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Characterization and PI-RADS version 2 assessment of prostate cancers missed by prebiopsy 3-T multiparametric MRI: Correlation with whole-mount thin-section histopathology

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ABSTRACT

Objectives: To determine the clinical and histopathologic characteristics of missed prostate cancers and their Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) score on a pre-biopsy MRI and subsequent MR-ultrasound (US) fusion biopsy.

Methods: We analysed 59 prostate cancer patients who underwent a 3-T MRI prior to an MR-US fusion biopsy and subsequent radical prostatectomy. A radiologist initially reviewed these cases to correlate target lesions and pathology-proven lesions. The patients were categorized as detected or missed prostate cancer cases. Three radiologists independently assigned the PI-RADS v2 score for each case. The missed lesions were further categorized as suspicious or invisible by consensus. The clinical characteristics, PI-RADS v2 scores, and histopathologic features were thereby obtained.

Results: Thirty seven (62.7%) of the 59 study cases had a detected prostate cancer and 22 (37.3%) as having missed cancer. Seventeen (77.3%) of the 22 missed patients had a clinically significant lesion. The missed cancer cases had a smaller tumour volume, and higher ADC ratio than the detected cancer cases. Fourteen (63.6%) of the missed lesions were not visible on MRI, even though 71.4% of these cancers were clinically significant. Invisible but clinically significant cancers had a tumour volume below 1 cm^3 in 70% of cases.

Conclusions: A negative MRI result does not rule out the current PI-RADS v2 definition of a clinically significant prostate cancer as these tumours can be missed if their volume is below 1 cm^3.

1. Introduction

The emergence of multiparametric magnetic resonance imaging (mpMRI) has led to improved prostate cancer detection and has enabled targeted biopsies. A recent randomized controlled trial has reported that a prebiopsy mpMRI and an MR-targeted biopsy is superior to transrectal ultrasound (TRUS)-guided systematic biopsy for the detection of clinically significant prostate cancer, even omitting systematic biopsy [1]. In addition, although the strategies for targeted biopsy and/or subsequent systematic biopsy may differ between trials, it has also been suggested that mpMRI and MR-targeted biopsy may better detect and distinguish more clinically significant cancer than TRUS-guided systematic biopsy [2–4]. Furthermore, this may reduce the number of patients who require a prostate biopsy.

Despite the promising results from these methods to date, several issues remain. Negative MRI results can be false-negatives in cases of clinically significant cancer [5,6]. There may be uncertainty with regard to further follow-ups or diagnostic strategies in such instances although a number of studies have mentioned close follow-up or systematic biopsy were done [2,3,7]. It has not yet been standardized which is the best approach to diagnosing prostate cancer, whether using a targeted biopsy alone or in conjunction with a subsequent systematic biopsy [8]. A better understanding of the characteristics of missed prostate cancers on mpMRI may provide further clarity to this situation.

The typical characteristics of missed prostate cancers have been reported in previous studies to be a small tumour volume and a low grade lesion [9,10]. However, those studies are likely to have been limited by the use of either systematic biopsy or the whole-mount

Abbreviations: mpMRI, multiparametric magnetic resonance imaging; TRUS, transrectal ultrasound; PI-RADS v2, the Prostate Imaging–Reporting and Data system version 2; RP, radical prostatectomy; MR-US, magnetic resonance-ultrasound; PSA, prostate-specific antigen; GS, Gleason score; ROI, region-of-interest; ICC, intraclass correlation coefficient

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pathology reference standards used in one report and post-biopsy MRI imaging analysis conducted in the other. These procedures can lead to an underestimation of the tumour volume or grade. Furthermore, those two prior studies had been performed before the Prostate Imaging–Reporting and Data system version 2 (PI-RADS v2) was developed. A recent study showed that 51.9% of prostate cancers and 21.4% of index lesions had been missed on mpMRI [11]. Of them, missed lesions which were larger than 1 cm had PI-RADS v2 score 1 or 2 in 61.5% of patients. Except for a study as mentioned above, missed prostate cancers have been incompletely evaluated under the PI-RADS v2 scoring system.

We sought in our present study to determine the clinical and histopathologic characteristics and the PI-RADS v2 score of missed prostate cancers. These data were obtained from multiple readers with varying degrees of expertise in prostate mpMRI. The study patients had all undergone a pre-biopsy MRI and MR-ultrasound (US) fusion biopsy, using whole-mount pathology as the reference standard.

2. Materials and methods

2.1. Study populations

The institutional review board of our institution approved this retrospective study and waived the requirement for written informed consent. A total of 239 patients underwent a pre-biopsy prostate MRI and subsequent MR-US fusion biopsy between November 2015 and May 2018 at our hospital. Among these cases, we recruited 59 patients with an elevated PSA (prostate specific antigen) that also received a radical prostatectomy (RP) for prostate cancer with a shorter than six month time interval between the MRI and MR-US fusion biopsy. We excluded 161 of the initially screened patients from our analysis due to a longer than six month interval between the MRI and biopsy ($n = 3$), too highly elevated PSA or metastatic prostate cancer ($n = 4$), biopsy finding of urothelial carcinoma ($n = 3$) or a benign tumour ($n = 141$), previous antiandrogen or radiation treatment ($n = 6$), and insufficient MR quality due to hip prosthesis ($n = 4$). The remaining 19 patients were excluded because they had not undergone a RP as depicted in Fig. 1.

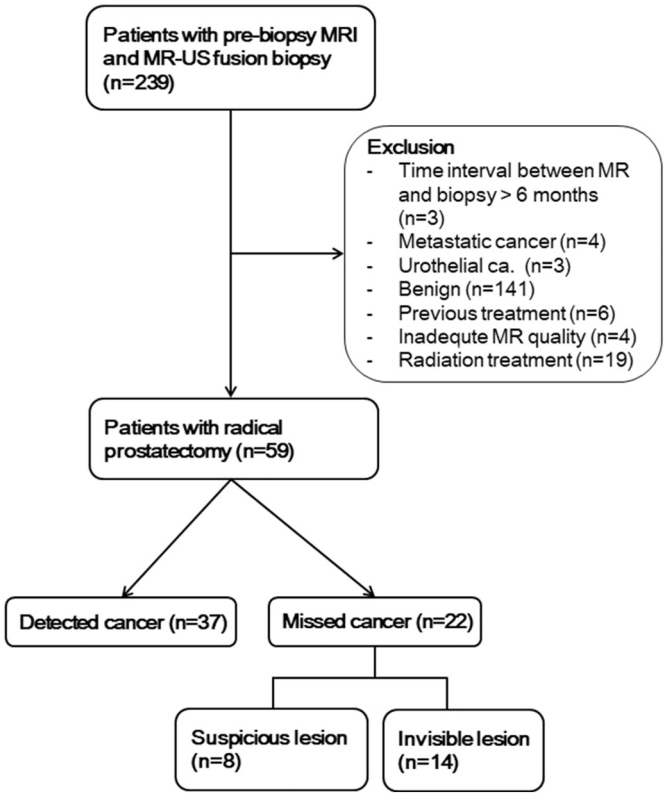

Fig. 1. Patient accrual process for this study.

2.2. Data analysis

2.2.1. Clinical and pathologic parameters

Preoperative clinical parameters were retrospectively collected and included patient age, the serum prostate-specific antigen (PSA) level, history of previous biopsies, and the number of positive cores on a 12-core TRUS-guided biopsy. Postoperative parameters such as the surgical Gleason score (GS), tumour volume, tumour diameter, presence of extracapsular extension (ECE), and seminal vesicle invasion were recorded. The whole-mount step section (5- to 7-mm section thickness, total of 7–12 slices) of the prostate gland was used as the reference standard. Clinically significant cancer was defined by a Gleason score ≥ 7 (3 + 4), and/or a volume ≥ 0.5 cm^3, and/or ECE according to the PI-RADS v2 score [12].

2.2.2. Image acquisition and MR-US fusion biopsy

Details of image acquisition and techniques of MR-US fusion biopsy was displayed in supplementary material.

2.2.3. Image analysis

2.2.3.1. Identification of the target lesion and classification of detected and missed prostate cancers. A genitourinary radiologist reviewed all of the medical records and MR-US fusion biopsy images for the study subjects and noted the target lesion. Target lesion was defined as the most suspicious lesion at the initial MRI interpretation prior to biopsy, which had been targeted on MR-US fusion biopsy. This reader then checked whether there was agreement between these target lesions and the final pathology-proven lesions using a pathologic map of the RP specimen generated by the hospital pathologists. If the target lesion was concordant with that of the pathology-proven lesion, this lesion was classified as detected cancer. If it was discordant and determined to benign lesion, the tumour was classified as a missed cancer. Additionally, all of the target lesions and missed lesions were marked with arrows on the T2-WI. Satellite lesions which were smaller or had lower PI-RADS v2 score compared to target lesions were not evaluated in this study, because those lesions had not undergone targeted biopsy under the circumstances of trying to reduce biopsy cores in a clinical setting.

2.2.3.2. MRI analysis with PI-RADS version 2. Two genitourinary specialists with > 10 and 9 years of experience with prostate MRI analysis, respectively, and a radiologist on a second-year fellowship, independently reviewed the prostate MRI results and recorded the PI-RADS score for each lesion based on PI-RADS v2 [12]. These three readers were blind to the clinical data and pathologic results.

2.2.3.3. Categorization of missed cancer as a suspicious or invisible lesion. After completion of each individual review, missed prostate cancers in the study series were further categorized via a consensus review by three radiologists, after reviewing the whole-mount step sections and prostate MRI findings, as follows: (a) a suspicious lesion which is retrospectively visible but was initially overlooked or incorrectly interpreted or (b) an invisible lesion, which could not be reliably distinguished from other benign lesions or normal structures.

2.2.3.4. Quantitative MRI analysis. Normalized ADC ratio for detected cancers and suspicious lesions in missed cancer cases were calculated. The details of quantitative MRI analysis were described in Supplementary material.

2.3. Statistical analysis

All statistical analyses were conducted using SPSS software (version 21, SPSS Inc., Chicago, IL). Clinical characteristics and imaging parameters were compared between patients with a detected or a missed prostate cancer using an independent *t*-test, chi-square test and Fisher's exact test. Agreement on the PI-RADS scoring between the three readers was assessed using an intraclass correlation coefficient (ICC). In the comparison of normalized ADC values, the Mann-Whitney *U* test was used to compare patients with detected prostate cancers and those with missed but suspicious lesions. The threshold for statistical significance was set as $p < 0.05$.

3. Results

3.1. Patient characteristics and initial assessments of prostate MRI results prior to biopsy

The median serum PSA level among the 59 current study patients was 7.94 ng/mL (range, 2.4–34.5 ng/mL) and the median age was 64 years (range, 49–76 years). The median interval between MR-US fusion biopsy and RP was 73 days (range, 13–134 days). On MR-US fusion and systematic biopsy, systematic biopsy detected 21 prostate cancer patients with negative target biopsy (8 patients of GS 6; 6 of GS 3 + 4; 5 of GS 4 + 3; and 2 of GS 8). Thirty-seven patients (62.7%) were categorized as having a detected prostate cancer and the other 22 cases (37.3%) as having a missed prostate cancer (Table 1). The preoperative serum PSA level (mean, 11.6 vs. 7.79 ng/mL; $p = 0.010$) and PSA density (mean, 0.39 vs. 0.26; $p = 0.035$) were significantly lower in the missed cancer group. Patient age, prostate volume measured on MRI, and previous history of TRUS-guided biopsy were not significantly different between these two groups. The mean PI-RADS score of the target lesions was significantly higher in the detected cancer group (4.43 vs. 2.73; $p < 0.001$). The clinical parameters of the study subjects and results from the initial prostate MRI assessment are summarized in Table 1.

3.2. Histopathologic result of biopsy and RP between detected versus missed prostate cancers

Table 2 presents the pathologic results from the TRUS-guided biopsies and RP. The number of positive cores on a 12-core random biopsy was greater in the detected cancer group (mean, 3.16 vs. 1.86; $p = 0.011$). The diameter and volume of the main prostate tumour were also significantly greater in the detected cancer group (diameter, 24.7 vs. 15.3 mm; $p < 0.001$ and tumour volume, 5.15 vs. 1.64 mL; $p = 0.003$), as was the surgical Gleason score ($p = 0.001$) Fig. 2. In the missed prostate cancer group, 8 patients (36.4%) were GS 3 + 3, 9 (40.9%) were 3 + 4, and 5 (22.7%) were 4 + 3. There were no missed cancers of GS 8–10 found in our present study. The patients in the missed cancer group showed more frequent organ-confined disease (86.4% vs. 43.2%; $p = 0.001$). We found that 36 patients (97.3%) and 17 patients (77.3%) had a clinically significant prostate cancer in the detected and missed groups, respectively, thus demonstrating a higher frequency of clinically significant cancer in the detected group ($p = 0.023$).

Table 1
Clinical characteristics and PI-RADS scores between the detected cancer and missed cancer patients.

Characteristics	Detected cancer ($n = 37$)	Missed cancer ($n = 22$)	*p*
Age (y)[a]	64.5 ± 6.87	62.8 ± 7.54	0.388
PSA level (ng/mL)[a]	11.6 ± 7.40	7.79 ± 3.43	0.010
Prostate volume at MR imaging (mL)[a]	35.7 ± 18.8	32.5 ± 10.6	0.470
PSA density (ng/mL^2)[a]	0.39 ± 0.33	0.26 ± 0.14	0.035
No. of prior transrectal US-guided biopsy			0.388
Biopsy-naïve	17 (51.5%)	7 (38.9%)	
Prior negative biopsy	16 (48.5%)	11 (61.1%)	
Mean PI-RADS score of target lesion†	4.43 ± 0.65	2.73 ± 0.88	< 0.001

[a] Data values are presented as the mean ± standard deviation.

Table 2
Comparison of transrectal US-guided biopsy and radical prostatectomy pathologic results.

Findings	Detected cancer (n = 37)	Missed cancer (n = 22)	*p*
Number of positive cores on random biopsy[a]	3.16 ± 2.35	1.86 ± 1.42	0.011
Diameter of tumour on RP (mm)[a]	24.7 ± 9.10	15.3 ± 8.41	< 0.001
Tumour volume (mL)[a]	5.15 ± 6.01	1.64 ± 2.72	0.003
Location of cancer			0.598
Transition zone	11 (29.7%)	8 (36.4%)	
Peripheral zone	26 (70.3%)	14 (63.6%)	
Surgical Gleason score			0.001
3 + 3	1 (2.7%)	8 (36.4%)	
3 + 4	13 (35.1%)	9 (40.9%)	
4 + 3	14 (37.8%)	5 (22.7%)	
8–10	9 (24.3%)	0 (0.0%)	
Local stage			0.001
T2 or less	16 (43.2%)	19 (86.4%)	
T3a	18 (48.6%)	2 (9.1%)	
T3b	3 (8.2%)	1 (4.5%)	
Clinically significant cancer	36 (97.3%)	17 (77.3%)	0.023

[a] Data values are presented as mean ± standard deviation.

3.3. Comparison of the PI-RADS version 2 scores between the three readers and the quantitative MRI parameters

Table 3 lists the PI-RADS scores assigned by three independent readers and the quantitative results of MRI analysis. The proportion of missed lesions categorized as a very low or low probability of being a clinically significant cancer (PI-RADS 1 or 2) was 59% for reader 1, 63.6% for reader 2, and 68.2% for reader 3. The mean PI-RADS score was significantly lower in the missed group for all three readers compared with the detected group (4.54 vs. 2.64 for reader 1; $p < 0.001$, 4.35 vs. 2.50 for reader 2; $p < 0.001$, and 4.46 vs. 2.55 for reader 3; $p < 0.001$). The ICC was 0.680 (95% CI, 0.590–0.758) among the three readers, which indicated substantial reproducibility. The tumour diameter measured on MRI was significantly larger in the detected cancer group (mean, 17.8 mm vs. 5.05 mm; $p < 0.001$). The normalized ADC ratio was significantly lower in the detected cancer group (0.80 vs. 1.59; $p = 0.028$).

3.4. Categorization of missed prostate cancers as suspicious or invisible lesions

After a consensus review, missed prostate cancers were categorized as suspicious (8 of 22; 36.4%) or invisible lesions (14 of 22; 63.6%). In total, 13.6% (8 of 59) of the patients with a missed cancer had a tumour that was retrospectively detectable. However, 23.7% (14 of 59) of the missed cancers in our current study series were barely visible even after a retrospective review. In terms of clinically significant cancers, 28.8% (17 of 59) of the lesions in our current study series could be missed. Half of the invisible lesions had a tumour volume > 0.5 cm^3 and a GS > 3 + 4. By definition, 10 of the 14 invisible lesions (71.4%) were clinically significant cancers. Of these 10 prostate tumours, 30.0% (3 of 10) were GS 3 + 3 with a tumour volume of 0.5–1.0 cm^3, 40.0% (4 of 10) were GS 7 (3 + 4 or 4 + 3) with a tumour volume of 0.5–1.0 cm^3,

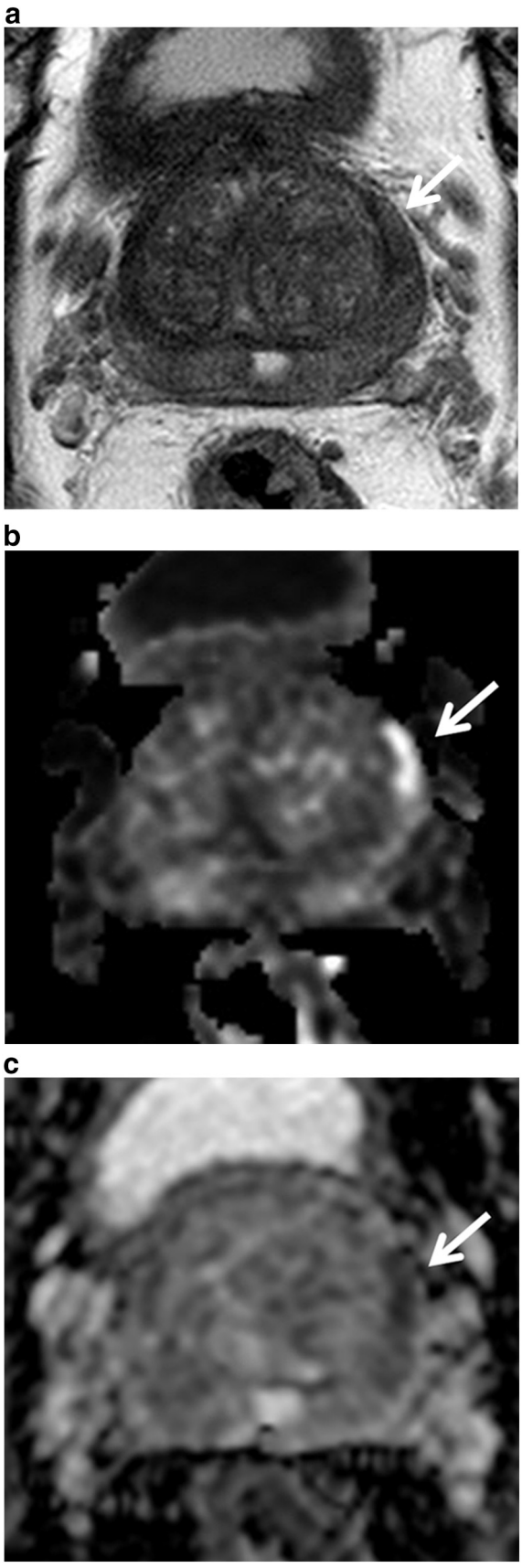

Fig. 2. A 56-year-old study patient with a prostate specific antigen level of 10.4 ng/mL and negative findings in a prior TRUS-guided biopsy.
A, axial T2-weighted image showing a suspicious T2-hypointense lesion in the left transition zone with an obscured margin (arrow), and not reliably distinguishable from the contralateral side. B and C, apparent diffusion coefficient map (B) and DWI with a *b* value of 1500 s/mm^2 (C) showing no apparent diffusion restriction (arrow). The lesion was assigned a T2-weighted imaging score of 2 and DWI score of 2 in the pre-biopsy setting. D, photomicrographs of thin sections showing a clinically significant prostate cancer (Gleason score, 3 + 4; tumour volume, 9.8 cm^3; with extracapsular extension) identified in the left transition zone (dotted line).

Table 3
PI-RADS scores from the three readers and quantitative indices.

	Detected cancer (n = 37)	Missed cancer (n = 22)	*p*
PI-RADS score			
Reader 1			< 0.001
1	0 (0.0%)	1 (4.5%)	
2	1 (2.7%)	12 (54.5%)	
3	1 (2.7%)	5 (22.7%)	
4	12 (32.4%)	2 (9.1%)	
5	23 (62.2%)	2 (9.1%)	
Reader 2			< 0.001
1	0 (0.0%)	1 (4.5%)	
2	0 (0.0%)	13 (59.1%)	
3	4 (10.8%)	4 (18.2%)	
4	16 (43.2%)	4 (18.2%)	
5	17 (45.9%)	0 (0.0%)	
Reader 3			< 0.001
1	0 (0.0%)	0 (0.0%)	
2	1 (2.7%)	15 (68.2%)	
3	3 (8.1%)	2 (9.1%)	
4	11 (29.7%)	5 (22.7%)	
5	22 (59.5%)	0 (0.0%)	
Mean PI-RADS score			
Reader 1	4.54 ± 0.69	2.64 ± 1.05	< 0.001
Reader 2	4.35 ± 0.68	2.50 ± 0.86	< 0.001
Reader 3	4.46 ± 0.77	2.55 ± 0.86	< 0.001
Diameter of tumour on MR (mm)	17.8 ± 8.18	5.05 ± 6.12	< 0.001
Normalized ADC ratio	0.80 ± 0.40	1.59 ± 1.30	0.028

Table 4
Histopathologic characteristics of the suspicious and invisible lesions.

	Suspicious lesion (*n* = 8)	Invisible lesion (n = 14)
Tumour volume		
≤ 0.5 cm^3	2 (25.0%)	7 (50.0%)
0.5–1.0 cm^3	2 (25.0%)	3 (21.4%)
> 1.0 cm^3	4 (50.0%)	4 (28.6%)
Surgical Gleason score		
3 + 3	1 (12.5%)	7 (50.0%)
3 + 4	5 (62.5%)	4 (28.6%)
4 + 3	2 (25.0%)	3 (21.4%)
8–10	0 (0.0%)	0 (0.0%)
Clinically significant cancer	7 (87.5%)	10 (71.4%)
GS 3 + 3 with tumour volume of 0.5–1.0 cm^3	0 (0.0%)	3/10 (30.0%)
GS 7 with tumour volume ≤ 1.0 cm^3	3/7 (42.9%)	4/10 (40.0%)
GS ≥ 7 and tumour volume > 1.0 cm^3	4/7 (57.1%)	3/10 (30.0%)

and the remaining 30.0% (3 of 10) were GS 7 (3 + 4 or 4 + 3) and had a tumour volume > 1.0 cm^3 (Table 4). The three invisible lesions with a tumour volume > 1.0 cm^3 were located in the central zone, transition zone, and peripheral zone, respectively, and could not be clearly distinguished from other structures on a T2WI without restricted diffusion (Figs. 3 and 4).

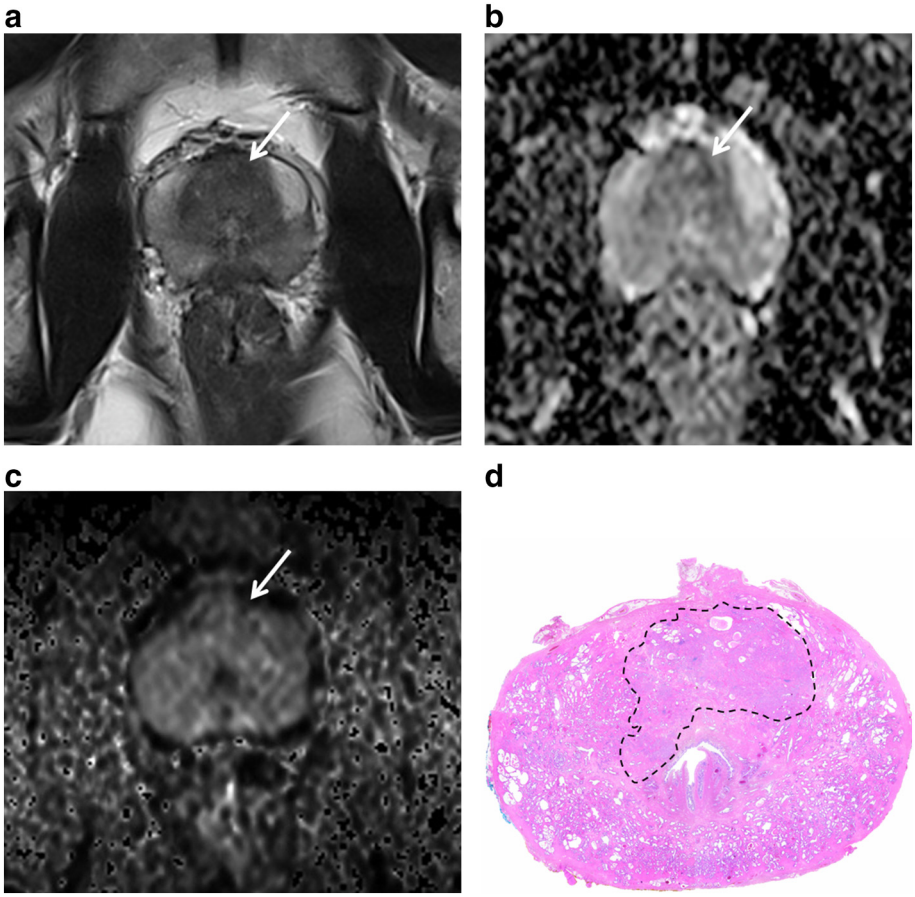

Fig. 3. A 64-year-old study patient with a prostate specific antigen level of 12.8 ng/mL and negative findings in a prior TRUS-guided biopsy.
A and B, axial (A) and coronal (B) T2-weighted images showing the symmetric appearance of a bilateral central zone without a non-circumscribed T2 low signal lesion. C, apparent diffusion coefficient map showing no apparent diffusion restriction. This lesion was not regarded as suspicious on the pre-biopsy MR reading. This patient underwent a TRUS-guided biopsy and MR-US fusion biopsy (target lesion was in the right transition zone; not shown here). D, photomicrographs of thin sections showing a clinically significant cancer (Gleason score, 4 + 3; tumour volume; 9.2 cm^3; with seminal vesicle invasion) identified in the right central zone (dotted line).

4. Discussion

Our present analyses indicate that up to a third of clinically significant prostate cancers may be missed on the initial mpMRI prior to an MR-US fusion biopsy. These missed tumours may have a lower PSA and PSA density, smaller tumour volume or diameter, lower surgical GS, and lower PI-RADS score than an initially detected lesion. By quantitative analyses, we further found in our current study that the missed cancers had a significantly higher normalized ADC ratio than the detected lesions. Approximately 60% (59–68.2% across the three readers) of the missed cancers in our study series were assigned a PI-RADS score of 2 or less. Among the missed prostate cancers, 63.6% of the lesions could not be reliably distinguished from normal or other structures, although 71.4% of these tumours were a clinically significant prostate cancer. These invisible but clinically significant cancers had a tumour volume ranging from 0.5 to 1 cm^3 in 70% of cases (Fig. 4).

Pokorny et al. reported that the lesions in 25% and 6% of their patients diagnosed with low risk and intermediate/high risk prostate cancer had been assigned a PI-RADS score of 1 or 2 [2]. Other studies have also reported a false-negative rate of 19.7–31.7% for the detection of prostate cancer by mpMRI [9,10]. The evidence from prior studies has indicated a negative predictive value (NPV) range of 68.6–85.7% for mpMRI in the detection of overall prostate cancer, with a PI-RADS cut-off of 3 or greater [5–7,13].

In our current study, 59–68.2% of the missed prostate cancers were assigned a PI-RADS score of 1 or 2 by three readers with varying degrees of expertise in assessing prostate MRI. The results of many previous reports and our current study findings indicate however that even an experienced radiologist can miss a clinically significant prostate cancer on an mpMRI. Some proportion of these missed cancers may be due to reader error but there are clearly some prostate tumours with a lower PI-RADS score, higher normalized ADC ratio or small volume that are not visible on these images.

Tan et al. have previously reported on a cohort of detected and missed prostate cancers after correlation with whole-mount thin-section histopathology. Their study demonstrated that missed lesions were more likely to be smaller than 1 cm in diameter, low-grade (75.2%), satellite lesions, and located at the prostatic apex [9]. De Visschere and colleagues reported that 31.7% of the prostate patients in their study had an initially negative mpMRI result but were subsequently diagnosed within 2 years. Among these prior cases, 67.7% of the lesions were low grade and 37.9% were < 1 cm in diameter [10]. In contrast to these earlier findings, our present study revealed that 40.9% and 22.7% of missed prostate cancers were intermediate or high grade based on the surgical GS. There are some possible explanations for these discrepancies. In the first instance, the study of Tan et al. was based on multiple lesion analysis, including index and satellite lesions, in patients who underwent a post-biopsy MRI scan. Satellite lesions are more likely to be low grade than index lesions, which may have resulted in a higher proportion of low grade cancers in prior report than in our current study series. Second, the study of De Visschere et al. included patients who had not undergone RP and used 12-core TRUS-guided biopsy results or RP specimens as reference standards. It has been suggested in multiple reports that the GS can be upgraded in approximately 39.9–50% of patients with a biopsy-proven cancer of GS 6 or less [14–16]. Hence, the proportion of intermediate to high grade prostate cancer could have been underestimated in these previous studies.

According to the PI-RADS version 2 grading system, the definition of a clinically significant prostate cancer includes a tumour volume ≥ 0.5 cm^3 [12]. However, this criterion has been considered to be too strict and a revised definition has been suggested in which a clinically insignificant prostate cancer may include index tumours with

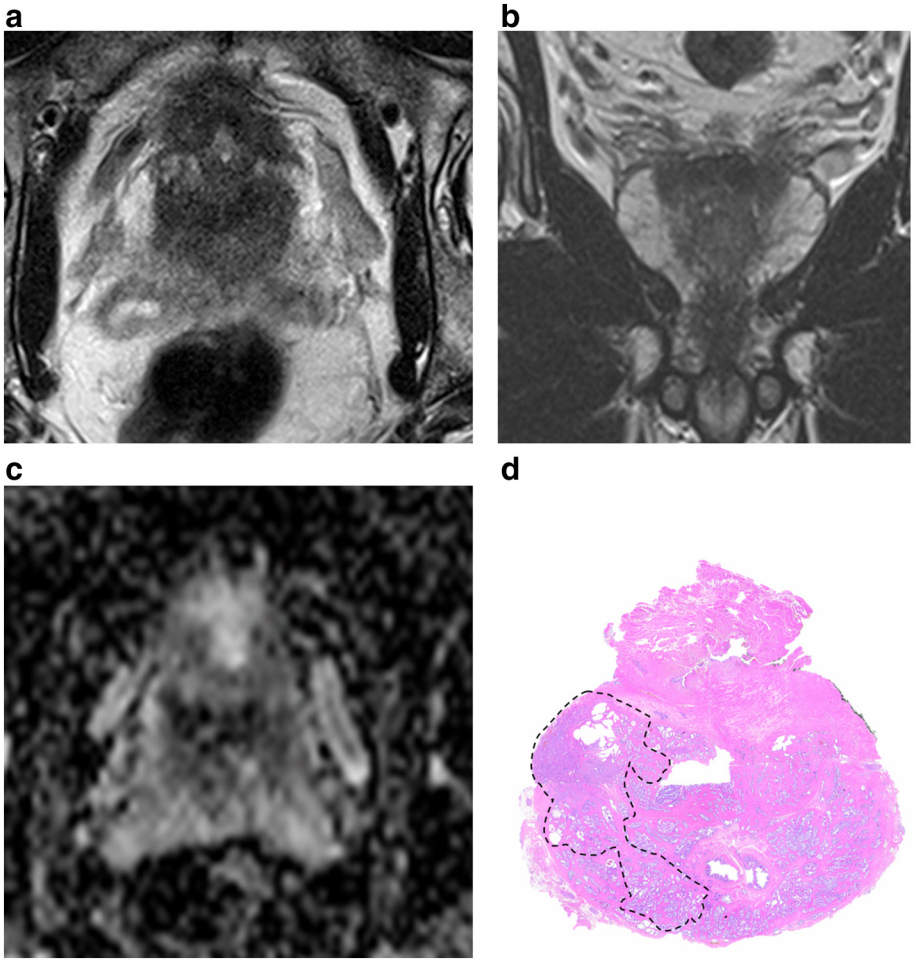

Fig. 4. A 65-year-old study patient with a prostate specific antigen level of 10.5 ng/mL and negative findings in a prior TRUS-guided biopsy.
A, axial T2-weighted image showing a T2-hypointense lesion (arrow) in the left peripheral zone. B and C, DWI with a *b* value of 1500 s/mm^2 (B) and apparent diffusion coefficient map (C) showing diffusion restriction. The lesion was assigned PI-RADS score of 5 on both T2-weighted image and DWI. This patient was diagnosed as a clinically significant cancer (Gleason score, 4 + 3; tumour volume, 1.3 cm^3; with extracapsular extension) after targeted biopsy and subsequent radical prostatectomy.

volume ≤ 1.3 cm^3 in patients with low-grade disease [17–19]. It has also been reported previously that mpMRI can miss a clinically significant prostate cancer of < 1 cm^3 [20]. Moreover, another prior study has indicated that mpMRI can underestimate the pathologic tumour volume in 49% of cases by a mean of 0.56 cm^3 using DWI [21]. The detection of clinically significant cancers of ≤1 cm^3 may therefore be limited when using the current PI-RADS v2 criteria. Hence, further studies are necessary to determine the optimal size for prostate cancer detection through an mpMRI.

One invisible prostate lesion with seminal vesicle invasion, a tumour volume of 9.2 cm^3 and a central zone location was found in our current study cohort. The detection of central zone cancer often poses a diagnostic challenge [22]. Despite the difficulty in detecting central zone lesions however, these tumours demonstrate a higher GS, and higher rates of extracapsular extension and seminal vesicle invasion. We found one case of an invisible lesion in the transition zone with a tumour volume of 9.8 cm^3 in our present cohort. It has been reported in this regard that transition zone cancers also show more limited detection accuracy [23]. As also shown in our current study, some central zone and transition zone prostate cancers may not be reliably visible on mpMRI which is another potential diagnostic pitfall.

There were several limitations of our present study of note. First, we conducted retrospective analysis of a small sample population. Also, our analysis was performed at a single institution at which all three readers were based. This may have reduced possible variability in the prostate MRI reporting patterns. Moreover, we only analysed index lesions with the highest GS in each patient and not satellite lesions. The strategy for prostate biopsy in our institution has been targeted biopsy for two or less suspicious lesions and subsequent systematic biopsy so far. The reason for limiting targeted biopsy within 1 or 2 lesions would be increasing number of biopsy cores could lead to increasing frequency of biopsy-related complications. We would contend in this regard that it may be important to choose the most suspicious lesion for targeted biopsy in a pre-biopsy MRI setting rather than finding out all prostate cancer foci. We thus believe that analysis of index lesions for each patient would be more practical in daily practice.

5. Conclusion

We here demonstrate that a pre-biopsy MRI can fail to detect a clinically significant prostate cancer in about a third of patients. Of the missed cancers in our current series, 71.4% were clinically significant and 63.6% were not reliably visible in a retrospective review. Invisible clinically significant prostate tumours had a volume < 1 cm^3 in 70% of our patients with a GS of 6 or 7. Although the PI-RADS v2 scoring system currently uses a tumour volume of ≥0.5 cm^3 as the cut-off for a clinically significant cancer, this may be too strict to observe all clinically significant cancers of < 1 cm^3. Our present findings thus have implications for future-decision making in prostate cancer patients with negative MRI or MR-targeted biopsy results.

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Appendix A. Supplementary data

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