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Prediction of pathologic upgrading in Gleason score 3+4 prostate cancer: Who is a candidate for active surveillance?

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Purpose: Whether active surveillance (AS) can be safely extended to patients with Gleason score (GS) 3+4 prostate cancer is highly debated. We examined the incidence and predictors of upgrading among patients with GS 3+4 disease.

Materials and Methods: The study involved 377 patients with biopsy GS 3+4 who underwent robot-assisted laparoscopic radical prostatectomy (RP) from 2014 to 2018 at a single institution. We analyzed the rate of GS upgrading and used logistic regression to determine the predictors of upgrading.

Results: A total of 168 (44.6%) patients with GS 3+4 experienced an upgrade in GS. In multivariable analysis, advanced age, prostate-specific antigen (PSA) level, PSA density (PSAD) and Prostate Imaging-Reporting and Data System version 2 (PI-RADS v2) score were significant predictors of GS upgrading. When structured into a predictive model that included age ≥65 years, PSA ≥7.7 ng/mL, PSAD ≥0.475 ng/mL^2 and PI-RADS v2 score 4–5, the probability of GS upgrading ranged from 36.4% to 65.7% when one to four of these factors were included.

Conclusions: A substantial proportion of patients with GS 3+4 prostate cancer were upgraded after RP. However, according to our model combining clinical and imaging predictors, patients with a low risk of GS upgrading may be eligible candidates for AS.

Keywords: Pathology; Prognosis; Prostate neoplasms; Prostatectomy

INTRODUCTION

Prostate cancer (PCa) has the highest incidence rate and the second-highest mortality rate of the common cancers in males [1]. However, many newly diagnosed PCa patients present in early stage when the disease is indolent or non-progressing and is unlikely to lead to morbidity or mortality [2]. For this reason, active surveillance (AS) has emerged as an attractive option for low-risk PCa to avoid overtreatment and reserve the opportunity for definitive therapy if the disease progresses. Whether or not AS can be safely extended to patients with Gleason 3+4 PCa remains a highly debated issue. Some data have shown that intermediate-risk (IR) PCa has similar oncologic outcomes to low-risk disease following curative treatment [3-5], suggesting that some Gleason score (GS) 3+4 patients may be candidates for AS. The National Comprehensive Cancer Network (NCCN) guidelines list AS as an option for males with favorable IR PCa (GS 3+4, <50%

positive biopsy cores and one additional IR factor) [6], while the America Society of Clinical Oncology endorses AS for select patients with low-volume Gleason 3+4 disease [7]. However, criteria identifying "favorable" IR have not yet been defined clearly due to lack of supporting oncologic evidence.

Although the GS score is regarded as the single most important determinant in risk assessment, evidence supporting AS in the majority of studies is based on biopsy results instead of whole-specimen pathology [8,9]. Many patients with GS 3+4 prostate cancer harboring higher grade disease than their biopsy need immediate active treatment, rather than AS, because of the high potential to progress [10]. We, therefore, examined the incidence and predictors of upgrading in GS 3+4 patients underwent radical prostatectomy (RP) to provide simple guidance on selecting GS 3+4 patients who would benefit from AS.

MATERIALS AND METHODS

This retrospective study was approved by Institutional Review Board of Seoul National University Bundang Hospital (IRB number: B-1706/402-115). We identified 1,791 males who underwent robot-assisted laparoscopic RP from 2014 to 2018. Transrectal ultrasound-guided prostate biopsy and multiparametric magnetic resonance imaging (mpMRI) were performed preoperatively on all of the patients according to the Prostate Imaging-Reporting and Data System version 2 (PI-RADS v2) guidelines. After excluding patients who had incomplete biopsy data (n=25) and those who had not assessed PI-RADS v2 classification in mpMRI (n=516), 1,250 patients with various GS score were examined to identify patients with GS 3+4 PCa. Eventually, a database of 377 patients was analyzed in our study.

The clinical and biopsy variables included age, prostate volume, prostate-specific antigen (PSA) level, PSAD density (PSAD), number of positive cores, maximum tumor length in a core, PI-RADS v2 score, number of lesions in mpMRI and clinical tumor stage. Pathologic variables were primary and secondary GS on biopsy samples and surgical specimens. GS was assigned according to the 2005 International Society of Urological Pathology (ISUP) modified Gleason scoring system. The primary outcome was GS upgrading, defined as an increase to GS ≥4+3 after RP.

The patients were divided into the upgraded and non-upgraded groups. We used chi-squared tests to compare the categorical variables and independent t-tests or Mann–Whitney test to compare the continuous variables. Univariable and multivariable logistic regression analyses were applied to determine the predictors of GS upgrading. All tests were two-sided with significance assumed at p<0.05. Statistical analyses were performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The baseline demographic and clinical features of 377 patients who were diagnosed with GS 3+4 PCa and underwent RP are shown in Table 1. Among the 377 total patients, the GS was upgraded in 168 (44.6%) after RP. Of these upgraded, 155 (92.3%) were upgraded to GS 4+3, four (2.4%) to GS 4+4, and nine (5.3%) to GS 4+5. In 209 subjects whose GS were not upgraded, only 1 (0.5%) was downgraded to GS 3+3 and 208 (99.5%) remained GS 3+4. Comparison of the non-upgraded and upgraded patients demonstrated that there was no statistical difference in prostate volume, number of positive cores, percentage of positive cores, maximum tumor length in a core, maximum percentage of tumor length in a positive core in biopsy samples, number of lesions in mpMRI and clinical tumor stages. In contrast, the upgraded group showed significantly higher age, preoperative PSA level, PSAD and PI-RADS v2 score.

Using receiver operating characteristic curve analysis, we identified the optimal cut-off value for continuous variables associated with GS upgrading, including age, PSA, and PSAD in order to change them into categorical variables for easily clinical application. Using univariate logistic regression analysis to determine the predictors, the results indicated that GS upgrading was positively associated with age ≥65 (p=0.032), PSA level ≥7.7 ng/mL (p<0.001), PSAD ≥0.475 ng/mL^2 (p<0.001) and PI-RADS v2 score 4–5 (p=0.007). In a further multivariate logistic regression model using these factors, all four elements were significantly related to GS upgrading (Table 2).

The GS upgrading predictive model was structured to stratify patients according to four risk factors: age ≥65, PSA level ≥7.7 ng/mL, PSAD ≥0.475 ng/mL^2, and PI-RADS v2 score 4–5. The rate of GS upgrading in patients with GS 3+4 PCa is shown in Table 3 and ranged from 36.4% when at least one of four predictive factors was included to 65.7% when all four factors were present (p<0.001).

DISCUSSION

Although AS is an alternative management strategy for patients who have mainly low-risk GS 3+3 cancer, several AS protocols include GS 3+4 PCa patients [11,12]. Males with GS 3+4 on biopsy were comparable to those with GS 3+4 in terms of biochemical recurrence and mortality [3,4].

Table 1. Patient demographics and clinicopathologic characteristics stratified by Gleason score

Variable	Total (n=377)	Non-upgraded (n=209)	Upgraded (n=168)	p-value
Age (y)	68 (63–72)	68 (62–72)	69 (64–73)	0.035
PSA (ng/mL)	7.45 (5.41–12.00)	6.80 (4.79–10.56)	8.72 (6.09–14.90)	<0.001
PV (mL)	32.0 (26.0–40.0)	33 (26.0–41.2)	31.1 (26.0–38.5)	0.217
PSAD (ng/mL^2)	0.24 (0.16–0.38)	0.20 (0.15–0.32)	0.28 (0.20–0.46)	<0.001
Number of positive cores	3 (2–5)	3 (2–5)	3 (1–6)	0.633
Percent of positive cores	25.0 (16.7–42.9)	25.0 (16.7–41.7)	25.0 (14.3–49.1)	0.840
Maximum tumor length in a core (mm)	0.5 (0.3–0.8)	0.5 (0.3–0.8)	0.6 (0.4–0.8)	0.560
Maximum percentage of tumor length in a positive core	31.7 (21.4–50.0)	30.7 (20.0–50.0)	33.3 (22.2–52.9)	0.262
PI-RADS v2 score				0.034
1	4 (1.1)	3 (1.4)	1 (0.6)	
2	2 (0.5)	2 (1.0)	0 (0.0)	
3	64 (17.0)	44 (21.1)	20 (11.9)	
4	166 (44.0)	93 (44.5)	73 (43.5)	
5	141 (37.4)	67 (32.1)	74 (44.0)	
Number of lesions in mpMRI				0.425
1	319 (84.6)	181 (86.6)	138 (82.1)	
2	55 (14.6)	27 (12.9)	28 (16.7)	
3	3 (0.8)	1 (0.5)	2 (1.2)	
Clinical T stage				0.324
T1b-c	249 (66.0)	143 (68.4)	106 (63.1)	
T2	82 (21.8)	44 (21.1)	38 (22.6)	
T3a-b	46 (12.2)	22 (10.5)	24 (14.3)	

Values are presented as median (interquartile range) or number (%).
PSA, prostate-specific antigen; PV, prostate volume; PSAD, PSA density; PI-RADS v2, Prostate Imaging-Reporting and Data System version 2; mpMRI, multiparametric magnetic resonance imaging.

Table 2. Uni- and multivariable logistic regression of clinicopathologic parameters on upgrading

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (y) (≥65 vs. <65)	1.627 (1.040–2.544)	0.032	1.594 (1.003–2.532)	0.049
PSA (ng/mL) (≥7.7 vs. <7.7)	2.062 (1.365–3.117)	<0.001	1.631 (1.032–2.579)	0.036
PV (mL)	0.994 (0.981–1.008)	0.414		
PSAD (ng/mL^2) (≥0.475 vs. <0.475)	2.707 (1.522–4.814)	<0.001	2.034 (1.076–3.845)	0.029
Number of positive cores	1.003 (0.925–1.088)	0.937		
Percent of positive cores	1.004 (0.994–1.015)	0.411		
Maximum tumor length in a core	1.191 (0.684–2.074)	0.536		
Maximum percentage of tumor length in a positive core	1.005 (0.996–1.014)	0.267		
PI-RADS v2 score (4–5 vs. 1–3)	2.144 (1.227–3.746)	0.007	1.998 (1.130–3.534)	0.017
Number of lesions in mpMRI	1.404 (0.834–2.365)	0.202		
Clinical T stage				
T1b-c	Reference			
T2	0.679 (0.362–1.277)	0.230		
T3a-b	0.792 (0.382–1.632)	0.527		

OR, odd ratio; CI, confidence interval; PSA, prostate-specific antigen; PV, prostate volume; PSAD, PSA density; PI-RADS v2, Prostate Imaging-Reporting and Data System version 2; mpMRI, multiparametric magnetic resonance imaging.

However, D'Amico et al. [13] reported that 40% of the males with low-grade disease at biopsy were found to have high grade disease at prostatectomy and other studies showed that a substantial percentage of patients with GS 3+4 were upgraded [10,14]. Additionally, GS ≥4+3 disease that has a significantly poor prognosis compared to GS 3+4 disease

Table 3. Probability of Gleason upgrading in patients presenting with risk factors (n=377)

Number of risk factors	n (%)	Probability of GS upgrading	p-value
0	12 (3.2)	0%	<0.001
1	88 (23.3)	36.4%	
2	141 (37.4)	36.9%	
3	101 (26.8)	60.4%	
4	35 (9.3)	65.7%	

GS , Gleason score.

[15,16], needs an active treatment rather than AS. Ploussard et al. [17] reported that the rate of GS upgrading from GS 3+4 to pathologic GS ≥4+3 was 25.3%. Their study solely enrolled patients diagnosed with biopsy GS 3+4 and clinical T1–2 stage, whereas our study included all patients with clinical T1–3 stage. As a predisposing risk factor in a few studies, the impact of clinical stage on GS upgrading was taken into account. Similarly, Yang et al. [10] demonstrated that 30.3% of patients were upgraded when more than 10,000 males with GS 3+4 PCa were analyzed. The subjects in that study fulfilled the NCCN categorization of favorable IR PCa (PSA <10 ng/mL, cT1c-2a, and positive biopsy score <50%) [10]. Recently, numerous studies reported that PSA level and number of positive biopsy cores were considered significant predictors for pathologic GS upgrading [10,14,17,18]. Therefore, the marked differences in the percentage of GS-upgraded patients between their study and ours can be contributed to these eligibility criteria.

As previously mentioned, high-grade PCa is associated with adverse pathology and an increased risk of PCa-related death [19,20]. Consequently, the prediction of GS upgrading plays an important role when considering AS, especially in GS 3+4 patients. In our study, we found that age, PSA level, PSAD, and PI-RADS v2 score were highly associated with GS upgrading. Ploussard et al. [17] reported that PSA, PSAD, clinical stage, and >2 positive cores were significant predictors. Similarly, Yang et al. [10] found the predictors, including age, higher PSA value, clinical stage cT2c versus cT1c, and the percentage of positive cores on multivariable analysis. However, Morlacco et al. [14] showed that only age, PSAD, and the percentage of surface involvement, not clinical stage, were associated with GS upgrading. These discrepancies were probably caused by the diverse population in their study with various selection criteria, such as restricted PSA level, clinical stage, and the number of positive cores.

Notably, age is an independent predictor of GS upgrading confirmed by previous studies of low- and intermediate-risk PCa patients [10,21]. Consistent with our results, Busch

et al. [22] reported that pathological upgrading was significantly higher among older (≥65 years) versus younger (<65 years). With increasing age, males are significantly more likely to have poor prognosis prostate cancer. A possible explanation is the growing tendency to use hormone therapy and watchful waiting/AS among elderly males and less local therapy, particular RP, compared to younger males [23]. A high proportion of young males with low-risk cancer enrolled in AS subsequently receive curative treatment. Alternatively, a large proportion of old males with more aggressive cancer receive watchful waiting than younger males with less aggressive cancer [24]. Additionally, more aggressive prostate cancers possibly arise during andropause when the plasma levels of free testosterone may be below the lower limit of normal. Prior studies found that high-grade prostate cancer was associated with low serum testosterone levels [25,26]. Although the precise mechanism of this phenomenon is incompletely understood, it might be related to the influence of aging on tumor biology, leading to more aggressive differentiation. In general, advanced age should be taken into consideration when discussing treatment for elderly males who have a higher risk of death from competing causes and more comorbidities.

Similar to the aforementioned studies, we found that PSA level was a consistent predictor for GS upgrading after surgery. This outcome supports PSA as a powerful prognostic factor in PCa. Interestingly, prostate volume did not show significant value in predicting GS upgrading, but PSAD was highly associated with GS upgrading in our study. Recent studies also proved that PSAD was an independent predictor of upgrading [14,17], suggesting a critical role in the GS upgrading predictive model.

Recently, mpMRI has become a promising tool in diagnosis and staging of PCa. Many studies confirmed the value of MRI within AS, which has a high specificity for low-risk PCa but in none of studies was MRI used as an indication for treatment [27]. Park et al. [28] revealed that PI-RADS v2 helped preoperatively predict clinically significant cancer, such as GS ≥7, tumor volume ≥0.5 cm^2, and positive extracapsular extension or seminal vesicle invasion. Song et al. [29] showed that the combination of MRI and clinical parameters had a significantly higher accuracy than clinical variables in GS 6 patients. Our study indicated that PI-RADS v2 score ≥4 was positively associated with an increased risk of upgrading in GS 3+4 cancer, proposing a powerful predictor to properly evaluate the GS upgrading probability of GS 3+4 PCa patients.

In recent years, much of research on the value of predictive factors has focused on the relationship between GS

upgrading and clinical parameters. The important question that emerges is how we can apply these results in daily challenging situation to determine risk classification and counsel patients regarding treatment decisions and disease prognosis. Ploussard et al. [17] assessed three factors including: PSAD >0.15 ng/mL^2, >2 positive cores, and clinical stage T2, and the rate of GS upgrading was 12% when any factors were present and up to 30.9% when all three factors were involved. In our study, we structured a simple predictive model with four factors: age ≥65, PSA ≥7.7 ng/mL, PSAD ≥0.475 ng/mL^2, and PI-RADS v2 score ≥4. The more risk factors the GS 3+4 PCa patient has, the higher GS upgrading probability is. Indeed, the rate of GS upgrading ranged from 36.4% to 65.7% when one to 4 factors were present.

Our study was not devoid of limitations. First, our findings came from a retrospective study at a single institution. The retrospective nature and the lack of a single experienced pathologist reexamination of all cases are potential limitations. Second, the patients were selected for RP and may be not representative of all patients with GS 3+4 who underwent radiotherapy, watchful waiting or another therapy and that introduced a selection bias in study. Finally, we did not analyze some characteristics of biopsy sample, such as percentage of GS 4 and tertiary GS 5, which might relate to poor PCa prognoses. Further studies with a larger data set analyzing adequate information on biopsy samples are necessary to estimate the relationship between variables and adverse pathology.

CONCLUSIONS

Approximately half of the patients with biopsy GS 3+4 cancer was upgraded after RP. The risk of GS upgrading included advanced age, high PSA, high PSAD, and PI-RADS score 4–5 identify patients as poor candidates for AS. Our results suggest a useful tool that can be applied easily in clinical circumstances to determine the risk classification and recommend patients for reasonable treatments.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Sang Eun Lee had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Duc Minh Pham, Jung Kwon Kim, and Sang Eun Lee.

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