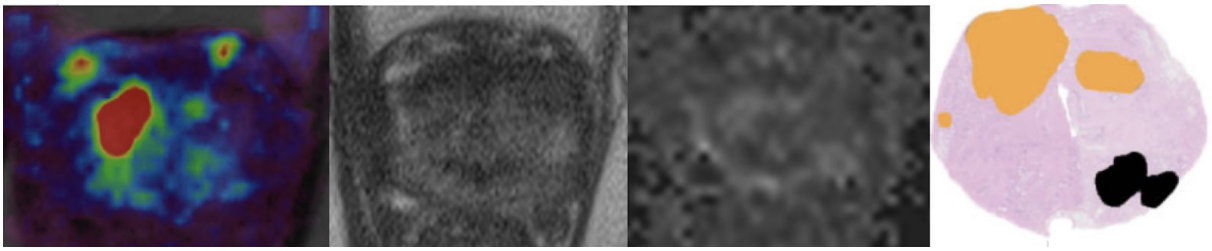


FIGURE 11: Dataset case of (left to right) axial DCE, axial T2, axial DWI and axially sliced wholemount radical prostatectomy with index tumour marked orange. The left AFMS tumour is subtle on T2 and DWI. There is early contrast enhancement on the DCE map.

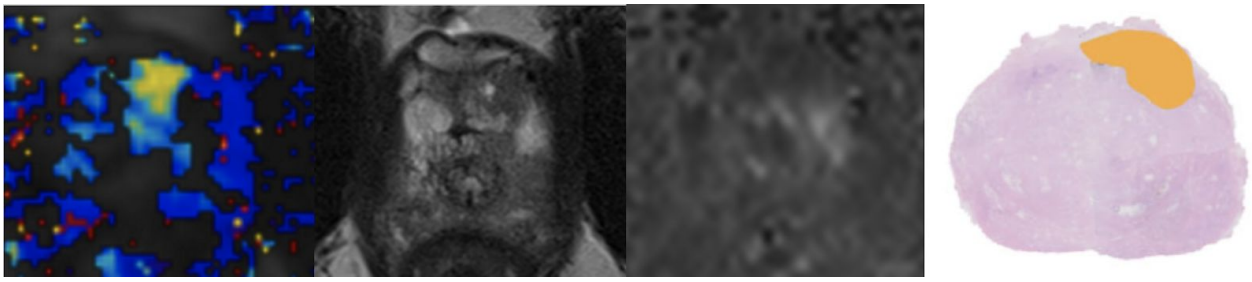
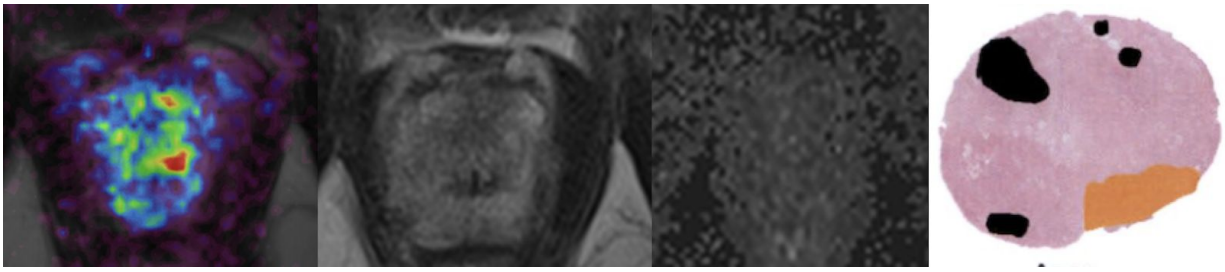


FIGURE 12: Dataset case of (left to right) axial DCE, axial T2, axial DWI and axially sliced wholemount radical prostatectomy with index tumour marked orange. The left PZ tumour is subtle on T2 and DWI. There is early contrast enhancement on the DCE map.



However, this retrospective analysis of false negative cases introduces a significant bias. As CHAPTER 3 demonstrates, when true negative cases were also considered, the discriminatory

ability of DCE was not statistically significant. The results of CHAPTER 3 present only the “true positive” results captured by DCE due to the study cohort; and not the additional false positive results which are a frequent criticism of DCE in literature [93-97]. Furthermore, although in retrospect there were several examples of prominent DCE that exactly matched the histopathology proven tumour location, it is uncertain whether this information would be at all useful in a prospective setting. It was only on heavy manipulation of the other series - T2 and DWI - that corresponding regions of suspicion not previously seen prospectively could be identified. Whether such heavy windowing of the DICOM dataset could be relied upon in a prospective setting to reliably call a PI-RADS 4 lesion is unknown. Evidently, the DCE series was not enough in the current cohort to make the radiologist suspicious, as each was described as a false negative. Whether radiologists, if specifically requested to assess the prostate apex and anterior fibromuscular stroma with the DCE series as a safety net, would find any additional lesions would require a specific prospective study which would be a useful area of future research. The effect size, based on the studies of Zawaideh et al and Stanzione et al, appears small, and therefore a large number of patients would be required to approach a statistically significant result. For example, the maximum size of this safety net effect within our own study in CHAPTER 3 can be calculated if we assume that each of the lesions demonstrating early contrast enhancement on DCE could have been subsequently confirmed on DWI/T2 (which is felt unlikely). This safety net effect existed in 11 of 34 false negative studies that proceeded to radical prostatectomy, of the 2,324 patients who were scanned in total. Such a small clinical effect size is consistent with the small effect size demonstrated in the two prospective studies of Stanzione et al [199] and Zawaideh et al [192]. Based on these results, and based on the potential size of the safety net effect from the number of possible safety net cases recorded in CHAPTER 3 (11 cases out of 2324 men scanned), it appears that DCE offers additional benefit in detecting clinically significant cancer in the order of 1-in-80 to 1-in-211 prostate MRI cases based on the safety net effect. Ultimately however, this remains an area that requires further prospective research, for example to examine whether this significantly increases false positive detection rates.

There are several avenues for ongoing research in this field. Prostate MRI now appears to be at an inflection point, characterized by widespread understanding of its benefits. The prior 10 years has focused on standardising prostate MRI (principally through the PI-RADS initiative) in order for prostate MRI to be reproducible enough to widely demonstrate its benefits. Now that these benefits are established, further research could focus on making testing as efficient as possible. At present, this focuses mainly on the ongoing role of the contrast series as described above. However, as each scan plane (axial/sagittal/transverse) takes incrementally longer, the additional value of

different scan planes is worth scrutinizing and remains a subject of discussion. For example, there are some preliminary studies that evaluate so-called "fast" biparametric protocols.These remove sagittal and coronal sequences from imaging. Van der Leest et al found that a fast monoplanar biparametric prostate MRI had an equal detection rate of clinically significant cancer to full mpMRI. However this took only 7 vs 15 minutes, although did result in 2% more biopsies and ~1% more overdetection of low-grade PCa[206]. Stanzione et al evaluated the same monoplanar protocol (axial T2/DWI/ADC only) against mpMRI in 2 experienced radiologists and 2 radiology registrars. Concordance with histopathology was slightly higher for mpMRI (83% vs 87%) amongst experienced readers and also amongst radiology residents (75% vs 77%) [207]. Kuhl et al evaluated fast bpMRI (acquisition time of 8 minutes) against full mpMRI (34 minutes) across 4 radiologists with 542 men. They found that mpMRI allowed detection of one additional clinically significant prostate cancer but caused 11 additional false-positive diagnoses.[186]. These preliminary results, whilst encouraging, require further research before monoplanar fast MRI protocols become routine in prostate cancer detection.

CONCLUSION

Establishing Prostate MRI as a Standard of Care in Early Prostate Cancer Detection

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Prostate cancer is a significant health burden amongst men and traditionally suffered from a flawed diagnostic pathway. But the increasing use of multiparametric prostate MRI likely represents a new paradigm in early detection. Despite its increasing use, literature demonstrates 'wide variability' in mpMRI accuracy [105]. Accurately characterising this is crucial because it has implications for ongoing management, such as whether men require biopsy, repeat interval scanning, or simply follow up PSA testing. This thesis therefore focused on evaluating the false negative rate of mpMRI (CHAPTER 1), and then evaluated factors known to influence false negative rates; tumour/gland histopathology (CHAPTER 2), radiologist experience (CHAPTER 3) and the use of contrast (CHAPTER 4).

The original contribution of this thesis is fourfold. Firstly it established a comprehensive understanding of the rate of clinically significant prostate cancer in reportedly normal (false negative) multiparametric prostate MRI studies using the best available comparator tests; conventional per-patient wholemount radical prostatectomy and transperineal template referencing, plus corroboration from a novel hemigland analysis. Between these three methods a false negative rate of 7.5% - 19.5% was established (depending on the type of comparison), producing a sensitivity for the detection of clinically significant disease between 89.6% - 92.5%.

Secondly, by analysing each radical prostatectomy in our dataset - which is novel for the method in which the pathologist has marked each tumour (guaranteeing lesion confirmation) - we were able to describe the histopathological characteristics of missed tumours. 15 of 34 missed tumours could not be seen in retrospect, and 8 of these were less than 0.5cc or low percentage Gleason pattern 4 disease. 5 cases appeared affected by artefact, and in 2 cases no cause was found. 5 of 19 cases where lesions could be seen in hindsight were lesions within the transition zone, which would have been upgraded to PI-RADS 3 based on the most recent PI-RADS Version 2.1 scoring system. Tumours which could otherwise be identified in hindsight were within the anterior fibromuscular stroma or prostate apex in 11 of 19 cases. These tumours were extremely subtle on their primary sequence (determined by the PI-RADS Version 2.0 scoring system). 80% of these tumours demonstrated early contrast enhancement on DCE series. However whether this means DCE increases the detection of such lesions is uncertain, given that they were inconspicuous on their primary series. In any case, the finding suggests radiologists should screen the anterior fibromuscular stroma and prostate apex for early contrast enhancement specifically.

Thirdly the importance of radiologist experience in prostate MRI accuracy was evaluated in a novel global analysis of 50 radiologists - a sample size approximately 10-fold larger than any prior study. This allowed a demonstration of the prostate MRI learning curve for the first time. Radiologists

were grouped in bins of prior prostate MRI caseload experience, which were plotted against overall PI-RADS accuracy, specificity, overall sensitivity and transition zone sensitivity. Apart from specificity (true negative detection), which was a skill established early in the prostate MRI learning curve, sensitivity and overall PI-RADS accuracy continued to improve across subgroups of experience, even between the highest and second highest tiers of prior experience in 300 and 1000 prior cases, respectively. This analysis demonstrated that the most difficult skill - or at least that which took longest to acquire - was accurate detection of transition zone lesions. The analysis also has implications for quality assurance. Radiologists should not perform single reader interpretation of prostate MRI scans when their prior experience is less than 100 cases. Ideally such readers would be paired with experts (those who have read more than 1000 prior cases) so that they can dual-read without compromising accuracy rates.

Finally this thesis performed the largest transperineal biopsy matched analysis of the marginal benefit of contrast in prostate MRI for cancer detection. Although there is one larger study of 1063 men by Boesen et al, their study used 10 core TRUS biopsy as the comparator [208]. Our analysis of 988 patients used transperineal biopsy with an average of 25 cores. Our results demonstrated that contrast was not required to determine the PI-RADS Version 2.0 score in 93% of cases. Furthermore, the actual discriminative ability of contrast for upgrading peripheral zone PI-RADS 3 lesions was not statistically significant. These results suggest that DCE is not routinely required in routine mpMRI reporting - a viewpoint recently acknowledged by the PI-RADS working group [209].

There are several limitations of this research. In CHAPTER 2 our study population had a prevalence of clinically significant disease of 68%. This influenced the negative predictive value of our analysis. On a screening basis, the prevalence of clinically significant disease would be closer to 40%. Furthermore, CHAPTER 3 focused on the retrospective identification of pathology. It remains to be seen whether these findings would falsely elevate false positive findings.

There are several avenues for further research. The role of contrast in specifically providing a safety-net could be clarified with large prospective studies. Similarly, the accuracy of fast monoplanar biparametric protocols for prostate cancer detection could be evaluated prospectively. Further attempts to subgroup PI-RADS 3 scans would provide greater clarification around management of these traditionally indeterminate lesions. Furthermore, methods of standardising radiologist interpretation, so that there is less experience-related variance in accuracy would be welcomed. Future studies of prostate MRI could focus on improving scan time without compromising diagnostic accuracy.

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