How accurate is multi-parametric MRI for predicting prostate cancer pathology and tumour staging in the real world? – An Australian multi-centre study

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Abstract

Objectives:

To assess the accuracy of multi-parametric MRI (mpMRI) for the detection of significant prostate cancer in men undergoing radical prostatectomy (RP) in an Australian multi-centre setting. Secondary aims were to assess concordance between mpMRI and RP for local tumour staging and index lesion locations.

Patients and Methods:

Patients who had an mpMRI performed within 12 months of RP between January 2013 and August 2016 at 3 Australian Sites were included (Central Coast, NSW, St Vincents Hospital, Melbourne, VIC, and Bendigo Hospital, VIC). The results of mpMRI were compared to the final RP specimen to analyse the performance of mpMRI for significant prostate cancer detection, index lesion localisation, prediction of T3 disease and lymph node metastasis. A comparison between mpMRI cases performed with technical and reporting specifications of PI-RADS version 1 and version 2 was also performed. Data analysis was performed using SPSS 24.0.

Results:

Two hundred and thirty-five cases were included for analysis. mpMRI PI-RADS score ≥ 3 had an 91% sensitivity and 95% positive predictive value for significant prostate cancer at

RP. Overall concordance between index lesion location on mpMRI and RP specimen was 75%. The sensitivity for predication of significant prostate cancer was higher in the PI-RADS version 2 cases compared to PI-RADS version 1 (87% to 99%, $p=0.005$). Index lesion concordance was higher in the PI-RADS version 2 group (68% vs. 91%, $p=0.002$). mpMRI had a 38% sensitivity, 95% specificity, 90% PPV and 57% NPV for extra-prostatic disease. Sensitivity for prediction of T3 disease improved from 30% to 62%, $p=0.008$ with PI-RADS version 2.

Conclusions:

In cases undergoing RP, an abnormal mpMRI is highly predictive (95% PPV) for significant prostate cancer with an index lesion concordance of 75%. There has been a significant improvement in accuracy after the adoption of PI-RADS version 2 technical specifications and reporting criteria however further study is required to determine if this is due to improved experience with mpMRI or changes of the PI-RADS system.

Introduction

Multi-parametric magnetic resonance imaging (mpMRI) is an expanding imaging modality used for the detection and local staging of prostate cancer. There is considerable variation in the reported accuracy of mpMRI for the detection of significant prostate cancer in the literature, with significant heterogeneity between studies including patient selection, mpMRI protocols, radiologist experience and definitions used for significant prostate cancer [1]. Furthermore, many studies only compare mpMRI results to histopathology from prostate biopsy, which only represents a small sample of tissue as opposed to whole mount radical prostatectomy, which should be considered the gold standard, bringing about study design flaws due to the known disparity between prostate biopsy results and final histopathological results at radical prostatectomy in a significant number of cases [2]. Some studies looking at the “real world” performance of mpMRI report significantly lower detection rates than those reported from academic tertiary centres in “ideal” situations with strict inclusion criteria and protocols[3]. Other studies also suffer from potential bias with the mpMRI performed after a biopsy confirming prostate cancer [4, 5].

The update to PI-RADS version 2 to standardise and simplify mpMRI technical specifications and reporting standards [6] has also had mixed results. One study found that reporting using PI-RADS version 2 slightly decreased the ability of mpMRI to predict significant prostate cancer at RP when compared to reporting with PI-RADS version 1 [7]. Other studies assessing the performance of PI-RADS version 2 have shown conflicting results with PI-RADS version 2 improving intra-reader reliability, increasing the specificity of mpMRI for detection of significant prostate cancer at biopsy[8] and increasing the predictive value for significant prostate cancer at radical prostatectomy [4].

Our study aims to provide a “real-world”, contemporary Australian assessment of the accuracy of mpMRI using radical prostatectomy specimens as our gold standard. We also aim to assess any changes in diagnostic accuracy with the change from PI-RADs version 1 to version 2.

Patients and methods

Patients who underwent an mpMRI within 12 months prior to a radical prostatectomy for prostate cancer between January 2013 and August 2016 were included in this study. Patients included in this study had their mpMRI scans performed at three Australian sites- 1. Gosford, New South Wales, 2. St Vincents Hospital, Melbourne, Victoria, and 3. Bendigo Hospital, Victoria. Institutional Review Board approval for this project was authorised (project 0715-056C) by the NSW Health Central Coast Local Health District Research Committee with additional authorisation by each individual site’s ethics committee.

Imaging

All patients underwent mpMRI with a 1.5T or 3T MRI at one of three imaging practices according to PIRADs version 1 or 2. Specific mpMRI protocols used at each site are detailed in Appendix 1.

The index lesion was defined as the largest lesion detected on mpMRI with the highest PI-RADS score. Extracapsular disease was defined as present or absent based on the mpMRI

reports. Reports which stated that “capsular contact” or “capsular bulge” was present with “no definite macroscopic extracapsular disease” were defined as equivocal cases for analysis.

Radical prostatectomy and histopathological assessment

Open, laparoscopic or robotic-assisted radical prostatectomy was performed in the standard fashion by several urological surgeons who were not blinded to the mpMRI results.

Histopathology was processed and reported according to ISUP protocols by pathologists from Douglas Hanly Moir, Pathology North, TissuPath and Australian Clinical Labs.

Significant cancer at radical prostatectomy was defined based on Wolter’s criteria 1) Gleason 7-10 with greater than 5% grade 4 and 0.7 cc or greater, 2) Gleason 6 and 1.3 cc or greater, 3) pT stage 3a or greater and 4) nodal metastasis[9].

Data analysis

All data was collected in a prospectively maintained database at each site which was then pooled for analysis. The results of mpMRI were compared to radical prostatectomy specimens. We analysed the ability of mpMRI to predict significant cancer, extracapsular extension, index lesion location and lymph node metastasis. Index lesion concordance was assessed by manually comparing the synoptic reports of mpMRI with RP to determine lesion location after dividing the prostate into 12 segments (Left/Right, apex/mid/base and ant/post). We also analysed for any differences in results after the adoption of PI-RADS version 2 technical and reporting specifications.

Data were analysed with Predictive Analytics SoftWare Statistics 24.0 (IBM, Chicago, Ill, USA). Normality tests were performed on all continuous variables. Comparisons between groups for normally distributed variables were performed with independent samples T-test for normally distributed values. Non-parametric Mann-Whitney U were performed for values which were not normally distributed. Fisher’s exact tests were performed on discrete variables.

Results

Our database identified 242 men who had an mpMRI prior to RP between January 2013 and October 2016. Seven cases were excluded as the mpMRI was performed over 1 year prior to RP, leaving 235 men meeting inclusion criteria for analysis. The mean age was 65 years and

mean pre-operative PSA was 9.5. There were no significant differences in patient demographics between the three sites. 91% of cases had their RP performed within 6 months of the mpMRI. 94.5% of men had significant prostate cancer at radical prostatectomy as defined by Wolter's criteria[9], with a mean tumour volume of 4.2cc. Tumour volume was significantly higher in patients with PI-RADS scores of 5, $p=0.001$ (**Error! Reference source not found.**).

Accuracy of mpMRI for prediction of significant prostate cancer

The predictive accuracy of mpMRI for detecting significant prostate cancer as defined by Wolter's criteria[9] is set out in **Error! Reference source not found.**. Overall mpMRI had an excellent sensitivity of 91% and positive predictive value (PPV) of 95% for the detection of significant prostate cancer. The negative predictive value of mpMRI for insignificant prostate cancer in patients undergoing radical prostatectomy was 14%.

Index lesion concordance between mpMRI and radical prostatectomy pathology

Overall index lesion concordance between mpMRI and radical prostatectomy pathology was 75% (177/235). Index lesion concordance improved significantly from 68% to 91%, $p=0.002$ after the adoption of PI-RADS version 2 technical and reporting specifications (Appendix 2).

Prediction of extra-prostatic disease

132 (56%) of cases had extra-prostatic disease at radical prostatectomy (Table 4). When mpMRI T3 equivocal cases (reported as capsular contact or capsular bulge with possible microscopic ECE) were excluded, mpMRI had a 38% sensitivity, 95% specificity, 90% PPV and 57% NPV for extra-prostatic disease. Cases with evidence of T3 disease on mpMRI had a significantly higher chance of pT3 disease at RP compared to mpMRI T3 equivocal cases (90% vs. 63%, $p=0.003$) and cases with no evidence of T3 disease on mpMRI (90% vs. 43%, $p<0.001$). mpMRI T3 equivocal cases had a significantly higher chance of pT3 disease than cases with no evidence of T3 disease on mpMRI ($p=0.01$). In mpMRI T3 equivocal group, the cases which had $\geq$ pT3a disease at RP had significantly more tumour capsular contact on mpMRI than the cases which only had pT2 disease, 11.0mm (95% CI 7.1-14.9mm) vs 14.5mm (95% CI 12.7-16.3mm), $U=83.5$, $p=0.014$.

Lymph node metastasis

Twenty-one cases had lymph node metastasis at RP. Only 2 of these cases had suspicious lymphadenopathy on mpMRI demonstrating a low sensitivity of only 9.5%.

PI-RADS version 1 compared to version 2

One hundred and sixty mpMRI cases were performed using PI-RADS version 1 technical and reporting specifications and 75 cases using PI-RADS version 2 (Appendix 2). A significantly higher number of patients had the mpMRI performed prior to prostate biopsy in the PI-RADS version 2 group (85% vs. 62%, $p=0.001$). There were no other significant differences in the demographics between these two groups. The sensitivity for predication of significant prostate cancer was higher in PI-RADS version 2 compared to PI-RADS version 1 cases (87% to 99%, $p=0.005$) (**Error! Reference source not found.**). Similarly, sensitivity for prediction of T3 disease was higher in PI-RADS version 2 cases (30% vs. 62%, $p=0.008$).

Discussion

Our study shows that mpMRI in contemporary, Australian practice has an acceptable sensitivity and specificity on par with that published in international literature. Only one other multi-centre Australian study has compared mpMRI to RP as the reference standard and our study is the first Australian study to assess index lesion concordance between mpMRI and RP. Furthermore, the other Australian study assessed the outcomes of patients treated at tertiary metropolitan hospitals and adjacent private hospitals in one city as opposed to our study that includes patients from three centres in two different states, including two large regional centres.

Our study demonstrated that mpMRI has a sensitivity of 91% and PPV of 95% for the detection of significant prostate cancer when a threshold of PI-RADS ≥ 3 is used. When the threshold is increased to PI-RADS ≥ 4 the sensitivity decreases to 75% with a PPV of 95%. Index lesion detection was also acceptable at 75%. For the detection of pT3 disease mpMRI had a 38% sensitivity and 95% specificity, demonstrating the known limitations of mpMRI

for predicting the present of pT3 disease. In comparing PI-RADS version 1 to version 2 there was a significant improvement in the diagnostic prediction of significant prostate cancer, pT3 disease and index lesion detection. This is despite a significantly higher number of patients in this group having an mpMRI prior to biopsy in the PI-RADS version 2 group.

Our study results are comparable to current Australian literature on mpMRI with the Australian study by Toner et al., [3] demonstrating that mpMRI has a 83% sensitivity and 47% specificity for significant prostate cancer at radical prostatectomy. Both this study and our current study demonstrated a higher sensitivity and a lower specificity than that reported in the meta-analysis by Hamoen et al., [10], 78% sensitivity and 79% specificity. This is mainly a reflection of the reference standards used, as the studies using radical prostatectomy are likely to have a higher sensitivity and a lower specificity as selection bias means that a significant portion of the patients are going to have significant prostate cancer compared to studies using prostate biopsy as their reference standard. The meta-analysis by Hamoen et al., pooled 14 studies of 1785 patients, with only one study using radical prostatectomy as their reference standard. Our study has shown that approximately 9% of patients with significant prostate cancer will have a normal mpMRI. A recent study by Truong et al., showed that the majority of these missed lesion are prostate cancer with poorly formed cribriform architecture [11]. Our study showed mpMRI had a 14% negative predictive value for insignificant cancer at radical prostatectomy which is far lower than those reported in comparisons of mpMRI to prostate biopsy. This highlights a major limitation of this study in its ability to determine the true negative predictive value of mpMRI. Only patients with significant prostate cancer found at biopsy would have proceeded to radical prostatectomy to be included in our study. Patients who had a true negative mpMRI would have had a negative biopsy and would not have proceeded to radical prostatectomy and therefore are excluded from our study. Therefore, our study cannot answer the question of the underlying pathology for patients with normal mpMRI who did not subsequently undergo a radical prostatectomy.

A known limitation of mpMRI is its ability to predict pT3 disease, particularly microscopic extracapsular extension. International literature is mixed with one meta-analysis demonstrating a 61% sensitivity and 88% specificity for prediction of pT3 disease at radical prostatectomy [12]. This study included 75 studies with 9796 patients using radical

prostatectomy as the reference standard. In an Australian context, mpMRI has been reported to have a 29% sensitivity and 94% specificity for pT3 disease [3], demonstrating similar results to our study that show mpMRI has significant limitations for the prediction of pT3 disease.

Unlike other publications ^{[4, 7], [8]}, we have found an improvement in diagnostic accuracy of mpMRI with the adoption of PI-RADS version 2 technical specifications and reporting standards. The difference in diagnostic accuracy when comparing the PI-RADS version 1 to version 2 scans is confounded by several factors. Firstly, the improvement in accuracy could simply be a surrogate of experience as the mpMRI radiologists improved their mpMRI interpretation with time and experience. Secondly if PI-RADS version 2 is truly superior to PI-RADS version 1, it is difficult to determine if this is due to an increase in the specified high-b value DWI sequences or standardisation of reporting. One study looking at the reporting of the same mpMRI images with both versions of PI-RADS scoring systems have shown that PI-RADS version 1 reporting had a higher accuracy than version 2 [7]. Another limitation of our study is that radiologists were not blinded to any of the patient demographics, PSA levels or biopsy results. Therefore, as a portion of our patients had an mpMRI performed after the initial biopsy confirming prostate cancer (38% for PI-RADS version 1 and 16% for PI-RADS version 2), there is likely to be significant bias with the performance of mpMRI artificially inflated.

In conclusion our study has shown that mpMRI in contemporary “real-world” Australian practices has an acceptable accuracy for the prediction of significant prostate cancer and index lesion detection. Similar to other studies, our study showed that mpMRI has a high PPV and specificity for pT3 disease, but a low sensitivity. Further studies are required to continue to validate the diagnostic accuracy of PI-RADS version 2 over version 1 in a RP cohort.

Conflicts of interest

None disclosed

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Table 1: Patient demographics and radical prostatectomy pathology results.

All patients (n=235)	
Age (yrs), mean (95% CI)	64.9 (63.9-65.9)
PSA (ng/L), mean (95% CI)	9.5 (8.2-10.8)
Abnormal DRE	75 (32%)
Prostate volume (cm³), mean (95% CI)	44.6 (42.0-47.3)
MRI performed prior to biopsy	162 (69%)
Time from MRI to RP (months), mean (95% CI)	3.4 (3.0-3.7)
PI-RADS score	
- 1 or 2	23 (10%)
- 3	38 (16%)
- 4 or 5	174 (74%)
Largest lesion diameter (mm), mean (95% CI)	16.3 (15.0-17.5)
ISUP Grade (RP)	
- 1	5 (2%)
- 2	98 (42%)
- 3	80 (34%)
- 4	18 (8%)
- 5	34 (14%)
Pathological Stage	
- 2	103 (44%)
- 3a	91 (39%)
- 3b	18 (8%)
- 4	2 (1%)
- Nodal Metastasis	21 (8%)

Significant Cancer^a	222 (94.5%)
Tumour Volume (cm³), mean (95% CI)	4.2 (3.4-4.9)

^a Significant cancer defined based on Wolter's criteria 1) Gleason 7-10 with greater than 5% grade 4 and 0.7 cc or greater, 2) Gleason 6 and 1.3 cc or greater, 3) pT stage 3a or greater and 4) nodal metastasis

Table 2: Comparison of PI-RADS score to Gleason score at radical prostatectomy and tumour volume. *There was significantly higher tumour volume in PI-RADS 5 cases, p=0.001.

		ISUP Grade					Tumour volume cm ³	Total
		1	2	3	4	5	mean (95% CI)	
PI-RADS score	1 and 2	0	12	9	0	2	3.2 (1.6-4.9)	23
	3	1	24	8	2	3	2.8 (1.8-3.8)	38
	4	3	28	29	5	11	3.6 (2.7-4.6)	76
	5	1	34	34	11	18	6.2 (4.9-7.5)*	98
Total		5	98	80	18	34		235

Table 3- Predictive accuracy of mpMRI for significant prostate cancer diagnosis at radical prostatectomy. ^a Unable to calculate as numerator 0, ^b unable to calculate as denominator 0

		Sensitivity	Specificity	PPV	NPV
Overall	PI-RADS ≥ 3	91%	23%	95%	13%
	PI-RADS ≥ 4	75%	38%	95%	8%
PI-RADS version 1	PI-RADS ≥ 3	87%	25%	93%	14%
	PI-RADS ≥ 4	70%	41%	94%	10%
PI-RADS version 2	PI-RADS ≥ 3	99%	N/A ^a	99%	N/A ^b

Table 4: MRI prediction of T3 disease compared to final histopathology. Equivocal cases on mpMRI were cases reported as capsular contact or capsular bulge with possible microscopic ECE.

Pathological stage ≥pT3		
MRI Evidence of T3 disease	No	55/129 (43%)
	Equivocal	42/67 (63%)

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