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ORIGINAL RESEARCH

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U.P.G.R.A.D.E. score: a new scoring system in predicting pathological upgrading after prostatectomy in patients with Gleason grade group 1 prostate cancer

Kaan Karamık[1,*], Hakan Anıl[2], Ali Yıldız[3], Ahmet Güzel[4], Serkan Akdemir[5], Murat Arslan[3]

[1]Department of Urology, Kemer State Hospital, 07980 Antalya, Turkey
[2]Department of Urology, Medical Park Seyhan Hospital, 01010 Adana, Turkey
[3]Department of Urology, Faculty of Medicine, Okan University, 34940 Istanbul, Turkey
[4]Department of Urology, Aydın State Hospital, 09000 Aydın, Turkey
[5]Department of Urology, Tınaztepe Hospital, 35390 İzmir, Turkey

***Correspondence**
kaan.karamik@saglik.gov.tr
(Kaan Karamık)

Abstract

Pathological upgrading poses a significant challenge in treatment decision-making, particularly for patients considered for active surveillance (AS). This study aimed to devise a novel scoring system to predict the risk of upgrading in patients with biopsy Gleason grade group 1 prostate cancer. We conducted a retrospective review of 235 patients who underwent radical prostatectomy between February 2014 and June 2022. Data on patient age, prostate-specific antigen (PSA) level, body mass index, clinical T-stage, prior biopsy history, Prostate Imaging-Reporting and Data System (PIRADS) score, time interval from biopsy to surgery, and pathological outcomes were collected. After a comprehensive review of the literature, multivariate analyses identified seven factors associated with upgrading in prostate cancer patients after radical prostatectomy: uninformative prior biopsy sample, PSA level, greatest percentage of tumor involvement, radiological PIRADS score, age, delay from biopsy to surgery and extension of positive cores. These factors were integrated into our devised U.P.G.R.A.D.E. model to form a scoring system. The U.P.G.R.A.D.E. score was calculated based on the cumulative score of these variables. The predictive performance of the U.P.G.R.A.D.E. scoring system was assessed, revealing a cohort with a mean age of 64.22 $\pm$ 5.88 years and a mean PSA value of 8.92 $\pm$ 5.05 ng/mL. The pathological samples of 95 patients (40.6%) were upgraded, and the upgraded patients exhibited significantly higher U.P.G.R.A.D.E. scores ($p < 0.001$). The area under the receiver operating characteristic (AUROC) curve for the U.P.G.R.A.D.E. scoring system demonstrated robust predictive ability for upgrading (AUROC = 0.952; 95% Confidence interval (CI): 0.926–0.978; $p < 0.001$). In addition, a higher U.P.G.R.A.D.E. score was strongly associated with an increased risk of upgrading in biopsy Gleason grade group 1 patients, suggesting potential limitations for active surveillance eligibility in these individuals. Further validation studies are warranted to confirm these initial findings.

Keywords

Prostate cancer; Pathology; Upgrading; Scoring system

1. Introduction

Prostate cancer (PCa) is the most frequently diagnosed cancer among men and ranks second in cancer-related mortality [1]. The widespread use of prostate-specific antigen (PSA) screening has led to an increase in the detection of small-volume and low-grade tumors. Therefore, active surveillance (AS) has emerged as a preferred initial management strategy for low-risk PCa patients to mitigate treatment-related morbidity [2, 3]. Treatment decisions in PCa primarily hinge on PSA levels, biopsy Gleason grade group (bGG) and clinical stage, necessitating accurate assessment of these clinical parameters to optimize treatment selection. However, there exists substantial discordance between bGG and prostatectomy GG (pGG), with reported underestimation rates ranging from 41.4% to 61% [4–6]. Moreover, upgrading from bGG to a higher pGG has been linked to poorer oncological outcomes [5, 7].

Accurately predicting bGG upgrading is essential for guiding appropriate treatment decisions, particularly in cases considered for AS. Herein, we performed this study to attempt solving the issue of significant challenges for pathological upgrading in patients initially diagnosed with bGG1 by developing a practical scoring system capable of estimating the risk of upgrading in bGG1 patients.

2. Materials and methods

2.1 Study design and participants

After approval from the ethics committee of our institution, we conducted a retrospective review of prospectively maintained database records covering 504 patients who underwent laparoscopic radical prostatectomy (LRP) via the extraperitoneal approach for PCa between February 2014 and June 2022. Only patients who had undergone multiparametric magnetic resonance imaging (mpMRI) before the prostate biopsy were included. Patients categorized as intermediate or high risk due to elevated PSA levels were also eligible. Exclusion criteria comprised patients with a history of radiation therapy (n = 3), incomplete data (n = 24), bGG higher than GG 1 (n = 174), prior hormonal therapy (n = 5), and those lacking mpMRI before biopsy (n = 63). The final study cohort consisted of 235 patients.

2.2 Biopsy and surgical technique

Prostate biopsy was indicated for patients with elevated PSA levels or abnormal digital rectal examination findings, and all of them underwent mpMRI before the prostate biopsy. The images were assessed by a dedicated radiologist who was blinded to the clinical outcomes according to Prostate Imaging-Reporting and Data System (PIRADS) v2.1. A transrectal ultrasound-guided 12-core prostate biopsy was performed under local anesthesia, preceded by single-dose antibiotic prophylaxis and gastrointestinal system preparation. The combined systematic biopsy, and cognitive MRI-targeted biopsy according to PIRADS lesion were conducted in all patients. The LRP procedures were performed by a senior surgeon (MA) with expertise in laparoscopic surgery, following previously described techniques [8]. Patients with a lymph node metastasis risk exceeding 5% per the Briganti nomogram underwent extended lymph node dissection.

2.3 Outcomes and definition of variables

For each case, data on patient age, PSA level, body mass index (BMI), clinical T-stage, history of negative prior biopsy, PIRADS score, and time from biopsy to surgery were recorded. Pathological outcomes included bGG, greatest percentage of tumor involvement, extension of positive cores, pGG, pathological T-stage and positive surgical margin (PSM) status. Upgrading was defined as a shift from bGG1 group to any higher grade on prostatectomy specimens.

The newly proposed U.P.G.R.A.D.E. scoring system consists of seven standardized variables identified through a comprehensive review of the literature on factors influencing PCa upgrading in multivariate analyses following radical prostatectomy (RP) [8–15]. These variables formed the acronym "U.P.G.R.A.D.E." (Table 1) and comprised of the following: Uninformative prior biopsy, PSA level, Greatest percentage of tumor, Radiological PIRADS score, Age, Delay from biopsy to surgery, and Extension of positive cores. In this scoring system, patients who were biopsy naive are assigned 1 point. A history of high-grade prostatic intraepithelial neoplasia (HG-PIN) or atypical small acinar proliferation (ASAP) diagnosis carries a score of 2 points. PSA levels were scored as follows: <10 ng/dL (1 point), 10–20 ng/dL (2 points), and >20 ng/dL (3 points). The greatest percentage of tumor involvement is categorized into three groups: <25% (1 point), 25–50% (2 points), and >50% (3 points). Radiological PIRADS scores ≤3 were assigned 1 point, while scores ≥4 were assigned 2 points. Patients younger than 65 years were scored as 1 point, whereas those 65 years or older were scored as 2 points. Surgical delay duration is categorized as <60 days (1 point), 61–120 days (2 points), and >120 days (3 points). The extension of the tumor is scored from 1 to 3 based on the involvement of a single core, one lobe or both lobes, respectively. The overall scores range from 7 to 18, with lower scores indicating a lower risk of upgrading and higher scores indicating a higher risk.

TABLE 1. Summary of U.P.G.R.A.D.E. scoring system.

Variables	Score
Uninformative prior biopsy	
Biopsy naive	1 pt
Negative prior biopsy	2 pt
PSA level	
<10 ng/dL	1 pt
10–20 ng/dL	2 pt
>20 ng/dL	3 pt
Greatest percentage of tumor	
<25%	1 pt
25–50%	2 pt
>50%	3 pt
Radiological PIRADS score	
PIRADS score ≤3	1 pt
PIRADS score ≥4	2 pt
Age	
<65	1 pt
≥65	2 pt
Delay from biopsy to surgery	
<60 d	1 pt
60–120 d	2 pt
>120 d	3 pt
Extension of positive cores	
Only single core	1 pt
Only one lobe	2 pt
Both lobes	3 pt

PSA: prostate-specific antigen; PIRADS: Prostate Imaging-Reporting and Data System.

2.4 Statistical analysis

Data were presented as n (%), mean ± standard deviation or median (interquartile range (IQR: 25th–75th)). Normality was assessed with Shapiro-Wilk test. Baseline differences in patient characteristics between the groups were analyzed using the independent—*t* test or Mann-Whitney U test for

continuous variables and the Pearson chi-square or Fisher's exact test for categorical variables. The predictive ability of the U.P.G.R.A.D.E. scoring system was evaluated by the area under the receiver operating characteristic (AUROC) curve. The cutoff point was determined using the Youden index method. Statistical analysis was completed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). A p-value < 0.05 was accepted as statistically significant.

3. Results

The study included 235 patients, with a mean age of 64.22 ± 5.88 years and a mean PSA level of 8.92 ± 5.05 ng/mL (Table 2). Among them, 95 patients (40.6%) were upgraded from bGG 1 to a higher grade during RP. Patients who underwent upgrading were notably older ($p = 0.010$) and had higher preoperative PSA levels ($p < 0.001$), advanced clinical T-stage ($p < 0.001$), elevated PIRADS score ($p < 0.001$), greater tumor involvement ($p < 0.001$), and more extensive positive cores ($p < 0.001$). They were also more likely to have a history of negative biopsy ($p = 0.005$) and experienced longer surgical delays ($p < 0.001$). The U.P.G.R.A.D.E. score was found to be significantly higher in the upgraded patients ($p < 0.001$).

As shown in Fig. 1, the AUROC curve of the U.P.G.R.A.D.E. scoring system for upgrading prediction was 0.952 (95% CI: 0.926–0.978; $p < 0.001$). When the cut-off value was set in 10.5, sensitivity, specificity, negative predictive value, and positive predictive value of the U.P.G.R.A.D.E. scoring system were 0.853, 0.943, 86.2% and 93.4%, respectively.

TABLE 2. Comparison of upgraded and non-upgraded patients.

Variables	Total (n = 235)	Upgraded (n = 95)	Not Upgraded (n = 140)	p
Age, yr, mean ± SD	64.22 ± 5.88	65.41 ± 6.31	63.41 ± 5.44	0.010
BMI, kg/m^2, mean ± SD	26.71 ± 3.11	26.82 ± 2.92	26.64 ± 3.23	0.676
PSA, ng/dL, median (IQR)	7.3 (5.4–11.0)	8.5 (5.9–12.6)	6.7 (5.1–9.4)	<0.001
Clinical Stage, n (%)				
T1c	186 (79.1%)	49 (51.6%)	137 (97.9%)	<0.001
T2	47 (20.0%)	44 (46.3%)	3 (2.1%)	
T3	2 (0.9%)	2 (2.1%)	0	
Negative Prior Biopsy, n (%)				
Yes	20 (8.5%)	14 (14.7%)	6 (4.3%)	0.005
No	215 (91.5%)	81 (85.3%)	134 (95.7%)	
PIRADS, n (%)				
≤3	188 (80.0%)	50 (52.6%)	138 (98.6%)	<0.001
≥4	47 (20.0%)	45 (47.4%)	2 (1.4%)	
Time from biopsy to surgery, n (%)				
<60 d	151 (64.3%)	45 (47.4%)	106 (75.7%)	<0.001
60–120 d	79 (33.6%)	45 (47.4%)	34 (24.3%)	
>120 d	5 (2.1%)	5 (5.6%)	0	
Greatest Percentage of Tumor, n (%)				
<25%	124 (52.8%)	11 (11.6%)	113 (80.7%)	<0.001
25–50%	63 (26.8%)	38 (40.0%)	25 (17.9%)	
>50%	48 (20.4%)	46 (48.4%)	2 (1.4%)	
Pathological Stage, n (%)				
T2	168 (71.5%)	36 (37.9%)	132 (94.3%)	<0.001
T3	67 (28.5%)	59 (62.1%)	8 (5.7%)	
Positive Surgical Margin, n (%)				
Yes	39 (16.6%)	31 (13.2%)	8 (3.4%)	<0.001
No	196 (83.4%)	64 (27.2%)	132 (56.2%)	
Extension of Positive Cores, n (%)				
Single Core	41 (17.4%)	2 (0.9%)	39 (16.6%)	<0.001
One Lobe	158 (67.2%)	63 (26.8%)	95 (40.4%)	
Both Lobe	36 (15.3%)	30 (12.8%)	6 (2.6%)	
U.P.G.R.A.D.E. score, mean ± SD	10.12 ± 1.99	12.03 ± 1.48	8.82 ± 1.01	<0.001

BMI: body mass index; PSA: prostate-specific antigen; PIRADS: Prostate Imaging-Reporting and Data System; SD: standard deviation; IQR: inter quartile range.

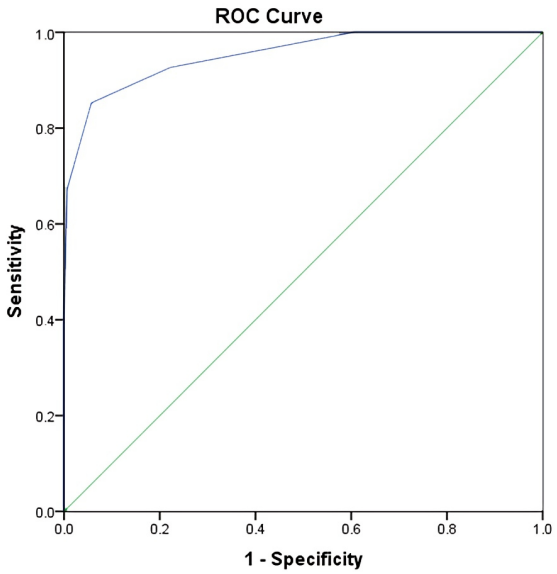

FIGURE 1. ROC analysis for U.P.G.R.A.D.E. scoring system to predict the pathological upgrading. ROC: Receiver operating characteristic.

4. Discussion

Scoring systems are pivotal in describing tumor characteristics and predicting outcomes in PCa. For example, the PSA level (P), ratio of positive biopsy needles (R), obesity (O), scores of Gleason (S), T stage by preoperative MRI scan (T), age (A), tumor volume (T) and experience of the surgeon (E) (PROSTATE) scoring system was introduced to predict of PSM after RP [16], while the Cancer of the Prostate Risk Assessment post-Surgical (CAPRA-S) score was developed to assess PCa recurrence [17]. An ideal scoring system should effectively estimate clinical events and be user-friendly. In this study, we have devised a novel scoring system based on clinical parameters to predict Gleason grade upgrading in PCa patients. Our findings indicate that patients with higher U.P.G.R.A.D.E. scores were significantly more likely to experience Gleason grade upgrading.

Current treatment options for PCa primarily depend on PSA levels, bGG and clinical stage classification. Options include AS, RP and radiotherapy. AS has gained increasing preference as a strategy to mitigate the complications associated with treatment in men with low-risk PCa [2]. However, pathological upgrading poses a significant challenge in treatment decision-making, particularly for AS candidates. Underestimation of high-grade disease can lead to inappropriate management decisions, potentially depriving patients of optimal treatment.

The incidence of GG upgrading in PCa ranges widely, from 20% to 65%. A meta-analysis involving 14,839 men reported an average upgrading frequency of 30% [18]. Higher rates of upgrading were observed in low-risk patients (55.7%) compared to intermediate (19.1%) and high-risk (24.3%) patients [19]. In our cohort, we observed a 40.6% rate of upgrading, consistent with recent literature [6, 9–11, 19, 20]. Pathological upgrading is a prevalent issue associated with an increased risk of biochemical recurrence [21], emphasizing the clinical significance of accurate grading.

The reasons for discrepancies between bGG and pGG remain uncertain. Possible explanations include the presence of unsampled high-grade disease, variability in pathological reporting, and the multifocality of PCa. Higher-grade tumor foci may go undetected during biopsy. In our study, we investigated whether upgraded tumors were localized to the same side of the prostate as reported in both biopsy and prostatectomy findings; we found concordance in 91 out of 95 upgraded cases. Interobserver variability could influence upgrading, particularly when borderline neoplastic lesions are encountered [22]. The multifocal and heterogeneous nature of PCa further complicates accurate GG determination [23]. Additionally, variations in biopsy techniques may affect tumor detection rates [24–26]. Lee *et al.* [27] showed that intensive sampling of the umbra and penumbra reduced risk of GG upgrading.

Numerous studies have extensively investigated clinical parameters associated with GG upgrading through multivariate analysis. Consistently, PSA has been identified as a significant risk factor for pathological upgrading in PCa [6, 9, 11–13, 15, 22, 28]. Similarly, advanced age has consistently shown an association with increased risk of upgrading [6, 10, 12, 13, 22], with a recent meta-analysis reinforcing this finding [29]. The number of positive cores and the maximum percentage of involvement have also emerged as independent predictors of upgrading [11, 13, 15, 22, 30]. Studies have highlighted surgical delay as another significant factor influencing upgrading risk [12, 31]. Additionally, the presence of ASAP or HGPIN has been consistently associated with GG upgrading [14, 32]. Following the widespread adoption of mpMRI before biopsy, the PIRADS score has independently predicted GG upgrading in several investigations [15, 28, 33]. Similar to the aforementioned studies, we found that PSA, age, positive core, tumor percentage, surgical delay, presence of ASAP/HGPIN and PIRADS score correlated with upgrading after RP.

The integration of these predictive variables into clinical practice underscores their utility in enhancing prognostic accuracy. Promising predictors have been incorporated into nomograms aimed at aiding clinical decision-making [15, 28, 34, 35]. For instance, Qi *et al*. [34] developed a nomogram incorporating age, PSA density, PIRADS score, and positive cores, while Wang *et al*. [15] reported a model using PSA, clinical stage, PIRADS score, and the greatest percentage of cancer with a C-index of 0.726. Moreover, ongoing efforts seek to mitigate GG upgrading through innovative tools such as ultrasound shear wave elastography, genetic tests and prostate-specific membrane antigen positron emission tomography (PSMA-PET) [36–40]. Nevertheless, research for more accessible, cost-effective and user-friendly prediction models with robust efficacy remains ongoing.

Several limitations should be acknowledged in this study. Firstly, the sample size was relatively small, which may have limited the statistical power of the results. Secondly, the retrospective and single-center design introduces potential selection biases. Thirdly, the histopathological evaluation was not centralized, potentially leading to interobserver variability. Lastly, the use of cognitive rather than fusion biopsy techniques might have influenced the accuracy of Gleason score determination. Future studies could externally validate the proposed U.P.G.R.A.D.E. scoring system using prospective cohorts involving larger sample size to address these limitations.

5. Conclusions

The likelihood of upgrading poses significant implications for PCa management and prognosis, particularly in men with bGG1. In this study, we successfully developed a novel scoring system that might reliably predict upgrading in bGG1 PCa, providing a robust reference for improving personalized treatment decisions based on risk assessment. Our study highlights that a high U.P.G.R.A.D.E. score substantially increases the risk of upgrading in this patient group, and men with elevated U.P.G.R.A.D.E. scores may not be suitable candidates for AS. The U.P.G.R.A.D.E. scoring system is easy to use, cost-effective, and demonstrates satisfactory predictive efficacy. However, further validation is required to confirm our study findings.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

KK and AY—designed the study. HA, AG and SA—performed the research. KK, AY, AG and SA—collected the data. HA—analyzed the data. KK, AY and AG—interpreted the data. KK, HA, AG and SA—wrote the first draft of the manuscript. MA—performed the surgeries and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of Okan University (approval number: 2023-988). The committee also waived written informed consent for this retrospective study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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