



Predictive model using prostate MRI findings can predict candidates for nerve sparing radical prostatectomy among low-intermediate risk prostate cancer patients

Gang Song^{1,2,3#}, Mingjian Ruan^{1,2,3#}, He Wang⁴, Zhiyong Lin⁴, Xiaoying Wang⁴, Xueying Li⁵, Peng Li⁶, Yandong Wang^{1,2,3,7}, Binyi Zhou^{1,2,3}, Xuege Hu^{1,2,3}, Hua Liu^{1,2,3}, Hao Wang^{1,2,3}, Yinglu Guo^{1,2,3}

¹Department of Urology, Peking University First Hospital, Beijing 100034, China; ²Institute of Urology, Peking University, Beijing 100034, China; ³National Urological Cancer Center of China, Beijing 100034, China; ⁴Department of Radiology, ⁵Department of Statistics, ⁶Department of Ultrasound, Peking University First Hospital, Beijing 100034, China; ⁷Department of Urology, the People's Hospital of Guizhou Province, Guiyang 550002, China

Contributions: (I) Conception and design: G Song, Y Guo; (II) Administrative support: None; (III) Provision of study materials or patients: G Song; (IV) Collection and assembly of data: M Ruan, P Li, Y Wang, B Zhou, X Hu, H Liu, H Wang; (V) Data analysis and interpretation: M Ruan, X Li, G Song; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Gang Song. Department of Urology, Peking University First Hospital, Beijing 100034, China. Email: sgbmupaper@163.com.

Background: In order to improve postoperative functional outcome, including urinary continence and erectile function, nerve sparing surgery is recommended for patients with clinically localized prostate cancer (PCa). However, due to poor diagnosis accuracy at the preoperative stage, upstaging occurs in a considerable proportion of patients. Multiparametric magnetic resonance imaging (mpMRI) and the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) have recently shown excellent performance in diagnosis and staging of PCa. The aim of this study was to develop a predictive model based on PI-RADS v2 for postoperative upstaging in patients with low-intermediate risk PCa.

Methods: The medical records of 314 patients with low-intermediate risk PCa [prostate-specific antigen (PSA) level ≤ 20 ng/mL, Gleason score (GS) < 8 , and clinical stage $< T3$] who underwent preoperative mpMRI and radical prostatectomy in the Department of Urology, Peking University First Hospital between January 2012 and July 2019 were reviewed retrospectively. Clinicopathological characteristics were collected. All MRI reports were done at our institution as part of routine clinical practice before prostate biopsy and there was no re-reporting occurred. Using PI-RADS v2, the mpMRI results were assigned to three groups: “negative”, “suspicious”, and “positive”. Multivariate logistic regression analysis was used to assess factors associated with postoperative pathological upstaging, defined as the presence of pT3 at final pathology. A regression coefficient based model for predicting postoperative upstaging was constructed and internally validated using 1,000 bootstrap resamples. The performance of the model was assessed using the area under the receiver operating characteristic curve (AUC). With the optimal cutoff point the performance of the model was assessed through analysis of sensitivity, specificity, positive predictive value, and negative predictive value.

Results: Upstaging was observed in 119 (37.9%) patients. The univariate and multivariate analyses revealed that PSA density, biopsy Gleason grade group (GGG), and mpMRI findings were significantly independent predictors for postoperative upstaging (all $P < 0.05$). A predictive model showing very favorable calibration characteristics and higher accuracy than the single variables was constructed (AUC = 0.74; $P < 0.001$). At the optimal cutoff point, the model demonstrated a sensitivity and negative predictive value of 87.4% and 87.0%, respectively.

Conclusions: PI-RADS v2 assessment proved to be one of the most valuable predictors for postoperative upstaging in patients with low-intermediate risk PCa. The predictive model, based on PI-RADS v2 assessment, PSA density, and biopsy GGG, may help to select suitable candidates for nerve sparing radical

prostatectomy among patients with low-intermediate risk PCa.

Keywords: Prostate cancer (PCa); multiparametric MRI; radical prostatectomy; nerve sparing

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Introduction

For the majority of patients with clinically localized prostate cancer (PCa), radical prostatectomy is the standard treatment, providing excellent oncological outcome. However, postsurgical urinary incontinence and erectile dysfunction, the most common postoperative complications, severely affect quality of life of the patients.

Since nerve sparing surgery was introduced, substantial improvement has been made in functional outcome in terms of urinary continence and erectile function (1,2). However, appropriate candidate selection for nerve sparing surgery is essential to balance the risks of oncologic safety and functional outcomes. According to American Urological Association guidelines, nerve sparing radical prostatectomy (NSRP) is recommended for patients with localized disease (3). Current European Association of Urology guidelines recommend not to preserve the neurovascular bundles in case of local advanced PCa or any biopsy Gleason score (GS) >7 (4).

Preoperative clinical staging based on digital rectal examination and prostate biopsy has limited accuracy, with understaging of locally extensive diseases in 30.4% to 37.2% of cases (5,6). In one study, 39.8% of patients who underwent NSRP were upstaged, leading to a higher rate of positive surgical margin and worse prognosis (7). NSRP was not suitable for these patients. These proportions confirmed the need for predicting the presence of upstaging at final pathology. Several predictive models have been constructed in order to predict postoperative upstaging (6,8,9). However, no models currently integrate the PI-RADS score to predict upstaging. Multiparametric magnetic resonance imaging (mpMRI) and the Prostate Imaging Reporting and Data System version 2 (PI-RADS v2) (10) currently play an important role in diagnosis and staging of PCa.

Therefore, the purpose of this study was to construct a new PI-RADS v2 based model for predicting postoperative upstaging in patients with clinically localized PCa. The developed predictive model may guide urologists in selecting appropriate candidates for nerve sparing operation.

Methods

Patient population

A total of 639 patients, who underwent preoperative mpMRI followed by radical prostatectomy for clinically localized PCa at our institution between January 2012 and July 2019, were reviewed retrospectively. Of the 639 patients, 401 were classified as low-intermediate risk PCa [prostate-specific antigen (PSA) level ≤ 20 ng/mL, GS < 8 , and clinical stage $< T3$] according to the NCCN 2019 Clinical Practice Guidelines in Oncology (11).

In all, 87 patients were excluded based on the following criteria:

- (I) prior hormonal therapy or radiotherapy [44];
- (II) less than 10 or >13 systematic biopsy cores taken [23];
- (III) incomplete data [20].

As a result, a total of 314 patients were enrolled in the study. Approval was obtained from the institutional review board.

Clinicopathological characteristics

Clinicopathological characteristics of the patients, i.e., age, preoperative PSA level, prostate volume (PV) measured by transrectal ultrasound (TRUS), the percentage of positive systematic biopsies which was defined as the proportion of the number of positive systematic cores to the number of total systematic cores, GS following prostate biopsy, and pathologic characteristics of specimens following radical prostatectomy, were collected. PSA density was calculated by dividing the preoperative PSA by the PV. Patients who were classified into the high-risk group were excluded because such patients can hardly be considered as candidates for nerve sparing procedures or other focal therapy.

Biopsy procedure and histopathology

All patients underwent 10- to 13-core TRUS guided systematic biopsy at our hospital. In those patients where

suspicious lesions at any area were found by ultrasonography or mpMRI, two targeted biopsies were performed, but these targeted biopsies were not analyzed.

All biopsy specimens were evaluated by two genitourinary pathologists, in order to determine the cancer stage and the GS in positive cases. The GS for individual TB and SB cores, as well as the overall GS for each patient, was assigned as the combination of the most common Gleason grade and highest Gleason grade. The new GS grading system was used to classify patients into the following five grades: grade group 1, GS 6; grade group 2, GS 3+4=7; grade group 3, GS 4+3=7; grade group 4, GS 4+4=8; and grade group 5, GS 9 and 10 (12). The pathological stage was determined in accordance with the AJCC 2017 TNM classification system. Upstaging was defined as showing pT3 features at final pathology, such as extra-capsular extension, defined as the extension of tumor beyond the boundaries of the prostate gland into periprostatic adipose.

MpMRI

MRI was performed using a 1.5T for 52 (16.6%) patients and 3.0T whole-body system (GE Healthcare, USA) for 262 (83.4%) with no endorectal coil used. The imaging protocol included axial T1-weighted images of the pelvis and biplanar T2-weighted fast spin-echo images centered on the prostate. In addition, axial diffusion-weighted imaging was performed with b-values of 0, 800, and 1,400 sec/mm². Dynamic contrast-enhanced images were made following intravenous administration of gadolinium-chelate.

MpMRI interpretation

MRI images were retrospectively interpreted by one of two experienced radiologists with >5 years' experience reading prostate MRIs. Any disagreement in the process of interpretation was resolved by the adjudicating senior radiologist. The probability of tumor was evaluated and scored on a three-point scale based on PI-RADS v2 scoring, where group "negative" (PI-RADS 1-2) = low probability, group "suspicious" (PI-RADS 3) = equivocal, and group "positive" (PI-RADS 4-5) = high or very high probability (10).

Statistical analysis

The end point of the study was identification of upstaging at postoperative pathology (T3 stage). Descriptive statistics

included frequencies and proportions for categorical variables and means, standard deviations, medians, and interquartile ranges (IQR) for continuously coded variables. Univariate and multivariate logistic regression analyses were performed to investigate potential independent predictors of upstaging at final pathology. The factors evaluated for prediction of upstaging at postoperative pathology were age, preoperative PSA level, PV by TRUS, PSA density, percentage of positive systemic biopsies, Gleason grade group (GGG) following prostate biopsy, and PI-RADS v2 score.

The logistic regression model for upstaging at postoperative pathology was constructed, utilizing selected variables based on the results of multivariate logistic regression analysis. Discrimination was measured using the area under the curve (AUC) derived from the receiver operating characteristic (ROC) curves. In addition, 1,000 bootstrap resamples were used for internal validation and to reduce overfit bias. With the optimal cutoff value according to Youden's index, the performance of the model was assessed through analysis of sensitivity, specificity, positive predictive value, and negative predictive value. All analyses were two-sided, with statistical significance set at $P < 0.05$. The statistical analyses were performed using SPSS (version 24.0; SPSS Inc., Chicago, IL, USA) and R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

The baseline clinical and pathological characteristics of the 314 patients in this cohort are described in *Table 1*. The median age was 67 (IQR, 62–71) years. The median preoperative PSA was 8.83 (IQR, 6.90–11.80) ng/mL.

Of all 314 patients, 119 (37.9%) presented with pT3 PCA at postoperative pathology, i.e., upstaging. Before operation, 107 cases (34.1%), 150 cases (47.8%), and 57 cases (18.2%) were stratified into GGG 1, 2 and 3, respectively. Of those who were diagnosed with GGG 1 cancer by biopsy, 26 (24.3%) were diagnosed with a locally advanced disease at final pathology; this number was 63 (42.0%) for those with GGG 2, and 30 (52.6%) for those with GGG 3.

The univariate and multivariate logistic regression analyses in this study cohort are described in *Table 2*. On univariate analysis, patients presenting upstaging in postoperative pathology showed significantly higher PSA [odds ratio (OR), 1.141; 95% confidence interval (CI), 1.072–1.215; $P < 0.001$] and PSA density values (OR, 51.743; 95% CI, 9.553–280.262; $P < 0.001$), lower free/total (f/t)

Table 1 Baseline clinical and pathological characteristics of the study cohort

Variable	Total (n=314)	Upstaging at RP	
		No (n=195)	Yes (n=119)
Age, median [IQR], years	67 [62–71]	66 [62–71]	68 [62–72]
PSA, median [IQR], ng/mL	8.83 [6.90–11.80]	8.18 [6.36–10.87]	10.09 [7.86–13.42]
f/t PSA, median [IQR]	0.13 [0.09–0.16]	0.13 [0.10–0.17]	0.11 [0.08–0.14]
PV, median [IQR], mL	41.10 [30.00–57.25]	44.0 [32.40–62.90]	36.80 [27.10–48.43]
PSAD, median [IQR], ng/mL ²	0.21 [0.14–0.32]	0.18 [0.12–0.27]	0.27 [0.19–0.39]
Percent positive systematic biopsies, median [IQR]	0.23 [0.08–0.42]	0.23 [0.08–0.38]	0.30 [0.16–0.50]
GGG, No. [%]			
1	107 [34.1]	81 [41.5]	26 [21.8]
2	150 [47.8]	87 [44.6]	63 [52.9]
3	57 [18.2]	27 [13.8]	30 [25.2]
PI-RADS, No. [%]			
Negative	54 [17.2]	47 [24.1]	7 [6.9]
Suspicious	102 [32.5]	69 [35.4]	33 [27.7]
Positive	158 [50.3]	79 [40.5]	79 [66.4]

RP, radical prostatectomy; IQR, interquartile range; BMI, body mass index; PSA, prostate-specific antigen; f/t PSA, free/total PSA ratio; PV, prostate volume; PSAD, PSA density; GGG, Gleason grade group; PI-RADS, Prostate Imaging Reporting and Data System.

Table 2 Univariate and multivariate analyses of predictors associated with upstaging prostate cancer

Variable	Univariate	P value	Multivariate	P value
	OR (95% CI)		OR (95% CI)	
Age (years)	1.027 (0.991–1.064)	0.144		
PSA (ng/mL)	1.141 (1.072–1.215)	<0.001*		
f/t	0.007 (0–0.521)	0.024*		0.678
PV (mL)	0.980 (0.969–0.992)	<0.001*		
PSAD (ng/mL ²)	51.743 (9.553–280.262)	<0.001*	26.577 (4.657–151.680)	<0.001*
Percent positive systematic biopsies	8.267 (2.563–26.662)	<0.001*		0.568
GGG	1.893 (1.353–2.650)	<0.001*	1.572 (1.095–2.257)	0.014*
1				
2				
3				
PI-RADS	2.401 (1.687–3.418)	<0.001*	2.022 (1.387–2.947)	<0.001*
Negative				
Suspicious				
Positive				

*, P value with <0.05 significance. OR, odds ratios; CI, confidence interval.

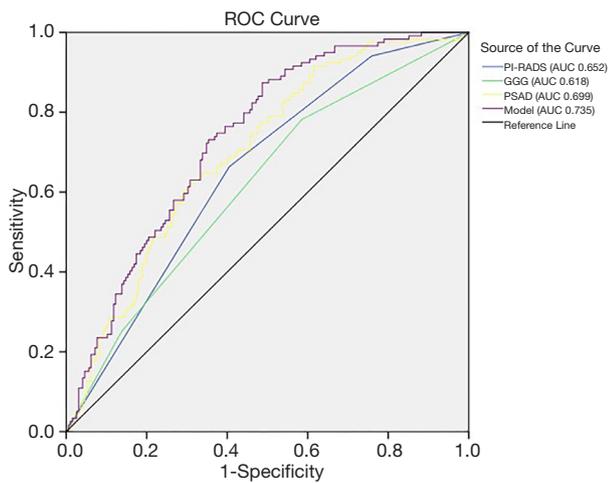


Figure 1 Receiver operating characteristic curves (ROC) for upstaging at final pathology for PSAD, PI-RADS score, GGG and predictive model. GGG, Gleason grade group; PI-RADS, Prostate Imaging Reporting and Data System.

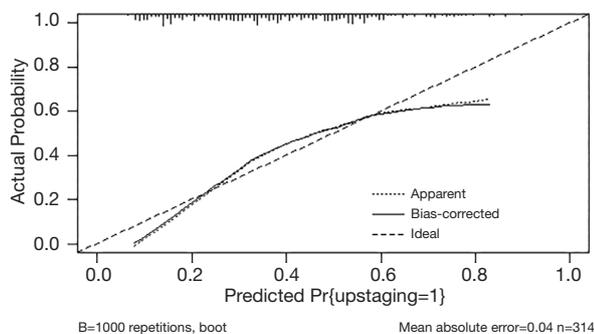


Figure 2 Calibration plot for predicting postoperative upstaging probability.

PSA values (OR, 0.007; 95% CI, 0–0.521; P=0.024), smaller prostates (OR, 0.980; 95% CI, 0.969–0.992; P<0.001), a higher percentage of positive systematic biopsies (OR, 8.267; 95% CI, 2.563–26.662; P<0.001), higher GGGs (OR, 1.893; 95% CI, 1.353–2.650; P<0.001), and a higher PI-RADS score (OR, 2.401; 95% CI, 1.687–3.418; P<0.001) compared to men without upstaging. No difference in age was observed between patients with or without postoperative upstaging.

The PSA and PV data were excluded from the multivariate analysis to avoid confounding. In the multivariate analysis, PSA density, GGG following biopsy, and PI-RADS score remained significantly associated with postoperative upstaging, suggesting that these variables are

independent risk predictors. Of those, the PI-RADS score was the most significant predictor according to the standard regression coefficient. Specifically, patients with high PI-RADS scores were at higher risk of upstaging at final pathology.

With application of the coefficients of the logistic function, a predictive model for postoperative upstaging was constructed using selected risk factors, including PSA density, GGG, and PI-RADS score, as follows:

$$\text{logit}(P) = \ln \left[\frac{P}{1-P} \right] \\ = -3.188 + 0.704 \times \text{PI-RADS} + 0.453 \times \text{GGG} + 3.280 \times \text{PSAD}.$$

In this equation, GGG 1, GGG 2, GGG3 were assigned to 0, 1, 2, respectively into the equation for calculation. PI-RADS outcome like negative, suspicious and positive results were also denoted as 0, 1, 2, respectively.

ROC analysis was performed to assess the accuracy of the model, as shown in *Figure 1*. The predictive model applied for postoperative upstaging yielded an AUC of 0.735, with a 95% CI of 0.681–0.790 (P<0.001), which was better than any single risk factor. At the optimal cutoff predictive value of 0.295, it showed a sensitivity of 87.4%, a specificity of 51.0%, a positive predictive value of 52.3%, and a negative predictive value of 87.0%. The calibration plot, exploring the relationship between observed and predicted values, before and after bootstrap validation, is depicted in *Figure 2*.

Discussion

Distinguishing organ-confined disease from disease with locally advanced PCa is of significance when planning treatment strategies for PCa. Among men with low-intermediate risk PCa before surgery, those presenting \geq pT3a PCa at final pathology should be excluded from the local control cohort (nerve sparing surgery or focal therapy) of PCa, so as to improve the likelihood of achieving negative margins and better prognosis. Moreover, patients with local advanced PCa will be given more aggressive treatment for the sake of cancer control and avoiding biochemical recurrence.

Current staging relies heavily on mpMRI, especially for patients with local advanced PCa. However, according to a contemporary critical meta-analysis, involving 9,796 patients from 75 different studies, MRI showed a poor sensitivity of 0.61 (95% CI, 0.54–0.67) for all patients with stage T3 PCa (13), which means a number of patients with local advanced PCa were missed, which may lead to relatively conservative management of PCa. Our results show an upstaging rate of 37.9% within the entire cohorts,

which is similar to results from previous studies (5,6). Nevertheless, unlike other authors, we did not consider those with documented loss of prostate capsule and irregularity of the capsule by mpMRI owing to its high positive predictive value. This may be due to the relatively high proportion of patients with biopsy GS 7 in this study. Moreover, a recent study focusing on Korean patients found that nearly 50% of patients with low risk disease were upstaged postoperatively (14), a number we cannot neglect.

Several models for postoperative upstaging prediction have been constructed. The probability nomogram developed by Partin considered PSA, clinical stage, and biopsy GS, but not mpMRI (8,15). This model has been confirmed to overestimate the probability of organ confinement and underestimate the probability of extraprostatic extension (EPE) during application. mpMRI has been considered as an important part of those models for the detailed anatomical information it provides. Feng *et al.* (6) have demonstrated that adding mpMRI findings to Partin tables and to the MSK nomograms could significantly improve their predictive accuracy, but those results were limited by the relatively small sample study [112]. Martini *et al.* (9) have developed an mpMRI based nomogram for the prediction of side-specific EPE, including the variables PSA, highest biopsy Gleason grade, and EPE. Despite its relative high AUC (82.11%), the clinical stage of patients with extracapsular extension on mpMRI should be considered as T3. The clinical stage of patients in those models was determined by digital rectal examination and prostate biopsy, which have been proved to have poor accuracy. Due to the relatively high cost, the adoption rate of mpMRI for staging PCa is low in Europe and the United States. In our cohort all patients underwent mpMRI before biopsy, which would make our model more generalizable.

Our previous studies have confirmed the value of PI-RADS in predicting PCa and clinically significant PCa in men undergoing repeat prostate biopsy and in predicting pelvic lymph node metastasis at radical prostatectomy (16,17). The aim of this study was to develop a new predictive model incorporating PI-RADS for the prediction of postoperative upstaging. The PSA density, GS, and PI-RADS score were found to be independent risk factors for the prediction of upstaging at final pathology. On that basis, we constructed a predictive model based on the cohort from a single institution, in order to predict the probability of upstaging after surgery. With three readily available variables, the combined predictive model performed

better than any single factor, with an AUC value of 0.735 ($P < 0.001$). With high sensitivity and negative predictive value, this model can precisely distinguish organ-confined disease from cases with locally advanced PCa and help in the selection of suitable candidates for nerve sparing surgery.

MpMRI and the PI-RADS v2 criteria (10,18) have improved visualization and characterization of PCa, leading to more accurate diagnosis and treatment. Kozikowski *et al.* (19) pointed out that with the optimal cutoff value of 5 for predicting side-specific EPE, the sensitivity of the PI-RADS score was twice as high as that of standard MRI staging and the specificity was slightly lower than that of standard MRI staging (83.5% *vs.* 92.0%). Bianchi *et al.* (20) analyzed 254 patients with low risk PCa and reported that PI-RADS was significantly correlated with upstaging at final pathology. Matsuoka *et al.* (21) showed that the system may serve as a valuable predictor of extracapsular extension, which may reduce the risk of understaging and facilitate precise preoperative planning.

PSA, a widely used prostate-specific serum marker, may be detected in cases of benign prostate hyperplasia, prostatitis, and PCa. A smaller PV was proved to be significantly associated with a higher risk of PCa in prior studies. In the current study, PSA (OR, 1.141; $P < 0.001$) and PV (OR, 0.980; $P < 0.001$) were strong predictors for postoperative upstaging. PSA density, the combination of PSA and PV, proved to be one of the most valuable markers to predict upstaging in patients with clinically localized PCa, which is consistent with a previous study (22). However, the predictive value of f/t PSA remains controversial in the literature. Aus *et al.* (23) reported that f/t PSA was a predictor of non-organ-confined PCa (stage pT3), whereas other studies reported that f/t PSA did not provide additional information about the pathological stage (24,25). Similarly, although age was proved to be associated with aggressive PCa in our previous study, it was not of predictive value for postoperative upstaging. Systematic biopsy is recommended as the method of choice for patients with elevated PSA or abnormal digital rectal examination in general, whereas there is a certain bias in percentage of positive cores on account of different biopsy strategies, PV, and lesions size. The predictive value of the percentage of positive cores for postoperative upstaging evidently remains unclear. In this study, in the multivariate analysis era, f/t PSA and percentage of positive cores were not independent significant predictors of upstaging at final pathology. Thus, these variables were excluded from our final model.

The present study is not devoid of limitations. First, there is a certain risk of selection bias due to the retrospective nature of our study. Second, the predictive model was constructed on the basis of a sample size that was not very large from a single institution. Third, our model will require external validation in a multicenter study to assess its wider applicability. Fourth, due to improvement in data quality over time and the different MRI protocol performed in patients, there might be a certain of difference in the outcome of the MRI.

Conclusions

PI-RADS assessment was proved to be one of the most valuable predictors for postoperative upstaging in patients with low-intermediate risk PCa. The predictive model on the basis of PI-RADS assessment, PSA density, and biopsy GGG may guide the treatment strategy and select suitable patients for nerve sparing surgery among patients with low-intermediate risk PCa.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tau.2020.01.28>). GS serves as an unpaid editorial board member of *Translational Andrology and Urology* from Jun 2019 to May 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Approval was obtained from the institutional review board.

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