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ORIGINAL ARTICLE

Prostate Cancer

Clinicopathological factors associated with pathological upgrading from biopsy to prostatectomy in patients with ISUP grade group ≤2 prostate cancer

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We performed this study to investigate pathological upgrading from biopsy to prostatectomy and clinicopathological factors associated with grade group (GG) upgrading in patients with International Society of Urological Pathology (ISUP) GG 1 and 2 prostate cancer (PCa) in a Chinese cohort. We included patients diagnosed with PCa with ISUP GG 1 and 2 at biopsy, who underwent RP at our institution. Pre- and postoperative clinical variables were examined. Univariate and multivariate logistic regression analyses were conducted to identify independent factors associated with GG upgrading. Patients in GG upgraded group had higher total prostate-specific antigen (tPSA; median: 14.43 ng ml^{-1} *vs* 10.52 ng ml^{-1}, *P* = 0.001) and PSA density (PSAD; median: 0.45 ng ml^{-2} *vs* 0.27 ng ml^{-2}, *P* < 0.001) than those in GG nonupgraded group. Patients in upgraded group had a higher ratio for Prostate Imaging-Reporting and Data System (PI-RADS) score >3 (86.4% *vs* 67.9%, *P* < 0.001). Those with GG 1 in biopsy were more likely to experience GG upgrading after RP than those with GG 2 (71 *vs* 54, *P* = 0.016). Independent preoperative factors predicting GG upgrading were PI-RADS score >3 (odds ratio [OR]: 2.471, 95% confidence interval [CI]: 1.132–5.393; *P* = 0.023), higher PSAD (*P* = 0.001), and GG in biopsy (OR: 0.241, 95% CI: 0.123–0.471; *P* < 0.001). The histopathological analyses of RP specimens revealed that perineural invasion (PNI; OR: 1.839, 95% CI: 1.027–3.490; *P* = 0.041) was identified as an independent factor associated with GG upgrading. Our results revealed that GG in the biopsy, PSAD, PI-RADS score >3, and PNI were independent factors of GG upgrading. These factors should be considered for patients with ISUP grade ≤2 PCa.

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Keywords: biopsy; grade group; prostate cancer; radical prostatectomy; upgrading

INTRODUCTION

Despite growing concerns about overtreatment of insignificant prostate cancer (PCa) during the past decades, radical prostatectomy (RP), the standard therapeutic procedure, has remained the primary curative method in the management of clinically localized PCa. As an alternative approach to radical treatment, active surveillance (AS) is recommended for carefully selected low-risk patients, to reduce the occurrence of treatment-related adverse events and corresponding costs.[1]

Gleason score (GS) is one of the main factors for risk stratification, and it plays a crucial role in deciding the treatment option. Currently, GS estimated by transrectal ultrasound (TRUS)-guided prostate biopsy specimen is most commonly used in the evaluation of aggressiveness of PCa; however, a major limitation of GS obtained through biopsy specimens is that biopsy samples only represent a small part of the tumor and may be limited in representing the real Gleason grade of the whole tumor. It is well documented that, following RP, there is Gleason grade discordance between the biopsy and postoperative specimens in nearly 40% of patients.[2] Moreover, if a higher Gleason grade tumor was missed at biopsy, high-grade conditions might be misclassified to low-grade conditions, which may underestimate the potential aggressiveness of PCa. Additionally, in some cases, it might lead to inappropriate management or clinical decisions. This concern is further highlighted by the histopathological analyses of patients with AS; a considerable number of patients with grade group (GG) ≤2 in biopsy have a higher grade pathology following RP.[3,4] Those patients, if included for AS, would have an increased risk of tumor progression and mortality. Thus, GG upgrading is a nonnegligible concern for patients with ISUP grade ≤2 in the biopsy.

Therefore, we examined the clinicopathological factors associated with GG upgrading in patients with ISUP grade ≤2 and evaluated independent predictors to improve risk assessment in such patients.

PATIENTS AND METHODS

Patients

In this study, 921 patients consecutively treated by laparoscopic or robotic RP between June 2016 and November 2020 at Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) were retrospectively reviewed. All patients underwent a multiparametric magnetic resonance imaging (mpMRI); TRUS-guided prostate biopsy (10–12 cores)

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was subsequently performed for the histopathological diagnosis of PCa. All patients underwent surgery within 3 months after the histopathological diagnosis. The exclusion criteria were as follows: patients who had incomplete medical records (n = 137), who had not scored according to Prostate Imaging-Reporting and Data System version 2 (PI-RADS v2) in mpMRI (n = 132), and who had received neoadjuvant hormonotherapy (n = 88). A database of 564 patients with PCa GG 1–5 was collected. Eventually, 228 patients with PCa GG 1 and 2 were selected and included in our study. Informed consent was obtained from all participants included in the study. This study was conducted according to the Declaration of Helsinki, 7th version. All data were anonymized and were retrospectively collected from the hospital information system. Ethical approval was waived by the institutional review board of Tongji Hospital given the retrospective nature of the study and all the procedures being performed were part of the routine care.

Data collection

Preoperative clinical variables including age at surgery, total prostate-specific antigen (tPSA), free PSA (fPSA), fPSA/tPSA, prostate volume assessed by mpMRI (calculated by height × width × length × 0.52), PSA density (PSAD), family cancer history (which included cancer history of all first-degree relatives), clinical T stage (≤T2a, T2b, and ≥T2c), PI-RADS score assessed by mpMRI, biopsy GG (defined as the GG of the most prevalent core in all biopsy cores), total biopsy cores, the maximum percentage of cancer per core, and the number of positive cores. For the pathology analyses of resection specimens after RP, details of tumor such as pathological T stage, Gleason GG, and adverse pathological findings (extracapsular extension, apical involvements, seminal vesicle and bladder neck invasion, surgical resection margin status, perineural infiltration or perineural invasion [PNI], vascular invasion, and lymph node dissection) were included in this study.

Pathological analyses of biopsy and postoperative specimens were routinely performed and reported by two senior pathologists. The RP specimens were embedded in paraffin after formalin fixation and serially sliced into 3-mm sections from apex to base, followed by hematoxylin and eosin staining. All whole-mount slides were reviewed by two experienced pathologists following the 2014 International Society of Urological Pathology (ISUP) Gleason grading system. In cases with multiple tumor foci, Gleason GG evaluation was performed for each tumor, and the highest Gleason GG was considered the final GG.

Increased Gleason GG at postoperative pathology compared with that in the previous biopsy was referred to as GG upgrading. Based on the GG upgrading status, the participants in this study were divided into two groups, namely, nonupgraded and upgraded groups. Clinical predictive factors and postoperative pathological findings related to GG upgrading were compared between the two groups.

Statistical analyses

Chi-square test or Fisher's exact test was used to compare the categorical variables, and Mann–Whitney U test was used to compare the continuous variables. Continuous variables were expressed as median (interquartile range [IQR]), and categorical variables were expressed as number (percentage). Univariate and multivariate logistic regression analyses were performed to examine the independent factors associated with GG upgrading. We conducted separate multivariate logistic regression analyses to identify independent preoperative clinical predictors and postoperative pathologic factors related to GG upgrading. A receiver operating characteristic (ROC) curve was used to determine the predictive value of the model. All tests were two sided. $P < 0.05$ was considered statistically significant. The odds ratio (OR) with 95% confidence interval (CI) was reported based on the results of the logistic regression analysis. Statistical analyses were performed using SPSS software version 24.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Baseline demographic and clinical characteristics of 228 patients diagnosed with PCa GG ≤2 are shown in **Table 1**. The median age was 67 (IQR: 62–71) years; median tPSA was 12.42 (IQR: 7.71–19.92) ng ml^{-1}; and median PSAD was 0.35 (IQR: 0.21–0.59) ng ml^{-2}. The clinical T stage was T1–2a, T2b, and T2c–3 in 73 (32.0%), 61 (26.8%), and 94 (41.2%) patients, respectively. PI-RADS scores assigned for all patients were as follows: score 1 and 2, 3, 4, and 5 in 18 (7.9%), 32 (14.0%), 82 (36.0%), and 96 (42.1%) patients, respectively.

Among clinical and biopsy variables, no statistically significant difference was observed between upgraded and nonupgraded group in terms of age (median: 67 years *vs* 66 years, P = 0.517), fPSA (median: 1.74 ng ml^{-1} *vs* 1.42 ng ml^{-1}, P = 0.118), prostate volume (median: 35.19 ml *vs* 34.10 ml, P = 0.123), cancer history of first-degree relatives (13 *vs* 7, P = 0.338), clinical T stage (P = 0.103), total biopsy cores (median: 12 *vs* 12, P = 0.596), number of positive cores (median: 4 *vs* 3, P = 0.692), and maximum percentage of cancer per core (median: 50.0% *vs* 50.0%, P = 0.583). Upgraded group had significantly higher tPSA (median: 14.43 ng ml^{-1} *vs* 10.52 ng ml^{-1}, P = 0.001) and PSA density (median: 0.45 ng ml^{-2} *vs* 0.27 ng ml^{-2}, $P < 0.001$). Patients in upgraded group had a higher ratio for PI-RADS score >3 (86.4% *vs* 67.9%, $P < 0.001$). There were 113 patients with biopsy GG 1 and 115 patients with biopsy GG 2. Patients with biopsy GG 1 were more likely to have an increased GG RP than those with biopsy GG 2 (71 *vs* 54, P = 0.016). In RP specimens, 163 (71.5%) patients were reported to have stage as pT2, and 65 (28.5%) patients had locally advanced disease (stage pT3–4). The postoperative histopathological variables including advanced pathological T stage (41 *vs* 24, P = 0.114), extracapsular extension (26 *vs* 18, P = 0.527), bladder neck invasion (13 *vs* 7, P = 0.338), apical involvement (55 *vs* 39, P = 0.349), vascular invasion (7 *vs* 2, P = 0.190), lymph node dissection (18 *vs* 10, P = 0.283), and lymph node positivity (3 *vs* 2, P = 1.000) were higher in upgraded group; however, the difference was not significant (all $P > 0.05$). Seminal vesicle invasion (17 *vs* 4, P = 0.012), positive surgical margin (33 *vs* 16, P = 0.047), and PNI (54 *vs* 25, P = 0.003) were found to be significantly higher in upgraded group.

Gleason GG upgrading was observed in 125 (54.8%) patients; the total concordance rates were 43.4%. The rate of biopsy GG 1 upgrading was 71 (62.8%) in 113 patients; most patients were upgraded to GG 2 (n = 52, 46.0%), followed by GG 3 (n = 13, 11.5%), GG 5 (n = 4, 3.5%), and GG 4 (n = 2, 1.8%). Among patients with biopsy GG2, 54 (46.9%) patients had upgraded GG. Among these, 37 (32.2%), 12 (10.4%), and 5 (4.3%) patients were upgraded to GG 3, GG 4, and GG 5, respectively. Among 61 (53.0%) patients whose Gleason GG was not upgraded, 57 (49.6%) patients remained in GG 2, and only 4 (3.5%) patients were downgraded to GG 1 (**Table 2**).

Univariate and multivariate logistic regression analyses of factors predicting GG upgrading at final pathology are summarized in **Table 3**. Higher PSAD (P = 0.001), PI-RADS score >3 (OR: 2.471, 95% CI: 1.132–5.393; P = 0.023), and biopsy GG (OR: 0.241, 95% CI: 0.123–0.471; $P < 0.001$) were independently predictive parameters for GG upgrading. **Figure 1** shows the ROC curve for the previous multivariate logistic regression model, where the area under the curve (AUC) was 0.745 (95% CI: 0.683–0.808; $P < 0.001$), indicating that our model had a relatively acceptable predictive ability when

Table 1: Baseline demographic and clinical characteristics of included patients

Variable	*Overall*	*Nonupgraded*	*Upgraded*	*P*
Patient, *n* (%)	228 (100.0)	103 (45.2)	125 (54.8)	
Age (year), median (IQR)	67 (62–71)	66 (61–71)	67 (62–72)	0.517
Age (year), *n* (%)				0.655
<55	10 (4.4)	3 (2.9)	7 (5.6)	
55–64	81 (35.5)	40 (38.8)	41 (32.8)	
65–74	110 (48.2)	48 (46.6)	62 (49.6)	
≥75	27 (11.8)	12 (11.7)	15 (12.0)	
tPSA (ng ml^{-1}), median (IQR)	12.42 (7.71–19.92)	10.52 (6.82–17.64)	14.43 (9.32–24.31)	0.001
tPSA (ng ml^{-1}), *n* (%)				0.019
<10.00	84 (36.8)	48 (46.6)	36 (28.8)	
≥10.00 and <20.00	88 (38.6)	35 (34.0)	53 (42.4)	
≥20.00	56 (24.6)	20 (19.4)	36 (28.8)	
fPSA (ng ml^{-1}), median (IQR)	1.52 (0.94–2.41)	1.42 (0.81–2.33)	1.74 (1.02–2.61)	0.118
fPSA/tPSA, median (IQR)	0.11 (0.08–0.17)	0.14 (0.09–0.18)	0.10 (0.08–0.16)	0.023
fPSA/tPSA, *n* (%)				0.068
≤0.16	160 (70.2)	66 (64.1)	94 (75.2)	
>0.16	68 (29.8)	37 (35.9)	31 (24.8)	
Prostate volume (ml), median (IQR)	34.45 (28.46–46.79)	34.10 (28.93–47.70)	35.19 (26.43–46.12)	0.123
PSAD (ng ml^{-2}), median (IQR)	0.35 (0.21–0.59)	0.27 (0.19–0.42)	0.45 (0.25–0.71)	<0.001
PSAD (ng ml^{-2}), *n* (%)				<0.001
<0.30	100 (43.9)	62 (60.2)	38 (30.4)	
≥0.30 and <0.60	74 (32.5)	26 (25.2)	48 (38.4)	
≥0.60	54 (23.7)	15 (14.6)	39 (31.2)	
Cancer history of first-degree relatives, *n* (%)	20 (8.8)	7 (6.8)	13 (10.4)	0.338
Clinical T stage, *n* (%)				0.103
≤T2a	73 (32.0)	39 (37.9)	34 (27.2)	
T2b	61 (26.8)	29 (28.2)	32 (25.6)	
≥T2c	94 (41.2)	35 (34.0)	59 (47.2)	
PI-RADS score >3, *n* (%)	178 (78.1)	70 (67.9)	108 (86.4)	<0.001
PI-RADS score, *n* (%)				0.008
1 and 2	18 (7.9)	13 (12.6)	5 (4.0)	
3	32 (14.0)	20 (19.4)	12 (9.6)	
4	82 (36.0)	34 (33.0)	48 (38.4)	
5	96 (42.1)	36 (34.9)	60 (48.0)	
Biopsy grade group, *n* (%)				0.016
1	113 (49.6)	42 (40.8)	71 (56.8)	
2	115 (50.4)	61 (59.2)	54 (43.2)	
Total biopsy cores, median (IQR)	12 (10–14)	12 (10–15)	12 (10–14)	0.596
Number of positive cores, median (IQR)	3 (2–5)	3 (2–5)	4 (2–6)	0.692
Maximum percentage of cancer per core (%), median (IQR)	50.0 (30.0–70.0)	50.0 (20.0–70.0)	50.0 (30.0–70.0)	0.583
Pathologic stage, *n* (%)				0.114
<pT3	163 (71.5)	79 (76.7)	84 (67.2)	
≥pT3	65 (28.5)	24 (23.3)	41 (32.8)	
Extracapsular extension, *n* (%)	44 (19.3)	18 (17.5)	26 (20.8)	0.527
Seminal vesicle invasion, *n* (%)	21 (9.2)	4 (3.9)	17 (13.6)	0.012
Bladder neck invasion, *n* (%)	20 (8.8)	7 (6.8)	13 (10.4)	0.338
Perineural invasion, *n* (%)	79 (34.6)	25 (24.3)	54 (43.2)	0.003
Positive surgical margin, *n* (%)	49 (21.5)	16 (15.5)	33 (26.4)	0.047
Vascular invasion, *n* (%)	9 (3.9)	2 (1.9)	7 (5.6)	0.190
Apical involvement, *n* (%)	94 (41.2)	39 (37.9)	55 (44.0)	0.349
Lymph node dissection, *n* (%)	28 (12.3)	10 (9.7)	18 (14.4)	0.283
Lymph node positivity, *n* (%)	5 (2.2)	2 (1.9)	3 (2.4)	1.000

IQR: interquartile range; PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; tPSA: total PSA; fPSA: free PSA; T: tumor; PI-RADS: Prostate Imaging Reporting and Data System

used to discriminate individuals with high GG upgrading risk from those with biopsy GG ≤2 PCa. **Table 4** shows the univariate and multivariate logistic regression analyses of postoperative pathological factors related to GG upgrading. PNI (OR: 1.839, 95% CI: 1.027–3.490; $P = 0.041$) was identified as an independent factor of GG upgrading in the multivariate analysis.

DISCUSSION

In this study, we analyzed the association between clinicopathological parameters and GG upgrading among patients with PCa GG ≤2 in a Chinese cohort. For all preoperative clinical parameters, PSAD, PI-RADS score, and biopsy GG were independent predictors of upgrading after RP. The predictive model had an AUC of 0.745 (95% CI: 0.683–0.808), indicating that our model had a relatively acceptable discrimination ability. In recent years, numerous studies have focused on this issue. Pham *et al.*[5] reported that tPSA, age, PI-RADS score, and PSAD were the independent predictors of GG upgrading. Yang *et al.*[4] showed that age, tPSA, percentage of positive cores, and clinical T stage were associated with GG upgrading. Erdem *et al.*[6] revealed that PSAD, age, and higher tumor-positive cores were the clinical predictors of GG upgrading. Additionally, Moussa *et al.*[7] reported that tPSA, clinical T stage, prostate volume, PNI, and presence of inflammation were the factors related to GG upgrading. The discrepancies among the results of this study and previous studies might be because of diverse populations, uneven sample sizes, and various selection criteria (*i.e.*, tPSA level, biopsy features, and clinical T stage). In addition, most previous findings were based on the old Gleason grading system, and specimens in this study were graded following the modified ISUP Gleason grading system.

In our study, we reported the rate of pathological upgrading was 62.8% (71/113) in patients with GG 1 PCa in the biopsy, and upgrading

Table 2: The number and percentage of grade group in biopsy and postoperative specimens

Radical prostatectomy	*Prostate biopsy*		
	GG 1	*GG 2*	*Total, n (%)*
GG 1	42 (37.2)	4 (3.5)	46 (20.2)
GG 2	52 (46.0)	57 (49.6)	109 (47.8)
GG 3	13 (11.5)	37 (32.2)	50 (21.9)
GG 4	2 (1.8)	12 (10.4)	14 (6.1)
GG 5	4 (3.5)	5 (4.3)	9 (3.9)
GG upgrading, *n* (%)	71 (62.8)	54 (46.9)	125 (54.8)
GG concordance, *n* (%)	42 (37.2)	57 (49.6)	99 (43.4)

GG: grade group

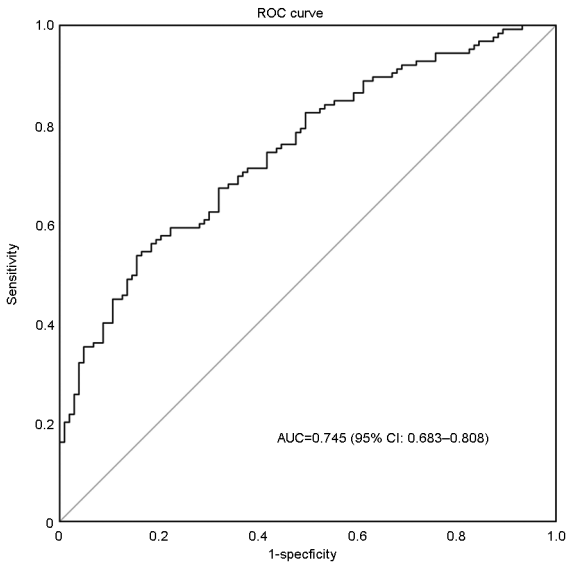

Figure 1: ROC curve of clinicopathological factors to predict grade group upgrading. ROC: receiver operating characteristic; AUC: area under the curve; CI: confidence interval.

Table 3: Univariate and multivariate logistic regression analyses of preoperative and postoperative clinicopathological factors

Variable	*Univariate*		*Multivariate*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age (year)	1.010 (0.971–1.051)	0.608	NA	NA
tPSA (ng ml^{-1})	1.034 (1.010–1.058)	0.005	1.004 (0.970–1.038)	0.825
fPSA (ng ml^{-1})	1.073 (0.973–1.184)	0.153	NA	NA
fPSA/tPSA	0.262 (0.023–2.952)	0.278	NA	NA
Prostate volume (ml)	0.983 (0.967–1.000)	0.052	NA	NA
PSAD (ng ml^{-2})		<0.001		0.001
<0.30	1 (reference)		1 (reference)	
≥0.30 and <0.60	3.012 (1.612–5.628)	0.001	3.807 (1.781–8.134)	0.001
≥0.60	4.242 (2.066–8.711)	<0.001	5.675 (1.729–18.633)	0.004
Cancer history of first-degree relatives	1.592 (0.610–4.151)	0.342	NA	NA
Biopsy grade group		0.017		<0.001
1	1 (reference)		1 (reference)	
2	0.524 (0.309–0.889)		0.241 (0.123–0.471)	
Clinical T stage		0.106		0.554
≤T2a	1 (reference)		1 (reference)	
T2b	1.266 (0.640–2.501)	0.498	0.815 (0.376–1.765)	0.604
≥T2c	1.934 (1.039–3.600)	0.038	1.227 (0.573–2.626)	0.599
PI-RADS score		<0.001		0.023
≤3	1 (reference)		1 (reference)	
>3	2.995 (1.551–5.782)		2.471 (1.132–5.393)	
Total biopsy cores	0.993 (0.919–1.074)	0.869	NA	NA
Number of positive cores	1.003 (0.921–1.092)	0.943	NA	NA
Maximum percentage of cancer per core (%)	1.003 (0.993–1.014)	0.510	NA	NA

NA: not analyzed; PSA: prostate-specific antigen; tPSA: total PSA; fPSA: free PSA; PSAD: prostate-specific antigen density; T: tumor; PI-RADS: Prostate Imaging Reporting and Data System; CI: confidence interval; OR: odds ratio

Table 4: Univariate and multivariate logistic regression analyses of postoperative pathological factors

Variable	*Univariate*		*Multivariate*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Pathologic stage		0.115	NA	NA
<pT3	1 (reference)		NA	NA
≥pT3	1.607 (0.891–2.898)		NA	NA
Extracapsular extension	1.240 (0.636–2.417)	0.527	NA	NA
Seminal vesicle invasion	3.896 (1.268–11.974)	0.018	2.739 (0.857–8.750)	0.089
Bladder neck invasion	1.592 (0.610–4.151)	0.342	NA	NA
Perineural invasion	2.373 (1.338–4.208)	0.003	1.839 (1.027–3.490)	0.041
Positive surgical margin	1.950 (1.003–3.793)	0.049	1.454 (0.717–2.948)	0.300
Vascular invasion	2.996 (0.609–14.746)	0.177	NA	NA
Apical involvement	1.289 (0.757–2.195)	0.349	NA	NA
Lymph node dissection	1.564 (0.688–3.557)	0.286	NA	NA
Lymph node positivity	1.242 (0.204–7.577)	0.814	NA	NA

T: tumor; NA: not analyzed; CI: confidence interval; OR: odds ratio

to GG 2 at final pathology was most commonly observed in those patients. Similarly, Erdem *et al.*[6] reported that 64.0% of patients with GG 1 had upgraded GG at final pathology, and a majority of them were upgraded to GG 2. Kaye *et al.*[3] reported that 40% of very low-risk patients and 59% of low-risk patients upgraded to GG ≥2. For biopsy GG 2, our data revealed that 46.9% of patients experienced upgrading at RP among clinical T1–3 PCa. This result was consistent with the findings by Pham *et al.*,[5] which demonstrated an upgrading rate of 44.6% for patients with biopsy GG 2 and clinical T1–3 PCa.

Similar to previous studies, we found that PSAD was remarkably associated with GG upgrading. PSAD was first proposed by Benson *et al.*[8] in the early 1990s, which is PSA concentration divided by prostate volume ratio. It is an important parameter that increases the detection specificity of PCa. Although it has been proven to be a better predictor of PCa than PSA, the application of PSAD in the diagnosis and prognosis of PCa is unclear. Moreover, it is inconsistently applied in clinical practice over the years.[9] Various studies have demonstrated that PSAD tended to be higher in patients with more aggressive disease.[10] Several studies highlighted the importance of PSAD in predicting adverse pathological features and biochemical recurrence (BCR) after RP.[10] In recent years, PSAD has been proposed as a powerful independent predictor of Gleason grade upgrading, particularly in disease with low Gleason Grade.[6,11] Given the evidence supporting the value of PSAD in the Gleason grade upgrading predictive model, some studies even reported that PSAD may have a role in current risk assessment not only for low-risk PCa but also for intermediate-risk and high-risk PCa.[12] The role of PSAD in low- and intermediate-risk PCa was illustrated by Corcoran *et al.*[13] They revealed that PSAD had independent predictive value for Gleason grade upgrading of Gleason 3 + 3 and 3 + 4 tumors. However, little independent predictive value of PSAD was observed when analyzing its role in GG upgrading of high-grade PCa. Corcoran *et al.*[13] believed that this could be because PSA secreted per unit tumor volume tend to be lower in tumors with a higher grade. Some researchers hypothesized that these higher grade PCa cells are poorly differentiated and their ability to produce PSA is decreased.[14] Our findings are consistent with those described by Corcoran *et al.*[13] Among Gleason GG ≤2 PCa patients with PCa in this study, PSAD was higher in the upgraded group and identified as an independent predictor for GG upgrading.

In recent years, mpMRI has emerged as a powerful tool in diagnosis, estimation of aggressiveness, staging, and monitoring of PCa. A recent Cochrane systematic review reported that MRI has a high negative predictive value in the detection of clinically significant PCa, with a negative predictive value of 91% for GG ≥ 2 PCa,[15] thus helping to improve candidate selection for AS and to reduce unnecessary biopsy. Some studies revealed that including MRI in an AS program may improve the ability to predict GG upgrading. Liss *et al.*[16] reported that the risk of GG upgrading in following AS biopsy is much lower in patients with a negative MRI. Mamawala *et al.*[17] reported that positive mpMRI (PI-RADS score ≥3) was an independent predictive factor for GG upgrading in follow-up biopsy after controlling several predictive factors such as age, PSAD, and tumor volume. Although the role of MRI in risk stratification of PCa has been increasingly appreciated in previous studies, the application of PI-RADS score for the prediction of GG upgrading after RP has not been fully understood. Song *et al.*[18] demonstrated that the rate of postoperative GG upgrading was 68.9% and 85.6% for PI-RADS scores 4 and 5, respectively, and the combination of clinical variables and mpMRI refined prediction accuracy of postoperative upgrading in GG 1 PCa. Similarly, when a lesion has a PI-RADS score of 4 or 5, a higher GG upgrading rate was observed among patients with biopsy GG 2 PCa.[19] Our data revealed that the PI-RADS score was an independent predictor of GG upgrading in PCa GG ≤2, which is consistent with the aforementioned studies. Patients with PI-RADS score ≤3 were less likely to experience GG upgrading than those with PI-RADS score >3. Moreover, Gondo *et al.*[20] reported that mpMRI helps to predict Gleason score downgrading for patients with biopsy Gleason 3 + 4 PCa. Additionally, Woo *et al.*[21] reported that a negative mpMRI is an independent predictor of postoperative Gleason grade downgrading for biopsy Gleason score 3 + 4 PCa. Accordingly, a prebiopsy mpMRI can be performed to predict GG upgrading or downgrading.

Furthermore, we analyzed the association between adverse pathological findings and GG upgrading. Only PNI was identified as an independent factor. PNI, characterized by cancer cell infiltration around or through the nerves, is a common pathological finding in PCa.[22] According to the previous literature, the prevalence of PNI in RP specimens varies from 32% to 80%.[23–26] Given the high prevalence of this condition, numerous studies have reported the prognostic and clinical value of PNI in PCa, but the results are conflicting. Some studies indicated that PNI was an independent prognostic factor for predicting BCR,[23,26] whereas other studies reported no prognostic value of PNI for predicting BCR.[25,27] Nevertheless, most studies agreed that PNI in RP specimen correlated with several adverse pathological factors such as a high Gleason score and advanced pathologic T stage.

A multi-institutional study by Kraus *et al.*[27] reported that PNI in RP specimen was associated with higher PSA and Gleason score and advanced pathological T stage but not with BCR. Erdem *et al.*[6] reported that PNI in RP specimen was independently associated with Gleason grade upgrading in multivariate analyses. These findings are relatively similar to our data. Based on the results, it appears that patients with PNI may experience GG upgrading. However, several recent studies about PNI on biopsy suggested that biopsy PNI seems less likely to predict GS upgrading.[28] Therefore, the association between biopsy PNI and Gleason grade upgrading warrant further investigation. For patients with biopsy PNI who are selected for AS, a repeat biopsy might be necessary.

AS is an attractive therapeutic option for low-risk PCa because it potentially reduces harmful overtreatment, wastage of medical resources, and treatment-related adverse events. In the original Epstein criteria for AS, only patients with GG 1 PCa were included. However, in recent years, various AS criteria have extended AS to low volume GG 2.[29] National Comprehensive Cancer Network guidelines endorse AS as a management method for men with favorable intermediate-risk PCa.[30] Unfortunately, in China, AS would be more difficult to implement in clinical practice for some complex reasons. One of the major clinical problems is Gleason GG discordance between biopsy and final pathology due to sampling error, and it is difficult to precisely distinguish indolent tumors from aggressive tumors in low-grade disease as per biopsy. The potential aggressiveness of disease might be obscured by the discrepancies, resulting in an inaccurate risk assessment and eventually leading to inadequate treatment. Corcoran *et al.*[31] revealed that the risk of BCR was significantly higher for patients with GG upgrading even after adjusting several clinical variables (including clinical T stage, PSA, number of positive cores, percentage of positive cores, and the total number of cores). Given that the underestimation of true Gleason grade poses a significant risk to the prognosis of PCa, patients are prone to choose radical treatment rather than AS. Besides, current evidence for AS is mainly based on western populations, and evidence from Asian populations is still limited. However, considerable differences may exist between Asian and Western populations, including differences in genetic background, dietary habits, and lifestyle, which may determine different disease characteristics. Since biopsy sampling errors are hard to avoid, evaluation of GG upgrading is crucial for appropriate treatment selection. This study is based on data obtained from Tongji hospital, one of the largest medical centers in central China. Our analyses aimed to provide a more precise assessment of GG upgrading risk in Chinese patients with the low-grade disease on biopsy. According to the present study, low biopsy GG, higher PSAD, and higher PI-RADS score were associated with a significantly increased risk of GG upgrading. Thus, risk factors associated with GG upgrading should be comprehensively assessed for patients with low-grade disease, particularly for those who are considering AS or are under AS program. A repeat systemic biopsy or MRI-ultrasound fusion-guided biopsy might be needed for those with high GG upgrading risk, to avoid delay in the appropriate management and to improve outcomes.

This study has some limitations, which could be considered when interpreting the data and attempting to apply the results to daily clinical practice. First, our study was conducted in a single institution with small sample size and was retrospective in design, which could have an inherent selection bias. Second, we lacked other clinical outcome and follow-up data, and it would be better to incorporate them into analyses. Third, biopsy information such as PNI, cribriform architecture, and percentage Gleason 4 disease, which are potential predictors of unfavorable diseases, were not available in our data; and we could not conduct a more complete comparison. Last, for patients with GG ≤2 PCa, including the highly heterogeneous population with advanced T stage and different PSA levels, there was no further stratification analysis for tumor stage and PSA level because of limited sample size. Thus, further prospective, large-scale studies are warranted to confirm these results.

CONCLUSION

This study suggested that biopsy GG, PSAD, and PI-RADS score >3 are independent predictors of postoperative GG upgrading in low-grade disease at biopsy, and PNI in RP specimens was considerably associated with GG upgrading. These factors could provide additional information in the current risk assessment. These results suggested us that a comprehensive evaluation of the risk of GG upgrading is essential before providing management options.

AUTHOR CONTRIBUTIONS

XL, ZXW, YPZ, and JW collected the dataset and participated in data analyses. XL, XYZ, and ZXW conceived the study and participated in its design, and XL, YSY, XYZ, and YPZ made substantial contributions to manuscript preparation and manuscript editing. XYZ has reviewed and polished the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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