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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

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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,

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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

Table 1 Distribution of Gleason scores.

Gleason score	Tertiary pattern	Number of cases
3 + 4 = 7		940
3 + 4 = 7	5	33
4 + 3 = 7		265
4 + 3 = 7	5	120
4 + 4 = 8		37
4 + 4 = 8	5	3
	Total	1398

secondary patterns with a comment regarding the tertiary score, if present [14]. However, without formal parameters to guide tertiary Gleason component reporting, and since the evaluation of involvement is subjective based on visual inspection, there is some variability in the literature.

Among a total of 1962 RP specimens that were reviewed in this study, 159 cases with TP5 were reported. Three pathology reports included comments that the tertiary Gleason 5 component comprised approximately 15% of the index tumor. These cases with relatively large tertiary components were excluded from our analysis based on previous studies [12,13]. We set the cut-off point at 10% for our study and hence all other cases that reported a tertiary component remained in our analysis. These remaining 156 cases with TP5 were analyzed compared to control patients with the same primary and secondary Gleason patterns without tertiary components. Among the cohort of patients with TP5, majority of patients were histologically determined to have either Gleason score 3 + 4 or 4 + 3 disease. The breakdown of Gleason scores (GS) is detailed in Table 1.

General characteristics of all GS 7 and 8 patients included in this study are presented in Table 2. Tumor grades and histopathological characteristics are detailed in Table 3. GS 3 + 4 with TP5 tumors were significantly associated with EPE and larger tumor diameters (TD) than GS 3 + 4 alone ($p < 0.0001$ for both). GS 3 + 4 with TP5 tumors also tended to present with positive SM, LNI, SVI, and have higher pre-operative PSA than GS 3 + 4 tumors, but without significance. GS 4 + 3 with TP5 tumors were more likely to demonstrate EPE, positive SM, SVI, have larger TD, and

Table 2 Gleason 7 and 8 patient characteristics ($n = 1398$).

Variable	Value
Age (years), mean ± SD	60.7 ± 7.1
Pre-operative PSA	
Mean	7.10
Median	7.14
EPE, *n* (%)	257 (18.3)
SM, *n* (%)	235 (16.8)
SVI, *n* (%)	56 (4.0)
LNI, *n* (%)	13 (0.9)
Tumor diameter (mm)	
Mean	1.70
Median	1.60

PSA, prostate-specific antigen; EPE, extraprostatic extension; SM, surgical margins; SVI, seminal vesicle invasion; LNI, lymph node invasion; Tumor diameter, maximum tumor diameter.

Table 3 Tumor grades and histopathological characteristics.

Tumor grade	EPE, *n* (%)	*p*	SM, *n* (%)	*p*	SVI, *n* (%)	*p*	LNI, *n* (%)	*p*	TD, (mm)	*p*	Pre-op PSA, (ng/mL)	*p*
Gleason score 3 + 4	85 (9%)	<0.0001	139 (15%)	0.11	5 (0.53%)	0.08	2 (0.22%)	0.77	1.60	<0.0001	6.26	0.16
Gleason score 3 + 4 with TP5	12 (36%)		7 (21%)		1 (3%)		0 (0%)		2.12		8.75	
Gleason score 4 + 3	77 (29%)	<0.0001	49 (18%)	0.02	12 (5%)	<0.0001	4 (1.5%)	0.12	1.76	<0.0001	7.83	<0.0001
Gleason score 4 + 3 with TP5	64 (53%)		32 (27%)		30 (25%)		5 (4.2%)		2.16		12.77	
Gleason score 4 + 4	18 (45%)	0.59	7 (18%)	0.47	8 (22%)	0.48	1 (2.7%)	0.14	1.71	0.11	9.97	0.21
Gleason score 4 + 4 with TP5	1 (33%)		1 (33%)		0 (0%)		1 (33%)		2.70		15.17	

EPE, extraprostatic extension; SM, positive surgical margins; SVI, seminal vesicle invasion; LNI, lymph node involvement; TD, tumor diameter; Pre-op PSA, pre-operative PSA level. *P* values, comparison between same Gleason score with and without TP5.

present with higher pre-operative PSA levels than GS 4 + 3 alone ($p < 0.0001$, $p = 0.02$, $p < 0.0001$, $p < 0.0001$, and $p < 0.0001$, respectively). GS 4 + 3 with TP5 also tended to present with LNI more often than GS 4 + 3, but without significance.

Kaplan–Meier PSA recurrence-free survival curves for GS 3 + 4 and 4 + 3 patients with and without TP5 were compared using log rank tests. When comparing GS 3 + 4 patients to those with GS 3 + 4 with TP5, there was no significant difference in PSA recurrence-free survival, and only one patient with GS 3 + 4 with TP5 recurred. However, there was a shorter time to PSA recurrence among GS 4 + 3 with TP5 patients compared to GS 4 + 3 patients ($p = 0.005$, Fig. 1).

Since TP5 was associated with other adverse pathologic features, a multivariable analysis was performed to investigate whether TP5 was independently associated with biochemical-free survival (BFS). Gleason score was categorized into four compartments (GS 2–6, 3 + 4, 4 + 3, and 8–10), as the majority of our patient population had GS 7 disease. When multivariate analysis of BFS was conducted, the presence of TP5 was associated with decreased BFS with an HR of 1.8 (95%CI: 1.1–2.7, $p = 0.017$; Table 4). Pre-operative PSA, GS, and EPE were also significant factors related to PSA recurrence. However, in our patient population, patients with GS 7 were the most likely to have TP5, so we performed another multivariate analysis limited to those patients (GS 3 + 4 and GS 4 + 3). Again, TP5 was an independent risk factor for PSA recurrence with an HR of 1.9 (95%CI: 1.1–3.3, $p = 0.035$; data not shown).

Table 4 Effect of various variables on biochemical recurrence based on Cox Proportional Hazards Model.

Covariate	HR	95%CI	*p*-value
PSA (continuous)	1.02	1.01–1.03	<0.0001
Gleason score			
GS 2-6 (reference)			
GS 3 + 4	1.70	0.63–4.40	0.31
GS 4 + 3	6.30	2.50–16.30	<0.0001
GS 8-10	11.00	4.10–29.10	<0.0001
TP5			
No (reference)			
Yes	1.80	1.10–2.70	0.017
EPE			
No (reference)			
Yes	2.10	1.30–3.30	0.003
Positive SM			
Negative (reference)			
Positive	1.10	0.76–1.60	0.53
SVI			
No (reference)			
Yes	0.94	0.56–1.60	0.83
Node stage			
Negative or n/a (reference)			
Positive	1.50	0.75–3.20	0.24

PSA, prostate-specific antigen; HR, hazard ratio; 95% CI, 95% confidence interval; GS, Gleason score; TP5, tertiary Gleason pattern 5; EPE, extraprostatic extension; SM, surgical margins; SVI, seminal vesicle invasion.

4. Discussion

The Gleason scoring system remains one of the most important prognostic parameters for prostate cancer. Over nearly 50 years, this grading system has remained largely intact aside from minor modifications to adapt to changes in the clinical practice of screening and management of prostate cancer [4–6]. In 2005, the ISUP met to establish a new consensus regarding prostatic carcinoma grading.

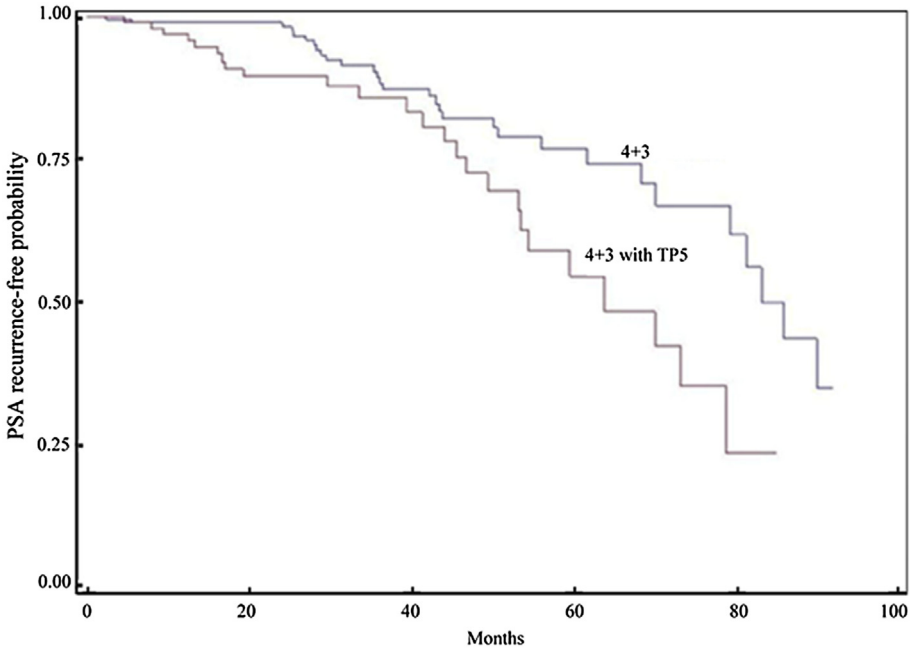

Figure 1 PSA recurrence-free survival in patients with Gleason score 4 + 3 disease without a tertiary component and Gleason score 4 + 3 with TP5 disease. Log rank chi-square 7.80, $p = 0.005$.

Among the debatable topics within the field of urologic pathology is the presence of a tertiary architectural pattern within a prostate specimen. For RP specimen, the ISUP stated that "one assigns the Gleason score based on the primary and secondary patterns with a comment as to the tertiary pattern" [14].

However, to date, pathologists have variable criteria of when to report this tertiary pattern. At our institution, TP5 was reported in 8.1% of pathology specimens. Although this was a somewhat lower incidence compared to other studies reporting TP5 in 10%—27% of cases, this may be reflective of the variable interpretation of when to report a tertiary pattern [12,16]. Some pathologists report the presence of any Gleason pattern that is less prevalent than the primary or secondary grades [8,10]. Others only report the third most prevalent pattern if it is higher grade than the primary and secondary patterns [11,15]. Recently, several authors suggested that a tertiary Gleason pattern only be reported if the area is higher grade than the primary and secondary patterns, and the area comprises less than 5% of the tumor volume [12,13,16]. In our current study, all cases where comments reported a TP comprising less than 10% of the tumor were included for this analysis.

In general, it is well established that the presence of a high grade Gleason pattern is a poor prognostic indicator. In fact, McNeal et al. [18,19] suggested modifying the Gleason scoring system to include the proportion of high grade (Gleason 4 or 5) cancer in a tumor specimen, as their studies found poor architectural differentiation to correlate with tumor volume, nodal metastasis, and tumor progression. Similarly, Cheng et al. [20] concluded that the combined percentage of Gleason patterns 4 and 5 was superior to conventional Gleason scoring in predicting patient outcome and PSA recurrence. Stamey and his colleagues [21] found the percentage of Gleason grade 4 or 5 disease to be independently associated with prostate cancer progression while other common predictors of progression, such as positive margins and capsular invasion, did not reliably predict recurrence following RP. A recent study at our institution found that the presence of Gleason pattern 5 was the single strongest pathological predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following RP [22].

Several groups have investigated whether high grade Gleason patterns are correlated with tumor aggressiveness and poor outcomes, even when present in small amounts and reported as a tertiary component. Similar to our study, Mosse et al. [12] reported that Gleason 7 tumors with TP5 were more likely to be higher stage and have worse prognostic clinico-pathological features. A systematic review and meta-analysis on the significance of high grade TP published in 2007 concluded that high tertiary grades were associated with poorer outcomes [17]. However, that review only included one study published after the ISUP Consensus Conference on Gleason grading and the meta-analysis failed to take into account the variable definitions of the tertiary Gleason pattern. More recent studies such as those by Turker et al. [15], Trock et al. [16], Pierorazio et al. [23], and Servoll et al. [24] concluded that high-grade TP is important as an independent predictor of PSA recurrence in Gleason 7 and 8 prostate cancers. In fact, Nanda et al. [25] found the risk of PSA recurrence in patients with Gleason 7 disease with TP5 to be similar to patients with Gleason 9 or 10 diseases. In contrast to those studies, others found that tertiary Gleason patterns were not consistently independent predictors of PSA recurrence [8,11].

In our study, Gleason 7 tumors with TP5 were more likely to present at higher stages and have larger tumor diameters. In the sub-group of GS 4 + 3 tumors, those with TP5 were also more likely to have positive SM, SVI, and present with higher pre-operative PSA values than those tumors with the same Gleason score without TP5. GS 3 + 4 and 4 + 4 tumors with TP5 also tended to present with those worse clinico-pathological parameters and higher pre-operative PSA levels, however, differences were not statistically significant perhaps due to the relatively small sample size in those subgroups.

In regards to BFS, as defined by undetectable PSA, TP5 was found to be an independent predictor of worse outcome. GS 4 + 3 with TP5 tumors demonstrated a shorter time to recurrence compared to GS 4 + 3 tumors. However, GS 3 + 4 with TP5 tumors did not significantly differ from GS 3 + 4 tumors in terms of time to recurrence. Again, this may be a reflection of the small number of patients with GS 3 + 4 with TP5. Nevertheless, even when accounting for these other pathologic and clinical features on multivariate analysis, the presence of TP5 remained a strong prognostic factor imparting a 1.8-fold increase in the risk of biochemical recurrence.

In current practice, many clinicians rely on various tables or algorithms, such as Partin tables and Kattan nomograms, in order to predict pathological stage and outcomes and to guide treatment strategies in prostate cancer [5,26]. However, when assessing tumor grades, the comments and notes from pathological reports are often not included in prognostic models. Therefore, although recent evidence seems to suggest that a high-grade tertiary component worsens prognosis in prostate cancer, that parameter is often dismissed when crucial decisions about cancer management are made. The ISUP conference in 2005 acknowledged the importance of high-grade tertiary patterns in RP specimens, but did not propose any formal criteria for diagnosis and simply recommended that its presence be commented upon. Therefore, based upon our study we recommend the inclusion of several concepts. Firstly, standardized criteria for TP scoring needs to be established. Secondly, further prospective studies should be conducted to evaluate for the role of tertiary Gleason components in multivariable predictive and prognostic models.

There are some limitations to our study. One limitation is its retrospective design. Additionally, despite the large overall sample size, there were certain subgroups which were relatively small and the power of analysis may have been too low to detect small differences. We were not able to compare the differences between patients with TP5 comprising less than 5% of the index tumor versus cases where TP5 comprised less than 10% due to inconsistent detail in pathology comments. However, during this time period at our institution, Gleason pattern 5 in less than 10% of the tumor was primarily used as the criteria for reporting tertiary patterns. Another limitation of this study was that we were not able to confidently report which patients received salvage or adjuvant treatment after RP as some

patients may have received subsequent treatment at other institutions, but were lost for primary follow-up at our hospital. Based on our institutional experience, the number of patients with Gleason 7 disease receiving adjuvant therapy is very low, but this information was not reliably available in our current dataset. It is also unusual that SVI, LNI, and margin status were not predictive of biochemical recurrence after prostatectomy at the multivariate level in this cohort. We suspect that an interplay of factors including strong influence of TP5, impact of unknown adjuvant therapies, and a relatively small number of cases might have influenced this pattern.

In conclusion, our study using a large population of prostate cancer patients who underwent RP at a single institution with consistent pathologic evaluation demonstrates that prostate cancer with TP5 is associated with aggressive features and is an independent risk factor of biochemical recurrence. Given the strong evidence that TP is a relevant risk factor in prostate cancer, prospective studies are needed to evaluate for the potential role of high-grade tertiary patterns in prostate cancer prognostic models.

Conflicts of interest

The authors declare no conflict of interest.

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