In this issue

The effect of limited (tertiary) Gleason pattern 5 on the new prostate cancer grade groups☆

Alexander S. Baras MD[a], Joel B. Nelson MD[b], Misop Han MD[a], Anil V. Parwani MD, PhD[b], Jonathan I. Epstein MD[a],*

[a]The Johns Hopkins Medical Institutions, Baltimore, MD 21231, USA
[b]University of Pittsburgh Medical Center, Pittsburgh, PA 15213, USA

Summary The risk of recurrence for prostatic adenocarcinoma after prostatectomy, as detected by prostate-specific antigen or other modalities, is based primarily on Gleason score along with pathologic tumor stage and surgical margin status. Recent large multi-institutional data spanning the last decade have supported modification of risk of recurrence stratification based on grade groups: grade group 1 (3 + 3 = 6), grade group 2 (3 + 4 = 7), grade group 3 (4 + 3 = 7), grade group 4 (4 + 4 = 8), and grade group 5 (Gleason scores 9 and 10). Using currently accepted grading definitions of grade patterns and grading rules, this study examines how the introduction of a limited, less than 5%, Gleason pattern 5 component at prostatectomy affects prognosis and fits into the grade group schema and reporting. The aggregate data from 2 independent major academic medical centers comprising 7606 patient records were analyzed with respect to biochemical recurrence–free survival. The presence of a limited (tertiary) Gleason pattern 5 component in the context of Gleason scores 3 + 4 = 7 (grade group 2) and 4 + 3 = 7 (grade group 3) imparts an intermediate prognosis relative to the next highest grade group. As such, we suggest that an additional comment and designation to the grade groups be provided reflecting the increased risk of recurrence in such cases (such as grade group 2+ or 3+). In contrast, the presence of limited (<5%) Gleason pattern 5 in the context of Gleason score 4 + 4 = 8 imparts a poor prognosis equivalent to grade group 5 and therefore should be reported as grade group 5.
© 2017 Elsevier Inc. All rights reserved.

1. Introduction

Traditionally, the risk of recurrence for prostatic adenocarcinoma after prostatectomy, as detected by prostate-specific antigen or other modalities, is based primarily on Gleason score but also on pathologic tumor stage and surgical margin status. Even with the recent modifications of Gleason patterns and the total Gleason score assessment [1], the risk stratification schema most commonly used clinically is based on the distinction between Gleason scores 6 and 7 and 8-10. Recent multi-institutional data spanning the last decade (comprised >20 000 patients from 5 major academic institutions) have supported modification of how risk of recurrence is stratified based on the grade groups for prostatic adenocarcinoma of grade group 1 (3 + 3 = 6), grade group 2 (3 + 4 = 7), grade group 3 (4 + 3 = 7), grade group 4 (4 + 4 = 8.3 + 5 = 8.5 + 3 = 8), and grade group 5 (Gleason scores 9-10) [2-4]. Salient features of the proposed schema

favoring adaptation over conventional approaches include the following:

1. A better characterization of the heterogeneity of the risk of recurrence with Gleason score 7, in which $4 + 3 = 7$ carries a 5-year risk of recurrence of 30% to 35%, whereas $3 + 4 = 7$ exhibits a 5-year risk of recurrence of only 5% to 10%.
2. A better characterization of the heterogeneity of the risk of recurrence in Gleason scores 8-10, in which Gleason scores 9-10 carry a 5-year risk of recurrence of greater than 75%, whereas Gleason score 8 exhibits a significantly decreased 5-year risk of recurrence of 40% to 50%.
3. A better characterization of the uniformly indolent behavior of lesions with only Gleason pattern 3, which exhibit no metastatic potential with a 5-year recurrence risk of less than 3%, all of which are effectively due to local recurrence [5,6].

Another feature of the proposed Gleason grade group schema is its characterization of the spectrum of the percentage of Gleason pattern 4 that can be seen in a background of Gleason pattern 3: the percent of Gleason pattern 4 in grade group 1 is zero, that in grade group 2 is less than 50%, that in grade group 3 is greater than 50%, and Gleason score $4 + 4 = 8$ (grade group 4) is entirely Gleason pattern 4. The proposed grade group 5 can be thought of as the presence of Gleason pattern 5 in the absence of any significant Gleason pattern 3. The importance of tertiary Gleason pattern 5 in prostatectomies was first proposed by our group in 2000 with follow-up studies in 2004 and 2009 in which we documented that the presence of tertiary Gleason pattern generally is associated with higher-stage disease and imparts a worse post-prostatectomy prognosis [7-9]. Most of prior studies on tertiary patterns used the pre-2005 grading criteria for prostate adenocarcinoma, which varies significantly compared with contemporary prostate cancer grading. Using currently accepted grading definitions of grade patterns and grading rules, the current study seeks to characterize precisely how the introduction of a limited (<5%) Gleason pattern 5 component at prostatectomy affects prognosis and how tertiary patterns fit into the grade group schema and reporting.

2. Materials and methods

The data from the Johns Hopkins cohort encompassed 9686 patients with paired biopsy and prostatectomy specimens from 2004 to 2014. Of these patients, 5483 had adequate post-prostatectomy follow-up (median time of 3 years) along with complete documentation of primary, secondary, and any limited (<5%) Gleason pattern 5 at prostatectomy. The data from the University of Pittsburgh cohort encompassed 2123 patients with adequate follow-up (median follow-up time of 3.9 years)

along with complete documentation of primary, secondary, and any limited (<5%) Gleason pattern 5 at prostatectomy. These 2 cohorts represent a subset of the data previously reported on in which the presence of limited (<5%) Gleason pattern 5 was recorded [2,4]. This work is retrospective in nature without the need for patient identification. As such, it does not require informed consent and has been approved by each respective institution's review board under the appropriate waiver.

Cases with less than 5% Gleason pattern 4 recorded at prostatectomy in the background of Gleason pattern 3 were grouped into grade group 2 (Gleason score $3 + 4 = 7$ with <5% Gleason pattern 4). The effect of limited Gleason pattern 5, defined as less than 5%, on biochemical recurrence–free survival (BRFS) was examined specifically in the context of Gleason scores $3 + 4 = 7$, $4 + 3 = 7$, and $4 + 4 = 8$ in the combined data from the 2 cohorts described above. The rationale for restricting the term "tertiary" to cases with less than 5% pattern 5 is not only to equate tertiary for the third most common pattern but that it is very limited in nature. A radical prostatectomy with 20% pattern 5 as the third most common pattern is still a lot of pattern 5 and would be expected to have an aggressive course. Also, by having a cutoff of 5%, cases with tertiary pattern 5 will be comparable in their extent of high-grade cancer.

The spectrum of biopsy Gleason scores observed stratified by Gleason scores at radical prostatectomy was examined using the paired biopsy and prostatectomy data available only in the Johns Hopkins cohort. Cases of Gleason scores $3 + 5 = 8$ and $5 + 3 = 8$ at prostatectomy (n = 86 and n = 18, respectively) were specifically excluded from this study, because their relationship to the grade groups is controversial, the number of these cases is small, and we wanted a uniform population within grade group 4 for the purposes of this study.

Biochemical recurrence was defined as serum prostate-specific antigen level of 0.2 ng/mL or higher. Biochemical recurrence–free survival was plotted using the Kaplan-Meier method. Biochemical recurrence–free survival across patient strata is compared using the log-rank test. Hazard ratios were calculated from Cox proportion hazard models. All analyses were performed in Matlab (R2015b; The Mathworks; Natick, MA 01760).

3. Results

3.1. The effect of limited Gleason pattern 5 at prostatectomy on BRFS is most pronounced in the context of Gleason score $4 + 4 = 8$ and intermediate in the context of Gleason score 7

The aggregate data from 2 independent major academic medical centers comprising 7606 patient records are presented in Fig. 1A. Cases with less than 5% Gleason pattern 5 have been characterized separately from Fig. 1A in Fig. 1B-D. The BRFS across the proposed grade groups is shown in