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ORIGINAL RESEARCH

Significance of tertiary Gleason pattern 5 in patients with Gleason score 7 after radical prostatectomy: a retrospective cohort study

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Purpose: To evaluate the association between tertiary Gleason pattern 5 (TGP5) and biochemical recurrence (BCR) in patients with prostate cancer (PCa) with a Gleason score (GS) of 7 after radical prostatectomy (RP).

Patients and methods: This retrospective study identified 350 patients who received RP and were graded as GS 7 (3+4 or 4+3) at the West China Hospital from January 2009 to December 2017. Initially, the patients were divided into two groups, TGP5 absence and TGP5 presence, independent of Gleason score. We further stratified the patients by adding the Gleason score into four groups: GS 3+4, GS 3+4/TGP5, GS 4+3, and GS 4+3/TGP5. Cox proportional-hazards models were used to evaluate the association between the status of TGP5 and BCR after adjusting for the confounding factors.

Results: The risk of BCR was significantly higher in patients with TGP5 when compared to patients without TGP5 (P=0.04, HR=2.17 95%, Cl: 1.03–4.59). For patients with primary Gleason pattern 4, the risk of BCR for patients with Gleason 4+3/TGP5 was statistically significantly higher than Gleason 4+3 (P=0.04, HR=2.45, 95% Cl: 1.04–5.76).

Conclusion: The TGP5 in patients with GS 7 had strong association with the risk of BCR and was an independent predictor for BCR. Further research on larger data sets is needed to confirm these findings.

Keywords: prostate cancer, biochemical recurrence, Gleason score, tertiary Gleason pattern, radical prostatectomy

Introduction

Prostate cancer (PCa) is one of the most common malignancies among males in developed countries and is the third leading cause of cancer-related death. In the United States, PCa has the highest incidence, with an estimated 164,690 new cases in 2018. This pattern has been consistent from 1975 to 2014.[1] In China, the percent change in the incidence of PCa is the highest amongst cancers in males.[2] PCa is a heterogeneous and multifactorial disease complicating accurate diagnosis, treatment, and assessment of prognosis of PCa.

The Gleason system is based on the microscopic examination of prostate cancer tissue and has aided by guiding therapy and predicting outcomes.[3–6] The tradition Gleason system is calculated using the first and second most prevalent histologic patterns. Adding tertiary patterns to the Gleason score has been debated as a way to increase the accuracy of the PCa prognosis.[7–9] Some research has shown that tertiary Gleason pattern (TGP5) is related to disease-free survival of patients after

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radical prostatectomy (RP).[10–13] Among RP specimens, PCa with a Gleason Score (GS) 7 is the most common grade with prevalence from 30% to 50%.[14,15]

In patients with GS 7, some studies have indicated that TGP5 presence has worse outcomes, including biochemical recurrence (BCR) compared with those without TGP5.[10–13,16,17] For this study, we assessed the impact of TGP5 on the BCR in GS 7 patients after RP at the West China Hospital.

Materials and methods

This retrospective study identified 604 patients who received RP and were diagnosed with GS 7 (3+4 or 4+3) in the West China Hospital. In total, 350 patients were included in this analysis (Figure 1). Data were excluded from patients without records of BCR (n=217) and on patients who received neoadjuvant hormone therapy (NHT) (n=37). Exclusions were not affected by the pathological diagnosis such as GS and T/N stage. A flowchart of patients who met the study's inclusion/exclusion criteria is provided as Figure S1. We collected clinicopathological data of included patients who visited the hospital between January 1, 2009 and December 31, 2017. The follow-up time was measured from the date of RP surgery to the date of emigration, date of death, or December 31, 2017, whichever was earliest. To determine the influence of TGP5 on

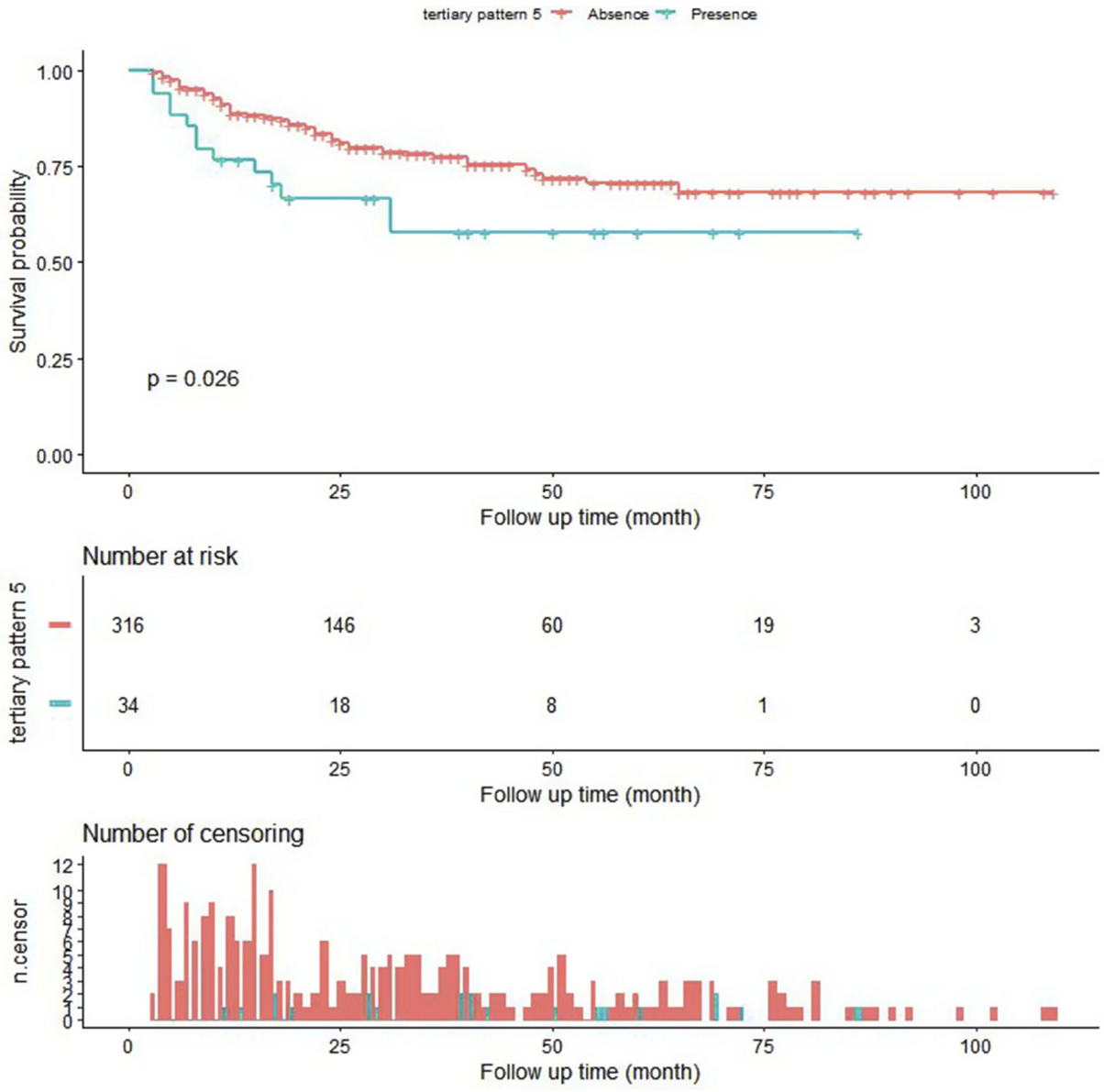

Figure 1 Kaplan–Meier analysis of TGP5 absence and presence regardlessly the primary Gleason pattern. The survival probability of patients with TGP5 absence and presence.

prognosis, patients were evaluated for the presence or absence of TBP5 that was independent of the primary Gleason pattern. We identified 316 patients with absence of TGP5 and 34 patients with the presence of TGP5. We stratified our sample by the primary Gleason pattern to address heterogeneity. Our sample was stratified into 4 groups: 165 patients with primary Gleason pattern 3 with TGP5 absence (GS 3+4), 7 patients with primary Gleason pattern 3 with TGP5 presence (GS 3+4/TGP 5), 151 patients with primary Gleason pattern 4 with TGP5 absence (Gleason 4+3), and 27 patients with primary Gleason pattern 4 with TGP5 presence (Gleason 4+3/TGP 5).

The clinical and pathological characteristics included the age at surgery, surgical approach, body mass index (BMI), tumor node metastasis (TNM) stage, and serum prostate-specific antigen (PSA) level. Grading and description of surgical samples were determined by 1 or 2 experienced pathologists without knowledge of grouping. TGP5 was defined as the third component of a Gleason pattern which is higher than the primary and secondary grades with the tertiary pattern. And TGP5 visually is deemed to be less than 5% of the whole tumor. As the primary endpoint, BCR of PCa was defined by two consecutive PSA increases of ≥0.2 ng/mL after RP.[18] The patient was seen quarterly to semiannually where follow-up PSA was performed and other clinicopathological information was collected. After 2 years, the patients were seen annually. No informed consent was needed by the Institutional Review Board West China Hospital as we analyzed de-identified patient data.

We summarized baseline characteristics with and without stratification of TGP5 status. Continuous variables using Kruskal–Wallis test were reported as means and standard deviations, while categorical variables using chi-square or Fisher's exact test were reported as counts and proportions.

We used univariate Cox regression model to evaluate the association between the status of TGP5 and BCR. Cox proportional-hazards models were used to assess the association between TGP5 and BCR controlling for other factors.

Model 1 included surgical approach, age at surgery, BMI, preoperative PSA, and biopsy GS as covariates. Model 2 included the surgical approach, age at surgery, BMI, preoperative PSA, biopsy GS, positive surgical margin (PSM), and TNM stage as covariates. We adjusted the covariates in the model using a change in the hazard ratio of 10% as a guideline.[19]

All analyses were performed using the statistical programs R (http://www.R-project.org, The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc, Boston, MA). We used stratified linear regression models for the subgroup analyses. The likelihood ratio test was used to compare the stratified samples as well as test interactions. All the statistical tests were two-sided and *P*-values of less than 0.05 were considered statistically significant.

The Institutional Review Board of West China Hospital has approved this study.

Results

A total of 350 patients with GS 7 treated with RP were analyzed in this study. The range of age was 48 to 84 years (Mean 67.92±6.75) and the follow-up time was from 3 to 109 months (Mean 29.05±22.98). The clinicopathological information is listed in Table 1. For pathological characteristics at baseline, pathological GS, biopsy GS, pathological ISUP, and BCR have differences ($P<0.05$). There is no statistically significant difference in other clinical and pathological characteristics at baseline when stratified by GS 7 and TGP5 as well as stratified by TGP5 alone. We applied univariate Cox regression model to evaluate the unadjusted association between TBP5 and BCR. The results of the univariate Cox regression model are presented in Table S1.

In the Cox proportional-hazards models, we controlled clinical and pathological characteristics, including surgical approach, age at surgery, BMI, preoperative PSA, NHT, PSM, and TNM stage. The risk of BCR for patients with TGP5 presence was significantly higher than the absence of TGP5 ($P=0.04$, HR=2.17 95%, Cl: 1.03–4.59) independent of primary Gleason score (Table S2). BCR survival was significantly different between patients with and without TGP5 as assessed by Kaplan–Meier curves and log-rank tests ($P=0.026$, Figure 1).

In patients with primary Gleason pattern 4, the risk of BCR for patients with Gleason 4+3/TGP5 was significantly higher than Gleason 4+3 alone ($P=0.04$, HR=2.45, 95% Cl: 1.04–5.76) (Table S3). BCR survival within these strata was significant (log-rank $P=0.073$, Figure 2).

There was no significant difference in risk of BCR or BCR survival between patients with Gleason 3+4/TGP 5 compared to patients with Gleason 3+4 (Table S3 and Figure 3).

Hierarchical regression analysis for subgroups showed a stronger association between TGP5 and BCR among subgroups of patients with PSA ≥20 ng/mL ($p=0.02$), pathological T stage=2c ($P=0.04$), pathological N stage=0

Table 1 Baseline characteristics of participants

Tertiary pattern 5	Absence	Presence	*P*-value	Mean+SD	N (%)
N	316	34			
Age at surgery (year, Mean+SD)	67.78±6.76	69.26±6.64	0.202	67.92±6.75	
Postoperative hospital stay (day, Mean+SD)	7.36±3.67	8.15±4.67	0.069	7.44±3.78	
BMI (Mean+SD)	23.79±2.79	23.53±2.14	0.787	23.76±2.74	
Intraoperative bleeding (mL, Mean+SD)	305.63±258.64	230.75±136.46	0.183	298.36±250.27	
Preoperative PSA (ng/mL, Mean+SD)	17.95±16.31	21.40±20.11	0.415	18.28±16.72	
Follow-up time (month, Mean+SD)	28.88±23.02	30.59±22.90	0.607	29.05±22.98	
Surgical approach (N, %)			0.154		
Open RRP	70 (22.15%)	8 (23.53%)			78 (22.29%)
LRP	112 (35.44%)	17 (50.00%)			129 (36.86%)
RARP	134 (42.41%)	9 (26.47%)			143 (40.86%)
Pathological GS (N, %)			<0.001		
3+4	165 (52.22%)	7 (20.59%)			172 (49.14%)
4+3	151 (47.78%)	27 (79.41%)			178 (50.86%)
Biopsy GS (N, %)			<0.001		
3+3	48 (15.19%)	4 (11.76%)			52 (14.86%)
3+4	156 (49.37%)	9 (26.47%)			165 (47.14%)
3+5	0 (0.00%)	2 (5.88%)			2 (0.57%)
4+3	88 (27.85%)	13 (38.24%)			101 (28.86%)
4+4	18 (5.70%)	3 (8.82%)			21 (6.00%)
4+5	2 (0.63%)	2 (5.88%)			4 (1.14%)
5+3	0 (0.00%)	1 (2.94%)			1 (0.29%)
5+4	1 (0.32%)	0 (0.00%)			1 (0.29%)
NA	3 (0.95%)	0 (0.00%)			3 (0.86%)
Pathological ISUP (N, %)			<0.001		
2	165 (52.22%)	7 (20.59%)			172 (49.14%)
3	151 (47.78%)	27 (79.41%)			178 (50.86%)
Intraoperative blood transfusion (N, %)			0.239		
No	296 (93.67%)	34 (100.00%)			330 (94.29%)
Yes	20 (6.33%)	0 (0.00%)			20 (5.71%)
Damico grade (N, %)			0.505		
Low risk	7 (2.22%)	1 (2.94%)			8 (2.29%)
Medium risk	119 (37.66%)	10 (29.41%)			129 (36.86%)
High risk	190 (60.13%)	23 (67.65%)			213 (60.86%)
T stage (N, %)			0.121	-	
T2a	48 (16.44%)	3 (10.00%)			51 (15.84%)
T2b	90 (30.82%)	9 (30.00%)			99 (30.75%)
T2c	131 (44.86%)	12 (40.00%)			143 (44.41%)
T3a	13 (4.45%)	2 (6.67%)			15 (4.66%)
T3b	10 (3.42%)	4 (13.33%)			14 (4.35%)
N stage (N, %)			0.195		
N0	303 (95.89%)	31 (91.18%)			334 (95.43%)
N1	13 (4.11%)	3 (8.82%)			16 (4.57%)
M stage (N, %)			1		
M0	306 (96.84%)	33 (97.06%)			339 (96.86%)
M1b	10 (3.16%)	1 (2.94%)			11 (3.14%)

(*Continued*)

Table 1 (Continued).

Tertiary pattern 5	Absence	Presence	*P*-value	Mean+SD	N (%)
PSM (N, %)			0.653		
No	251 (80.19%)	26 (76.47%)			277 (79.83%)
Yes	62 (19.81%)	8 (23.53%)			70 (20.17%)
BCR (N, %)			0.013		
No	257 (81.33%)	21 (61.76%)			278 (79.43%)
Yes	59 (18.67%)	13 (38.24%)			72 (20.57%)

Abbreviations: RRP, retropubic radical prostatectomy; LRP, laparoscopic radical prostatectomy; RARP, robotic-assisted laparoscopic radical prostatectomy; ISUP, International Society of Urologic Pathology grade; PSM, positive surgical margin.

(*P*=0.03), or pathological M sge=0ta (*P*=0.03) (Table S4). Stratified analysis in other clinical and pathological characteristics was not statistically significant. The test for interactions was showed in Table S5.

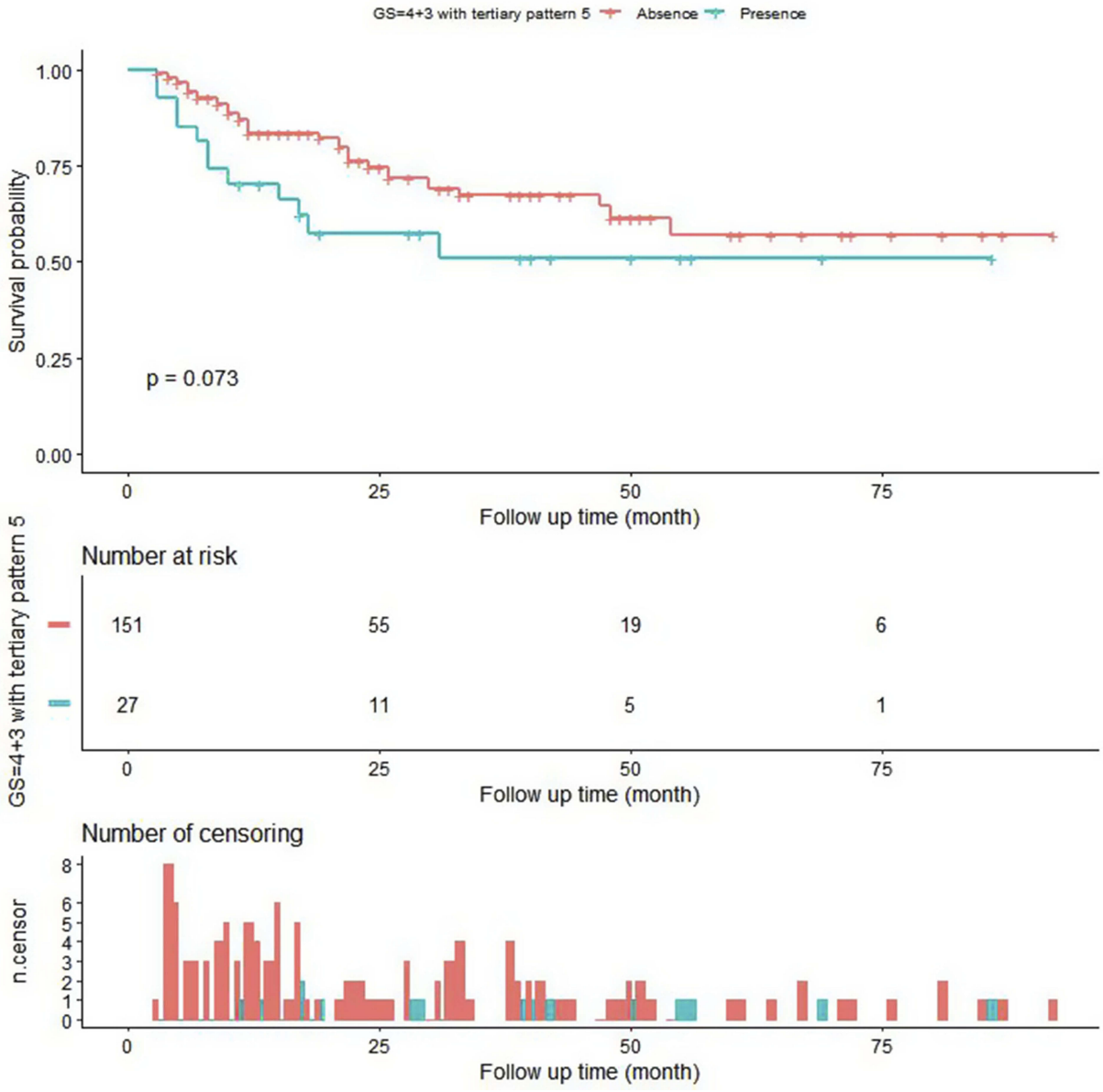

Figure 2 Kaplan–Meier analysis of GS 4+3 and GS 4+3/TGP5. The survival probability of patients with GS 4+3 and GS 4+3/TGP5. The log-rank *p*=0.073.

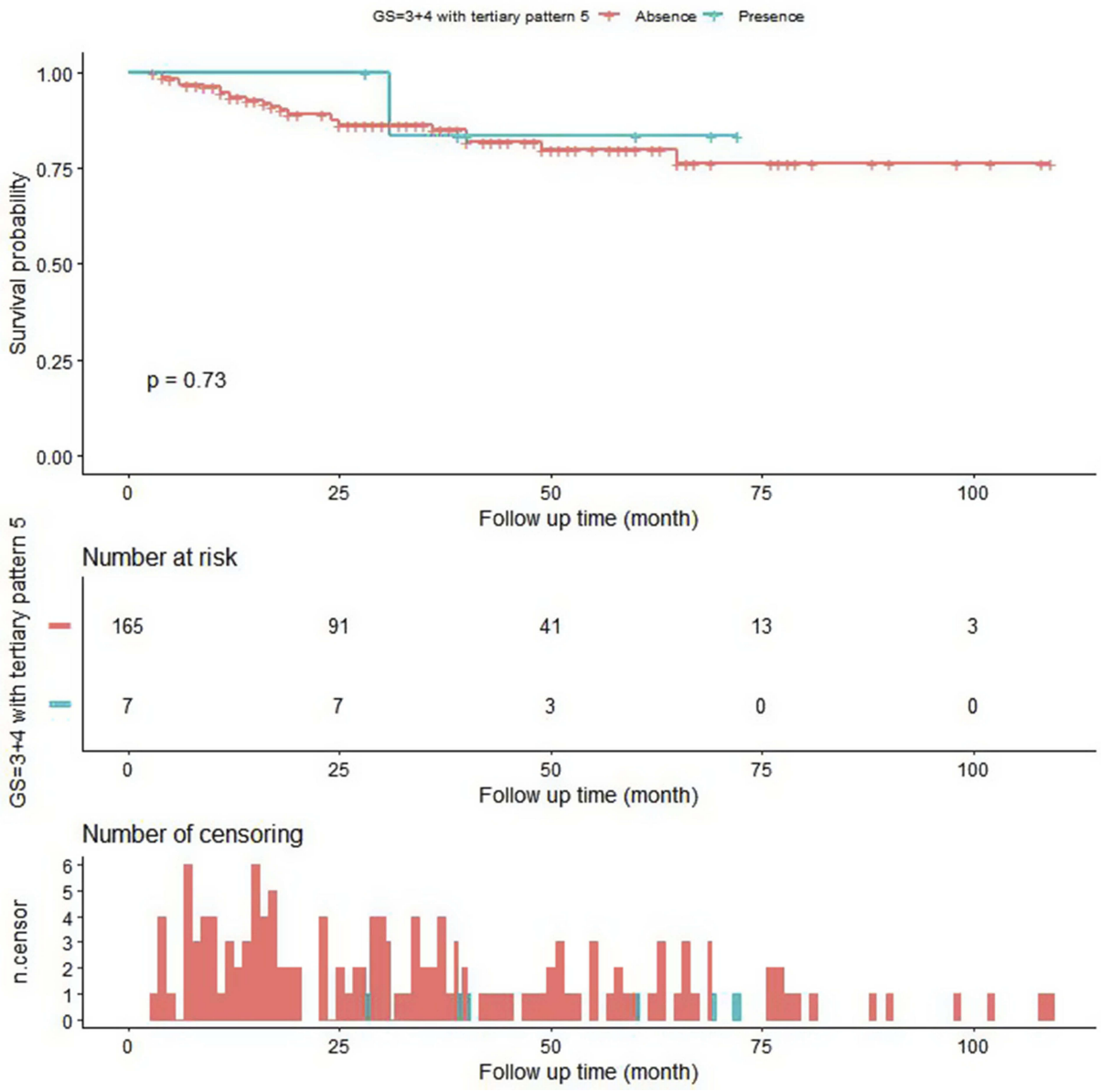

Figure 3 Kaplan–Meier analysis of GS3+4 and GS3+4/TGP5. The survival probability of patients with GS3+4 and GS3+4/TGP5. There was no significant difference in BCR survival between patients with Gleason 3+4/TGP 5 compared to patients with Gleason 3+4 (log-rank *P*=0.73).

Discussion

Although the relevance of TGP5 to more advanced PCa has reached consensus, the effects of TCG on BCR are still controversial. Some studies[20–24] reported TGP is an independent predictor of BCR, while other studies[25,26] did not find a significant association.

In this study, we identified patients with GS 7 and found that TGP5 was associated with BCR in patients after RP, confirming the results of previous studies. Overall, we showed a worse prognosis with individuals with TGP5, and this relationship persisted regardless of the primary Gleason pattern ($P<0.05$). When stratifying by primary Gleason pattern, there was a significant difference showing Gleason 4+3/TGP5 had a worse prognosis than Gleason 4+3 ($P<0.05$).

Even a small amount of TGP 5 leads to serious deterioration of the prognosis and TGP 5 is relative with the further clinical expansion negatively impacts prognosis.[16] Özsoy M et al reported that TGP5 increased the risk of BCR within the same GS group, which including patients with GS 7 (4+3) and (3+4).[27] Sim et al also reported that TGP was significantly associated with increased risk of BCR in GS 7 groups in 1100 cases.[21] Baras et al, stated that, in patients with GS 7, the effect of TGP5 in pattern 4+3 was greater than pattern

3+4 with respect to BCR,[28] which is consistent with our findings. Jang et al reported the presence of TGP5 is an independent predictor of BCR in patients with GS 7[29] presence of TGP5 in patients with GS 7 increased the risk of BCR to mimic the rate of GS 8. Trock et al found that patients with GS 7 (4+3) and TGP5 had the same risk of BCR in patients with GS 8 (4+4).[20] Moul et al[6] found patients with GS 7 and higher-grade tertiary patterns had the same risk of BCR with patients with GS8. Sauter et al even defined an integrated quantitative GS by considering TGP5 to reflect their finding that TGP5 had powerful prognostic impact in patients with GS 7.[23]

Our study found a significant association of the presence of TGP5 and the risk of BCR in patients with GS 7 had a significant association with the risk of BCR, supporting inclusion of TGP5 in the evaluation of patients with PCa. They may consider TGP5 when calculating the risk of BCR for patients with GS 7 after PR. The evidence, including this study, suggests that the current Gleason grading system should be updated to include TGP5.

Our study is the first research of this topic to analyze the patients in this region of China, where there is an estimated incidence (60.3%) of PCa and associated mortality (26.6%) within the 4,292,000 invasive cancer cases in 2015.[2]

There were several limitations of our study including relatively small sample size. Our data were collected from clinical records at the West China Hospital. Although it was the top medical institution for the western part of China, it is only a single institution, and our results may not be generalizable. We found interesting non-significant differences in the stratified analysis result, but could not make conclusions because of our sample size. Further studies with larger sample sizes can more fully test these associations.

We are constructing a database which includes additional data and more extended follow-up information, providing a valuable resource to further study the association between TGP5 in patients with GS 7 and the risk of BCR. Finally, the Gleason grading system should consider including TGP5 information to improve the assessment of prognosis in patients with PCa.

Conclusion

We found a significant association between TGP5 and BCR in patients with GS 7 after RP. The TGP5 in patients with GS 7 had strong association with the risk of BCR and it was an independent predictor for BCR. This result was stronger in patients with GS 7 (4+3). Further research with larger dataset is needed to confirm these findings.

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Disclosure

The authors report no conflicts of interest in this work.

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