Outcome of Gleason 3 + 5 = 8 Prostate Cancer Diagnosed on Needle Biopsy: Prognostic Comparison with Gleason 4 + 4 = 8

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Abbreviations and Acronyms

GS = Gleason score

PSA = prostate specific antigen

Accepted for publication May 20, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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Purpose: ISUP (International Society for Urologic Pathology) and WHO adopted prognostic Grade Groups 1 to 5 that simplify prostate cancer grading for prognosis. Grade Group 4 is Gleason score 8 cancer, which is heterogeneous, and it encompasses Gleason score 4 + 4 = 8, 3 + 5 = 8 and 5 + 3 = 8. The comparative prognostic implications of these various Gleason scores had not been studied by urological pathologists after a re-review of slides.

Materials and Methods: Patients with a highest biopsy Gleason score of 3 + 5 = 8 or 4 + 4 = 8 were included in the study. Controls were cases with a highest Gleason score of 4 + 3 = 7 or 9-10. A total of 423 prostatic biopsy cases accessioned from 2005 to 2013 at 2 institutions were reviewed. Clinicopathological findings and followup (median 33.4 months) were assessed.

Results: Among Gleason score 8 cancers the cancer status outcome in 51 men with Gleason score 3 + 5 = 8 was marginally worse than in 114 with Gleason score 4 + 4 = 8 ($p = 0.04$). This was driven by a persistent nonmetastatic (after radiation/hormone therapy) cancer rate of 37% among Gleason score 3 + 5 = 8 cases vs 24% among Gleason score 4 + 4 = 8 cases. Conversely, cancer specific survival at 36-month followup was 97.8% in 3 + 5 cases vs 92.6% in 4 + 4 cases but this was not significant ($p = 0.089$). Cancer specific survival in the Gleason score 8 group was dichotomized by the presence of cribriform growth ($p = 0.018$). All Gleason score categories did not differ in the fraction of biopsy cores positive, clinical presentation or pathological findings, including the frequency of Gleason pattern 5, in 70 patients who underwent prostatectomy.

Conclusions: Using the most current standards of prostate cancer grading the prognosis is not different in Gleason score 3 + 5 = 8 and 4 + 4 = 8 cancers. This justifies including both in Grade Group 4.

Key Words: prostatic neoplasms; neoplasm grading; biopsy; neoplasm recurrence, local; World Health Organization

Gleason score is used to stratify prostatic adenocarcinoma based on the dominant and secondary architectural patterns. Accordingly, a GS of 8 may represent an architecturally homogeneous 4 + 4 cancer or a combination of heterogeneous patterns in the case of 3 + 5 or 5 + 3 cancer. Whether the presence of Gleason pattern 5 in GS 8 cancer imparts a different prognosis than pure 4 + 4 = 8 is uncertain. The

0022-5347/16/1964-1076/0
THE JOURNAL OF UROLOGY®
© 2016 by American Urological Association Education and Research, Inc.
http://dx.doi.org/10.1016/j.juro.2016.05.105
Vol. 196, 1076-1081, October 2016
Printed in U.S.A.

urgency to resolve this question is heightened by the recent adoption by ISUP and WHO of a simplified patient centric grading system composed of 5 prognostic Grade Groups[1,2] as proposed in 2013 based on data from The Johns Hopkins Medical Institutions[3] and subsequently validated by biochemical recurrence HRs in cases from 5 large academic centers.[4] Grade Groups 1, 2, 3, 4 and 5 were designated GS 3 + 3 = 6, GS 3 + 4 = 7, GS 4 + 3 = 7, GS 8 and GS 9-10, respectively. The divisions of GS 3 + 4 = 7 from GS 4 + 3 = 7 and GS 8 from GS 9-10, which had often been bundled together for prognostic and research purposes, is supported by studies showing significantly different outcomes.[5,6] Grade Group 4 is heterogeneous as it includes GS 4 + 4 = 8, GS 3 + 5 = 8 and GS 5 + 3 = 8. Three recent studies without re-review of slides by urological pathologists suggested that cases with any pattern 5 may behave worse than GS 4 + 4 = 8 cancer.[7–9]

The current detailed clinicopathological study with pathology re-review according to the standards agreed on at the 2014 ISUP conference[1] was done to determine whether cases with the highest biopsy finding of GS 8 with pattern 5 have a different prognosis than those without pattern 5. Cases with pattern 5 were limited only to GS 3 + 5 = 8 cancer because of the extreme rarity of GS 5 + 3 = 8 cases.[3,10]

MATERIALS AND METHODS

Patients and Data Collection

We reviewed the records of 428 prostatic biopsy cases accessioned from 2005 to 2013 at Medical College of Wisconsin/Froedtert Hospital and University of Miami Miller School of Medicine. All biopsy slide sets that had a highest GS (on a single tissue core of at least 1 part) of 4 + 4 = 8, 3 + 5 = 8 or 5 + 3 = 8 were included in the study (table 1). ISUP 2014 rules[1] were applied as inclusion criteria for this study, in which any amount of Gleason 5 cancer qualifies as a secondary grade 5 (unlike in prostatectomy specimens).[10] If more than 1 core was submitted in the container, each core with a different GS was assigned an individual grade. Control groups comprised all biopsy sets with the highest GS of 4 + 3 = 7 (Grade Group 3) or 9-10 (Grade Group 5) that were acquired in the same years. All slide sets were reviewed by urological pathologists (KAI and ONK). For study purposes GS was divided into 7 categories, including 1) 4 + 3, 2) 3 + 5, 3) 5 + 3, 4) 4 + 4, 5) 4 + 5, 6) 5 + 4 and 7) 5 + 5. Only 5 cases of GS 5 + 3 = 8 were excluded from analysis due to the small size of the category, leaving 423 cases. The 3 + 5 = 8 category included 6 cases that met criteria for that diagnosis after review but had been signed out with another GS. The presence of a cribriform or intraductal growth pattern was assessed in GS 8 cases when feasible.

The fraction of positive cores was recorded based on the sum of cores in all parts of the specimen. Clinical followup was obtained for as long as available, including type of intervention, PSA recurrence and survival. Cancer status was defined as 1) metastatic at diagnosis or later, 2) persistent with cancer not treated with surgery and clinically present at last followup, 3) recurrent with biochemical recurrence after definitive surgical or radiation treatment with achievement of a serum PSA nadir of 0.2 ng/ml or less, 4) relapse with cancer clinically cured by definitive treatment but recurrent, 5) negative or 6) unknown. In 70 men treated with radical prostatectomy who had available pathological data GS, percent of gland involvement by cancer, stage and margin status were recorded.

Statistical Analysis

The Kruskal-Wallis test was used to assess differences in continuous measures (eg age and followup). Associations between categorical measures such as cribriform growth were assessed by the chi-square test using exact or Monte Carlo methods. The log-rank test was used to determine overall survival differences. Pairwise comparisons for the log-rank test were considered significant in a stepdown manner. A generalized linear model with the logit link function and normal error was used to model the percent positive of each core sample while controlling for the data source. Generalized estimating equations were used to account for repeat measures in the data. All results were considered statistically significant at the 0.05 level. Analysis was performed with SAS®, version 9.4.

RESULTS

Clinicopathological Characteristics of Study Patients

Median followup was 33.4 months in the study set of 423 men. For the GS 4 + 3, 4 + 4, 3 + 5, 4 + 5, 5 + 4 and 5 + 5 categories followup was 47.9, 35.6, 46.1, 6.6, 23.6 and 13.8 months, respectively ($p < 0.001$). Followup did not differ for the 3 + 5 vs 4 + 4 categories. Overall differences were attributable to patients diagnosed with higher GS cancer dying sooner or being lost to followup sometimes as little

Table 1. *Clinicopathological characteristics*

	Medical College of Wisconsin		University of Miami		p Value
No. pts	197		226		
Median age (range)	67 (45–91)		64 (43–87)		<0.001 (Wilcoxon rank sum test)
No. 1st treatment course (%):					
Prostatectomy	50	(25)	23	(10)	<0.001 (chi-square test)
Androgen deprivation + radiation	81	(41)	101	(45)	
Androgen deprivation only	18	(9)	58	(26)	
Watchful waiting	22	(11)	3	(1)	
Cryotherapy	17	(9)	0		
Chemotherapy/other	9	(5)	41	(18)	
No. biopsy GS (%):					
4 + 4 = 8	53	(27)	68	(30)	<0.001 (chi-square test)
3 + 5 = 8	15	(8)	43	(19)	
Other	129	(65)	115	(51)	

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