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Platinum Priority – Prostate Cancer – Editor's Choice

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Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging

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Abstract

Background: Multiparametric magnetic resonance imaging (mpMRI) undoubtedly affects the diagnosis and treatment of localized prostate cancer (CaP). However, clinicians need a better understanding of its accuracy and limitations in detecting individual CaP foci to optimize management.
Objective: To determine the per-lesion detection rate for CaP foci by mpMRI and identify predictors of tumor detection.
Design, setting, and participants: We carried out a retrospective analysis of a prospectively managed database correlating lesion-specific results from mpMRI co-registered with whole-mount pathology (WMP) prostatectomy specimens from June 2010 to February 2018. Participants include 588 consecutive patients with biopsy-proven CaP undergoing 3-T mpMRI before radical prostatectomy at a single tertiary institution.
Outcome measurements and statistical analysis: We measured mpMRI sensitivity in detecting individual CaP and clinically significant (any Gleason score ≥7) CaP foci and predictors of tumor detection using multivariate analysis.
Results and limitations: The final analysis included 1213 pathologically confirmed tumor foci in 588 patients with primarily intermediate- (75%) or high-risk (12%) CaP. mpMRI detected 45% of all lesions (95% confidence interval [CI] 42–47%), including 65% of clinically significant lesions (95% CI 61–69%) and nearly 80% of high-grade tumors. Some 74% and 31% of missed solitary and multifocal tumors, respectively, were clinically significant. The majority of missed lesions were small (61.1% ≤1 cm); 28.3% were between 1 and 2 cm, and 10.4% were >2 cm. mpMRI missed at least one clinically significant focus in 34% of patients overall, and in 45% of men with multifocal lesions. On multivariate analysis, smaller, low-grade, multifocal, non-index tumors with lower prostate-specific antigen density were more likely to be missed. Limitations include selection bias in a prostatectomy cohort, lack of specificity data, an imperfect co-registration process, and uncertain clinical significance for undetected lesions.
Conclusions: mpMRI detects less than half of all and less than two-thirds of clinically significant CaP foci. The moderate per-lesion sensitivity and significant proportion of men with undetected tumor foci demonstrate the current limitations of mpMRI.
Patient summary: Magnetic resonance imaging of the prostate before surgical removal for prostate cancer finds less than half of all individual prostate cancer tumors. Large, solitary, aggressive tumors are more likely to be visualized on imaging.
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1. Introduction

In developed countries worldwide, prostate cancer (CaP) is the most common malignancy and third most common cause of cancer death among men [1]. Screening, diagnosis, and treatment for CaP are fraught with uncertainty and challenges: poor test characteristics of the prostate-specific antigen (PSA) test; significant morbidity and sampling errors for prostate biopsy; difficulty in distinguishing indolent from aggressive cancers; the morbidity of local and systemic treatments; and the multifocal nature of CaP. In the past decade, prostate multiparametric magnetic resonance imaging (mpMRI) emerged to help address these challenges, including biopsy risk stratification [2–4], increasing the detection of clinically significant cancer while reducing the diagnosis of insignificant cancer [5–8], identifying appropriate active surveillance candidates [9,10], as an adjunct to biopsy in active surveillance protocols [11,12], and improving local staging and surgical planning [13,14].

Whole-mount pathology (WMP) is the ideal reference standard for minimizing biopsy sampling errors and correlating individual prostate lesions to mpMRI findings. The current study updates our previous analysis of mpMRI performance using the Prostate Imaging-Reporting and Data System version 2 (PI-RADS v.2) scoring system [15] for per-lesion CaP detection in WMP radical prostatectomy specimens. We identify predictors of tumor detection on mpMRI, with particular attention to tumor focality, and include a secondary analysis of mpMRI performance for detection of clinically significant CaP (csCaP).

2. Patients and methods

2.1. Study population

A total of 588 consecutive patients underwent 3-T mpMRI within 6 mo before radical prostatectomy at a single institution between June 2010 and February 2018. mpMRI was performed for clinical suspicion of CaP or for surgical planning. We excluded patients with mpMRI performed at an outside facility, prior prostate radiation, androgen deprivation therapy, or transurethral procedure, and cases involving technical limitations (Fig. 1). Research staff extracted clinicodemographic, MRI, and histopathologic data into our prospectively maintained integrated diagnostics database. We calculated PSA density using mpMRI prostate volume. The institutional review board approved this study.

2.2. mpMRI

Radiology technicians performed mpMRI scans according to a standardized protocol (Supplementary Table 1). Consistent with the standard clinical workflow of an academic teaching institution, one of three board-certified abdominal imaging radiologists with 10–18 yr of prostate mpMRI experience (600, 2000, and 3000 prostate MRI reads) jointly interpreted all images with the on-service abdominal imaging fellow (postgraduate yr 6). Radiologists had access to clinical information and assigned a PI-RADS v.2 suspicion score to each region of interest (ROI).

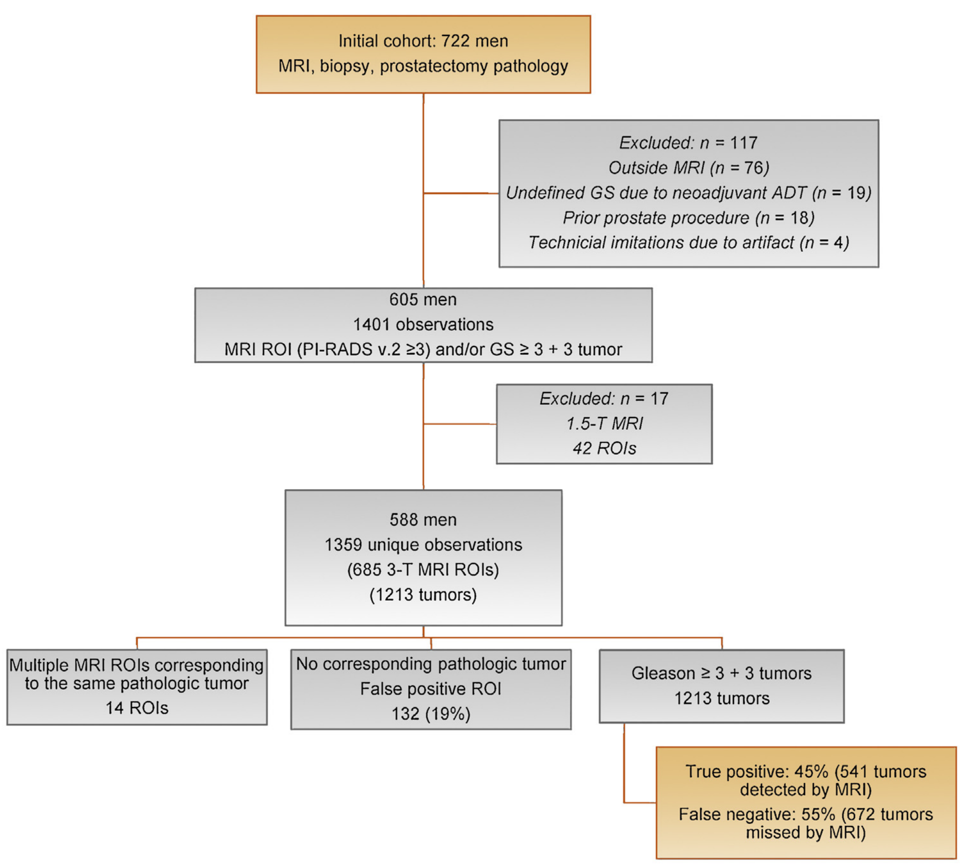

Fig. 1 – Flow chart for study inclusion. ADT = androgen deprivation therapy; GS = Gleason score; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; ROI = region of interest.

For mpMRI scans interpreted before the adoption of PI-RADS v.2 (n = 462), a genitourinary radiologist (6 yr of experience, 1000 prostate MRI reads), blinded to clinical and biopsy information, retrospectively assigned PI-RADS v.2 to each ROI. Lesions with PI-RADS v.2 scores ≥3 were considered positive. We could not evaluate inter-reader variability as two different reads were not available. When radiologists identified multiple ROIs, we designated the index ROI as the lesion with the highest PI-RADS v.2 score, or the larger of two lesions with the same PI-RADS v.2 score.

2.3. Radiology-pathology correlation (Fig. 2)

Two genitourinary pathologists with 4–12 yr of CaP experience localized, measured, and outlined tumors after WMP slide preparation, which involved sectioning each prostate in the axial plane from the inked basal margin to the apex in approximately 4–5-mm intervals and mounting the sections on large slides. At a separate monthly multidisciplinary meeting, a genitourinary radiologist and pathologist came to a consensus about the concordance of radiographic ROIs and pathologic tumors on

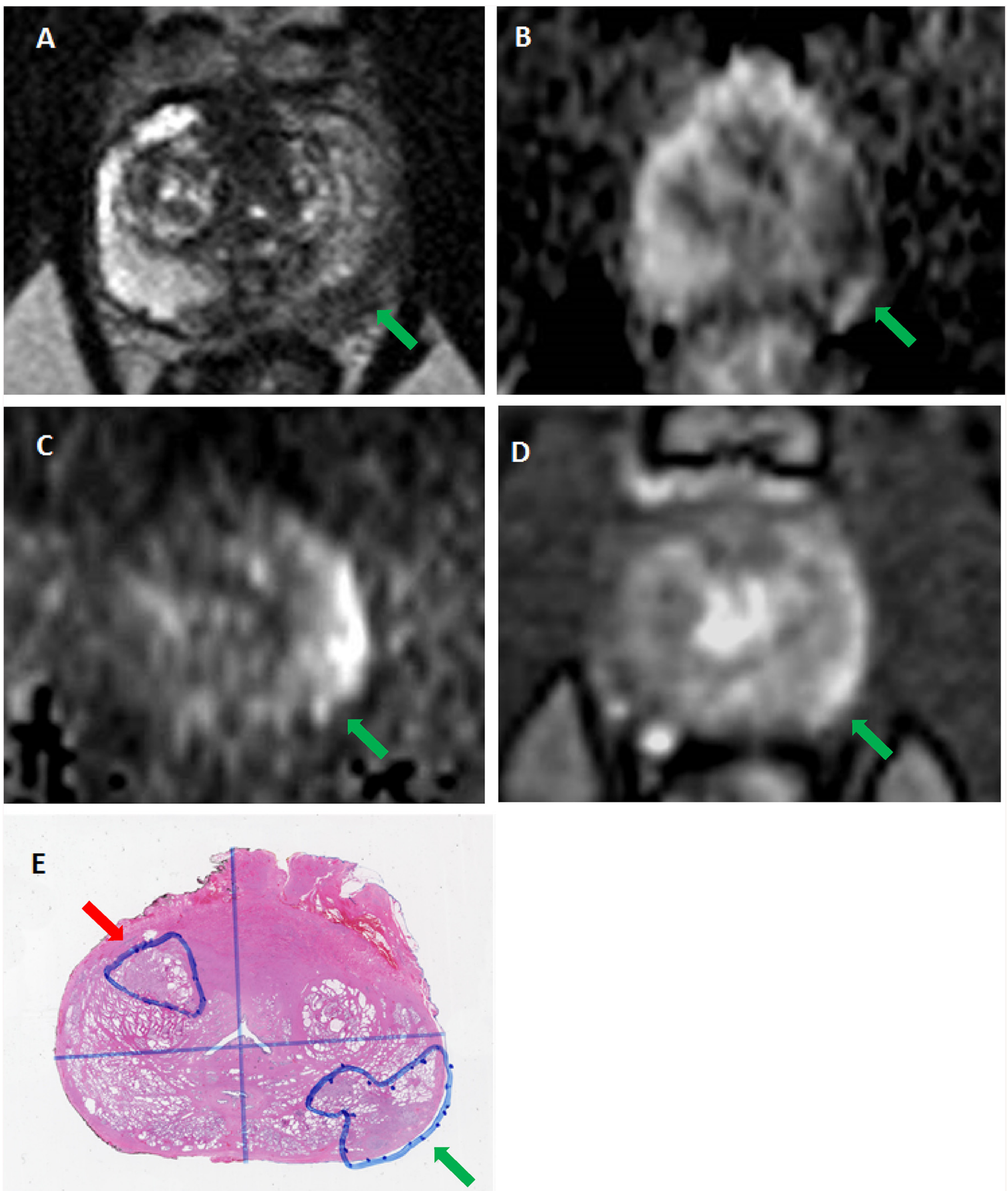

Fig. 2 – Imaging for a 57-yr-old patient with serum prostate-specific antigen of 6.3 ng/ml and an index lesion detected (green arrow) with Gleason score 3 + 4 and a false-negative satellite lesion (red arrow) with Gleason score 3 + 3. (A) Axial T2-weighted magnetic resonance image. (B) Axial apparent diffusion coefficient map. (C) Diffusion-weighted image (b = 1400 s/mm^2). (D) Dynamic contrast-enhanced magnetic resonance image. (E) Whole-mount pathologic specimen obtained at robot-assisted prostatectomy.

WMP. Concordant lesions were in the same quadrant (left, right, anterior, posterior) and segment (base, mid-gland, apex) on both mpMRI and WMP. False-negative lesions lacked an mpMRI correlate and false-positive ROIs had no corresponding histopathologic lesion. We recorded the maximum diameter for radiographic ROIs and histopathologic tumors, which was nearly always in the axial plane. The pathologic index tumor was the lesion with the highest Gleason score (GS) or the tumor with the largest diameter if multiple lesions had the same GS. We determined whether two foci on adjacent slides were separate lesions if there was no overlap with clear evidence of benign prostate tissue between nodules for more than 5 mm in two or more consecutive slides. We defined lesion-specific csCaP as GS $\geq$ 3 + 4 [16].

2.4. *Statistical analysis*

We described characteristics for each patient, mpMRI study, and WMP specimen. We compared size, GS, and tumor focality between detected and missed lesions and stratified this analysis according to tumor focality (solitary vs multifocal). We compared detection rates using a χ^2 test. To identify characteristics associated with missed tumor detection, we screened variables using univariate logistic analysis and included variables with $p < 0.20$ in the forward stepwise model selection process to build our multilevel multivariate logistic regression. We repeated the analyses for csCaP only. We excluded false-positive mpMRI lesions from positive predictive value (PPV) calculations. To assess for potential bias from blinded yet retrospective PI-RADS v.2 assignment, we assessed linear time trends in the detection rate using a Mantel-Haenszel χ^2 test for the entire study period and stratified by pre- and post-PIRADS v.2 adoption. To account for within-patient correlations, we ran a multilevel model for both univariate and multivariate analyses using PROC GENMOD in SAS (SAS Institute, Cary, NC, USA) with a binary distribution, a REPEATED statement, and compound symmetry for the correlation matrix structure. All tests were two-sided with $\alpha = 0.05$. All analyses were conducted using SAS version 9.4 (SAS Institute).

3. Results

Table 1 lists patient, mpMRI, and WMP specimen characteristics for all 588 men with 1213 histopathologic lesions. We identified 685 individual radiographic ROIs in 420 men. The majority of all ROIs (75%), index ROIs (81%), and nonindex ROIs (58%) were highly or very highly suspicious (PI-RADS v.2 score 4 or 5). Overall GS was 6 in 74 (13%), 7 in 442 (75%), and >8 in 72 patients (12%). CaP was non–organ-confined in 188 patients (32%); 150 men (26%) had extracapsular extension and 37 (6%) had seminal vesical involvement. One patient had pT4 disease, 27 (5%) had pelvic lymph node involvement, and 372 (63%) had multifocal cancer (mean 2.7 foci, range 2–7). The median pathologic tumor size was 2.0 cm (interquartile range [IQR] 1.5–2.7) for index lesions and 1.4 cm (IQR 0.7–2.1) for nonindex lesions. Compared to index lesions, nonindex lesions were more likely to be of low risk according to multilevel modeling (13% vs 76% GS 6; $p < 0.00001$; Table 1).

3.1. *mpMRI performance*

Overall, mpMRI detected 541/1213 pathologic lesions, which represents sensitivity of 45% (95% confidence interval [CI] 42–47%) and a PPV of 81% (95% CI 78–84%). Larger, higher-grade, index, and solitary tumors were more likely to

Table 1 – Patient and lesion characteristics for 588 men with histopathologically confirmed prostate cancer

Parameter	Result
Median age, yr	62.2 (57.3–67.4)
Median time from MRI to prostatectomy, mo	2.3 (0.9–3.5)
Median prostate-specific antigen, ng/ml	6.0 (4.6–8.3)
Median MRI prostate volume, cm^3	37 (29.5–48)
Median MRI prostate-specific antigen density, ng/ml/cm^3	0.16 (0.11–0.23)
Median MRI ROI diameter, cm	
Index ROI only (n = 420)[a]	1.4 (1.0–1.9)
All ROIs (n = 541)	1.3 (0.9–1.8)
Median pathology tumor diameter, cm	
Index lesion only (n = 587)[b]	2.0 (1.5–2.7)
All lesions (n = 1212)	1.4 (0.7–2.1)
Median prostate weight at surgery, g	42 (34–54)
Histopathology	
Gleason score distribution: index pathologic lesions (n = 588)[b]	
3 + 3	13 (74)
3 + 4	53 (309)
4 + 3	23 (133)
≥8	12 (72)
Gleason score distribution: nonindex pathologic lesions (n = 625)	
3 + 3	76 (474)
3 + 4	20 (125)
4 + 3	2 (15)
≥8	2 (11)
Gleason score distribution: all pathologic lesions (n = 1213)	
3 + 3	45 (548)
3 + 4	36 (434)
4 + 3	12 (148)
≥8	7 (83)
Pathologic stage	
T2	68 (399)
T3a	26 (150)
T3b	6 (37)
T4	0.2 (1)
N0/Nx	95 (561)
N1	5 (27)
Solitary tumor	37 (216)
Multifocal cancer	63 (372)
2 foci	34 (198)
3 foci	19 (110)
4 foci	9 (53)
≥5 foci	2 (11)
Multiparametric MRI	
Endorectal coil	
Yes	49 (290)
No	51 (298)
MRI relative to biopsy	
On/before biopsy	49 (283)
After biopsy	51 (290)
Median ROIs per patient, n (range)	2 (1–7)
ROI PI-RADS score: index ROIs (n = 420)[a]	
3	19 (80)
4	43 (180)
5	38 (160)
ROI PI-RADS score: nonindex ROIs (n = 121)	
3	42 (51)
4	50 (60)
5	8 (10)
ROI PI-RADS score: all ROIs (n = 541)	
3	24 (131)
4	44 (240)
5	31 (170)

IQR = interquartile range; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging-Reporting and Data System; ROI = region of interest. Data are presented as n (IQR) or % (n).
[a] The index MRI lesion was the lesion with the highest PI-RADs score or the largest ROI if there were more than one ROI with the same PI-RADs score.
[b] The index pathologic lesion was the lesion with the highest Gleason score or the largest lesion if there were more than one lesion with the same Gleason score.

be detected (Fig. 3). Specifically, mpMRI detected 10%, 19%, 54%, and 78% of tumors of 1–5, 6–10, 11–20, and >20 mm, respectively. PPV increased with radiographic suspicion (64%, 85%, and 92% for PI-RADS 3, 4, and 5, respectively). Some 132/685 ROIs had no corresponding pathologic tumor, which represents a false positive rate of 19% (95% CI 16–22%). The PI-RADS v.2 score for these ROIs was 3, 4, and 5 in 56%, 33%, and 11% of cases, respectively. The sensitivity was 71% (420/588) for index lesions and 19% (121/625) for nonindex lesions ($p < 0.0001$). Index tumor detection was significantly lower for patients with multifocal tumors compared to those with solitary tumors (66% vs 80%; $p < 0.0001$; Fig. 4).

mpMRI more accurately detected csCaP lesions, with overall sensitivity of 65% (95% CI 61–69%; 435/665), and 83% (157/189) for solitary and 58% (278/476) for multifocal tumors. The overall PPV for csCaP was 65% (95% CI 61–69%; 446/685) and increased with suspicion score (40%, 68%, and 89% for PI-RADS 3, 4, and 5). Some 74% (32/43) of all missed solitary tumors were clinically significant, including ten (23%) with GS $\geq 4+3$. Of all the missed multifocal tumors, 31% (198/629) were clinically significant, including 46 (7%) with GS $\geq 4+3$. Supplementary Table 2 includes additional details for missed csCaP lesions.

We found no significant linear trend in detection rates over the entire study period ($p = 0.07$) or between pre- and post-PI-RADS v.2 adoption ($p > 0.1$), indicating that blinded retrospective assignment of PI-RADS v.2 score was not associated with the detection rate.

On multivariate analysis for detection of any cancer, smaller size, lower PSA density, GS $\leq 3+4$ vs GS ≥ 8, nonindex status, and multifocality were associated with a higher risk of missing any lesion. Secondary analysis for csCaP detection revealed that smaller size, nonindex status, and multifocality increased the risk of missed csCaP (Table 2). GS was no longer significant for csCaP detection. Tumor size was the strongest predictor of detection.

4. Discussion

To the best of our knowledge, this is the largest evaluation of preoperative mpMRI performance for CaP detection using WMP as the reference standard. We found that mpMRI detected less than half of all lesions, including less than two-thirds of all csCaP foci. In contrast to our prior report, we found that multifocality was negatively associated with tumor detection after controlling for other factors. A larger sample size of patients with multifocal tumors (997 vs 243) in the current analysis probably explains these disparate findings [17].

Greater detection of csCaP and lower detection of clinically insignificant CaP are the primary benefits of mpMRI and MRI-fusion biopsy that are driving widespread adoption in routine practice worldwide [5–7], along with help in identifying appropriate candidates for active surveillance and focal therapy [9,10,18]. While the former is supported by our findings (mpMRI misses 81% of GS 6 tumors and 90% of tumors <5 mm), the characteristics of missed lesions highlight the limitations of mpMRI. Nearly 75% of missed solitary lesions were clinically significant, including nearly 25% with GS $\geq 4+3$. While the vast majority of missed multifocal tumors were clinically insignificant, we found a substantial percentage (31%) of the 629 missed multifocal tumors contained some pattern 4 pathology. In a similar retrospective study, mpMRI missed

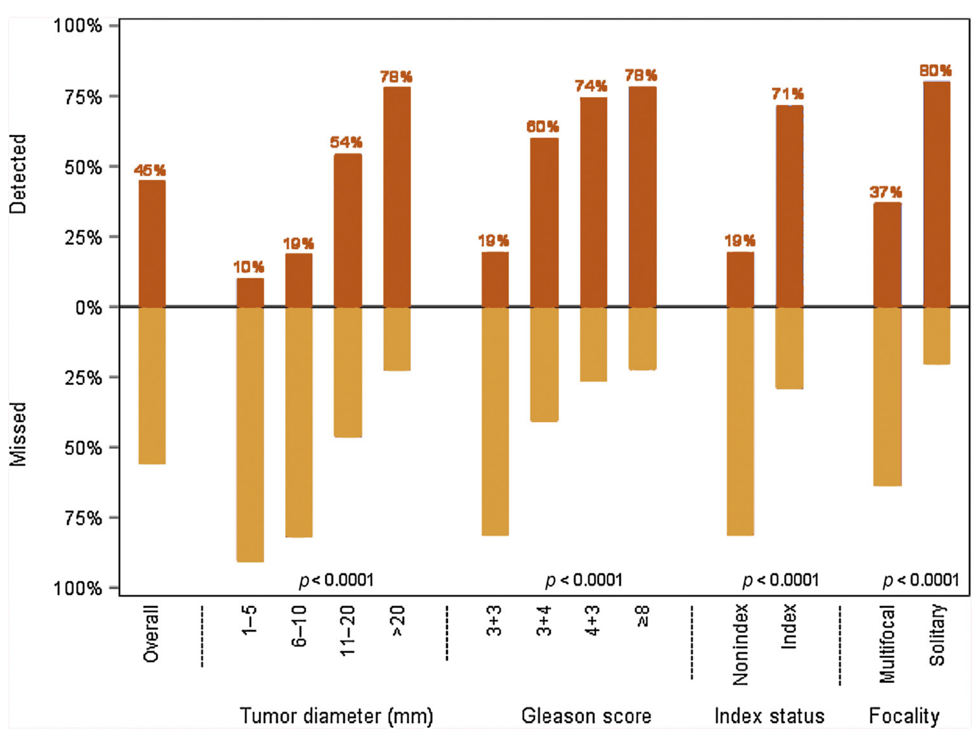

Fig. 3 – Overall tumor detection rates by final pathologic tumor features.

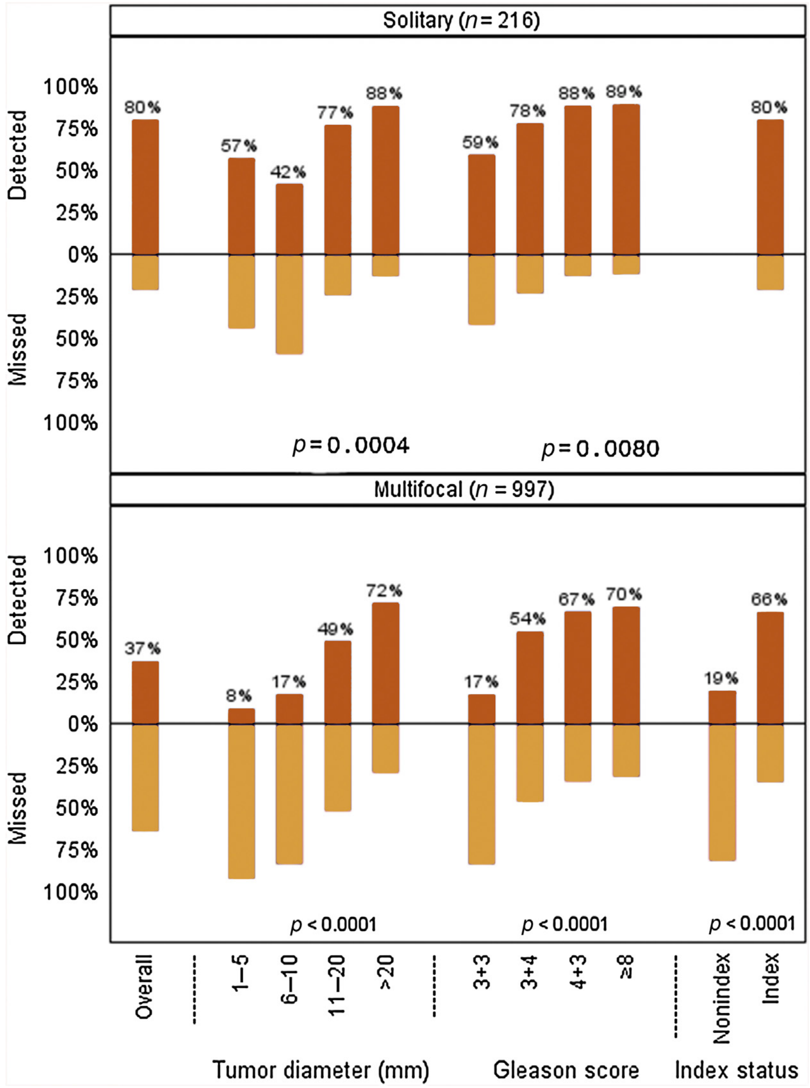

Fig. 4 – Tumor detection rates by final pathologic tumor features, stratified by focality.

16% (26/162) of all csCaP, defined as GS 6 > 5 mm or any GS $\geq$ 7 [19]. In this study, mpMRI missed at least one csCaP focus in 26% of patients, compared to 34% (177/514) in our study, including 45% (145/325) of patients with multifocal lesions.

Our study should be interpreted in the context of two recently published studies evaluating patient-level detection of csCaP by mpMRI [5,20]. In a paired validating confirmatory study evaluating the diagnostic accuracy of 1.5-T mpMRI and systematic transrectal ultrasound-guided prostate biopsy (TRUS) using template prostate mapping biopsy (TPMB) as the reference standard in 576 men, mpMRI accurately detected csCaP (defined as GS $\geq$ 4 + 3 or GS 3 + 4 with maximum cancer core length $\geq$6 mm) in 93% of patients compared to 48% with TRUS biopsy alone. The 89% negative predictive value for mpMRI in this study suggests that 27% of patients could avoid primary biopsy. Under the assumption that targeted MRI-fusion biopsy achieves comparable diagnostic accuracy to TPMB, a biopsy strategy that utilizes mpMRI may detect up to 18% more cases of csCaP with the tradeoff of and up to 21% increase in the diagnosis of clinically insignificant CaP [20]. This study found a similar patient-level diagnostic accuracy for mpMRI as a prior study of 388 patients undergoing TPMB plus cognitively targeted biopsies as the reference standard (sensitivity 95%) [21].

A multicenter, randomized, noninferiority trial compared an mpMRI-directed biopsy strategy with TRUS biopsy for detection of csCaP (GS $\geq$ 3 + 4). Men randomized to MRI-directed biopsy with suspicious mpMRI findings (PI-RADS v.2 $\geq$ 3) underwent targeted biopsy only, without standard systematic cores. Men with negative mpMRI findings were observed. Detection of csCaP was superior in the mpMRI-directed algorithm compared to TRUS only (38% vs 26%; p = 0.005) [5].

Taken together, these studies demonstrate the utility of mpMRI in identifying patients harboring any csCaP. By contrast, we investigated per-lesion detection rates. Our current study indicates that mpMRI may miss up to 35% of clinically significant lesions (30% when using GS $\geq$ 3

Table 2 – Odds of missed tumor detection by multiparametric MRI from multilevel modeling

	Univariate		Multivariate (n = 1213)		Multivariate for csCaP (n = 665)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.00 (0.99–1.02)	0.7338				
MRI PV	1.01 (1.00–1.02)	0.0052				
Pathology TD, mm						
1–5	33.43 (20.25–55.20)	<0.0001	9.25 (5.18–16.55)	<0.0001	15.52 (5.30–45.41)	<0.0001
6–10	15.60 (10.09–24.14)	<0.0001	5.27 (3.18–8.74)	<0.0001	6.85 (3.60–13.03)	<0.0001
11–20	3.04 (2.17–4.26)	<0.0001	1.79 (1.22–2.62)	0.0028	1.87 (1.21–2.89)	0.0047
>20	Reference		Reference		Reference	
MRI PSAD	0.15 (0.05–0.49)	0.0018	0.26 (0.08–0.85)	0.0255	0.21 (0.03–1.43)	0.1112
Endorectal coil[a]						
No	1.34 (1.07–1.68)	0.0108	1.09 (0.74–1.61)	0.6695	0.94 (0.55–1.61)	0.8231
Yes	Reference		Reference		Reference	
Gleason pattern						
3 + 3	16.11 (8.88–29.20)	<0.0001	3.86 (1.89–7.89)	0.0002	N/A	–
3 + 4	2.53 (1.39–4.60)	0.0023	2.01 (1.01–4.01)	0.0463	1.06 (0.62–1.84)	0.8260
4 + 3	1.28 (0.66–2.51)	0.4557	1.70 (0.79–3.64)	0.1759	0.63 (0.30–1.36)	0.2431
≥8	Reference		Reference		Reference	
Pathologic stage						
T2	1.68 (1.32–2.15)	<0.0001				
T3/T4	Reference					
Index status						
Nonindex	10.29 (7.84–13.51)	<0.0001	2.68 (1.77–4.07)	<0.0001	2.25 (1.31–3.85)	0.0032
Index	Reference		Reference		Reference	
Tumor focality						
Multifocal	7.04 (4.93–10.05)	<0.0001	1.92 (1.23–3.01)	0.0042	1.92 (1.15–3.19)	0.0124
Solitary	Reference		Reference		Reference	
MRI with SPY						
Yes	1.80 (0.80–4.04)	0.1551				
No	Reference					

CI = confidence interval; csCaP = clinically significant prostate cancer; MRI = magnetic resonance imaging; OR = odds ratio; PSAD = prostate-specific antigen density; PV = prostate volume; SPY = spectroscopy; TD = tumor diameter.
[a] Adjusted for interaction between timing of MRI.

+ 4 with cancer core length ≥6 mm as the csCaP definition) and result in at least one missed csCaP focus in 34–45% of men undergoing radical prostatectomy. While the true clinical significance of these missed tumor foci remains uncertain, our data suggest that a considerable proportion of missed solitary (23%) and multifocal (7%) tumors harbor predominantly pattern 4 pathology. In addition, while the highest grade pathology typically resided in the largest tumor, a smaller lesion contained the most aggressive pathology in 11% (42/372), suggesting that systematic biopsy remains important for active surveillance, patient selection, and focal therapy treatment planning despite its inherent sampling error [22,23].

Our multivariable analysis confirms prior findings that mpMRI performs better in detecting larger, higher-grade index tumors [17,24–26]. In contrast to our previous findings, multifocal tumors, including clinically significant foci, are more likely to be missed than solitary tumors.

Our study has several limitations, primarily stemming from the selection bias inherent to a surgical population required for WMP analysis. While this bias probably contributes to the high PPV of mpMRI, we believe that eliminating biopsy sampling errors outweighs this potential bias when considering our study objective. We acknowledge the potential for bias in the retrospective PI-RADS v.2 scoring. However, statistical analyses of linear time trends and detection rates before and after the date of PI-RADS v.2 adoption were non-significant, indicating that this bias is unlikely to meaningfully affect our results. Second, we did not report specificity as this would have required calculation of true negative rates for each MRI-negative segment. The overall true negative population is unknown because all men in this database had biopsy-proven CaP. Third, our objective was to characterize tumor detection by mpMRI only so we did not incorporate biopsy results into sensitivity calculations. Fourth, mpMRI-pathologic concordance relies on an imperfect system of co-registration, as it is not feasible to match the pathologic tumors according to the 39-sector PI-RADS v.2 sector map [27]. However, we believe that our technique affords the most accurate method possible for direct comparison of mpMRI with pathologic findings. Fifth, we considered a PI-RADS v.2 score ≥3 as a positive radiographic ROI. While this is an accepted clinically relevant cutoff, PI-RADS v.2 1–2 lesions occasionally harbor CaP, and excluding them may falsely decrease our sensitivity [28]. Sixth, we included patients who underwent mpMRI with and without an endorectal coil (ERC). Radiologists may be biased by the knowledge that an ERC was predominantly used for presurgical planning, which, along with higher pretest probability of csCaP, may partly account for the higher detection rate with an ERC. However, after adjusting for MRI timing (pre- vs post-biopsy), ERC use was no longer associated with detection and the interaction between mpMRI timing and ERC for detection of csCaP is not significant. Seventh, our results are from a high-volume academic institution with significant expertise in image acquisition and prostate mpMRI interpretation, potentially rendering our detection rates optimistic compared to lower-volume, less-experienced community centers. Furthermore, our institution has longstanding quality control protocols to ensure optimal image acquisition for all mpMRI scanners and maintain high-quality training of mpMRI technicians, which may be lacking at lower-volume, less-experienced community imaging centers. Lastly, the oncologic implication of missed lesions is indeterminate, as all patient underwent definitive extirpative surgery. In particular, the clinical significance of minimal pattern 4 pathology is controversial and multifactorial [29,30]. Nonetheless, image guidance remains useful for CaP diagnosis and treatment. Further imaging advances and greater experience may improve per-lesion detection and reduce uncertainty associated with active surveillance and focal therapy.

5. Conclusions

On a per-lesion basis, mpMRI has moderate sensitivity for detecting CaP and csCaP, and multifocality appears to increase the odds of missed tumors on mpMRI. A substantial percentage of missed lesions are clinically significant, and mpMRI misses at least one csCaP in nearly half of patients. Despite significant progress and greater experience, prostate mpMRI has room to improve. Our findings underscore the need to further refine risk stratification methods and support the continued use of systematic biopsy. Ongoing studies will help to elucidate the pathophysiologic mechanisms behind MRI-invisible lesions and their clinical significance.

Author contributions: David C. Johnson had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Johnson, Mirak, Raman, Reiter.
Acquisition of data: Johnson, Mirak, Kwan, Bajgiran, Hsu, Maehara, Ahuja, Felker, Raman, Reiter.
Analysis and interpretation of data: Johnson, Kwan, Raman, Reiter.
Drafting of the manuscript: Johnson, Mirak, Kwan.
Critical revision of the manuscript for important intellectual content: Johnson, Faiena, Pooli, Raman, Reiter.
Statistical analysis: Kwan.
Obtaining funding: Johnson, Raman, Reiter.
Administrative, technical, or material support: Bajgiran, Hsu, Maehara, Ahuja.
Supervision: Raman, Reiter.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.11.031.

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Radtke JP, Wiesenfarth M, Kesch C, et al. Combined clinical parameters and multiparametric magnetic resonance imaging for advanced risk modeling of prostate cancer—patient-tailored risk stratification can reduce unnecessary biopsies. Eur Urol 2017;72:888–96.
[3] Mehralivand S, Shih JH, Rais-Bahrami S, et al. A magnetic resonance imaging-based prediction model for prostate biopsy risk stratification. JAMA Oncol 2018;4:678–85.
[4] Moldovan PC, Van den Broeck T, Sylvester R, et al. What is the negative predictive value of multiparametric magnetic resonance imaging in excluding prostate cancer at biopsy? A systematic review and meta-analysis from the European Association of Urology prostate cancer guidelines panel. Eur Urol 2017;72:250–66.
[5] Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. N Engl J Med 2018;378:1767–77.
[6] Sonn GA, Chang E, Natarajan S, et al. Value of targeted prostate biopsy using magnetic resonance–ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen. Eur Urol 2014;65:809–15.
[7] Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging–ultrasound fusion targeted biopsy: a systematic review. Eur Urol 2015;68:8–19.
[8] Tonttila PP, Lantto J, Pääkkö E, et al. Prebiopsy multiparametric magnetic resonance imaging for prostate cancer diagnosis in biopsy-naive men with suspected prostate cancer based on elevated prostate-specific antigen values: results from a randomized prospective blinded controlled trial. Eur Urol 2016;69:419–25.
[9] Pessoa RR, Viana PC, Mattedi RL, et al. Value of 3-Tesla multiparametric magnetic resonance imaging and targeted biopsy for improved risk stratification in patients considered for active surveillance. BJU Int 2017;119:535–42.
[10] Fütterer JJ, Briganti A, De Visschere P, et al. Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging?. A systematic review of the literature. Eur Urol 2015;68:1045–53.
[11] Felker ER, Wu J, Natarajan S, et al. Serial magnetic resonance imaging in active surveillance of prostate cancer: incremental value. J Urol 2016;195:1421–7.
[12] Frye TP, George AK, Kilchevsky A, et al. Magnetic resonance imaging-transrectal ultrasound guided fusion biopsy to detect progression in patients with existing lesions on active surveillance for low and intermediate risk prostate cancer. J Urol 2017;197:640–6.
[13] de Rooij M, Hamoen EHJ, Witjes JA, Barentsz JO, Rovers MM. Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 2016;70:233–45.

[14] McClure TD, Margolis DJA, Reiter RE, et al. Use of MR imaging to determine preservation of the neurovascular bundles at robotic-assisted laparoscopic prostatectomy. Radiology 2012;262:874–83.
[15] American College of Radiology. PI-RADS™ Prostate Imaging-Reporting and Data System. ACR; 2015 www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2.pdf?la=en
[16] Kryvenko ON, Epstein JI. Improving the evaluation and diagnosis of clinically significant prostate cancer. Curr Opin Urol 2017;27:191–7.
[17] Le JD, Tan N, Shkolyar E, et al. Multifocality and prostate cancer detection by multiparametric magnetic resonance imaging: correlation with whole-mount histopathology. Eur Urol 2015;67:569–76.
[18] Nassiri N, Chang E, Lieu P, et al. Focal therapy eligibility determined by magnetic resonance imaging/ultrasound fusion biopsy. J Urol 2018;199:453–8.
[19] Borofsky S, George AK, Gaur S, et al. What are we missing? False-negative cancers at multiparametric MR imaging of the prostate. Radiology 2018;286:186–95.
[20] Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815–22.
[21] Thompson JE, van Leeuwen PJ, Moses D, et al. The diagnostic performance of multiparametric magnetic resonance imaging to detect significant prostate cancer. J Urol 2016;195:1428–35.
[22] Filson CP, Natarajan S, Margolis DJA, et al. Prostate cancer detection with magnetic resonance-ultrasound fusion biopsy: the role of systematic and targeted biopsies. Cancer 2016;122:884–92.
[23] Catto JWF, Robinson MC, Albertsen PC, et al. Suitability of PSA-detected localised prostate cancers for focal therapy: experience from the ProtecT study. Br J Cancer 2011;105:931–7.
[24] Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. Eur Radiol 2013;23: 2019–2029.
[25] Turkbey B, Mani H, Shah V, et al. Multiparametric 3 T prostate magnetic resonance imaging to detect cancer: histopathological correlation using prostatectomy specimens processed in customized magnetic resonance imaging based molds. J Urol 2011;186: 1818–1824.
[26] Rosenkrantz AB, Mendrinos S, Babb JS, Taneja SS. Prostate cancer foci detected on multiparametric magnetic resonance imaging are histologically distinct from those not detected. J Urol 2012;187: 2032–2038.
[27] Isebaert S, Van den Bergh L, Haustermans K, et al. Multiparametric MRI for prostate cancer localization in correlation to whole-mount histopathology. J Magn Reson Imaging 2013;37:1392–401.
[28] Wysock JS, Mendhiratta N, Zattoni F, et al. Predictive value of negative 3 T multiparametric magnetic resonance imaging of the prostate on 12-core biopsy results. BJU Int 2016;118:515–20.
[29] Trock BJ, Guo CC, Gonzalgo ML, Magheli A, Loeb S, Epstein JI. Tertiary Gleason patterns and biochemical recurrence after prostatectomy: proposal for a modified Gleason scoring system. J Urol 2009;182: 1364–1370.
[30] Schraml P, Struckmann K, Hatz F, et al. VHL mutations and their correlation with tumour cell proliferation, microvessel density, and patient prognosis in clear cell renal cell carcinoma. J Pathol 2002;196:186–93.