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Original Article

Upgrade in Gleason score between biopsy and radical prostatectomy pathology indicates poor outcomes in prostate cancer

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Abstract: Gleason score (GS) plays an important role in determining the biology of prostate cancer but prognostic information is scanty. A total of 966 patients with paired biopsy and radical prostatectomy histology were enrolled from 8 academic hospitals in China from January 2005 to March 2013, with median follow-up of 53 months. Kaplan-Meier curves and multivariate models were generated to compare the GS upgrade to those in whom the Gleason score remains the same on the risk of postoperative biochemical recurrence/progression and death. Overall, 331 patients (34.26%) experienced a GS upgrade post Radical Prostatectomy (RP). We found that patients with upgraded GS experienced a significantly higher rate of biochemical recurrence/clinical progression/death/cancer-specific mortality compared to those with concordant GS (P<0.001). According to the biopsy GS, patients were divided into 3 groups (biopsy GS≤6, GS=7, and GS≥8), patients with upgraded GS suffered a significantly higher biochemical recurrence (P<0.005) than those with concordant GS in the 3 groups. In multivariate models, a change in GS was an independent predictor of biochemical recurrence (2.01 (1.45-2.80), P<0.001), progression (1.77 (1.06-2.96), P=0.003) and death (1.83 (0.83-4.04), P=0.036) in the preoperative setting only. Patients experiencing an upgrade in their GS between biopsy and post RP exhibited significantly more aggressive pathological features than corresponding concordant tumors, and a higher risk of biochemical recurrence/progression and death post RP.

Keywords: Biochemical recurrence, clinical progression, Gleason score, prostate cancer, radical prostatectomy

Introduction

An accurate assessment of the risk of tumor progression and metastases within the lifetime of the patient is crucial to optimal management of localized prostate cancer [1]. Estimated risk may also affect the decision of technical treatments, such as a decision to nerve-spare during radical prostatectomy or the duration of androgen deprivation therapy with external beam radiotherapy [2-5].

Donald F. Gleason in 1966 created a unique grading system for prostatic carcinoma based solely on the architectural pattern of the tumor [6]. Another innovative aspect of this system was, rather than assigning the worst grade as the grade of the carcinoma, the grade was defined as the sum of the two most common grade patterns and reported as the Gleason score. The biopsy Gleason score sum (GS) is one of the most important determinants for accurately assessing risks and making informed

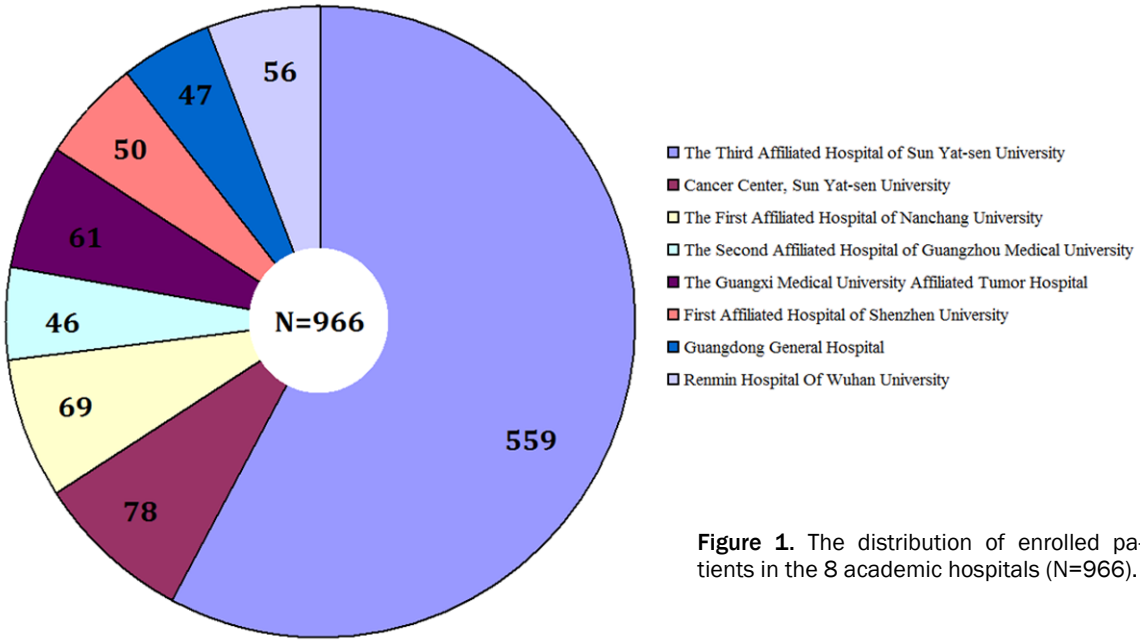

Figure 1. The distribution of enrolled patients in the 8 academic hospitals (N=966).

choices regarding treatment options in patients with prostate cancer [7, 8]. However, it has been well documented that the biopsy GS is prone to error, because it is based on the examination of a small portion of the prostate. Consequently, it is not surprising that the GS obtained after an examination of the "entire gland" often is higher than the GS examined by biopsy [9]. As Gleason score can be more accurately assessed preoperatively than other prognostic tumor features, continued effort is required to identify those most at risk of upgrading and to refine biopsy strategies to reduce sampling error [10, 11]. In 2005 and 2014, International Society of Urological Pathology (ISUP) obtained consensus in specific areas of Gleason grading, including areas where there is currently either a lack of data or scant information as to the optimal method of grading [12, 13].

It is well documented that following radical prostatectomy there is discordance in the Gleason score between the initial biopsy and the final specimen in up to 50% of patients, with the vast majority experiencing an upgrade from their initial pathology [14, 15]. Given the obvious implications, this may be useful for pretreatment decision-making, particularly for patients choosing non-surgical options. The discrepancy in Gleason score from prostate biopsy to radical prostatectomy specimen has been an interesting area of intense recent investigation [16, 17]. However, it is less clear what if any effect a change in Gleason score has upon pathological outcomes following radical prostatectomy. We therefore assessed the impact of an upgrade in Gleason score on biochemical recurrence/progression/death post radical prostatectomy.

Materials and methods

Patients

All experimental procedures involving human were in accordance with the sixth version of Declaration of Helsinki (revised 2008), and were performed in compliance with the institutional ethical guidelines for animal and human experimentation. The participants all signed the informed consent. This study was approved by the Institutional Review Board of The Third Hospital Affiliated to Sun Yat-sen University. From January 2005 and March 2013, 966 consecutive prostate cancer patients undergoing RP from 8 academic hospitals in China were enrolled (mainly in south of China). The distribution of patients in the 8 hospital was shown in **Figure 1**.

Treatment

Patients with prostate biopsies based on elevated prostate-specific antigen (PSA) levels, or abnormal digital rectal exam or clinical suspi-

Table 1. Clinicopathological characteristics of the 966 patients

Items	All patients	Concordant GS	Upgraded GS
No. of cases	966	635	331
Median age, y (range)	69 (45-85)	69 (46-85)	69 (45-83)
Median PSA (ng/ml, range)	12.06 (0.56-104.25)	11.63 (0.56-98.14)	12.86 (0.77-104.25)
No. of cores, median (range)	12 (6-24)	12 (6-24)	12 (6-24)
Positive cores, median (range)	3 (1-14)	3 (1-11)	3.5 (1-14)
6 cores (cases, percentage)	57 (5.90%)	13 (2.05%)	44 (13.29%)
8 cores (cases, percentage)	82 (8.49%)	22 (3.46%)	60 (18.14%)
10 cores (cases, percentage)	183 (18.94%)	105 (16.54%)	78 (23.56%)
12 cores (cases, percentage)	521 (53.94%)	397 (62.52%)	124 (37.46%)
>12 cores (cases, percentage)	123 (12.73%)	98 (15.43%)	25 (7.55%)
Biopsy Gleason sum n			
≤6	497 (51.45%)	328 (51.65%)	169 (51.06%)
7	328 (33.95%)	194 (30.55%)	134 (40.48%)
8-10	111 (11.49%)	89 (4.02%)	22 (6. 65%)
NA	30 (3.11%)	24 (3.78%)	6 (1.81%)
Clinical T stage n			
T1c	269 (27.86%)	186 (29.29%)	83 (25.08%)
T2a	301 (31.16%)	200 (31.50%)	101 (30.51%)
T2b	274 (28.36%)	175 (27.56%)	99 (29.91%)
T2c	107 (11.08%)	64 (10.08%)	43 (12.99%)
T3a	15 (1.54%)	10 (1.57%)	5 (1.51%)
Pathological Gleason sum n			
≤6	324 (33.54%)	310 (48.82%)	14 (4.23%)
7	443 (45.86%)	236 (37.17%)	207 (62.54%)
8-10	199 (20.60%)	89 (14.01%)	110 (33.23%)
Pathological T stage n			
T2a	194 (20.08%)	140 (22.05%)	54 (16.31%)
T2b	326 (33.75%)	225 (35.43%)	101 (30.52%)
T2c	267 (27.64%)	172 (27.09%)	95 (28.70%)
≥T3a	179 (18.53%)	98 (15.43%)	81 (24.47%)
Seminal Vesicle Invasion n			
Negative	831 (86.04%)	567 (89.29%)	264 (79.76%)
Positive	97 (10.04%)	50 (7.87%)	47 (14.20%)
NA	38 (3.93%)	18 (2.84%)	20 (6.04%)
Surgical Margin n			
Negative	827 (85.61%)	561 (88.35%)	266 (80.36%)
Positive	87 (9.01%)	47 (7.40%)	40 (12.08%)
NA	52 (5.38%)	27 (4.25%)	25 (7.56%)
Lymph node invasion n			
Negative	807 (83.54%)	570 (89.76%)	237 (71.60%)
Positive	143 (14.80%)	57 (8.98%)	86 (25.98%)
NA	16 (1.66%)	8 (1.26%)	8 (2.42%)
Biochemical recurrence n	328 (33.95%)	151 (23.78%)	177 (53.47%)
Clinical progression n	144 (14.91%)	56 (8.82%)	88 (26.59%)
Death n (%)	57 (5.90%)	21 (3.31%)	36 (10.88%)
Follow-up Months, median (range)	53 (11-119)	52 (18-119)	55 (11-110)

cion of PCa were included. All patients underwent at least 6-core transrectal ultrasound-guided biopsies, and at least 6 paraffin blocks per patient and at least 20 paraffin blocks post RP were prepared. Patients receiving neo-adjuvant androgen deprivation therapy, chemotherapy or experimental agents that might interfere with the histological assessment of the radical prostatectomy specimen were excluded from analysis. Patients receiving cancer nodules puncture were excluded. In addition, patients without complete clinical information were excluded. Information regarding the Gleason score of the preoperative biopsy, the histological assessment of the surgical specimen and detailed PSA follow-up was available in all cases. All information was recorded prospectively and analyzed retrospectively.

Gleason score evaluation

The final analysis of GS was based on the 2005 ISUP Gleason Grading of Prostatic Carcinoma [12]. The protocol for processing surgical specimens was consistent over the years of the study. The prostate was step-sectioned with 3-mm to 5-mm intervals. All sections were embedded for analysis. The biopsy and postoperative RP paraffin blocks were available for analysis and all corresponding hematoxylin and eosin-stained and immunostaining slides were reviewed. All slides were reviewed by two independent urological pathologists. Preoperative analysis was performed. In cases in which the review diagnosis differed from the diagnosis at the source institution, the samples were further reviewed by another two urological pathologist (J. Wang and H.J. Shi), who acted as arbiters. Then, the GS in biopsy and postoperative RP were compared.

Patients were categorized as concordant if there was agreement in Gleason score between prostate biopsy and radical prostatectomy, and discordant if there was not. Data on continuous variables are presented as means or medians with their respective ranges, and differences between groups were analyzed with Student's t test. Differences between categorical variables were determined using Pearson's chi-squared test or Fisher's exact test as appropriate. To determine differences in biochemical recurrence/progression/death-free survival between groups, Kaplan-Meier curves were generated and compared using the log-rank test. For this analysis, biochemical recurrence was defined as any postoperative PSA≥0.2 ng/mL and rising, or a rising PSA below this level that led to the initiation of salvage therapy. For the generation of survival curves, patients without recurrence were censored at the date of their last PSA.

Statistical analysis

All data were analyzed with SPSS 18.0 (Chicago, IL, USA). All statistics were two-sided with significance considered at $P<0.05$.

Results

There were 1109 cases of patients during the investigation recruited, of which 143 cases were overestimated and 331 cases were underestimated. In the follow-up, the 143 cases were withdrawn. The remaining 966 patients met the inclusion criteria and there clinical and pathological information is listed in **Table 1**. There was overall agreement in 635 cases (57.26%), with 331 patients (29.8%) experiencing GS upgrade on final review. There were no significant differences in terms of mean age, mean PSA, frequency of clinical stages or number of cores between the concordant group and upgraded group. Consistent with the move away from traditional sextant biopsies, the median number of biopsy cores taken was 12 (6-24). A comparison of the concordance rates between Gleason sum on needle biopsy and final prostatectomy histology is shown. For patients experiencing an upgrade in Gleason score, in 76.4% (253/331) of cases this involved a change by a single Gleason point. Patients with a biopsy Gleason sum of 7 had the highest rates of agreement with final pathology, with a concordance rate of 74.0% (328/443). Of patients with Gleason 7 disease, information on the predominant pattern in both the biopsy and final histology was available in 328 cases. We found within this specific subset that there was agreement regarding the predominant Gleason grade in 207 cases, with 78 patients being upgraded from Gleason pattern 3+4 to 4+3. In contrast, patients with Gleason sum 6 or 8-10 were significantly more likely to experience a change in Gleason score. In the cohort of the present study, 22/331 (6.65%) patients had a Gleason score of 8-10 in the biopsy specimen and 110/331 (33.23%) in prostatectomy specimen. Comparison of pathological features revealed that patients with

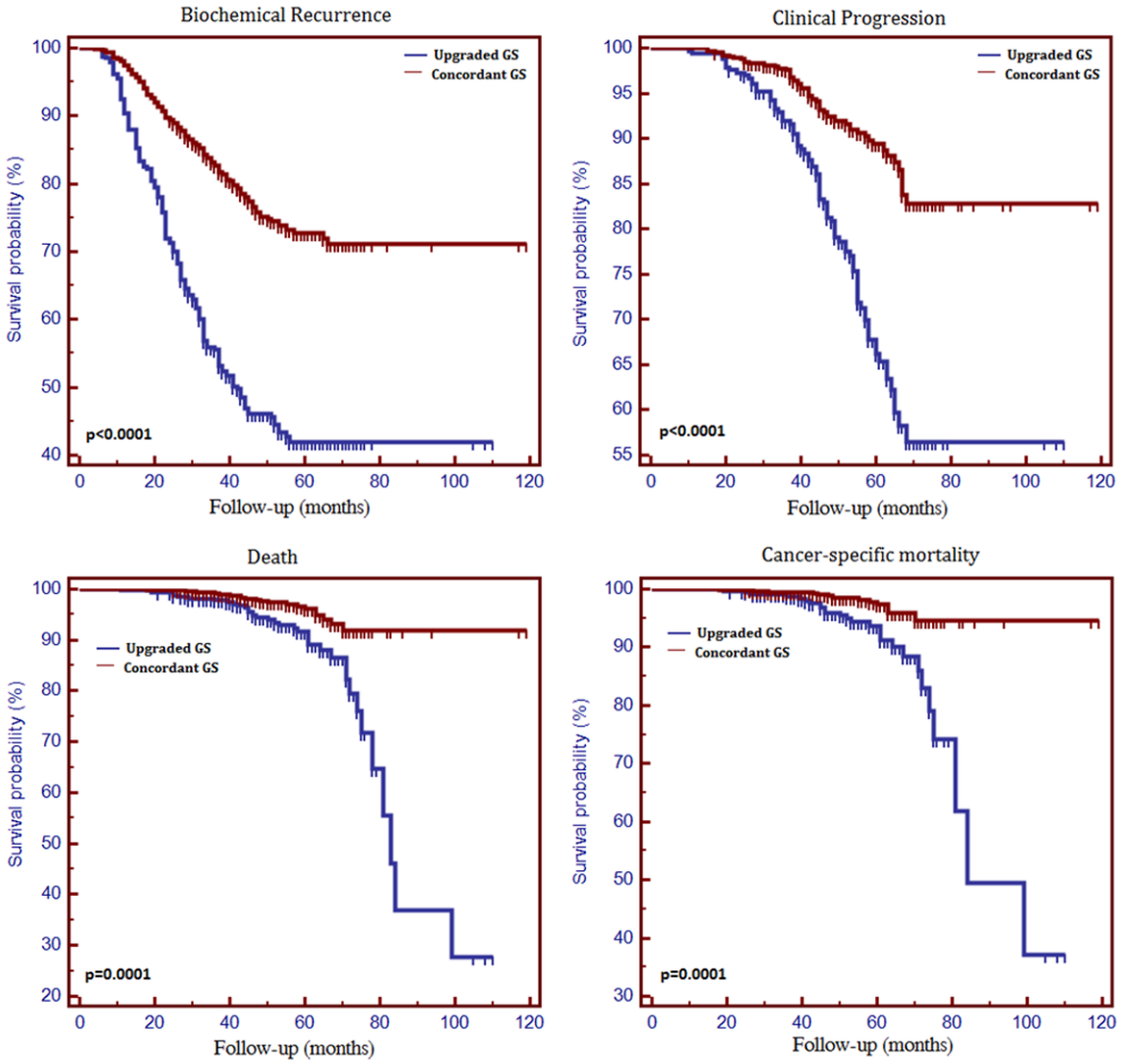

Figure 2. Kaplan-Meier curves of clinical outcomes-survival in upgraded tumors compared to corresponding concordant tumors in the total patients (N=966), 635 cases with concordant GS and 331 cases with upgraded GS.

upgraded GS were significantly more likely to have positive seminal vesicle invasion (14.20% *vs* 7.87%), surgical margin (12.08% *vs* 7.40%) and lymph node invasion (25.98% *vs* 8.98%) (P<0.05).

With regard to survival outcomes, over a median follow-up of 53 months (11-119), 328 men (33.95%), 144 men (14.91%), and 57 (5.90%) experienced a biochemical recurrence, clinical progression and death, respectively. To examine the effect of Gleason score upgrade on pathological outcomes following radical prostatectomy, we generated Kaplan-Meier curves of biochemical recurrence/clinical progression/death/specific death from PCa-survival over the entire cohort by Gleason score, and compared survival distribution with the log-rank test (**Figure 2**). We found that patients with upgraded GS experienced a significantly higher rate of biochemical recurrence compared to those with concordant GS (53.47% vs 23.78%) (P<0.001). Similar results were found in other outcomes, including clinical progression/death/cancer-specific mortality (P≤0.001).

We have recorded the number of biopsy cores for all cases, and five different groups were divided. There was a significantly higher rate of GS upgrading in patients evaluated with 6 cores (2.05% VS 13.29%) or 8 cores (3.46% VS 18.14%). However, an opposite result was

Table 2. Clinicopathological characteristics of the GS=7 (3+4→4+3) patients

Items	GS 3+4	GS 4+3
No. of cases	201	78
Median age, y (range)	69 (48-85)	68 (49-82)
Median PSA (ng/ml, range)	12.1 (0.56-54.50)	13.94 (1.96-102.74)
No. of cores, median (range)	12 (6-24)	12 (6-24)
Positive cores, median (range)	3.5 (1-14)	4 (1-11)
Clinical T stage n		
T1c	45 (22.39%)	13 (16.67%)
T2a	76 (37.81%)	24 (30.76%)
T2b	60 (29.85%)	28 (35.90%)
T2c	20 (9.95%)	13 (16.67%)
T3a	0	0
Pathological T stage n		
T2a	38 (18.91%)	9 (11.54%)
T2b	74 (36.82%)	29 (37.18%)
T2c	59 (29.35%)	32 (41.03%)
≥T3a	30 (14.92%)	8 (10.25%)
Seminal Vesicle Invasion n		
Negative	185 (92.04%)	67 (85.90%)
Positive	15 (7.46%)	9 (11.54%)
NA	1 (0.50%)	2 (2.56%)
Surgical Margin n		
Negative	180 (89.55%)	66 (84.62%)
Positive	16 (7.96%)	8 (10.25%)
NA	5 (2.49%)	4 (5.13%)
Lymph node invasion n		
Negative	178 (88.56%)	62 (79.49%)
Positive	19 (9.45%)	14 (17.95%)
NA	4 (1.99%)	2 (2.56%)
Biochemical recurrence n	46 (22.89%)	39 (50.00%)
Clinical progression n	21 (10.45%)	20 (25.64%)
Death n (%)	12 (5.97%)	6 (7.69%)
Follow-up Months, median (range)	52 (25-78)	57 (25-83)

found in patients evaluated with 12 or more biopsy cores, the rate of upgrading was lower (2.52% VS 37.46% & 15.43% VS 7.55%). In case of 10 cores, there was no significant difference between concordant GS group and upgraded GS group. These results suggested that a higher rate of under-estimate would result from less number of biopsy cores, because of the limited region selected by the biopsy.

To determine if the tumors in patients experiencing an upgrade in their Gleason scores were more closely related clinicopathologically to tumors concordant with their initial lower biopsy Gleason score or tumors concordant for the higher, upgraded, Gleason score, we performed a detailed analysis across Gleason score strata (**Table 1**). All of the patients were divided into three groups (GS≤6, GS=7, GS≥8) according to the GS by biopsy. In the GS≤6 group (N=517), there were 172 cases with upgraded GS and 345 cases with concordant GS. Tumors of Gleason 6 upgrading have a significantly higher rate of biochemical recurrence, clinical progression and death compared with Gleason 6 concordant tumors (P<0.001) (Figure S1). Over the follow-up, the tumors with upgraded GS also showed a significantly worse outcome in cancer-specific mortality than concordant GS tumors (P< 0.001). Similar analysis of Gleason 7 and Gleason 8 concordant tumors revealed that the clinical outcomes of upgraded tumors were significantly worse than concordant tumors (P≤ 0.001) (Figures S2, S3).

Interestingly, there was only a trend towards an improved positive lymph node invasion with Gleason 4+3 tumors than Gleason 3+4 concordant tumors (15.16% vs 9.69%), while not found in vesicle invasion and surgical margin (**Table 2**). Similar analysis of Gleason 7 concordant tumors revealed that the biochemical recurrence rates of upgraded 4+3 tumors were significantly worse than 3+4 concordant tumors (42.42% *vs* 24.43%, P<0.001), also worse in clinical progression (21.21% vs 11.36%, P=0.024). However, there were no significant differences in death and cancer-specific mortality comparing the Gleason 4+3 tumors and Gleason 3+4

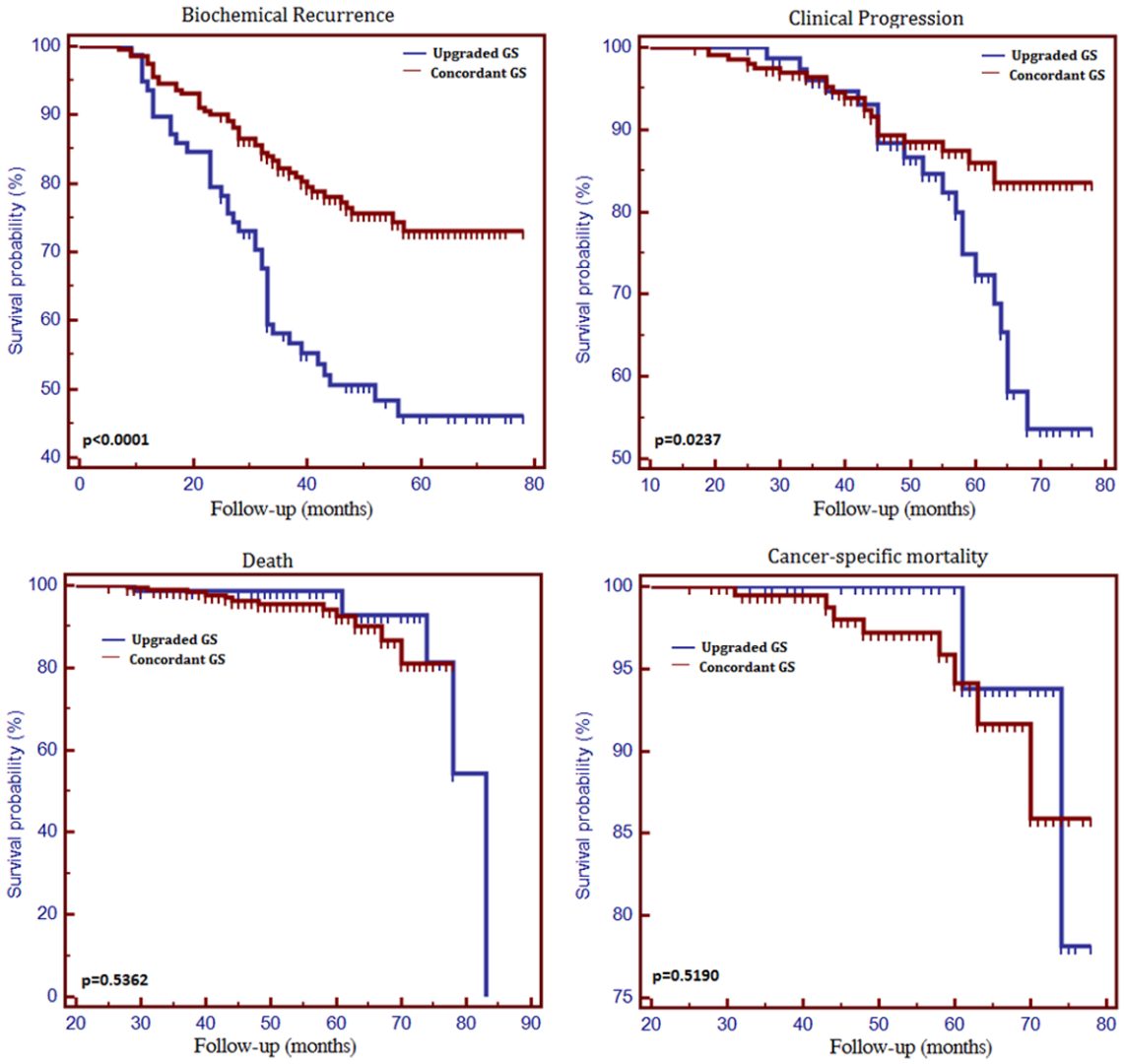

Figure 3. Kaplan-Meier curves of clinical outcomes-survival in upgraded tumors compared to corresponding concordant tumors in Gleason 3+4→4+3 (N=278), 201 cases with concordant GS and 78 cases with upgraded GS.

tumors (P=0.536 and P=0.519, respectively) (**Figure 3**).

To determine if a potential upgrade in Gleason score was a significant predictor of biochemical recurrence in the preoperative setting, we examined its ability to predict biochemical recurrence in univariate regression models along with risk stratification (**Table 3**). In each case, although a difference in Gleason score between concordant tumors was a strong and independent predictor of biochemical recurrence, while upgrade in Gleason score in discordant tumors was not. In patients with higher-risk, there was no significant difference in cancer-specific mortality between upgraded GS group and concordant GS group during the median follow-up 53 months (P=0.069).

The association of upgraded Gleason score and clinicopathological variables with clinical outcomes was examined by generating univariate and multivariate Cox proportional hazard models (Table S1). To determine if a potential change in Gleason score was a significant predictor of biochemical recurrence in the preoperative setting, we examined its ability to predict biochemical recurrence/progression/death in univariate and multivariate regression models along with established predictors of outcome including clinical stage, pathological stage, preoperative PSA, Gleason score strata

Table 3. Preoperative risk stratification of the patients

Items	All patients	Upgraded GS	Concordant GS
No. of cases	966	331	635
Risk stratification n (%)			
Low risk	123 (12.73%)	42 (12.69%)	81 (12.76%)
Intermediate risk	554 (57.35%)	186 (56.19%)	368 (57.95%)
High risk	289 (29.92%)	103(31.12%)	186 (29.29%)

and GS change. We found that across all Gleason score strata an upgraded GS in on final histology was a significant independent predictor of postoperative outcomes.

Discussion

In this study, the coincidence of GS in biopsy and pathology was 57.26%, with an overestimate rate of 12.89% and an underestimate rate of 29.85%. In Epstein's report, there were only 6 cases with Gleason 5 in 7643 patients, the rest with Gleason≥6 based on the 2005 ISUP system. The concordance of biopsy and post RP was only 50%, with an overestimate rate of 16% and an underestimate rate of 34%, which was similar with our results. During the evaluation of GS, it is inevitable to obtain discordance between biopsy and pathology, which may results from subjective or objective reasons, including the followings. First, the sampling sections in different angles would bring misdiagnosis. For example, a bad gland of original Gleason 3 would be misdiagnosed to Gleason 4 by biopsy; while the original cribriform glands of Gleason 4 would be misdiagnosed to Gleason 3 as the appearance of glandular lumina. Second, the Gleason score is a continuous constant, so it is ambiguous to score the gland which is intermediate between two adjacent levels. Third, the scores with low frequency in all of the samples would be easy to ignore. Fourth, PCa is a type of multifocal disease, so it is difficult to sampling all of the lesions with limited section. Fifth, in case of tertiary patterns on biopsy, it was the consensus that these tumors on needle biopsy should be graded by listing the primary pattern and highest grade, not the primary and secondary pattern. If the frequency of the highest grade is less than 5%, the grades could not be added into the Gleason sum. This could cause a discrepancy with the fact. Sixth, there is subjective tendentiousness to underestimate the GS for pathologists. It is suggested that the growth of carcinoma with different metastases is different. Briefly, poorly differentiated carcinoma (such as latent or sporadic carcinoma) grew slowly and exhibited nodule, which was an important sampling site in biopsy [19, 20]. This could result in an underestimated score. As time goes by, the proportion of poorly differentiated carcinoma with slow-growth became less and less, while well-differentiated carcinoma exhibited a quick-growth and became more and more. Therefore, the constituents of these two types of carcinoma post RP is different from those in biopsy. It is suggested to assign a professional doctor who can independently complete and accurately evaluate the biopsy in the urological department, in order to assure the coincidence in criteria. A regular familiar pathological doctor, who specializes in PCa tissue selection method, tissue section, hematoxylin-eosin (HE) staining, and and microscopic examination of organs, diagnosis through pathological analysis, is needed to do the clinicopathological analysis. Before puncture, a multifunctional MRI is useful to accurately locate the PCa lesion with high suspicious and guide the doctor for targeted biopsy [19]. These strategies would be benefit to reduce the misdiagnosis and avoid the missed diagnosis.

The results of the prostate biopsy and the surgical specimen may differ for several reasons, such as incorrect evaluation by the pathologist, sampling errors and the presence of borderline grading. Many patients undergo repeat biopsies because clinicians do not have a clear basis for stratifying individuals who need intensive follow-up and those who do not. Several studies have demonstrated that a higher number of cores, compared to the sextant biopsy, may lead to a lower percentage of upgrading. Jong analyzed the biopsy GS in low-risk prostate cancer patients, and found that higher positive cores and higher tumor percentage in cores in upgraded GS group than that in concordant GS group [21]. Capitanio evaluated the relationship between biopsy cores and the GS scores. In patients evaluated with 10-12 core biopsies, the upgrading was 47.9%, compared to 31.6 and 23.5% with 13-18 or >18 cores, respectively, with a statistically significant *P*-value, demonstrating that a larger sampling of the gland may avoid subsequent upgrading

and may help in planning an appropriate treatment approach [22]. The finding in our study was coincident with these previous reports, a lower under-estimate in GS score with the increase of positive cores, and a higher under-estimate in GS score in patients evaluated with less biopsy cores (6 cores-8 cores). Meanwhile, although the recruit patients were from different hospitals, we actually recorded the exact number of cores sampled of all our cases, we could address the relation of the number of cores sampled to predict upgrading and downgrading. The patients with 12 biopsy cores explained for 53.94% and more than 12 biopsy cores for 66.67%. The sample size of 966 was efficient to support the main finding. Meanwhile, it was found that the volumes of prostate from patients were ≤38 ml when using 6 cores or 8 cores for biopsy.

A key question for patients experiencing an upgrade in their Gleason score after RP that remains to be resolved is whether their clinical outcome is similar to that of concordant tumors. We have found that between Gleason score strata, in general, tumors in upgraded patients more closely resembled the clinico-pathological features of the higher grade concordant tumors, with a similar risk of biochemical recurrence over time. This also applied within Gleason 7 tumors, when the predominant Gleason pattern switched from 3 to 4 in the final pathology. The more critical point where the potential for Gleason score upgrade can impact upon outcome is at the time of initial diagnosis, when decisions concerning subsequent management are part influenced by the biopsy Gleason score. We showed that even adjusting for other preoperative variables including clinical stage, PSA, number of positive cores and percentage of positive cores, upgrade to a higher Gleason score remained a strong and independent predictor of biochemical recurrence after attempted local curative therapy, and this must be taken into account particularly when considering non-operative approaches.

There are still some limitations in this study. First, we studied a highly selected population, thus the findings may not be general; second, biopsy reclassification and pathology assessment may not correlate with important health outcomes, such as death from prostate cancer and freedom from metastatic disease in all cases; third, the results contain small numbers in subset analyses, although the present study presents the largest dataset to evaluate this issue to date.

In summary, we have identified that patients with an upgrade in their Gleason score between biopsy and specimen pathology have significantly more aggressive tumors and a higher risk of biochemical recurrence than patients with concordant histology. The upgrading from prostate biopsy to radical prostatectomy is an important topic of discussion and may be of significant value at the clinical level. Hence, new tools are required to predict upgrading and upstaging of our patients, in order to ensure better counseling for optimal treatment planning. Continued effort is required to identify patients most at risk and to optimize biopsy strategies to reduce sampling error.

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Disclosure of conflict interest

None.

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Supplementary information for upgrade in Gleason score between biopsy and radical prostatectomy pathology indicates poor outcomes in prostate cancer

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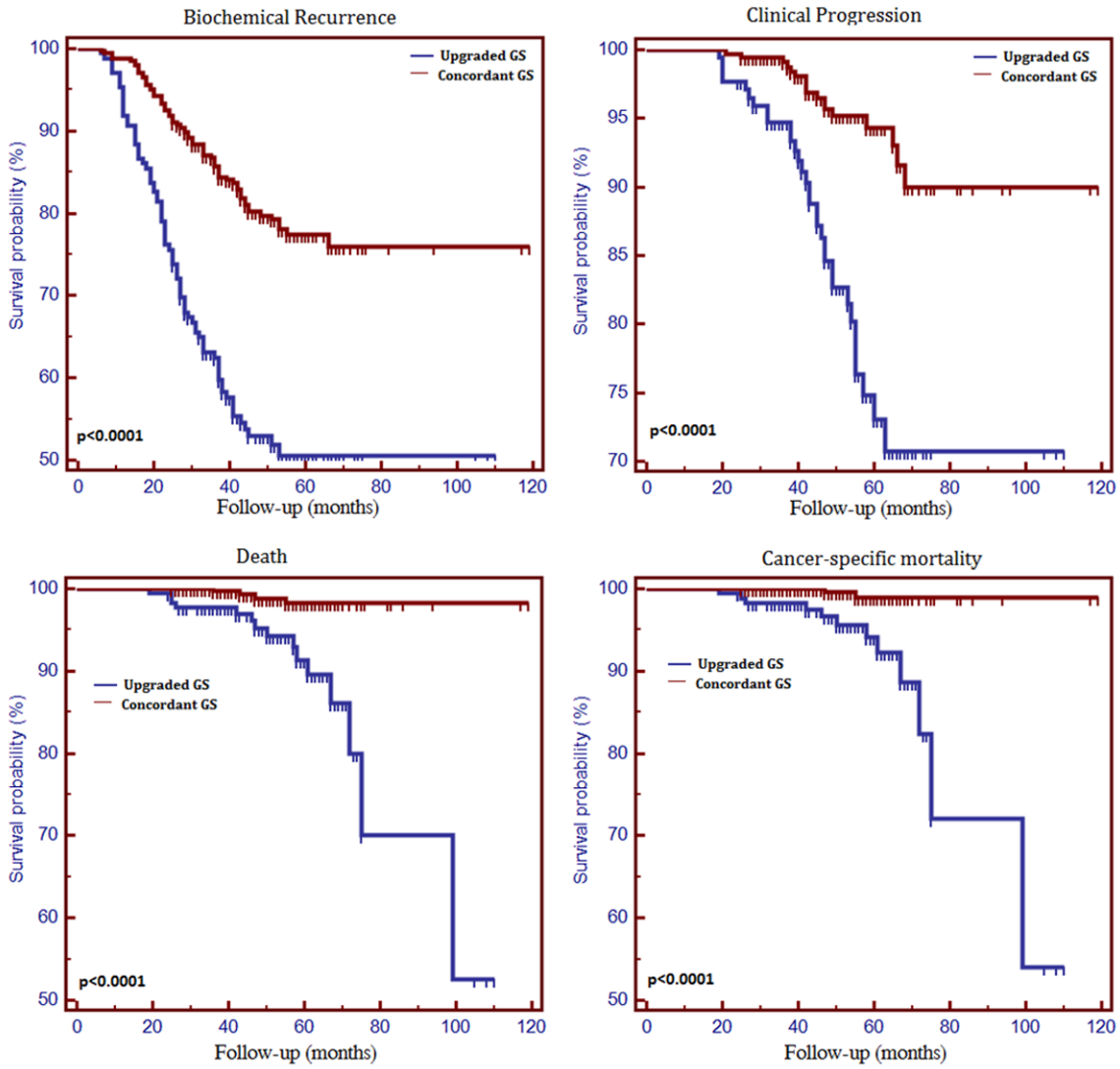

Figure S1. Kaplan-Meier curves of clinical outcomes-survival in upgraded tumors compared to corresponding concordant tumors in patients of Gleason 6 at biopsy (N=517), 345 cases with concordant GS and 172 cases with upgraded GS.

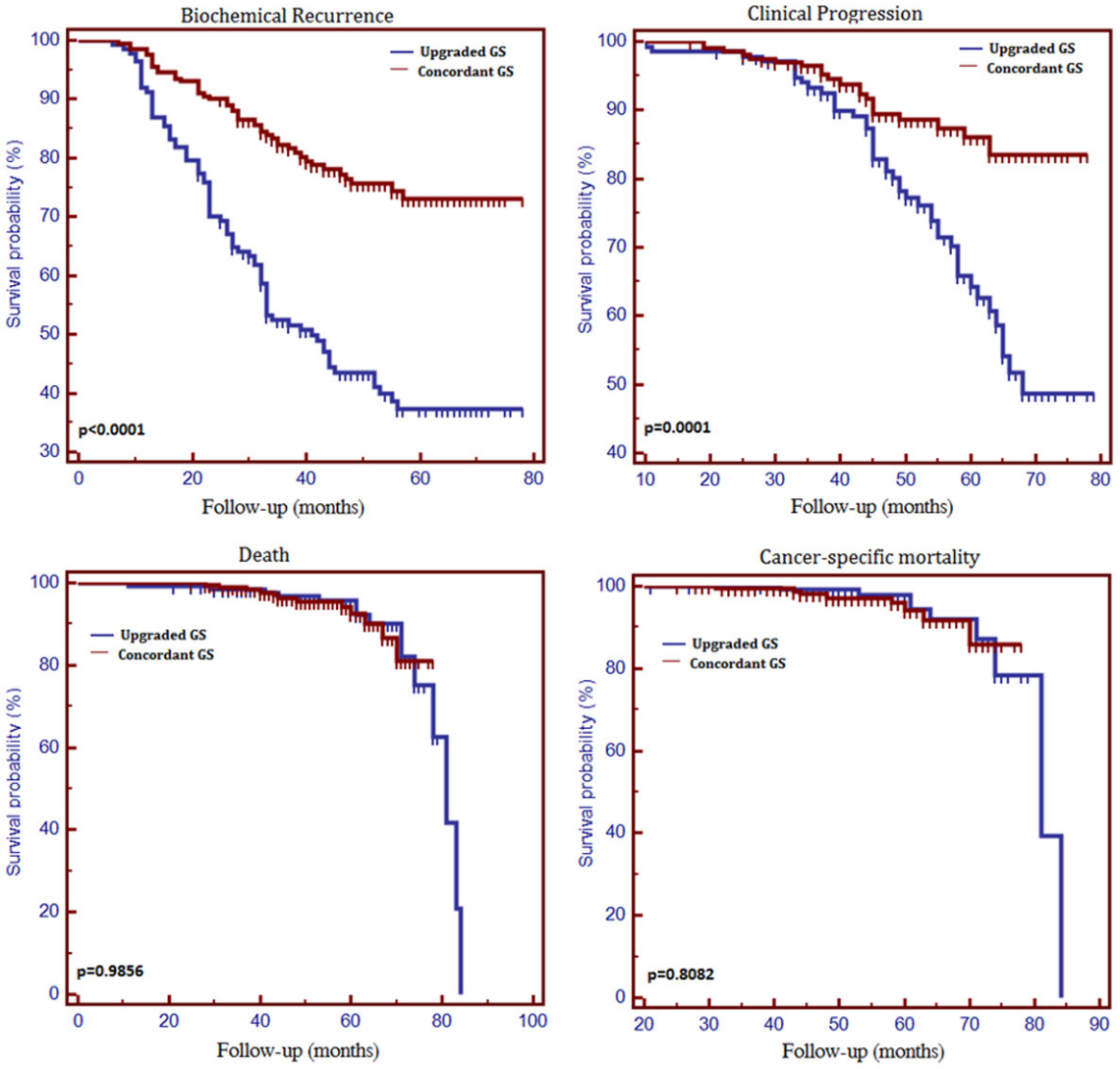

Figure S2. Kaplan-Meier curves of clinical outcomes-survival in upgraded tumors compared to corresponding concordant tumors in patients of Gleason 7 at biopsy (N=338), 201 cases with concordant GS and 137 cases with upgraded GS.

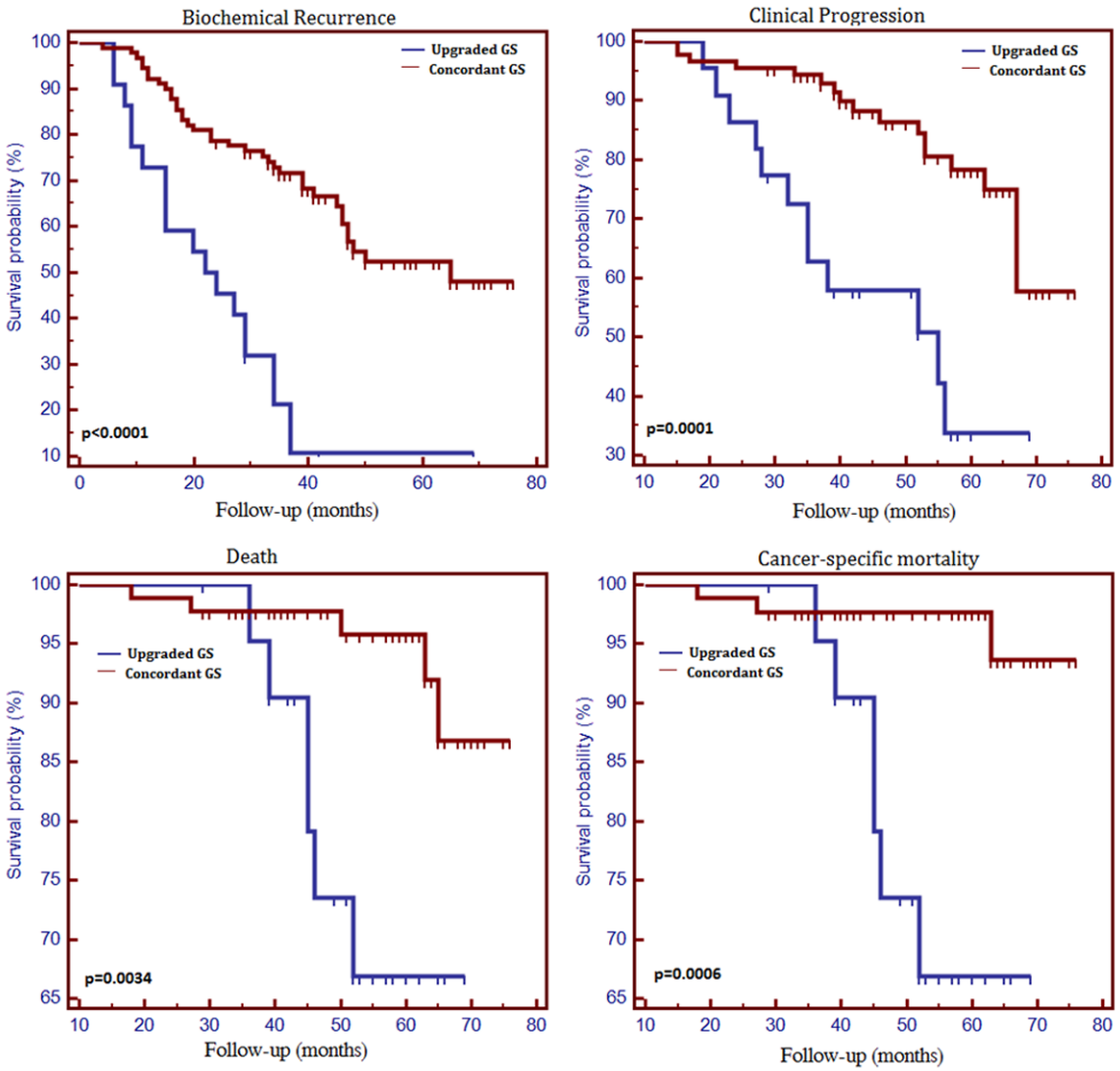

Figure S3. Kaplan-Meier curves of clinical outcomes-survival in upgraded tumors compared to corresponding concordant tumors in patients of Gleason ≥8 at biopsy (N=111), 89 cases with concordant GS and 22 cases with upgraded GS.

Table S1. Multivariate Cox Regression Analysis of Time to Biochemical Recurrence/progression/death (n=966)

Variable	Univariate analysis (BCR)			Univariate analysis (Progression)			Univariate analysis (Death)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
1<PSA<10 (ng/ml)	1.13	0.88 to 1.45	0.349	0.61	0.40 to 0.94	0.025	0.58	0.28 to 1.20	0.144
10≤PSA≤20 (ng/ml)	1.33	1.02 to 1.83	0.082	0.93	0.82 to 1.75	0.479	0.67	0.39 to 1.02	0.356
PSA>20 (ng/ml)	1.56	1.17 to 2.08	0.003	1.39	0.93 to 2.08	0.111	1.01	0.53 to 1.92	0.968
Clinical≤T2a	/	/	/	/	/	/	/	/	/
Clinical=T2b	0.99	0.77 to 1.29	0.996	1.00	0.68 to 1.49	0.981	0.6	0.31 to 1.17	0.134
Clinical≥T2c	1.03	0.74 to 1.42	0.878	1.36	0.87 to 2.14	0.178	1.05	0.52 to 2.14	0.891
Biopsy GS≤6	0.44	0.21 to 0.73	0.687	0.22	0.19 to 0.83	0.531	0.62	0.41 to 1.33	0.687
Biopsy GS=7	0.68	0.47 to 0.97	0.034	0.79	0.46 to 1.38	0.415	1.15	0.48 to 2.77	0.750
Biopsy GS≥8	1.02	0.60 to 1.78	0.930	1.07	0.47 to 2.44	0.878	1.63	0.58 to 3.91	0.259
Pathological≤T2a	0.14	0.09 to 0.23	<0.001	0.13	0.05 to 0.33	<0.001	0.08	0.02 to 0.37	0.001
Pathological=T2b	0.42	0.32 to 0.55	<0.001	0.41	0.26 to 0.64	0.001	0.24	0.11 to 0.53	0.001
Pathological≥T2c	1.23	1.06 to 2.68	<0.001	1.33	1.10 to 2.96	0.002	1.04	0.87 to 2.46	0.007
Pathological GS≤6	0.67	0.45 to 1.01	0.051	0.49	0.24 to 1.00	0.052	0.21	0.06 to 0.73	0.015
Pathological GS=7	1.12	1.06 to 1.81	0.045	0.89	0.82 to 1.45	0.058	0.7	0.29 to 1.69	0.435
Pathological GS≥8	1.65	1.14 to 2.39	0.008	1.68	1.03 to 2.93	0.041	0.95	0.53 to 1.42	0.024
Gleason Upgraded	2.01	1.45 to 2.80	<0.001	1.77	1.06 to 2.96	0.003	1.83	0.83 to 4.04	0.036