Research Article

Diagnostic yield of multiparametric MRI for local recurrence at biochemical recurrence after radical prostatectomy

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A R T I C L E   I N F O

A B S T R A C T

Purpose: To validate the diagnostic yield of multiparametric magnetic resonance imaging (mpMRI) for local biochemical recurrence after radical prostatectomy in patients with biochemical recurrence using large consecutive patient data.

Materials and methods: Of 4632 patients who underwent radical prostatectomy for prostate adenocarcinoma, 748 patients with prostate-specific antigen > 0.2 ng/mL and second confirmatory level were retrospectively identified. Among them, 468 patients who underwent multiparametric magnetic resonance imaging were analyzed. The primary outcome measure was the diagnostic yield of multiparametric magnetic resonance imaging for local recurrence, and the secondary measure was its accuracy, using the response to salvage radiotherapy as reference.

Results: Only 33 patients (7.1%) showed positive imaging findings. The positive and negative predictive values were 84.8% (28/33) and 37.5% (45/120), respectively. The sensitivity and specificity were 27.2% (28/103) and 90% (45/50), respectively. The overall accuracy was 47.7% (73/153). In multivariate logistic regression analysis, prostate-specific antigen level at recurrence was found to be the only factor significantly higher in the positive image findings group.

Conclusions: The universal use of multiparametric magnetic resonance imaging resulted in a low-diagnostic yield for local recurrence in patients with biochemical recurrence after radical prostatectomy. The results suggest that selective use of multiparametric magnetic resonance imaging should be considered in patients with a higher prostate-specific antigen threshold.

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1. Introduction

Radical prostatectomy (RP) is the primary treatment modality for localized prostate cancer. According to the guidelines of the American Urological Association/American Society for Radiation Oncology, biochemical recurrence (BCR) after radical prostatectomy is defined as a serum prostate-specific antigen (PSA) $\geq$ 0.2 ng/mL followed by a second confirmatory level.[1] BCR indicates a high risk of progression of PSA[2] and implies the presence of either locally recurrent or distant disease. In general, guidelines recommend that physicians offer salvage radiotherapy (SRT) to patients with BCR and no evidence of distant metastatic disease.[1,3]

Over the past 20 years, several studies have investigated the ability of multiparametric magnetic resonance imaging (mpMRI) to detect locally recurrent tumors after RP.[4–16] Its reported sensitivity and specificity vary, but mostly range between 80 and 100%, showing high diagnostic yield and accuracy in localizing the recurrent tumors. Nevertheless, there are no established guidelines for the use of MRI to guide SRT in patients with BCR. Since accurate localization of a recurrent tumor may potentially benefit patients by minimizing or avoiding unnecessary radiation exposure through a more targeted therapy, it is important that MRI shows consistent high yield and accuracy for detecting local recurrence in patients with BCR.

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However, in most studies, the selection process of the study population has not been clearly described, raising the fundamental question of whether it properly represents the target population. Furthermore, the study population usually involved less than 100 participants, with a few exceptions analyzing up to a maximum 262 patients.[9] This study aimed to validate the diagnostic performance of multiparametric MRI after RP in a large cohort of patients with BCR.

2. Methods

2.1. Patient Selection

This retrospective observational study was approved by the institutional review board, which waived the requirement for informed consent owing to its retrospective nature. A total of 4632 patients who underwent radical prostatectomy for prostate adenocarcinoma between January 2005 and June 2020 were retrospectively enrolled. Among them, 748 patients with initial baseline PSA levels < 0.2 ng/mL which increased thereafter over that threshold and followed by a second confirmatory PSA level

were identified. Of these, 473 patients underwent mpMRI within one month of the second confirmatory PSA test. The remaining 275 patients who did not undergo MRI were excluded from the study. Of 473 patients with mpMRI, five patients were excluded due to lack of contrast-enhanced imaging results (n = 3) and poor image quality (n = 2). A flowchart of the patient selection process is shown in Fig. 1.

2.2. MRI Protocol

MRI examinations were performed using a 3-Tesla scanner (Achieva or Ingenia, Philips, the Netherlands) or a 1.5-Tesla scanner (Amira, Siemens, Germany) with a 6-channel external phased array coil. Sequences included triplanar T2 weighted images (TR, 2500−3000 ms; TE, 70−90 ms; slice thickness, 3 mm; interslice gap, 1 mm; field of view, 160 × 160 mm; matrix, 320 × 320; and number of excitations, 1), axial T1 weighted images, and axial diffusion-weighted images (DWI; b-values 0, 100, 1000, or 1500 s/mm^2). Dynamic contrast-enhanced acquisition (DCE) was used in 137 of 468 patients and obtained by axial 3D gradient-echo-fat-suppressed sequence after IV administration of 0.1 mmol/kg
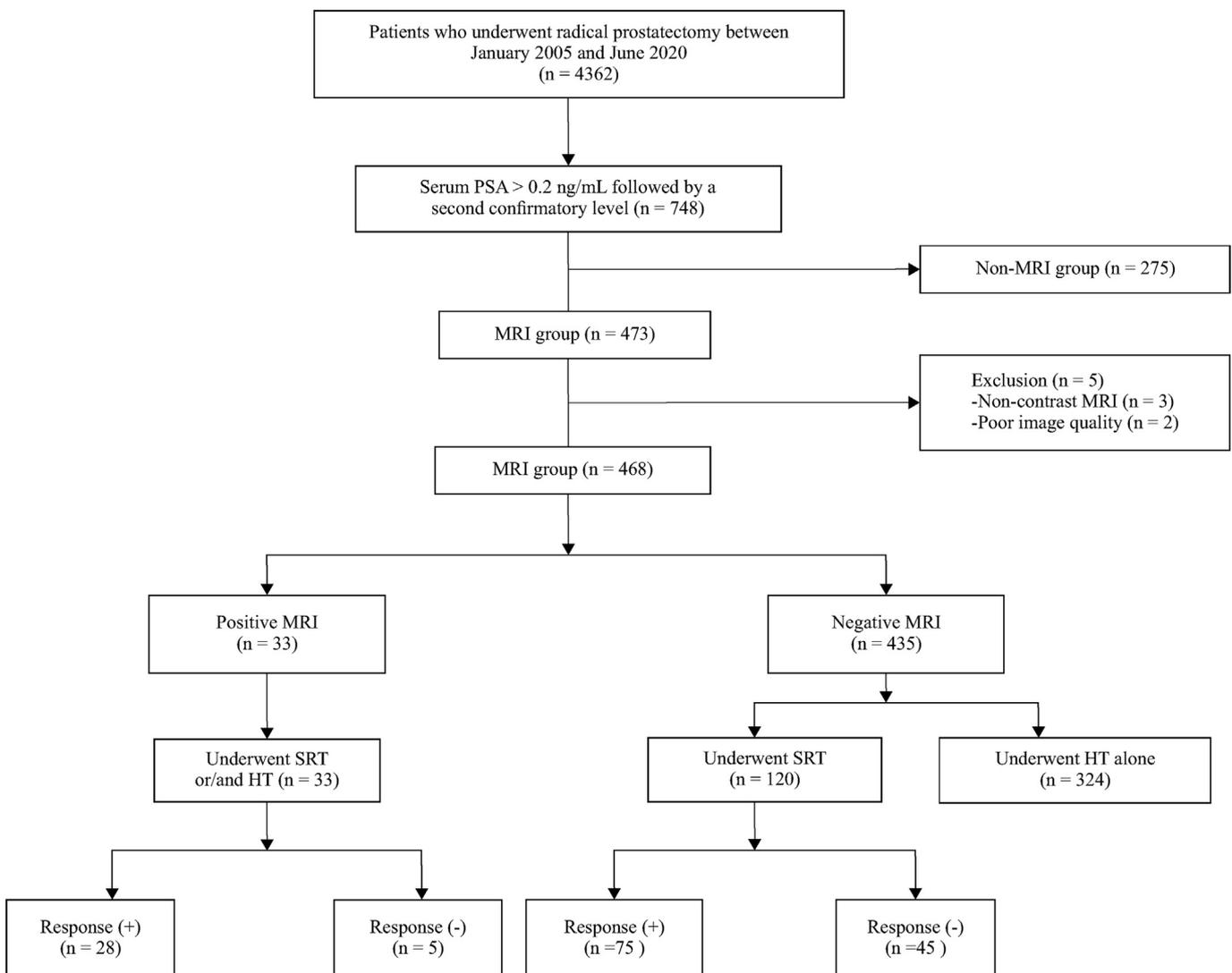

Fig. 1. A flowchart of the patient selection process.

Table 1
Baseline clinical and pathologic characteristics of the study population

	MRI group (N = 468)	Non-MRI group (N = 275)	*P*-value
Mean age (in yr)	66.2 ± 6.9	66.2 ± 6.6	0.993
Mean preop PSA (in ng/mL)	26.3 ± 108.2	19.8 ± 28.4	0.343
Mean postop nadir PSA (in ng/mL)	0.0 ± 0.0	0.0 ± 0.0	0.937
Mean PSA at BCR (in ng/mL)	1.3 ± 4.6	1.0 ± 2.6	0.257
Mean time to BCR from RP (in d)	1042.7 ± 820.5	1100.4 ± 865.3	0.371
PSADT (in mo)	3.9 ± 55.3	5.3 ± 20.7	0.615
Adjuvant RT before MRI	33 (7.1%)	17 (6.2%)	0.762
Gleason's score			0.522
6	5 (1.1%)	5 (1.8%)	
7	291 (62.2%)	175 (63.6%)	
8	42 (9.0%)	30 (10.9%)	
9	130 (27.7%)	65 (23.6%)	
T stage			0.800
pT2	155 (33.7%)	99 (36.0%)	
pT3	299 (65.0%)	173 (62.9%)	
pT4	6 (1.3%)	3 (1.1%)	
pN1	33 (7.1%)	18 (6.5%)	0.881
Positive margin	225 (48.1%)	150 (54.5%)	0.095
Capsular penetration	298 (63.7%)	170 (61.8%)	0.637
Invasion to bladder neck	62 (13.2%)	27 (9.8%)	0.198
Seminal vesicle invasion	153 (32.7%)	71 (25.8%)	0.057

Data are presented as mean ± standard deviation or n (%).
PSADT, PSA doubling time; BCR, biochemical recurrence; RP, radical prostatectomy

gadopentetate dimeglumine. In the other 331 patients, single-phase contrast enhancement was acquired 180–210 s after IV administration of 0.1 mmol/kg gadopentetate dimeglumine.

2.3. MR Image Analysis

Two radiologists (reader 1 with 3 years and reader 2 with 20 years of experience in prostate MR image interpretation, respectively) analyzed the MR images independently and retrospectively, blinded to clinical information except for the presence of BCR before reviewing the cases. After independently analyzing the images, a final consensus was reached. MRI was interpreted by the prostate magnetic resonance imaging for local recurrence reporting (PI-RR),[17] and an imaging score of 4 or 5 was regarded as positive for local recurrence. Accordingly, 1) any focal or mass-like dynamic early enhancement or 2) non-dynamic enhancement plus focal marked hyperintensity on DWI and marked hypointensity on the ADC map, were regarded as positive for local recurrence.

2.4. Standard of Reference

Response to SRT or hormonal therapy was used as a standard of reference, considering that radiotherapy is highly effective in degrading tumors including their neo-vascularization.[10] The presence of local recurrence was confirmed when 1) the tumor size decreased on positive MRI after SRT or hormonal therapy with a 50% reduction in PSA levels, or 2) a 50% reduction in PSA levels was observed in patients with negative MRI after SRT.

2.5. Statistical Analysis

Inter-reader reproducibility was evaluated by calculating the κ coefficients. κ coefficients between 0–0.20, 0.21–0.40, 0.41–0.60, 0.61–0.80, and 0.81–1.00, indicate no to slight, fair, moderate, substantial, and almost perfect agreement, respectively.[18] The diagnostic yield, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated for mpMRI. We also compared several clinical and pathological characteristics between the MRI and non-MRI groups and between the positive and negative MRI groups. Postoperative nadir PSA level

was defined as the lowest PSA level first measured after radical prostatectomy and before BCR. PSA doubling time was calculated as described by Pound et al.[19] using PSA levels and the time interval (months) between the first and second measurements of BCR. For continuous variables, we used Student's t-test between the MRI and non-MRI groups and the Mann–Whitney U-test between the positive and negative MRI groups. The chi-squared test was used for categorical data. Logistic regression analysis with enter method was used for comparison between positive MRI group with negative MRI group. Statistical significance was set at P < 0.05. All statistical analyses were performed using IBM SPSS Statistics, version 20 (IBM Corporation, Somers, NY, USA).

3. Results

3.1. Clinical and pathological characteristics in the MRI and non-MRI groups

The mean age in the MRI group (n = 468) was 66.2 ± 6.9 years, which was not significantly different from that in the non-MRI group (n = 275, 66.2 ± 6.6, p = 0.993). There was no significant difference in mean preoperative PSA levels (ng/mL) (26.3 ± 108.2 vs. 19.8 ± 28.4, p = 0.343), postoperative nadir PSA levels (ng/mL) (0.0 ± 0.0 vs. 0.0 ± 0.0, p = 0.937), PSA levels at BCR (ng/mL) (1.3 ± 4.6 vs. 1.0 ± 2.6, p = 0.257) and mean time (days) to BCR from radical prostatectomy (1042.7 ± 820.5 vs. 1100.4 ± 865.3, p = 0.371), respectively.

Gleason scores 7 (62.2%) and pT3 (65.0%) were found in most patients in the MRI group, followed by Gleason's score 9 (27.7%) and pT2 (33.7%). The proportions of other pathological features were as follows: pN1 (7.1%), positive resection margin (48.1%), capsular penetration (63.7%), invasion to bladder neck (13.2%), and seminal vesicle invasion (32.7%), which were not significantly different from those in non-MRI group. Table 1 shows the clinical and pathological characteristics of the MRI and non-MRI group.

3.2. MRI diagnostic yield and accuracy

Among the 468 patients who underwent MRI, reader 1 interpreted 24 cases of MRI positivity, while reader 2 interpreted 30
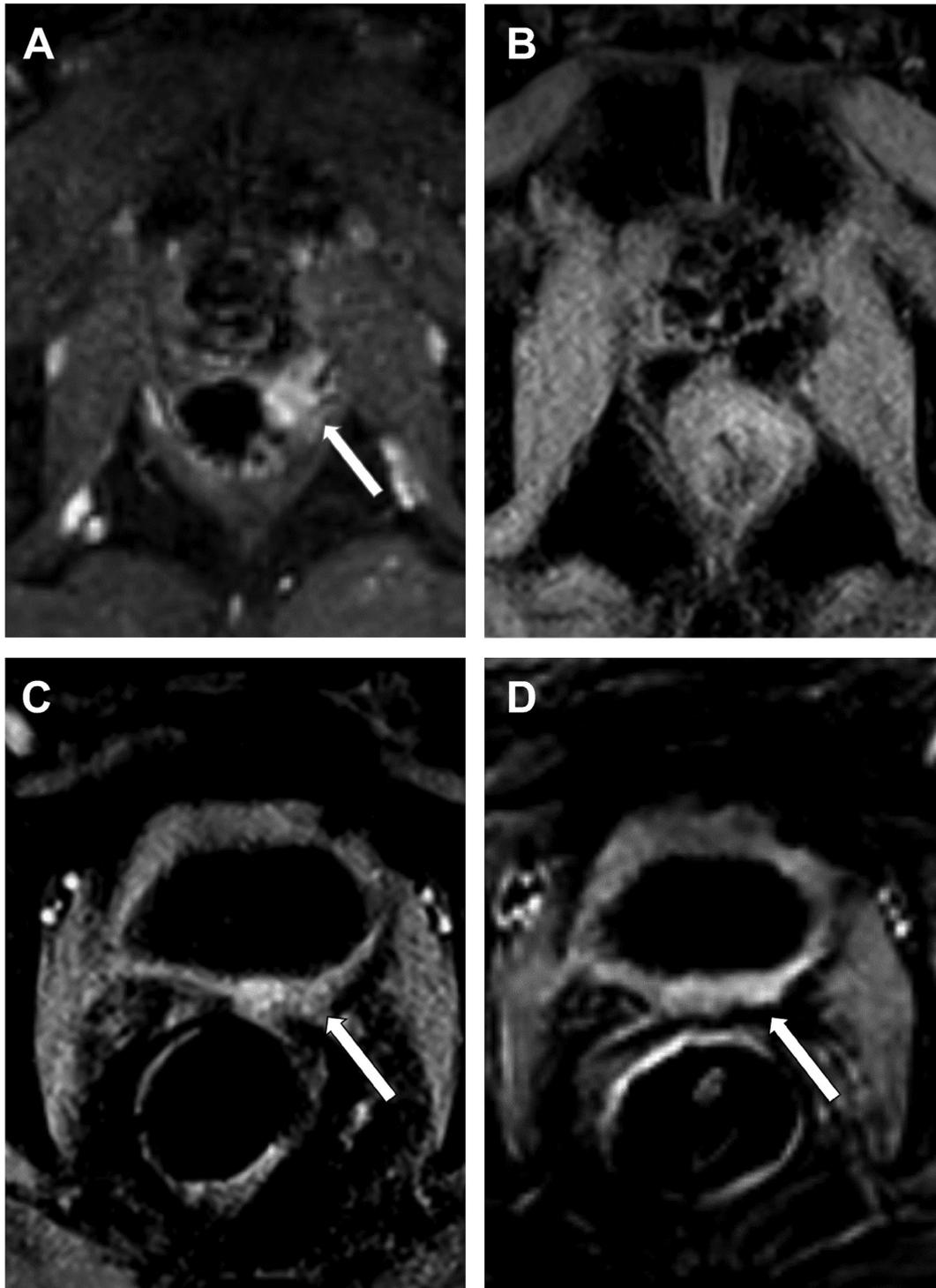
Fig. 2. A. A 64-year-old patient with prostate-specific antigen (PSA) level of 0.342 ng/mL after radical prostatectomy. Dynamic contrast-enhanced (DCE) MRI shows early enhancement of a 15 × 8-mm mass-like lesion at the left-sided vesicourethral junction. B. After undergoing salvage radiotherapy, the PSA level decreased to 0.018 ng/mL. Follow-up DCE MRI demonstrates disappearance of the lesion, suggestive of a true-positive lesion.

cases of MRI positivity. The inter-reader agreement was substantial ($\kappa = 0.80$, p < 0.05). Final consensus led to confirm 33 (7.1%) of 468 MRIs as positive and the other 435 as negative (Fig. 1). When different PSA cutoff values for BCR were applied, the prevalence of positive MRI was as follows: 10.1% (22/217) for PSA $\geq$ 0.4, 13.0% (9/69) for PSA $\geq$ 1.0, 50.0% (5/10) for PSA $\geq$ 10.0, and 5.0% (1/20) for PSA $\geq$ 20.0. In a subgroup analysis by different MRI methods (combination of DCE, single phase, 3T, and 1.5T), the prevalence of positive MRI was as follows: 7.9% (5/63) for 3T DCE, 6.8% (5/74) for 1.5T DCE, 5.6% (12/214) 3T single phase, and 9.4% (11/117) for 1.5T single phase study. No significant difference was observed in the proportion of positive MRI findings by MRI methods (p > 0.05).

Table 2
Comparison of clinical and pathologic characteristics between positive and negative MRI

	Positive MRI (N = 33)	Negative MRI (N = 435)	*P*-value
Mean age (in yr)	68.2 ± 7.5	66.02 ± 6.8	0.097
Mean preop PSA (in ng/mL)	20.7 ± 28.3	19.8 ± 28.5	0.636
Mean postop nadir PSA (in ng/mL)	0.0 ± 0.0	0.0 ± 0.0	0.159
Mean PSA at BCR (in ng/mL)	4.5 ± 11.3	1.0 ± 3.5	0.004
Mean time to MRI from RP (in d)	1196.3 ± 957.0	1034 ± 808.1	0.383
PSADT (in mo)	1.3 ± 22.9	4.1 ± 57.1	0.463
Adjuvant RT before MRI	0 (0%)	33 (7.6%)	0.154
Gleason's score (all)			0.061
6	0 (0.0%)	5 (1.1%)	
7	15 (45.5%)	276 (63.4%)	
8	3 (9.1%)	39 (9.0%)	
9	15 (45.5%)	115 (26.4%)	[a]0.026
T stage			0.051
pT2	12 (38.7%)	143 (32.9%)	
pT3	18 (58.1%)	287 (66.0%)	
pT4	1 (3.2%)	5 (1.1%)	
pN1	4 (12.1%)	29 (6.7%)	0.277
Positive margin	19 (57.6%)	206 (47.4%)	0.282
Capsular penetration	20 (60.6%)	278 (63.9%)	0.710
Invasion to bladder neck	9 (27.3%)	53 (12.2%)	0.028
Seminal vesicle invasion	17 (51.5%)	136 (31.3%)	0.021

Statistical significance test was done by Mann–Whitney U-test for continuous variables.
Data are presented as mean ± standard deviation or n (%).
PSADT, PSA doubling time; BCR, biochemical recurrence; RP, radical prostatectomy
[a] When only the proportion of Gleason's score 9 were compared.

Additionally, subgroup analysis by Tesla showed no significant difference in proportions of positive findings (6.1%, 17/277 in 3T MRI group vs 8.4%, 16/191 in 1.5T MRI group, p > 0.05).

Thirty-three patients with positive MRI findings underwent salvage RT and/or HT. Among them, 28 patients showed size reduction of the presumed recurrent tumors, with > 50% decrease in PSA levels. Among the 435 patients with negative MRI findings, 120 initially underwent RT. Of these, 75 patients showed > 50% decrease in follow-up PSA levels, whereas the other patients showed persistent elevation in PSA levels. Using response to salvage treatment as reference, the positive and negative predictive values of MRI for detection of local recurrence were 84.8% (28/33) and 37.5% (45/120), respectively. The sensitivity and specificity of MRI for detection of local recurrence were 27.2% (28/103) and 90% (45/50), respectively. The overall accuracy was 47.7% (73/153).

3.3. MRI findings of local recurrence

Thirty-three cases of local recurrence showed a mass with an average size of 14 mm along the long diameter (range: 5–30 mm). The most frequent location was the vesicourethral junction (27/33), followed by the bladder wall (6/33), and vas deference (2/33) (Fig. 2A and B). In five cases of false-positive MRI, focal nodular dynamic enhancement did not show significant change in size, morphology, or enhancement pattern on follow-up MRI, after SRT, or a decrease in PSA levels (Fig. 2C and D).

3.4. Comparison of positive and negative MRI

Both clinical and pathological features between patient groups with positive and negative MRI findings are compared with univariate analysis in Table 2. The mean PSA level at the BCR in the positive MRI group was significantly higher than that in the negative MRI group (4.5 ± 11.3 vs. 1.0 ± 3.5 ng/mL, p < 0.01). Regarding pathological characteristics, significantly higher proportions of patients in the positive MRI group showed a Gleason score 9 (45.5% vs. 26.4%, p < 0.05), seminal vesicle invasion (51.3% vs. 31.3%, p < 0.05), and bladder neck invasion (27.3% vs. 12.2%, p < 0.05) than

the negative MRI group. There were no other significant differences between groups in terms of age, preoperative PSA levels, or postoperative nadir PSA levels, nor were there no significant differences in pathological T staging or other pathological features.

On multivariate logistic regression analysis, however, only PSA level at recurrence was significantly higher in the positive MRI group (p = 0.02), among other clinical and pathologic factors (Table 3).

4. Discussion

To the best of our knowledge, our study included the largest number of patients (n = 468) with BCR after RP who underwent mpMRI so far. Multiparametric MRI showed low prevalence (7.1%) and sensitivity (27.2%) in our study. In subgroup analysis, different MRI methods did not affect the diagnostic yield.

These results are far lower than those of previous studies that demonstrated the high diagnostic performance of mpMRI. Casciani et al. analyzed DCE-MRI in 51 patients with suspected local recurrence after RP, demonstrating 88% sensitivity and 100% specificity.[4] Panebianco et al. included the highest number of patients (n = 262) with BCR, showing 98–100% sensitivity and 94–97% specificity of combined T2-weighted and DCE-MRI, and 93–94% sensitivity and 89–92% specificity of combined T2-weighted and DWI(b value, 1,000 s/mm^2).[9] In a meta-analysis conducted by Wu et al., the pooled sensitivity and specificity of MRI after RP in detection of local recurrence were 82% and 87%, respectively,[16] while in a subgroup analysis, DCE MRI showed higher pooled sensitivity (85%) and specificity (95%) than T2-weighted imaging.

The low-diagnostic yield and sensitivity of mpMRI in our study could be mainly attributed to our study population, which differed with respect to the selection process and number. Most prior studies lacked a description of the selection process for patients who underwent RP showing BCR thereafter. The data in our study represent patients followed up since RP was found to have BCR thereafter and underwent MRI. In addition, > 60% of the patients with BCR (473/748) underwent mpMRI owing to the high availability of MR scanning in the national health care system.

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Table 3
Association of positive MRI with clinical or pathologic features by logistic regression analysis

	OR (CI 95%)	*P*-value
Mean age	1.02 (0.89–1.023)	0.231
Mean preop PSA	0.998 (0.983–1.012)	0.873
Mean postop nadir PSA	0.820 (0.899–1.233)	0.110
Mean PSA at BCR	1.260 (1.109–1.413)	0.020
Mean time to MRI from RP	1.011 (0.989–1.001)	0.383
PSADT	0.991 (0.772–1.023)	0.235
Adjuvant RT before MRI	0.683 (0.232–1.231)	0.113
T2	0.903 (0.910–1.023)	0.645
T3	1.112 (0.72–2.301)	0.167
T4	0.829 (0.520–2.432)	0.121
Gleason's score 6	1.333 (0.553–2.830)	0.523
Gleason's score 7	0.770 (0.428–1.540)	0.783
Gleason's score 8	1.430 (0.728–1.297)	0.422
Gleason's score 9	1.526 (0.658–3.540)	0.408
pN1	1.057 (0.273–4.094)	0.277
Positive margin	0.864 (0.350–2.134)	0.282
Capsular penetration	1.473 (0.423–3.212)	0.231
Invasion to bladder neck	1.720 (0.668–4.431)	0.222
Seminal vesicle invasion	1.411 (0.592–3.367)	0.287

Enter method was used in logistic regression analysis.
CI: confidence interval; OR: odds ratio
PSADT, PSA doubling time; BCR, Biochemical recurrence; RP, radical prostatectomy

Compared with the non-MRI group, the MRI group showed no significant differences in either clinical or pathologic characteristics as presented by Table 1, implying that the study population is randomized. In most of the patients in our study, BCR was detected at very early stages, as reflected by > 50% patients (251/468) having PSA levels < 0.4 ng/mL at the time of MRI. Few previous studies included patients with mean or median PSA levels at BCR ≤ 0.4 ng/mL[14, 16, 21]. In all these studies, the prevalence of local recurrence observed on mpMRI was < 25%.[13,15,20] While previous studies showed higher rate of BCR in patients with high Gleason scores or/and positive surgical margin,[21,22] both univariate and multivariate analysis of our study showed significantly higher PSA level at recurrence in the positive MRI group than negative MRI group. Considering low-diagnostic yield of MRI in our study population altogether, these results suggest MRI should be restricted to patients with higher PSA at BCR. Future multicenter prospective studies analyzing cost-effectiveness are needed to consolidate these results and provide evidence for more specific indications for mpMRI at BCR.

Another reason for the low-diagnostic performance of mpMRI may be MRI data interpretation. Unlike the prostate imaging reporting and data system (PI-RADS) version 2.1, where DCE plays a minor role in providing additional information on DWI or T2WI findings than in detecting prostate cancer,[23] localization of recurrent tumors after RP largely depends on DCE.[17] In our study, the surgical bed after RP showed not only areas of delayed enhancement but also some areas of arterial enhancement on DCE unchanged in size and morphology after SRT and associated with a decrease in PSA levels. To evaluate the true positive predictive value of DCE, further studies are warranted to compare the results between BCR and non-BCR patients after radiologists interpret DCE and other imaging sequences (DWI and T2WI) blinded to BCR status.

This study had some limitations. First, it was a retrospective study conducted at a single institution. Second, among the 435 patients with negative MRI findings, only 153 underwent SRT, which was used as a reference standard to calculate the sensitivity and negative predictive value.

In conclusion, the universal application of mpMRI at BCR showed low-diagnostic performance in detecting local recurrence after RP. The present results suggest that selective application of mpMRI should be considered in patients with higher PSA levels. Further prospective and comparative studies are required to validate the diagnostic performance of DCE-MRI.

Conflicts of interest

All authors have no disclosure of any relationship with industry for this study or have no conflict of interest to declare.

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