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Clinical Significance of Prospectively Assigned Gleason Tertiary Pattern 4 in Contemporary Gleason Score 3+3 =6 Prostate Cancer

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Abstract

OBJECTIVE—To determine the oncologic impact of prospectively assigned tertiary pattern 4 in contemporary Gleason score (GS) 3 +3 =6 radical prostatectomy (RP) specimens.

PATIENTS AND METHODS—Oncologic outcomes were retrospectively reviewed for 720 consecutive patients from a single National Comprehensive Cancer Network (NCCN) center with at least 6 months follow-up after RP for GS3 +3 =6 (GS6, N =222), GS6 with tertiary pattern 4 (GS6t4, N =62), or GS3 +4 =7 (N =436) prostate cancer, as prospectively graded since 2006 using the 2005 International Society of Urologic Pathologists criteria. Preoperative NCCN risk category, RP pathology, progression-free survival (PFS) and metastasis-free survival (MFS) were compared among the GS6, GS6t4, and GS3 +4 =7 groups using χ^2 , Kaplan–Meier, and log-rank analyses.

RESULTS—The incidence of low NCCN preoperative risk classification for GS6t4 patients (63%) was less than that for GS6 patients (77%) while greater than that for GS3 +4 =7 patients (30%, $P<0.001$). GS6t4 patients had RP pathologic features which were intermediate in risk between that of GS6 and GS3 +4 =7 based on extraprostatic extension (27% vs. 6% vs. 31%, respectively, $P<0.001$) and mean percentage of prostate gland involvement (13% vs. 10% vs. 16%, respectively, $P<0.001$). With a mean overall follow-up of 42 months, PFS for GS6t4 patients (5-year 85%) was intermediate between that of GS6 (5-year 93%) and GS3 +4 =7 (5-year 76%) patients ($P<0.001$). The 5-year MFS rate was 100% for GS6 and GS6t4 patients compared to 97% for GS3 +4 =7 patients ($P=0.07$).

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CONCLUSIONS—This study provides the longest follow-up to date for RP patients with prospectively assigned GS6t4 and supports a risk for adverse RP pathology and postoperative disease progression that is intermediate between GS6 and GS3 +4 =7. Whether a tertiary pattern 4 in GS6 disease increases the risk of metastasis is uncertain and requires longer term study. Given favorable oncologic outcomes, less stringent postoperative surveillance for both GS6 and GS6t4 patients may be warranted.

Keywords

prostate cancer; radical prostatectomy; tertiary Gleason pattern; biochemical failure

INTRODUCTION

The Gleason scoring system predicts prostate cancer aggressiveness and provides an important tool for guiding patient management decisions [1,2]. As described by Dr. Gleason, a total score is generated by summation of the first (primary) and second (secondary) most prevalent differentiation patterns individually scored from 1 (most differentiated) to 5 (least differentiated) that comprise at least 5% of the tumor volume [1,3]. A wealth of scientific literature has validated this grading system based on worse oncologic outcomes after radical prostatectomy in association with a higher primary, secondary or total Gleason score (GS) [1,4,5]. Among Gleason 7 patients, a primary pattern 4 (GS4 +3 =7) carries a worse prognosis than a primary pattern 3 (GS3 +4 =7) [4,6].

In addition to a primary and secondary Gleason pattern, the clinical significance of a tertiary Gleason pattern, defined as a small volume (<5% of the cancer) or a third most prevalent differentiation pattern, has also been suggested. A tertiary pattern of prostate cancer can be identified in approximately one in four prostatectomy specimens, although reported rates vary widely (10–48%) [7–15]. Early investigations of a retrospectively assigned tertiary Gleason pattern indicated an increased risk for systemic and local relapse after radical prostatectomy, particularly when higher in grade than the primary or secondary pattern [10,15–17]. Among GS 6 prostatectomy patients with a tertiary patterns 4 or 5, the incidence of both adverse surgical pathology and postoperative progression was concluded to be intermediate between that of conventional GS6 and GS7 [16]. These initial findings drove the International Society of Urological Pathologists (ISUP) to standardize tertiary Gleason reporting in 2005 [18]. The 2005 ISUP recommendations also included stricter histologic criteria for distinguishing Gleason pattern 3 from pattern 4 that result in many historical cases of GS6 to be now considered GS7.

In contemporary practice, radical prostatectomy patients with GS6 and a tertiary pattern 4 (GS6t4) are thus presumed to have higher risk of postoperative relapse than conventional GS6 patients. However, data supporting this conclusion are limited by: (i) retrospective assignment of a tertiary Gleason pattern after knowledge of postoperative relapse, allowing for potential grading bias; (ii) statistical grouping of GS6t4 cases together with tertiary pattern 5 cases; and (iii) grade assignment prior to the 2005 ISUP updated guidelines, translating into frequent contamination of GS6/GS6t4 cohorts with contemporary GS7 disease. The prognostic significance of a tertiary pattern 4 that is assigned prospectively at

the time of prostatectomy has not been validated despite recent attempt [19], however there has been only short follow-up available for patients undergoing prostatectomy since the 2005 ISUP adoption of tertiary grading. The absence of prognostic validation is relevant given recent observations which suggest a limited amount of Gleason pattern 4 prostate cancer may be insufficient for clinically relevant disease progression [20,21].

The current study investigates the hypothesis that a limited amount of Gleason pattern 4, as in GS6t4, fails to alter the oncologic risk of contemporary GS6 prostate cancer after radical prostatectomy. To test this hypothesis, intermediate length oncologic outcomes were compared among prostate cancer patients diagnosed prospectively at the time of radical prostatectomy with GS6t4, GS6, or GS3 +4 =7 using the 2005 ISUP grading modifications. These outcomes include the longest follow-up reported to date for a GS6t4 cohort diagnosed prospectively using these contemporary grading criteria.

METHODS

Patients

Institutional review board approval was obtained for this study. A prospectively populated departmental database was queried to identify all patients undergoing radical prostatectomy at Roswell Park Cancer Institute between January 2006 and December 2013 for prostate cancer prospectively graded at the time of operation as GS6, GS6t4, or GS3 +4 =7 without tertiary pattern 5. Patients with less than 6 months of postoperative follow-up were excluded. Clinical, operative, and pathologic variables extracted from the database were compared retrospectively among the three GS groups. Preoperative clinical risk was classified as low, intermediate, or high according to National Comprehensive Cancer Network (NCCN) guidelines [2]. Postoperative surveillance was conducted in accordance with NCCN guidelines [2]. Postoperative disease progression was defined by either the occurrence of biochemical failure or the administration of any postoperative prostate cancer treatment, which includes radiation or androgen deprivation therapy. Metastatic workup was initiated at the time of progression and included cross-sectional pelvic imaging and radionuclide bone scan.

Statistics

Patient characteristics were reported as means and medians for continuous measures, and as frequencies and relative frequencies for categorical variables. Comparisons were made between groups using the Kruskal–Wallis exact and Pearson χ^2 tests for continuous and categorical variables, respectively. Progression-free survival (PFS) and metastasis-free survival (MFS) were summarized for each group using Kaplan–Meier curves, from which 3- and 5-year survival rates were calculated. Comparisons were made between groups using the log-rank test. All analyses were conducted in SAS v9.4 (Cary, NC) at a nominal significance level of 0.05.

RESULTS

Clinical Features

A total of 720 patients including 222 GS6 patients, 62 GS6t4 patients, and 436 GS3 +4 =7 patients were identified (Table I). Median and mean preoperative PSA values for GS6t4 patients (4.9 and 5.2 ng/dl, respectively) were slightly higher than PSA values for GS6 patients (4.6 and 5.1 ng/dl, respectively), while lower than those of GS3 +4 =7 patients (5.3 and 6.0 ng/dl, respectively, $P<0.001$). Similarly, the incidence among GS6t4 patients of low NCCN preoperative risk category (63%) was lower than that for GS6 patients (77%) while higher than that for GS3 +4 =7 patients (30%, $P<0.001$).

Pathologic Features

The incidence of adverse pathologic features among GS6t4 prostatectomy specimens was intermediate between that of GS6 and GS3 +4 =7 specimens, based on extraprostatic extension rates (27% vs. 6% vs. 31%, respectively, $P<0.001$) and mean percentage of prostate gland involvement (13% vs. 10% vs. 16%, respectively, $P<0.001$, Table I). The positive margin rate among GS6t4 specimens was nearly twice that of GS6 specimens and no different than among GS3 +4 =7 patients (Table I).

Postoperative Oncologic Outcomes

Postoperative follow-up duration approached 4 years on average (mean/median 42/39, 46/49, 40/36, and 42/36 months for all patients, GS6, GS6t4, and GS3 +4 =7, respectively). Postoperative radiation was administered to 3% of GS6 patients, 5% of GS6t4 patients, and 9% of GS3 +4 =7 patients. Ten patients, all GS3 +4 =7, received postoperative androgen deprivation therapy. PFS for GS6t4 patients (3-year 92%, 5-year 85%) was intermediate between PFS for GS6 patients (96% and 93%, respectively) and GS3 +4 =7 patients (86% and 76%, respectively, $P<0.001$, Fig. 1).

Clinical and pathologic features of all GS6t4 patients with postoperative progression (N =6) were further evaluated (Table II). Palpable disease, extracapsular extension, and positive surgical margins were common features among GS6t4 patients with progression. All three GS6t4 progressing patients treated postoperatively with radiation had a complete biochemical response.

No GS6 or GS6t4 patients developed metastasis compared to 9 (2%) GS3 +4 =7 patients. The 5-year MFS rates for GS6 and GS6t4 patients were each 100% compared to 97% for GS3 +4 =7 patients ($P=0.07$, Fig. 2). There were no cancer-specific mortalities.

DISCUSSION

The prognostic impact of primary and secondary Gleason patterns in radical prostatectomy specimens is well established, but the clinical significance of a tertiary Gleason pattern is less clear, particularly for GS6t4. Prior research has suggested an intermediate prognosis for GS6t4 relative to GS6 and GS7 but has been limited by retrospective assignment of GS6t4, use of outdated histologic criteria for differentiating Gleason patterns 3 versus 4, and data contamination with tertiary pattern 5. Validation of an intermediate prognosis for GS6t4

prospectively diagnosed at the time of prostatectomy using contemporary grading criteria has not been previously reported.

Herein oncologic outcomes for prostatectomy patients prospectively diagnosed with GS6t4 since the implementation of the 2005 ISUP updated grading criteria were compared to outcomes for prospectively diagnosed GS6 and GS3 +4 =7 prostatectomy patients from the same period. The average follow-up interval for a prospectively diagnosed GS6t4 cohort in this study of approximately three and a half years is the longest reported to date. The findings confirm that GS6t4 patients have intermediate risk for adverse prostatectomy pathology relative to GS6 and GS3 +4 =7 patients based on both extraprostatic extension and cancer volume. More importantly, the findings support a risk for postoperative progression among GS6t4 patients that is intermediate between GS6 and GS3 +4 =7 patients. Although conclusions must be tempered in the absence of long-term follow-up, the 5-year outcomes data reported here are expected to capture the vast majority (>80%) of lifetime biochemical failure events [22,23].

Considerable prior research has investigated the clinical significance of a tertiary Gleason pattern after Dr. Gleason and others first described its frequent occurrence [24–26]. In 2000, investigators from Johns Hopkins University proposed the prognostic significance of a tertiary Gleason pattern identified in 114 patients, based on increased risks of advanced pathological tumor stage, biochemical recurrence, and metastasis [16]. Follow-up studies from these researchers and others concluded that a tertiary pattern 5 among GS7 patients conferred a higher risk for adverse pathology and progression [10,17]. Subsequently, van Oort et al. showed that any retrospectively assigned tertiary pattern, whether higher or lower grade, increased the risk of postoperative relapse [15]. Such studies collectively prompted international experts in urological pathology (ISUP) to establish updated criteria in 2005 for reporting tertiary patterns and distinguishing Gleason patterns 3 and 4 [18].

Since the 2005 ISUP convention, others have substantiated the prognostic significance of a tertiary Gleason pattern [8,11–14,27–29], with rare exception [7]. However, only few of these studies focused on GS6 (or GS<7) patients, and each grouped tertiary patterns 4 and 5 together in all analyses [11,13,14,29]. Turker et al. regraded 331 prostatectomy specimens and identified 36 GS<7 patients with tertiary patterns 4 or 5, and found a tertiary pattern was associated with worse pathology and higher progression rates, similar to those observed among GS3 +4 =7 patients [14]. Servoll et al. reported on 148 prostatectomy specimens, only eight of which had GS<7 and a tertiary pattern [11,29]. The tertiary pattern did not alter oncologic risk among GS<7 patients even with long-term follow-up, although the small cohort may have compromised statistical power. In both the Turker et al. and Servoll et al. studies, tertiary patterns were diagnosed retrospectively by specimen reexamination, introducing the potential for grading bias with knowledge of postoperative outcomes.

In contrast, investigators from Johns Hopkins University have reported outcomes of a prospectively assigned tertiary pattern [13]. However, prostatectomy specimens were graded prior to 2005 and the establishment of contemporary ISUP grading criteria. This study concluded the risk for progression among GS6 patients with any tertiary component (GS6-tertiary) was higher compared to GS6 patients but similar to GS3 +4 =7 patients. Potential

contamination of their GS6-tertiary cohort with contemporary GS7 cases and inclusion of tertiary Gleason pattern 5 might have exacerbated GS6-tertiary outcomes.

To our knowledge, only one prior study has addressed oncologic outcomes for prospectively assigned tertiary disease among contemporary prostatectomy patients [19]. Investigating a cohort of prostatectomy patients since 2007, Adam et al. recently concluded that a prospectively assigned tertiary Gleason pattern increased the risk of extraprostatic extension in GS6 specimens, as in the current study, but without increased risk for postoperative progression after a median follow-up of 24 months. The discrepancy in progression risk between the current study and the Adam et al. study may relate to differences in follow-up duration. In the current study, no difference in progression rates among GS6 and GS6t4 patients was detected during an earlier interval evaluation (data not shown) which included a similar median follow-up as in the Adam et al. study; only with additional follow-up past 2–3 years do the PFS curves begin to separate for GS6 and GS6t4 patients (Fig. 1). Increased progression among GS6t4 patients relative to GS6 patients is consistent with worse prostatectomy pathology for GS6t4 patients observed in both the Adam et al. study and the current study.

Although a tertiary pattern 4 increased progression risk relative to pure GS6 disease, it did not increase the risk of early metastasis in the current study, as both GS6 and GS6t4 cohorts remained metastasis-free for the study duration. GS6t4 progressors had frequently positive margins, suggesting residual disease in the surgical bed as the likely site of relapse, rather than systemic disease. Consistent with a pelvic-only location for disease recurrence, all GS6t4 progressors who underwent radiation had a complete response. Hence, it is possible that a small Gleason pattern 4 may have limited-to-no potential for metastasis, as recently suggested for contemporary GS6 prostate cancer [30,31], although longer term study is needed. The potential clinical insignificance of a small volume of Gleason pattern 4 is consistent with conclusions of Cooperberg et al. who has suggested such patients can be safely monitored with active surveillance [20]. Additional support includes the PIVOT trial indicating no cancer-specific survival benefit for biopsy Gleason 7 patients undergoing prostatectomy versus observation, although the study was not designed to detect differences in this subgroup [21]. If outcomes of the current study can be validated with longer follow-up, relaxation of postoperative surveillance regimens for both GS6 and GS6t4 patients may be warranted.

Additional limitations of this study include potential biases inherent in a single institutional investigation and a retrospective study design. Validation in larger cohorts using multi-institutional collaboration is needed. Quantitative estimations of the precise volume of Gleason pattern 4 were not available in this study but warrant future investigation as perhaps a more clinically useful measure than overall tumor volume estimations.

CONCLUSIONS

This study provides the first data to our knowledge which supports that GS6t4 prostate cancer prospectively diagnosed using updated ISUP grading criteria carries an intermediate risk for both adverse pathology and postoperative progression compared to GS6 and GS3 +4

=7. A tertiary Gleason pattern 4 may still be insufficient for metastasis, and future investigation with longer term follow-up is needed. Awaiting these important data, the clinical significance of limited Gleason pattern 4 relative to pure GS6 disease remains uncertain. Given favorable 5-year outcomes for either GS6 or GS6t4, future investigation of less stringent postoperative follow-up for both groups is warranted.

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Fig. 1. Progression-free survival among GS6, GS6t4, and GS3 +4 =7 patients. Kaplan–Meier survival curves and log-rank *P*-values are displayed for GS6 versus GS6t4 versus GS3 +4 =7 patient groups.

Fig. 2. Metastasis-free survival among GS6, GS6t4, and GS3 +4 =7 patients. Kaplan–Meier survival curves and log-rank *P*-values are displayed for GS6 versus GS6t4 versus GS3 +4 =7 patient groups.

TABLE I

Patient Characteristics

	GS6	GS6t4	GS3 +4 =7	GS6 versus GS6t4 versus GS3 +4 =7
Total patients, n (%)	222 (26%)	62 (7%)	436 (52%)	—
Age, years				
Mean	59	59	60	0.17
Median	60	59	60	
Preoperative PSA, ng/dl				
Mean	5.1	5.2	6.0	<0.001
Median	4.6	4.9	5.3	
Biopsy Gleason score, n (%)				
<7	206 (93%)	47 (76%)	142 (32%)	<0.001
7	16 (7%)	14 (23%)	283 (65%)	
>7	0 (0%)	1 (1%)	11 (3%)	
cT stage, n (%)				
1	159 (72%)	41 (66%)	296 (68%)	0.15
2	63 (28%)	21 (34%)	131 (30%)	
3–4	0 (0%)	0 (0%)	9 (2%)	
NCCN clinical risk, n (%)				
Low	171 (77%)	39 (63%)	132 (30%)	<0.001
Intermediate	50 (23%)	22 (36%)	282 (65%)	
High	1 (0%)	1 (1%)	22 (5%)	
pT stage, n (%)				
2	205 (92%)	45 (73%)	281 (64%)	<0.001
3–4	17 (8%)	17 (27%)	155 (36%)	
Surgical margins, n (%)				
Negative	193 (87%)	48 (77%)	337 (77%)	0.009
Positive	29 (13%)	14 (23%)	99 (23%)	
Prostatectomy cancer volume, % of prostate gland				
Mean	10.5%	13.5%	15.7%	<0.001
Median	8.0%	12.0%	10.0%	
pN stage, n (%)				
0	20 (9%)	10 (16%)	203 (47%)	<0.001
1	0 (0%)	0 (0%)	1 (0%)	
X	202 (91%)	52 (84%)	232 (53%)	

TABLE II
Clinical and Pathological Features of GS6t4 Patients With Postoperative Progression

Patient #	Age (years)	PSA (ng/dl)	cT stage	pT stage	Surgical margins	Cancer volume (% of prostate)	Post-op XRT	
							Received	Complete PSA response
1	57	5.9	2b	3a	Positive	12%	Yes	Yes
2	65	4.3	2c	3a	Positive	25%	No	(NA)
3	50	4.4	1c	3a	Negative	15%	No	(NA)
4	46	4.3	2a	2c	Positive	20%	Yes	Yes
5	64	10.6	1c	2c	Negative	5%	Yes	Yes
6	53	3.4	2a	2c	Positive	5%	No	(NA)

NA, not applicable.