

## Original Article

# Correlation of Prognostic Gleason Grade Grouping and Histopathological Parameters: Can the “New System” Reflect the Pathological Perspective for Prognosis?

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**Background:** Gleason score is one of the strongest prognostic predictors of prostate cancer; however, a change was published which is a 5 step grouping system of prostatic adenocarcinomas according to their Gleason scores. The aim of this study is to determine the relationship between histopathological findings and prognosis of tumors subgrouped according to the new Gleason grade grouping system.

**Methods:** A total of 163 radical prostatectomies subgrouped into 5 prognostic groups were investigated for prognostic features such as pathological stage, extraprostatic extension, surgical margin status, involvement of seminal vesicles, perineural invasion, necrosis, vascular invasion, ganglionic involvement, concomitant high grade prostatic intraepithelial neoplasia (HPIN) in addition to other microscopic features of tumors such as the presence of mucin and foamy cytoplasmic change between groups.

**Results:** The mean age of patients was  $65.72 \pm 6.67$  (min = 46, max = 82). Among 131 patients who completed the study, the mean prostate specific antigen (PSA) value was  $11.29 \pm 10.88$ . The statistically significant factors were significantly related to both the original Gleason and the prognostic grade groups. The recurrence rate of grade group 4 patients (57%) was significantly higher than grade group 3 patients (8%) ( $P = 0.038$ ). But no significant difference was found between grade group 4 and 5 ( $P = 0.25$ ).

**Conclusion:** Grade grouping systems reflect prognostic differences but adapting this new system into routine evaluation of patients may confuse the clinicians; however, pathology reports stating both the traditional Gleason score and the new prognostic group may soften the transition.

**Keywords:** Gleason grading, Grade grouping, Prostate cancer, Prostate, Prognosis

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**Introduction**

Prostate cancer is the most common cancer in men worldwide and has a different grading system from other carcinomas (the Gleason grading system) which was developed in the 1960s. Gleason grade/score remains the strongest prognostic predictor of prostate cancer which is defined as the sum of the first and the second most common architectural grades<sup>1</sup> in biopsies which do not have a worse tertiary pattern and radical prostatectomies (RP).

Gleason grading system was first modified by Gleason and Mellinger in 1974<sup>2</sup> and another revision in 2005 was done by the International Society of Urological Pathology (ISUP).<sup>3</sup> Depending on the controversial results of different studies and the complexity of the new modified ISUP Gleason scoring system, a change in the reporting of prostatic adenocarcinomas is offered by Epstein et al,<sup>4</sup> which was accepted by the WHO and published in the last version of the WHO “blue book”.<sup>5</sup> This is a 5 step grouping system of

prostatic adenocarcinomas according to their Gleason scores.

The aim of this study was to determine the relationship between histopathological findings and prognosis of tumors subgrouped according to the offered Gleason prognostic grouping.

**Materials and Methods**

A total number of 163 cases diagnosed with acinar prostatic adenocarcinoma and treated by RP in İzmir Atatürk Training and Research Hospital Urology Clinic between January 2001 and December 2012 were included in this study. Patients out of follow up for any reason and whose paraffin blocks were out of reach were excluded.

All of the specimens were evaluated with same procedure as all surgical margins were inked and all of the specimens were handled and blocked. All the hematoxylin-eosin slides were reviewed, staged according to 2010 AJCC staging system. Demographic data were obtained from hospital records and

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an informed consent was taken from each patient for the study. Gleason score was modified according to ISUP 2015 revision as all cribriform glands were accepted as Gleason pattern 4, comedonecrosis as Gleason pattern 5 etc. for the cases diagnosed before the revision. Tumor volume was measured by eye-ball estimation. Normal distribution was analyzed by chi-square test. In addition to Gleason score; many histological prognostic parameters such as tumor volume, stage, high grade prostatic intraepithelial neoplasia (HPIN), extraprostatic extension, perineural invasion, lymphovascular invasion, surgical margins and lymph node status were also noted.

Then the cases were subgrouped into 5 prognostic groups as Epstein et al<sup>4</sup> offered and WHO accepted.<sup>5</sup> Many prognostic features such as pathological stage, extraprostatic extension, surgical margin status, the involvement of seminal vesicles, perineural invasion, necrosis, vascular invasion, ganglionic involvement, concomitant HPIN were investigated in addition to the other microscopic features of tumors such as the presence of mucus and foamy cytoplasmic change (<20% of the entire tumor) between the groups. In order to enlighten the importance of Gleason grade grouping among our cases, all of the possible histological parameters mentioned above that may effect prognosis were compared between the original Gleason score and the new prognostic grade groups and evaluated in statistical analysis. Biochemical recurrence was accepted as postoperative prostate specific antigen (PSA) level >0.2 ng/mL.

### Statistical Analysis

The Mann-Whitney-Wilcoxon and Welch *t*-tests were used to assess the difference between patients who relapsed and those who did not in terms of their pathological stages, tumor volumes, original total Gleason scores (G-total score) and prognostic groups that were designed based on the total Gleason scores (Gleason grade group), PSA levels, and ages. A *P* value of <0.05 was considered statistically significant.

To determine whether there was any significant association between recurrence of the disease and histopathological parameters, chi-square and Fisher exact tests were used. Kruskal-Wallis test was used to determine if there was a statistically significant difference in term of the PSA level between the Gleason grade groups. The pairwise comparisons were done by the Mann-Whitney-Wilcoxon test with Bonferroni adjustment. All statistical analyses were performed using the computing environment R.

### Results

In this study, the pathological features of 163 cases were examined. The mean age of those patients was  $65.72 \pm 6.67$  (min = 46, max = 82). There were 32 cases lost to follow-up. 131 patients completed the study.

A total of 131 patients with a mean age of  $65.44 \pm 7.00$  (minimum 46 and maximum 82) were included in this study. The mean PSA value of the studied patients was  $11.29 \pm 10.88$ . According to the pathological stage 61 cases were PT2 and 70 cases were PT3.

The distribution of the original total Gleason scores and the cases subgrouped into 5 prognostic groups were given in Table 1. The important histopathological and prognostic factors of these patients were given in Table 2.

All of the patients were revised for biochemical recurrence which was defined as PSA level >0.2 ng/mL. According to this; 21 cases (16%) had recurrent disease. Minimum relapse time was 8 months and maximum was 72 months. Average relapse time was  $20.81 \pm 14.01$  months.

There was a statistically significant difference in PSA level between the G-total scores ( $P < 0.001$ , Kruskal-Wallis test), with a median PSA level of 6.4 for G-total = 6, 8.2 for G-total = 7, 9.3 for G-total = 8, and 20.4 for G-total = 9. Post-hoc comparisons (Mann-Whitney-Wilcoxon test with Bonferroni adjustment) indicated that the median PSA level of the G-total=9 group was significantly higher than the groups G-total = 6 and G-total = 7 (both  $P < 0.001$ ). However, G-total = 8 was not significantly differ from the G-total = 9 ( $P = 0.32$ ).

Also, there was a statistically significant difference in PSA level between the G-prognostic groups ( $P < 0.001$ , Kruskal-Wallis test), with a median PSA level of 6.4 for grade group 1, 8.1 for grade group 2, 10.7 for grade group 3, 9.3 for grade group 4 and 20.4 for grade group 5. Post-hoc comparisons indicated that the median PSA level of the grade group 5 was significantly higher than the grade group 2 and grade group 1 (both  $P < 0.001$ ). However, grade group 5 was not significantly differ from the grade group 4 and grade group 3 ( $P = 0.32$ ,  $P = 0.03$ , respectively). In addition, PSA levels of the grade group 4 did not significantly differ from the grade group 3 ( $P = 0.65$ ).

The volume and the pathological stage of the tumor, the original total Gleason score and the prognostic Gleason grade group number were significantly higher in relapsed patients ( $P < 0.001$ , Mann-Whitney-Wilcoxon test). The relapse rate was significantly higher in PT3 cases ( $P = 0.001$ , proportion test). The original total Gleason score was significantly higher in relapsed cases ( $P < 0.001$ , Fisher exact test) as well as Gleason grade groups ( $P < 0.001$ , Fisher exact test). The lymph node involvement was seen in 4 cases (3.05%) and 3 of them were in grade group 3, whilst one was in grade group 4. Lymph node involvement showed significant relation with recurrence ( $P = 0.013$ , Fisher exact test) and between the groups ( $P < 0.001$ , Fisher exact test).

The age ( $P = 0.981$ , Welch *t* test), HPIN ( $P = 0.999$ , Fisher's exact test), intraluminal mucin ( $P = 0.663$ , chi-square test), ganglionic involvement ( $P = 0.157$ , Fisher exact

**Table 1.** Distribution of Gleason Grade Groups

	Prognostic Grade Group				
	Grade Group 1 (3+3=6) No. (%)	Grade Group 2 (3+4=7), No. (%)	Grade Group 3 (4+3=7), No. (%)	Grade Group 4 (4+4=8, 3+5=8, 5+3=8), No. (%)	Grade Group 5 (4+5,5+4), No. (%)
Number of patients	67 (51%)	35 (27%)	12 (9%)	7 (5%)	10 (8%)

**Table 2.** The Important Histopathological and Prognostic Factors of the Patients

Prognostic Factor	Number of Patients, No. (%)	
	Positive	Negative
EPE	68 (52)	63 (48)
PNI	95 (73)	36 (27)
Presence of HPIN	100 (76)	31 (24)
Lymphovascular invasion	11 (8)	120 (92)
Necrosis	9 (7)	122 (93)
Tumor positive surgical margin	68 (52)	63 (48)
Involvement of the seminal vesicles	18 (14)	113 (86)
Ganglionic involvement	9 (7)	122 (93)
High grade tertiary pattern	15 (11)	116 (89)
Intraluminal mucin	46 (35)	85 (65)
Foamy cytoplasm	22 (17)	109 (83)

HPIN: High grade prostatic intraepithelial neoplasia; EPE, extraprostatic extension; PNI, perineural invasion.

test), foamy cytoplasm ( $P=0.754$ , Fisher exact test) and high grade tertiary pattern ( $P = 0.999$ , Fisher exact test) was unrelated to recurrence. Other histopathological factors related to recurrence was given in Table 3.

All of the parameters were compared with the original Gleason score and Gleason grade group according to the presence of recurrence. In both types of grouping; the presence of HPIN and high grade tertiary pattern was unrelated to recurrence ( $P = 0.877$  and  $0.260$  for the original Gleason scoring and  $P = 0.911$  and  $0.153$  for the prognostic grade grouping, respectively). The statistically significant factors (EPE, PNI, LVI, necrosis, positive surgical margins, involvement of the seminal vesicles and ganglion, foamy cytoplasmic change) were both significantly related to both the original Gleason and the prognostic grade groups (Table 4). The only exception in these prognostic parameters is the intraluminal mucin. Intraluminal mucin was significantly related to recurrence when compared with the original Gleason scores ( $P=0.004$ ). However, intraluminal mucin was not statistically related when compared to prognostic grade grouping ( $P=0.09$ ).

The presence of high grade tertiary pattern was not statistically different among all the scores and groups. The effect of high grade tertiary pattern was also investigated among the gleason score 3+3 and 4 + 4 group and no significant difference was observed in these groups ( $P = 0.521$  and  $P=0.429$ , respectively) for the recurrence.

In our study group we observed no significant difference for recurrence between grade group 1 and 2 ( $P=1$ , Fisher exact test) but there was a significant relation grade group 3 and grade group 4 for recurrence ( $P=0.038$ , Fisher's exact test). In other words, the recurrence rate of grade group 4 patients (57%) was significantly higher than the grade group 3 patients (8%) ( $P=0.038$ , Fisher exact test). But no significant difference was found between grade group 4 and 5 ( $P=0.25$ , Fisher exact test). However; there were no patients with score 10 in our study group.

## Discussion

The current Gleason grading system, first announced by

**Table 3.** The Relationship Between the Prognostic Factors and Recurrence

Prognostic Factors	Recurrence		P Value
	Positive	Negative	
Pathological stage 2	3	58	0.003
Pathological stage 3	18	52	
Gleason score of 6	4	63	< 0.001
Gleason score of 7	4	43	
Gleason score of 8	4	3	
Gleason score of 9	9	1	
EPE positive	17	51	0.008
EPE negative	4	59	
PNI positive	20	75	0.008
PNI negative	1	35	
HPIN positive	16	5	0.999
HPIN negative	84	26	
Necrosis positive	5	4	0.008
Necrosis negative	16	106	
LVI positive	6	15	0.002
LVI negative	5	105	
Surgical margin positive	19	2	<0.001
Surgical margin negative	49	61	
Seminal vesicles involved	11	10	<0.001
Seminal vesicles not involved	7	103	
Intraluminal mucin positive	6	40	0.663
Intraluminal mucin negative	15	70	
Ganglion involved	3	18	0.157
Ganglion not involved	6	104	
Foamy cytoplasmic change positive	4	17	0.999
Foamy cytoplasmic change negative	18	92	
High grade tertiary pattern positive	2	19	0.999
High grade tertiary pattern negative	13	97	

EPE, Extraprostatic extension, PNI, Perineural invasion, HPIN, high grade prostatic intraepithelial neoplasia, LVI, Lymphovascular invasion.

Gleason and Mellinger in 1974,<sup>2</sup> has changed from its original description and most recently revised in 2014 by the International Society of Urological Pathology (ISUP).<sup>3,4</sup> The major reasons for these revisions were the histopathological discordance of the scoring patterns and the difference in the clinical impacts of these scores. For example; overtreatment of Gleason score 6 prostate cancer is an important problem; however, undertreatment and a missed opportunity for cure is also a real risk of trying to treat a cancer.<sup>6</sup> Some studies even question whether a Gleason score 6 or less should be labeled as cancer.<sup>7</sup> Another clinical problem about Gleason scores was the prognostic difference between the cases with Gleason score of 3 + 4 = 7 and 4 + 3 = 7. Many studies in the literature investigated the prognostic difference of these two groups. The major view of these studies was that Gleason score 7 with 4 + 3 patterns had a worse prognosis when compared with Gleason score of 3 + 4.<sup>8-12</sup> After the Gleason grade grouping, the major target of many studies was to put forth the prognostic value of this system. Many of these studies supported the prognostic grade grouping as it correlates more with the clinical aspects.<sup>3-15</sup>

In contrast, some of the studies suggested that the novel grading does not have an improved effect on prostate cancer grading and has less sensitivity in differentiating 3 + 4 and 4 + 3 tumors on radical prostatectomy.<sup>16</sup> Some studies offer that this system does not improve the clinical view of

**Table 4.** Comparison of Histopathological Parameters With Prognostic Grade Groups

	G-prog = 1 (n = 67)	G-prog = 2 (n = 35)	G-prog = 3 (n = 12)	G-prog = 4 (n = 7)	G-prog = 5 (n = 10)	P Value
Stage						
2	49 (80%)	8 (13%)	2 (3%)	1 (2%)	1 (2%)	< 0.001
3	18 (26%)	27 (39%)	10 (14%)	6 (9%)	9 (13%)	
Recurrence						
Yes	4 (19%)	3 (14%)	1 (5%)	4 (19%)	9 (43%)	< 0.001
No	63 (57%)	32 (29%)	11 (10%)	3 (3%)	1 (1%)	
EPE						
Yes	16 (24%)	28 (41%)	10 (15%)	5 (7%)	9 (13%)	< 0.001
No	51 (81%)	7 (11%)	2 (3%)	2 (3%)	1 (2%)	
PNI						
Yes	35 (37%)	34 (36%)	10 (11%)	6 (6%)	10 (11%)	< 0.001
No	32 (89%)	1 (3%)	2 (6%)	1 (3%)	0 (0%)	
HPIN						
Yes	52 (52%)	26 (26%)	10 (10%)	5 (5%)	7 (7%)	0.911
No	15 (48%)	9 (19%)	2 (6%)	2 (6%)	3 (10%)	
Necrosis						
Yes	1 (11%)	1 (11%)	2 (22%)	0 (0%)	5 (56%)	< 0.001
No	66 (54%)	34 (28%)	10 (8%)	7 (6%)	5 (4%)	
LVI						
Yes	0 (0%)	1 (9%)	3 (27%)	1 (9%)	6 (55%)	< 0.001
No	67 (56%)	34 (28%)	9 (8%)	6 (5%)	4 (3%)	
Positive surgical margins						
Yes	22 (32%)	22 (32%)	10 (15%)	4 (6%)	10 (15%)	< 0.001
No	45 (71%)	13 (21%)	2 (3%)	3 (5%)	0 (0%)	
Involvement of the seminal vesicles						
Yes	2 (11%)	3 (17%)	5 (28%)	2 (11%)	6 (33%)	< 0.001
No	65 (58%)	32 (28%)	7 (6%)	5 (4%)	4 (4%)	
Intraluminal mucin						
Yes	20 (43%)	17 (37%)	5 (11%)	0 (0%)	4 (9%)	0.09
No	47 (55%)	18 (21%)	7 (8%)	7 (8%)	6 (7%)	
Ganglionic involvement						
Yes	2 (22%)	2 (22%)	2 (22%)	0 (0%)	3 (33%)	0.023
No	65 (53%)	33 (27%)	10 (8%)	7 (6%)	7 (6%)	
Foamy cytoplasmic change						
Yes	6 (27%)	12 (55%)	2 (9%)	1 (5%)	1 (5%)	0.026
No	61 (56%)	23 (21%)	10 (9%)	6 (6%)	9 (8%)	
High grade tertiary pattern						
Yes	11 (73%)	1 (7%)	2 (13%)	1 (7%)	0 (0%)	0.153
No	56 (48%)	34 (29%)	10 (9%)	6 (5%)	10 (9%)	

EPE, Extraprostatic extension, PNI, Perineural invasion, HPIN, high grade prostatic intraepithelial neoplasia, LVI, Lymphovascular invasion.

prognosis.<sup>17</sup> We observed no significant difference between grade group 1 and grade group 2 but there was a real significant relation between grade group 3 and grade group 4. This finding supports the prognostic difference between 4 + 3 and 4 + 4 tumors and that's why we have to mention the Gleason pattern 3 if existing.

Lymph node involvement is one of the most important prognostic factors not only in prostate cancer but also in all epithelial malignant tumors. The presence of regional lymph node involvement is seen in 5–12% of the cases with organ-confined disease.<sup>5</sup> In our study, 3.05% of our cases had lymph node involvement similar with the literature. Patients with visceral organ metastasis had been shown to have worse prognosis than the patients with only nodal metastasis.<sup>18</sup> However, we did not find studies focusing on the correlation of histopathological prognostic factors between groups. We observed that not only the poor clinical prognostic factors such as PSA levels, high tumor stages but also worse histopathologic features such as perineural invasion, lymphovascular invasion, extraprostatic extension

were more common in prognostic groups of IV and V.

In our study, we found a significant difference of recurrence supporting the data of Pierorazio et al.<sup>19</sup> and Epstein et al.<sup>4</sup> The most classically known prognostic factors were also significant in our study but we wanted to determine a few novel factors that may affect prognosis such as intraluminal mucin, ganglionic involvement and foamy cytoplasmic change. Foamy glands are one of the most common benign mimickers of prostatic carcinoma. Foamy gland carcinoma was described as a distinct type of carcinoma by Epstein and Nelson.<sup>20</sup> Foamy gland carcinomas show crowded glands with abundant foamy cytoplasm in various rates. But classical acinar low-grade adenocarcinomas may have a small amount (<20%) of foamy cytoplasmic change.<sup>20,21</sup> In our study, we observed foamy cytoplasmic change in 17% of our cases but it had no prognostic effect. However foamy cytoplasmic change was significantly different between the grade groups as mostly seen in grade group 1 and 2. Ganglionic involvement is generally associated with perineural involvement; however, we wanted to see the

distinct effect of ganglionic involvement and it was found to be significantly different between the prognostic groups.

Intraluminal mucin can be seen as amorphous basophilic secretions in the lumina of carcinomatous glands and rarely recognized in benign prostatic hyperplasias.<sup>22</sup> Intraluminal mucin can be observed not only in adenocarcinomas but also in atrophy and basal cell hyperplasia. Noiwani et al studied subtypes of mucin produced in prostatic adenocarcinomas.<sup>22</sup> They suggested that actual mucin production may be more common in prostatic adenocarcinomas. However as there is no certain study focusing on the prognostic effect of mucin production in prostate adenocarcinomas, the effect on prognosis is not clearly stated in the literature. We observed intraluminal mucin in 46 (35.1%) of our cases and only 6 of them had recurrent disease (4.5%). Most of cases which show intraluminal mucin production were grade group 1 (n = 20) and 2 (n = 15) but the presence of intraluminal mucin was not statistically different between the grade groups ( $P = 0.09$ ). As most of intraluminal mucin positive cases belong to lower grade groups, we thought that the presence of intraluminal mucin might be related with well differentiation of the prostate cancer. However the relation was not significant and this may be related to the unequal distribution of the cases and the low number of high grade cases.

One of the most important reasons for Gleason grade grouping was the prognostic difference between 3 + 4 and 4 + 3; 4 + 4 and score 9,10; and prognostic similarity of 3 + 3 and 3 + 4. Our results also showed the prognostic difference of grade group 3 and grade group 4, the most conflicting groups of the Gleason system. We did not find any significant difference between grade group 4 and 5 but this result may be due to the small number of cases in our grade group 5 due to inclusion of only patients treated by RP.

In conclusion; our results also supported the revision of the Gleason scores for their prognostic indications. Prognostic grouping of prostate cancer can enlighten personalized treatment and prevent patients from over/undertreatment because of the strict differences in each group. However, pathology reports stating both the traditional Gleason score and the new prognostic group as Epstein et al suggested may soften the transition and provide familiarization with this new classification.

#### Authors' Contribution

Collecting data: YD, AAA, EY, KB, AAS, Case selection: KB, YD, Histopathological evaluation of the cases: YD, AAA, AAS Statistical analysis: KT, YD, Writing the manuscript: YD, AAS, EY, Critical revision of the written manuscript: AAS.

#### Conflict of Interest Disclosures

The authors have no conflicts of interest.

#### Ethical Statement

Not applicable.

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