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Authors	Hogan, Donnacha;Yao, Henry Han-I;Kanagarajah, Abbie;Ogluszko, Cindy;Tran, Phillip Vinh Phu;Dundee, Phil;O'Connell, Helen Elizabeth
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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

Can multiparametric magnetic resonance imaging and prostate specific antigen density accurately stratify patients prior to prostate biopsy?

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Keywords:	Prostate cancer, Multiparametric Magnetic Resonance Imaging, Prostate Specific Antigen Density, Transperineal Biopsy, Radiology
Abstract:	Objective This study examines the diagnostic accuracy of mpMRI in a high-volume centre to potentially stratify patients prior to prostate biopsy. Methods All biopsy naïve patients who had mpMRI prostate and transperineal biopsy of prostate (TPBx) in 2017 and 2018 were included. There were no exclusion criteria. All patients, regardless of mpMRI result, underwent systematic template biopsy under general anaesthesia with cognitive target biopsy if indicated. Clinicopathological data were extracted from medical records. The primary outcome was the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of mpMRI prostate in the detection of PCa compared with template TPBx. Results In total 140 patients were included. Overall, 57.1% had a positive biopsy. A higher Prostate Imaging-Reporting and Data Systems (PI-RADS) score was associated with a higher risk of diagnosing clinically significant PCa (ISUP ≥2) ($p<0.001$). The sensitivity, specificity, NPV, and PPV of mpMRI in detecting clinically significant PCa with a PI-RADS ≥3 lesion, was 95% (95% CI 83.0-99.3%), 41% (95% CI 31.3-51.3%), 95.3% (95% CI 84.2-99.4%) and 39.2% (95%CI 29.4-49.6%), respectively. Combining this with prostate specific antigen density (PSAD) of <0.15 further improved the negative predictive value to 100% (86.3-100). Binomial logistic regression to understand the effects of PSA, DRE and PI-RADS score on predicting clinically significant PCa (ISUP ≥2) found increasing PSA (OR 1.06, [95% CI 1.00-1.11, $p=0.022$]) and PI-RADS (OR3.17, [95% CI 1.94-5.18, $p<0.001$]) to be significant predictors. Malignant DRE was not a significant predictor ($p=0.087$).

	Conclusion This study demonstrates that the high sensitivity and NPV of mpMRI combined with PSAD may play a pivotal role in stratifying men for prostate biopsy and help avoid biopsy and its associated morbidity in select patients.

Can multiparametric magnetic resonance imaging and prostate specific antigen density accurately stratify patients prior to prostate biopsy?

Dr D Hogan[1,2]

Mr H.H. Yao[1,3]

Dr A Kanagarajah[1,3]

Ms C Ogluszko[1]

Dr P Tran[4]

Mr P Dundee[1]

Professor H.E. O'Connell[1]

1. Department of Urology, Western Health, Melbourne, Victoria, Australia
2. University College Cork, College Road, Cork, Ireland
3. Eastern Health Clinical School, Monash University, Melbourne, Australia
4. Department of Radiology, Western Health, Melbourne, Australia

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Corresponding author

Name: Dr Donnacha Hogan

Address: Western Health, 160 Gordon Street, Footscray, Melbourne, Australia, 3011

Email: donnacha.hogan@umail.ucc.ie

Phone: +353(21)4922000

Twitter: @HoganDonnacha

Abstract

Objective –This study examines the diagnostic accuracy of mpMRI in a high-volume centre to potentially stratify patients prior to prostate biopsy.

Methods – All biopsy naïve patients who had mpMRI prostate and transperineal biopsy of prostate (TPBx) in 2017 and 2018 were included. There were no exclusion criteria. All patients, regardless of mpMRI result, underwent systematic template biopsy under general anaesthesia with cognitive target biopsy if indicated. Clinicopathological data were extracted from medical records. The primary outcome was the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of mpMRI prostate in the detection of PCa compared with template TPBx.

Results – In total 140 patients were included. Overall, 57.1% had a positive biopsy. A higher Prostate Imaging-Reporting and Data Systems (PI-RADS) score was associated with a higher risk of diagnosing clinically significant PCa (ISUP ≥2) ($p<0.001$). The sensitivity, specificity, NPV, and PPV of mpMRI in detecting clinically significant PCa with a PI-RADS ≥3 lesion, was 95% (95% CI 83.0-99.3%), 41% (95% CI 31.3-51.3%), 95.3% (95% CI 84.2-99.4%) and 39.2% (95%CI 29.4-49.6%), respectively. Combining this with prostate specific antigen density (PSAD) of <0.15 further improved the negative predictive value to 100% (86.3-100). Binomial logistic regression to understand the effects of PSA, DRE and PI-RADS score on predicting clinically significant PCa (ISUP ≥2) found increasing PSA (OR 1.06, [95% CI 1.00-1.11, $p=0.022$]) and PI-RADS (OR3.17, [95% CI 1.94-5.18, $p<0.001$]) to be significant predictors. Malignant DRE was not a significant predictor ($p=0.087$).

Conclusion – This study demonstrates that the high sensitivity and NPV of mpMRI combined with PSAD may play a pivotal role in stratifying men for prostate biopsy and help avoid biopsy and its associated morbidity in select patients.

Level of Evidence: 2b (Oxford Centre for Evidence-Based Medicine: Levels of Evidence)

Introduction

Prostate cancer (PCa) is the most frequently diagnosed solid organ cancer in men and is the second most common cause of cancer-related death (1). Prostate biopsies remain the cornerstone of PCa diagnosis. Both the transrectal and transperineal routes for prostate biopsy are associated with complications such as urosepsis and urinary retention (2). The decision to perform a biopsy has traditionally been based on the patient's serum prostate specific antigen (PSA), combined with their digital rectal examination (DRE) findings. The advent of multiparametric magnetic resonance imaging (mpMRI) of the prostate has allowed the identification of lesions amenable for target biopsy thus improving the positive yield and reducing the need for repeat prostate biopsies (3). In recent times, there has been an increased uptake of mpMRI prior to prostate biopsy. A previous prospective, multi-centre, paired-cohort, confirmatory study has shown mpMRI to have a high sensitivity in detecting clinically significant PCa of 93% for ISUP ≥3 and 88% for ISUP ≥2 PCa (4). A recent systematic review and meta-analysis has demonstrated the pooled negative predictive value (NPV) of mpMRI to be 93.4% (5). As such, mpMRI still cannot be relied on alone in the diagnosis of PCa.

Currently mpMRI is used pre-biopsy to identify target lesions and thereby improve the yield of a biopsy. Its use to identify those men who do not require a biopsy has not yet been clearly defined. One suggestion has been to include adjuvant tools such as PSA density (PSAD), to further the utility of mpMRI in this context (6-8). Prostate biopsy is not a risk-free procedure and carries a small risk of urinary retention, erectile dysfunction, sepsis and associated risk of general anaesthesia in centres not performing prostate biopsies under local anaesthesia (2, 9-14). . It is useful to assess the utility of mpMRI in reducing the number of biopsies performed thereby reducing the morbidity associated with prostate biopsies (2, 9-14). The use of mpMRI to avoid biopsy and diagnosis of low-risk PCa can also reduce the morbidity associated with

such a diagnosis. Although the majority of patients are now enrolled in active surveillance (AS), a small portion of patients will elect to undergo curative treatment and experience the associated side effects of treatment (15). AS also carries with it some morbidity associated with a confirmatory biopsy, as well as anxiety of diagnosis and progression (16, 17). At least one third of men enrolled in AS report cancer-specific anxiety that affects their quality of life (15, 16, 18-23).

One reason mpMRI prostate has not replaced biopsy is the broad variation in the degree of sensitivity and NPV of mpMRI (5, 6). A recent multi-centreseries on mpMRI has shown the sensitivity and specificity to be variable across centres, resulting in an overall pooled value to be below the reported values in the meta-analysis by *Sathianathen et al*. (5, 24). This study's institution performs a high volume of prostate biopsy with the majority of mpMRI reported by a single radiologist experienced in MRI reporting who regularly attends multidisciplinary (MDT) meeting to correlate their MRI reporting to histopathological findings. Our hypothesis is that using an experienced trained radiologist who actively takes part in MDT can achieve a high mpMRI reporting quality. This study aims to determine the sensitivity, specificity, NPV and positive predictive value (PPV) of mpMRI in the detection of PCa in a high-volume centre and assess the role of PSAD and DRE in combination with mpMRI in stratification of patients for prostate biopsy.

Methods

This retrospective study included 140 consecutive biopsy naïve patients with no prior diagnosis of PCa who underwent pre-biopsy mpMRI followed by transperineal biopsy of the prostate (TPBx) at the study institution from January 1st, 2017 to December 31st, 2018. Patients were recommended to have biopsy based on the Prostate Cancer Foundation of Australia guidelines

(25). As per local guidelines all patients with a clinical suspicion of prostate cancer underwent mpMRI prostate prior to biopsy. A normal MRI did not exclude patients from having a biopsy in the setting of raised PSA or abnormal DRE. All patients in the study period had a biopsy regardless of mpMRI results. Clinicopathological data were collected from hospital electronic medical records and included demographic information; age at time of biopsy, date of biopsy, pre-operative PSA, DRE findings (as reported by the operating surgeon at time of biopsy), lower urinary tract symptoms (LUTS), family history of PCa, prostate volume, number of cores sampled, mpMRI Prostate Imaging-Reporting and Data System (PI-RADS) score, and International Society of Urological Pathology (ISUP) histopathological findings. The majority of MRI scans (>90%) were performed using a 3T MRI scanner with an external phased array body coil. Standard multiparametric prostate MRI sequences were obtained including T1-weighted images, high resolution small field of view T2-weighted images, high B-value (up to 1500) diffusion-weighted imaging, apparent diffusion coefficient map and dynamic contrast enhanced T1 imaging. Intravenous Buscopan was administered if there were no contra-indications to reduce bowel motion artefact. PI-RADS score were reported according to the PI-RADS version 2 reporting system. Similarly, the majority of scans performed (>90%) were reported by a single abdominal fellowship trained radiologist specialising in mpMRI prostate imaging who had been reporting prostate MRI for 7 years prior to the study. Complications were recorded retrospectively from documentation of the two-week post-operative follow up appointment. Ethics approval for this study was granted by the Human Research Ethics Committee of the study institution (Project ID QA2019.26).

Two definitions were used for a positive MRI: 1) PI-RADS 3 and above, and 2) PI-RADS 4 and above. Two definitions were used for clinically significant cancer: 1) ISUP 2 and above, and ISUP 3 and above. The sensitivity, specificity, PPV, NPV for each of the definition were

calculated. The more widely adopted definition of positive MRI is PI-RADS 3 and above and clinically significant cancer is ISUP 2 and above. The results of this definition are reported as the primary outcome of this study. Subgroup analysis was performed for those with negative MRI to determine if the use of PSAD and DRE improved the diagnostic value.

All patients during the study period underwent systematic template biopsy under general anaesthesia. Cognitive target biopsy was performed in addition to the systematic biopsy in patients with a lesion present on pre-biopsy mpMRI. Patients were placed in the high lithotomy position. Template biopsies utilised the brachytherapy 5mm grid and stepper unit (Enovare, Pennsylvania, United States). Transrectal ultrasound guidance was provided with the BK™ endocavity 8848 ultrasound probe (BK Medical, Massachusetts, United States) in the axial and sagittal planes. All biopsies were performed either by or under the supervision of the urology fellow or a urologist.

Data analysis was performed using *Stata Statistical Software: Release 16* (STATACorp, LLC, Texas, United States). Data were tested for normality using the Shapiro-Wilks test and are given as the mean (standard deviation) if normally distributed or median (interquartile range) if non-normally distributed. Categorical data was analysed using χ^2 test or Fisher's exact test. An exact (Clopper-Pearson) 95% confidence interval was calculated. A p-value of <0.05 was considered significant. Binomial logistic regression was performed and assumptions were assessed prior to analysis.

Results

A total of 140 patients were included in this retrospective study. The mean age was 61.3 (±9.65). The median PSA was 6 ng/mL (IQR 4.5-8.8). The DRE finding was benign in 63.6% (n=89), malignant in 32.9% (n=46), and not documented in 3.6% (n=5) of men. Pre-operative LUTS was present in 45.7% (n=64) of men. A family history of PCa was present in 14.3% of men (n=20). The median prostate volume on mpMRI was 38 mL (IQR 26-55). The median PSAD was 0.15 (IQR 0.09-0.26). Just 10% of patients (n=14) had a life expectancy of less than 10 years based on 2017 average Australian life expectancy. Staging using nuclear medicine bone scan and computed tomography identified 2 (1.4%) patients with suspicious lymphadenopathy and 1 (0.7%) patient with metastatic disease to bone. Pre-operative mpMRI findings and patient demographics are summarised in Table 1.

The median number of cores sampled at TPBx was 26 (IQR 22-33). Specific target cores were taken in 30% of patients (n=42). The mean core density was 0.79 (± 0.45). Out of the 97 patients who had lesions amenable to target (PI-RADS 3-5), specific target cores were documented in 43.3% (n=42). It should be noted that it was the preference of some surgeons performing systematic biopsy, particularly on small glands, to incorporate a target lesion into their systematic biopsy. Therefore, those patients did not have a target core labelled separately for histology purposes and were not captured as targeted biopsies in this study. The median number of cores taken per mL of prostate gland was 0.7 (IQR 0.5-1.1). PCa was detected in 57.1% of patients (n=80). Of the patients with malignant findings on biopsy, 50% were ISUP 1 (n=40), 20% ISUP 2 (n=16), 11.3% ISUP 3 (n=9), 8.9% ISUP 4 (n=7) and 10% ISUP 5 (n=8).

The percentage of clinically significant PCa diagnosed on TPBx stratified by PI-RADS score on mpMRI of the prostate is shown in Figure 1. The detection rate of clinically significant PCa

increased with increasing PI-RADS score for both definitions of clinically significant PCa ($p<0.001$ for both definitions).

Using PI-RADS ≥3 on mpMRI as the definition of positive MRI and ISUP ≥2 as the definition of clinically significant PCa, the sensitivity, specificity, NPV and PPV of mpMRI prostate was 95% (95% CI 83.0-99.3), 41% (95% CI 31.3-51.3%), 95.3% (95% CI 84.2-99.4%) and 39.2% (95% CI 29.4-49.6%), respectively. When a PSAD of <0.15 was also taken into consideration, the NPV and PPV of mpMRI in detecting clinically significant PCa was 100% (95% CI 86.3-100) and 17% (95% CI 7.2-32.1%), respectively. Further including a benign DRE into this diagnostic consideration resulted in an NPV and PPV of 100% (95% CI 83.9-100%) and 9.1% (95% CI 1.1-29.2%), respectively. The sensitivity, specificity, NPV and PPV of mpMRI was also calculated using the varying definitions of positive mpMRI and clinically significant PCa as well as varying levels for PSAD and is summarised in Table 2.

Binomial logistic regression was performed to understand the effects of PSA, DRE and PI-RADS score on cancer detection. This was performed for both definitions of clinically significant cancer. Excluded were patients with missing data (n=5). When taking ISUP ≥2 as the definition for clinically significant PCa; PSA was found to be a significant predictor of PCa (OR 1.06 [95% CI 1.00-1.11, p=0.022]), as was increasing PI-RADS score (OR 3.17 [95% CI 1.94-5.18, p<0.001]). However, malignant DRE was not a significant predictor (p=0.087). When taking ISUP ≥3 as the definition for clinically significant PCa; PSA was again found to be a significant predictor of PCa (OR 1.06 [95% CI 1.01-1.12, p=0.006]), as was increasing PI-RADS score (OR 3.63 [95% CI 1.89-6.93, p<0.001]). Malignant DRE was not a significant predictor (p=0.190).

There were no documented urinary tract infections on follow-up. Post-operative urinary retention occurred in 3.6% of the men who were not catheterised pre-operatively (n=5/139).

Discussion

This high sensitivity of 95% and NPV of 95.3% of mpMRI in the detection of PCa demonstrated in this study appears better than the recently published Australian series (24) and is consistent with the meta-analysis published recently showing a pooled NPV of 91.3% for patients with no previous diagnosis of PCa (5). Compared to other studies included in the systematic review on the predictive value of mpMRI by *Sathianathen et al.* and *Stonier et al.*, the findings of the present study demonstrate a sensitivity and NPV that are towards the higher range of published studies (5, 26). Although our data demonstrated a relatively high sensitivity of mpMRI and a correspondingly lower specificity, it did not increase the rate of negative biopsy. Therefore, we do not believe we are over-referring for biopsy in our population. Furthermore, the relatively high NPV in our cohort, is unlikely to be due to a low pre-test probability as our positive biopsy rate was 57.1% of whom 50% had clinically significant PCa, which is similar to other series (27). The authors propose that our favourable outcomes may be due to the reporting of our mpMRI by a single radiologist, highly skilled in prostate mpMRI reporting, and regularly attends urology MDT that reviews both histopathology and radiology imaging for prostate biopsies. Although, we acknowledge the power of this study is much lower compared with some multi-centre studies with only 140 participants examined. Furthermore, studies comparing MRI reporting at high and low volume centres is required to prove this definitively. In addition, the low specificity and PPV of mpMRI has been examined, however as seen in other cancer screening tests such as mammography, the high NPV is at the expense of the PPV and accounts for a significant number of false positives (28).

This differences in sensitivity and NPV between this study and other case series further highlights the high variability of MRI reporting and the importance of subspecialty training for the interpretation of mpMRI prostate, as recently described by *De Rooij et al.* (29). In synthesising local practice guidelines, the use of published literature, even domestic literature, is suboptimal due to the high levels of variation. This study supports the concept that institutions should conduct their own audit to help standardise their local prostate biopsy policy. In line with the report from *De Rooij et al.* deficiencies in reporting can be rectified with sufficient training and as demonstrated with high quality mpMRI reporting. Local institutional data can personalise the care specific to the involved institution and select patients who may be able to avoid a biopsy and its associated morbidity.

This study found that when assessing patients with a benign mpMRI defined as PI-RADS ≤2 the use of PSAD <0.15 was demonstrated to further improve the NPV to 100%. The use of a very strict PSAD of <0.1 also increases the NPV to 100% however such a low cut-off runs the risk of performing many unnecessary biopsies. Conversely relaxing the cut-off for PSAD to <0.2 does not significantly increase the NPV (97%) and risks missing patients with potentially clinically significant PCa. The cohort of men with PSAD <0.15 may be counselled to potentially avoid a biopsy. This improvement in diagnostic value of mpMRI using PSAD is consistent with findings from other studies by by *Washino et al.* and *Distler et al*. (30, 31). Current risk tools, including the MRI European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC) do not factor PSAD into their calculations (32, 33). However, the EAU and NICE guidelines support its use in stratifying men for prostate biopsy and with the ongoing development of newer nomograms, we suggest that this valuable tool should not be overlooked by institutions offering prostate biopsy (7, 8). In contrast, the addition of DRE to the decision-making tool in this study

did not improve the NPV. DRE continues to be one of the main screening tools at the disposal of urologists however, it is a crude assessment and its prominence over other adjuvant investigations has not been justified (34). The findings of this study therefore support the recommendation by the Prostate Cancer Foundation of Australia (PCFA) on DRE not being a routine test at the general practitioner's office for men wishing to be tested for the presence of PCa (25). Urologists will continue find DRE useful for clinical staging of PCa. PSAD is not always routinely provided in mpMRI reporting but there is strong evidence in support of its utility which out data support.

There are several limitations to this study. Firstly, this is a retrospective study and comes with all the limitations of such a study design. For example, the accuracy of complications rates was dependent on meticulous clinical documentation. Therefore, it is possible that the rates of complication may have been under-reported. However, the primary outcome of this study should not have been affected as all patients had mpMRI reported PI-RADS scores as well as histopathology findings. Secondly, not all patients who underwent TPBx at our institution underwent mpMRI and therefore these patients were not included in this study. This may present a selection bias. The reason for not undergoing a pre-biopsy mpMRI is usually due to cost and access and most of the patients in this study were recruited prior to the MBS funding of mpMRI was available. Thirdly, unlike the PROMIS trial, our study did not employ saturation biopsy of 5mm and therefore some cancer may have been missed (4). However, the use of target biopsy in 30% (n=42) of patients as well as the high number of cores taken, with a mean of 26 (±7.21), is expected to have provided adequate sampling. As previously mentioned, in patients who did not have a target core, the surgeon aimed to incorporate the target lesion into their systematic biopsy and did not label this separately. In line with EAU guidelines, in the first biopsy setting, the samples taken concentrate on the peripheral zone (PZ) rather than the

transitional zone (TZ), therefore a lower number of cores is generally sampled from the TZ rather than the PZ (11-14). Although all patients did not have a saturation biopsy or prostatectomy specimen as a gold standard for cancer detection rate, there was a high mean core density of 0.79 (± 0.45) which allowed us to determine the performance of mpMRI. Fourthly, this study did not perform a per MRI positive lesion analysis and therefore cannot conclude on the sensitivity and specificity on a per lesion basis. As discussed previously, some surgeons include the target lesion in the template and therefore it is not possible to determine per lesion analysis for these patients. ~~Fourthly~~Finally, this study of a high-volume tertiary referral single-centre with an experienced single-radiologist may limit the generalisability of the results to some biopsy centres. This does support the move in many parts of the world to centralise cancer services in order that diagnosis and treatment is performed by high-volume surgeons. It has been well documented that high volume centres have better oncological outcomes than low-volume centres (35). The results of this study further support this.

Conclusion

This study demonstrates that mpMRI has a high sensitivity (95%) and NPV (95.3%) for the detection of PCa on TPBx at our institution, a high-volume tertiary referral centre with an experienced MRI radiologist. For men with a negative MRI defined as PI-RADS 1-2, using a PSAD further improves the NPV to 100% when including a PSAD of <0.15 into the diagnostic algorithm. Based on the findings of this study, mpMRI can be used to stratify patients for prostate biopsy and allow patients with PI-RADS 1-2 and PSAD <0.15 to potentially avoid biopsy and its complications.

Acknowledgements

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Table 1: Pre-operative Clinical and Demographic Characteristics

	Patients (n=140)
Age (years)	61.3 (±9.65)
PSA (ng/mL)	6 (4.5-8.8)
DRE	
Benign	63.6% (n=89)
Malignant	32.9% (n=46)
Unknown	3.6% (n=5)
Prostate Volume (mL)	38 (26-55)
PSA Density	0.15 (0.09-0.26)
PI-RADS Score	
1	1% (n=2)
2	29% (n=41)
3	24% (n=33)
4	25% (n=35)
5	21% (n=29)
LUTS	45.7% (n=64)
Family History of PCa	14.3% (n=20)

Data are given as mean (standard deviation), median (interquartile range) or percentage (n), unless otherwise stated.

DRE= Digital Rectal Examination, LUTS = Lower urinary tract symptoms, mL= millilitre, PCa = Prostate Cancer, PSA= Prostate Specific Antigen.

Table 1: Sensitivity, specificity. positive predictive value and negative predictive value of mpMRI prostate.

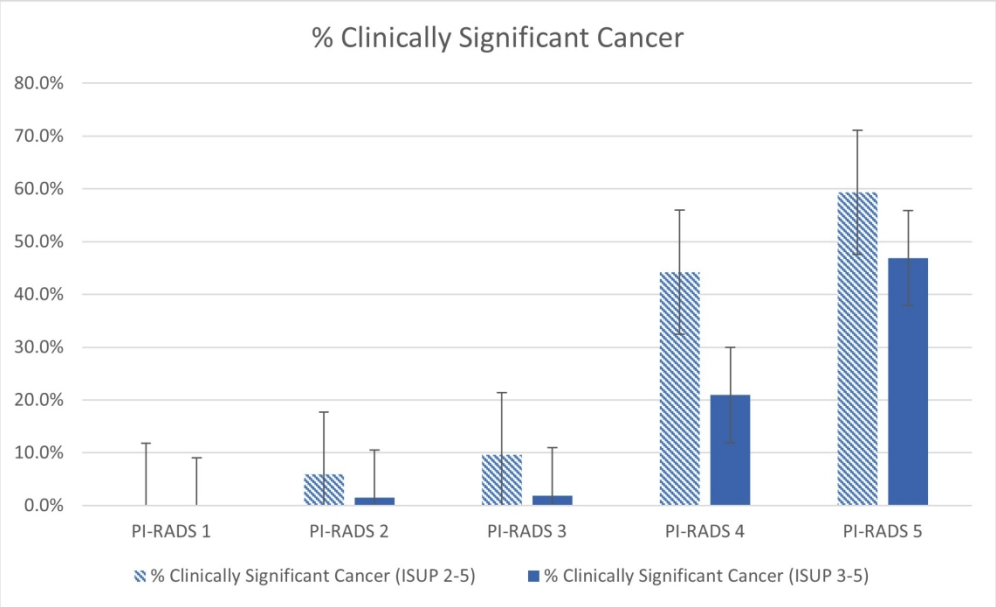
	Sensitivity	Specificity	NPV	PPV
PI-RADS ≥3 and ISUP≥2	95.0 (83.0-99.3)	41.0 (31.3-51.3)	95.3 (84.2-99.4)	39.2 (29.4-49.6)
PI-RADS ≥3 and ISUP≥3	95.8 (78.9-99.9)	36.2 (27.5-45.6)	97.7 (87.7-99.9)	23.7 (15.5-33.4)
PI-RADS ≥4 and ISUP≥2	87.5 (73.2-95.8)	71 (61.0-79.6)	93.4 (85.3-97.8)	54.7 (41.7-67.2)
PI-RADS ≥4 and ISUP≥3	91.7 (73.0-99.0)	63.8 (54.4-72.5)	97.3 (90.8-99.7)	34.4 (22.9-47.3)
PI-RADS ≥3, ISUP≥2 and PSAD <0.1	-	-	100 (82.4-100)	5.1 (0.1-26.0)
PI-RADS ≥3, ISUP≥3 and PSAD <0.1	-	-	100 (82.4-100)	0 (0-17.6)
PI-RADS ≥4, ISUP≥2 and PSAD <0.1	-	-	96.6 (82.2-99.9)	0 (0-33.6)
PI-RADS ≥4, ISUP≥3 and PSAD <0.1	-	-	100 (88.1-100)	0 (0-33.6)
PI-RADS ≥3, ISUP≥2 and PSAD <0.15	-	-	100 (86.3-100)	17.0 (7.2-32.1)
PI-RADS ≥3, ISUP≥3 and PSAD <0.15	-	-	100 (86.3-100)	9.8 (2.7-23.1)
PI-RADS ≥4, ISUP≥2 and PSAD <0.15	-	-	97.8 (88.5-99.9)	30.0 (11.9-54.3)
PI-RADS ≥4, ISUP≥3 and PSAD <0.15	-	-	100 (92.3-100)	8.9 (5.7-43.7)
PI-RADS ≥3, ISUP≥2 and PSAD <0.2	-	-	97.0 (84.2-99.9)	22.6 (12.3-36.2)
PI-RADS ≥3, ISUP≥3 and PSAD <0.2	-	-	97.0 (84.2-99.9)	13.2 (54.8-25.3)
PI-RADS ≥4, ISUP≥2 and PSAD <0.2	-	-	96.6 (88.1-99.6)	39.3 (21.5-59.4)
PI-RADS ≥4, ISUP≥3 and PSAD <0.2	-	-	98.3 (90.8-99.9)	25.0 (10.7-44.9)
PI-RADS ≥3, ISUP≥2, PSAD <0.15 and benign DRE	-	-	100 (83.9-100)	9.1 (1.1-29.2)
PI-RADS ≥3, ISUP≥3, PSAD <0.15 and benign DRE	-	-	100 (83.9-100)	4.5 (0.1-22.8)
PI-RADS ≥4, ISUP≥2, PSAD <0.15 and benign DRE	-	-	97.2 (85.5-99.9)	14.3 (0.4-57.9)
PI-RADS ≥4, ISUP≥3, PSAD <0.15 and benign DRE	-	-	100 (90.3-100)	14.3 (0.4-57.9)

Data is displayed as percentage (%) and Exact 95% confidence interval.

ISUP = International Society of Urological Pathology, NPV = Negative Predictive Value, PPV = Positive Predictive Value, PI-RADS = Prostate Imaging-Reporting and Data System, PSAD = Prostate Specific Antigen Density, DRE = Digital Rectal Examination.

Figure Legends

Figure 1: Percentage of clinically significant PCa found stratified by PI-RADS score on mpMRI prostate using ISUP ≥2 or ISUP≥3 as definition of clinically significant PCa.



Percentage of clinically significant PCa found stratified by PI-RADS score on mpMRI prostate using ISUP ≥2 or ISUP≥3 as definition of clinically significant PCa.

158x96mm (330 x 330 DPI)

Declarations

Conflicting interests: There are no declarations by any author of competing interests, financial or otherwise.

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Research ethics: The ethics committee of Western Health approved with study (Project ID GA2019.26)

Guarantor: DH

Contributorship: DH, HY researched the literature and conceived the study. DH, CO and HY were involved in protocol development, gaining ethical approval, patient recruitment, and data analysis. DH wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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