Prostate International 12 (2024) 224–230

Contents lists available at ScienceDirect

Prostate International

journal homepage: https://www.journals.elsevier.com/prostate-international

Research Article

Oncological outcomes after radical prostatectomy of localized prostate cancer: stratified by magnetic resonance imaging and risk classification

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ARTICLE INFO

Article history:
Received 21 June 2024
Received in revised form
19 September 2024
Accepted 25 September 2024
Available online 28 September 2024

Keywords:
Biochemical recurrence
Magnetic resonance imaging
Metastasis
Prostate cancer
Risk stratification

ABSTRACT

Background: We investigated whether combining T2-weighted magnetic resonance imaging (MRI) findings and clinical risk categories improves upon established prognostic indicators of oncological outcomes in prostate cancer.

Methods: Patients who underwent radical prostatectomy, but not preoperative hormone therapy, radiotherapy, or chemotherapy, for localized prostate cancer at Seoul National University Bundang Hospital from October 2007 to April 2016 were included. MRIs were classified according to the Prostate Imaging-Reporting and Data System (PI-RADS). Patients were divided into the following five groups: 1, no focal suspicious lesion; 2, organ-confined suspicious lesion PI-RADS $\leq$3; 3, organ-confined suspicious lesion PI-RADS 4 or 5; 4, suspicious lesion with extraprostatic extension (EPE), no seminal vesicle invasion (SVI); 5, suspicious lesion with EPE and SVI. Risk classified according to the National Comprehensive Cancer Network (NCCN) and MRI findings were combined to analyze survival curves for biochemical recurrence (BCR)-free and metastasis-free survival. The area under a time-dependent receiver operating characteristic was analyzed for event prediction after 5 years.

Results: We analyzed 1,290 patients. In multivariate Cox regression models, PI-RADS $\geq$4 (hazard ratio [HR] 2.33, $P < 0.001$), EPE (HR 1.46, $P = 0.027$), SVI (HR 5.03, $P < 0.001$) and NCCN high-risk (HR 2.33, 95% CI 1.66-3.26, $P < 0.001$) were associated with BCR. For metastasis, EPE (HR 2.33, $P = 0.047$), SVI (HR 13.08, $P < 0.001$) and NCCN high-risk (HR 2.78, $P = 0.026$) were independent risk factors. Depending on MRI group, BCR-free survival significantly decreased in NCCN intermediate-risk ($P = 0.001$) and high-risk ($P < 0.001$) groups, and metastasis-free survival decreased in the intermediate-risk group ($P = 0.39$) and significantly decreased in the high-risk ($P < 0.001$) group. Adding MRI group to NCCN risk classification significantly improved the predictive accuracy for BCR in comparison with NCCN risk classification alone ($P = 0.042$), but not for metastasis ($P = 0.012$).

Conclusion: Combining prostate MRI with NCCN risk classification improves the prediction value of BCR following radical prostatectomy for localized prostate cancer.

1. Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men, with the sixth highest mortality worldwide.[1]

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https://doi.org/10.1016/j.prnil.2024.09.003

As the clinical behavior of PCa is extremely heterogeneous, a precise risk stratification tool is necessary for personalized decision-making for managing PCa. A clinical risk classification system for PCa was first developed in 1998 based on serum prostate-specific antigen (PSA) testing, digital rectal examination, and Gleason score at transrectal ultrasound-guided prostate biopsy.[2] The D'Amico risk classification for PCa has been adapted by the National Comprehensive Cancer Network (NCCN). Although NCCN risk categories are widely used for PCa risk stratification, substantial heterogeneity has been reported in oncological outcomes within each group, specifically for the high-risk group.[3]

Over the past decade, multiparametric magnetic resonance imaging (mpMRI) has become an increasingly useful diagnostic tool for the evaluation, localization, and staging of PCa, improving diagnostic accuracy.[4] Therefore, current guidelines recommend mpMRI prior to biopsy if possible.[5,6] As mpMRI has been widely adopted in the clinical field of urology, standardization of multiple factors that contribute to the multiparametric nature of MRI was needed. Therefore, the European Society of Urogenital Radiology published the Prostate Imaging-Reporting and Data System (PI-RADS) in 2012,[7] which was revised as version 2.1 in 2019.[8] The PI-RADS in mpMRI provides a significant correlation with adverse pathologic features in radical prostatectomy (RP) specimens.[9]

Although mpMRI may improve the prediction of BCR following RP,[10–14] the PI-RADS in mpMRI has not yet been incorporated into conventional risk stratification based on clinical factors. Several patients with negative mpMRI findings have been diagnosed with clinically significant PCa, suggesting that clinical factors, such as abnormal digital rectal examination or PSA density, should be considered in addition to mpMRI.[15]

In addition to the predictive value for the presence of clinically significant PCa, the PI-RADS on mpMRI presents the prognostic value in each NCCN risk group.[16,17] Wimber et al introduced the risk stratification including PI-RADS, extraprostatic extension (EPE), and seminal vesicle invasion (SVI) status for localized PCa, which was correlated with the oncological outcome.[18]

However, those studies are based on a Caucasian population. Korean and Japanese populations showed a higher grade of PCa than Caucasian populations, even in men with low levels of serum PSA.[19] However, Asians showed lower mortality-to-incidence ratios and higher survival rates despite the higher degree of PCa at diagnosis.[20]

We aimed to assess the additional value of mpMRI to predict biochemical recurrence (BCR) or metastasis after RP in each NCCN risk group, especially in an Asian population.

2. Materials and methods

2.1. Ethics statement

This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-2108-701-101). The IRB waived the informed consent requirement owing to the retrospective study design. Personal identifiers were removed and the data were anonymously analyzed. All methods were performed according to the relevant guidelines and regulations.

2.2. Study design and population

Patients were included if they were diagnosed with PCa through biopsy; underwent prostate MRI within 6 months before surgery; had localized PCa clinical stage T3 or lower, N0, and M0; and underwent RP for localized PCa at a single large tertiary center between October 2007 and April 2016. Patients were excluded if they had other primary tumors; were treated with hormone therapy, chemotherapy, or radiation therapy before surgery; had poor-quality MRI images that could not be reevaluated with PI-RADS. There were no patients with previous history of surgical intervention for benign prostatic hyperplasia in our cohort.

2.3. MRI evaluations and risk group stratification

Patients were divided into five groups according to the MRI findings, as follows: group 1, no focal suspicious lesion; group 2, organ-confined suspicious lesion PI-RADS $\leq$3; group 3, organ-confined suspicious lesion PI-RADS 4 or 5; group 4, suspicious lesion with EPE and no SVI; and group 5, suspicious lesion with EPE and SVI. Medical records were reviewed and the patients were classified into low, intermediate, and high-risk groups according to the NCCN risk classification. The NCCN risk classification and MRI findings were combined to analyze survival curves for BCR-free and metastasis-free survival. The area under a time-dependent receiver operating characteristic (ROC) curve (AUC) was analyzed for event prediction after 5 years.

2.4. Study outcomes and statistical analysis

To evaluate the association between MRI group and BCR or metastasis, univariate and multivariate Cox proportional hazards regression models were performed, and groups were compared using Kaplan–Meier survival curves and log-rank tests.

We sought to develop and verify a model that predicts BCR-free survival and metastasis-free survival by MRI classification alone and by combining MRI findings with risk classification. For the prediction model, the model derivation and test groups were divided in a ratio of 3:1, a scoring system was created in the derivation group, and the model was verified in the test group. A score was created using the beta coefficient of the Cox model, and prediction accuracy was evaluated using the AUC for each survival outcome after 5 years.

The time-dependent ROC curve considers ROC curves as a function of time and can estimate and test the statistical significance of AUCs at a specific time. We used the R package 'timeROC' proposed by Blanche et al, which used inverse probability of censoring weighting.[21,22] Detailed explanations on the use of time-dependent ROCs[23] and comparison with the conventional concordance index are described elsewhere.[24]

Chi-square tests were used to compare categorical variables, and one-way analysis of variance and t tests were used to compare continuous variables. A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM-SPSS® version 25.0 (IBM, Chicago, IL, USA) and R statistical package version v.4.3.0 (R Core team, Vienna, Austria).

3. Results

A total of 1,290 patients were analyzed. Baseline characteristics are shown in Table 1. The median age at the time of surgery was 68 (interquartile range 62–72) years, and the median follow-up was 43.0 months. The NCCN intermediate-risk group comprised 58.1% of the patients, with no low-risk group. The MRI classification group 3 (organ-confined suspicious lesion PI-RADS 4 or 5) showed the largest distribution at 54.3%. In comparison with patients with PI-RADS $\leq$3 patients, those with PI-RADS $\geq$4 showed higher PSA (9.0 vs. 7.0, $P < 0.001$), higher PSA density (0.27 vs. 0.20, $P < 0.001$), worse Gleason score at biopsy ($P < 0.001$), and more frequent NCCN high-risk group (51.1% vs. 14.1%, $P < 0.001$). Furthermore, the patients with PI-RADS $\geq$4 presented a worse pathologic outcome after prostatectomy, including pathologic T stage ($P < 0.001$), pathologic Gleason score ($P < 0.001$) and surgical margin positivity ($P < 0.001$),

Table 1
Baseline characteristics of patients (n = 1,290).

Variables	Overall	PI-RADS ≤3	PI-RADS ≥4	*P* value
Patients	1290	320 (24.8%)	970 (75.2%)	
Median age, year (IQR)	68 (62-72)	67 (61-71)	68 (63-72)	0.273
Median BMI, kg/m^2 (IQR)	24.5 (22.8-26.2)	24.5 (22.7-26.3)	24.5 (22.8-26.2)	0.865
Hypertension (%)	625 (48.4%)	163 (50.9%)	462 (47.6%)	0.304
Diabetes mellitus (%)	240 (18.6%)	53 (16.6%)	187 (19.3%)	0.279
Median PSA, ng/ml (IQR)	8.5 (5.6-13.6)	7.0 (4.8-11.4)	9.0 (6.0-14.6)	<0.001
Median PSAD, ng/ml/cc (IQR)	0.26 (0.17-0.42)	0.20 (0.14-0.34)	0.27 (0.18-0.46)	<0.001
Clinical stage (%)				<0.001
cT1	733 (56.8%)	255 (79.7%)	478 (49.3%)	
cT2	288 (22.3%)	65 (20.3%)	223 (23.0%)	
cT3a	230 (17.8%)	0	230 (23.7%)	
cT3b	39 (3.0%)	0	39 (4.0%)	
Biopsy Gleason score (%)				<0.001
6	106 (8.2%)	37 (11.6%)	69 (7.1%)	
7				
3 + 4	540 (41.9%)	188 (58.8%)	352 (36.3%)	
4 + 3	321 (24.9%)	62 (19.4%)	259 (26.7%)	
8	270 (20.9%)	27 (8.4%)	243 (25.1%)	
≥9	53 (4.1%)	6 (1.9%)	47 (4.8%)	
NCCN risk stratification				<0.001
Intermediate-risk	749 (58.1%)	275 (85.9%)	474 (48.9%)	
High-risk	541 (41.9%)	45 (14.1%)	496 (51.1%)	
EPE (+) on MRI	230 (17.8%)	0	230 (23.7%)	<0.001
SVI (+) on MRI	39 (3.0%)	0	39 (4.0%)	<0.001
MRI group (%)				
Group 1	184 (14.3%)	184 (57.5%)	0	
Group 2	136 (10.5%)	136 (42.5%)	0	
Group 3	701 (54.3%)	0	701 (72.3%)	
Group 4	230 (17.8%)	0	230 (23.7%)	
Group 5	39 (3.0%)	0	39 (4.0%)	
Operation type				0.040
Open	58 (4.5%)	21 (6.6%)	37 (3.8%)	
Robot-assisted	1232 (95.5%)	299 (93.4%)	933 (96.2%)	
% of tumor volume (%)	11 (6-20)	7 (3-12)	13 (7-23)	<0.001
Pathologic stage (%)				<0.001
T2	826 (64.0%)	270 (84.4%)	556 (57.3%)	
T3a	327 (25.3%)	34 (10.6%)	293 (30.2%)	
T3b	137 (10.6%)	16 (5.0%)	121 (12.5%)	
Pathologic Gleason score (%)				<0.001
6	5 (0.4%)	4 (1.3%)	1 (0.1%)	
7				
3 + 4	444 (34.4%)	178 (55.6%)	266 (27.4%)	
4 + 3	619 (48.0%)	122 (38.1%)	497 (51.2%)	
8	107 (8.3%)	8 (2.5%)	99 (10.2%)	
≥9	115 (89%)	8 (2.5%)	107 (11.0%)	
Lymph node (+) (%)	29 (2.2%)	4 (1.3%)	25 (2.6%)	0.165
Positive surgical margin (%)	253 (19.6%)	36 (11.3%)	217 (22.4%)	<0.001
Biochemical recurrence (%)	238 (18.4%)	20 (6.3%)	218 (22.5%)	<0.001
Metastasis (%)	47 (3.6%)	5 (1.6%)	42 (4.3%)	0.022
Follow-up, months (IQR)	43.0 (28.2-59.9)	49.8 (36.6-61.1)	38.3 (26.1-59.5)	<0.001

BMI, body mass index; EPE, extraprostatic extension; IQR, interquartile range; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density; SVI, seminal vesicle invasion.

except for lymph node positivity (P = 0.165). They also showed higher rate of BCR (P < 0.001) and metastasis (P = 0.022).

In multivariate Cox regression models, PI-RADS ≥4 [Hazard ratio (HR) 2.33, 95% confidence interval (CI) 1.04−2.05, P < 0.001), EPE (HR 1.46, 95% CI 1.04−2.05, P = 0.027), SVI (HR 5.03, 95% CI 3.15−8.01, P < 0.001), and NCCN high-risk (HR 2.33, 95% CI 1.66−3.26, P < 0.001) were associated with BCR. Meanwhile, EPE (HR 2.33, 95% CI 1.10-5.35, P = 0.047), SVI (HR 13.08, 95% CI 5.60−30.57, P < 0.001), and NCCN high-risk (HR 2.78, 95% CI 1.13−6.85, P = 0.026) were independent risk factors for metastasis (Table 2).

Estimated probabilities of BCR-free survival stratified by MRI category revealed a significant decrease in BCR-free survival, depending on the MRI group, in the NCCN intermediate (P = 0.001) and high-risk (P < 0.001) groups (Fig. 1).

Furthermore, estimated probabilities of metastasis-free survival stratified by MRI category revealed a decrease, although not significant, in metastasis-free survival in the intermediate-risk group (P = 0.39) and a significant decrease in the high-risk group (P < 0.001) (Fig. 2).

In time-dependent ROC curves of the Cox models for BCR-free survival and metastasis-free survival at 5 years, adding NCCN risk classification to MRI group significantly improved the Cox model for BCR-free survival in comparison with NCCN risk classification alone (0.79 vs. 0.74, P = 0.042), but this was not significant for metastasis-free survival (0.78 vs. 0.71, P = 0.122) (Fig. 3).

4. Discussion

mpMRI is regularly used to assess men with elevated PSA to stratify the personal risk of clinically significant PCa, minimizing the risk of over-detection of clinically nonsignificant PCa. Indeed,

Table 2
Multivariate cox regression models of biochemical recurrence- and metastasis-free survival with National Comprehensive Cancer Network (NCCN) categories.

	Biochemical recurrence		Metastasis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age	0.99 (0.98-1.01)	0.424	1.00 (0.96-1.04)	0.821
MRI PI-RADS				
PI-RADS ≤3	Reference		Reference	
PI-RADS ≥4	2.33 (1.66-3.26)	<0.001	1.27 (0.45-3.61)	0.652
EPE (+) on MRI	1.46 (1.04-2.05)	0.027	2.33 (1.01-5.35)	0.047
SVI (+) on MRI	5.03 (3.15-8.01)	<0.001	13.08 (5.60-30.57)	<0.001
NCCN risk group				
Intermediate	Reference		Reference	
High	2.33 (1.66-3.26)	<0.001	2.78 (1.13-6.85)	0.026
Operation type				
Open	Reference		Reference	
Robot-assisted	0.62 (0.35-1.10)	0.103	1.04 (0.24-4.41)	0.961

EPE, extraprostatic extension; MRI, Magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PI-RADS, Prostate Imaging-Reporting and Data System; SVI, seminal vesicle invasion.

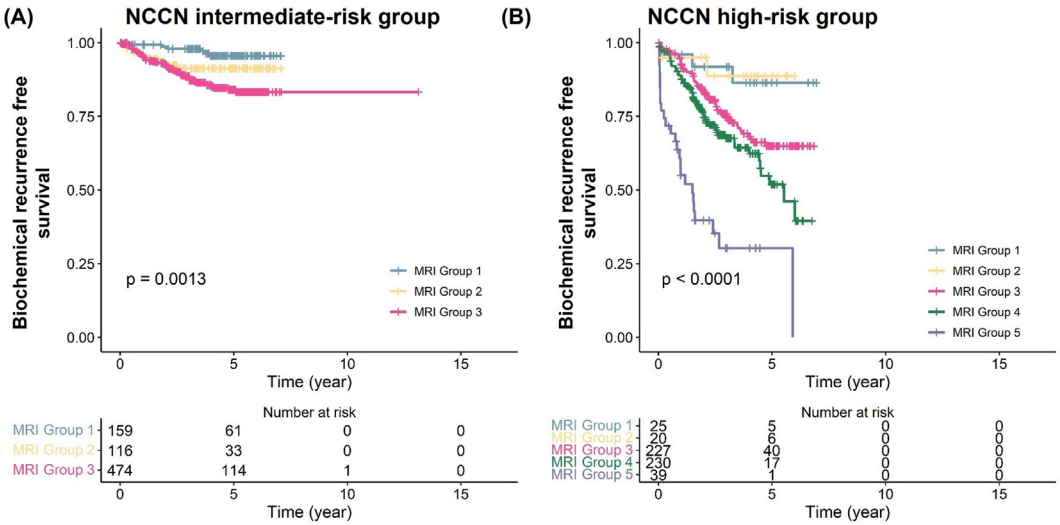

Fig. 1. Estimated probabilities of biochemical recurrence-free survival stratified by magnetic resonance imaging (MRI) category, separately for National Comprehensive Cancer Network (NCCN) intermediate-risk (A) and high-risk group (B).

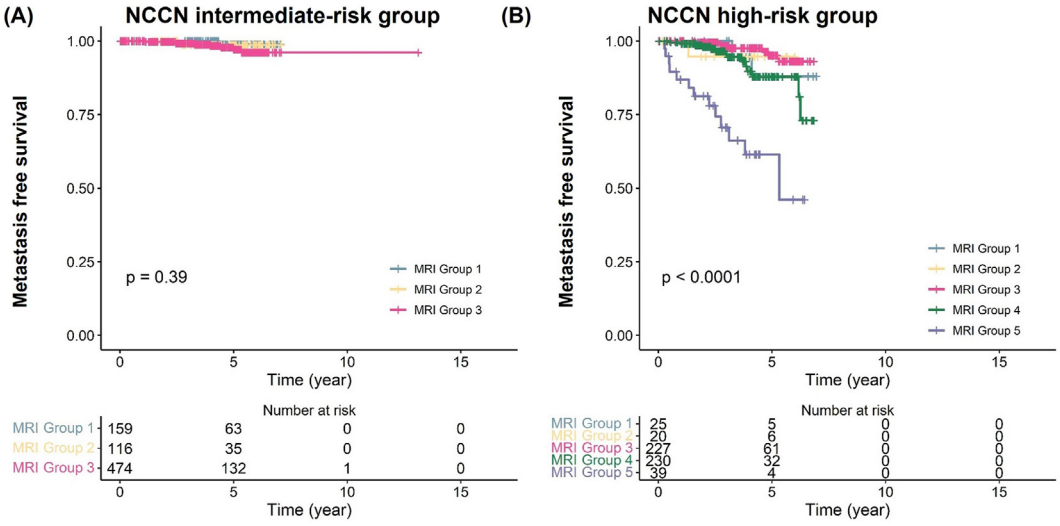

Fig. 2. Estimated probabilities of metastasis-free survival stratified by magnetic resonance imaging (MRI) category, separately for National Comprehensive Cancer Network (NCCN) intermediate-risk (A) and high-risk (B).

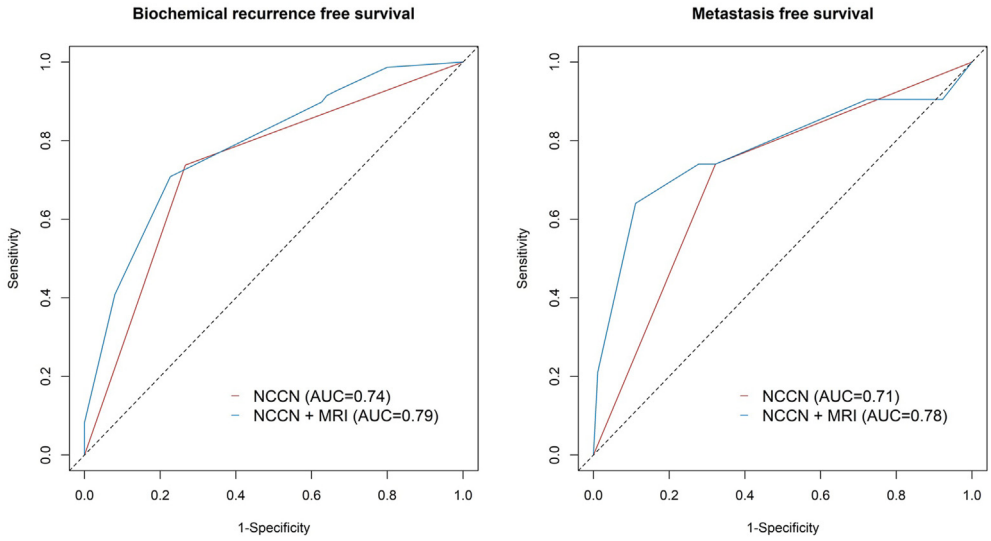

Fig. 3. Comparison of time-dependent receiver operating characteristic curves between the Cox model of National Comprehensive Cancer Network (NCCN) risk classification alone and that of the combination of NCCN risk classification and magnetic resonance imaging (MRI) category for biochemical recurrence-free survival (A) and metastasis-free survival (B), respectively.

mpMRI is well-known for diagnostic accuracy for clinically significant PCa.[25,26]

As mpMRI has been widely used in clinical practice, the PI-RADS classification was introduced to standardize the interpretation of mpMRI, which was last updated in 2019.[8] According to PI-RADS scoring, a PI-RADS ≥4 lesion is considered to be likely to show PCa, whereas a PI-RADS 3 lesion is considered equivocal. A multicenter randomized controlled study showed PCa detection rates within PI-RADS 3, 4, and 5 to be 34%, 69%, and 94%, respectively.[27] Furthermore, a higher PI-RADS score was associated with adverse histopathologic features[9] and poor oncological outcomes.[28]

However, mpMRI findings alone have limitations as a risk stratification tool for PCa. First, there are debates over how to consider equivocal PI-RADS 3 lesions. Furthermore, novel multivariate risk models are required for those unclear and diagnostic equivocal results.[29] Even 34% of the patients with negative mpMRI lesions, such as PI-RADS 1 and 2, presented clinically significant PCa on prostate biopsy, suggesting the need to combine mpMRI and clinical factors for risk stratification of PCa.[15]

In our study, we aimed to assess the prognostic value of the combination of mpMRI and NCCN risk stratification after RP. Indeed, our results suggested that a higher PI-RADS score on mpMRI could stratify the risk of postoperative BCR in the NCCN-based intermediate or high-risk group, congruent with the results of previous studies. A meta-analysis revealed that a higher PI-RADS score on mpMRI was associated with a higher BCR rate following definitive treatment for PCa.[30] Gandaglia et al[11] showed that a risk tool based on mpMRI and MRI-targeted prostate biopsy may improve the prediction accuracy for early postoperative BCR. They suggested that a multivariable model based on mpMRI variables, such as PI-RADS score and the presence of EPE or SVI on mpMRI and the maximum diameter of the index lesion was superior to that based on clinical factors and target biopsy factors alone.

In our cohort, the presence of EPE and SVI were also predictors of BCR following RP among patients with PI-RADS 5 lesions on mpMRI. Suspicion for EPE on mpMRI was associated with adverse pathology ≥ T3b.[31] Furthermore, clinical T stage ≥3 on mpMRI was related to postoperative BCR. Mazzone et al also suggested a novel risk stratification method including mpMRI for predicting BCR.[19] Their model included serum PSA, Gleason grade at biopsy, and clinical T stage and maximum diameter of lesion on mpMRI. Cassin et al[10] concluded that the combination of preoperative Gleason score ≥4 + 3 and clinical T stage ≥3 on preoperative MRI show the best prediction for BCR. Patel et al[14] revealed that an MRI-based diagnostic approach failed to result in significantly reduced positive surgical margin rates, although it provided a greater utilization of bilateral nerve-saving and an improved BCR outcome. In an Asian population, Yang et al[13] showed clinical T3 stage on mpMRI and PSA density predicting BCR after RP in NCCN-defined high- and very-high-risk patients.

In our study, time-dependent ROC analysis revealed that the combination of MRI with NCCN risk stratification provided additional predictive value for BCR in comparison with NCCN risk stratification alone. Gandaglia et al[11] also suggests that a novel model including PI-RADS score, presence of SVI, diameter of the index lesion, and other clinicopathologic factors can be superior to the existing risk stratification systems for PCa.

Meanwhile, among patients in the NCCN-based high-risk PCa group, those with PI-RADS ≥4 lesions, along with EPE and SVI on mpMRI, were likely to show metastasis after RP, whereas the other MRI groups failed to show significant differences in metastasis-free survival. Moreover, mpMRI showed no additional value in predicting postoperative metastasis in the NCCN-based intermediate-risk PCa group. Our results are consistent with those of the previous studies. Turchan et al[16] showed that distant metastasis only occurred in patients with PI-RADS 5 lesions among those with NCCN-based intermediate- and high-risk PCa, whereas Pockros et al[17] revealed that lymph node metastasis only occurred in patients with PI-RADS ≥4 lesions. However, according to time-dependent ROC analysis, the combination of MRI with NCCN risk stratification failed to provide additional predictive value for distant metastasis in comparison with NCCN risk stratification alone. This is partially because PI-RADS ≥4 was not significantly associated with metastasis after adjusting NCCN risk stratification and other MRI-based feature, such as EPE and SVI. Indeed, the median follow-up period in patients with PI-RADS ≥4 was 38.0 months, which was significantly shorter than that in those with PI-RADS ≤3 (43.0 months, $P < 0.001$). Further study with long-term follow-up should be performed.

The results of the present study should be carefully interpreted in view of several limitations. First, our study design was retrospective and subject to selection bias. Therefore, several clinical data that might be associated with oncological outcomes were unavailable, such as the diameter of the index lesions on mpMRI and the ratio of tumor volume in each biopsy core. Moreover, as the present study was performed at a single institution, generalizability might be limited. Considering that our study included a single race, the Korean population, a further multicenter, large population-based study should be performed. Interobserver inconsistency in interpretation of the same mpMRI has been reported when using the PI-RADS.[32] To generalize our results, a multicenter study should be performed that evaluates interobserver reproducibility.

Despite these limitations, this study is still noteworthy and remains the largest study to date that evaluates the predictive value of mpMRI in addition to the existing NCCN risk stratification for BCR and metastasis in an Asian population with PCa.

5. Conclusion

Recently, mpMRI has been reported to prevent not only high sensitivity in the detection of clinically significant PCa, but also potential prognostic value for PCa. In the current study, the addition of mpMRI features, such as PI-RADS, EPE, and SVI status with conventional NCCN risk stratification presented a better predictive value for BCR after RP, in comparison with NCCN risk stratification alone. These findings might enable clinicians to present more personalized information to further predict prognosis based on mpMRI findings.

Author contributions

GJ: Data collection, Data analysis, Manuscript writing. JKK: Project development, Manuscript editing. HK: Data management, Data analysis. JL: Data management, Data analysis. SKH: Project development, Manuscript editing. All the authors approved and contributed to the final manuscript.

Data availability statement

All data disclosure is not possible due to the policy of National Health Insurance Corporation.

Conflicts of interest

This study was conducted in the absence of commercial or financial relationships that could be interpreted as potential conflicts of interest. The authors declare no conflicts of interest.

Acknowledgments

The authors declare that they did not receive institutional, private, and/or corporate financial support. This work was supported by Grant No. 02-2021-0044 from the Seoul National University Bundang Hospital (SNUBH) Research Fund.

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