Prospective evaluation of the value of dynamic contrast enhanced (DCE) imaging for prostate cancer detection, with pathology correlation

Ishaq Al Salmi, MD,[1] Terence Menezes, MD,[1] Mohamed EL-Khodary, FRCPC,[1] Sandra Monteiro, PhD,[2] Ehsan A. Haider, FRCPC,[1] Abdullah Alabousi, FRCPC[1]

[1]Department of Radiology, St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada

[2]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

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Introduction: *The aim of this study was to evaluate the value of dynamic contrast enhanced (DCE) imaging in multi-parametric prostate MRI (mpMRI) for the detection and staging of prostate cancer in comparison with T2W and DWI images alone in biparametric MRI (bpMRI) in treatment naïve patients.*

Materials and methods: *One hundred consecutive patients who underwent a prostate MRI at our institution from June-August 2017, as well as a systematic ultrasound-guided prostate biopsy or prostatectomy, were included. Strictly following PIRADSv2, the MRI studies were independently interpreted by a body radiologist and a body-imaging fellow on two different occasions 8-10 weeks apart. Initially, with all mpMRI sequences and then without the DCE sequence (bpMRI). The readers were blinded to the clinical information. Ethics approval was obtained.*

Results: *One hundred treatment-naïve patients were included (median age 64, age range 48-81, mean PSA 10.3). There was almost perfect intra-observer agreement for mpMRI versus bpMRI for both readers [Cohen's Kappa (k) 0.88-0.86] and substantial inter-observer agreement (k = 0.74 for mpMRI and 0.76 for bpMRI). The sensitivity and specificity did not significantly change between multi-parametric and bi-parametric MRI (Sensitivity 91.7% and 90%, Specificity of 85.5% and 85% for mpMRI and bpMRI, respectively).*

Conclusion: *Based on our findings, prostate MRI without DCE (bpMRI) is of comparable diagnostic accuracy to mpMRI in treatment-naïve patients. Performing prostate MRI without DCE (bpMRI) will reduce acquisition time, decrease cost and potentially improve patient safety.*

Key Words: imaging, prostate cancer, MRI

Introduction

Magnetic resonance imaging (MRI) of the prostate plays a major role in the work up of patients suspected to have or at high risk of having prostate cancer.[1] A standard prostate MRI study currently consists of three essential sequences: T2, diffusion-weighted imaging (DWI) and dynamic contrast enhanced (DCE) images. This is referred to as multi-parametric MRI (mpMRI).

Prostate MRI is interpreted according to the Prostate Imaging Reporting and Data System (PI-RADS) Version 2.[2] The two essential sequences for prostate MRI according to PI-RADS are T2 and DWI. DCE imaging plays a relatively minor role in detecting clinically significant prostate cancer.

The main objective of this study is to evaluate the added value of DCE imaging in the detection and staging of clinically significant prostate cancer. Our hypothesis is that DCE imaging does not offer significant added value for treatment-naïve patients. In fact, we suspect that DCE imaging can be omitted in treatment-naïve patients without significant effect on imaging-pathology correlation. The goal is to correlate MRI findings with histopathology, as the gold standard, to validate our results.

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Address correspondence to Dr. Abdullah Alabousi, Department of Radiology, St. Joseph's Healthcare Hamilton, 50 Charlton Ave E., Hamilton, ON L8N 4A6 Canada

Materials and methods

Patient selection

Patients were included if they met the following criteria: (a) had a standard 3T prostate MRI with no endorectal coil; (b) had a systematic 14-core transrectal ultrasound (TRUS) guided prostate biopsy, focused TRUS guided prostate biopsy or prostatectomy within a 12-month period from the prostate MRI examination.

Patients were excluded if: (a) The prostate MRI acquisition was incomplete, or the examination was non-diagnostic due to artifact; (b) The prostate biopsy or prostatectomy was performed in a time frame beyond 12 months from the prostate MRI examination; (c) No histopathology results were available; (d) They have received prior surgical or non-surgical treatment for prostate cancer.

Research ethics board approval was obtained from our institution. All patients gave written informed consent prior to their prostate MRI study.

Imaging protocol

All patients underwent a prostate MRI examination on a 3T MRI system (Philips Achieva 3T, Philips Healthcare, MA, USA) equipped with a 16-channel torso phased-array surface coil. The following MRI sequences were obtained: axial T1-WI (3D THRIVE whole pelvis, THRIVE fat-saturated and THRIVE non-fat-saturated), T2-WI in the three orthogonal planes, axial DWI (b0, b400, b800, b1400), axial DCE with subtraction images as well as axial delayed post contrast images of the pelvis with fat saturation. The prostate MR protocol at our institution is detailed in Table 1. Endorectal coils were not utilized in all patients. No pre-imaging patient preparation was performed. Intramuscular Butylscopolamine (Buscopan) was administered for all patients.

The total scanner occupation time for the standard mpMRI study is 45 minutes including patient positioning and intravenous access time. The exclusion of the DCE and delayed post contrast enhanced images from the examination reduces the total scanner occupation time to 30 minutes, with actual scanning time of 22 minutes and 10 seconds.

Clinical data and histopathology

The PSA was extracted from the patients' clinical records and PSA density (PSAD) was calculated after obtaining the prostate volume by MRI using the formula PSA/prostate volume. The histopathology findings, including the Gleason score, location and size of the index lesion (defined as the lesion with the highest Gleason score), were extracted from each patient's medical record. A Gleason score of 7 or higher was considered to represent clinically significant prostate cancer.

Data collection and validation

The MRI images for all patients were reviewed by a fellowship trained body imaging radiologist and a

Variables	Localizer	Ax T2WI	Sag T2WI	Cor T2WI	Ax DWI	Ax 3D THRIVE	Ax THRIVE FS (Mask)	Ax THRIVE Non-FS (Mask)	Ax THRIVE RUN C+ (DCE)	Ax THRIVE FS C+ PELVIS
PLANE	3 Orthogonal planes	Axial	Sagittal	Coronal	Axial	Axial	Axial	Axial	Axial	Axial
Echo time (msec)	4.6	100	90	90	69	2.3	2.3	2.3	2.3	2.3
Repetition time (msec)	6.2	3738	3386	3347	3000	4.15	4.3	4.3	4.3	4.1
Field of view (mm)	400	220	180	180	300	340	180	180	180	340
Acquisition matrix	256/128	365/358	300/293	270/272	92/94	244/242	120/116	120/116	120/116	244/242
Voxel size	1.56 x 1.56 x 15.0	0.312 x 0.312 x 3.0	0.312 x 0.312 x 3.0	0.352 x 0.352 x 3.0	1.88 x 1.88 x 5.0	0.89 x 0.89 x 4.4	0.63 x 0.63 x 6.0	0.63 x 0.63 x 6.0	0.63 x 0.63 x 6.0	0.66 x 0.66 x 4.4
b-values					0, 50, 400, 800, 1400					
No. of dynamic frames									31	
Acquisition time	0 minutes 30 seconds	4 minutes 0 seconds	4 minutes 0 seconds	5 minutes 0 seconds	8 minutes 0 seconds	0 minutes 40 seconds	0 minutes 40 seconds	0 minutes 40 seconds	3 minutes 30 seconds	0 minutes 40 seconds

Table 1. Summary of the prostate MR protocol at our institution.

radiology body imaging fellow who independently interpreted the 100 prostate MRI examinations. The examinations were interpreted in two different sessions 8-10 weeks apart. The first session involved study interpretation with all mpMRI sequences provided including the dynamic post contrast enhanced (DCE) images. Each reader then re-interpreted the same examinations at a later time point, without the DCE images. The PI-RADS version 2 guidelines were strictly followed for the scoring of all suspicious lesions.[2] A PI-RADS score of 4 or 5 was expected to correlate with clinically significant prostate cancer.

Both readers were blinded to the clinical information including the clinical history, PSA level and histopathology results. Correlation between the MRI findings and histopathology was performed after the completion of data acquisition. The tumor location based on MRI was considered to match histopathology findings if they were described on the same side and zone (peripheral versus transitional).

Statistical analysis

The data were analyzed using the SPSS version 20 (IBM corporation, Armonk, NY, USA). The intra-observer and inter-observer agreement between the mpMRI and bpMRI was analyzed using the Cohen's Kappa (k) test. The sensitivity, specificity, positive predictive value and negative predictive value were calculated for each reader and compared. A 95% confidence interval was used to determine significance. A Gleason score of 7 (3+4) and above was considered positive on pathology. The pathology results of the TRUS-guided-biopsy, radical prostatectomy or TURP were used as gold standard. Gleason score of 6 (3+3) was considered positive if the MR findings were positive in the same location.

Results

Initially, a total of 104 patients who underwent a prostate MRI at our institution from June 2017-August 2017 and met the inclusion criteria were included in this study (mean age 64, age range 48-81 years). One patient was excluded due to the lack of DCE-MR sequence. Two patients had left total hip replacement with significant artifact on the DWI and were therefore excluded from the study. One examination was performed on a 1.5T MR unit and was also excluded. Therefore, 100 patients who met the inclusion and exclusion criteria were included in this study. The mean PSA is 10.3 (range 0.2-42). The mean PSA density is 0.17 (range 0.01-0.64). The mean prostate volume is 69.9 cc (range 15-240), Table 2.

TABLE 2. **Summary of patient age, PSA levels and prostate volumes**

Patient age (years)	**48-81 (mean 64.1)**
< 50	1
50-60	29
61-70	55
71-80	14
> 80	1
PSA level at MRI (ng/mL)	**0.2-42 (mean 10.3)**
< 5.1	15
5.1-7.0	14
7.1-10.0	37
> 10.0	34
Prostate volume at MRI (mL)	**15-240 (mean 69.9)**
< 30	8
30-50	29
> 50	63

The mean lesion size was 9 mm in maximum dimension (range 5-51 mm). The lesion size was measured according to the PIRADSv2 guidelines.[2] The number of index tumors fulfilling the criteria of PIRADS 3 or above was capped at 4 as per PIRADSv2 guidelines. There were no patients fulfilling the PIRADS 1 category from the study population. For reader one (Body imaging fellow), there were 46 patients with a final score of PIRADS 2, 6 patients with PIRADS 3, 25 patients with PIRADS 4 and 23 patients with PIRADS 5 with mpMRI (compared to 43 patients with PIRADS 2, 5 patients with PIRADS 3, 25 patients with PIRADS 4 and 27 patients with PIRADS 5 with bpMRI). For reader two (staff radiologist), there were 44 patients with a final score of PIRADS 2, 1 patient with PIRADS 3, 29 patients with PIRADS 4 and 26 patients with PIRADS 5 with mpMRI (compared to 45 patients with PIRADS 2, 5 patients with PIRADS 3, 30 patients with PIRADS 4 and 20 patients with PIRADS 5 with bpMRI). Those results are summarized in the flow chart, Figure 1.

A total of 79 patients underwent TRUS-guided-biopsy, 20 patients underwent radical prostatectomy and one patient underwent transurethral resection of the prostate lesion. On histopathology, Figure 2, there were 37 patients who had negative biopsy results, 28 patients had Gleason 6 (3+3) disease, 23 patients had Gleason 7 (3+4) disease, 8 patients had Gleason 7 (4+3) disease, 2 patients had Gleason 8 disease and

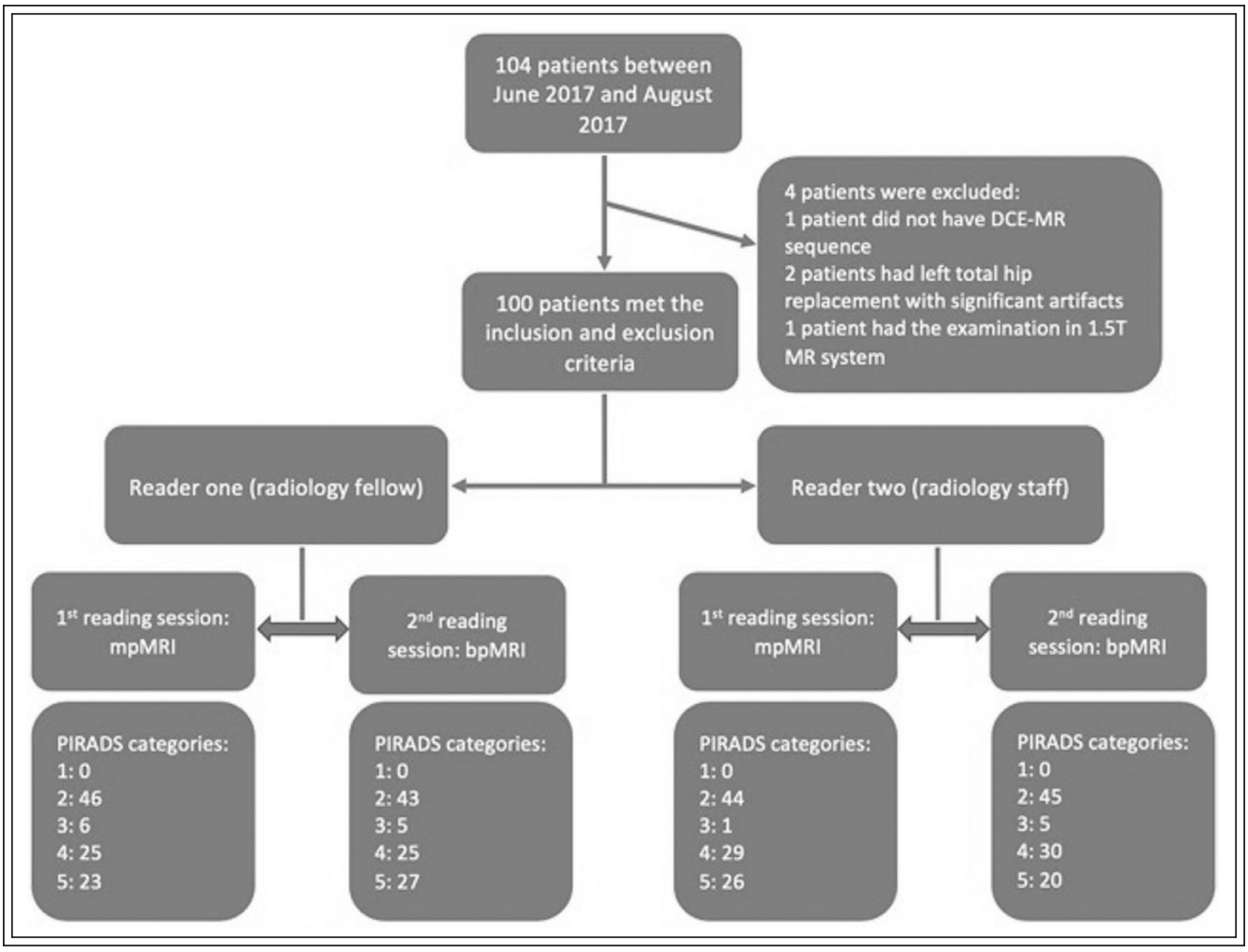

Figure 1. Flow chart outlining the study methodology and patient population.

2 patients had Gleason 9 disease. In total, 35 patients had a Gleason score of > 6 and 63 patients had a Gleason score of 6 and above. The locations of the lesions were as follows: 19 lesions within the transition zone (10 lesions on the right side, 7 lesions on the left side and 2 lesions were bilateral), 29 lesions within the peripheral zone (15 lesions within the right side and 14 lesions within the left side) and 8 lesions were diffuse involving both the transition and peripheral zones. There were 40 patients who had unifocal lesions, 9 patients had 2 foci of disease, 8 patients had 3 foci of disease and 6 patients had 4 foci of disease on pathology.

The calculated sensitivity, specificity, positive predictive values and negative predictive values are as follows: for reader one, the sensitivity was 91.3% versus 91.3% and specificity of 89.9% versus 81.5% for mpMRI and bpMRI, respectively. The PPV for

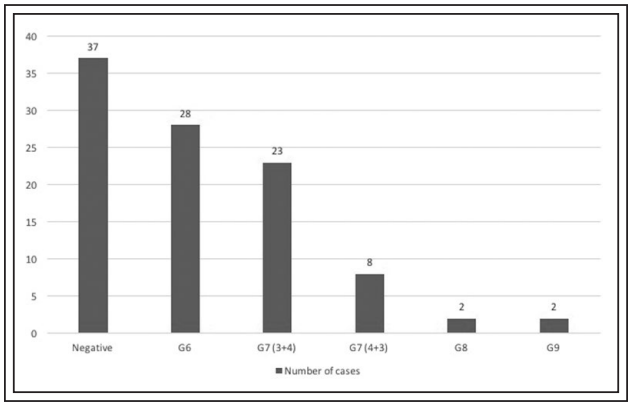

Figure 2. Bar graph demonstrating the distribution of patients according to the Gleason score on pathology results based on the 14-core TRUS-guided biopsy or radical prostatectomy results.

TABLE 3. **Summary of the sensitivity, specificity, positive predictive values and negative predictive values for each reader**

	Reader 1 mpMRI	Reader 1 bpMRI	Reader 2 mpMRI	Reader 2 bpMRI
Sensitivity	91.3%	91.3%	92.0%	89.6%
Specificity	89.9%	81.5%	82.0%	86.5%
PPV	87.5%	80.8%	83.6%	86.0%
NPV	92.3%	91.7%	91.1%	90.0%

reader one was 87.5% versus 80.8% and NPV of 92.3% versus 91.7%, for mpMRI and bpMRI, respectively. For reader two, the sensitivity was 92% versus 89.6% and specificity of 82% versus 86.5% for mpMRI and bpMRI, respectively. The PPV for reader two was 83.6% versus 86.0% and NPV of 91.1% versus 90.0%, for mpMRI and bpMRI, respectively, Table 3.

Using the Cohen's kappa, there was almost perfect intra-observer agreement between the mpMRI and bpMRI (k: 0.88 for reader one and k: 0.86 for reader two). There was substantial inter-observer agreement for both mpMRI (k: 0.74) and bpMRI (k: 0.76), Table 4.

Discussion

Clinically insignificant prostate cancer on radical prostatectomy specimen is defined as a Gleason score 6 without Gleason pattern 4 or 5, organ-confined disease (no extra-prostatic extension, seminal vesicle invasion, or lymph node involvement and/or tumour volume < 0.5 cc. On core biopsies, clinically insignificant cancer is defined as a Gleason score less than or equal to 6, with fewer than three positive cores < 50% of cancer involvement in any core. Any lesion exceeding the above criteria is considered clinically significant prostate cancer.[3]

According to PI-RADS version 2, the DCE sequence plays a relatively limited rule in the diagnosis of clinically significant prostate cancer. It is primarily utilized in the assessment of lesions within the peripheral zone.[2] Furthermore, its utilization is limited to lesions, which are categorized as PI-RADS 3 based on the T2WI and DWI sequences.[2] Some of these can be upgraded to PI-RADS 4 based on their enhancement characteristics on DCE.[2] The added value of DCE imaging in prostate MRI, therefore, appears limited given the added time, expense and potential safety concerns with Gadolinium-based contrast. Our study evaluated the sensitivity, specificity, PPV and NPV of prostate MRI without DCE, referred to as biparametric MRI (bpMRI) and compared it to that of mpMRI in the same population in an attempt to determine the role and value of DCE imaging. Figure 3 demonstrates an example of a PIRADS 3 lesion, which is upgraded to PIRADS 4 based on DCE findings and Figure 4 demonstrates an example of a PIRADS 4 lesion in which DCE findings did not affect the final score.

Based on our study, the sensitivity and specificity for detection of clinically significant cancer were not significantly affected by omitting the DCE sequence (sensitivity: 92% versus 89.6% and specificity: 82% versus 86.5% for mpMRI and bpMRI, respectively). The PPV and NPV were also not significantly affected (PPV: 83.6% versus 86.0% and NPV: 91.1% versus 90.0%, for mpMRI and bpMRI, respectively).

These results are similar to prior studies.[4-6] Additionally, a systematic review and meta-analysis by Woo et al showed that the prostate MRI protocol (bpMRI versus mpMRI) was not a significant factor

TABLE 4. **Summary of the intra-observer and inter-observer agreement**

	Intra-observer agreement (reader 1)	Intra-observer agreement (reader 2)	Inter-observer agreement mpMRI (reader 1 vs. reader 2)	Inter-observer agreement bpMRI (reader 1 vs. reader 2)
Cohen's kappa	0.88	0.86	0.74	0.76
Level of agreement	Almost perfect agreement	Almost perfect agreement	Substantial agreement	Substantial agreement

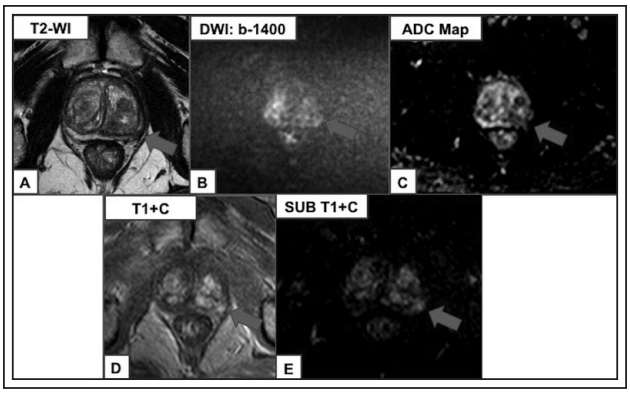

Figure 3. Axial T2WI image **(A)** demonstrates a hypointense lesion in the posterolateral peripheral zone of left mid gland (arrow), DWI b-value 1400 **(B)** demonstrates equivocal hyperintense signal corresponding to the findings on T2WI, ADC map **(C)** demonstrates questionable mildly hypointense signal equivocal for mild diffusion restriction, dynamic contrast-enhanced image **(D)** demonstrates early avid arterial hyperenhancement, subtracted image of the DCE **(E)** demonstrates avid arterial hyperenhancement. The findings from T2WI and DWI are in keeping with a PIRADS 3 lesion. It is upgraded to PIRADS 4 due to the findings on the DCE.

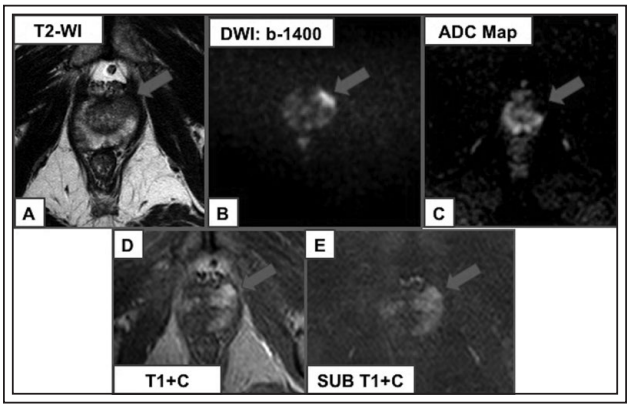

Figure 4. Axial T2WI image **(A)** demonstrates a hypointense lesion in the anterior peripheral zone of left mid gland (arrow), DWI b-value 1400 **(B)** demonstrates marked hyperintense signal corresponding to the findings on T2WI, ADC map **(C)** demonstrates marked hypointense signal in keeping with diffusion restriction, dynamic contrast-enhanced image **(D)** demonstrates avid early arterial hyperenhancement, subtracted image of the DCE **(E)** demonstrates avid arterial hyperenhancement. This is a PIRADS 4 lesion given its size and findings on T2WI and DWI. The findings on the DCE sequence added no value in this patient.

in the heterogeneity of the sensitivity and specificity of 20 published studies comparing the two protocols.[6]

In this study, only 1 out of the 100 patients with a clinically significant prostate cancer of Gleason score > 6 was detected only on the mpMRI and missed on the bpMRI. It was missed by reader one on both mpMRI and bpMRI but detected by reader two on mpMRI. This particular patient had a Gleason score of 7 (4+3). Upon analyzing the subsequent pathology results of radical prostatectomy, the disease was involving 3% of the gland only. There was no extra-prostatic extension and no seminal vesicle invasion.

Furthermore, in our study, a positive mpMRI or bpMRI which corresponded to a Gleason score of 6 on biopsy was considered a true positive result. However, a Gleason score of 6 on biopsy with negative MRI (both mpMRI and bpMRI) was considered a true negative. This is because a lesion detected by MRI is likely to correspond to a higher-grade lesion (higher than Gleason 6) and we assume that the random systematic biopsy could have missed the observed abnormality. In addition, there is some variability in the Gleason scoring especially in distinguishing between Gleason 6 and Gleason score 7 (3+4) lesions. There are a number of published studies addressing this issue.[7-11] As well, we assume that a Gleason score of 6 on biopsy does not usually qualify to be clinically significant especially if there are no corresponding findings on the prostate MRI and therefore a Gleason score of 6 with negative MRI is regarded as a true negative.

We have taken into account the experience level of the radiologists. A fellowship-trained body imaging staff radiologist and a body-imaging fellow independently read the examinations. The level of experience did not significantly affect the sensitivity, specificity, PPV or NPV for mpMRI and bpMRI as the results were similar between the two readers with substantial inter-observer agreement.

Theoretically, while adopting PIRADS version 2, utilizing the two different protocols (mpMRI and bpMRI) is not expected to affect the detection rate of clinically significant prostate cancer as the potential difference will only be in peripheral zone lesions, which are scored as PI-RADS 3 based on T2WI and DWI. Therefore, the expected difference between the two protocols is in a peripheral zone lesion, which has been scored as PI-RADS 3 based on T2WI and DWI but cannot be upgraded to PIRADS 4 while using bpMRI. However, a PIRADS 3 lesion is still suspicious for a clinically significant prostate cancer and needs to either undergo a targeted biopsy or a follow up MRI. From our experience, most of the final PIRADS scoring comprised PIRADS2, PIRADS 4 and PIRADS 5. Lesions within the peripheral zone of

the prostate were less frequently assigned a PIRADS 3 category. This is because the PIRADS version 2 criteria is very strict for this particular category and the lesion must not fulfill the criteria for PIRADS 2, PIRADS 4 or PIRADS 5 categories in order to be assigned as PIRADS 3. For example, out of the 100 cases in our study, there were 6 examinations, which were given a final score of PIRADS 3 on mpMRI and 5 examinations on bpMRI, for reader one. Interestingly, for reader two, there was one examination with a score of PIRADS 3 on mpMRI and 5 examinations on bpMRI. The single lesion, which was assigned PIRADS 3 category on mpMRI for reader 2 was negative on biopsy. Further analysis of the 5 cases which were assigned a PIRADS 3 score in bpMRI for reader two revealed the following: one was negative on biopsy (was assigned PIRADS 4 on mpMRI), one corresponded to Gleason 6 disease, two were negative on biopsy (were assigned as PIRADS 2 on mpMRI) and one was positive for a Gleason 7 (4+3) prostate cancer on biopsy (was assigned as PIRADS 2 on mpMRI). Therefore, we feel that either follow up MRI or targeted biopsy for PIRADS 3 lesions are reasonable approaches regardless of the MR protocol used (mpMRI versus bpMRI).

A study by Puech et al suggested that DCE imaging can be useful in determining the aggressiveness of a prostatic tumor.[12] However, there is variability in the interpretation of the post-contrast images between radiologists and histopathology remains the standard for the determination of tumour aggressiveness. Of note, a study by Oto et al showed that there was no significant correlation between the quantitative DCE-MRI parameters of a prostatic lesion and the pathologic Gleason score.[13] Additional studies have suggested that the DCE sequence is useful in the evaluation of extra-prostatic disease extension and seminal vesicle invasion.[12,14] However, according to those studies, this was true for less experienced radiologists only and did not apply for experienced radiologists. And, in any case, when a significant disease burden is suspected on a bpMRI, a repeat mpMRI can be arranged for this small proportion of patients.

We anticipate that adopting a new prostate MRI protocol with lack of the DCE sequence is going to be relatively difficult at the beginning. Therefore, we suggest that each patient should undergo the full protocol (mpMRI) at baseline. Any follow up and/or surveillance imaging can then be abbreviated, and bpMRI can be utilized. In any instance where there is uncertainty or a possible PIRADS 3 lesion in the peripheral zone, calling the patient back for additional DCE imaging is a feasible option. Alternatively, such PIRADS 3 lesions within the peripheral zone can be further assessed with targeted biopsy or follow up MRI.

The two main advantages of using bpMRI over mpMRI are shorter acquisition time and reduced cost.[4,6,12,15-18] From our study, the estimated actual acquisition time for the bpMRI is 22 minutes and 10 seconds, compared to 27 minutes and 30 seconds for mpMRI with an estimated difference of about 5 minutes and 20 seconds for each patient. Moreover, the total scanner occupation time, which included patient positioning and intravenous access can be reduced from 45 minutes to 30 minutes. This will allow for an increased volume of cases. In terms of cost savings, at our institution, the Gadolinium contrast material costs $75 per patient and the intravenous access/contrast injection kit costs an additional $25 per patient, for a total cost reduction of $100 per patient. Depending on the number of prostate MRIs being performed, this can translate into significant cost savings.

There are several limitations of this study. This includes patient recruitment from a single center and MRI imaging on a single unit from one vendor. The sample size is relatively small. Although consecutive patients were selected, there is an inherent selection bias due to a relatively high pretest probability of prostate cancer compared to the general population. However, this does not affect the sensitivity and specificity of the test. It may have some effect on the PPV and NPV. Additionally, we have considered the systematic 14-core TRUS biopsy as a gold standard, which has its own limitations in detection of clinically significant prostate cancer. Moreover, our study was limited to treatment-naïve patients and patients with prior surgical intervention or radiation therapy are highly likely to still benefit from the DCE-MR sequence.

Conclusion

Our study showed that there is no significant difference in the sensitivity, specificity, PPV and NPV between bpMRI and mpMRI of the prostate in detecting clinically significant cancer in a treatment-naïve population. The advantages of bpMRI include shorter acquisition time and reduced cost while maintaining comparable diagnostic accuracy. □

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