available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

Evaluation of the 2015 Gleason Grade Groups in a Nationwide Population-based Cohort

Stacy Loeb [a,*], *Yasin Folkvaljon* [b], *David Robinson* [c], *Ingela Franck Lissbrant* [d], *Lars Egevad* [e], *Pär Stattin* [c,f]

[a] *Department of Urology and Population Health, New York University and Manhattan Veterans Affairs Medical Center, NY, USA;* [b] *Regional Cancer Centre, Uppsala University Hospital, Uppsala, Sweden;* [c] *Department of Surgical and Perioperative Sciences, Urology and Andrology, Umeå University Hospital, Umeå, Sweden;* [d] *Department of Oncology and Radiation Physics, Sahlgrenska University Hospital, Gothenburg, Sweden;* [e] *Department of Pathology, Karolinska University Hospital, Stockholm, Sweden;* [f] *Department of Urology, Uppsala University Hospital, Uppsala, Sweden*

Article info

Article history:
Accepted November 30, 2015

Associate Editor:
James Catto

Keywords:
Prostate cancer
Gleason grade
Pathology
ISUP
Epstein

Abstract

Background: New five-tiered Gleason grade groups (GGGs) were recently proposed, in which Gleason 6 is GGG 1, Gleason 3 + 4 is GGG 2, Gleason 4 + 3 is GGG 3, Gleason 8 is GGG 4, and Gleason 9-10 is GGG 5.
Objective: To examine the performance of the new GGGs in men with prostate cancer from a nationwide population-based cohort.
Design, setting, and participants: From the National Prostate Cancer Register of Sweden, we identified 5880 men diagnosed with prostate cancer from 2005 to 2007, including 4325 who had radical prostatectomy and 1555 treated with radiation therapy.
Outcome measurements and statistical analysis: Kaplan–Meier survival analysis, Cox proportional hazards models, and concordance indices were used to examine the relationship between the GGGs and biochemical recurrence after radical prostatectomy and radiation therapy.
Results and limitations: Among men treated with surgery, the 4-yr biochemical recurrence-free survival rates were 89%, 82%, 74%, 77%, and 49% for GGG 1–5 on biopsy, and 92%, 85%, 73%, 63%, and 51% based on prostatectomy GGG, respectively. For men treated by radiation therapy, men with biopsy GGG of 1–5 had 4-yr biochemical recurrence-free survival rates of 95%, 91%, 85%, 78%, and 70%. Adjusting for preoperative serum prostate-specific antigen and clinical stage, biopsy GGGs were significant independent predictors of biochemical recurrence after radical prostatectomy and radiation therapy. The new 5-tier system resulted in virtually no change in predictive accuracy compared with the current 3- and 4-tier classifications. Limitations include a median follow-up of 4.6 yr, precluding the ability to examine long-term oncologic outcomes.
Conclusions: The newly proposed GGGs offer a simplified, user-friendly nomenclature to aid in patient counseling, with similar predictive accuracy in a population-based setting to previous classifications.
Patient summary: The new Gleason grade groups, ranging from 1–5, provide a simplified, user-friendly classification system to predict the risk of recurrence after prostatectomy and radiation therapy.

* Corresponding author. 550 First Avenue, VZ30, 6th floor 612, NY, NY 10016, USA.
Tel. +1-646-501-2559; Fax: +1-2122634549.
E-mail address: stacyloeb@gmail.com (S. Loeb).

http://dx.doi.org/10.1016/j.eururo.2015.11.036
0302-2838/Published by Elsevier B.V. on behalf of European Association of Urology.

1. Introduction

A new prostate cancer grading scheme has recently been proposed in an effort to better reflect true biologic aggressiveness and guide clinical management [1]. Unlike contemporary Gleason scores which range from 6–10, the new prognostic grade groups use a scale of 1–5. Specifically, Gleason grade group (GGG) 1 is Gleason 6, GGG 2 is 3 + 4 = 7, GGG 3 is 4 + 3 = 7, GGG 4 is Gleason 8, and GGG 5 is Gleason 9–10. Thus, using this new system, tumors with the most favorable features are now considered a "1" rather than a "6," and Gleason 7 is split into two separate categories.

As yet, there are limited published data evaluating the new GGGs. A single-institution series of 7869 men undergoing radical prostatectomy (RP) at Johns Hopkins showed that GGGs predicted biochemical recurrence (BCR) at a median follow-up of 2 yr [2]. The 5-yr rates of BCR-free survival were 95%, 83%, 65%, 63%, and 34% for men with GGG 1–5 on biopsy, and 97%, 88%, 70%, 64%, and 34% for GGG 1–5 at prostatectomy, respectively ($p < 0.001$).

More recently, Epstein et al [3] examined the GGGs in 20 845 men undergoing RP at five academic centers and 5501 men treated with radiation therapy at two academic centers, with a median follow-up of 3 yr. On multivariable analysis, the new GGGs predicted a higher risk of BCR after both RP and radiation therapy.

To date, there are no published studies evaluating the GGGs in a population-based setting, and their predictive value for men undergoing radiation therapy has not yet been examined in an independent population. The objective of our study was to examine the newly proposed grade groups in men undergoing RP and radiation therapy in The National Prostate Cancer Register (NPCR) of Sweden.

2. Materials and methods

Since 1998, the NPCR of Sweden has data on 98% of all prostate cancer cases diagnosed nationwide compared with the Swedish Cancer Register to which registration is mandatory [4,5]. As previously described, in the Prostate Cancer data Base, the data from NPCR have been cross-linked to other national health care registers and demographic databases using each individual's personal identity number. As such, Prostate Cancer data Base contains detailed information on both cancer features and primary treatment, as well as data on other important patient characteristics such as Charlson comorbidity index based on discharge diagnoses from the patient register, and educational level, income, and marital status from the Longitudinal Integration Database for health insurance and labor market.

For cases diagnosed in 2003–2007, the NPCR performed a follow-up study of men aged $\leq$ 70 yr diagnosed with localized prostate cancer (serum prostate-specific antigen [PSA] $<$ 20 ng/ml, clinical stages T1/T2). Due to changes in Gleason grading at the 2005 International Society of Urological Pathology (ISUP) meeting [6], we limited the current study to men from the follow-up study diagnosed with prostate cancer from 2005 to 2007 (n = 7596), as in the recent study by Epstein et al [3]. Of these men, 6119 underwent RP or radiation therapy. We excluded 114 men with missing biopsy Gleason grade, an additional 64 men with incomplete data on prostatectomy Gleason grade and 61 men with missing date of treatment. Following these exclusions the final study population included 5880 men, including 4325 who had RP and 1555 who received radiation therapy (Supplementary Fig. 1). Outcomes were assessed uniformly in all men by chart review at 5 yr after diagnosis.

Gleason scores were assigned by local pathologists across Sweden. For prostate biopsy, common practice in Sweden is to submit each specimen in a separate container and to separately embed each specimen. Each core is assigned a Gleason score and a global Gleason score is reported in the bottom line. For RP, the specimen is completely embedded with a whole mount preparation to facilitate identification of individual tumor foci.

Biopsy Gleason scores were classified into GGGs as described above: Gleason score 6 is GGG 1, Gleason 3 + 4 = 7 is GGG 2, Gleason 4 + 3 = 7 is GGG 3, Gleason 8 is GGG 4, and Gleason 9–10 is GGG 5 [1,2]. For men who underwent RP, the final Gleason scores were also categorized in the same way. BCR was defined as two PSA measurements $\geq$ 0.2 ng/ml for men undergoing RP, and two PSA measurements $\geq$ 2 ng/ml over the nadir for radiation therapy, with the first of these considered the date of BCR.

Among men in the RP subset, the chi-square test was used to examine associations between biopsy GGG with the following individual pathology features: RP GGG, organ-confined disease, positive surgical margins, and lymph node metastasis. Multivariable logistic regression was used to assess the relationship between biopsy GGG and a composite definition of adverse pathology after prostatectomy (defined as the presence of extracapsular extension, seminal vesicle invasion, or lymph node metastases). Additional covariates in the main multivariable models were PSA (continuous, in 1 ng/ml units) and clinical stage (T2 vs T1).

Kaplan–Meier survival analysis was used to examine progression-free survival after prostatectomy (using biopsy and prostatectomy GGG) and after radiation therapy (using biopsy GGG), and curves were compared using the log-rank test. We also created Kaplan–Meier curves for prostate cancer specific survival based on biopsy and RP GGG. Follow-up for mortality was complete through December 31, 2013.

Multivariable Cox proportional hazards models were also used to examine BCR, with separate models for patients undergoing RP and radiation therapy. In the main analysis, these models were adjusted for serum PSA (continuous, in 1 ng/ml units) and stage (clinical stage T2 vs T1 in models using biopsy GGG, and organ-confined vs non organ-confined the model with RP GGG). In order to adjust for the age distribution in different grade groups, age was used as the time scale. Separate models were performed adjusting for marital status (not currently married vs married), education level (low, middle, high), Charlson comorbidity index (0, 1, 2+), and hospital type (nonuniversity vs university). In men undergoing radical prostatectomy, a separate Cox model was performed adjusting for pathologic stage and surgical margin status. In the radiation therapy cohort, separate models were performed adjusting for use of neoadjuvant hormonal therapy.

Finally, we also calculated the concordance index for the following Gleason grade classifications for BCR using 10-fold cross-validation: 3-tier system ($\leq$6, 7, and 8–10), 4-tiered system ($\leq$6, 7, 8, and 9–10), and the 5-tier GGG. R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analysis. The study was approved by the research ethics board at Umeå University Hospital.

3. Results

Table 1 shows the demographics of the study population. Overall, 3953 (67%) men had GGG 1 (former Gleason score 6), 1181 (20%) had GGG 2 (Gleason score 3 + 4), 417 (7%) had GGG 3 (Gleason score 4 + 3), 255 (4%) had GGG 4 (Gleason score 8), and 74 (1%) had GGG 5 (Gleason score 9–10) on biopsy. The proportion of biopsies positive for cancer is shown in Supplementary Table 1.

Table 2 shows the relationship between GGG in biopsy and prostatectomy specimens as well as the pathology

Please cite this article in press as: Loeb S, et al. Evaluation of the 2015 Gleason Grade Groups in a Nationwide Population-based Cohort. Eur Urol (2016), http://dx.doi.org/10.1016/j.eururo.2015.11.036