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Outcomes of Gleason score 3 + 4 = 7 prostate cancer with minimal amounts (<6%) vs ≥6% of Gleason pattern 4 tissue in needle biopsy specimens☆

Gozde Kır, MD *, Hatice Seneldir, MD, Eyup Gumus, MD

Umraniye Education & Research Hospital, Istanbul, Turkey

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ABSTRACT

Objective: The International Society of Urological Pathology Gleason grading system was modified in 2005. Since the modified system was introduced, many cancers that previously would have been categorized as Gleason score (GS) 6 are now categorized as GS 7 based on biopsy specimens that only contain minimal amounts (<6%) of Gleason pattern (GP) 4 tissue. However, the clinical significance of observing <6% of GP 4 tissue in biopsies of GS 7 prostate cancer has not been studied.

Material and methods: This study was based on needle biopsy specimens that were categorized as GS 6 or GS 7 and were obtained from patients who underwent radical prostatectomy (RP) with available follow-up data. We assessed the quantity of GP 4 tissue in biopsy specimens of GS 7 prostate cancer. Further, we evaluated the correlation between the quantity of GP 4 tissue and disease progression after RP.

Results: GP 4 comprising 26–49% of the specimen, GS 4+3 and percentage of total core tissue scored as positive were significant and independent predictors of prostate-specific antigen (PSA) failure after RP, as assessed using a multivariate Cox regression model that included the quantity of GP 4 in the prostate biopsy specimen, preoperative PSA, perineural invasion, clinical stage, number of positive cores, and percentage of core tissue scored as positive. Cases with GS 3+3 and cases in which the observed GP 4 area was <6% did not differ significantly in terms of biochemical PSA recurrence (BPR) status. In contrast, cases with 6–25% GP 4 tissue, 26–49% GP 4 tissue, and GS 4+3 showed more frequent BPR than cases with GS 3+3.

Conclusions: Our data suggest that the quantity of GP 4 tissue in GS 7 cancer has clinical significance. However, there is a need for larger studies of the clinical significance of biopsy specimens that include <6% GP 4 tissue. We should reconsider whether the amount of GP 4 should be included in standart pathology reports.

1. Introduction

A modification to the International Society of Urological Pathology (ISUP) Gleason grading system was published in 2005. Since this modified system was introduced, certain patterns that were originally scored as Gleason pattern (GP) 3 have now been recategorized as GP 4 [1]. For example, cribriform and other poorly formed glands are now graded as GP 4. Furthermore, following the modified Epstein criteria, all cribriform glands are now assessed as pattern 4 [2]. The ISUP consensus statement also recommends grading needle biopsy specimens with the most common GP as the primary pattern and the highest GP as the secondary pattern. This is a significant change from the previous grading method, in which the Gleason score (GS) was assigned by adding the most common and the second-most common GPs [1,3,4]. The ISUP-modified Gleason grading system has significantly changed the distribution of GSs among needle biopsy specimens of prostate cancer. Many GS 3 + 3 = 6 prostate carcinomas are now scored as GS 3 + 4 = 7. Indeed, the percentage of GS 6 cancers has decreased from 48% to 22%, whereas the percentage of GS 7 cancers has increased from 26% to 68% [5–8].

In a recent study, Huang et al [9] considered cases of GS 3 + 4 = 7 prostate cancer in which needle biopsy specimens contained a minimal amount (<6%) of tissue that was scored as GP 4. They found that cases with these features were associated with low-risk tumors in corresponding radical prostatectomy (RP) specimens. Huang et al concluded that further studies were needed to evaluate the clinical significance of minimal amounts (<6%) of GP 4 tissue in biopsy specimens taken from GS 7 prostate cancers. Furthermore, the authors noted that their findings needed to be corroborated using data on clinical outcomes.

In this study, we assessed the quantity of GP 4 in biopsy specimens of GS 7 prostate cancer. Furthermore, we evaluated the correlation between GP 4 quantity and disease progression after RP.

☆ Conflict of interest: None declared.

* Corresponding author at: Pathology Department, Umraniye Education & Research Hospital, Umraniye, Istanbul, Turkey. Tel.: +90 5434935054.

E-mail addresses: gozkir@yahoo.com (G. Kır), hkodabas@yahoo.com (H. Seneldir), eyupg@superonline.com (E. Gumus).

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Table 1
Consort diagram of patients.

Prostate core biopsy/total (n)	Benign (n)	Aciner adenocarcinoma (n)
1712	1205	557
RP	–	382
GS 3 + 3	–	216
GS 3 + 4	–	130
GS 4 + 3	–	26
GS ≥ 4 + 4 (excluded)	–	10

RP, patients underwent radical prostatectomy; GS, Gleason score.

2. Materials and methods

2.1. Patients and treatment

This study included patients with prostate cancer who received needle biopsies, who were assigned a GS of 6 or 7, who subsequently underwent RP and for whom follow-up data were available (Table 1). Cases were collected from 2006 to 2015 at the Department of Pathology of Umraniye Education and Research Hospital.

None of the patients had a history cryotherapy, radiotherapy, or androgen deprivation therapy. A postoperative serum prostate-specific antigen (PSA) level above 0.1 ng/mL was considered to be indicative of biochemical PSA recurrence (BPR) [10]. In all cases, slides were examined independently by 2 pathologists (G. Kir and H. Seneldir) who were blinded to the cases' outcomes. Each case with scoring discrepancies was subsequently placed under joint review and was assigned a score that both pathologists agreed upon. Each case was assigned a GS according to the 2005 ISUP criteria [1]. In accordance with the modified Epstein criteria, we assessed all cribriform foci as GP 4 [2]. In addition, the proportion of the area scored as GP 4 was recorded for each biopsy in 5% increments. The number of cores involved by cancer, the presence of perineural invasion, and histopathologic type of GP 4 were recorded.

The biopsies and subsequent RPs were performed at the same institution.

2.2. Statistical analysis

Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software (NCSS LLC, Kaysville, UT) were used for statistical analysis. Descriptive statistics were shown in Table 2. Categorical values were shown as number and percentage, and associations were tested with Fisher exact test or Yates continuity correction test (Table 3). The BPR-free survival rates were estimated by the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were used to explore the association between preoperative characteristics and the primary end point (Table 4). All tests were 2 sided, and significance levels were set at a P value less than .05.

Table 2
Preoperative clinicopathologic characteristics of patients.

		n	%
Quantity of GP 4	3 + 3	216	58.1
	<6%	50	13.4
	6%-25%	52	14.0
	26%-49%	28	7.5
	4 + 3	26	7.0
BPR	Positive	34	9.1
	Negative	338	90.9
Perineural invasion	Positive	62	16.7
	Negative	310	83.3
Clinical stage	cT1	268	72.0
	cT2	98	26.3
	cT3	6	1.6
		Min-max (interquartile range)	Median
Preoperative PSA		0.38-74	6.3
No. of positive cores		1-12	3
Percentage of total core tissue scored as positive		0.4-85	5

BPR, biochemical prostate-specific antigen recurrence; GP, Gleason pattern; PSA, prostate-specific antigen.

Table 3
Association of the quantity of GP 4 with BPR for GSs 3 + 3, 3 + 4, and 4 + 3.

Quantity of GP 4	BPR		P	OR	95% CI
	n	%			
3 + 3	8	3.7	1.000	1.083	0.223-5.265
<6%	2	4			
3 + 3	8	3.7	.034	3.391	1.123-10.245
6%-25%	6	11.5			
3 + 3	8	3.7	.001	10.400	3.524-30.689
26%-49%	8	28.6			
3 + 3	8	3.7	0.001	16.250	5.632-46.888
4 + 3	10	38.5			
<6%	2	4	.270	3.130	0.601-16.310
6%-25%	6	11.5			
<6%	2	4	.003	0.600	1.872-49.240
26%-49%	8	28.6			
<6%	2	4	.001	15.000	2.968-75.810
4 + 3	10	38.5			
6%-25%	6	11.5	.070	3.067	0.941-9.995
26%-49%	8	28.6			
6%-25%	6	11.5	.013	4.792	1.501-15.301
4 + 3	10	38.5			
26%-49%	8	28.6	.630	1.563	0.500-4.879
4 + 3	10	38.5			

The P values were calculated by the Fisher exact test and the Yates continuity correction test. BPR, biochemical prostate-specific antigen recurrence; CI, confidence interval; GP, Gleason pattern.

3. Results

The preoperative clinicopathologic characteristics of the study population are presented in Table 2. Of 372 cases, 216 (58.1%) resulted in a GS of 3 + 3 = 6, 130 (34.9%) resulted in a GS of 3 + 4 = 7, and 26 (7%) resulted in a GS of 4 + 3 = 7. Of the 130 biopsies with a GS of 3 + 4 = 7, 50 (13.4%) showed GP 4 in less than 6% of the tissue, 52 (14%) showed GP 4 in 6% to 25% of the tissue, and 28 (7.5%) showed GP 4 in 26% to 49% of the tissue. In all cases, the tissues scored as GP 4 had similar histologic patterns. Thirty-four (9.1%) of the 372 cases showed BPR.

At univariate Cox regression analysis, several clinicopathologic factors were significantly associated with BPR: GP 4 in 6% to 25% of the tissue (hazard ratio [HR], 3.242; 95% confidence interval [CI], 1.124-9.345; $P = .029$), GP 4 in 26% to 49% of the tissue (HR, 8.062; 95% CI, 3.025-21.487; $P < .001$), GS of 4 + 3 = 7 (HR, 12.186; 95% CI, 4.800-30.937; $P < .001$), perineural invasion (HR, 4.775; 95% CI, 2.435-9.366; $P < .001$), cT3 (HR, 6.958; 95% CI, 2.079-23.290; $P = .002$), preoperative PSA levels (HR, 1.045; 95% CI, 1.026-1.065; $P < .001$), the number of positive cores (HR, 1.236; 95% CI, 1.109-1.378; $P < .001$), and the percentage of total core tissue scored as positive (HR, 1.039; 95% CI, 1.025-1.054; $P < .001$) (Table 4).

We subsequently performed a multivariate Cox regression analysis to identify clinicopathologic parameters with independent prognostic value. We found the following independent predictors of BPR after RP: GP 4 in 26% to 49% of the tissue (HR, 7.612; 95% CI, 2.855-20.294; $P < .001$), GS of 4 + 3 = 7 (HR, 6.380; 95% CI, 2.190-18.583; $P < .001$), and percentage of total core tissue scored as positive (HR, 1.028; 95% CI, 1.011-1.046; $P < .001$) (Table 4).

A key outcome measured in this study was BPR-free survival after RP, for which the median duration of follow-up was 54 months (range, 25-107 months; mean, 58.42 ± 19.43 months). There were significant differences in BPR-free survival between groups of patients with GS 7 disease who were stratified by the quantity of GP 4 tissue observed in prostate biopsy samples (log-rank test, $P = .001$; Figure). However, BPR-free survival did not differ significantly between patients