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ORIGINAL ARTICLE

Prostate Cancer

The performance of the new prognostic grade and stage groups in conservatively treated prostate cancer

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We evaluated the prognosis of the new grade groups and American Joint Committee on Cancer (AJCC) stage groups in men with prostate cancer (PCa) who were treated conservatively. A total of 13 798 eligible men were chosen from the Surveillance Epidemiology and End Results database. The new grade and AJCC stage groups were investigated on prostate biopsy specimens. Kaplan–Meier survival analysis and multivariable hazards models were applied to estimate the association of new grade and stage groups with overall survival (OS) and PCa-specific survival (CSS). Mean follow-up was 42.65 months (95% confidence interval: 42.47–42.84) in the entire cohort. The 3-year OS and CSS rates stepped down for grade groups 1–5 and AJCC stage groups I–IVB, respectively. After adjusting for clinical and pathological characteristics, all grade groups and AJCC stage groups were associated with higher all-cause and PCa-specific mortality compared to the reference group (all $P \leq 0.003$). In conclusion, we evaluated the oncological outcome of the new grade and AJCC stage groups on biopsy specimens of conservatively treated PCa. These two novel clinically relevant classifications can assist physicians to determine different therapeutic strategies for PCa patients.

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Keywords: mortality; neoplasm grading; neoplasm staging; prostatic neoplasms

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer of men in the world.[1] Men with newly diagnosed PCa are often assigned a clinical staging, which includes physical examination, prostate-specific antigen (PSA), the biopsy Gleason score as well as imaging studies. For patients who undergo radical prostatectomy (RP), additional information is obtained from histological examination of the surgically resected specimen, which forms the basis for pathologic staging. Men who do not undergo prostatectomy are not assigned a pathologic stage and treatment decisions are based on the clinical stage.

The Gleason grade for the two most prevalent differentiation patterns is combined to create the Gleason score, which is now incorporated into a newly adopted grade group system. The revised system was endorsed and accepted by the International Society of Urological Pathology (ISUP) in 2014 and then included in the World Health Organization (WHO) in 2016.[2,3] In new grade groups, tumors are separated into five categories based on the primary and secondary Gleason patterns: group 1 (Gleason score 3 + 3), group 2 (3 + 4), group 3 (4 + 3), group 4 (4 + 4, 3 + 5, or 5 + 3), and group 5 (4 + 5, 5 + 4, or 5 + 5). Previous studies have substantially proven the prognostic performance of this grading system in men who underwent radical prostatectomy[4–8] using biochemical recurrence (BCR), clinical recurrence, and overall survival (OS). Several studies also discussed the differences in the new grade groups in radiotherapy-treated[4,5,9] or conservatively treated patients.[10] A recent study published in *European Urology* demonstrated that new grade groups are associated with the risk of PCa-specific survival (CSS) and bone metastasis in nondefinitive therapy and RP-only cohort.[11] The eighth (2017) American Joint Committee on Cancer (AJCC) staging system[12,13] added the new grade groups and pretreatment PSA to the anatomic tumor-node-metastasis (TNM) staging to create prognostic stage groups for PCa, which to our knowledge, has not been validated up to now. Therefore, in our study, all-cause and PCa-specific mortality were used as the outcome to evaluate the prognostic performance of both the new grading system and AJCC staging system in conservatively treated PCa cohort.

PATIENTS AND METHODS

Study population

All patients were selected in the Surveillance, Epidemiology, and End Results (SEER) database with prostate adenocarcinoma in 2010. All men had an explicit Gleason Score of primary and secondary pattern values on needle core biopsy. Patients who underwent initial primary management with RP or radiation therapy were excluded. As more experience has been gained with Gleason grading, pathologists generally will not diagnose PCa with composite Gleason scores of 2–5.[2] Therefore, the range of composite Gleason scores was chosen as 6 (3 + 3) to 10 (5 + 5) on prostate

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biopsies. The permission to access the research data was obtained by reference number 12027-Nov2016.

Covariates

Demographic characteristics included age, race, and marital status. Clinical characteristics included preoperative PSA value, clinical T and N stages, distant metastasis, and Gleason score at biopsy. We defined prostate needle biopsy-positive rate as the number of positive cores over total needle biopsy cores. The new AJCC stage group was determined according to the AJCC Eighth Edition Cancer Staging Manual.[12,13]

Statistical analysis

Variables of **Table 1** presented as medians (interquartile range, IQR) were analyzed by Mann–Whitney U-test and percentages were analyzed by Chi-squared test. The Kaplan–Meier method was used to calculate survival in PCa patients and the log-rank test was used to estimate the differences in OS and CSS probabilities. The association of the new grade groups and AJCC stage groups with OS and CSS was analyzed using the Cox proportional hazards model. Predictive accuracy calculations of the model were assessed using the Harrell's concordance index (C-index).[14] Statistical analyses were performed using SPSS version 21 (IBM, Chicago, IL, USA) and R (version 3.0.0, The R Foundation for Statistical Computing, Vienna, Austria), and a two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Data pertaining to 13 798 patients diagnosed with prostate adenocarcinoma as well as information on biopsy Gleason score and TNM stage in 2010 were extracted. A total of 2180 (15.8%) men experienced all-cause death and 771 (5.6%) experienced PCa-specific death. The baseline characteristics are summarized in **Table 1**.

Among the 13 798 patients, 7604 (55.1%) patients were assigned to grade group 1, 2347 (17.0%) were allocated to grade group 2, 1170 (8.5%) were assigned to grade group 3, 1237 (9.0%) were assigned to grade group 4, and the remaining 1440 (10.4%) were designated as grade group 5. The new grade groups were associated with age, race, and marital status, and higher grade groups were related to higher preoperative PSA, higher biopsy-positive rate, higher T stage, more lymph node metastases, and more distant visceral metastasis ($P < 0.001$). A total of 8762 (63.5%) cases could be assigned to specific AJCC stage group according to the definition.[12] Among them, 3482 (25.2%) belonged to stage group I, 548 (4.0%) belonged to IIA, 1315 (9.5%) to IIB, 879 (6.4%) to IIC, 678 (4.9%) to IIIA, 93 (0.7%) to IIIB, 618 (4.5%) to IIIC, 124 (0.9%) to IVA, and 1025 (7.4%) to IVB.

Correlation of new grade groups with OS and CSS

The mean follow-up time was 42.65 months (95% confidence interval [CI]: 42.47–42.84) and 45.40 months (95% CI: 45.28–45.52) for patients with OS and CSS, respectively. Remarkable differences concerning OS and CSS were found between each grade group ($P < 0.001$, **Figure 1**). Pairwise comparisons of prognostic grade groups were significantly different using the log-rank test (all $P < 0.001$, **Supplementary Table 1** and **2**). The 1, 2, and 3-year estimated OS rates, CSS rates, and the mean survival time for grade groups 1–5 were declining step by step, respectively (**Supplementary Table 3** and **4**).

Relative to grade group 1, all the other grade groups were closely correlated with an increased hazard of OS and CSS on univariate analyses (all $P < 0.001$, **Table 2** and **3**). After adjusting for age, preoperative PSA, needle core biopsy-positive rate, race, marital status, and clinical TNM stage, all the other grade groups remained associated with an elevated higher risk of OS and CSS (all $P < 0.001$, **Table 2** and **3**). However, the multivariable prognostic model based on the new five-tier grade groups failed to provide a better predictive accuracy than the old classification (improvements of C-index <0.01, **Table 4**).

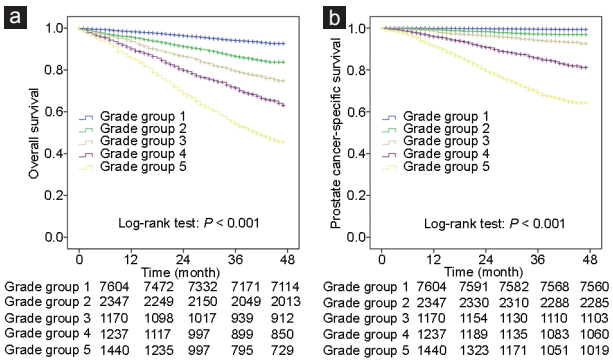


Figure 1: The Kaplan–Meier plot of (**a**) overall survival and (**b**) prostate cancer-specific survival stratified by the new grade groups.

Correlation of new AJCC stage groups with OS and CSS

The mean follow-up time was 42.06 months (95% CI: 41.82–42.30) and 44.87 months (95% CI: 44.71–45.04) for patients with OS and CSS, respectively. Remarkable differences on OS and CSS were observed between the new AJCC stage groups ($P < 0.001$, **Figure 2**). Pairwise comparisons of prognostic AJCC stage groups were significantly different in OS with the exception of stage group IIIA versus Group IIIB ($P = 0.058$), IIIA versus IVA ($P = 0.296$), IIIB versus IIIC ($P = 0.832$), IIIB versus IVA ($P = 0.455$), and IIIC versus IVA ($P = 0.200$) (**Supplementary Table 5**) and in CSS with the exception of stage group IIA versus Group IIB ($P = 0.512$), IIA versus IIC ($P = 0.185$), IIIA versus IIIB ($P = 0.655$), and IIIC versus IVA ($P = 0.860$) (**Supplementary Table 6**). The 1, 2, and 3-year estimated OS rates, CSS rates, and the mean survival time for AJCC stage groups I–IVB were declining step by step, respectively (**Supplementary Table 7** and **8**).

Compared to stage group I, all the other stage groups were in good correlation with an incremental hazard of OS and CSS on univariate analyses (all $P \leq 0.001$, **Table 2** and **3**). After adjusting for age, race, and marital status, relative to stage group I, all the other groups were still in good correlation with an increased hazard of OS and CSS (all $P \leq 0.003$, **Table 2** and **3**).

DISCUSSION

Our study shows that, in PCa men who did not receive definitive treatment for their cancer, both the new grade grouping and AJCC stage grouping system can effectively predict the risk of OS and CSS as the end point.

The Gleason grade for the two most prevalent differentiation patterns has been used to create the Gleason score and is now being used in the newly adopted grade group system, which provides a more accurate risk stratification than the current composite Gleason score.[4] Tumors are separated into five categories based on the primary and secondary Gleason patterns. Gleason 3 + 4 and 4 + 3 tumors were formally grouped as Gleason score 7. However, as these groups differ substantially in prognosis, they have now been divided into groups 2 and 3, respectively. Men with Gleason 4 + 3 tumors (where grade 4 is more prevalent than grade 3) have a less favorable outcome than those with Gleason 3 + 4 disease.[15–20] For example, a multivariate analysis of PCa men with Gleason 7 found a remarkable incremental risk of

Table 1: Association of new grade group with clinicopathological variables in the entire cohort

	All patients	*Grade group*					*P*
		1	*2*	*3*	*4*	*5*	
Total, *n* (%)	13 798 (100)	7604 (55.1)	2347 (17.0)	1170 (8.5)	1237 (9.0)	1440 (10.4)	
Age (year), median (IQR)	69 (62–76)	67 (61–73)	71 (63–78)	74 (66–81)	74 (66–81)	74 (65–81)	<0.001
Preoperative PSA (ng ml^{-1}), median (IQR)	7.1 (4.9–13.9)	5.8 (4.5–8.1)	7.65 (5.2–13.2)	11.3 (6.2–27.3)	19.55 (8.8–67.2)	40.95 (14.65–98)	<0.001
Needle core biopsy-positive rate, median (IQR)	0.3 (0.1–0.7)	0.2 (0.1–0.3)	0.4 (0.2–0.7)	0.5 (0.3–0.8)	0.7 (0.4–1.0)	1.0 (0.7–1.0)	<0.001
Race, *n* (%)							
White	9771 (70.8)	5573 (57.0)	1566 (16.0)	788 (8.1)	831 (8.5)	1013 (10.4)	<0.001
Black	1996 (14.5)	891 (44.6)	421 (21.1)	207 (10.4)	221 (11.1)	256 (12.8)	
Other	674 (4.9)	339 (50.3)	97 (14.4)	60 (8.9)	83 (12.3)	95 (14.1)	
Marital status, *n* (%)							
Single	1371 (9.9)	666 (48.6)	261 (19.0)	111 (8.1)	138 (10.1)	195 (14.2)	<0.001
Married	6331 (45.9)	3675 (58.0)	962 (15.2)	494 (7.8)	523 (8.3)	677 (10.7)	
Divorced/separated	977 (7.1)	517 (52.9)	162 (16.6)	89 (9.1)	93 (9.5)	116 (11.9)	
Widowed	583 (4.2)	194 (33.3)	106 (18.2)	74 (12.7)	91 (15.6)	118 (20.2)	
Clinical T stage, *n* (%)							
T1	7045 (51.1)	4494 (63.8)	1154 (16.4)	498 (7.1)	460 (6.5)	439 (6.2)	<0.001
T2	4893 (35.5)	2397 (49.0)	909 (18.6)	493 (10.1)	514 (10.5)	580 (119)	
T3	297 (2.2)	10 (3.4)	26 (8.8)	35 (11.8)	71 (23.9)	155 (52.2)	
T4	174 (1.3)	0	14 (8.0)	18 (10.3)	40 (23.0)	102 (58.6)	
Tx	1389 (10.1)	703 (50.6)	244 (17.6)	126 (9.1)	152 (10.9)	164 (11.8)	
Lymph node status, *n* (%)							
N0	11 509 (82.3)	6683 (58.1)	1996 (17.3)	955 (8.3)	927 (8.1)	948 (8.2)	<0.001
N1	359 (2.6)	4 (1.1)	12 (3.3)	40 (11.1)	91 (25.3)	212 (59.1)	
Nx	1930 (13.8)	917 (47.5)	339 (17.6)	175 (9.1)	219 (11.3)	280 (14.5)	
M stage, *n* (%)							
M0	12 773 (92.6)	7578 (59.3)	2269 (17.8)	1078 (8.4)	985 (7.7)	863 (6.8)	<0.001
M1	1025 (7.4)	26 (2.5)	78 (7.6)	92 (9.0)	252 (24.6)	577 (56.3)	
Summary stage, *n* (%)							
Localized	11 183 (81.0)	6868 (61.4)	2005 (17.9)	910 (8.1)	779 (7.0)	621 (5.6)	<0.001
Regional	286 (2.1)	12 (4.2)	27 (9.4)	47 (16.4)	75 (26.2)	125 (43.7)	
Distant	1034 (7.5)	26 (2.5)	78 (7.5)	93 (9.0)	256 (24.8)	581 (56.2)	
Distant visceral metastasis, *n* (%)							
Bone metastasis	876 (6.3)	24 (2.7)	65 (7.4)	79 (9.0)	215 (24.5)	493 (56.3)	<0.001
Brain metastasis	3 (0.0)	0	0	1 (33.3)	0	2 (66.7)	0.014
Liver metastasis	34 (0.2)	1 (2.9)	3 (8.8)	3 (8.8)	9 (26.5)	18 (52.9)	<0.001
Lung metastasis	58 (0.4)	0	3 (5.2)	6 (10.3)	22 (37.9)	27 (46.6)	<0.001
Gleason score, *n* (%)							
3+3=6	7604 (55.1)	7604 (100)	0	0	0	0	<0.001
3+4=7	2347 (17.0)	0	2347 (100)	0	0	0	
4+3=7	1170 (8.5)	0	0	1170 (100)	0	0	
4+4=8	1134 (8.2)	0	0	0	1134 (91.7)	0	
3+5=8	79 (0.6)	0	0	0	79 (6.4)	0	
5+3=8	24 (0.2)	0	0	0	24 (1.9)	0	
4+5=9	932 (6.8)	0	0	0	0	932 (64.7)	
5+4=9	322 (2.3)	0	0	0	0	322 (22.4)	
5+5=10	186 (1.3)	0	0	0	0	186 (12.9)	
The new AJCC stage group, *n* (%)							
I	3482 (25.2)	3842 (100)	0	0	0	0	<0.001
IIA	548 (4.0)	548 (100)	0	0	0	0	
IIB	1315 (9.5)	0	1315 (100)	0	0	0	
IIC	879 (6.4)	0	0	507 (57.7)	372 (42.3)	0	
IIIA	678 (4.9)	166 (24.5)	154 (22.7)	157 (23.2)	201 (29.6)	0	
IIIB	93 (0.7)	9 (9.7)	18 (19.4)	26 (28.0)	40 (43.0)	0	
IIIC	618 (4.5)	0	0	0	0	618 (100)	
IVA	124 (0.9)	2 (1.6)	5 (4.0)	18 (14.5)	32 (25.8)	67 (54.0)	
IVB	1025 (7.4)	26 (2.5)	78 (7.6)	92 (9.0)	252 (24.6)	577 (56.3)	

AJCC: The American Joint Committee on Cancer; IQR: interquartile range; PSA: prostate-specific antigen

Table 2: Uni- and multivariate analyses of overall survival in the entire cohort

	Univariate analyses			*Multivariate analyses*		
	HR	*95% CI*	*P*	*Adjusted HR*	*95% CI*	*P*
Grade group						
1	1.000 (reference)			1.000 (reference)		
2	2.372	2.064–2.726	<0.001	1.766	1.375–2.270	<0.001
3	3.762	3.235–4.374	<0.001	2.181	1.646–2.891	<0.001
4	5.706	4.994–6.520	<0.001	2.496	1.899–3.280	<0.001
5	9.922	8.841–11.134	<0.001	3.047	2.331–3.984	<0.001
The new AJCC stage group						
I	1.000 (reference)			1.000 (reference)		
IIA	2.267	1.649–3.116	<0.001	1.816	1.275–2.586	0.001
IIB	3.143	2.517–3.924	<0.001	2.379	1.846–3.065	<0.001
IIC	4.394	3.504–5.510	<0.001	3.415	2.650–4.402	<0.001
IIIA	7.268	5.844–0.039	<0.001	5.052	3.932–6.490	<0.001
IIIB	10.395	7.128–15.161	<0.001	6.451	4.215–9.873	<0.001
IIIC	10.765	8.757–13.234	<0.001	6.905	5.417–8.802	<0.001
IVA	8.722	6.172–12.327	<0.001	7.255	5.006–10.515	<0.001
IVB	20.289	16.942–24.297	<0.001	15.853	13.010–19.317	<0.001

Adjusted HR: adjusted for age, preoperative PSA, needle core biopsy-positive rate, race, marital status, clinical TNM stage in grade groups and adjusted for age, race, marital status in the new AJCC stage groups. HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen; TNM: tumor-node-metastasis; AJCC: The American Joint Committee on Cancer

Table 3: Uni- and multivariate analyses of prostate cancer-specific survival in the entire cohort

	Univariate analyses			*Multivariate analyses*		
	HR	*95% CI*	*P*	*Adjusted HR*	*95% CI*	*P*
Grade group						
1	1.000 (reference)			1.000 (reference)		
2	4.907	3.335–7.222	<0.001	2.682	1.455–4.943	0.002
3	10.902	7.453–15.948	<0.001	3.722	1.980–6.998	<0.001
4	29.156	20.956–40.564	<0.001	5.754	3.205–10.331	<0.001
5	65.767	48.200–89.737	<0.001	7.735	4.355–13.739	<0.001
The new AJCC stage group						
I	1.000 (reference)			1.000 (reference)		
IIA	5.854	2.258–15.172	<0.001	4.753	1.769–12.774	0.002
IIB	4.391	1.901–10.145	0.001	3.746	1.577–8.898	0.003
IIC	10.011	4.585–21.858	<0.001	7.411	3.268–16.805	<0.001
IIIA	30.374	14.848–62.134	<0.001	22.481	10.760–46.967	<0.001
IIIB	36.440	13.570–97.848	<0.001	25.795	9.157–72.662	<0.001
IIIC	77.066	38.959–152.446	<0.001	46.085	22.757–93.324	<0.001
IVA	80.758	37.368–174.529	<0.001	63.360	29.005–138.405	<0.001
IVB	244.961	126.569–474.094	<0.001	181.480	93.552–352.050	<0.001

Adjusted HR: adjusted for age, preoperative PSA, needle core biopsy-positive rate, race, marital status, clinical TNM stage in grade groups and adjusted for age, race, and marital status in the new AJCC stage groups. HR: hazard ratio; CI: confidence interval; PSA: prostate-specific antigen; TNM: tumor-node-metastasis; AJCC: The American Joint Committee on Cancer

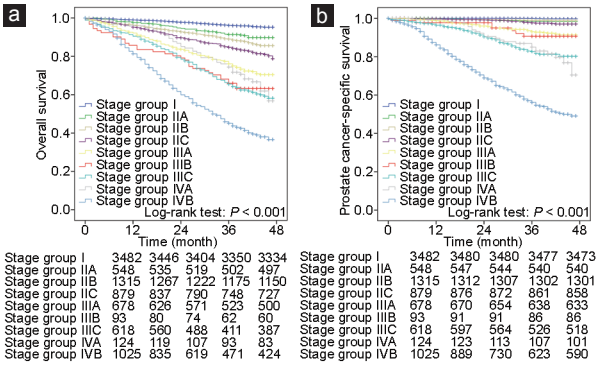
Table 4: Results of Harrell's C-index for the entire cohort with the standard three-tier Gleason groups and the new five-tier grade groups

	C-index[*]	
	Overall survival	*Prostate CSS*
Three-tier grade groups (6 *vs* 7 *vs* 8–10)	0.795	0.907
New five-tier grade groups (6 *vs* 3+4 *vs* 4+3 *vs* 8 *vs* 9–10)	0.795	0.908

[*]Adjusted for age, preoperative PSA, needle core biopsy-positive rate, race, marital status, and clinical TNM stage. C-index: concordance index; PSA: prostate-specific antigen; TNM: tumor-node-metastasis; CSS: cancer-specific survival

seminal vesicle invasion in those with Gleason 4 + 3 disease.[21,22] The new group grading system, as discussed above, separates Gleason score 7 into grade group 2 (Gleason 3 + 4) and grade group 3 (Gleason 4 + 3) to address the different risks associated with each group. The grade group system was comprehensively validated in RP patients between 2005 and 2014. There was an increasing risk of BCR and PCa mortality with increasing grade.[10] Relative to grade group 1, hazard ratio (HR) was 1.9, 5.4, 8.0, and 11.7 in grade groups 2, 3, 4, and 5, respectively. In our study, the prognostic grade grouping system offered incremental prediction of the risk of OS and CSS with adjusted HR ranging from 1.77 to 3.05 and 2.68 to 7.74, respectively. A higher histologic grade group indicated a greater likelihood of having nonorgan-confined disease as well as a worse outcome. These results are in line with those of previous studies.

It remains unclear whether the new grade groups provide a greater predictive accuracy than the old ones. A multi-institutional validation study from European PCa men proved that the new grade groups do not improve the accuracies of prognostic models compared to the current three-tier classification.[8] Similar to previous studies,[8,23] we



	0	12	24	36	48
Stage group I	3482	3446	3404	3350	3334
Stage group IIA	548	535	519	502	497
Stage group IIB	1315	1267	1222	1175	1150
Stage group IIC	879	837	790	748	727
Stage group IIIA	678	626	571	523	500
Stage group IIIB	93	80	74	62	60
Stage group IIIC	618	560	488	411	387
Stage group IVA	124	119	107	93	83
Stage group IVB	1025	835	619	471	424

	0	12	24	36	48
Stage group I	3482	3480	3480	3477	3473
Stage group IIA	548	547	544	540	540
Stage group IIB	1315	1312	1307	1302	1301
Stage group IIC	879	876	872	861	858
Stage group IIIA	678	670	654	638	633
Stage group IIIB	93	91	91	86	86
Stage group IIIC	618	597	564	526	518
Stage group IVA	124	123	113	107	101
Stage group IVB	1025	889	730	623	590

Figure 2: The Kaplan–Meier plot of (**a**) overall survival and (**b**) prostate cancer-specific survival stratified by the new AJCC stage groups. AJCC: The American Joint Committee on Cancer.

found that, despite an independent association with OS and CSS, the new grading system failed to add more prognostic value than the old classification using concordance index, which may be explained by a short follow-up time.

The serum PSA level provides important prognostic information that is useful for determining the degree of workup required after the initial biopsy and for planning subsequent treatment. A higher baseline serum PSA is linked to an increased risk of more advanced disease as well as subsequent disease progression. The use of a combination of serum PSA level, the new grade groups, and clinical T stage allows a more reliable prediction of pathologic stage and treatment outcome. These three parameters have been incorporated into prognostic stage groups in the eighth (2017) edition of the AJCC TNM staging system. The new AJCC prognostic stage group was also evaluated in PCa men in our study for the first time, which offered increased prediction of the risk of OS and CSS with adjusted HR ranging from 1.82 to 15.85 and 4.75 to 181.48, respectively.

Limitations do exist in this study. First, the retrospective nature results in selection bias in this study. Second, the clinical staging based on needle biopsy can under- or over-estimate the extent and aggressiveness of the disease when compared to results based on a resection specimen after radical prostatectomy.[24,25] Third, a central pathologic review is lacking in SEER data, which has been proven to be important when interpreting pathology results.[26] Forth, inaccurate PSA data within SEER[27] could have a negative impact on further AJCC stage classification. Fifth, as the grade and stage of PCa patients increase, their comorbidity is also increasingly severe so as to be considered for "conservative" or no treatment. Hence, untreated patients tend to experience more noncancer-specific mortality than treated men. The lack of reporting comorbidity and competing risk reduces the credibility of this study. Sixth, PSA biochemical recurrence and metastatic recurrence rates were unavailable in this study, which would be more informative as the end point than OS and CSS, subject to a too short follow-up time (<4 years). Moreover, the effect of adjuvant hormone therapy was also not factored in this analysis, where many PCa patients would have likely received hormone therapy, especially for grade groups 4–5. Finally, there was no access to data on positive surgical margin or prostate gland volume, which are all important prognostic factors for PCa patients and may have added further clarification to this analysis.

CONCLUSION

There is a strong correlation between the new grading system and AJCC staging system with all-cause and prostate cancer-specific mortality in biopsy specimens obtained from the conservatively treated population. However, more prospective and multicenter studies are necessary to confirm and validate these findings.

AUTHOR CONTRIBUTIONS

XZH and RFX designed the study. YC collected the data. CCJ and LKH performed the statistical analysis. CC prepared the manuscript. RFX and XZH reviewed the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

Supplementary Information is linked to the online version of the paper at *Asian Journal of Andrology* website.

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; 67: 7–30.
2 Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, *et al*. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. *Am J Surg Pathol* 2016; 40: 244–52.
3 Gasparrini S, Cimadamore A, Scarpelli M, Massari F, Doria A, *et al*. Contemporary grading of prostate cancer: 2017 update for pathologists and clinicians. *Asian J Androl* 2017; 19: 1–5. [doi: 10.4103/aja.aja_24_17], [Epub ahead of print].
4 Epstein JI, Zelefsky MJ, Sjoberg DD, Nelson JB, Egevad L, *et al*. A contemporary prostate cancer grading system: a validated alternative to the Gleason score. *Eur Urol* 2016; 69: 428–35.
5 Loeb S, Folkvaljon Y, Robinson D, Lissbrant IF, Egevad L, *et al*. Evaluation of the 2015 Gleason grade groups in a nationwide population-based cohort. *Eur Urol* 2016; 69: 1135–41.
6 Spratt DE, Cole AI, Palapattu GS, Weizer AZ, Jackson WC, *et al*. Independent surgical validation of the new prostate cancer grade-grouping system. *BJU Int* 2016; 118: 763–9.
7 Djaladat H, Amini E, Xu W, Cai J, Daneshmand S, *et al*. Oncological Outcomes after radical prostatectomy for high-risk prostate cancer based on new Gleason grouping system: a validation study from university of Southern California with 3,755 cases. *Prostate* 2017; 77: 743–8.
8 Mathieu R, Moschini M, Beyer B, Gust KM, Seisen T, *et al*. Prognostic value of the new grade groups in prostate cancer: a multi-institutional European validation study. *Prostate Cancer Prostatic Dis* 2017; 20: 197–202.
9 Spratt DE, Jackson WC, Abugharib A, Tomlins SA, Dess RT, *et al*. Independent validation of the prognostic capacity of the ISUP prostate cancer grade grouping system for radiation treated patients with long-term follow-up. *Prostate Cancer Prostatic Dis* 2016; 19: 292–7.
10 Berney DM, Beltran L, Fisher G, North BV, Greenberg D, *et al*. Validation of a contemporary prostate cancer grading system using prostate cancer death as outcome. *Br J Cancer* 2016; 114: 1078–83.
11 Leapman MS, Cowan JE, Simko J, Roberge G, Stohr BA, *et al*. Application of a prognostic Gleason grade grouping system to assess distant prostate cancer outcomes. *Eur Urol* 2017; 71: 750–9.
12 Buyyounouski MK, Choyke PL, McKenney JK, Sartor O, Sandler HM, *et al*. Prostate cancer – Major changes in the American joint committee on cancer eighth edition cancer staging manual. *CA Cancer J Clin* 2017; 67: 245–53.
13 Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, *et al*. AJCC Cancer Staging Manual. Switzerland: Springer; 2017.
14 Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996; 15: 361–87.
15 Tollefson MK, Leibovich BC, Slezak JM, Zincke H, Blute ML. Long-term prognostic significance of primary Gleason pattern in patients with Gleason score 7 prostate cancer: impact on prostate cancer specific survival. *J Urol* 2006; 175: 547–51.
16 Kang DE, Fitzsimons NJ, Presti JC, Kane CJ, Terris MK, *et al*. Risk stratification of men with Gleason score 7 to 10 tumors by primary and secondary Gleason score: results from the SEARCH database. *Urology* 2007; 70: 277–82.
17 Burdick MJ, Reddy CA, Ulchaker J, Angermeier K, Altman A, *et al*. Comparison of biochemical relapse-free survival between primary Gleason score 3 and primary Gleason score 4 for biopsy Gleason score 7 prostate cancer. *Int J Radiat Oncol Biol Phys* 2009; 73: 1439–45.
18 Stark JR, Perner S, Stampfer MJ, Sinnott JA, Finn S, *et al*. Gleason score and lethal prostate cancer: does 3 + 4 = 4 + 3. *J Clin Oncol* 2009; 27: 3459–64.
19 Wright JL, Salinas CA, Lin DW, Kolb S, Koopmeiners J, *et al*. Prostate cancer specific mortality and Gleason 7 disease differences in prostate cancer outcomes between

cases with Gleason 4 + 3 and Gleason 3 + 4 tumors in a population based cohort. *J Urol* 2009; 182: 2702–7.
20 Koontz BF, Tsivian M, Mouraviev V, Sun L, Vujaskovic Z, *et al.* Impact of primary Gleason grade on risk stratification for Gleason score 7 prostate cancers. *Int J Radiat Oncol Biol Phys* 2012; 82: 200–3.
21 Vira MA, Tomaszewski JE, Hwang WT, D'Amico AV, Whittington R, *et al.* Impact of the percentage of positive biopsy cores on the further stratification of primary grade 3 and grade 4 Gleason score 7 tumors in radical prostatectomy patients. *Urology* 2005; 66: 1015–9.
22 Gonzalgo ML, Bastian PJ, Mangold LA, Trock BJ, Epstein JI, *et al.* Relationship between primary Gleason pattern on needle biopsy and clinicopathologic outcomes among men with Gleason score 7 adenocarcinoma of the prostate. *Urology* 2006; 67: 115–9.
23 Sun GX, Shen PF, Zhang XM, Gong J, Gui HJ, *et al.* Predictive efficacy of the 2014 international society of urological pathology Gleason grading system in initially diagnosed metastatic prostate cancer. *Asian J Androl* 2017; 19: 573–8.
24 Caster JM, Falchook AD, Hendrix LH, Chen RC. Risk of pathologic upgrading or locally advanced disease in early prostate cancer patients based on biopsy Gleason score and PSA: a population-based study of modern patients. *Int J Radiat Oncol Biol Phys* 2015; 92: 244–51.
25 Winters BR, Wright JL, Holt SK, Lin DW, Ellis WJ, *et al.* Extreme Gleason upgrading from biopsy to radical prostatectomy: a population-based analysis. *Urology* 2016; 96: 148–55.
26 Netto GJ, Eisenberger M, Epstein JI. Interobserver variability in histologic evaluation of radical prostatectomy between central and local pathologists: findings of TAX 3501 multinational clinical trial. *Urology* 2011; 77: 1155–60.
27 Sun M, Trinh QD. A surveillance, epidemiology and end results (SEER) database malfunction: perceptions, pitfalls and verities. *BJU Int* 2016; 117: 551–2.

Supplementary Table 1: Pairwise comparison of new grade groups in prostate overall survival using the log-rank test

	P				
	Grade group 1	*Grade group 2*	*Grade group 3*	*Grade group 4*	*Grade group 5*
Grade group 1	—	<0.001	<0.001	<0.001	<0.001
Grade group 2	<0.001	—	<0.001	<0.001	<0.001
Grade group 3	<0.001	<0.001	—	<0.001	<0.001
Grade group 4	<0.001	<0.001	<0.001	—	<0.001
Grade group 5	<0.001	<0.001	<0.001	<0.001	—

Supplementary Table 2: Pairwise comparison of new grade groups in prostate cancer-specific survival using the log-rank test

	P				
	Grade group 1	*Grade group 2*	*Grade group 3*	*Grade group 4*	*Grade group 5*
Grade group 1	—	<0.001	<0.001	<0.001	<0.001
Grade group 2	<0.001	—	<0.001	<0.001	<0.001
Grade group 3	<0.001	<0.001	—	<0.001	<0.001
Grade group 4	<0.001	<0.001	<0.001	—	<0.001
Grade group 5	<0.001	<0.001	<0.001	<0.001	—

Supplementary Table 3: Survival rates of new grade groups in the follow-up years and the mean overall survival time

	12 months (%)	*24 months (%)*	*36 months (%)*	*Mean survival time (95% CI)*
Grade group 1	98.2	96.3	94.1	45.297 (45.138–45.456)
Grade group 2	95.6	91.2	86.5	42.992 (42.556–43.429)
Grade group 3	93.7	86.5	79.4	40.890 (40.165–41.615)
Grade group 4	90	79.9	71.4	38.249 (37.445–39.052)
Grade group 5	85.6	68.7	54.2	33.488 (32.681–34.295)

CI: confidence interval

Supplementary Table 4: Survival rates of new grade groups in the follow-up years and the mean cancer-specific survival time

	12 months (%)	*24 months (%)*	*36 months (%)*	*Mean survival time (95% CI)*
Grade group 1	99.8	99.7	99.5	46.849 (46.801–46.898)
Grade group 2	99.2	98.3	97.2	46.198 (45.989–46.406)
Grade group 3	98.6	96.3	94.2	45.333 (44.920–45.746)
Grade group 4	95.9	90.8	85.6	42.829 (42.223–43.435)
Grade group 5	91.4	79.5	69.1	38.210 (37.465–38.955)

CI: confidence interval

Supplementary Table 5: Pairwise comparison of new American Joint Committee on Cancer Stage groups in prostate overall survival using the log-rank test

	P								
	Stage group I	*Stage group IIA*	*Stage group IIB*	*Stage group IIC*	*Stage group IIIA*	*Stage group IIIB*	*Stage group IIIC*	*Stage group IVA*	*Stage group IVB*
Stage group I	—	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIA	<0.001	—	0.040	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIB	<0.001	0.040	—	0.003	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIC	<0.001	<0.001	0.003	—	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIIA	<0.001	<0.001	<0.001	<0.001	—	0.058	<0.001	0.296	<0.001
Stage group IIIB	<0.001	<0.001	<0.001	<0.001	0.058	—	0.832	0.455	<0.001
Stage group IIIC	<0.001	<0.001	<0.001	<0.001	<0.001	0.832	—	0.200	<0.001
Stage group IVA	<0.001	<0.001	<0.001	<0.001	0.296	0.455	0.200	—	<0.001
Stage group IVB	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	—

Supplementary Table 6: Pairwise comparison of new American Joint Committee on Cancer stage groups in prostate cancer-specific survival using the log-rank test

	P								
	Stage group I	*Stage group IIA*	*Stage group IIB*	*Stage group IIC*	*Stage group IIIA*	*Stage group IIIB*	*Stage group IIIC*	*Stage group IVA*	*Stage group IVB*
Stage group I	—	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIA	<0.001	—	0.512	0.185	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIB	<0.001	0.512	—	0.014	<0.001	<0.001	<0.001	<0.001	<0.001
Stage group IIC	<0.001	0.185	0.014	—	<0.001	0.001	<0.001	<0.001	<0.001
Stage group IIIA	<0.001	<0.001	<0.001	<0.001	—	0.655	<0.001	<0.001	<0.001
Stage group IIIB	<0.001	<0.001	<0.001	0.001	0.655	—	0.047	0.060	<0.001
Stage group IIIC	<0.001	<0.001	<0.001	<0.001	<0.001	0.047	—	0.860	<0.001
Stage group IVA	<0.001	<0.001	<0.001	<0.001	<0.001	0.060	0.860	—	<0.001
Stage group IVB	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	—

Supplementary Table 7: Survival rates of new American Joint Committee on Cancer stage groups in the follow-up years and the mean overall survival time

	12 months (%)	*24 months (%)*	*36 months (%)*	*Mean survival time (95% CI)*
Stage group I	99.0	97.7	96.1	45.931 (45.746–46.116)
Stage group IIA	97.6	94.6	91.3	44.607 (43.926–45.289)
Stage group IIB	96.3	92.8	89	43.597 (43.057–44.136)
Stage group IIC	95.2	89.7	84.7	42.448 (41.716–43.180)
Stage group IIIA	92.1	83.6	76.1	39.718 (38.704–40.733)
Stage group IIIB	85.7	79.1	65.9	36.674 (33.472–39.875)
Stage group IIIC	90.5	78.5	65.5	37.156 (36.019–38.294)
Stage group IVA	95.9	86.8	74.4	39.937 (37.897–41.977)
Stage group IVB	81.3	59.9	45.1	30.502 (29.525–31.478)

CI: confidence interval

Supplementary Table 8: Survival rates of new American Joint Committee on Cancer stage groups in the follow-up years and the mean cancer-specific survival time

	12 months (%)	*24 months (%)*	*36 months (%)*	*Mean survival time (95% CI)*
Stage group I	99.9	99.9	99.8	46.948 (46.909–46.988)
Stage group IIA	99.8	99.2	98.4	46.636 (46.373–46.898)
Stage group IIB	99.8	99.4	98.9	46.690 (46.517–46.862)
Stage group IIC	99.6	99.1	97.7	46.453 (46.200–46.705)
Stage group IIIA	98.7	96	93	45.136 (44.578–45.694)
Stage group IIIB	97.7	97.7	90.6	44.807 (43.137–46.477)
Stage group IIIC	96.4	90.3	82.7	42.425 (41.556–43.294)
Stage group IVA	99.2	90.5	85	42.982 (41.374–44.591)
Stage group IVB	86.2	68.9	56.2	34.083 (33.108–35.058)

CI: confidence interval