Published in final edited form as:

Eur Urol. 2016 August ; 70(2): 248–253. doi:10.1016/j.eururo.2015.10.026.

Size-adjusted Quantitative Gleason Score as a Predictor of Biochemical Recurrence after Radical Prostatectomy

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Abstract

Background—The risk of biochemical recurrence (BCR) following radical prostatectomy for pathologic Gleason 7 prostate cancer varies according to the proportion of Gleason 4 component.

Objective—We sought to explore the value of several novel quantitative metrics of Gleason 4 disease for the prediction of BCR in men with Gleason 7 disease.

Design, setting, and participants—We analyzed a cohort of 2630 radical prostatectomy cases from 1990–2007. All pathologic Gleason 7 cases were identified and assessed for quantity of

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Author contributions: Nicholas Donin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Deng, Benito, Melamed, Nobin, Zhou, Ma, Wang, Donin, Lepor.

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Obtaining funding: Deng, Benito, Melamed, Zhou, Lepor.

Administrative, technical, or material support: Deng, Benito, Melamed, Nobin, Zhou, Lepor.

Supervision: Deng, Benito, Melamed, Nobin, Zhou, Wang, Donin, Lepor.

Other: None.

Financial disclosures: Nicholas Donin certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Gleason pattern 4. Three methods were used to quantify the extent of Gleason 4: a quantitative Gleason score (qGS) based on the proportion of tumor composed of Gleason pattern 4, a size-weighted score (swGS) incorporating the overall quantity of Gleason 4, and a size index (siGS) incorporating the quantity of Gleason 4 based on the index lesion.

Outcome measurements and statistical analysis—Associations between the above metrics and BCR were evaluated using Cox proportional hazards regression analysis.

Results and limitations—qGS, swGS, and siGS were significantly associated with BCR on multivariate analysis when adjusted for traditional Gleason score, age, prostate specific antigen, surgical margin, and stage. Using Harrell's c-index to compare the scoring systems, qGS (0.83), swGS (0.84), and siGS (0.84) all performed better than the traditional Gleason score (0.82).

Conclusions—Quantitative measures of Gleason pattern 4 predict BCR better than the traditional Gleason score.

Patient summary—In men with Gleason 7 prostate cancer, quantitative analysis of the proportion of Gleason pattern 4 (quantitative Gleason score), as well as size-weighted measurement of Gleason 4 (size-weighted Gleason score), and a size-weighted measurement of Gleason 4 based on the largest tumor nodule significantly improve the predicted risk of biochemical recurrence compared with the traditional Gleason score.

Keywords

Gleason score; Humans; Prognosis; Risk assessment; Prostatectomy; Tumor volume; Neoplasm grading; Neoplasm recurrence; Prostatic neoplasms

1 Introduction

Gleason score (GS) represents one of the most important determinants of prognosis in prostate cancer [1]. Interpretative modifications of the Gleason scoring system were adopted in 2005 at a consensus meeting of the International Society of Urological Pathology in order to improve disease risk stratification [2]. Today, the overwhelming majority of cancers in both biopsy and radical prostatectomy (RP) specimens fall into the GS 6–7 groups [3]. A cluster of GS in the 6–7 range limits the discriminative ability of GS to stratify risk of the disease. The ability to reliably predict risk of disease progression at the time of diagnosis and following curative intervention would influence decisions regarding assignment of primary and adjuvant treatment, respectively. As a result, algorithmic tools factoring in a number of different variables, including but not limited to GS, are being used in the preoperative and post-RP settings in order to better predict pathological stage and risk of biochemical recurrence (BCR) following curative intervention [4]. It has long been hypothesized that high-grade elements within prostate tumors drive disease progression. In 1999, Stamey et al [5] published seminal work demonstrating that the percentage of high-grade carcinoma within a tumor, as well as the size of the tumor, independently predict the risk of BCR. This initial study included patients with a wide range of tumor characteristics, including GSs ranging from 6–10. Subsequent studies in other cohorts have been carried out in a variety of risk groups with a range of follow-up, and the majority have found that

quantification of high-grade components within the tumor enhances the ability to predict disease recurrence [5–8].

Given the increasing appreciation of the indolent course of treated Gleason 6 disease [9,10], post-treatment risk stratification and management are most needed in patients with higher-grade tumor elements, the lion's share of which are represented by Gleason 7 tumors. While prior studies have evaluated the improvements in risk stratification using quantification of high-grade disease in this population, these studies did not evaluate the absolute quantity of high-grade disease in this population, and were performed in cohorts of limited size with limited follow-up. We aimed to address this knowledge gap by evaluating the performance of several novel metrics of high-grade disease to predict BCR in a large cohort of patients with Gleason 7 disease with substantial follow-up. To our knowledge this is the first study to look at both the proportion and absolute quantity of high-grade disease exclusively in patients with Gleason 7 tumors.

2. Materials and methods

2.1. Dataset

This study was performed via analysis of the New York University (NYU) School of Medicine RP dataset, collected by the NYU Prostate Cancer Biorepository Network under a protocol approved by the NYU Institutional Review Board. All prostatectomy cases performed at the institution between 1990 and 2011 were acquired by the Biorepository for standardized pathology review. The individual slides were reviewed by two uropathologists. Consecutive cases performed from 1990–2007 were included. Quantitative data outside of this period was not available as data was collected as part of a specified study protocol. The processing of RPs at our institution has followed the same protocol of entirely embedding the specimen since 1991 unless the prostate is massively enlarged, in which case it has been partly embedded in a systematic fashion (posterior quadrants entirely submitted and anterior portions sampled). This process has remained consistent over the study period.

Patient follow-up included periodic serum prostate-specific antigen (PSA) measurements. BCR was defined by a serum PSA >0.2 ng/ml. Follow-up data was derived from electronic medical records, tumor registry databases, and clinical research datasets.

2.2. Histological characterization

All hematoxylin and eosin stained microscopic slides were reviewed by biorepository uropathologists. The central pathology review graded using the International Society of Urological Pathology 2005 modified Gleason system, assessed quantity of Gleason 4/5, and assessed cases for standard pathology criteria including tumor volume, size of index tumor, margin status, and stage.

For the percentage of gland occupied by tumor, the areas of tumor were marked on slides and the area estimated over all slides of the prostate to provide a semiquantitative percentage estimate of the extent of the tumor. For Gleason percentage 4/5, resource pathologists evaluated the percentage of Gleason 4/5 in the overall tumor. The size of the index lesion was measured on slides using a ruler to assess linear extent.

2.3. Quantitative Gleason score

The quantitative Gleason score (qGS) has been previously described and was calculated as follows: $2 \times (3 \times \%GS3 + 4 \times \%GS4)$ [6]. This formula provides a greater weight to the Gleason 4 pattern compared with Gleason 3 and yields a sum between 6 and 8. For example, a case with 100% Gleason 4 pattern would result in a qGS of 8, while a case with equally distributed Gleason pattern 3 (50%), Gleason 3 and Gleason 4 (50%) would provide a qGS of 7. Gleason 3 + 3 with tertiary 4 would result in a qGS of $2 \times (3 \times 0.95 + 4 \times 0.05) = 6.1$.

2.4. Size-weighted Gleason score

The size-weighted Gleason score (swGS) was calculated as follows: prostate gland weight $\times$ % gland with tumor $\times$ (Gleason 4)%. This calculation thus provides a weight in grams of the absolute amount of Gleason pattern 4 in the prostate. For example, a 50-g prostate with 10% composed of tumor that was 30% Gleason 4 would yield a swGS of 1.5 g.

2.5. Size index Gleason score

The size index Gleason score (siGS) was calculated as follows: the greatest diameter of the index lesion within the prostate in mm $\times$ (Gleason 4)% within that lesion. A 10 mm lesion comprised of 60% Gleason pattern 4 would yield a siGS of 6 mm. The index lesion was defined as the lesion with the greatest amount of Gleason pattern 4 present, independent of lesion size.

2.6. Statistical analyses

Biochemical disease free survival was defined as the time between RP and BCR or latest PSA follow-up for nonrecurrent cases. In order to determine if qGS improved the risk assessment of BCR, qGS was compared with traditional GS using Cox proportional hazards regression analysis adjusted for age at RP, PSA at diagnosis, surgical margin status, extraprostatic extension, and seminal vesicle invasion. Subsequently, additional assessments were performed to determine whether swGS and siGS were also associated with BCR by using separate Cox proportional hazards regression analyses. Harrell's c-index was used to compare the Gleason scoring systems.

3. Results

The demographic and disease characteristics of the study population are summarized in Table 1. Of 2630 cases, 995 (38%) GS 7 cases comprised the study sample. Of the GS 7 cases, 79% and 21% are GS 3 + 4 and 4 + 3, respectively. The median (interquartile range) percentage Gleason 4 was 20 (10–40). A positive surgical margin was observed in 26%, extraprostatic extension in 36% and seminal vesicle invasion in 9%. The median follow-up was 71 mo in both men who did and did not experience BCR.

We stratified our Gleason 7 cohort into three subgroups according to percentage of Gleason 4 in the tumor (<11%, 11–50%, >50%). Risk of BCR increased in a step-wise manner according to progressive increases in percentage Gleason 4 amongst the three subgroups ($p < 0.0001$, Fig. 1A).

The Gleason 7 cohort was subdivided into three groups based on the linear amount of Gleason 4 (cm) within the index lesion (0.1cm, 0.1 cm to 0.5cm, and >0.5cm). BCR increased in a step-wise manner according to progressive increases in mm of Gleason 4 in the index lesion ($p < 0.0001$, Fig. 1B).

A similar result was found when the cohort was stratified by swGS. BCR increased in a step-wise manner according to progressive increases in swGS ($p < 0.0001$, Fig. 1C).

Table 2 displays the results of Cox proportional hazards regression models investigating parameters associated with BCR after RP. In the presence of other predictor variables, and traditional GS, qGS, swGS, and siGS were independently associated with the risk of BCR. Using Harrell's c-index to compare the scoring systems, qGS (0.83), swGS (0.84), and siGS (0.84) all performed better than the traditional GS (0.82).

4. Discussion

One of the most powerful predictors of BCR following RP is the GS [15]. Multiple contemporary studies have questioned whether Gleason 6 tumors have the capacity to produce metastasis [9,10,16,17]. At the other end of the spectrum lies high-grade (GS 8) disease, while representing a significant threat for metastasis and disease-specific death, represents approximately 5% of contemporary RP specimens [3]. As such, the majority of men at risk for BCR after RP have Gleason 7 disease.

It has previously been recognized that the proportion of pattern 4/5 disease within prostatectomy specimens is predictive of both BCR and cancer-specific survival following RP [5,8,18,19].

There is compelling evidence that differentiating between Gleason 4 + 3 versus 3 + 4 disease is a significant predictor of BCR following RP [20]. A more discriminative quantitative scoring system within the Gleason 7 group might improve the ability to predict which patients with Gleason 7 disease will experience BCR.

Reese et al [6] evaluated a novel method for quantifying GS from RP surgical specimens in a cohort of men with Gleason 7 disease. They demonstrated that qGS was an independent predictor of BCR. Hensen et al [7] utilized a similar quantitative approach, but did so in a group of men with exclusively high-risk disease, and looked at early (2-yr) BCR. While they found that percentage of high-grade tumor volume was an independent predictor of BCR in their multivariable Cox regression model, adding it to the model did not result in a meaningful increase in predictive accuracy, and they concluded that its incorporation was not clinically meaningful. The explanation for these conflicting conclusions is likely related to the significantly different cohorts (intermediate vs high risk patients), as well as differing time-points examined. Our study adds substantially to the body of knowledge in this area in several important ways. The first advantage of our series is the 4-fold greater number of RP specimens (compared with Reese et al [6]), as well as almost twice the duration of mean follow-up (71 mo vs 40 mo). Secondly, ours is the first study to evaluate both proportion and extent of Gleason 4 in both the entire surgical specimen as well as within the index lesion as predictors of BCR risk. Both size of Gleason 4 in the index lesion (in cm) and percent

volume of Gleason 4 in the entire gland (%) were independent predictors of BCR when examined in separate models that included traditional GS.

Quantification of the tumor within RP specimens remains controversial. Measurement of tumor volume, percentage of gland occupied by the tumor, or the largest linear dimension of the tumor have all been proposed as possible metrics of tumor quantity [23–25]. A recent consensus meeting of the International Society of Urological Pathology recommended reporting a size-based estimate of tumor without a consensus on whether to use tumor diameter or volume [26]. We utilized three methods to quantify high-grade tumor within the prostate gland, and compared their ability to predict BCR using Harrell's c-index. In our dataset, siGS and swGS provided the highest values. The statistical differences we demonstrated were modest, and as such, the clinical utility of these quantified metrics in pathologic specimens remains unknown. However, we believe our findings are hypothesis generating and deserve further evaluation. Given the heterogeneity of tumor aggressiveness within Gleason 7 disease, we feel that every effort should be made to attempt to risk stratify patients to the best of our capability, and while the quantified metrics we present herein may not ultimately represent a significant clinically meaningful tool at present, we feel that there is adequate evidence to justify further investigation into quantified metrics of high grade disease.

Limitations of this study deserve a mention. The study was based on a standardized review of cases; therefore, the interobserver reproducibility of assigning percentage Gleason 4 is not specifically addressed. The initial criticism to the adaptation of Gleason 4 as a standard diagnostic measure was that it was difficult to reproduce using Stamey et al's [5] method of calculating the proportion of overall tumor volume. Other more contemporary adaptations of Gleason 4/5 evaluation showed significant association despite using a simpler semiquantitative method. In our study, the measurements were performed by two pathologists using a semiquantitative method and resulted in good interobserver reproducibility (data not shown). The Reese et al [6] study, which utilized data from at least 10 different pathologists, demonstrates the generalizability of this method, but further studies amongst a wider group of pathologists are required to assess reproducibility for assigning Gleason 4 percentage.

In summary, our study demonstrates that several novel metrics quantifying the high-grade tumor elements within the prostate better predict BCR than traditional GS. These findings validate the concept that in men with Gleason 7 disease, a quantified Gleason scoring system improves the ability to risk stratify these men.

Acknowledgments

We would like to acknowledge Monica Gorman, Max Kong, and Rachel Ruoff for assistance with Biorepository data collection.

Funding/Support and role of the sponsor: This work was supported in part by Department of Defense PCRP grant numbers W81XWH-10-2-0046 and W81XWH-14-2-0185 and NCI/NIH grant number UO1 CA99-012.

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We found that in men with Gleason 7 tumors, the quantity of Gleason pattern 4 within the tumor, as well as within the dominant tumor nodule, allows a more precise determination of the risk of biochemical recurrence than traditional the Gleason score.

Fig. 1. Biochemical disease free survival of patients with Gleason 7 cancers stratified by (A) percentage of Gleason 4 disease (<11%, 11–50%, >50%), (B) size index Gleason score (<0.1, 0.1–0.5, >0.5), and (C) size-weighted Gleason score (<0.1, 0.1–0.5, >0.5). GS = Gleason score; siGS = size index Gleason score; swGS = size-weighted Gleason score.

Table 1

Demographic and disease characteristics of study population (Gleason 7 radical prostatectomy cases at New York University between 1990 and 2007)^a

		GS 7 RP cohort (n = 995)
Age (yr)		62 (56–67)
	<55	193 (19)
	55–65	486 (49)
	>65	316 (32)
PSA at diagnosis (ng/ml)		6.0 (4.3–9.6)
	<4	179 (18)
	4–10	590 (59)
	>10	226 (23)
Clinical T stage	T1	547 (55)
	T2	202 (20)
	T3	16 (1.6)
Pathological T stage	pT2	602 (61)
	pT3	314 (32)
	pT4	3 (0.3)
Traditional pathological Gleason grade	3 + 4	782 (79)
	4 + 3	213 (21)
% Gleason 4		20 (10–40)
Surgical margins	Negative	729 (73)
	Positive	263 (26)
EPE	Negative	636 (64)
	Positive	356 (36)
SVI	Negative	902 (91)
	Positive	90 (9.0)
Follow-up in men without BCR (mo)		71 (41–102)
Follow-up in men with BCR (mo)		71 (47–95)

BCR = biochemical recurrence; EPE = extraprostatic extension; GS = Gleason score; PSA = prostate specific antigen; RP = radical prostatectomy; SVI = seminal vesicle invasion.

^aContinuous data are presented as median (interquartile range) and categorical data as *n* (%).

Cox proportional hazards model of factors associated with biochemical recurrence after radical prostatectomy

Table 2

	Traditional pathologic Gleason score		Quantitative pathologic Gleason score		Size-weighted Gleason score		Size index Gleason score	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Traditional pathologic Gleason score 3 + 4 versus 4 + 3	2.2	1.7–2.9	–	–	–	–	–	–
Quantitative pathologic Gleason score	–	–	1.2	1.1–1.2	–	–	–	–
Size-weighted Gleason score	–	–	–	–	1.8	1.4–2.4	–	–
Size index Gleason score	–	–	–	–	–	–	2.6	2.0–3.3
Surgical margins	2.0	1.5–2.7	2.0	1.5–2.6	1.9	1.4–2.5	1.8	1.4–2.4
EPE	1.3	1.0–1.8	1.3	0.99–1.7	1.4	1.1–1.9	1.2	0.9–1.6
SVI	1.7	1.2–2.3	1.4	1.0–2.0	1.6	1.1–2.3	1.2	0.84–1.8
Harrell c-index	0.82		0.83		0.84		0.84	

CI = confidence interval; EPE = extraprostatic extension; HR = hazard ratio; SVI = seminal vesicle invasion.