Original Article

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Do Subgroup Evaluations Provide Additional Contributions to Biochemical Recurrence in Grade Group 4 and 5 Patients? A Multicenter Study by the Turkish Urooncology Association Prostate Cancer Working Group

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Abstract

Objective: To investigate the effect of the International Society of Urological Pathology (ISUP) grade group 4 (GG4) and ISUP GG5 subgroups according to prostate biopsy on biochemical recurrence (BCR).

Materials and Methods: Patients who underwent radical prostatectomy (RP) after being diagnosed with GG4 and GG5 prostate cancer according to prostate biopsy and who had follow-up data were retrospectively evaluated. Patient data were obtained from the Urologic Cancer Database-Prostate of the Turkish Urooncology Association. GG4 and GG5 pathologies were evaluated using Gleason subgroups. The effect of clinicopathological parameters on BCR after RP was investigated separately in the GG4 and GG5 patient groups.

Results: In GG4, 73 of 188 patients developed BCR. When GG4 patients were evaluated for BCR, only lymphovascular invasion was significant for BCR (p=0.004). In addition, seminal vesicle invasion (SVI) and high ISUP grade according to RP pathology were significant in patients with BCR (p=0.004 and p=0.005). In the follow-up of 145 patients with GG5, 80 patients developed BCR. When GG5 patients were evaluated for BCR, no predictive factor was found for developing BCR. However, surgical margin positivity, extraprostatic extension, and SVI after RP were found to be significant in patients with BCR (p=0.031, p=0.011 and p=0.007).

Conclusion: According to our results, the ISUP GG system, which does not include Gleason subgroups, is an appropriate classification system for GG4 and GG5 patients for the prediction of BCR in the Turkish patient population, in parallel with the current literature.

Keywords: Prostate cancer, Gleason score, biochemical recurrence, ISUP grade group

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Introduction

Prostate cancer (PC) is the most common solid organ malignancy in men and the second most common cause of cancer-related death (1). Many studies have reported that a high Gleason score (GS) is a prognostic factor for survival (2,3). For better management of the disease by the clinician, Gleason patterns are combined as primary and secondary patterns to increase their prognostic value (4,5). Tumor grading using grade groups (GG) was first described by Epstein et al. (6) and was validated in a multicenter study (2). This grading was finally approved by the International Society of Urological Pathology (ISUP) in 2014. However, there are studies suggesting that it may be difficult to evaluate these patients under a single group because of the heterogeneity in GG4 and GG5 patients. In this context, there are different biological and oncological outcomes between the subgroups according to these studies (6-9). In addition, another limitation is that cribriform and intraductal tumor variants do not have clear ISUP grading.

The aim of the study was to investigate the effect of Gleason subgroups on biochemical recurrence (BCR) in ISUP GG4 and ISUP GG5 patients according to prostate biopsy and to simultaneously evaluate the possible predictive factors for BCR after radical prostatectomy (RP) in each GG.

Materials and Methods

Patients with data entry completed in the Urological Cancer Database-Prostate of the Turkish Urooncology Association (TUOA) and who underwent RP due to PC and had follow-up data were retrospectively reviewed for this study (TUO-PR-21-04). Among them, patients diagnosed with GG4 and GG5 PC according to prostate biopsy and other clinicopathological parameters were investigated in the study. All parameters obtained from the database, clinical findings (digital rectal examination, preoperative PSA, BMI, prostate volume), multiparametric prostate magnetic resonance imaging findings [PIRADS score, lesion number, lesion size, extracapsular extension (ECE), seminal vesicle invasion (SVI)], prostate biopsy findings [type of biopsy and MR fusion biopsy technique (cognitive or MR fusion and transperineal or transrectal), GS, ISUP GG, total number and percentage of positive cores on biopsy, percentage of cores removed from the lesion and presence of perineural invasion, lymphovascular invasion (LVI), and high-grade prostatic intraepithelial neoplasia] and RP pathological findings [ISUP GG, surgical margin positivity (pSM), ECE, SVI, lymph node status] were evaluated. In addition, according to the follow-up data, the BCR status of the patients was investigated. In parallel with the literature, BCR was considered an increase above 0.2 ng/mL of PSA after falling to undetectable levels (PSA nadir) in the postoperative period (10). All patients and GG patients were assessed according to the BCR status after RP.

Patients who had GG4 on prostate biopsy were divided into three subgroups according to the GS as 4+4, 3+5, and 5+3 subgroups. Similarly, GG5 patients were also divided into three subgroups as GS subgroups of 4+5, 5+4, and 5+5. The effects of these Gleason subgroups and other clinicopathological findings on BCR were separately investigated for each GG.

Statistical Analysis

The study data were obtained from Research Electronic Data Capture (REDCap) electronic data tools hosted by TUOA (11,12). REDCap is a secure, web-based software platform designed to support data capture for research studies. In the statistical analysis, the t-test, Mann-Whitney U test and χ^2 test were used to analyze continuous and categorical variables according to BCR status. Values of $p<0.05$ were considered statistically significant.

Results

In this study, 188 and 145 patients with GG4 and GG5 were investigated, respectively. In the follow-up of the GG4 patients, 73 (38.8%), 13 (6.9%), and 21 (11.1%) patients developed BCR, castration-resistant prostate cancer (CRPC), and metastasis, respectively. In the follow-up of GG5, 80 (55.2%), 31 (21.4%), and 27 (18.6%) patients developed BCR, CRPC, and metastasis, respectively. Lymph node dissection (LND) was performed in 155 patients (82.4%) and 130 patients (89.7%) in GG4 and GG5. None of the patients received neoadjuvant androgen deprivation therapy (ADT). Among GG4 and GG5 patients, 76 (40.4%) and 79 (54.5%) received additional treatment because of the development of BCR after RP ± LND, respectively. In GG4, 38 (20.2%), 15 (8%) and 6 (3.2%) patients received only radiotherapy (RT), RT + ADT and only ADT, respectively. In GG5, 42 (29%), 24 (16.5%), and 3 (2.1%) patients received only RT, RT + ADT and only ADT, respectively.

For evaluating GG4 patients, clinicopathological data and comparison results according to BCR status are given in Table 1 and 2. According to the results, only the presence of LVI on biopsy was found to be significantly higher in the BCR group (p=0.004). For RP pathological findings, while pSM (p=0.054), ECE (p=0.078) and LND status (p=0.35) were similar, SVI and high ISUP grade were significantly higher in the BCR group (p=0.004 vs p=0.005 respectively).

For evaluating GG5 patients, clinicopathological data and comparison results according to BCR status are given in Table 3 and 4. In this cohort, pSM (p=0.031), ECE (p=0.011) and SVI (p=0.007) on RP pathology were found to be higher in the BCR0-positive group.

For each GG4 and GG5 group, the Gleason subgroup according to biopsy pathology did not affect BCR after RP.

Discussion

In this study, the effect of Gleason subgroups on BCR was investigated separately in GG4 and GG5 patients according to prostate biopsy. Although the hypothesis of our study was that Gleason subgroups have a possible effect on BCR in GG4 and GG5 patients, it could not be demonstrated for the GG groups in our cohort. However, in GG4 patients in our cohort, only one factor (LVI) on prostate biopsy and two factors (SVI and high GG) on RP pathology were associated with BCR after RP. For GG5 patients in our cohort, no factor was found on prostate biopsy, and three factors (pSM, ECE, and SVI) on RP pathology were related to BCR after RP.

Validation studies for PC grading combine a GS of 8 into a single prognostic group (13). However, according to previous

Table 1. Grade group 4 patient's clinical and demographical features				
GG 4		**No BCR (n=115)**	**BCR (n=73)**	**p-value**
Digital rectal examination	Benign	96 (88.1%)	53 (79.1%)	0.084
	Malign	13 (11.9%)	14 (20.9%)	
Extracapsular extention on MRI	Positive	4 (28.6%)	0 (0%)	0.258
	Negative	10 (71.4%)	5 (100%)	
Seminal vesicle invasion on mpMRI	Positive	1 (7.2%)	1 (16.7%)	0.521
	Negative	13 (92.8%)	5 (83.3%)	
Targeted lesion side on mpMRI	Right	19 (90.5)	7 (77.8%)	0.547
	Left	2 (9.5%)	2 (22.2%)	
Targeted lesion location on mpMRI	Anterior	11 (84.6%)	4 (80%)	0.868
	Posterior	2 (15.4%)	1 (20%)	
Targeted lesion area on mpMRI	Apex	16 (80%)	9 (90%)	0.413
	Mid	3 (15%)	0 (0%)	
	Base	1 (5%)	1 (10%)	
Prostate biopsy technique	Transperineal	2 (16.7%)	1 (16.7%)	0.730
	Transrectal	10 (83.3%)	5 (83.3%)	
PIRADS	3	0 (0%)	1 (11.1%)	0.130
	4	11 (52.4%)	2 (22.2%)	
	5	10 (47.6%)	6 (66.7%)	
PSA (ng/mL)		13.1±16.6	16.2±19.4	0.273
BMI		28.6±3.3	28.7±1.4	0.317
Prostate volume		40.9±19.3	37.9±17.9	0.460
Targeted lesion length (mm)		17.1±7.2	19.0±7.0	0.509
Positive core number		4.5±2.9	5.6±3.4	0.083
Positive core ratio (%)		65.4±30.2	73.6±29.5	0.141
Biopsy technique	Conventional	103 (88.6%)	67 (91.8%)	0.408
	MRI directed	12 (11.4%)	6 (8.2%)	
Number of targeted lesion		2.1±1.2	1±0	0.060

BCR: Biochemical recurrence, GG: Grade groups, mpMRI: Multiparametric prostate magnetic resonance imaging, PSA: Prostate-specific antigen, BMI: Body mass index

Table 2. Grade group 4 patient's biopsy and radical prostatectomy pathology results				
GG 4		**No BCR (n=115)**	**BCR (n=73)**	**p-value**
Biopsy ISUP subgroups	3+5	19 (16.5%)	9 (12.3%)	0.289
	4+4	94 (81.7%)	60 (82.2%)	
	5+3	2 (1.8%)	4 (5.4%)	
Biopsy PNI positivity	Positive	25 (28.7%)	21 (41.2%)	0.096
	Negative	62 (71.3%)	30 (58.8%)	
Biopsy LVI positivity	Positive	1 (1.2%)	7 (14%)	0.004
	Negative	85 (98.8%)	43 (86%)	
Biopsy HGPIN	Positive	13 (15.6%)	10 (20.4%)	0.320
	Negative	70 (84.4%)	39 (79.6%)	
RP PSM	Positive	53 (46.4%)	43 (59.7%)	0.054
	Negative	61 (53.6%)	29 (40.3%)	
RP ECE positivity	Positive	52 (46.8%)	39 (59.1%)	0.078
	Negative	59 (53.2%)	27 (40.9%)	
RP SVI	Positive	28 (24.6%)	32 (44.4%)	0.004
	Negative	86 (75.4%)	40 (55.6%)	
Lymph node invasion	Positive	93 (89.4%)	62 (84.9%)	0.35
	Negative	21 (10.6%)	11 (15.1%)	
RP grade group	1	6 (5.3%)	3 (4.1%)	0.005
	2	31 (26.9%)	7 (9.6%)	
	3	29 (25.2%)	16 (21.9%)	
	4	30 (26.1%)	20 (27.4%)	
	5	19 (16.5%)	27 (37.0%)	

BCR: Biochemical recurrence, GG: Grade groups, ISUP: International Society of Urological Pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High-grade prostatic intraepithelial neoplasia, RP: Radical prostatectomy, PSM: Surgical margin positivity, ECE: Extracapsular extension, SVI: Seminal vesicle invasion

Table 3. Grade group 5 patient's clinical and demographical features				
GG 5		No BCR (n=65)	BCR (n=80)	p-value
Digital rectal examination	Benign	49 (82.1%)	58 (81.7%)	0.513
	Malign	10 (16.9%)	13 (18.3%)	
Extracapsular extention on MRI	Positive	3 (42.9%)	5 (71.4%)	0.296
	Negative	4 (57.1%)	2 (28.6%)	
Seminal vesicle invasion on mpMRI	Positive	1 (12.5%)	5 (62.5%)	0.059
	Negative	7 (87.5%)	3 (37.5%)	
Targeted lesion side on mpMRI	Right	10 (90.9%)	8 (72.7%)	0.500
	Left	1 (9.1%)	3 (27.3%)	
Targeted lesion location on mpMRI	Anterior	7 (100%)	7 (77.8%)	0.248
	Posterior	0 (0%)	2 (22.2%)	
Targeted lesion area on mpMRI	Apex	10 (90.9%)	7 (70%)	0.609
	Mid	1 (9.1%)	2 (20%)	
	Base	0 (0%)	1 (10%)	
Prostate biopsy technique	Transperineal	2 (25%)	1 (12.5%)	0.500
	Transrectal	6 (75%)	7 (87.5%)	
PIRADS	3	1 (8.3%)	0 (0%)	0.280
	4	3 (25.0%)	1 (9.1%)	
	5	8 (66.7%)	9 (81.8%)	
PSA (ng/mL)		18.2±24.9	35.8±139.6	0.074
BMI		26.8±2.6	27.8±4.5	0.352
Prostate volume		58.6±36.0	43.5±30.3	0.104
Targeted lesion length (mm)		17.1±6.8	21.7±5.8	0.131
Positive core number		6.4±3.6	7.0±3.6	0.514
Positive core ratio (%)		72.5±30.5	80.2±26.9	0.215
Biopsy technique	Conventional	57 (87.7%)	72 (90%)	0.428
	MRI directed	8 (12.3%)	8 (10%)	
Number of targeted lesion		1.88±1.8	1.75±1.2	0.749

BCR: Biochemical recurrence, GG: Grade groups, mpMRI: Multiparametric prostate magnetic resonance imaging, PSA: Prostate-specific antigen, BMI: Body mass index

studies, in both 3+5 and 5+3 subgroups of GG4 patients, the proportional excess of the Gleason 3 pattern is considered protective in terms of oncologic outcomes. In addition, it was suggested that 3+5 has the same results as GG2, whereas tumors with 5+3 should be grouped together with GG5 (14). The presence of GS 5 was the strongest pathologic predictor of BCR, metastasis, and cancer-specific mortality (CSM). In this context, the presence of GS 5 may play an important role in oncologic outcomes within GG4 and classifying these patients into a single category (GG4) may be insufficient to assess the subgroups of patients (GSs of 3+5, 4+4 and 5+3) (6,15). In parallel, another study reported that the mortality in the subgroup of GS 5+3 patients was almost doubled compared with GS 4+4 patients. A difference in mortality was not detected between patients with GSs of 3+5 and 4+4. This situation shows that different oncologic results may be obtained for the GG4 subgroups (8). However, our results do not support the importance of a primary GS 5 in GG4 patients for BCR after RP. In conclusion, our results are consistent with the validation studies.

For GG5 patients, there was a similar discussion that the presence of GS 5 and primary GS 5 indicated worse oncologic outcomes. In a study, for CSM, GSs 5+4 or 5+5 were detected to be disadvantageous compared with GSs of 4+5. It was also stated that the rarest subtype was Gleason 5+5 (9.9%), whereas Gleason 5+4 was found in 19.1% of cases. The 10-year CSM was found to be highest in the 5+5 subgroup (39.1%), followed by 5+4 (28%) and 4+5 (18.2%) subgroups (16).

In another study, the authors suggested that biopsy GSs 4+5, 5+4, and 5+5 should be evaluated separately in pretreatment risk stratification because of differences in CSM (17), contrary to Epstein et al. (13). However, the patient distribution and scarcity of subgroups of GG5 make it difficult to evaluate this group. As such, the Cancer of the Prostate Strategic Urologic Research Endeavor - based study evaluated 225, 81 and 48 patients treated with both RP and EBRT in the GS 4+5, 5+4 and 5+5 subgroups according to biopsy, respectively (17). Similar results were obtained in other studies due to the sample size (18,19). Although the discussion in this field is ongoing, our results obtained from 145 patients show that there is no difference in BCR after RP between the subgroups of GG5 patients.

Study Limitations

First, because of its multicenter nature, patient selection and evaluation of adjuvant and salvage therapies may be heterogeneous. Second, only the effect on BCR was investigated

Table 4. Grade group 5 patient's biopsy and radical prostatectomy pathology results				
GG 5		**No BCR (n=65)**	**BCR (n=80)**	**p-value**
Biopsy ISUP subgroups	4+5	48 (73.8%)	52 (65%)	0.375
	5+4	14 (21.5%)	20 (25%)	
	5+5	3 (4.7%)	8 (10%)	
Biopsy PNI	Positive	22 (40.7%)	36 (53.7%)	0.108
	Negative	32 (59.3%)	31 (42.3%)	
Biopsy LVI	Positive	7 (13.5%)	11 (16.7%)	0.415
	Negative	45 (86.5%)	55 (83.3%)	
Biopsy HGPIN	Positive	10 (20%)	8 (12.3%)	0.320
	Negative	40 (80%)	57 (87.7%)	
RP PSM	Positive	39 (60%)	60 (75.9%)	0.031
	Negative	26 (40%)	19 (24.0%)	
RP ECE	Positive	32 (53.3%)	56 (73.7%)	0.011
	Negative	28 (46.7%)	20 (26.3%)	
RP SVI	Positive	27 (41.5%)	50 (63.3%)	0.007
	Negative	38 (58.5%)	29 (36.7%)	
Lymph node invasion	Positive	61 (93.8%)	69 (87.3%)	0.152
	Negative	4 (6.2%)	10 (12.7%)	
RP grade group	1	0 (0%)	1 (1.25%)	0.091
	2	2 (3.1%)	2 (2.5%)	
	3	13 (20%)	5 (6.25%)	
	4	7 (10.8%)	6 (7.5%)	
	5	43 (66.1%)	66 (82.5%)	

BCR: Biochemical recurrence, GG: Grade groups, ISUP: International Society of Urological Pathology, PNI: Perineural invasion, LVI: Lymphovascular invasion, HGPIN: High-grade prostatic intraepithelial neoplasia, RP: Radical prostatectomy, PSM: Surgical margin positivity, ECE: Extracapsular extension, SVI: Seminal vesicle invasion

because of the difficulty in obtaining survival data. Third, pathology was not evaluated in a single center, and patients were dependent on their own pathologists for identification and reporting of GSs. All these limitations raise concerns about the generalizability of the study. However, our results reflect real-world data in a limited patient population.

Conclusion

In conclusion, evaluations of GG4 and GG5 patients according to GS subgroups (GG4: 4+4, 3+5 and 5+3; GG5: 4+5, 5+4 and 5+5) found no significant differences in terms of BCR after RP. Accordingly, the ISUP GG system that does not include Gleason subgroups for GG4 and GG5 patients is an appropriate classification system for the prediction of BCR after RP in the Turkish patient population. Prospective studies with homogeneous patient distribution will provide stronger evidence in the future.

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Ethics

Ethics Committee Approval: The project approval number of Turkish Urooncology Association: TUO-PR-21-04.

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: E.S., S.S., V.İ., B.A., L.T., G.A., H.Ö., S.Y., Concept: S.Ç., B.Ş., Design: T.Ç., S.Ç., B.Ş., Data Collection or Processing: S.Ç., B.Ş., Analysis or Interpretation: S.Ç., Literature Search: T.Ç., Writing: T.Ç.

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