Prostate MRI evolution in clinical practice: Audit of tumour detection and staging versus prostatectomy with staged introduction of multiparametric MRI and Prostate Imaging Reporting and Data System v2 reporting.

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Abstract

Introduction: We conducted a retrospective audit to compare dominant nodule detection and local staging before and after the introduction of functional sequences and PI-RADS v2 reporting to MRI prostate scans in routine private practice.

Method: A retrospective audit was performed of 245 patients in 4 separate groups undergoing robotic prostatectomy for prostate cancer by a single urologist between 2009 and 2017. The initial 100 consecutive patients had T2 imaging only. The next 43 patients had T2 and DWI. 52 subsequent patients had T2, DWI and DCE sequences (mpMRI). A final 50 consecutive patients had mpMRI using PI-RADS v2 reporting. Preoperative MRI reports were compared with prostatectomy histopathology to determine the sensitivity of MRI in detecting dominant tumour nodule and T3 extension.

Results: The addition of DWI and DCE sequences improved sensitivity for detection of dominant tumour nodule, with a significant further increase using PI-RADS v2 reporting (38% for T2 vs. 62% for T2/DWI vs. 67% for mpMRI vs 91% for PI-RADS v2). The accuracy of detecting T3 disease was initially very low. The use of additional imaging techniques did not significantly influence this, but the use of a 3 category likelihood of extraprostatic extension in the PI-RADS v2 group had a significant increase in detection of T3 disease (sensitivity 27% vs. 23% vs. 38% vs 63%)

Conclusion: This audit tracks the significant improvements in MRI detection of prostate cancer dominant tumour nodule and T3 extension in patients undergoing prostatectomy with changing techniques and reporting standards in routine clinical practice.

Introduction:

Magnetic resonance imaging for detection of prostate cancer has evolved significantly over the past decade. Initially, high resolution T2 imaging provided reasonable glandular detail, but suffered from limitations due to post biopsy hemorrhage, fibrosis and prostatitis in the peripheral zone (PZ) and the lack of awareness of the T2 appearances of tumours in the transitional zone (TZ)[1, 2, 3]. At this time the primary aim of MRI was to stage cases of biopsy proven carcinoma. The addition of functional sequences including diffusion weighted imaging (DWI) and dynamic contrast enhanced imaging (DCE), resulted in significant improvements in tumour detection[4,5,6,7,8]. The combination of T2, DWI and DCE to perform multiparametric MRI (mpMRI) lead to significant improvements in cancer detection and tumour localisation within the prostate, with an increasing focus on tumour detection over staging[9,10].

As many centres around the world adopted mpMRI, there was a lack of standardised criteria for the interpretation of results, leading to substantial variability in interpretation - generally based on the overall impression of the radiologist[11]. To standardise the evaluation and reporting of prostate MRI, the European Society of Urogenital Radiology (ESUR) published guidelines based on expert consensus in 2012, termed the Prostate Imaging Reporting and Data System (PI-RADS)[12]. The original PI-RADS system was relatively complex, scoring for all three sequences and then converting them into a Likert scale, which lead to variable uptake, as well as substantial heterogeneity across centres using PI-RADS[13]. The PI-RADS version 2 revision simplified the system with a single score recognising the dominant sequences for the PZ and TZ being DWI and T2-weighted sequences respectively[14]. This was more widely adopted by the radiology community and became the standard for reporting prostate MRI in our practice in 2015.

MRI had been acknowledged to have relatively low sensitivity for identifying extraprostatic extension (EPE)[15]. This is understandable as even extensive EPE at pathological analysis can demonstrate microscopic disease which will not necessarily be visible on MRI[16]. As a result there have been a number of secondary signs proposed to predict the likelihood of EPE such as broad capsular contact, bulge, and irregularity. The use of a binary system on MRI calling EPE present or absent is therefore problematic and many radiologists have moved to reporting three groups, including likely or possible microscopic EPE as an intermediate option.

We performed an initial audit of MRI prostate cases versus prostatectomy for quality control and learning, looking at dominant nodule detection and T3 extension just prior to the introduction of mpMRI. Our stepwise introduction of mpMRI allowed further audit of groups with T2 and DWI and then T2, DWI and DCE. Our hypotheses were that mpMRI would improve dominant nodule detection rate, and due to an improved knowledge of the location of disease we would improve our rate of T3 detection. As a consequence of these initial results

we altered our reporting of T3 disease to use three categories, as outlined above. A fourth group of patients, assessed after experience using PI-RADS v2 and three categories of EPE reporting, was included with the hypothesis that we would have a further improvement in dominant nodule detection and some improvement in predicting T3 disease.

Methods:

Study Groups:

This retrospective, observational audit consists of four groups of consecutive robotic prostatectomy patients from a single urologist in Adelaide, South Australia who also had a pre-operative MRI. Comparison of MRI reports was made with histopathological analysis performed at the Institute of Medical and Veterinary Science (IMVS), Adelaide (now SA Pathology).

Group 1 [T2 group] consists of 100 consecutive patients who underwent pre-operative MRI and prostatectomy between December 2009 and March 2011. The MR imaging protocol was; T1 axial and high resolution T2 sagittal, axial and coronal sequences (slice thickness 3mm)

Group 2 [DWI group] consists of 43 consecutive prostatectomy patients scanned between February and November 2012. The MRI protocol was as for the T2 group, with additional DWI sequence (b= 50, 400, 800 s/mm^2 and ADC map).

Group 3 [DCE group] consists of 52 patients scanned between October 2012 and August 2013. A dynamic contrast enhanced sequence was added to the DWI protocol. DCE enhancement curves were assessed on Cadstream (Bayer, Imaxeon).

All 195 patients in the T2, DWI and DCE groups were scanned on a 1.5T magnet with external surface coil and had interpretation of images prior to the introduction of the PI-RADS structured reporting. Reports did not typically use a template. Radiologists indicated the presence or absence of a dominant nodule, its location using side and often apex / mid / base descriptors, and the presence or absence of extraprostatic extension (EPE).

Group 4 [PI-RADS v2 group] consisted of 50 consecutive prostatectomy patients scanned between February 2016 and August 2017. Diffusion sequence b = 50, 500, 1000 and calculated b=1600. Contrast sequences were no longer analysed on a CAD product. 13 patients were scanned on a 1.5T Siemens Aera and 37 patients were scanned on a 3T Siemens Skyra. Interpretation of images was performed according to the PI-RADS v2 structured reporting scheme[14] with tumour location recorded in 12 segments (right / left, anterior / posterior, apex / mid / base). T-staging was reported using three categories: no evidence of EPE, likely microscopic EPE or macroscopic EPE visible for T3a disease. Both likely EPE and macroscopic EPE were recorded as T3 on the MRI report for the purposes of the audit.

Pathological analysis:

The robotic prostatectomy specimens were submitted in their entirety for histological assessment in accordance with standard practice. Histological assessment included dominant nodule location, volume (using Chen's method) and Gleason score. Local pathological staging information was provided using the AJCC TNM 7th edition (before 2016) criteria and 8th criteria (after 2016). Cases of extra-prostatic extension (EPE) described as focal pT3a (extra-prostatic glands are identified which occupy no more than one high power field in no more than two sections[16]) were classified as pT2 for the purposes of the audit as per RANZCR audit recommendations of 2011. This was kept consistent between all groups. The MRI report and the histopathology report were considered to be concordant if there was agreement on the side (left vs right) of the dominant nodule. More precise determination of the concordance of the site of dominant nodule and size measurements was not possible because of significant heterogeneity in MRI reporting, particularly in the earlier groups in this audit.

Data Analysis

Dominant nodule detection rate and T-staging were compared between all groups. Statistical analysis was performed using non-parametric methods as the data did not conform to a normal distribution. Statistical analyses were performed in R[17]. The 2x2 contingency table were assessed with Bernard's exact test. Larger tables were assessed using Chi-square tests and Fisher's exact tests for independence. The remainder of the numerical analyses were performed with Microsoft Excel.

Ethics approval was obtained from the St Andrew's Hospital Ethics Committee.

Results:

There was no significant difference in the baseline characteristics of each of the four groups with respect to PSA, and overall tumour volume at the time of prostatectomy (Table 1). Pathological Gleason score and tumour stage were statistically different between the groups (p=0.027 and p=0.039, respectively). The routine use of 3T MR was also significantly different between the groups as it was used in 74% of the PI-RADS v2 group and was not used at all in the original 3 groups.

Table 1: Baseline characteristics of the four patient groups

Parameter	T2†	DWI‡	DCE§	PI-RADS 2¶
Total patients (n)	100	43	52	50
MRI > 1 year from surgery	0 (0)	0 (0)	0 (0)	4 (9)
3T MRI (n (%))	0 (0)	0 (0)	0 (0)	37 (80)
PSA (ng/ml) (median (IQR))	7.0 (5.0-11.0)	7.0 (4.5-9.0)	6.9 (5.8-8.9)	8.5 (6-13)
Volume (cc) (median (IQR))	3.8 (2.4-6.8)	2.9 (1.5-4.9)	3.2 (1.7-6.9)	3 (2-7)
pGleason score (n (%))				
• 6	8 (8)	1 (2)	0 (0)	2 (4)

• 7 (<=0.5cc)	2 (2)	3 (7)	0 (0)	1 (2)
• 7 (>0.5cc)	78 (78)	32 (74)	44 (85)	27 (59)
• 8	2 (2)	3 (7)	1 (2)	6 (13)
• 9	10 (10)	4 (9)	7 (13)	10 (22)
pT staging (n (%))				
• T2	52 (52)	17 (40)	20 (39)	14 (30)
• T3a	40 (40)	24 (55)	24 (46)	22(48)
• T3b	8 (8)	2 (5)	8 (15)	10 (22)

† T2 only, ‡ T2 and DWI, § T2, DWI and DCE, ¶T2, DWI, DCE using PI-RADS v2 reporting.
3T, 3 Tesla MRI used (0 implies 1.5 Tesla MRI); PSA, Prostate specific antigen; pT, pathological T-stage; pGleason, pathological Gleason score at prostatectomy.

In the initial 3 groups, a total of 11 radiologists provided the reports and in the PI-RADS v2 group, 6 radiologists were responsible for the final report. Experience in reporting prostate MRI ranged from 3 to >10 years. The largest percentage of cases in the PI-RADS v2 group were reported by two radiologists with <5 years experience, neither of whom reported any cases in groups 1-3.

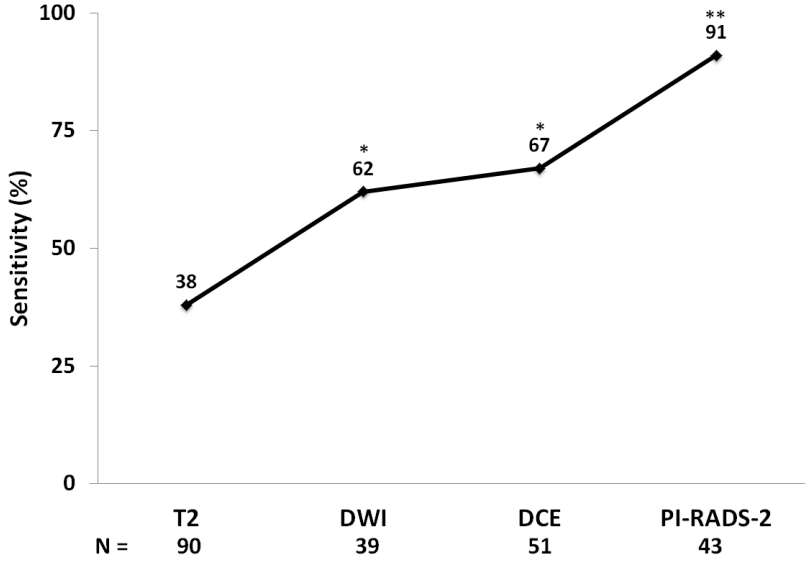
Dominant nodule detection:

As MRI is not expected to reliably detect Gleason 6 or very low volume (< 0.5cc) Gleason 7 disease[12], these cases were excluded from analysis of dominant nodule detection only. Cases where the MRI was performed greater than one year before the prostatectomy were also excluded due to potential for significant change in the intervening time. In a single DCE case, the dominant nodule location was not available, although staging was. This case was excluded from calculation of dominant nodule detection only. These exclusions (summarized in Table 1) resulted in a total of 90 T2 cases, 39 DWI cases, 51 DCE cases and 43 PI-RADS v2 cases (total =223) left for analysis of dominant nodule detection.

The sensitivity of dominant nodule detection (DND) for the four groups is shown in Figure 1. T2 weighted imaging alone detected the dominant tumour nodule in 34 out of 90 (38%) cases. T2 weighted imaging combined with DWI detected the dominant nodule in 24 out of 39 (62%) cases and T2, combined with DWI and DCE (mpMRI) detected the dominant nodule in 34 out of 51 cases (67%). mpMRI combined with PI-RADS v2 reporting detected the dominant nodule in 39 of 43 cases (91%).

The DWI and DCE groups demonstrated a statistically significant ($p<0.05$) improvement in dominant nodule detection when compared to the T2 group. Furthermore the PI-RADS v2 group demonstrated a statistically significant increase in dominant nodule detection when compared to the DWI ($p=0.006$) and DCE ($p=0.02$) groups.

Figure 1. Improving sensitivity for prostate cancer dominant nodule detection on MRI



Sensitivity (%) for detection of dominant nodule on MRI, using histological assessment of prostatectomy specimens as the gold standard, is represented as a percentage on the y-axis. The MRI techniques with corresponding number of cases (N) are represented on the x-axis. The actual sensitivity (%) for each MRI technique is displayed above the (♦).

T2 = T2 only group

DWI = T2 and diffusion weighted imaging (DWI) group

DCE = T2, DWI and dynamic contrast enhanced (DCE) group

PI-RADS-2 = DCE using PI-RADS version 2 imaging technique and reporting system.

*$p<0.05$ compared to the T2 group

**$p<0.05$ compared to T2, DWI, and DCE groups

T Staging:

Of the 245 original cases, only the 4 PI-RADS v2 cases where prostatectomy was performed > 1 year from MRI were excluded from analysis of T-staging leaving N=241 cases remaining for analysis. For the purposes of this audit, staging was considered concordant if the radiological and pathological T- stage matched. Stages T2a, T2b and T2c were grouped as stage T2 and stages T3a and T3b were grouped as stage T3. Focal EPE was considered pT2 (a total of 30 of 241 cases).

There were 138 cases of pT3a or pT3b disease in the entire patient cohort. Combining all four groups, pre-operative MRI reported only 65 cases of T3a or T3b disease. Overall there were 51 of 138 (37%) cases where MRI correctly identified T3 disease and 87 of 138 cases (63%) where MRI undercalled T3 disease. In 14 of 103 cases (14%) of pT2 disease, MRI overcalled T3 disease.

There was no significant difference observed in sensitivity and specificity between the first three groups for T3 detection (Table 2), however there was a significant improvement in sensitivity between the PI-RADS v2 group and the T2, and DWI groups ($p<0.05$) with a non significant trend to improvement in sensitivity between the PI-RADS v2 group and the DCE group ($p=0.06$). There was a non-significant slight decrease in specificity.

Table 2 – Detection of T3 disease on MRI

	Sensitivity (%)	Specificity (%)	Overcall (%)	Undercall (%)
T2†	27	90	10	73
DWI‡	23	94	6	77
DCE§	38	80	20	63
PIRADS-2¶	63*	71	29	38*

† T2 only group, ‡ T2 and DWI group, § T2, DWI and DCE group, ¶T2, DWI, DCE group
*$p<0.05$

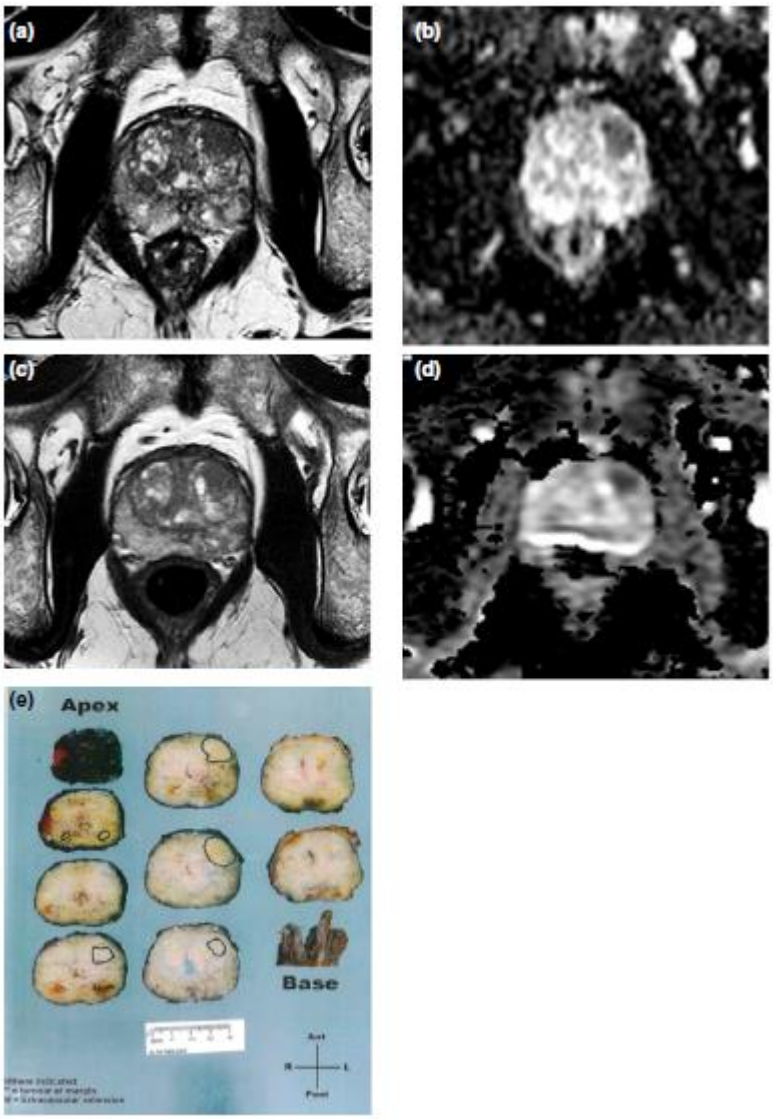
Discussion:

This audit illustrates the significant improvements which have been made to prostate cancer dominant nodule detection and local staging over the past 10 years in a private radiology practice in South Australia, with the staged introduction of DWI and DCE sequences and PI-RADS version 2 reporting.

The audit of the first three groups captured significant improvements in dominant nodule detection based largely on the technical advances associated with the addition of functional sequences. The largest improvement was seen with the addition of the DWI sequence, which is logical as diffusion is now the dominant sequence for assessing the more common PZ rs. While T2 is now the dominant sequence for TZ tumours, the characteristic appearance of TZ tumours was unknown at the time of reporting the initial group, so many of these tumours were missed. Anecdotally, some patients presenting for follow up MRI after the introduction of mpMRI and awareness of the appearance of TZ tumours, had TZ tumours identified retrospectively on their earlier scans (Figure 2a-e). Only a further slight improvement was noted in dominant nodule detection with the introduction of DCE sequences, which was not statistically significant. This is consistent with the recent de-emphasis on the role of DCE compared to T2 and DWI sequences in PI-RADS v2.

Figure 2(a-e). Improved detection of anterior tumour

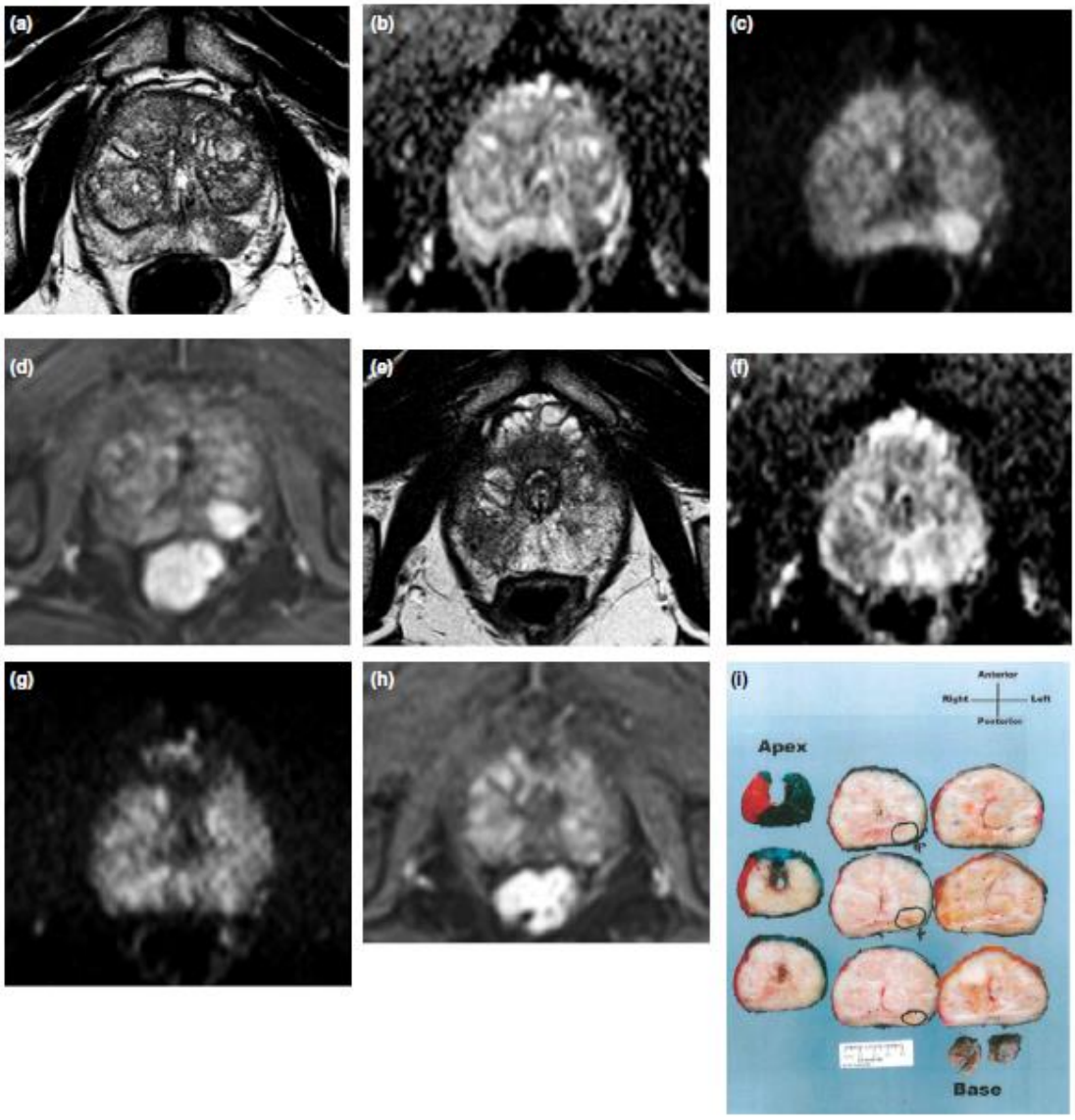
Left anterior transitional zone PI-RADS 5 lesion, highly suspicious for tumour, identified on axial T2 (a) and ADC (b) sequences using PI-RADS v2 reporting. Retrospectively seen on MRI two years earlier on T2 (c) and ADC (d) sequences, and confirmed at histopathology (e).



The fourth group using PI-RADS v2 and the 3 category system of EPE reporting showed significant further improvement in both dominant nodule detection (DND) and local staging. This improvement in DND can be at least partly attributed to the structured scoring system of PI-RADS v2 with clear guidelines for using dominant sequences in the PZ and TZ (Figure 3a-i). Studies using PI-RADS v2 have shown sensitivities for dominant nodule detection ranging from 78% to 95% and our result of 91% is consistent with this [18,19,20,21]. While our patients all had prostate cancer as they are consecutive prostatectomy cases, Group 4 did not have known cancer at the time of the MRI report as by this time MRI was typically performed prior to biopsy, so there was no bias on the reporting radiologist (although all cases are biased by selection for biopsy proven cancer). This is compared to the initial group where almost all patients had a known cancer at the time of MRI, but we could still only detect the nodule in 38% of cases. As the reference standard in this audit was whole prostate histopathology, and therefore no normal prostate specimens were included for comparison, true positive predictive and negative predictive values of MRI in our series were not able to be determined.

Figure 3 (a-i). Use of PI-RADS v2 for detection of dominant nodule

Left posterior peripheral zone (PZ) PI-RADS 4 lesion, suspicious for tumour, with possible extraprostatic extension (EPE), with T2 hypointensity (a), ADC hypointensity (b), DWI hyperintensity (c) and focal enhancement (d). Right posterior PZ PI-RADS 3 lesion, equivocal for tumour, with T2 hypointensity (e), ADC hypointensity (f), no DWI hyperintensity (g) and without focal enhancement (h). Histopathology (i) confirms tumour in the left PZ only with EPE.



The improved results will be contributed to by other technological advances, such as the increased use of 3T and higher b-value diffusion sequences over time. The learning curve is a potential significant confounder, which is not specifically tested in our audit. Groups 2 and 3 were assessed during the introduction of new sequences and reporting knowledge, so even those radiologists with significant prior reporting experience were on a relatively even par with newer reporters. Group 4 was assessed at least 12 months after the introduction of PI-RADS v2 reporting, allowing time for significant upskilling by regular reporters. There was significant heterogeneity in the range of reporters and individual radiologist experience amongst those who reported prostate MRI in this audit,

which was not designed to assess how such heterogeneity affected the results. It is interesting to note that good results were achieved in the final PI-RADS v2 group by radiologists who had the least experience, although the exact reasons for this are unclear. The literature suggests reasonable agreement between both experienced readers and those with at least 1 year experience[21,22] and our findings are consistent with that. It appears that regular reporting using the PI-RADS v2 structured reporting system is enough to achieve good results in routine practice. In addition to improvement in the performance of individual radiologists, better results over time would be expected due to the increased cumulative institutional experience involving radiologists, technicians and referring surgeons.

MRI has average sensitivity for detecting pT3 disease with a meta-analysis by de-Rooij et. al. showing a pooled sensitivity for combined pT3 stage of 61%[23]. This is predominantly due to the high rate of microscopic disease which is not visible on MRI, leading to the use of secondary signs such as an irregular or spiculated margin and a tumour-capsule interface of >10-12mm to predict EPE[24,25,26]. The clinical significance of small volume EPE, particularly in the setting of negative surgical margins, is questionable. However, prospectively identifying the site of potential EPE is valuable for the surgeon, as it may allow for a wider surgical margin at this site, thereby reducing the risk of a positive surgical margin. Conversely, if there is no indication of EPE, a closer surgical margin and potential preservation of the neurovascular bundle can be attempted with increased confidence[24]. We introduced a 3 category system for reporting EPE following the poor results of our initial pre-PI-RADS v2 audit, with the additional middle category of possible (likely microscopic) EPE based on secondary signs. Our recording of both likely microscopic and visible macroscopic EPE as positive on the MRI report will be largely responsible for our increased T3 detection rates, though it should be noted we still missed 38% of pT3 cases. The non significant decrease in specificity in group 4 (71%) would be corrected to 82% if we included focal pT3a cases as pT3 positive. These had been reassigned pT2 due to initial RANZCR recommendations for prostate audit pre mpMRI and the requirement to keep the data consistent across all four groups.

A significant confounder is the heterogeneity of the magnet type and field strength. All studies were initially done on a 1.5T MRI with external coil, which at the time was not the highest standard of care, but common in routine clinical practice. With further research into the use of mpMRI it is useful to note that a 1.5T magnet and external coil are now accepted as a satisfactory system for diagnosis[14]. During groups 2 and 3 we changed to performing prostate scans on a new 1.5T MRI (Siemens Aera) and the spatial resolution was noticeably improved. Further improvements were also seen with the adoption of 3T MRI, which was increasingly used in our PI-RADS v2 group due to magnet replacement. We still perform a significant number of prostate MRI scans on 1.5T magnets across our practice.

There was no significant change in surgical selection by the urologist over the audit period, other than operating on fewer Gleason 6 cancers in more recent

years. As these cases are consecutive prostatectomy patients rather than consecutive MRI referrals, the more recent changes in MRI referral patterns should not play a significant role. This audit did not capture patients who had an MRI but did not proceed to prostatectomy due to active surveillance or radiotherapy and/or chemotherapy treatment pathways. While MRI was part of the clinical pathway, all patients had biopsy proven cancer prior to prostatectomy. A negative MRI with a positive biopsy of ≥ Gleason 7 would not have precluded surgery. No particular data was analysed about patients with prior negative biopsy and positive MRI, nor the use of targeted biopsy post-MRI.

All of these limitations reflect the real life environment of the evolution of mpMRI in routine clinical practice. They are expected and unavoidable, but allowing for all the variables there is an unequivocal improvement in performance of MRI over time. Multiple factors likely contributed to the observed improvement, including technical factors (e.g. hardware, pulse sequences), radiologist factors (e.g. reporting strategy, experience), and the change in workflow (post-biopsy vs pre-biopsy MRI), and these factors are likely not independent of each other. It is difficult to determine the main reasons for the improved performance, although these results are applicable to the way in which mpMRI has been introduced into many radiology practices, which will experience similar confounders.

Conclusion:
This longitudinal, retrospective audit demonstrates significant improvements that have been achieved with prostate MRI in routine clinical practice over the past decade from T2 imaging alone to the current standard of mpMRI technique and PI-RADS v2 reporting. Our results are in line with those reported internationally and are likely to reflect the current capabilities of prostate MRI in radiology practices within Australia.

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