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External validation of the Gleason grade group system in Argentinian patients that underwent surgery for prostate cancer

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Introduction The aim of this article was to evaluate the effectiveness of the Gleason grade groups (GGG) system on a group of Argentinian patients with prostate cancer (PC) who underwent radical prostatectomy (RP).

Material and methods We retrospectively studied 262 patients who underwent RP between 1996 and 2014. To determine the performance and validity of the GGG system, a Kaplan-Meier analysis and multivariate analysis with Cox proportional method were performed to evaluate biochemical recurrence, distance metastases and specific cancer mortality. The area under the curve (AUC) was calculated to compare new groups of degrees of the GGG system with the classical scheme of stratification into 3 groups.

Results The median follow-up was 84 months. As the groups ascend, there is less confined organ disease ($p < 0.001$) and greater extraprostatic extension ($p < 0.001$), greater invasion of seminal vesicles ($p < 0.001$) and greater lymph node involvement ($p < 0.001$). The biochemical recurrence-free survival at 5 years was 68%, 55%, 22%, 9%, 0% of the 1–5 groups, respectively. Ten-years cancer-specific survival was 96%, 95%, 78%, 64%, 25% for group 1–5, respectively. In the multivariate analysis, the GGG system is presented as the only independent predictor of biochemical recurrence and specific cancer mortality. The AUC indicates that the GGG system has a higher prognostic discrimination compared to the classic 3-group system (6, 7, ≥8).

Conclusions The International Society of Urological Pathology (ISUP) GGG system is an independent predictor of biochemical recurrence and mortality from prostate cancer in patients treated with RP. The classification into 5 groups shows greater discrimination in the prognosis than the traditional Gleason classification.

Key Words: prostate cancer ‹› Gleason grade ‹› International Society of Urological Pathology ‹› radical prostatectomy

INTRODUCTION

The Gleason scoring system (GSS) has been universally accepted as the grade system for prostate cancer since its introduction by Donald Gleason in 1996 [1]. In the same way, this histological classification has proven to be a strong prognostic predictor in men diagnosed with this neoplasm [2, 3]. However, this system has undergone significant modifications since its introduction and in 2005, the International Society of Urological Pathology (ISUP), recommended the use of higher grades while defining the Gleason group (GG), principally due to false lower scores and marked differences in grades from

biopsy cylinders and radical prostatectomy (RP) specimens [4].

After these revisions, the original Gleason score that had 25 possibilities evolved into a traditional 3 level classification (6, 7, ≥8). This last version, however, shows marked heterogeneity in intermediate-risk groups (3 + 4 vs. 4 + 3), as well as in the high-risk group (8 vs. 9–10). For this reason, a new classification scheme formulating Gleason grade groups (GGG) was proposed by Pieropazio et al., in an effort to most adequately reflect the true histopathological aggressiveness of GGS [5]. Specifically, the groups were divided in the following way: Group 1 GGS 6, Group 2 GGS 3 + 4 = 7, Group 3 GGS 4 + 3 = 7, Group 4 GGS 8, Group 5 GGS 9–10. Several groups have validated such system in relation to the biochemical recurrence and specific cancer mortality to primary end points in patients treated with RP, external radiotherapy and brachytherapy [6, 7, 8]. In 2016, the ISUP accepted a new system as the new gold standard for regulating prostate cancer (PC) according to the World Health Organization [9]. However, to our knowledge, the new classification system has not been validated in Argentinian patients with prostate cancer after RP. Therefore, the objective of this study was to check the effectiveness of the GGG system on a group of Argentinian patients with PC who underwent RP.

MATERIAL AND METHODS

A retrospective and descriptive study was carried out evaluating 262 patients who underwent RP by localized prostate cancer between 1996 and 2014. A total of 35 patients with history of external radiotherapy, neoadjuvant with androgenic blockage before or lack of follow-up were excluded. All prostate biopsies and RP specimens were assigned a traditional Gleason score informed by our own Department of Pathological Anatomy. Tertiary patterns were not routinely used and were not included in the analysis. All of the cases were evaluated by a specialized uropathologist. The follow-up of the patients consisted of a prostate-specific antigen (PSA) examination performed every 3–6 months. Clinical, pathological and evolutionary variables were studied. In order to evaluate the new GGG system, patients were categorized as it was previously described (6, 3 + 4, 4 + 3, 8, 9 - 10) and assigned into groups 1-5, respectively. The groups system was analyzed along with the RP specimen. Biochemical recurrence was defined as the consecutive increase of two examinations of PSA >0.2 ng/ml. The presence of distant metastasis was determined by imaging methods [computed tomography (CT) or bone scan]. The univariate analysis was carried out with the chi-square method evaluating different GGG groups with pathological characteristics in the RP surgical pieces. The Kaplan-Meier analysis with survival rate curve was used for evaluating biochemical recurrence, distance metastasis and cancer specific mortality.

The log-rank test was used in order to determine the survival rate differences between the different GGG system groups. The multivariate analysis was carried out with the Cox proportional method comparing the GGG system with other known clinical and pathological

prognostic variables in PC. Finally, the area under the curve (AUC) was calculated in order to compare the new GGG grade groups with the classical scheme of the 3 stratification groups (Gleason 6 vs. 7 vs. ≥8). In all statistical analyses, a $p < 0.05$ was considered statistically significant. The statistical analysis was performed with the SPSS program version 18.0.

RESULTS

The population study included 227 patients with a mean follow-up of 84 months. Patients were dived according to the GGG system: 110 patients in Group 1 (48%), 66 in Group 2 (29%), 32 in Group 3 (14%), 11 in Group 4 (5%) and 8 in Group 5 (4%). The demographic characteristics of the study population are described in Table 1.

In Table 2, the relationship between GGG with several pathological characteristics found in the RP surgical specimen is shown. As the groups increase there is lower organ-confined disease and greater extraprostatic extension (EPE), greater seminal vesicle invasion (SVI) and greater lymph node invasion.

Figure 1 shows biochemical recurrence-free survival rate according to each risk group, which decreased as the groups ascended (log-rank test <0.001). Biochemical-free survival rate at 5 years was 68%, 55%, 22%, 9%, 0% for groups 1–5, respectively.

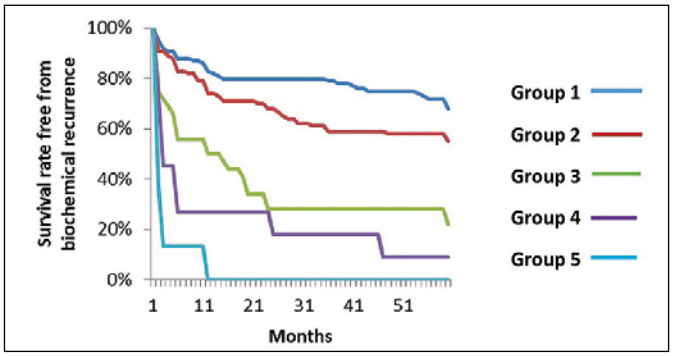

Figure 1. *Biochemical recurrence-free survival rate in Gleason grade groups.*

Similarly, metastasis-free survival rate and cancer-specific survival rate was lower in patients with higher GGG (log-rank test <0.001). Metastasis-free survival rate at 10 years was 95%, 92%, 75%, 64%, 25% for groups 1–5, respectively (Figure 2). Cancer-specific survival rate at 10 years was 96%, 95%, 78%, 64%, 25% for groups 1–5 respectively (Figure 3).

While performing the multivariate analysis, we showed that PSA level and the GGG system, are independent predictors for biochemical recurrence. Nevertheless, when we evaluated mortality by CAP only the GGG system was expressed as an independent predictive factor (Table 3).

In order to compare the differential power of the new GGG system in relation to the classical 3 grade system (6, 7, ≥8), the area under the curve was calculated (Table 4). There was an improvement in the AUC for biochemical recurrence (0.70 vs. 0.66), distant metastasis (0.72 vs. 0.75) and mortality by CAP (0.76 vs. 0.79), when comparing both systems

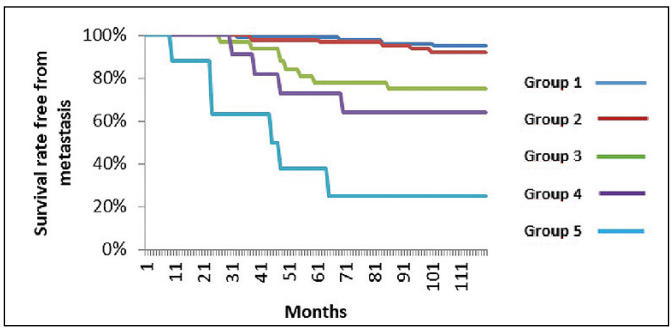

Figure 2. *Metasis-free survival rate in Gleason grade groups.*

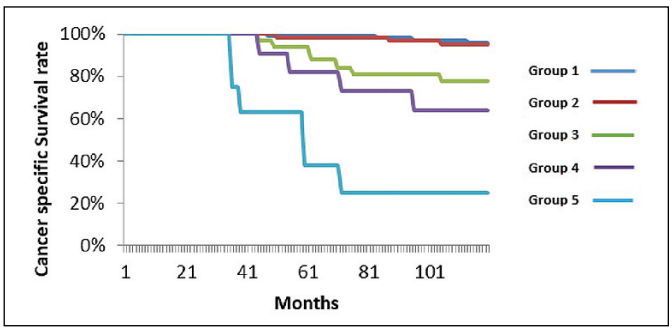

Figure 3. *Cancer-specific survival rate in Gleason grade groups.*

Table 1. *Demographic characteristics of the study population*

GGG System	G1	G2	G3	G4	G5
Number of patients	110 (48%)	66 (29%)	32 (14%)	11 (5%)	8 (4%)
Age (mean)	64	64	65	64	66
Surgery					
Before 2010	83 (75.4%)	43 (65.1%)	21 (65.6%)	7 (63.7%)	4 (50%)
After 2010	27 (24.6%)	23 (34.9%)	11 (34.4%)	4 (36.3%)	4 (50%)
PSA (mean)	8.9	9.3	11.8	9	20
Clinical stage					
T1	63 (57%)	24 (36%)	10 (31%)	1 (9%)	1 (12%)
T2	47 (43%)	42 (64%)	22 (69%)	10 (91%)	7 (88%)
No. of core biopsies					
<6	26 (23.6%)	15 (22.7%)	3 (9.4%)	1 (9%)	3 (37.5%)
6–10	38 (34.5%)	24 (36.3%)	6 (18.7%)	5 (45.5%)	0
>10	46 (41.9%)	27 (41%)	23 (71.9%)	5 (45.5%)	5 (62.5%)
No. of positive core biopsies					
<3	57 (51.8%)	22 (33.3%)	10 (31.2%)	2 (18.2%)	0
4–6	43 (39.1%)	32 (48.5%)	14 (43.8%)	3 (27.3%)	2 (25%)
>6	10 (9.1%)	12 (18.2%)	8 (25%)	6 (54.5%)	6 (75%)

GGG – Gleason grade groups; PSA – prostate-specific antigen

Table 2. *Pathological characteristics according to Gleason grade groups from radical prostatectomy specimens*

Pathological characteristics	Group 1	Group 2	Group 3	Group 4	Group 5	p
Organ-confined disease	89 (80.9%)	40 (60.6%)	16 (50%)	2 (18.2%)	0	<0.001
EPE	18 (16.4%)	18 (27.3%)	12 (37.5%)	6 (54.5%)	5 (62.5%)	<0.001
Seminal vesicle invasion	9 (8.2%)	11 (16.7%)	10 (31.2%)	6 (54.5%)	7 (87.5%)	<0.001
Lymph node invasion	0	0	1 (3.1%)	2 (18.2%)	3 (37.5%)	<0.001
Margins (+)	25 (22.7%)	17 (25.7%)	11 (34.4%)	5 (45.5%)	5 (62.5%)	0.06

EPE – extraprostatic extension

Table 3. *Independent predictors of biochemical recurrence and mortality from PC after RP*

Variable	Biochemical recurrence			Cancer specific mortality		
	OR	p	CI 95%	OR	p	CI 95%
PSA	7.46	0.006	1–1.03	0.01	0.99	0.96–1.03
cT2	0.51	0.47	0.76–1.81	0.10	0.75	0.17–3.57
Extraprostatic extension	0.72	0.39	0.77–1.90	0.54	0.87	0.32–2.63
Margins (+)	0.17	0.68	0.71–1.69	0.26	0.87	0.36–2.37
Seminal vesicle invasion	3.27	0.07	0.97–2.27	0.09	0.76	0.41–3.40
Lymph node invasion	0.98	0.32	0.61–4.38	1.68	0.19	0.64–8.64
GGG System	6.95	0.008	1.06–1.52	6.10	0.01	1.10–2.39

PC – prostate cancer; RP – radical prostatectomy; OR – odds ratio; IC – confidence interval; PSA – prostate-specific antigen; GGG – Gleason grade groups

Table 4. *Area under the curve results comparing the classical system vs. the new GGG system*

Evolution characteristics	3 pattern classical classification (6, 7, ≥8)	GGG System
Biochemical recurrence	0.66	0.70
Distant metastasis	0.72	0.75
Mortality from PC	0.76	0.79

GGG – Gleason grade groups; PC – prostate cancer

in RP specimens and correlating with their prognostic capacity.

DISCUSSION

In the 1960's, Donald Gleason was the first to propose a grading system for PC based on cellular architectural patterns. Afterwards, it was demonstrated that the sum of primary and secondary patterns (Gleason score) had a strong correlation with mortality [1]. From then on, GG has remained as the major result predictor in CAP in relation to biochemical recurrence and cancer-specific mortality [10, 11, 12]. In 2005, the ISUP conducted a consensus conference in order to evaluate contradictory points of the Gleason system which had not undergone any variations for 40 years, whereas the PC presentation and its management in clinical practice had substantial changes in biopsy schemes [13]. This consensus consisted of multiple modifications and the refinement of several histopathological variants, limiting the definition of pattern 3 and increasing that of pattern 4 [4]. These changes originated in the use of 3 groups (6, 7, ≥8) and they evidenced a better prognosis according to several validations carried out [14]. Because of this, the GG ≤6 was reduced considerably according to the Surveillance, Epidemiology and End Results (SEER) and National Cancer Data Base (NCDB) analysis carried out between 2004 and 2011 [15]. In the same way, several investigations reported that GG 2–5 have remained unused in clinical practice [16]. However, this new 3 groups system has demonstrated to be heterogeneous, specifically for the lack of distinction of GG 7 (3 + 4 vs. 4 + 3) and GG 8–10.

Multiple studies have demonstrated the differences in prognosis between GG 3 + 4 vs. 4 + 3 in relation to biochemical recurrence, distance metastasis and mortality from PC [17, 18]. However, in our field both are called intermediate risk patterns regardless of the prognosis differences. In the same way, the 3 groups scheme of the ISUP 2005 classifies patients with GG ≥8 as high-risk, not distinguishing between 8 vs. 9–10. In spite of this, multiple studies have revealed even worse significant results in the presence of pattern 5 [19, 20].

In light of this evidence, in 2013 the Johns Hopkins Hospital proposed a new classification system based on 5 groups after analyzing 7869 patients with radical prostatectomy between 1982 and 2011, concluding that this new GGG system had better abilities to distinguish aggressiveness than the 3 groups system, based principally on the separation of GG 7 in 3 + 4 (group 2) and 4 + 3 (group 3) as well as in GG ≥8 in 8 (group 4) and 9–10 (group 5) [5].

Our series clearly shows an important association of the GGG system with unfavorable pathological findings in the surgical specimen, demonstrating a higher proportion of extraprostatic extension, seminal vesicle invasion and lymph node invasion as the group increases from 1 to 5. This coincides with previous observations where similar findings have been observed [6].

When evaluating evolution characteristics, it was shown that as the GGG group system increases, biochemical recurrence-free survival rate, metastasis-free survival rate and cancer-specific survival rate are reduced substantially. These observations concur with similar results documented previously [6, 21, 23].

While comparing both schemes (3 pattern system vs. GGG), we demonstrated a better distinguishing

power in the new grading system in relation with the predictive abilities of biochemical recurrence (0.66 vs. 0.70), distant metastasis (0.72 vs. 0.75) and mortality from PC (0.76 vs. 0.79). Since 2014 this system has been externally validated in centers in Europe, the U.S.A., Canada and Asia [6, 7, 8, 21, 22, 23].

In all cases there are significant differences between the 5 groups, confirming a better diagnosis separating the 7 score in 3 + 4 and 4 + 3 and the score ≥8 in 8 and 9–10. To our knowledge this is the first external validation of the innovative ISUP GGG system in a contemporary group of Latin American PC patients treated with RP.

One limitation of our research is its retrospective nature. A group of patients in the study presented before 2005, making possible grade differences to our present day recommendations in ISUP 2005 an inevitable limitation. Secondly, we only have 19 patients with group 4–5 classification, which may reduce significant findings. The complete study of the surgical specimen in RP is not carried out routinely in our Institution although this should have the same impact on all groups. Lastly, the study included 227 cases collected within a timeframe of 18 years; we know that during such a long period of time the general urological treatment of prostate cancer, especially operational technique, have all changed significantly. This is why the clinical and biochemical tools to assess the quality of both classifications in such a small group are exposed to bias.

CONCLUSIONS

The ISUP GGG system is an independent predictor of biochemical recurrence and prostate cancer mortality in patients treated with RP. Classification into 5 groups demonstrates higher distinguishing abilities of prognosis than in the traditional Gleason classification system. These findings support the inclusion of the ISUP GGG system as part of the pathological report in patients with PC treated with RP in the Argentinian population.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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