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Accuracy of multiparametric magnetic resonance imaging to detect significant prostate cancer and index lesion location

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Abstract

Background: Multiparametric magnetic resonance imaging (mpMRI) of the prostate appears to improve prostate cancer detection, but studies comparing mpMRI to histopathology at the time of radical prostatectomy (RP) are lacking. This retrospective study determined the accuracy of mpMRI predicting Gleason score and index lesion location at the time of RP, the current gold standard for diagnosis.

Methods: Between April 2013 and April 2016, a database of all men aged more than 40 years who underwent RP after positive transrectal ultrasound biopsy by an experienced urological surgeon was collated at a single regional centre. This was cross-referenced with a database of all men who had mpMRIs performed at a single centre and reported according to Prostate Imaging Reporting and Data System (PI-RADS version 1) during this period to generate a sample size of 64 men. A Spearman's rho test was utilized to calculate correlation.

Results: Median age of patients was 64 years, the median prostate-specific antigen at RP was 6.22 ng/mL. mpMRI was positive (≥PI-RADS 3) in 85.9% of patients who underwent RP. More than 92% of participants had Gleason ≥7 disease. A positive relationship between mpMRI prostate PI-RADS score and RP cancer volume was demonstrated. An anatomical location correlation calculated in octants was found to be 89.1% accurate.

Conclusion: mpMRI accurately detects prostate cancer location and severity when compared with gold standard histopathology at the time of RP. It thus has an important role in planning for future prostate biopsy and cancer treatment.

Key words: anatomical correlation, biopsy, cancer detection, magnetic resonance imaging, prostate cancer.

Introduction

Over the last 10 years, multiparametric magnetic resonance imaging (mpMRI) of the prostate has emerged as a tool for the assessment and diagnosis of focal prostate cancer (PCa), especially amidst concerns about the accuracy of screening measures [1].

Interest in the accuracy of PCa assessment using mpMRI has increased in response to the low specificity/sensitivity of digital rectal examination [2] and issues with transrectal ultrasound (TRUS)-guided prostate biopsy, including inadequate sampling of the anterior part of the prostate and the disparity between Gleason score at biopsy and pathological analysis at the time of radical prostatectomy (RP) [2–4]. There have been multiple recent studies published about the diagnostic accuracy of mpMRI, comparing preoperative MRI findings with biopsy results and cohorts of RP histopathology [5–7]. The aforementioned literature demonstrated that mpMRI had high sensitivity and high negative predictive value for detecting PCa, with limited specificity [4].

mpMRI compares favourably with established tests such as mammography for breast cancer screening [8]. It has been demonstrated that men in regional areas receive PCa diagnoses later, receive delayed treatment and have increased morbidity and mortality when compared with men in metropolitan areas [9]. Therefore, it is important to explore and contextualize the role of mpMRI in a regional setting where risk stratification for biopsy and treatment must be performed with access and resource limitations in mind. The current gold standard treatment for clinically significant, non-metastatic PCa is aimed at total removal of the gland via RP, with pelvic lymph node clearance [10,11]. This retrospective study utilized RP specimens to correlate Prostate Imaging Reporting and Data System (PI-RADS) score with definitive Gleason score and PCa volume. It also aims to document the accuracy of mpMRI by demonstrating anatomical concordance between mpMRI and RP pathology.

Methods

Study population characteristics

Between April 2013 and April 2016, a database of all men who underwent RP by an experienced urological surgeon after positive biopsy was collated at a regional centre. A database of patients who underwent mpMRI for clinical suspicion of PCa was also collated. These databases identified 64 patients aged ≥40 years who underwent mpMRI prostate within 18 months prior to RP. The surgeon used mpMRI to guide TRUS cognitive-fusion biopsy, informing the decision to proceed to RP. Regions of interest (ROI) appeared visible on TRUS as a hypoechoic area, which assisted targeted biopsy.

Exclusion criteria included men who had their first mpMRI prostate post radiotherapy, men who had mpMRI but had not yet undergone RP and men with an mpMRI prostate reported by an inexperienced radiologist (less than 50 mpMRI previously reported).

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Ethics approval was granted by The University of Notre Dame Australia's Human Research Ethics Committee. Informed consent was gained from all patients prior to their database inclusion.

Study protocol

mpMRIs were performed at a single centre using the Discovery MR750w 3.0T (GE Healthcare, Chicago, IL, USA), 3-Tesla magnet and a standardized protocol as per published mpMRI prostate studies [1,5]. In RP-naïve men, a cognitive-fusion biopsy with 16–24 cores was utilized to obtain a Gleason score. Indications for RP adhered to a definition of clinically significant PCa. Significant PCa was defined as either Gleason score ≥7, PCa volume >0.5 cm3 at RP specimen analysis or extra-prostatic extension, in line with current literature [2,4,11].

MRI was prospectively anatomically correlated to RP in octants. The data collectors entering mpMRI and RP anatomic locations were blinded to prevent bias. An index lesion (IL) based on size was analysed on a per-patient basis for apparent diffusion coefficient and RP specimen. RP histopathology was performed at two regional centres as per established World Health Organization (WHO) reporting guidelines.

Reporting protocol

Two radiologists (ID and NS) reported mpMRIs independently as ordered by the clinician (SS). Each radiologist had reported more than 50 prior prostate MRIs. Standard PI-RADS version 1 was used. Radiologists were given clinical data including PSA, digital rectal examination and family history.

Standardized PI-RADS is on a five-point scale, which describes clinically significant PCa; 1, extremely unlikely; 2, unlikely; 3, equivocal; 4, likely or 5, extremely likely [12]. Using objective criteria, ROI were assigned a score for each parameter including T2-weighted imaging (T2WI), dynamic contrast-enhanced imaging and diffusion weighted imaging. For the purpose of the study, positivity was defined as PI-RADS ≥3, in line with other mpMRI prostate studies [3,4,13–16]. The study's primary end point was to demonstrate a correlation between PI-RADS and Gleason score/PCa volume.

A blinded investigator correlated location according to retrospective mpMRI radiology reports and pathology reports. MRI ILs were retrospectively defined by the investigator as lesions with the highest PI-RADS score. The prostate was divided into octants at histopathology to characterize IL. mpMRI ILs were described in octants in order to determine correlation between mpMRI and RP specimen. Secondary lesions were reported descriptively.

Statistical analysis

Statistics were performed using Microsoft Excel Professional Plus 2013 (Windows 10 Enterprise; Microsoft, Redmond, WA, USA) and IBM SPSS version 22 (IBM, Armonk, NY, USA). Tests were two-tailed and a p-value of <0.05 was considered significant. A Spearman's rank correlation was utilized

to determine the correlation between PI-RADS and Gleason score at TRUS biopsy and RP, and PI-RADS and PCa volume at RP given the distribution of the data. A Kruskal–Wallis H-test was used to assess statistical difference between PI-RAD categories and mean PCa volume.

Results

Baseline characteristics

The median age of the study population was 64 (35–79) years, and 92% of participants had at least Gleason 7 disease. The median PSA at the time of surgery was 6.22 ng/mL. Seventy-five percent of patients had a volume of PCa >0.5 cm3 at RP histopathology.

Biopsy results

There was 75% correlation between cognitive-fusion biopsy Gleason score and RP specimen Gleason score. Of the 16 patients whose Gleason scores did not correlate, 13 were upgraded from biopsy to RP. This corresponded to a 20.3% rate of Gleason score upgrade from biopsy to RP. Table 1 shows a cross-tabulation of the distribution of biopsy Gleason results within PI-RADS score categories.

RP specimen results

Sixty-four patients underwent RP after mpMRI and TRUS biopsy. Table 1 demonstrates the distribution of Gleason scores at the time of RP specimen histopathology and their percentage within each PI-RADS score category. The five patients who were found to have Gleason 6 disease were all found to have PCa volumes ≥0.5 cm3.

Table 1: Gleason score at biopsy and at radical prostatectomy according to PI-RADS

Gleason Score		PI-RADS [n (%)]			
		2	3	4	5
At biopsy	6	3 (33.3)	1 (9.1)	4 (25.0)	8 (28.6)
	7	4 (44.4)	9 (81.8)	12 (75.0)	15 (53.6)
	8	2 (22.2)	1 (9.1)	0	2 (7.1)
	9	0	0	0	3 (10.7)
At radical prostatectomy	6	2 (22.2)	1 (9.1)	0	2 (7.1)
	7	5 (55.6)	10 (90.9)	16 (100)	22 (78.6)
	8	2 (22.2)	0	0	1 (3.6)
	9	0	0	0	3 (10.7)

Forty-six (71.9%) patients had PCa volumes ≥0.5 cm3 at the time of RP specimen analysis. Figure 1 demonstrates the relationship between PCa and volume at RP when compared with mpMRI PIRADS.

Significant PCa (volume ≥0.5 cm3) was found in 55.6% of patients reported as PI-RADS 2, 54.5% of patients reported as PIRADS 3, 87.5% of patients reported as PI-RADS 4 and 82.1% of patients reported as PI-RADS 5.

There was no correlation between PI-RADS and Gleason scores; however, there was a positive correlation between PI-RADS score and PCa volume (Spearman's ρ = 0.356, *p* = 0.004). Gleason score was also positively associated with PCa volume (Spearman's ρ = 0.347, *p* = 0.005).

Cancer volume increased with increasing PI-RADS score (*p* = 0.018). Mean cancer volume at the time of RP histopathology was reported as 0.79 cm3 for PI-RADS 2 PCa, 0.95 cm3 for PIRADS 3 PCa, 1.87 cm3 for PI-RADS 4 PCa and 2.47 cm3 for PIRADS 5 PCa.

There were nine patients whose PCa was reported as insignificant (PI-RADS 2), of whom seven were found to have ≥Gleason 7 disease at RP. Fifty-five patients had significant disease on mpMRI (≥PI-RADS 3), three of whom had Gleason 6 disease reported at RP.

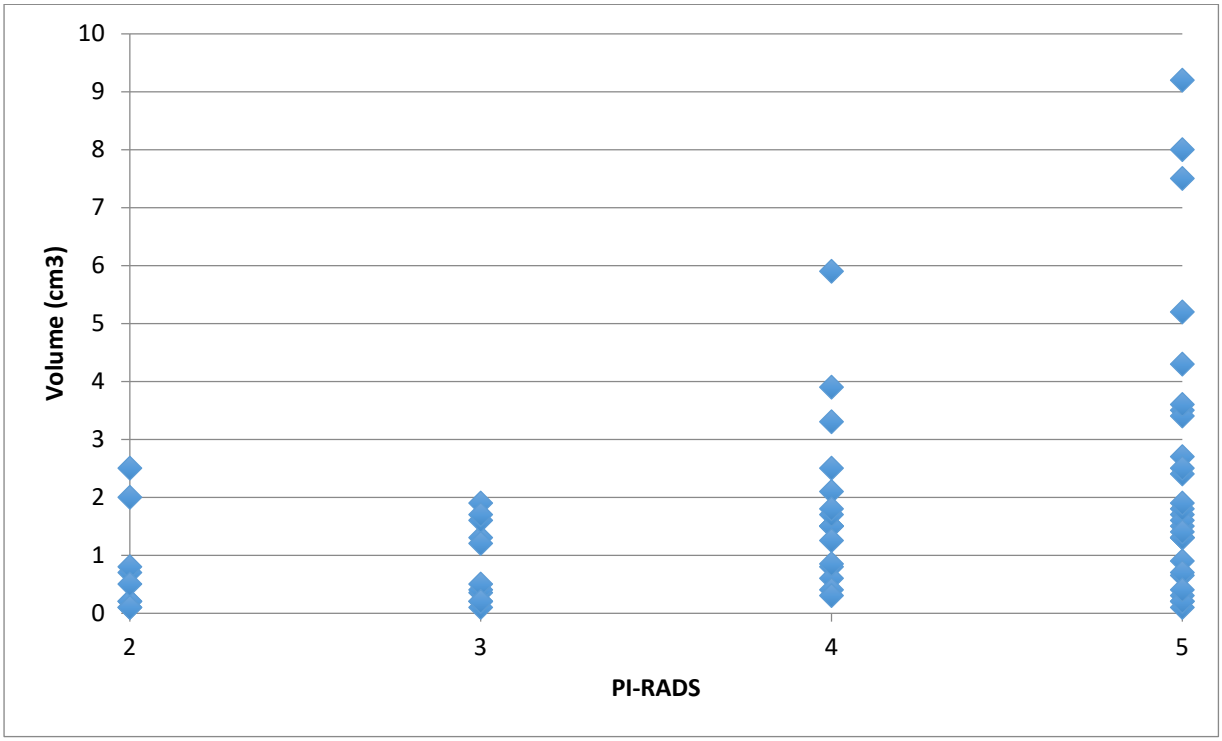

Figure 1: Prostate cancer volume versus Prostate Imaging Reporting and Data System (PI-RADS) score.

Correlation location

Fifty-seven (89.1%) patients had an IL described on mpMRI that corresponded with the IL reported at RP. Table 2 describes features of ILs on mpMRI that did not correspond with IL at RP. Seven significant PCas found at RP were not identified on mpMRI (Table S1). The majority (5/7) of

significant PCa missed was intermediate risk with Gleason score 3 + 4 = 7 (n = 3) or Gleason 4 + 3 = 7 (n = 1). Two patients were found to have Gleason 8 disease at the time of RP. Both patients had an mpMRI demonstrating diffuse low-grade signal abnormality, attributed to benign glandular hyperplasia.

Table 2: MRI IL versus radical prostatectomy IL locations

Patient No.	MRI IL	Other regions MRI	RP IL	Other regions RP
4	Left anterolateral mid	Left anterior apex	Postero-lateral right	Left posterior apex
10	Left posterior	Right PZ	Right posterior peripheral	
30	Diffuse bilateral non-specific change	-	Posterior–left and right	-Right PZ
33	Central bilateral	Left PZ	Apex, peripheral zones bilaterally	
40	Minor left and right change		Multifocal cancer in all quadrants, largest volume in right PZ	
45	Left base with seminal vesical invasion		Left and right apex, no seminal vesical invasion	
56	Diffuse central gland abnormality		Extensive bilaterally in PZ	Foci in left and right posterior quadrants

IL - index lesion; MRI – magnetic resonance imaging; PZ – peripheral zone

Discussion

Accurately sampling the prostate during biopsy has become increasingly important amidst concerns that men are presenting later and with more advanced disease as a result of the recommendations against routine PSA screening released in 2012 [1].

mpMRI prostate has been widely adopted by Australian urologists to characterize PCa prior to initial biopsy, with approximately one in five urologists ordering pre-biopsy MRI in 2015 [17]. Its use has been promoted by the Urological Society of Australia and New Zealand (USANZ) to aid cognitive-fusion or in-gantry biopsy for active surveillance of low-risk disease and to stage newly diagnosed PCa [18]. USANZ lodged an application to the Medicare Benefits Schedule for funding both cognitive-fusion and in-gantry MRI biopsies which was only recently opposed in April 2017 [19].

In this study, the primary surgeon utilized mpMRI to guide cognitive-fusion TRUS biopsy. This is a widely accessible technology, which allows the surgeon to prioritize the ROI pre-identified on mpMRI. Our study demonstrated a significant positive correlation between PI-RADS score and PCa volume at the time of RP. Tumour volume was not assessed on MRI in this patient group but the PI-RADS score itself contains a relevant quantitative component, with increasing PI-RADS score indicating increasing capsular contact by the PCa [8].

There are limited published studies reporting anatomical correlation between lesions with a high PI-RADS and IL at RP histopathology [1,15,20]. One retrospective study comparing cognitive-fusion biopsy of 63 patients with robotic RP whole-mount pathology found MRI was anatomically accurate in 73% of cases [21]. Patel *et al.* [21] mapped the prostate into 24 segments on MRI and histopathology to correlate ILs, which likely accounts for its decreased accuracy compared with our study, despite a similar sample size. Thompson *et al.* compared ROIs in the transperineal template-guided mapping biopsy and whole-mount RP histopathology of 109 men with an 18-segment prostate map and found 97% anatomical concordance, of which 86.5% matched exactly and 13.5% matched but had separate missed significant PCa on MRI [16]. This breakdown of results would have been a useful addition to the data collected by our investigators, but we were unable to confidently correlate the results, given we retrospectively defined the MRI IL. Whole-mount pathology was not available to us at our regional pathology provider. In the current study, the prostate was divided into octants in order to describe lesions, as this is how they were reported at the time of histopathological analysis.

PCa is the only solid organ malignancy that is diagnosed by blind biopsy, i.e. without visualization of the tumour [22]. Without image guidance, systematic TRUS biopsy inadequately samples lesions in the apex, anterior and midline of the prostate [23]. Attempts to increase sampling with additional cores can increase morbidity from bleeding [24] and lower urinary tract symptoms and infection, with readmission rates as high as 2% [3,25]. The inaccuracy of blind biopsy is evident in the frequent disparity between biopsy Gleason score at biopsy when compared to RP, with a recent study of 5339 cases finding only 54.5% concordance [26].

Techniques proposed to increase accuracy include increasing biopsy cores (16, 24, 28 or 36), MRI prior to standard TRUS biopsy with additional targeted cores and ultrasound/MRI (cognitive) fusion biopsies, designed to improve the specificity of the lesions targeted [8,16]. There is no consensus on the optimal core number for PCa detection without an increase in morbidity, which ranges between 12 and 36 for some template-mapped and perineal biopsy protocols [7,15,25,27]. The primary operator has reduced from an 18–24 core biopsy protocol to an aforementioned 12 core with four additional cores in mpMRI identified ROIs.

This research adds to the body of evidence that IL can be identified on prostate mpMRI prior to TRUS biopsy and RP in the majority of men. The ability of mpMRI to accurately detect the anatomical location of PCa ILs is important for cognitive-fusion biopsy, where the urologist uses ‘visual registration’ to aim biopsy cores at known mpMRI targets. This technique is simple, inexpensive and does not require additional equipment [28]. 89.1% of patients’ IL was correctly identified on mpMRI

prior to TRUS biopsy and RP, which supports the validity of targeted cognitive fusion biopsy by an experienced operator.

Cognitive-fusion biopsy is more readily available in regional centres, given the absence of transperineal biopsy mapping and in-gantry biopsy techniques. Utilizing this technique with 12–18 cores is less time-consuming, less costly and involves a reduced general anaesthesia time for the patient when compared with techniques aforementioned [23,25]. Whilst access to specialist and radiology services is improving in Australian regional centres, there is a recognized discrepancy between Medicare-funded services, health workforce and individual health status between rural and metropolitan areas [28].

There is minimal extra requirement of urologists, radiographers or local health services when utilizing cognitive-fusion biopsy. Ultrasound-MRI fusion and in-gantry biopsy techniques require more ancillary staff including appropriately trained radiographers and registered nurses. Additionally, the Medical Services Advisory Committee costed these three procedures at $925.72, $1149.72 and $2375.11, respectively [19]. Cognitive-fusion biopsy is a sensible option to reduce the human and financial cost whilst maintaining accuracy.

There is ongoing debate about the reference standard to which mpMRI is compared [28]. A systematic review found that ‘various authors advocate comparing MRI with transrectal biopsy, TPB or prostatectomy specimens’ but concluded that even studies which compared both biopsy and RP specimens to MRI produced similar results, a high negative predictive value of MRI specimens [2,4,14–16,18,24,28]. Transperineal biopsy can provide a more comprehensive sample of the prostate for comparison [24]. This was a limitation of our study; however, it is not currently available in regional New South Wales centres.

In this study, there was no significant correlation between PIRADS and Gleason score at RP, likely due to the skew of our small sample size towards Gleason 7 disease, reducing the spread at the higher Gleason range. However, the characteristics of patients who underwent RP were similar to other studies conducted in tertiary centres [4,15,17,18,20].

Four patients who had Gleason ≥7 with volumes >0.5 cm3 were reported as PI-RADS 2 on initial mpMRI. A limitation of this retrospective study was the presence of sample bias. All patients in our study population had significant PCa, thus a high false negative rate. This indicates that although mpMRI enables the targeted sampling of potential PCa focus, it is not a reliable substitute for initial biopsy.

At the time of database collation, PI-RADS version 1 was the most current reporting system [20]. PI-RADS version 2 (2015) places greater emphasis on T2WI and DWI for PCa detection in the transition peripheral zones and places less emphasis on DCE [7,17] which was weakly correlated in this study compared with T2WI and DWI. Our findings support the changes made to the PI-RADS reporting score.

Conclusions

mpMRI was able to detect clinically significant PCa with greater accuracy for PCa volume than Gleason score. Location correlation between mpMRI IL and RP specimen tumour focus demonstrated high accuracy in a small sample size. This study supports the use of cognitive-fusion biopsy, especially in regional centres with limited access to in-bore MRI or MRI-ultrasound fusion technology. Further prospective studies comparing mpMRI cognitive-fusion biopsy with RP specimens are needed to support more widespread use of mpMRI-targeted biopsy in clinical practice.

Conflicts of interest

None declared.

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Table S1: Features of significant prostate cancer missed on mpMRI

Patient Number	**PI-RADS Score**	**Gleason Score**	**Volume (cm^3)**	**PSA (ng/mL)**
3	2	7	0.1	2.8
12	2	7	0.7	6.4
45	2	8	2.0	7.0
50	2	7	0.2	4.8
52	2	7	0.8	6.6
55	2	8	0.8	8.1
64	2	7	0.2	4.8