Original Study

Utility of Multiparametric Magnetic Resonance Imaging With PI-RADS, Version 2, in Patients With Prostate Cancer Eligible for Active Surveillance: Which Radiologic Characteristics Can Predict Unfavorable Disease?

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Abstract

We investigated the utility of multiparametric magnetic resonance imaging using Prostate Imaging Reporting and Data System version 2 (PI-RADSv2) in patients with prostate cancer eligible for active surveillance. We found that multiparametric magnetic resonance imaging with PI-RADSv2 has high negative predictive value in active surveillance candidates. Moreover, multiple PI-RADS 4-5 lesions were associated with unfavorable disease compared with solitary lesions, and multiple PI-RADS 5 lesions were strongly associated with Gleason score ≥ 4 + 3 or pathologic stage T3 disease.

Background: We investigated the utility of multiparametric magnetic resonance imaging (mpMRI) using Prostate Imaging Reporting and Data System, version 2 (PI-RADSv2), scoring in patients with prostate cancer eligible for active surveillance (AS). **Materials and Methods:** The medical records of the patients who had undergone mpMRI before radical prostatectomy from 2014 to 2018 were reviewed. All the patients had met the Prostate Cancer Research International AS criteria. PI-RADSv2 scores were assigned to 12 prostate regions. Unfavorable disease was stratified using the American Joint Committee on Cancer (AJCC) prognostic scale as stage IIB (Gleason score [GS], 3+4 and pathologic stage T2) and IIC-III (GS, ≥ 4+3 or pathologic stage T3). **Results:** Of 376 eligible patients, 184 (48.9%), 129 (34.3%), and 63 (16.8%) had AJCC stage I, IIB, and IIC-III disease, respectively. The patients with IIC-III disease were older and had a higher prostate-specific antigen density than those with stage I or IIB disease. PI-RADS 5 lesions were more frequent in patients with stage IIC-III than in patients with stage I or IIB disease. Multivariable analysis revealed that ≥ 2 lesions with a PI-RADS 5 score was an independent predictor for unfavorable disease (hazard ratio [HR], 3.612; $P < .001$ for IIB; HR, 6.562; $P < .001$ for IIC-III), and PI-RADS score of ≥ 4 was limited for predicting AJCC stage IIB disease (HR, 2.387; $P = .01$). **Conclusion:** mpMRI with PI-RADSv2 showed high negative predictive value for patients with prostate cancer eligible for AS. Multiple PI-RADS 4-5 lesions were associated with unfavorable disease compared with solitary lesions. Multiple PI-RADS 5 lesions were strongly associated with GS ≥ 4+3 or pathologic T3 disease. Targeted biopsy or radical treatment should be considered for these patients.

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Introduction

Active surveillance (AS) has emerged in the past decade as an acceptable option for patients with low-risk prostate cancer.[1] The new National Comprehensive Cancer Network guidelines have recommended AS for very low-risk and low-risk prostate cancer groups with life expectancies of ≥ 10 years. However, standardized criteria for determining AS eligibility have not yet been well established, and misclassification or reclassification has occurred for a significant number of AS candidates,[1-3] highlighting the importance of identifying clinically significant cancer before or during AS.

Multiparametric magnetic resonance imaging (mpMRI) plays an important role in AS programs owing to its high detection rate and high negative predictive value for significant prostate cancer.[4] For standardization of the interpretation and reporting of mpMRI, the European Society of Urogenital Radiology first reported the Prostate Imaging Reporting and Data System (PI-RADS) guidelines in 2012 and announced PI-RADS, version 2 (PI-RADSv2), in 2015 with fixes and complements to the problems that had appeared in the first version.[5] Recent studies have reported that MRI findings might be associated with clinically significant cancer in AS candidates.[6-9] However, the mpMRI factors and clinical parameters associated with unfavorable disease in patients eligible for AS have not yet been fully determined.

In the present study, we investigated the utility of mpMRI plus PI-RADSv2 scoring in patients with prostate cancer eligible for AS. We assessed the diagnostic accuracy of mpMRI for AS candidates. Moreover, we aimed to identify the mpMRI factors associated with unfavorable disease, including the number of MRI-positive lesions and PI-RADSv2 scores.

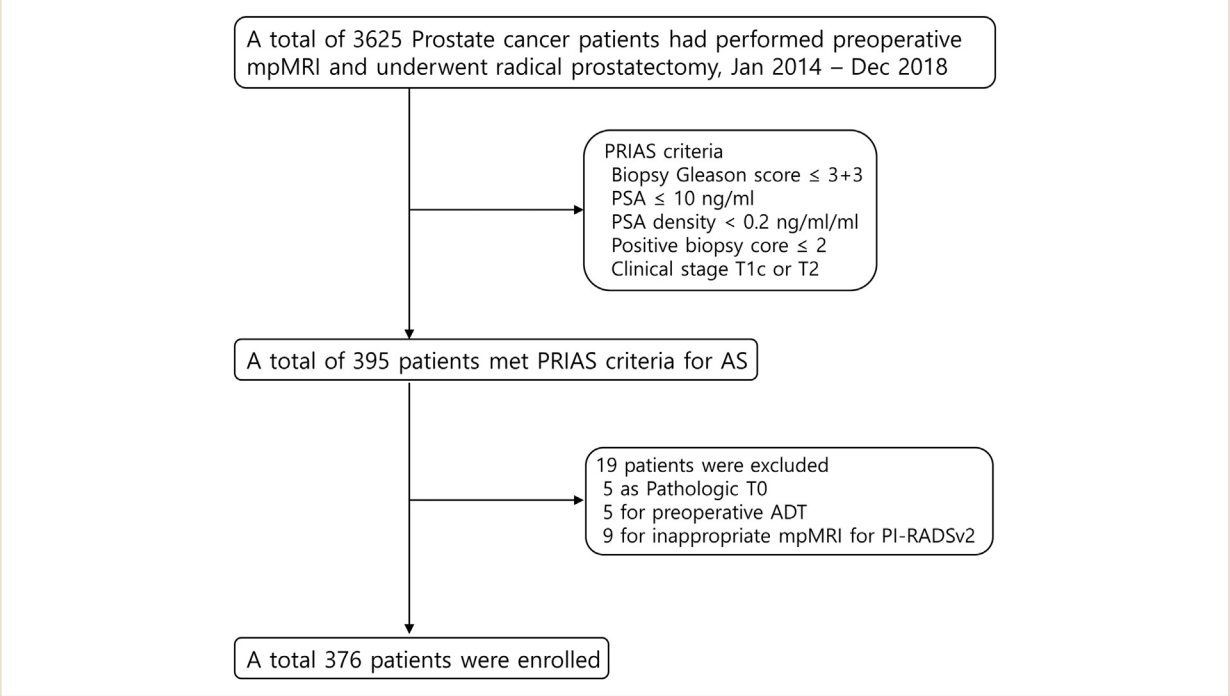
Materials and Methods

Study Design

The Asan Medical Center institutional review board approved the present retrospective study, which examined the medical records of patients with prostate cancer (approval no. 2017-1037). The medical records of 3625 patients who had undergone preoperative mpMRI and radical prostatectomy from January 2014 to December 2018 were reviewed. Of these 3625 patients, 395 had met the Prostate Cancer Research International: Active Surveillance (PRIAS) criteria (core needle biopsy Gleason score [GS], ≤ 6; prostate-specific antigen [PSA], ≤ 10 ng/mL; PSA density, < 0.2 ng/mL/mL; clinical stage T1c or T2; and positive biopsy cores, ≤ 2). Patients with pathologic T0 disease (n = 5), those who had received neoadjuvant therapy (n = 5), and those who had not undergone mpMRI according to the study protocol (n = 9) were excluded, for a total of 376 included men (Figure 1).

In the present study, unfavorable disease was defined using to the 8th edition of the American Joint Committee on Cancer (AJCC) criteria as prognostic stage IIB or ≥ IIC according to the pathology results.[10] The patients were divided into 3 groups as follows: pathologic T2 and GS 6 (AJCC stage I), pathologic T2 and GS 3+4 (AJCC stage IIB), and pathologic T3 or GS ≥ 4+3 (AJCC stage

Figure 1 Flow Chart of Study Enrollment



Abbreviations: ADT = androgen deprivation therapy; AS = active surveillance; mpMRI = multiparametric magnetic resonance imaging; PI-RADSv2 = Prostate Imaging Reporting and Data System, version 2; PRIAS = Prostate Cancer Research International: Active Surveillance; PSA = prostate-specific antigen.

Table 1 Clinical and Pathologic Information Eligible for PRIAS Criteria for AS (n = 376)

Variable	Overall	AJCC Stage			*P* Value
		I (n = 184)	IIB (n = 129)	≥ IIC (n = 63)	
Age, y	65.6 ± 6.7	64.7 ± 6.7	65.8 ± 6.5	67.9 ± 6.7	.004
BMI, kg/m^2	24.9 ± 2.6	25.1 ± 2.7	24.8 ± 2.4	24.8 ± 2.7	.463
PSA, ng/mL	4.65 ± 1.8	4.71 ± 1.9	4.59 ± 1.7	4.55 ± 1.6	.736
PSA density, ng/mL/mL	0.116 ± 0.04	0.108 ± 0.04	0.121 ± 0.04	0.125 ± 0.04	.004
Prostate volume, cm^3	43.3 ± 19.6	46.7 ± 21.6	39.8 ± 14.8	40.3 ± 19.6	.003
Tumor proportion on biopsy core, %	15.7 ± 14.6	12.6 ± 10.7	18.2 ± 17.6	19.9 ± 16.5	<.001
Pathologic stage		NA	NA	NA	NA
T2	342 (91.0)				
T3a	32 (8.5)				
T3b	2 (0.5)				
N1	0 (0)				
Pathologic Gleason score		NA	NA	NA	NA
6	189 (50.3)				
3+4	152 (40.4)				
4+3	30 (8.0)				
8	4 (1.1)				
9 (4+5)	1 (0.3)				
Index tumor location		NA	NA	NA	NA
Anterior	191 (50.8)				
Posterior	185 (49.2)				
Apex	145 (38.5)				
Mid-gland	215 (57.2)				
Base	16 (4.3)				

Data presented as mean ± standard deviation or n (%).
Abbreviations: AJCC = American Joint Committee on Cancer; AS = active surveillance; BMI = body mass index; NA = not applicable; PRIAS = Prostate Cancer Research International: Active Surveillance; PSA = prostate-specific antigen.

≥IIC). Because all the patients included in the present study had met the PRIAS criteria, none had had AJCC stage IIA disease.

mpMRI Protocol and Interpretation

mpMRI was performed using 1.5 T or 3.0 T MRI systems with 6- or 8-channel phased-array coils. All the patients had undergone standard transrectal ultrasound-guided biopsy with ≥ 12 cores. However, MRI-targeted biopsy was not performed in the present study cohort. All MRI examinations included sagittal, coronal, axial T1- and T2-weighted sequences, and diffusion-weighted imaging with 0, 100, and 1000 s/mm^2 b-value to build an apparent diffusion coefficient map. Dynamic contrast-enhanced imaging before, during, and after injection of gadolinium contrast (meglumine gadoterate, 15 mL) was also performed. Three radiologists from our institute interpreted the mpMRI findings using PI-RADSv2 scoring in 12 sections of the prostate and 12 sections of extracapsular extension.[5] The mpMRI examinations performed from January 2014 to December 2015 were reviewed retrospectively, because our institution had not used PI-RADSv2 for interpretation before January 2016. The investigators were kept unaware of the clinical and pathologic information. PI-RADS scores of 4 or 5 were considered indicative of likely prostate cancer.

Pathologic Analysis

All pathologic specimens were examined by 2 pathologists for cancer location, tumor size, GS of the index tumor, extraprostatic extension, and seminal vesicle invasion. mpMRI–histopathologic correlations were assessed by whole-mount section analysis to measure the diagnostic accuracy of PI-RADSv2. Diagnostic accuracy is expressed as the sensitivity, specificity, positive predictive value, and negative predictive value.

Statistical Analysis

Clinical variables such as age, PSA, PSA density, tumor proportion of biopsy core, and prostate volume for each group were analyzed. The χ^2 test, 1-way analysis of variance, and post hoc tests were used to evaluate the differences in the study groups. The kappa coefficient was used to measure the interobserver variability of the radiologists. Multivariable analysis was performed to identify the factors associated with unfavorable disease. *P* values < .05 indicated

Table 2 MRI Characteristics Stratified by AJCC Stage

Characteristic	AJCC Stage			*P* Value
	I (n = 184)	IIB (n = 129)	≥IIC (n = 63)	
Presence of PI-RADS ≥ 4	140 (86.1)	113 (87.6)	54 (85.7)	.023
PI-RADS ≥ 4 lesions, n				.001
0	44 (23.9)	16 (12.4)	9 (14.3)	
1	50 (27.2)	26 (20.2)	7 (11.1)	
≥2	90 (48.9)	87 (67.4)	47 (74.6)	
Presence of PI-RADS 5	36 (19.6)	54 (41.9)	36 (57.1)	<.001
PI-RADS 5 lesions, n				<.001
0	148 (80.4)	75 (58.1)	27 (42.9)	
1	18 (9.8)	14 (10.9)	6 (9.5)	
≥2	18 (9.8)	40 (31.0)	30 (47.6)	

Data presented as n (%).
Abbreviations: AJCC = American Joint Committee on Cancer; MRI = magnetic resonance imaging; PI-RADS = Prostate Imaging and Reporting Data System.

statistical significance. SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY), was used for all statistical analyses.

Results

The baseline patient characteristics are summarized in Table 1. The preoperative PSA and PSA density was 4.7 ± 1.8 ng/mL and 0.12 ± 0.04 ng/mL/mL, respectively. Overall, unfavorable disease was found in 192 patients. GS upgrading was found in 187 patients (GS 3+4, n = 152; GS 4+3, n = 30; GS 4+4, n = 3; and GS 4+5, n = 1). Pathologic upstaging was observed in 34 patients (T3a, n = 32; T3b, n = 2). A total of 185 patients (49.2%) had undergone pelvic lymph node dissection, with an average of 5.4 lymph nodes removed. AJCC stage I, IIB, and ≥IIC disease was observed in 184, 129, and 63 patients, respectively. Patient age (64.7 vs. 65.8 vs. 67.9 years; $P = .004$), PSA density (0.11 vs. 0.12 vs. 0.13; $P = .004$), prostate volume (46.7 vs. 39.8 vs. 40.3 cm^3; $P = .003$), and tumor proportion in biopsy core (12.6% vs. 18.2% vs. 19.9%; $P < .001$) differed significantly between the patients with AJCC I, IIB, and ≥IIC disease, respectively.

The overall sensitivity, specificity, positive predictive value, and negative predictive value for PI-RADSv2 were 0.55, 0.87, 0.45, and 0.82, respectively. The kappa coefficient was 0.560 ($P < .001$) for PI-RADS 4 or 5 among the radiologists, suggesting moderate agreement. The distribution of PI-RADS scores for each group is presented in Table 2. The prevalence of PI-RADS score 4-5 lesions was similar among patients with stage I, IIB, and IIC-III disease. However, PI-RADS 5 lesions were more frequently found in patients with unfavorable disease (stage I vs. IIB vs. ≥IIC, 19.6% vs. 41.9% vs. 57.1%, respectively; $P < .001$). Two or more PI-RADS 4-5 lesions occurred more frequently in patients with unfavorable disease (stage I vs. IIB vs. ≥IIC, 48.9% vs. 67.4% vs. 74.6%, respectively; $P = .001$), and the proportion of multiple PI-RADS 5 lesions differed significantly according to AJCC stage (stage I vs. IIB vs. ≥IIC, 9.8% vs. 31.0% vs. 47.6%, respectively; $P < .001$). In addition, PI-RADS 5 lesions on the anterior prostate were frequently found in patients with unfavorable disease (stage I vs. IIB vs. ≥IIC, 8.7% vs. 23.3% vs. 25.4%, respectively; $P = .001$).

The results of multivariable analysis for the prediction of unfavorable disease in patients eligible for AS are presented in Tables 3 and 4. On univariate analysis, the significant factors were PSA density, number of positive cores on prostate biopsy, and number of PI-RADS 4-5 lesions. The data presented in

Table 3 Multinomial Logistic Regression Analysis for Prediction of Unfavorable Disease With PI-RADS ≥ 4 Lesions

Variable	Unfavorable Pathologic AJCC Stage			
	IIB		≥IIC	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.032 (0.995-1.070)	.092	1.090 (1.038-1.145)	.001
PSA density ≥ 0.10	1.576 (0.959-2.589)	.073	2.142 (1.091-4.206)	.027
Positive biopsy core, 2 vs. 1	0.996 (0.589-1.684)	.989	1196 (0.625-2.289)	.590
Tumor proportion on biopsy core	1.030 (1.011-1.049)	.002	1.033 (1.011-1.056)	.003
PI-RADS 4-5, n				
0	Reference	NA	Reference	NA
1	1.382 (0.644-2.966)	.407	0.629 (0.209-1.896)	.410
≥2	2.394 (1.231-4.655)	.010	2.078 (0.898-4.807)	.087

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; MRI = magnetic resonance imaging; NA = not applicable; PI-RADS = Prostate Imaging and Reporting Data System; PSA = prostate-specific antigen.

Table 4 Multinomial Logistic Regression Analysis for Prediction of Unfavorable Disease Using PI-RADS 5

	Unfavorable Pathologic AJCC Stage			
	IIB		≥IIC	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age	1.021 (0.984-1.059)	.263	1.071 (1.019-1.127)	.007
PSA density ≥ 0.10	1.597 (0.971-2.627)	.065	2.106 (1.063-4.174)	.033
Positive biopsy core (2 vs. 1)	0.997 (0.590-1.687)	.992	1.187 (0.610-2.311)	.613
Tumor proportion on biopsy core	1.026 (1.007-1.045)	.007	1.027 (1.004-1.050)	.020
PI-RADS 5 lesions, n				
0	Reference		Reference	
1	1.430 (0.663-3.085)	.362	1.547 (0.545-4.391)	.412
≥2	3.619 (1.906-6.874)	<.001	6.413 (3.045-13.507)	<.001

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; HR = hazard ratio; MRI = magnetic resonance imaging; NA = not applicable; PI-RADS = Prostate Imaging and Reporting Data System; PSA = prostate-specific antigen.

Tables 3 and 4 show that ≥ 2 PI-RADS 4-5 lesions was an independent predictor of IIB disease (hazard ratio [HR], 2.39; 95% confidence interval [CI], 1.23-4.66; $P = .010$) but not of ≥IIC disease (HR, 2.08; 95% CI, 0.90-4.81; $P = .087$). On multivariable analysis that included the number of PI-RADS 5 lesions, ≥ 2 PI-RADS 5 lesions independently predicted for stage IIB (HR, 3.62; 95% CI, 1.91-6.87; $P < .001$) and ≥IIC disease (HR, 6.41; 95% CI, 3.05-13.51; $P < .001$).

Discussion

In the present study, preoperative mpMRI with PI-RADSv2 scoring had a high negative predictive value in patients eligible for AS. Moreover, our results showed that multiple PI-RADS 5 lesions were associated with GS ≥ 4 + 3 or pathologic T3 disease.

Although AS can reduce overtreatment in those with low-risk prostate cancer, a substantial proportion of patients eligible for AS could harbor unfavorable disease.[11] MRI has been increasingly considered an important diagnostic tool for detecting, staging, and planning treatment of prostate cancer.[6,12,13] Although most contemporary AS programs have been based on PSA-related parameters, transrectal ultrasound-guided biopsy factors, and clinical staging,[1,14] MRI has the potential to more accurately detect clinically significant cancer and has demonstrated superior performance compared with standard models for identifying patients suitable for AS.[4,6,8,13,15] Many studies have investigated the role of mpMRI for both enrollment and follow-up of patients in AS programs. Moreover, MRI-targeted biopsy, compared with standard transrectal ultrasound-guided biopsy, has been associated with the increased detection of clinically significant cancer and decreased serendipitous detection of low-risk prostate cancer.[16,17] One systematic review reported that positive MRI findings resulted in reclassification after MRI-targeted biopsies or radical prostatectomy.[4] In addition, a recent prospective multicenter trial demonstrated that MRI-targeted biopsies identified most, but not all, clinically significant cancers.[18]

The high negative predictive value of MRI has been used as a rationale for the role of MRI in ruling out clinically significant prostate cancer. In the present study, mpMRI of patients eligible for AS had a negative predictive value of 82%, indicating that mpMRI with PI-RADSv2 could be useful for ruling out clinically significant cancer lesions, consistent with the findings from previous studies.[7,13,19]

Reducing the risk of misclassification is most important in the selection of AS candidates. In general, GS 3+4 disease has been considered clinically significant, and the role of AS for the treatment of GS 3+4 prostate cancer is highly controversial.[20,21] Moreover, patients with GS ≥ 4+3 or pathologic T3 disease require radical treatment. The present study used the 8th edition of the AJCC Prostate Cancer Prognostic Staging Guidelines to distinguish unfavorable (GS 3+4) and very unfavorable (GS ≥ 4+3 or pathologic T3) disease in candidates for AS. Previous studies using the Surveillance, Epidemiology, and End Results database reported a significant difference in cancer-specific and overall survival among those with stage I, IIB, and ≥IIC disease according to the 8th edition of the AJCC Prognostic Staging Guidelines.[22,23]

Previous studies have investigated the utility of PI-RADS scoring in low-risk prostate cancer.[4,7-9,12,13,18,19,24] In prostatectomy data for patients meeting AS criteria, PI-RADS of ≥ 4 was significantly associated with an initial biopsy misclassification.[8,9] A recent study reported that PI-RADS 5 (HR, 4.38) and PI-RADS 4 (HR, 2.62) lesions were associated with disease progression in men with prostate cancer receiving AS.[7] In the present study cohort, 54.4% and 71.4% of patients with PI-RADS 4 and 5, respectively, had adverse pathologic features. These results are consistent with those of 2 seminal MRI-targeted biopsy studies.[16,17]

Although many studies have demonstrated that PI-RADS scoring is useful for predicting unfavorable disease in AS candidates, most had evaluated the maximum PI-RADS scores. The present study focused on the association between the number of MRI-positive lesions and unfavorable disease. A previous study developed a nomogram to replace confirmative biopsy according to the number of visible lesions on MRI using a Likert scale.[15] We found that a solitary PI-RADS 4 or 5 lesion did not independently predict for unfavorable disease. When PI-RADS ≥ 4 lesions were present in multiple regions, the mpMRI findings were significantly associated with unfavorable disease. In particular, ≥ 2 PI-RADS 5 lesions was a strong predictor for GS ≥ 4+3 or pathologic T3 disease. Differences in the predictability between PI-RADS 4 and 5 lesions can be explained by

the strong correlation of tumor size and grade.[25,26] To the best of our knowledge, the present study is the first to show that the number of PI-RADSv2 4-5 lesions is associated with unfavorable disease. Our results suggest that targeted biopsy or radical treatment should be considered for patients with multiple PI-RADS $\geq$ 4 lesions, especially those with multiple PI-RADS 5 lesions. Careful surveillance might be a feasible option for patients with solitary MRI-positive lesions, depending on the other clinical parameters.

The present study had several limitations. First, we had enrolled a relatively small number of patients from a single center. Thus, a multicenter cohort with a large pool of patients might better define the role of mpMRI to identify clinically significant disease. Second, only patients who had undergone radical prostatectomy were enrolled, which could have caused a significant bias. This population did not include AS- or biopsy-naive populations, which might have affected the diagnostic performance of mpMRI. In the present study, 27 patients who had met the PRIAS criteria had undergone AS. We found no significant differences in the MRI characteristics between the AS and radical prostatectomy populations. However, the present study had unavoidable indication and selection biases owing to its retrospective nature. Third, our study contained a retrospective interpretation of mpMRI scans performed from 2014 to 2015, which might have resulted in a bias for the radiologists. Despite these limitations, we believe that the results of our investigation reflect real-world practice and have provided useful information to support the role of mpMRI with PI-RADSv2 for patients with prostate cancer eligible for AS.

Conclusion

mpMRI with PI-RADSv2 scoring had a high negative predictive value and might be useful for predicting unfavorable disease in patients with prostate cancer eligible for AS. The presence of multiple PI-RADS 4-5 lesions was associated with unfavorable disease compared with solitary lesions. In particular, multiple PI-RADS 5 lesions were associated with GS $\geq$ 4+3 or pathologic T3 disease. Targeted biopsy or radical treatment should be considered for these patients.

Clinical Practice Points

- The mpMRI factors and clinical parameters associated with unfavorable disease in patients eligible for AS have not been fully determined.
- We assessed the diagnostic accuracy of mpMRI in AS candidates and sought to identify the mpMRI factors associated with unfavorable disease, including the number of MRI-positive lesions and PI-RADSv2 scores.
- Two or more PI-RADS 4-5 lesions occurred more frequently in patients with unfavorable disease and the proportion of multiple PI-RADS 5 lesions differed significantly according to AJCC stage.
- The presence of multiple PI-RADS 4-5 lesions was associated with unfavorable disease compared with solitary lesions.
- Two or more PI-RADS 5 lesions independently predicted for stage IIB (HR, 3.62; 95% CI, 1.91-6.87; $P < .001$) and $\geq$IIC (HR, 6.41; 95% CI, 3.05-13.51; $P < .001$) disease.
- Targeted biopsy or radical treatment should be considered for patients with multiple PI-RADS $\geq$ 4 lesions.

Disclosure

The authors declare that they have no competing interests.

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