Impact of ISUP grade group on cancer-specific mortality in radical prostatectomy-treated prostate cancer patients with organ-confined disease

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ABSTRACT

Introduction: We aimed to test the impact of International Society of Urological Pathology (ISUP) grade group (GG) on cancer-specific mortality (CSM) in organ-confined (pT2) prostate cancer (PCa) at radical prostatectomy (RP).

Methods: RP organ-confined prostate cancer (PCa) patients were identified (Surveillance, Epidemiology, and End Results 2004−2015). Cancer-specific survival (CSS) rates were tested in Kaplan-Meier plots and multivariable Cox regression (MCR) models according to GG: 1–3 vs. 4 vs. 5. Sensitivity analyses addressed GG4 and GG5 patients with available primary and secondary Gleason score (GS).

Results: Overall, 61 172 patients with RP organ-confined PCa were identified. Of these, 57 715 (94.4%), 2036 (3.3%) and 1421 (2.3%) harbored GG1–3, 4, and 5, respectively. In Kaplan-Meier analyses, seven-years' CSS estimates were 99.6 vs. 98.2 vs. 93.8% for GG1–3 vs. 4 vs. 5, respectively (p<0.001). In MCR models, GG4 (hazard ratio [HR] 2.72, p<0.001) and 5 (HR 9.95, p<0.001) independently predicted higher CSM, relative to GG1–3. Furthermore, GG5 also independently predicted higher CSM (HR 3.72, p<0.001) vs. GG4. In sensitivity analyses, 1.2, 1.6, and 2.4 CSM events per 1000 person-years of followup were respectively recorded for GS 4+4, 3+5, and 5+3 patients. Conversely, 4.8 vs. 5.3 CSM events per 1000 person-years of followup were respectively recorded for GS 4+5 vs. 5+4/5+5 patients.

Conclusions: In organ-confined PCa, at RP, a small proportion of patients harbor GG4–5. These patients exhibit higher CSM than their GG1–3 counterparts. Moreover, detectable mortality rate differences indicate a dose-response effect according to primary and secondary GS. This phenomenon applies in both GG4 and GG5, as well as between GG4 and GG5.

KEY MESSAGES

- Overall, 61 172 patients with RP organ-confined PCa were identified. Of these, 57 715 (94.4%), 2036 (3.3%), and 1421 (2.3%) harbored GG1–3, 4, and 5, respectively.
- In Cox regression models, GG4 (HR 2.72, p<0.001) and 5 (HR 9.95, p<0.001) independently predicted higher CSM, relative to GG1–3.
- In organ-confined Pca, at RP, a small proportion of patients harbor GG4–5; these patients exhibit higher CSM than their GG1–3 counterparts.

INTRODUCTION

Organ-confined (pT2) prostate cancer (PCa), in patients treated with radical prostatectomy (RP), is associated with favorable oncological outcomes[1–3]. However, patients with organ-confined PCa at RP might harbor high-grade ISUP grade group (GG, e.g. GG4-5) PCa (0.1-2%)[4,5]. The latter represents a well-established risk factor for worse cancer control outcomes[6,7]. The impact of GG on cancer-specific mortality (CSM) has been mainly addressed in studies that relied on cohorts, where organ- and non-organ-confined PCa stages were assessed[4,7]. In

consequence, it is not clear whether GG4-5 affects CSM in RP organ-confined patients. We addressed this void and tested for predictors of CSM based on the hypothesis that high-grade GG might predispose to higher CSM risk for organ-confined PCa at RP. We tested these hypotheses using the Surveillance, Epidemiology and End Results (SEER) database (2004-2015).

METHODS

Study population

Within the SEER database (2004 to 2015)[8], we focused on patients 18 years or older with histologically confirmed prostate adenocarcinoma (International Classification of Disease for Oncology [ICD-O-3]; site code C61.9; histologic code 8140). We only considered patients with histologically confirmed localized prostate cancer. Only pathological organ-confined (pT2) cases at RP were included. Patients harboring pathologically confirmed nodal metastases (pN1) were excluded from the analyses. Primary and secondary Gleason score (GS), which was addressed in sensitivity analyses, was available from 2010 onwards. Cancer-specific mortality (death from prostate cancer) was defined according to the SEER mortality code. Exclusion criteria consisted of unavailable information on stage, grade and follow-up. All autopsy and death certificate only diagnoses were also excluded.

Statistical analyses

Descriptive statistics included frequencies and proportions for categorical variables. Medians and interquartile ranges (IQR) were reported for continuously coded variables. Survival analyses focused on cancer-specific survival (CSS) using Kaplan-Meier analyses and multivariable Cox-regression (MCR) models. Results were stratified according to ISUP GG: 1-3 vs 4 vs 5. In MCR models, covariates consisted of age, PSA and surgical margin status. Sensitivity analyses focused on GG4 and GG5 patients in whom GS primary and secondary pattern were available. All statistical tests were two-sided with a level of significance set at $P < 0.05$. Analyses were performed using the R software environment for statistical computing and graphics (version 4.2.1; http://www.r-project.org/).

RESULTS

Descriptive characteristics of the study population

The study population consisted of 61,172 RP organ-confined PCa at RP (2004-2015). Patient median age and PSA (Table 1) were 61 years (56-66) and 5.5 ng/ml (4.4-7.6), respectively. Overall, GG distribution was as follows: GG1-3 57,715 (94.4%), GG4 2,036 (3.3%), GG5 1,421 (2.3%).

Survival analyses assessing CSM-free survival

Kaplan-Meier analyses depicted CSS rates in organ-confined PCa at RP, according to GG (Figure 1). Specifically, seven-years' CSS rates were 99.6 (95% CI 99.5-99.7) vs 98.2 (95% CI 97.1-99.5) vs 93.8% (95% CI 90.8-96.9) for GG 1-3 vs 4 vs 5 (p-value < 0.001). Median follow-

up was 54 (32-70) months. In MCR models, relative to GG1-3, GG4 (HR 2.72, 95% CI 1.56-4.74, p-value < 0.001) and GG5 (HR 9.95, 95% CI 6.84-14.47, p-value < 0.001) achieved independent predictor status for CSM, after adjusting for all covariates (Table 2). Furthermore, in MCR models, GG5 exhibited higher CSM (HR: 3.65, 95% CI 1.96-6.77, p-value < 0.001) relative to GG4 (Supplementary Table).

Sensitivity analyses in GG4 patients with available GS primary and secondary patterns
In GG4 organ-confined PCa at RP, GS primary and secondary patterns were available in 1,922 (94,4%) patients. Rates of GS4+4, 3+5 and 5+3 were 71.3 (n=1,371), 23.4 (n=430) and 5.3% (n=101), respectively. In Kaplan-Meier analyses five-years' CSS rates were 99.2 (95% CI 98.5-99.9) vs 99.5 (95% CI 98.7-99.9) vs 98.2% (95% CI 94.7-99.9) for GS4+4 vs 3+5 vs 5+3 (p-value = 0.8). Median follow-up was 47 (28-66) months. For the same groups, at 5,187, 1,855, 414 person-years of follow-up 1.2, 1.6, 2.4 CSM events per 1,000 person-years of follow-up were respectively recorded (Table 3).

Sensitivity analyses in GG5 patients with available GS primary and secondary patterns
In GG5 organ-confined PCa at RP, GS primary and secondary patterns were available in 1,340 (94,3%) patients. Rates of GS4+5 and 5+4/5+5 were 81.5 (n=1,092) and 18.5% (n=248), respectively. In Kaplan-Meier analyses five-years' CSS rates were 97.7 (95% CI 96.5-98.9) vs 96.4% (95% CI 93.4-99.5) for GS 4+5 and 5+4/5+5 (p-value = 0.9). Median follow-up was 46 (28-64) months. For the same groups, at 4,194 and 952 person-years of follow-up, 4.8, 5.3 CSM events per 1,000 person-years of follow-up were respectively recorded (Table 3).

DISCUSSION

High-grade GG is a rare entity in organ-confined PCa at RP [4,5]. Based on its rarity and the combination of unfavorable GG with favorable pathological stage, some clinicians might be uncertain of its natural history. Based on the lack of data regarding this entity, we tested for the rates and differences in CSM in contemporary organ-confined PCa at RP, according to GG. Moreover, we tested for differences regarding primary and secondary GS in GG4-5. Our analyses led to several noteworthy observations.

First, presence of high-grade GG in organ-confined PCa at RP is rare. Specifically, we identified 2,036 (3.3%) and 1,421 (2.3%) individuals, respectively harboring GG4 and GG5 at RP. Our findings are consistent with Ham et al[4]. The authors, within a large single-center RP cohort (n=14,501; 1984-2014), recorded a 2% rate of organ-confined PCa with GG4-5. Conversely, Preisser et al[5], within a large single-center cohort of RP organ-confined PCa patients (n=10,855; 1992-2017), reported substantially lower rates of GG4 (0.1%) and GG5 (0.1%) PCa. Of note, in the latter study, patients exhibiting positive surgical margins were excluded from the analyses. These observations confirm the rarity of high-grade GG in RP organ-confined PCa patients. Moreover, observations reported by Preisser et al[5], suggest that even in the largest single institution series, the rates of such rare entity might be remarkably different from those identified in population-based cohorts. In consequence, both types of data

origin are needed to assess the rate and effect of GG4-5 in organ-confined PCa at RP from markedly different perspectives, institutional vs population-based data.

Second, given the lack of data assessing the impact of high-grade GG on CSM in organ-confined PCa at RP, we tested for CSM differences in such patients, according to pathological GG. Specifically, seven-years' CSS rates were 99.6, 98.2 and 93.8% for GG 1-3, GG4 and GG5, respectively. Furthermore, presence of GG4 (HR: 2.72, p<0.001) or GG5 (HR: 9.95, p< 0.001) reached independent predictor status for higher CSM in organ-confined PCa at RP, relative to GG1-3. In consequence, presence of high-grade GG is associated with higher risk of CSM, even in organ-confined PCa at RP. Our observations are consistent with Preisser et al[5], who identified GG4 (HR 6.09, p=0.02) and GG5 (HR 30.1, p<0.001) as independent predictors of higher CSM in organ-confined PCa at RP, relative to GG2-3. Moreover, we tested for potential differences between GG4 and GG5. Here, MCR models revealed a statistically significant difference between GG4 and GG5 (HR: 3.72, p<0.001) in organ-confined PCa at RP. Our results confirm the association between ISUP grade grouping and CSM, even in organ-confined PCa at RP. This observation is consistent with Ham et al[4], where the authors reported worse CSM associated with GG5 (HR 2.20, p<0.001) vs GG4 at RP. However, their observation was not specific to organ-confined PCa at RP. Specifically, 59% of patients harbored non-organ-confined PCa at RP.

Third, we performed even more detailed subgroup analyses focusing on the importance of primary vs secondary GS. This approach was applied to RP GG4-5. Specifically, 1.2, 1.6 and 2.4 CSM events per 1,000 person-years of follow-up were respectively recorded for GS 4+4, 3+5 and 5+3 patients. Conversely, 4.8 vs 5.3 CSM events per 1,000 person-years of follow-up were respectively recorded for GS 4+5 vs 5+4/5+5 patients. The above observations confirm important differences between GG4 (1.2 to 2.4 CSM events per 1,000 person-years of follow-up) vs GG5 (4.8 to 5.3 CSM events per 1,000 person-years of follow-up) regarding CSM. However, it should be emphasized that these differences are based on absolute, marginally low, CSM rates. In consequence, a formal comparison using conventional survival methodology, such as MCR modeling, could not be performed. Instead, a computation of CSM event rate per 1,000 person-years of follow-up was applied. Using this approach, the above described differences between GG4 vs GG5 were identified. Moreover, using this approach, we also identified heterogeneity within GG4, as well as within GG5. Specifically, within GG4 patients we recorded a dose-response effect according to increasing aggressiveness of GS pattern: 1.2, 1.6 and 2.4 CSM events per 1,000 person-years of follow-up for GS 4+4, 3+5 and 5+3, respectively. The above observations are in agreement with Mori et al.[9]. The authors, reported CSM differences among RP GG4 PCa patients, according to primary and secondary GS. Specifically, they reported worse CSM for GS5+3 RP treated patients (HR 5.3, p=0.008) vs GS3+5 patients, after adjusting for confounders. However, in the Mori et al. [9] study, approximately half of the overall cohort exhibited non-organ-confined PCa at RP. Furthermore, in the latter study, the median follow-up was longer (86 vs 47 months) than in the current study. Moreover, we also

recorded heterogeneity of CSM rates within GG5 patients, where we recorded a dose-response effect according to increasing aggressiveness of GS pattern: 4.8 vs 5.3 CSM events per 1,000 person-years of follow-up for GS 4+5 vs 5+4/5+5, respectively. Similarly, Tilki et al.[10] reported higher CSM after RP in biopsy GS 5+4/5+5 (HR: 2.44, $p < 0.001$) vs GG5 with primary GS4, after adjusting for confounders. However, it should be noted that Tilki et al.[10] findings are not based on RP GS patterns but, instead, are based on biopsy findings. Moreover, the authors did not perform formal analyses distinguishing organ-confined from non-organ-confined PCa at RP.

Taken together, our study identified a small, albeit non-negligible proportion of organ-confined PCa at RP with GG4 or GG5 disease (n=3,457; 5.6%). These individuals clearly exhibit worse cancer control outcomes (GG4 HR: 2.72, $p < 0.001$; GG5 HR: 9.95, $p < 0.001$) than their GG1-3 counterparts. Within GG4-5 patients, GG5 exhibit significantly higher CSM (HR:3.64, $p<0.001$). Finally, more aggressive GS patterns within GG4 resulted in increasingly worse cancer control outcomes. The same phenomenon applies to GG5 patients. The clinical implications of the above observations are important at individual patient-level since RP GG4-5 organ-confined PCa patients clearly require longer and more detailed follow-up than their GG1-3 counterparts. Moreover, the implications of our findings are also applicable to planning of prospective studies and allocation of health-care resources. For purpose of study planning, equal distribution of GG4 and GG5 between study arms might prove of importance even when most study subjects harbor organ-confined PCa. Finally, allocation of health-care resources may require adjustment, according to rates of GG4 and GG5, even in organ-confined PCa at RP. Additionally, this data should be taken into account also when evaluating patients with presence of positive surgical margins. Indeed, as reported by Pellegrino et al. [11] assessing long term outcomes of RP PCa patients, only in patients exhibiting adverse pathological features (such as RP ISUP GG 4-5), presence of positive surgical margins might impact on CSM risk. In consequence, such individuals will clearly require higher proportion of subsequent therapies.

Despite the novelty of our findings, several limitations need to be acknowledged. The first and foremost limitation consists of patient origin. Specifically, our findings are applicable to individuals, who were identified within the SEER database. In consequence, the observations made within the current study cannot be applied to tertiary-care referral centre, since they rather reflect population based outcomes. Moreover, our observations may not be applicable to patients diagnosed and treated from outside of the United States. Second, no standardized specimen handling, as well as central pathologic review was applied within the SEER database. Third, our endpoint consisted of CSS. However, in other studies evaluating cancer control outcome after RP, earlier endpoints may be used, such as biochemical-recurrence or metastatic progression. Fourth, in the SEER database, GS primary and secondary patterns were only available from 2010 onwards. In consequence, earlier data could not be stratified according to primary and secondary GS. Fifth, androgen deprivation therapy (ADT) exposure status is unavailable in the SEER database. However, a very small proportion of organ-confined PCa patients would be expected to

receive it. Finally, our report represents a retrospective analysis with high potential for selection biases.

CONCLUSIONS

In organ-confined PCa at RP a small proportion of patients harbor GG4-5. These patients exhibit higher CSM than their GG1-3 counterparts. Moreover, detectable mortality rate differences indicate a dose-response effect according to primary and secondary GS. This phenomenon applies in both GG4 and GG5, as well as between GG4 and GG5.

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FIGURES AND TABLES

Figure 1. Kaplan-Meier analyses depicting cancer-specific survival (CSS) estimates of 61 172 organ-confined at radical prostatectomy prostate cancer patients identified within the Surveillance, Epidemiology, and End Results database (2004–2015). Data were stratified according to ISUP grade group (GG) (1–3 vs. 4 vs. 5).

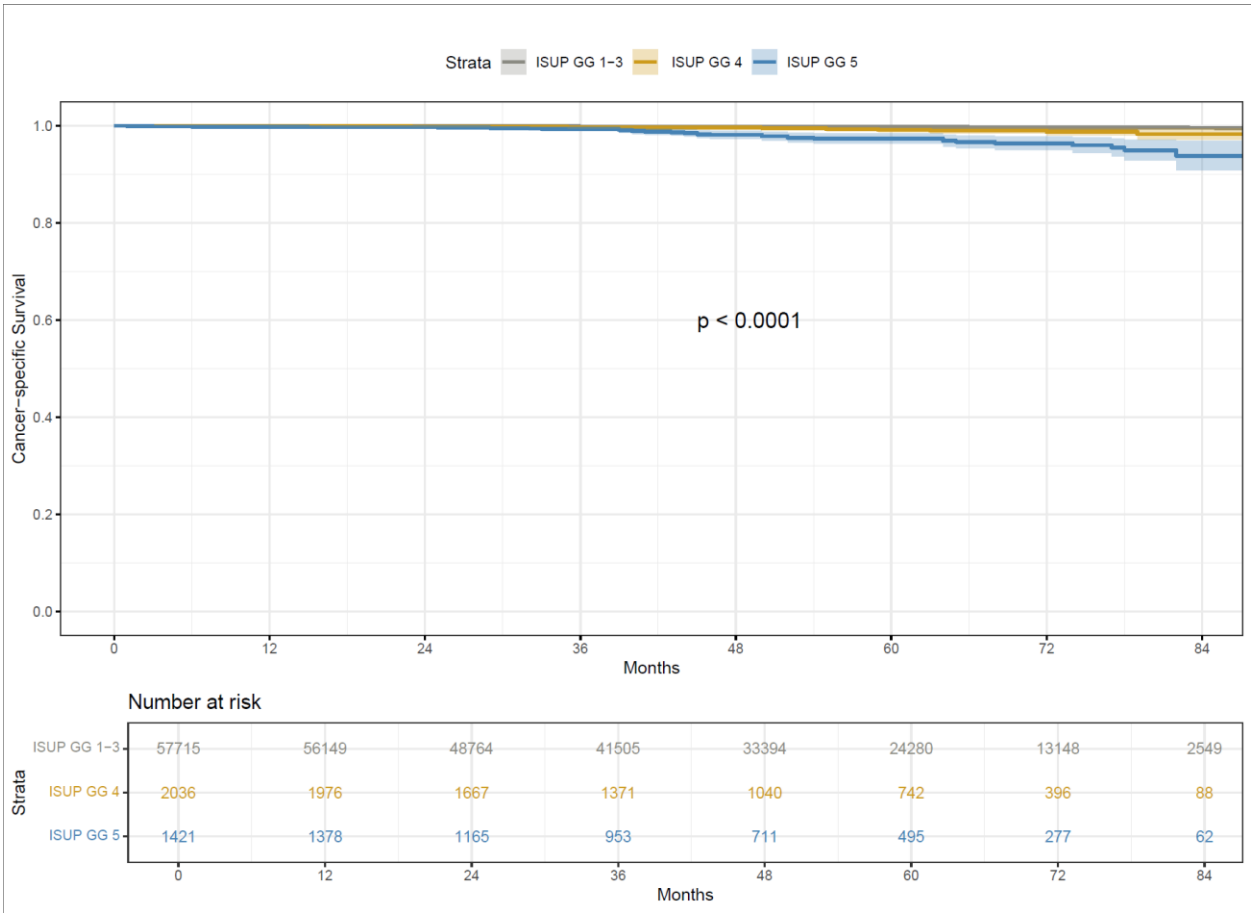

Table 1. Descriptive characteristics of 61 172 organ-confined at radical prostatectomy prostate cancer patients identified within the Surveillance, Epidemiology, and End Results database (2004–2015)

Variables	**Overall (N=61 172)**
Age at diagnosis (years) Median (IQR)	 61 (56–66)
PSA (ng/ml) Median (IQR)	 5.5 (4.7–7.6)
ISUP grade group (%) 1–3 4 5	 57 715 (94.4) 2036 (3.3) 1421 (2.3)
pN stage (%) pNx pN0	 27,734 (45.3) 33,438 (54.7)
Postoperative radiotherapy (%)	1,088 (1.8)
Positive surgical margins (%)	5,354 (8.8)
Followup (months) Median (IQR)	 54 (32–70)

ISUP: International Society of Urological Pathology; IQR: interquartile range.

Table 2. Multivariable Cox-regression models testing predictors of cancer-specific-mortality in 61,172 organ-confined at radical prostatectomy prostate cancer patients identified within the Surveillance, Epidemiology, and End Results database (2004–2015)

Predictors	**HR (95%CI)**	**p**
ISUP grade group 1–3 4 5	 Ref. 2.72 (1.56–4.74) 9.95 (6.84–14.47)	 – <0.001 <0.001
Positive surgical margins 0 1	 Ref. 1.76 (0.62–4.96)	 – 0.3
Age at diagnosis (years)	1.03 (1.01–1.03)	0.001
PSA (ng/ml)	1.01 (1–1.03)	0.04

CI: confidence interval; HR: hazard ratio; ISUP: International Society of Urological Pathology; PSA: prostate-specific antigen.

Table 3. Descriptive characteristics of 3262 ISUP grade group 4–5 organ-confined at radical prostatectomy prostate cancer patients, with available Gleason score primary and secondary pattern, identified within the Surveillance, Epidemiology, and End Results database (2010–2015)

Variables	ISUP grade group 4 n=1922 (58.9%)			ISUP grade group 5 n=1340 (41.1%)	
	GS 4+4 1371 (71.3%)	GS 3+5 450 (23.4%)	GS 5+3 101 (5.3%)	GS 4+5 1092 (81.5%)	GS 5+4/5+5 248 (18.5%)
Age (years) Median (IQR)	61 (56–66)	60 (55–65)	62 (56–66)	59 (55–65)	59 (54–65)
PSA (ng/ml) Median (IQR)	6.7 (5–9.9)	6 (4.7–8.2)	5.7 (4.5–7.9)	5.1 (4.1–6.9)	5.4 (4.3–7.1)
Followup, months Median (IQR)	45 (27–64)	51 (33–69)	52 (29–69)	46 (28–64)	46 (26–64)
Person-years of followup	5187	1855	414	4194	952
CSM events per 1000 person-years of followup	1.2	1.6	2.4	4.8	5.3

Data stratified according to ISUP grade group (4 vs. 5) and Gleason score primary and secondary pattern (4+4 vs. 3+5 vs. 5+3; 4+5 vs. 5+4/5+5). CSM: cancer-specific mortality; GS: Gleason score; ISUP: International Society of Urological Pathology; IQR: interquartile range