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ORIGINAL ARTICLE

Impact of tertiary Gleason pattern 5 on prostate cancer aggressiveness: Lessons from a contemporary single institution radical prostatectomy series

Zachary B. Koloff [a], Daniel A. Hamstra [b], John T. Wei [a], Jeffrey S. Montgomery [a], Scott A. Tomlins [c], Angela J. Wu [c], Todd M. Morgan [a], Javed Siddiqui [a], Kellie Paich [a], Arul M. Chinnaiyan [c], Felix Y. Feng [c], Alon Z. Weizer [a], Lakshmi P. Kunju [c], Brent K. Hollenbeck [a], David C. Miller [a], Ganesh S. Palapattu [a], Rohit Mehra [c,*]

[a] *Department of Urology, University of Michigan Medical School, Ann Arbor, MI, USA*
[b] *Department of Radiation Oncology, University of Michigan Medical School, Ann Arbor, MI, USA*
[c] *Department of Pathology, University of Michigan Medical School, Ann Arbor, MI, USA*

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Abstract *Objective:* To better evaluate tertiary Gleason pattern reporting and to evaluate the impact of tertiary Gleason pattern 5 (TP5) on prostate cancer pathological features and biochemical recurrence at our large single institution.
Methods: We retrospectively reviewed 1962 patients who underwent radical prostatectomy (RP) for prostate cancer; TP5 was reported in 159 cases (8.1%). Men with Gleason score (GS) 7 and GS 8 disease were divided into subgroups with and without TP5, and histopathological features were compared. Multivariate analyses were conducted to assess the impact on TP5 on biochemical-free survival (BFS).
Results: Tumors possessing GS 3 + 4 with TP5 were more likely to exhibit extraprostatic extension (EPE) and had a larger tumor diameter (TD) than GS 3 + 4 alone. GS 3 + 4 with TP5 was also associated with positive surgical margins (SM), seminal vesicle involvement (SVI), and higher pre-operative prostate-specific antigen (PSA) values, but without statistical significance. GS 4 + 3 with TP5 more commonly presented with EPE, positive SM, SVI, and greater TD and pre-operative PSA level than GS 4 + 3 alone. In multivariate analysis, Gleason score,

* Corresponding author.
E-mail address: mrohit@med.umich.edu (R. Mehra).
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EPE, and TP5 were overall independent risk factors for PSA recurrence in this cohort. Additionally, GS 4 + 3 with TP5 was associated with shorter time to recurrence versus GS 4 + 3 alone. *Conclusion:* Our results emphasize the importance of TP5 and suggest that criteria for tertiary pattern reporting in prostate cancer should be standardized. Further studies are needed to evaluate the role of tertiary patterns in prognostic models.

1. Introduction

The original Gleason scoring system proposed that the overall grade of prostate cancer was best determined by the sum of the two most common architectural patterns of the tumor [1—3]. The most prevalent pattern was described as the primary grade and the second most prevalent pattern the secondary grade. These primary and secondary patterns have been well studied, and higher Gleason scores are significantly associated with adverse pathological factors (e.g., positive surgical margins [SM], seminal vesicle invasion [SVI], lymph node involvement [LNI], and extraprostatic extension [EPE]) and prostate-specific antigen (PSA) recurrence [1—3]. Over the years, the Gleason scoring system has continued to demonstrate strong prognostic power [4—6].

Although Gleason scores or sums are typically reported based on a combination of primary and secondary grades (for example, 3 + 4 = 7), even in 1977 Donald Gleason noted that "occasionally, small areas of a third pattern were observed" [7]. Increasingly in recent years there has been investigation into the criteria and relevance of this third, "tertiary" Gleason component. Currently, however, there is no consensus definition of this tertiary component. Some pathologists might report a tertiary pattern (TP) as any third most common architectural pattern, while others only report a TP when it is higher grade than the two more prevalent patterns [8—11]. Several authors have suggested that TP should be reported if the area is higher grade and comprises less than 5% of the tumor volume, and reported as the secondary grade if it is more prevalent [12,13]. In 2005, an international consensus conference on urologic pathology recommended that the tertiary grade should be commented on in pathology reports, however, the specific criteria for reporting TP were not addressed then [14].

Despite the variable TP definitions of previous studies, some studies have demonstrated that high-grade TP is associated with adverse tumor characteristics and biochemical recurrence [11,12,15—17]. The current study was conducted using a database of patients who underwent RP for clinically localized prostate cancer to better evaluate TP reporting and to evaluate the impact of tertiary Gleason pattern 5 (TP5) on tumor pathological features and biochemical recurrence in this large single institution series.

2. Materials and methods

The study data were obtained retrospectively and analyzed in accordance with University of Michigan Medical School's Institutional Review Board (IRB) approved protocol. All men in this study underwent radical prostatectomy (RP) and all surgical specimens were uniformly processed. The prostate and seminal vesicles were fixed in formalin after inking the outer surface. The most proximal urethra at the prostate base and apical 3-mm were embedded on end after radial sectioning in a cone-like fashion to assess the inked bladder neck and apical margins. The remaining prostate was serially sectioned from apex to base at 3-mm intervals and submitted as quadrisected sections for examination. A subset of prostatectomy tissues underwent tissue procurement protocol for research purposes. In such cases, all peripheral margins were submitted from the procured sections to ensure a complete evaluation of margins and EPE (including extracapsular extension in any location and seminal vesicle invasion). Cases were signed out by a spectrum of pathologists including general surgical pathologists as well as sub-specialty trained genitourinary pathologists. A tumor component was designated as TP5 if it constituted less than 10% of the tumor mass by microscopic visual inspection (all cases where surgical pathology reports stated a TP comprising less than 10% of the tumor were included for this study). Small foci of a lower tertiary grade pattern were not recorded in this series.

Biochemical recurrence was defined as any postoperative elevation of PSA >0.2 ng/mL. There were incomplete data regarding PSA follow-up for a small proportion of patients (3%), therefore, these patients were excluded in the analysis of PSA recurrence. The data regarding which patients received adjuvant treatment following RP were not consistently available.

Statistical analyses were performed using SAS program version 9.3 (SAS Institute Inc., Cary, NC, USA) and MedCalc version 12.7 (MedCalc Software, Ostend, Belgium). Univariate analyses for subjects with and without tertiary Gleason scores were based on chi-square and Fisher's exact tests for categorical variables, and *t*-tests and Wilcoxon rank sums for continuous variables. Multivariate analyses were performed using Cox Proportional Hazards Model. The log rank test was used to compare Kaplan—Meier probabilities for PSA recurrence between subjects with and without tertiary Gleason components. *P*-values <0.05 were considered statistically significant.

3. Results

We retrospectively reviewed RP pathology reports between September 2005 and December 2012 to identify cases with a reported tertiary Gleason component. This time period was selected since the International Society of Urological Pathology (ISUP) released a consensus statement in September 2005 recommending that tumor grades be assigned a Gleason score based on the primary and