Comparison of Gleason scoring and the new grade-group system in prostate cancers: a 15-year retrospective study

Prostat kanserlerinde Gleason skorlaması ile yeni grade-group sisteminin karşılaştırılması: 15 yıllık retrospektif bir çalışma

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ABSTRACT

Aim: Prostate cancer is the most common malignant tumour in men. The most widely used histological grading scheme for prostate cancer is Gleason scoring. After the original, this system has been modified several times. In this study, we retrospectively investigated the new Grade-group system (GGS).

Material and Method: This study includes 486 cases diagnosed with prostate cancer between 2000 and 2015. All cases were re-grouped for the new Grade-group system and its relationship with prognosis was examined.

Results: Grade-group system subgroups had a statistically significant relationship between prognostic factors and this relationship was more significant between GGS 2 and GGS 3 [tumor status (p<0.001), age (p=0.045), PN invasion (p<0.001), stage (p=0.004), and LN status (p<0.001)]. In univariable survival analysis, there was a significant difference between Grade-group system subgroups (for GGS 2-GGS 3, RFS: p=0.035 and OS: p=0.012; for GGS 4-GGS 5, RFS: p=0.001 and OS: p=0.001). In multivariable survival analysis, GGS subgroups were found to be an independent survival parameter for prostate cancer (for GGS 2-GGS 3, OS: HR=2.56, p=0.012 and RFS: HR=2.69, p=0.038; for GGS 4-GGS 5, OS: HR=2.84, p=0.011 and RFS: HR=2.59, p<0.001).

Conclusions: According to our results, the new Grade-group system performs the prognostic risk grading more accurately than the old classification. Also, the fact that this system contains fewer categories and is simpler has increased the interobserver compatibility.

Keywords: Grade-group system, Gleason scoring, prostate cancer.

ÖZ

Amaç: Prostat kanseri (PK) erkeklerde en sık görülen malign tümördür. PK için en yaygın kullanılan histolojik derecelendirme şeması Gleason skorlamasıdır. Orijinalinden sonra bu sistem birkaç kez değiştirildi. Bu çalışmada, prostat kanseri için tanımlanan yeni Grade-group sistemini (GGS) geriye dönük olarak inceledik.

Gereç ve Yöntem: Bu çalışma 2000-2015 yılları arasında prostat kanseri tanısı konmuş 486 vakayı içermektedir. Tüm olgular yeni Grade-group sistemini için yeniden gruplandırıldı ve prognozla ilişkisi incelendi.

Bulgular: Grade-group sistemini alt gruplarının prognostik faktörler arasında istatistiksel olarak anlamlı bir ilişki vardı ve bu ilişki GGS 2 ve GGS 3 arasında daha anlamlı idi [tümör durumu (p<0,001), yaş (p=0,045), PN invazyonu (p<0,001), evre (p=0,004), ve LN durumu (p<0,001)]. Tek değişkenli sağkalım analizinde Grade-Group sistemini alt grupları arasında anlamlı bir fark vardı (GGS 2-GGS 3, RFS: p=0,035 ve OS: p=0,012; GGS 4-GGS 5, RFS için: p=0,001 ve OS: p=0,001). Çok değişkenli sağkalım analizinde Grade-Group sisteminin alt gruplarının prostat kanseri için bağımsız bir sağkalım parametresi olduğu bulundu (GGS 2-GGS 3, OS: HR=2,56, p=0,012 ve RFS: HR=2,69, p=0,038; GGS 4- için GGS 5, OS: HR=2,84, p=0,011 ve RFS: HR=2,59, p<0,001).

Sonuçlar: Çalışmamıza göre, yeni Grade-group sistemini sistemi prognostik risk sınıflandırmasını eski sınıflandırmadan daha doğru bir şekilde gerçekleştirmektedir. Ayrıca, bu sistemin daha az kategori içermesi ve daha basit olması, gözlemciler arası uyumluluğu artırdı.

Anahtar Kelimeler: Grade-grup sistemi, Gleason skorlaması, prostat kanseri.

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INTRODUCTION

Prostate cancer (PC) is one of the most common cancers worldwide. In 2018, 1,276,106 new PC cases were detected. Mortality rates for PC are reported as 9.3% and its incidence increases with age (1). The most common subtype of PC is acinar adenocarcinoma. PCs are usually multifocal and mostly originate from the peripheral region of the gland. Considering the incidence and heterogeneous clinical behaviour of prostate carcinoma, it is very important to classify patients according to the risk group correctly (1,2). Several clinical and pathological parameters (Gleason score [GS], serum prostate-specific antigen [PSA] level, radiological assessment, the status of surgical margin, regional lymph nodes, tumour stage, etc.) are used to identify risk groups. Among these factors, the GS system is still one of the most important prognostic parameters for the PC today (2,3).

Gleason scoring system was defined by Donald F. Gleason in the 1960s (4). This classification is based on the architectural structure of the glands. Gleason drew a basic diagram for this classification by visualizing five different patterns of the tumour. In this system, the most common first and second patterns of 5 different patterns are summed and the total GS is given. This system is performed by histopathological evaluation of hematoxylin and eosin (H&E) stained sections in x4 and x10 magnification. Modifications were made to this system in 1974 and 2005 (5,6). Lastly, in 2013, the foundation of a Grade-group system (GGS) was laid with a study from Johns Hopkins Hospital. In this study, Epstein et al. (7) proposed dividing GS into prognostic risk categories. Thus, this system groups classic GS cases from 1 to 5. This new rating system, which was later approved by many multicenter studies, was accepted at the 2014 International Society of Urological Pathology (ISUP) conference and entered WHO in 2016 (3).

In this study, we analyzed this new system retrospectively in terms of prognosis prediction, usefulness, and contribution to daily practice.

MATERIAL AND METHOD

Ethical Approval

The study was approved by the Kırıkkale University Health Research Ethics Committee (Permission granted/ date: 2020, decision number: 2020.06.18). In this retrospective study, all procedures and practices are in accordance with the ethical standards of the national/ institutional research committee and the 1964 Helsinki declaration.

Study Design

This study was carried out in Kırıkkale University Faculty of Medicine, Department of Pathology. All patients who underwent biopsy and resection due to PC between 2000 and 2015 were included in this study. Patients with second malignancy synchronized with PC were excluded from the study (n=9). Also, cases with tumour block deficiency (n=10) and insufficient tissue in the block (n=7) were excluded from the study. As a result, four hundred and eighty-six cases were collected. Tumour location and volume, GS, age, lymph node status, perineural and vascular invasion, stage, surgical margin, and survival information were recorded from the archive data.

Processing of Tissues

Necessary formalin-fixed paraffin-embedded tumour samples were collected from the tissue archives of the pathology department for cases deemed necessary (n=98). 4-micron thick sections prepared from paraffin blocks of these tissue samples were stained with H&E.

Assessment of Gleason Grade Group

In this study, archive records, H&E painted sections, conventional light microscope (Nikon Eclipse E600, Nikon AG Instruments, USA), and x4-x10 lenses were used for evaluation. Three experienced pathologists re-evaluated all cases. The scores of the cases varying between 2 and 10 were re-grouped in terms of GGS. GS ≤6 patients were GGS1 group, GS 3+4=7 patients GGS2 group, GS 4+3=7 patients GGS3 group, GS 8 patients GGS4 group and GS 9-10 patients GGS5 group. The relationship between GGS and clinicopathological parameters was evaluated statistically. American Cancer Joint Committee (8th) guidelines were used in evaluations.

Reproducibility of the study

Inter-observer agreement was investigated to assess reproducibility. Three experienced pathologists (MZ, ME and MAA) evaluated all cases without knowing the clinical and pathological information. Kappa test (κ), which is a variance ratio, was used for inter-observer agreement. κ was grouped as weak, medium and perfect for values of 0.41-0.60, 0.61-0.80 and 0.81-1, respectively.

Patients follow-up

The survival data for the outcome measures were obtained from the archive records. The start time was calculated from the day of the primary biopsy. 15 years of follow-up was considered appropriate to make a more reliable decision about the relapse of the disease. Recurrence-free survival (RFS) was defined as the time from primary biopsy day to local/regional recurrence day or death day. Overall survival (OS) was defined as the time from the day of primary biopsy to the day of death. All events after sixty months of follow-up were censored in sixty months.

Statistical Evaluation

Ranges, averages, and standard deviation were used to define continuous data and percentages and frequencies for categorical data. Chi-square test was used to analyze

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the relationships between clinicopathological prognostic factors and categorical variables. Significant differences between univariable survival groups were evaluated by the Log-rank test and survival curves were presented by the Kaplan-Meier method. Multivariable survival groups were evaluated by the Cox-regression model with a 95% confidence interval (CI) and a 1.0 hazard ratio (HR). All tests were two-sided and p values less than 0.05 were considered statistically significant. Statistical data were analyzed using SPSS 21.0 (IBM institute, North Castle, USA).

RESULTS

General Features

The mean of age and tumor volume were 65.54±8.77 (range: 50-89) and 4.50 cm±1.50 cm (range: 2 cm-5 cm). 135 (27.7%) of tumors were GGS 1, 120 (24.6%) were GGS 2, 114 (23.4%) were GGS 3, 60 (12.3%) were GS 4, and 57 (11.7%) were GS 5. Tumour was single lobe in 291 (60.0%) cases, and of tumour ratio was <50% in 310 (63.9%) cases.

Evaluation of GGS

Particular attention was paid when reassessing GS 3+4 and 4+3 cases because the GGS scores would be different. In general, our GS scores were compatible with archive records. There was a statistical relationship between GGS subgroups and prognostic factors, and there was more significant relationship, especially between GGS 2 and GGS 3 [tumour status (p<0.001), age (p=0.045), PN invasion (p<0.001), stage (p=0.004), LN status (p<0.001), and surgical margin (p=0.003)]. The statistical relationship between clinicopathological features and GGS is shown in **Table 1**.

Reproducibility of GGS

The inter-observer agreement was generally in the clinically useful range and ranged from moderate to significant (κ=0.51-0.70). We also found that the agreement between observers for GGS is generally higher (κ=0.63-0.70).

Follow-up of Patients

In the follow-up, one hundred and sixty-five cases died (n=25 for GGS1, n=89 for GGS 2 and GGS 3, n=51 for GGS 4 and GGS 5) and two hundred and ninety cases relapsed (n=32 for GGS 1, n=96 for GGS 2 and GGS 3, n=62 for GGS 4 and GGS 5). The 5-year RFS and OS rates were 81% and 83% for GGS 2 and 65% and 66% for GGS 3, respectively. Also, the 5-year RFS and OS rates were 55% and 58% for GGS 4 and 42% and 43% for GGS 5, respectively **(Table 2)**.
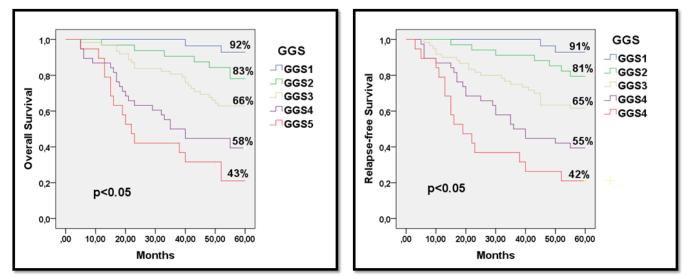
Survival Analyses

There was a significant difference in survival in univariate analysis for GGS subgroups (for GGS 2-GGS 3, RFS: p=0.035 and OS: p=0.012; for GGS 4-GGS 5, RFS: p=0.001 and OS: p=0.001) **(Table 2, Figure 2)**. Other parameters associated with poor survival were LN status, stage, and surgical margin. GGS subgroups were an independent survival parameter for survival in multivariate analysis (for GGS 2-GGS 3, OS: HR=2.56 [1.81-4.32], p=0.012 and RFS: HR=2.69 [1.49-4.52], p=0.038; for GGS 4-GGS 5, OS: HR=2.84 [1.34-3.49], p=0.011 and RFS: HR=2.59 [1.46-4.19], p<0.001). Other independent parameters associated with poor survival were LN status, stage and surgical margins **(Table 2).**
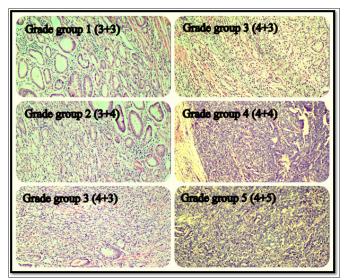
Table 1. Statistical relationship of GGS subgroups with prognostic factors							
		GGS (%)			GGS (%)		
		GGS 2	GGS 3	p-value	GGS 4	GGS 5	p-value
Tumour status	Single lobe	39 (32.5)	72 (63.1)	<0.001*	22 (36.6)	33 (57.8)	**0.021***
	Both lobes	81 (67.5)	42 (36.9)		38 (63.4)	24 (42.2)	
Age	<65	57 (47.5)	69 (23.4)	**0.045***	27 (45.0)	36 (63.1)	**0.048***
	≥65	63 (52.5)	45 (76.6)		33 (55.0)	21 (36.9)	
AL invasion	No	54 (45.0)	63 (55.2)	0.116	29 (48.3)	30 (52.6)	0.642
	Yes	66 (55.0)	51 (44.8)		31 (51.7)	27 (47.4)	
PN invasion	No	54 (45.0)	78 (68.4)	<0.001*	29 (48.3)	38 (66.6)	**0.045***
	Yes	66 (55.0)	36 (31.6)		31 (51.7)	19 (33.4)	
Tumour volume	<50%	54 (45.0)	63 (55.2)	0.116	24 (40.0)	34 (59.6)	**0.033***
	≥50%	66 (55.0)	51 (44.8)		36 (60.0)	23 (40.4)	
Stage	PT1	48 (40.0)	72 (63.1)	0.004	23 (38.3)	37 (64.9)	0.004*
	PT2	72 (60.0)	52 (36.9)		37 (61.7)	20 (35.1)	
LN status	Negative	52 (35.0)	81 (71.0)	***<0.001****	24 (40.0)	38 (66.6)	0.003*
	Positive	78 (65.0)	33 (29.0)		36 (60.0)	19 (33.4)	
Surgical margin	Negative	52 (35.0)	72 (63.1)	0.003*	22 (36.6)	35 (61.4)	0.007*
	Positive	78 (65.0)	52 (36.9)		38 (63.4)	22 (38.6)	
*. The limit of significance was accepted as 0.05 for the Chi-square test. Statistically significant results were recorded in italics. **Abbreviations:** GGS: Grade-Group system, AN: Angiolymphatic, PN: Perineural, LN: Lymph node							

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Table 2. Survival curves of GGS

	Univariate survival analysis(%)				Multivariate survival analysis(%)			
	OS		RFS		OS		RFS	
	5-year (%)	p-value	5-year (%)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Tumour status		0.248		0.233		NC		NC
Single lobe	89%		88%		-		-	
Both lobes	78%		77%		-		-	
Age		0.457		0.449		NC		NC
<65	85%		86%		-		-	
≥65	75%		84%		-		-	
AL invasion		0.559		0.489		NC		NC
No	87%		88%		-		-	
Yes	79%		88%		-		-	
PN invasion		0.162		0.168		NC		NC
No	87%		87%		-		-	
Yes	75%		76%		-		-	
Tumour volume		0.667		0.823		NC		NC
<50%	88%		87%		-		-	
≥50%	79%		80%		-		-	
Stage		0.007*		0.009*		0.041*		0.032*
PT1-2	90%		89%		1		1	
PT3-4	73%		73%		1.42 (1.23-4.56)		1.37 (1.33-2.44)	
LN status		0.003*		0.001*		0.021*		0.014*
Negative	79%		78%		1		1	
Positive	63%		60%		1.31 (1.11-4.12)		1.43 (1.52-3.88)	
Surgical margin		0.005*		<0.001*		0.0017*		0.003*
Negative	88%		89%		1		1	
Positive	72%		70%		1.42 (1.28-2.16)		1.54 (1.37-3.62)	
GGS		0.012*		0.003*		0.038*		0.012*
GGS 2	83%		81%		1		1	
GGS 3	66%		65%		2.56 (1.81-4.32)		2.69 (1.49-4.52)	
GGS		0.001*		<0.001*		0.011*		0.001*
GGS 4	58%		55%		1		1	
GGS 5	43%		42%		2.84 (1.34-3.49)		2.59 (1.46-4.19)	

*. The limit of significance was accepted as 0.05 for the Chi-square test. Statistically significant results were recorded in italics. **Abbreviations:** GGS: Grade-Group system, AN: Angiolymphatic, PN: Perineural, LN: Lymph node, OS: Overall survival, RFS: Relapse-free survival, HR: Hazard ratio, NC: Not calculable, CI: Confidence interval

Figure 2: Overall survival and relapse-free survival of Grade-Group system
Survival curves were presented with the Kaplan-Meier curves. The limit of significance was accepted as 0.05 for the Chi-square test.

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Figure 1. Representative examples of Grade-Group system (GGS) While examining prostate cancers in terms of GGS, x10-x20 lens, hematoxylin and eosin-stained sections, and classical microscope were used.

Table 3. Reproducibility of GGS	
N	Kappa values (Weighted)
GGS	0.70 **(A&B)**, 0.62 **(B&C)**, 0.63 **(A&C)**
GS	0.55 **(A&B)**, 0.51 **(B&C)**, 0.53 **(A&C)**
Abbreviations GS: Gleason scoring, GGS: Grade-Group system, A: First observer, B: Second observer, C: Third observer	

DISCUSSION

In this study, we compared the new GGS with the old system. According to our findings, this system classified patients more accurately in terms of survival. Also, due to the simplicity of the GGS, this system increased the inter-observer agreement.

Prostate cancer is one of the most common malignant tumours in the world and methods such as serum PSA level, transrectal prostate needle biopsy, and prostate ultrasound are used for its screening and diagnosis. Treatment options for PC are radical prostatectomy, chemotherapy, radiotherapy and hormonotherapy (8). The characteristics of the tumour should be evaluated correctly at the time of diagnosis for the correct treatment selection and correct prognosis estimation (9). While PC patients are divided into risk groups, GS and preoperative PSA level are very important (10,11). Between these two factors, the final GS may change before and after surgery. Therefore, much attention should be paid to the correct evaluation of GS at the time of diagnosis for an appropriate treatment decision (12,13).

Gleason scoringis a rating system developed in the 1960s and remains the strongest prognosis estimator for PC today. GS was first modified from its original definition in 1974 by Gleason and Mellinger (5). In 2005, the 2nd

modification was made by the ISUP, thereby achieving a better correlation between the Gleason degree, patient stage, and biochemical PSA values (6). Although these new changes were more complex than before, they showed better relationships with prognostic factors. As an example of the complexities, low-grade cancer, which covers less than 5% in needle biopsy of high-grade cancer, would not be included in GS (14). Also, the highest grade pattern was included in the biopsy score, but not in the resection score. However, many studies reported that GS 6 cases with pattern 4 differ in recurrence.That is, GS 6 cases with a high-grade component had a prognosis between GS 6 and GS 3+4=7 (15,16). In our study, we experienced that the GS system is more complex. Also, the prognosis of the groups containing pattern 4 was worse than pattern 3.

The last modification for the GS was made by ISUP in 2014. Accordingly, considering approximately 20000 radical prostatectomy data collected from different centres, PCs were categorized into 5 histological classes described above. Also, many multicenter studies have confirmed that GGS classifies PC patients more accurately in terms of prognosis (3). In addition, with the new grading system, the score that could have a value between 2-10 was reduced to 5 and a simpler stratification was created. Moreover, it was provided to express low and medium risk groups more easily (10, 13). In our study, it was seen that this system was easy to understand and useful. Also, the agreement between observers was higher. The GS 3+4 and GS 4+3 groups are scored as 7 in the GS system. However, studies have shown that the percentage of pattern 4 adversely affects patient prognosis in GS 7 patients. In the new system, GS 3+4=7 cases are considered as GGS2, and GS 4+3=7 cases are considered as GGS3 (17-19). In our study, we also found that GGS 3 has a worse prognosis than GG2.

In tumours with a GS score of 8 and above, the prognosis is significantly worse, but this is more pronounced at the 9-10 level. GS 8 and above are considered as a single category in most studies, including prediction tables and nomograms (20). This is because the number of patients with GS 9-10 is small and combined with GS 8 for meaningful statistical analysis. For this reason, some urologists consider GS 8 the same as GS 9-10. GS 9-10 patients are rarely seen, but GS 9-10 tumours have a worse prognosis than GS 8. Also, patients with these tumours are mostly not suitable for resection (20,21). In addition, there is a significant decrease in prognosis in the first three years in GS 9-10 patients. For the above reasons, GS 9-10 patients should be evaluated separately from GS8 patients (21,22). In our study, a significant difference was also observed between these two groups in terms of prognosis.

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The limitations of our study are as follows. Since our study is retrospective, there are some limitations inherent in retrospective studies. For example, it is not possible to overcome the sampling difference. Also, archive records were used for our study and individual records were not used. In addition, since our patients were treated according to protocols before 2015, there may be differences according to current treatment approaches.

CONCLUSION

According to our results, the new GGS divides patients more accurately into risk groups. Also, this system is very simple and this is an important advantage for daily practice, observers agreement and patient management.

Abbreviations

PC: Prostate cancer, GS:Gleason scoring, GGS:Grade-Group system, HPF: High power field, ISUP: International Society of Urological Pathology, AJCC: American Joint Cancer Committee, κ: Kappa, H&E: Hematoxylin and eosin, SD:Standard deviation, HR: Hazard ratio, OS: Overall survival, RFS: Relapse-free survival

ETHICAL DECLARATIONS

Ethics Committee Approval: Our study was approved by the Kırıkkale University Health Research Ethics Committee (Permission granted/date: 2020, decision number: 2020.06.18). Attention has been paid to ensure that all steps performed during our study comply with the 1964 Helsinki Declaration and national/institutional ethical standards

Informed Consent: Because the study was designed retrospectively, no written informed consentform wasobtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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