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From Biopsy to Pathology: A Retrospective Cohort Study of Predictors of Gleason Score Upgrading in Grade Group 1 Prostate Cancer

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Abstract

Background/Aim: This study aimed to identify pre-treatment predictors of Gleason score (GS) upgrading in patients with biopsy-confirmed Grade Group 1 (GS 3+3) prostate cancer (PCa) – those typically considered candidates for active surveillance according to National Comprehensive Cancer Network guidelines – so as to refine risk stratification and avoid under-treatment.

Patients and Methods: A retrospective analysis was conducted on patients with biopsy-proven GS 3+3 PCa who underwent radical prostatectomy (RP) at a tertiary referral center between 2010 and 2023. Preoperative clinical, pathological, and biochemical data were collected, including prostate-specific antigen (PSA) levels, PSA density, prostate volume (PV). Multivariable logistic regression was used to identify independent predictors of GS upgrading. Collinearity among PSA, PV, and PSA density was assessed using variance inflation factors and correlation matrix analysis.

Results: Among the 121 patients included in the study, 64.46% experienced GS upgrading at the final pathology. Patients with GS upgrading were older (median age 67.5 years), had higher PSA density (median 0.3 ng/ml/cm^3 *vs.* 0.18 ng/ml/cm^3, p=0.0033), and exhibited a smaller median PV (36.4 ml *vs.* 41 ml, p=0.0145) compared to those without upgrading. These findings highlight the limitations of biopsy-based grading in accurately assessing tumor aggressiveness.

Conclusion: GS upgrading is common in patients initially diagnosed with GS 3+3 PCa and is associated with pre-treatment clinical factors, including PSA density and smaller PV. Identifying these predictors preoperatively may improve risk stratification and guide personalized treatment strategies. Future research should focus on integrating genomic and molecular markers to increase the predictive accuracy and optimize patient management.

Keywords: Prostate cancer, Gleason score upgrading, risk stratification.

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Introduction

Prostate cancer (PCa) remains one of the most frequently diagnosed malignancies among men worldwide, representing a significant burden on healthcare systems globally (1). Accurate grading of prostate tumors is essential for determining appropriate treatment strategies and predicting patient outcomes, with the Gleason score (GS) system serving as the gold standard for assessing PCa aggressiveness. Patients diagnosed with initial biopsy-confirmed GS 3+3 PCa, corresponding to Grade Group 1, are generally classified as having low-risk, indolent disease. These patients are often managed conservatively through active surveillance (AS) to avoid overtreatment and preserve quality of life (2).

However, a subset of these patients may experience GS upgrading on subsequent pathological evaluation following radical prostatectomy (RP) or repeat biopsies, indicating more aggressive disease than initially perceived (3). Recent studies have shown that approximately one-quarter of patients experience GS upgrading or pathologic upstaging (4, 5). This observation highlights the limitations of biopsy-based risk stratification and underscores the need for improved predictive tools to identify patients at risk of GS upgrading.

Several clinical and pathological factors have been implicated in GS upgrading, including prostate-specific antigen (PSA) levels, tumor heterogeneity, biopsy sampling errors, and imaging findings from multiparametric magnetic resonance imaging (mpMRI) (6-8). Given that current guidelines recommend AS for most men with biopsy-confirmed Grade Group 1 disease, accurate identification of patients at risk for upgrading is particularly important to avoid under-treatment. A comprehensive understanding of pre-treatment predictors may therefore enhance risk stratification and support more individualized treatment decision-making.

The primary objective of this study was to evaluate the rate of GS upgrading in patients with an initial biopsy GS of 3+3 and to identify key clinical factors associated with pathological upgrading following RP. Additionally, this study sought to assess the impact of GS upgrading on patient outcomes to better inform risk stratification and treatment strategies for low-risk PCa patients.

Patients and Methods

Study design. This retrospective cohort study was conducted with data from a retrospectively maintained, single-center PCa registry at tertiary referral center. The dataset comprised patients diagnosed with biopsy-confirmed GS 3+3 PCa who underwent RP between 2010 and 2023. The study protocol was approved by the Institutional Review Board Ethics (IRB) Committee of Kaohsiung Medical University Hospital (KMUHIRB-E(I)-20230231). The requirement for written informed consent was waived by the IRB due to the retrospective nature of the study. The waiver covered both participation and publication of anonymized patient data. The study adhered to the principles outlined in the Declaration of Helsinki and complied with the International Conference on Harmonization guidelines for Good Clinical Practice. The authors assume full responsibility for the accuracy, completeness, and integrity of the study data, analysis, and reporting.

Participant selection. At our institution, RP is recommended for patients with low-risk disease who meet one or more of the following conditions:

(i) PSA >10 ng/ml or PSA density >0.15 ng/ml/cm^3; (ii) three or more positive biopsy cores or >50% cancer involvement in any single core; (iii) suspicious or high-grade lesion on mpMRI [prostate imaging-reporting and data system (PI-RADS) ≥4]; (iv) palpable nodule (clinical T2) on digital rectal examination; or (v) patient preference for definitive management after counseling.

Eligible participants included patients who underwent RP between 2010 and 2023 and had biopsy-confirmed GS 3+3 prostate cancer with complete final pathology reports available for review. Patients were excluded if they did not proceed with prostatectomy, or if preoperative clinical data required for the primary analysis (age, pre-biopsy PSA, PV, and final pathological GS) were missing. In

addition, patients with any prior surgical intervention for benign prostatic hyperplasia or PCa, such as transurethral resection of the prostate (TURP), were excluded, as previous procedures could alter prostate volume (PV) or pathology and potentially confound the analysis. Because this was a retrospective analysis including all eligible cases within the study period, no formal sample size calculation or power analysis was performed.

Data collection. Data, including demographic information (age, race, and comorbidities), clinical parameters (PSA levels, PSA density, and PV), and pathological findings [biopsy GS, final GS, perineural invasion (PNI), lymphovascular invasion (LVI), or margin status] were extracted from electronic health records. Imaging data from mpMRI, including Prostate Imaging-Reporting and Data System (PI-RADS) scores, were collected when available. The interval between prostate biopsy and RP was also recorded. Data collection was performed *via* standardized protocols to ensure consistency and accuracy.

Biopsy technique and operator experience. All patients underwent systematic transrectal ultrasound (TRUS)-guided prostate biopsy prior to surgery. A standard 12-core template was used, including six peripheral-zone and six far-lateral cores, obtained under local anesthesia with an 18-gauge needle. All procedures were performed by board-certified urologists at our medical center, each with more than five years of independent clinical experience in urologic oncology. While mpMRI and MRI-targeted biopsy were not routinely performed due to limited insurance coverage, findings from patients who did undergo mpMRI were incorporated into their preoperative assessments.

Study outcomes. The primary outcome of interest was GS upgrading, defined as an upgrade from GS 3+3 at biopsy to GS 3+4, 4+3, or higher on final pathology following RP.

Statistical analysis. Descriptive statistics were used to summarize patient demographics, clinical characteristics, and pathological findings. Continuous variables were reported as the means with standard deviations (SDs) or medians with interquartile ranges (IQRs), depending on their distributions. Categorical variables were presented as frequencies and percentages. Comparisons between patients with and without GS upgrading were conducted *via* chi-square tests for categorical variables and *t*-tests or Mann-Whitney *U*-tests for continuous variables, as appropriate.

Univariable logistic regression analyses were first performed to screen candidate preoperative predictors, including age, pre-biopsy PSA, PSA density, PV, clinical T stage, biopsy-core positivity, and mpMRI findings (when available). Prior to multivariable modeling, collinearity diagnostics – including variance inflation factor (VIF) and correlation matrix analyses – were conducted to assess interdependencies among parameters. Given that PSA density is mathematically derived from PSA and PV, and considering the severe multicollinearity identified between PSA and PV (VIF >9), candidate variables were selected hierarchically to prevent statistical redundancy and model instability.

A case analysis approach was applied to the full analyzed cohort of 121 patients with complete core clinical metrics. Variables that were mathematically derived or highly collinear (PSA, PSA density), non-significant in univariable screening (clinical T stage, biopsy-core features), or unavailable in a uniform subset due to historical reimbursement constraints during earlier study years (mpMRI) were excluded from the final multivariable regression model. Ultimately, the final adjusted multivariable logistic regression model retained age and PV as independent predictors to ensure model parsimony and stability. Statistical significance was set at a two-sided p-value <0.05. All analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

Missing data occurred only in postoperative pathological and follow-up variables (LVI, n=1; recurrence status, n=10). These variables were analyzed using available cases, and the denominator for each variable is reported in the tables. No missing data were present in the variables included in the regression models. Fisher's exact test was used when expected cell counts were <5.

Results

Patient characteristics. A total of 121 patients with biopsy-confirmed GS 3+3 PCa who underwent RP were included in this study (Supplementary Figure S1). The median age was 67 years, with a median preoperative PSA level of 9.06 ng/ml (IQR=6.58-14.84 ng/ml) and a median PSA density of 0.24 ng/ml/cm^3 (IQR=0.16-0.45 ng/ml/cm^3). All patients proceeded directly to RP without a preceding period of AS. The median interval between prostate biopsy and surgery was 2.62 (IQR=1.77-3.40) months. Among the cohort, 78 patients (64.46%) experienced GS upgrading on final pathology. LVI was identified in 9 of 120 evaluable patients (7.5%), and PNI in 50 of 121 (41.32%). Among the 111 patients with available follow-up PSA data, biochemical recurrence (BCR) occurred in 70 (63.06%) during follow-up (Table I).

Table I. *Clinical characteristics of 121 patients with GS 3+3.*

	n=121	%
Age		
Median (Q1, Q3)	67 (62-71)	
Pre-biopsy PSA		
Median (Q1, Q3)	9.06 (6.58-14.84)	
PV		
Median (Q1, Q3)	38.15 (29.85-49.15)	
PSA density		
Median (Q1, Q3)	0.24 (0.16-0.45)	
Interval between biopsy and RP		
Median (Q1, Q3)	2.62 (1.77-3.40)	
GS upgrading		
Yes	78	64.46
No	43	35.54
LVI (n=120)		
Yes	9	7.5
No	111	92.5
PNI		
Yes	50	41.32
No	71	58.68
Recurrence (n=111)		
Yes	70	63.06
No	35	31.53
Without nadir	6	5.41

GS: Gleason score; PSA: prostate specific antigen; PV: prostate volume; RP: radical prostatectomy; LVI: lymphovascular invasion; PNI: perineural invasion. Missing data: LVI, n=1; recurrence status, n=10. Percentages are calculated based on available data.

Comparison between patients with and without Gleason Score upgrading. We compared the clinical and pathological characteristics of patients with and without GS upgrading (Table II, Supplementary Figure S2). Patients with GS upgrading had significantly smaller PVs (median 36.4 ml *vs*. 41 ml, p=0.0145) and higher PSA densities (median 0.3 ng/ml/cm^3 *vs*. 0.18 ng/ml/cm^3, p=0.0033) compared to those without upgrading. The prevalence of LVI was similar between the two groups, but PNI was significantly more frequent in the upgrading group (53.25%), than in the non-upgrading group (20.93%; p=0.0004).

Predictors of Gleason Score upgrading. The results of univariable and multivariable analyses identifying predictors of GS upgrading are summarized in Table III. In the multivariable model, older age (adjusted OR=1.091, 95%CI=1.017-1.171; p=0.0147) and smaller PV (adjusted OR=0.959, 95%CI=0.931-0.987; p=0.0049) were significant independent predictors of GS upgrading. Although PSA density was significantly associated with GS upgrading in univariable analysis, it was not entered into the multivariable model because it is mathematically derived from PSA and PV.

Univariable predictors of Gleason Score upgrading. Forest plot analysis further demonstrated the univariable associations between clinical parameters and GS upgrading (Figure 1). Advancing age, elevated PSA density and reduced PV were significantly associated with upgrading from GS 3+3 to more aggressive disease. Notably, these findings are consistent with previous evidence suggesting that anatomical factors play significant roles in the underestimation of tumor aggressiveness at biopsy. The forest plot illustrates the effect estimates for the evaluated variables and their potential utility in preoperative risk stratification.

Assessment of multicollinearity. In Table IV, collinearity diagnostics were performed to assess potential interactions among covariates. VIF analysis revealed significant collinearity between pre-biopsy PSA

Table II. *Comparison of characteristics between patients with and without Gleason score (GS) upgrading.*

	GS upgrading		
	No (n=43)	Yes (n=78)	*p*-Value
Age, Median (Q1-Q3)	65 (59-71)	67.5 (63-72)	0.0594
Pre-biopsy PSA, Median (Q1-Q3)	8.35 (6.09-12.18)	9.53 (6.9-16.7)	0.2219
PSA Density, Median (Q1-Q3)	0.18 (0.14-0.31)	0.3 (0.19-0.48)	0.0033
PV, Median (Q1-Q3)	41 (33.94-58)	36.4 (27.9-46.5)	0.0145
LVI, n (%)		n=76	0.0838
Not present	42 (97.67)	68 (89.47)	
Present	1 (2.33)	8 (10.53)	
PNI, n (%)		n=77	0.0004
Not present	34 (79.07)	36 (46.75)	
Present	9 (20.93)	41 (53.25)	

PSA: Prostate specific antigen; PV: prostate volume; PNI: perineural invasion; LVI: lymphovascular invasion. Percentages are calculated based on available data. *p*-Values were calculated using the Mann–Whitney *U*-test, chi-square test, or Fisher's exact test, as appropriate.

(VIF=9.994) and PV (VIF=10.802). Correlation matrix analysis further demonstrated strong positive correlations between PSA and PV (Pearson r=0.839, $p<0.001$; Spearman ρ=0.759, $p<0.001$). PSA density showed moderate correlations with PSA and PV but remained within acceptable VIF thresholds (VIF=3.452). Other variables, including age, PNI, and LVI, demonstrated minimal collinearity (VIF range=1.061-1.202).

Discussion

Our findings highlight the importance of identifying reliable predictors of GS upgrading among patients with biopsy-confirmed Grade Group 1 disease who are potential candidates for AS. In accordance with National Comprehensive Cancer Network Guidelines 2026, these patients represent the subgroup in which upgrading has the greatest clinical impact, as it may shift management from AS to definitive therapy. We found that older age and smaller PV were significant predictors of GS upgrading. These results underscore the complex nature of seemingly indolent PCa and reinforce the need for a personalized approach to managing patients initially diagnosed with GS 3+3 disease. Therefore, the present results should primarily be interpreted in the context of refining patient selection and monitoring strategies for AS rather than in higher-risk groups already indicated for radical treatment.

The study cohort comprised patients with biopsy GS 3+3 disease who nevertheless underwent RP. The main indications for surgery were elevated PSA or PSA density, high tumor volume on biopsy, suspicious MRI findings, or patient preference for definitive treatment. Consequently, our population may represent a slightly higher-risk subset of Grade Group 1 patients, which could partially explain the relatively high rate of GS upgrading observed. Future studies including patients managed with AS would provide a more balanced estimate of upgrading across all low-risk subgroups.

Importantly, our study focused on clinically available pre-treatment indicators that can inform decision-making at diagnosis. This approach aligns with the clinical purpose of identifying risk factors relevant to patient counseling and AS eligibility. In line with this approach, recent research identified preoperative PSA levels, clinical T stage, and biopsy GS as the strongest predictors of LVI in PCa patients, highlighting the potential of preoperative data to refine risk stratification and treatment planning (9).

Aging and Gleason Score upgrading. Aging emerged as a significant predictor of GS upgrading in our study, likely reflecting the complex interplay between age-related changes in tumor biology and immune surveillance. Previous studies have demonstrated that advancing age is an independent predictor of GS upgrading on confirmatory biopsy, even when controlling for PV and PSA levels (6, 10-12). Notably, the odds of upgrading have been reported to increase by 4% to 7% per year of age (6, 12). Consistent with our findings, Porcaro *et al*. identified advanced age, palpable tumors, and pelvic lymph node invasion as independent predictors of PCa progression in a cohort of patients undergoing robot-assisted RP and extended lymph node dissection (13). These findings suggest that age-related changes in the tumor

Table III. *Univariable and Adjusted logistic regression for predicting Gleason score upgrading in patients after radical prostatectomy.*

	cOR	*p*-Value	aOR	*p*-Value
Age	1.065 (1.003-1.131)	0.0386	1.091 (1.017-1.171)	0.0147
Pre-biopsy PSA	1.035 (0.98-1.092)	0.2129		
PSA Density	24.275 (2.131-276.556)	0.0102		
PV	0.963 (0.939-0.988)	0.0035	0.959 (0.931-0.987)	0.0049

PSA: Prostate specific antigen; PV: prostate volume; cOR: crude odds ratio; aOR: adjusted odds ratio.

microenvironment may contribute to the development of more aggressive disease.

The correlation between advanced age and GS upgrading identified in our study likely stems from a combination of biological and procedural factors. Aging-related declines in androgen concentrations have been shown to trigger spontaneous stromal remodeling, primarily through increased fibroblast proliferation and reduced smooth muscle density (14). Furthermore, Malinen *et al.* demonstrated that pro-inflammatory signaling can profoundly alter the androgen receptor cistrome, potentially facilitating oncogenic progression (15). These physiological shifts may result in a greater degree of tumor heterogeneity, thereby increasing the likelihood that higher-grade components remain undetected during initial biopsy, only to be identified following RP.

Furthermore, prostate gland characteristics in older men – such as increased gland size, fibrosis, or atrophy – may also reduce sampling precision during biopsy. Collectively, these biological and technical factors may account for the higher probability of GS upgrading with advancing age. Given these observations, older patients initially classified as GS 3+3 PCa may require closer monitoring and additional diagnostic measures, such as targeted biopsy or advanced imaging. Tailoring management strategies to account for age-related biological changes could improve outcomes and optimize care in this population.

Small prostate volume and Gleason Score upgrading. The association between smaller PV and GS upgrading observed in our study underscores the potential influence of anatomical factors on the accuracy of PCa grading. Smaller prostates are more likely to harbor undetected higher-grade disease during biopsy due to limited sampling areas and the reduced likelihood of detecting tumor heterogeneity. A recent meta-analysis by Zou et al. involving 14,823 patients confirmed that smaller PV was a significant predictor of GS upgrading following radical prostatectomy (3). Consistently, a recent cohort study identified a prostate volume cutoff of <38 ml as being associated with an increased risk of pathological Gleason score upgrading (16). Additionally, Wang *et al.* reported that smaller PV independently predicted GS upgrading after surgery, suggesting an inverse relationship between gland size and tumor grade (17). These findings supported the integration of PV into risk stratification models for AS, particularly in men with small prostates (16). Directed biopsy methods and consideration of PV during initial risk assessment could improve the accuracy of grading and reduce the risk of underestimating tumor aggressiveness.

Several studies have proposed biological mechanisms for the association between PV and upgrading. Theory suggested that smaller prostates may exhibit reduced androgenicity and lower intraprostatic growth factor concentrations, creating a microenvironment conducive to aggressive tumor development (18). Additionally, larger prostates tend to have lower glandular density in the peripheral zone and thicker capsules, which may account for lower detection rates of higher-grade tumors during biopsy (19-21). However, some researchers have argued that this association may reflect ascertainment bias due to the performance of PSA in detecting clinically T1c disease (22). Future research is needed to clarify the relationship between PV and tumor aggressiveness.

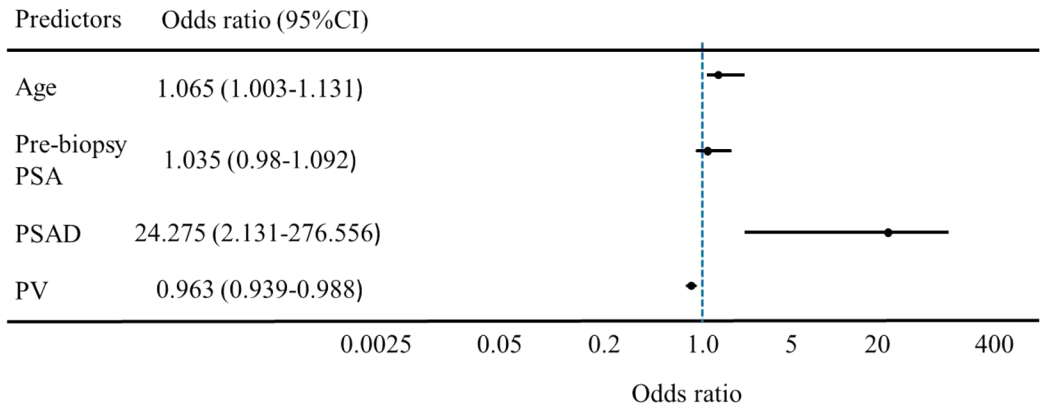


Figure 1. *Forest plot of univariable predictors associated with Gleason Score upgrading. This figure depicts the odds ratios for predictors such as age, pre-biopsy PSA, PSA density and PV. Among these predictive factors, older age, and smaller PV were confirmed determinants of possible GS upgrading. PSA: Prostate specific antigen; PSAD: PSA density; PV: prostate volume.*

Table IV. *Collinearity assessment.*

Variables	VIF	Correlation matrix					
		Age	Pre-biopsy PSA	PV	PSA Density	PNI	LVI
Age	1.061		0.001	–0.065	0.105	0.030	0.097
Pre-biopsy PSA	9.994	0.083		0.759***	0.129	0.129	0.104
PV	10.802	0.040	0.839***		–0.490***	0.219*	0.241**
PSA Density	3.452	0.153	0.132	–0.332**		–0.074	–0.216*
PNI	1.115	0.041	0.148	0.154	–0.101		0.278**
LVI	1.202	0.093	0.160	0.232*	–0.240**	0.278**	

*p<0.05; **p<0.01; ***p<0.001. VIF: Variance inflation factor; PNI: perineural invasion; PSA: prostate specific antigen; PV: prostate volume; LVI: lymphovascular invasion; The lower triangular matrix reports the estimated Pearson correlation coefficients, and the upper triangular matrix reports the Spearman correlation coefficients.

Role of MRI in diagnosis and upgrading prediction. MpMRI has become a cornerstone of prostate cancer diagnosis, enabling improved detection of clinically significant tumors and more accurate risk stratification (23-25). In our cohort, only a subset of patients underwent mpMRI prior to biopsy because of reimbursement limitations and the gradual implementation of MRI-based protocols during the earlier study years. The absence of routine MRI for all patients may have contributed to biopsy sampling error and subsequent GS upgrading. Future prospective studies incorporating MRI-targeted biopsy and standardized PI-RADS assessment are warranted to enhance diagnostic precision and reduce underestimation of tumor grade.

Impact of biopsy method and MRI-targeted techniques. The accuracy of prostate biopsy depends heavily on the sampling method and operator expertise. All biopsies in our series were systematic TRUS-guided procedures performed by experienced urologists, which minimizes sampling error. The absence of routine MRI-targeted biopsy during much of the study period likely contributed to the observed rate of GS upgrading. MRI-targeted biopsy has been shown to improve lesion localization and reduce grade underestimation (8, 26, 27), suggesting that such techniques could enhance diagnostic precision in future practice.

Variance inflation factors/collinearity analysis. In a recent study, Kuo *et al.* highlighted the utility of integrating PSA-

derived biomarkers to optimize biopsy and risk-stratification decisions (28). However, pre-biopsy PSA and PV exhibited strong correlation coefficients and VIF values approaching or exceeding conventional multicollinearity thresholds in our study. Such findings are biologically plausible, as serum PSA levels reflect not only tumor burden but also benign prostatic volume. This interdependence was previously highlighted by Huang *et al.* who observed significant correlations between PV and both total and free PSA ($p<0.05$) in a cohort of 1,620 patients (29). More recently, a meta-analysis of over 14,000 low-risk cases confirmed that PV acts as a critical confounder, with its biological overlap often destabilizing risk stratification models (3). Furthermore, studies focusing on predictive modeling for GG1 upgrading have increasingly highlighted that such collinearity can compromise the reliability of individual regression coefficients, leading to statistical instability in multivariable analyses (30). Given these findings, the high VIF observed between PV and PSA suggests that including both variables in the same multivariable model could lead to statistical instability.

Based on the results of the VIF and correlation analyses, PSA and PV were therefore not simultaneously included in the final multivariable models. Instead, we chose to prioritize PV in the final adjusted model to reflect its stronger independent predictive value for GS upgrading in this cohort. This methodological approach maintains the robustness of the identified predictors by minimizing the risk of model instability caused by the inherent correlation between PV and total PSA secretion.

Furthermore, other clinical parameters evaluated during initial screening – including clinical T stage and biopsy-core positive rates – did not demonstrate statistically significant independent associations during univariable testing and were omitted to maintain model parsimony. Preoperative mpMRI findings were analyzed descriptively due to variable historical availability across the long retrospective study window (2010-2023), thereby avoiding sample size attenuation in the primary multivariable model. Consequently, restricting the final adjusted model to age and PV provided the most stable, robust, and parsimonious predictive estimation for Gleason score upgrading in this cohort.

Clinical interpretation of key predictors. In our univariable analysis, several factors were associated with GS upgrading, as illustrated in the forest plot. Among preoperative variables, smaller PV and higher PSA density exerted the greatest relative impact on the likelihood of upgrading. These parameters likely reflect a higher tumor-to-gland ratio and potential under-sampling of aggressive foci during biopsy, emphasizing the need for careful selection and counseling of candidates for AS.

Future directions. Future research should focus on prospective, multicenter studies with standardized data collection protocols and long-term follow-up. Incorporating comprehensive clinical staging, surgical, pathological variables – including margin status and neurovascular bundle preservation – genomic and molecular testing could significantly improve the predictive accuracy of GS upgrading. Additionally, including patients managed with AS would provide a more comprehensive understanding of disease progression across all risk groups. Detailed analysis of the impact of adjuvant therapies on BCR in patients with GS upgrading is also needed to refine treatment strategies.

Study limitations. This study is limited by its retrospective, single-center design and by the inclusion of biopsy-confirmed Grade Group 1 patients who underwent RP rather than a representative AS population. Institutional indications for surgery included elevated PSA or PSA density, greater biopsy tumor volume, suspicious mpMRI findings, and patient preference, potentially enriching the cohort for patients with greater clinical suspicion of aggressive disease. Some patients also had PSA levels >10 ng/ml and did not meet Epstein criteria. Therefore, the observed upgrading rate should not be generalized directly to contemporary AS populations. The long

inclusion period (2010-2023), incomplete availability of mpMRI, and lack of routine MRI-targeted biopsy may also have introduced temporal and diagnostic heterogeneity.

The modest sample size and incomplete availability of some clinical variables limit the precision of the multivariable estimates, while the absence of genomic and molecular biomarkers limits comprehensive risk assessment. Follow-up was relatively short or heterogeneous for some patients, restricting conclusions regarding biochemical recurrence and other long-term outcomes. Prospective multicenter studies incorporating contemporary MRI-targeted biopsy, standardized pathological assessment, and both surgical and active-surveillance populations are needed to validate these findings.

Conclusion

This study identified older age and smaller PV as independent predictors of GS upgrading in biopsy-confirmed GS 3+3 prostate cancer. These findings underscore the limitations of biopsy-based grading and the need for individualized risk assessment in low-risk PCa patients. Integrating parameters such as PSA density, PV and imaging features into preoperative models may improve risk stratification for AS and prevent under-treatment. Future multicenter prospective studies incorporating molecular and genomic biomarkers are warranted to refine predictive accuracy and optimize personalized management strategies for early-stage prostate cancer.

Supplementary Material

Supplementary material is available at: https://doi.org/10.6084/m9.figshare.33996069

Conflicts of Interest

The Authors have declared that there are no conflicts of interest in relation to this study.

Authors' Contributions

All Authors contributed to the study conception and design. Material preparation, tables creation, data collection and analysis were performed by YCS, HYL, YSJ, WJW and KL. The first draft of the manuscript was written by HCS and all Authors commented on previous versions of the manuscript. All Authors read and approved the final manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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