Misclassification of Gleason grade and tumor stage in Asian-American patients with low-risk prostate cancer

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Research Article

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Abstract

Purpose: To investigate the misclassification rates of Asian-American patients with low-risk prostate cancer (PCa).

Methods: Patients diagnosed with low-risk PCa treated with radical prostatectomy (RP) between 2010 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) database were included in this study. Then, basic characteristics and pathological outcomes of the enrolled patients were retrospectively extracted. We compared the rates of upgrading and/or upstaging between Asian-American patients and White/Black patients. Moreover, temporal trend analyses were performed to explore the changes in upgrading and upstaging rates in each race over time. Finally, logistic regression models were constructed to explore the role of Asian race in upgrading and upstaging and to screen out potential risk factors for predicting upgrading and upstaging in Asian-American patients.

Results: Asian-Americans had a significantly higher rate of upgrading than Whites ($P < 0.001$), while no statistical difference was found in the comparison of upstaging rate ($P = 0.536$). Moreover, Asian-Americans were more likely to upgrade to diseases with higher International Society of Urological Pathology (ISUP) grade than Whites ($P = 0.010$). The rate of upgrading increased significantly over time in White and Black patients, but not in Asian-American patients. Finally, race seemed to be an independent risk factor for predicting upgrading, while the racial differences seemed to be more pronounced between White and Black patients.

Conclusion: Asian-American patients had a significantly higher rate of upgrading than White patients. Moreover, Asian-American patients were more likely to upgrade to diseases with higher ISUP grade. Further risk assessment before clinical decision for low-risk PCa patients with the help of significant clinical variables is required.

Introduction

Prostate cancer (PCa) is one of the most common malignant tumors in the urinary system, and its incidence ranks third among all malignancies worldwide [1]. In 2021, the estimated new cases and deaths of PCa are 248,530 and 34,130 in the United States [2]. Patients can be divided into different risk groups according to prostate specific antigen (PSA), pathological outcomes at biopsy (Gleason score, number of positive cores, core ratio) and clinical T stage. Whether in European Association of Urology (EAU) or National Comprehensive Cancer Network (NCCN) clinical practice guidelines, the most recommended/preferred treatment for patients with low-risk ($PSA < 10$ ng/ml, Gleason score < 7 and clinical T1-2a) PCa is active surveillance (AS), rather than invasive radical prostatectomy (RP) or radiotherapy (www.nccn.org/patients, <https://uroweb.org/>).

In recent years, many studies have discussed the best indication of AS for PCa. Clearly, it is essential and difficult to develop strategies to balance disease progression and over treatment. Hassan et al. [3] demonstrated that 3.9% of pure Gleason score 3+3 patients experienced focal extra-prostatic

extension at RP, while Gleason score 6 was rarely associated with seminal vesicle invasion and lymph node metastasis. Sato et al. [4] found that Gleason score 3+4 patients with the highest Gleason pattern 4 < 5% had a similar risk of adverse pathology and biochemical recurrence with Gleason score 3+3 patients.

However, most references included in the clinical guidelines were from European and American countries, and most of the enrolled patients were White. To have a better understanding of the racial disparities in low-risk PCa, many studies [5, 6] have investigated the role of Black race in AS. However, the lack of high-quality, well-designed clinical trials in Asian countries makes it difficult to explore the misclassification rates of Gleason grade and tumor stage for low-risk patients. Additionally, the risk of upgrading and upstaging after RP is an important evaluation criterion for assessing whether some patients should be treated with AS. Therefore, we performed this study to explore the misclassification of Gleason grade and tumor stage in Asian patients who met the AS criteria through the Surveillance, Epidemiology, and End Results (SEER) database, so as to develop the best personalized treatment strategy for these patients.

Materials And Methods

In this study, all data were extracted from the SEER database utilizing the SEER*Stat software (Version 8.3.6; NCI). As one of the largest tumor databases in the world, the SEER registry currently covers approximately 30% of the US population. We signed the data agreement and accessed this database with the username of 10977-Nov2019. Considering the publicity of the data itself, our study was exempt from Institutional Review Board (IRB) approval.

Patient identification

Patients diagnosed with low-risk PCa from 2010 to 2015 were retrospectively identified from the SEER 18 database. All patients should meet the following criteria: (1) diagnosed with prostate adenocarcinoma with positive pathology, (2) type of reporting source was not from death certificate/autopsy only, (3) patients were treated using RP. Furthermore, the exclusion criteria were as follows: (1) patients with unknown data on some important variables, such as prostate-specific antigen (PSA) values, Gleason score on needle core biopsy/transurethral resection of prostate (TURP) and RP, clinical T stage and race, (2) patients were treated with neoadjuvant radiotherapy or chemotherapy prior to RP, (3) patients with nonstandard records in some variables.

Data extraction

Baseline characteristics of the included patients were further obtained using the "Case Listing Session" function, variables including year of diagnosis, age, race and ethnicity, clinical and pathological T stage, N stage, administration of radiotherapy and chemotherapy, radiation sequence with surgery, PSA value prior to diagnostic biopsy, Gleason score on biopsy/TURP and RP, number of cores examined, number of cores positive and so on.

Age at diagnosis was categorized into < 45, 45-64, and $\geq$ 65 years old. International Society of Urological Pathology (ISUP) 2014 grade (group) system was used to divide Gleason score into five groups systematically. Race was classified into White, Black, Asian, and other. Moreover, the Asian population was further subdivided into Chinese, Japanese, South Asian (Asian Indian, Asian Indian, or Pakistani, Pakistani) and other Asian (Filipino, Hmong, Kampuchean, Korean, Laotian, Thai, Vietnamese). Core ratio was defined as the percentage of positive cores, which was calculated by dividing the number of positive cores by the number of cores examined. According to the EAU and NCCN guidelines, patients with low-risk PCa are strongly recommended as AS candidates. Definition of low-risk PCa is PSA value < 10 ng/mL, ISUP grade 1, and cT1-2a (Table 1).

Upgrading and upstaging

In this study, upgrading was defined as at least 1 ISUP grade increase from needle biopsy/TURP ISUP grade to the final pathology at RP, and upstaging was defined as a non-organ confined tumor ($\geq$ pT3 or pN1) at RP. In addition, upgrading and/or upstaging was a combination of both.

Firstly, our study made comparisons in the rate of upgrading, upstaging, and upgrading and/or upstaging between Asian race and White/Black race, and further analyzed the specific categories of upgrading in each group. Then, we investigated the potential interaction between upgrading and upstaging. Similarly, these comparisons were conducted within different Asian populations. Subsequently, we analyzed the temporal trends of upgrading and upstaging rates, and then calculated the average annual percent change (AAPC) of each race. Additionally, a multivariate logistic regression model was developed to explore the role of Asian race in upgrading and upstaging. Lastly, uni- and multivariate logistic regression analyses were performed to screen out potential risk factors for predicting upgrading and upstaging in Asian populations.

Statistical analyses

Categorical variables were presented in the form of n (%), and chi-square test or Fisher's exact test was used to test the statistical significance of proportion differences. Continuous variables that disobey the normal distribution were displayed in the form of median (IQR), and Mann-Whitney U or Kruskal-Wallis test was applied for the statistical significance of differences. Temporal trends of upgrading/upstaging rates were examined and AAPCs were calculated using Joinpoint software (version 4.9.0.0, <https://surveillance.cancer.gov/joinpoint/>). SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) was utilized for all statistical analyses, and two-sided $P < 0.05$ was statistically significant.

Results

Basic characteristics

The flowchart of patient selection is shown in Figure 1. As shown in Table 2, a total of 20,993 patients were enrolled in this study, including 17,475 (83.24%) White patients, 2,679 (12.76%) Black patients and

839 (4.00%) Asian-American (Asian-American) patients. Asian-American patients had an older age at diagnosis than White (median: 62.0 vs. 60.0 years old, $P<0.001$) and Black (median: 62.0 vs. 57.0 years old, $P<0.001$) patients. Similarly, a higher PSA value was detected in Asian-American patients than that in White (median 5.5 vs. 5.0 ng/mL, $P<0.001$) and Black (median 5.5 vs. 5.2 ng/mL, $P<0.001$) patients. Compared with White patients, Asian-American patients had higher ISUP grade at RP ($P<0.001$). Additionally, no significant differences were found in tumor characteristics at RP between Asian-American patients and White/Black patients, such as the proportion of pathological T stage and N stage. However, Black patients seemed to have a higher proportion of clinical T1 disease than Asian-American patients (96.08% vs. 92.13%, $P<0.001$).

In Asian populations, Japanese patients had the highest age at diagnosis and PSA at diagnosis, while patients from South Asian had the lowest age and PSA at diagnosis (all $P<0.05$, Table S1). Moreover, Japanese patients had the lowest proportion of ISUP grade 1 at RP than other Asian patients ($P<0.001$). Similarly, no meaningful differences were detected in the comparisons of tumor characteristics among Asian patients (all $P>0.05$).

Upgrading and upstaging

As shown in Table 3 and Figure 2, the total rate of upgrading, upstaging and upgrading and/or upstaging was 45.73% (9,601/20,993), 9.92% (2,082/20,993) and 48.24% (10,128/20,993), respectively. Asian-American patients had significantly higher rate of upgrading than White patients (51.25% vs. 45.18%, absolute $\Delta=6.07\%$, $P=0.001$). Similarly, the rate of upgrading and/or upstaging was higher in Asian-American patients when compared with that in White patients (53.04% vs. 47.67%, absolute $\Delta=5.37\%$, $P=0.002$). However, no statistical difference was found in the comparison of upstaging rate between Asian-American and White patients (10.01 vs. 10.01, $P=0.536$). Moreover, Asian-American patients had significant higher rate of upgrading to ISUP 3-5 diseases than White (9.18% vs. 6.07%, absolute $\Delta=3.11\%$, $P<0.001$) and Black (9.18% vs. 6.72%, absolute $\Delta=2.46\%$, $P<0.001$) patients. Notably, there were no significant differences in the comparisons of upgrading or upstaging rates between Asian-American and Black patients (all $P>0.05$).

In upgraded patients, Asian-American patients were more likely to upgrade to diseases with higher ISUP grade than White patients ($P=0.010$). Moreover, no significant differences were detected in the proportions of upgrading with concomitant upstaging in Asian-American and White/Black patients ($P=0.751$ and 0.201 , respectively). Similarly, in upstaged patients, no statistically significant differences were recorded between Asian-American and White patients in the proportion of upstaging with concomitant upgrading (82.14% vs. 75.07%, $P=0.142$). However, Asian-American patients had a significant higher proportion of upstaging with concomitant upgrading than Black patients (82.14% vs. 69.48%, $P=0.024$). In addition, in patients upgraded to ISUP grade 3-5, Asian-American patients had statistically higher proportions of upgrading with concomitant upstaging than Black patients (32.47% vs. 20.00%, $P=0.031$).

In Asian population (Table S2), Japanese patients had the highest rate of upgrading (66.00%), while patients from South Asian had the lowest upgrading rate (46.09%). Meanwhile, the rate of upgrading and/or upstaging was 69.00% in Japanese patients, which was significantly higher than that in patients from South Asian (47.66%). However, no significant differences were detected regarding the proportions of upgrading with concomitant upstaging (all $P>0.05$).

Temporal trends

As shown in Figure 2, the rate of upgrading increased significantly over time in White patients (average annual percentage change [AAPC]=4.2%, 95% confidence interval [CI]=2.9%-5.4%, $P<0.01$) and Black patients (AAPC=5.5%, 95% CI=0.3%-11.1%, $P<0.01$). However, upgrading rate did not change significantly in Asian-American patients from 2010 to 2015 (AAPC=3.4%, 95% CI=-3.0%-10.2%, $P=0.2$). Additionally, the rate of upstaging rate did not change significantly over time among Asian-American patients (AAPC=20.1%, 95% CI=-1.3%-46.0%, $P=0.1$), White patients (AAPC=-2.4%, 95% CI=-5.1%-0.4%, $P=0.1$) or Black patients (AAPC=-2.3%, 95% CI=-13.0%-9.7%, $P=0.6$).

Multivariate regression analyses

Finally, a multivariate logistic regression model was developed to investigate the effect of Asian Race on upgrading and/or upstaging in patients with low risk PCa. As shown in Table 4, race ($P=0.015$) seemed to be an independent risk factor for predicting upgrading in patients with low risk PCa after being adjusted by age at diagnosis, PSA, clinical T stage, number or biopsy cores, number of positive cores and core ratio. However, the racial differences seemed to be more pronounced between White and Black patients, rather than between Asian-American and White/Black patients. Older age at diagnosis, the higher PSA, the smaller number of biopsy core and larger number of positive cores could predict a higher risk of upgrading and upstaging. Moreover, clinical T stage (OR=1.297, 95% CI=1.047-1.608, $P=0.017$) was an important risk factor for predicting upstaging in low-risk PCa patients.

Univariate logistic regression analyses revealed that race, age at diagnosis, PSA, number of biopsy cores, number of positive cores and core ratio were predictive factors for upgrading in Asian-American patients. Finally, multivariate logistic regression analyses showed that Japanese, higher PSA, smaller number of biopsy cores and larger number of positive cores were tightly associated with higher risk of upgrading (Table S3). Similarly, higher PSA and larger number of positive cores were closely related to a higher risk of upstaging in Asian-American patients (Table S4).

Discussion

Low risk PCa is often indolent, and the affected patients are more likely to die from other causes than the tumor itself. In addition, invasive RP may bring unnecessary adverse events (urinary or bowel dysfunction, impotence) to these patients and reduce their quality of life [7, 8]. Hence, AS is recommended as the preferred treatment for low-risk PCa in major clinical guidelines. However, although many studies have confirmed the clinically feasibility of AS, some problems still exist that patients with low-risk PCa

confirmed by biopsy and clinical stage always exhibit high risk of upgrading and/or upstaging after RP, and these potential unfavorable pathological characteristics may have significant adverse effects on prognosis. Moreover, many famous and influential clinical guidelines are based on the research results from European and American countries [9-11], and most of the included patients are Whites. Obviously, racial disparities could affect the tumor heterogeneity seriously in PCa [12]. Some studies [5, 6] have separately explored the different effects of AS on Black and White patients. However, there was no study has explored the misclassification of ISUP grade group and tumor stage in Asian patients. And most studies were retrospective analyses of single institute with small sample size, which cannot bring high evidence support to guide clinical practice. Hence, we developed this research to investigate the role of Asian race in upgrading and upstaging in low-risk PCa patients.

In this study, the total rate of upgrading, upstaging and upgrading and/or upstaging was 45.73%, 9.92% and 48.24%, respectively. Asian-American patients had significant higher rate of upgrading than White patients. Obviously, the statistical differences of upgrading and/or upstaging rate between Asian-American and White patients was due to the racial difference of upgrading rate. In upgraded patients, Asian patients were more likely to upgrade to diseases with higher ISUP grade than White patients. In addition, in patients upstaged or upgraded to ISUP grade 3-5, the proportions of upgrading with concomitant upstaging in Asian-American patients were significantly higher than that in Black patients.

Singh et al. [13] analysed the rate of upgrading and upstaging in Asian males with low-risk PCa, and found that the total upgrading and upstaging rate was 50.00% and 17.4%, respectively. Jeon et al. [14] explored the impact of race on the upgrading and upstaging rate in an Asian and Western cohort. They demonstrated that the rate of upstaging to pathological T3 stage was not statistically different between Asian and White patients, while Asian patients had significant higher rate of upgrading to ISUP grade 3 or higher diseases than White patients (9.1% vs. 2.7%, $P=0.003$). Another study constructed by Kim et al. [15] showed that the upgrading and upstaging rate was 50.6% and 9.3% in Asian patients with low-risk PCa, which was comparable with our study. Combined with previous study [16] and our findings, conclusions can be drawn that Asian patients had a higher upgrading rate and a comparable upstaging rate than White patients. In Asian patients, the higher risk of upgrading may be associated with the ethnic differences in cancer behavior. Asian males are confirmed to have a lower rate of testosterone when compared with White population [17], and the reduced testosterone metabolism in Asian patients may result in worse cancer outcomes.

The rate of upgrading increased significantly from 2010 to 2015 in White and Black patients, while no significant change in Asian patients over time. Meanwhile, the starting point for upgrading rate in Asian-American patients (50.46%) was significantly higher than that in Black (45.70%) and White patients (42.45%), which can also explain the higher overall upgrading rate in Asian patients. However, it seemed to be clinically meaningless for individuals to explore the temporal trends of different races. We extracted patients diagnosed from 2010 to 2015 since the latest updated data in SEER database is up to 2016 (with additional treatment fields, including radiotherapy, chemotherapy).

In our study, patients had a higher rate of upgrading no matter in which race (ranging from 45.18% to 51.25%), which meant that upgrading should be expected in 1 in 2 individuals with low-risk PCa. Moreover, Asian-American patients were more likely to upgrade to ISUP grade 3-5 diseases than White patients. The rate of upgrading to ISUP 3-5 diseases was significantly higher in Asian-American patients than that in White and Black patients. Clearly, the prognosis and tumor characteristics of ISUP grade 3-5 diseases are significantly different from that of ISUP grade 1-2 diseases. Previous study [18] found that PCa patients with ISUP grade 1-2 (99.1%–99.5%) had better 8-year PCa-specific mortality than those with ISUP grade 3-5 (85.8%–97.4%, $P<0.001$) at biopsy. Although only 77 Asian-American patients were upgraded to ISUP 3-5, this also accounted for about 10% of the total Asian population. That is to say, one in ten people upgraded to PCa with Gleason score of 4+3 or higher, which did not include some patients who did not upgrade to ISUP 3-5 but upstage to pT3+ or pN1. Therefore, many low-risk PCa Asian-American patients will upgrade to intermediate or high-risk patients after RP. In addition, in patients upgraded to ISUP grade 3-5, Asian-American patients had statistically higher proportions of upgrading with concomitant upstaging than Black patients. Taken together, our study suggested that Asian-American patients with low-risk PCa who fulfilled the AS criteria had a higher risk of upgrading than other races. Hence, it is necessary to make personalized prediction of the risk of upgrading or upstaging before clinical decision.

Multivariate logistic regression model revealed that race, age at diagnosis, PSA, number of biopsy core and number of positive cores were risk factors of upgrading in low-risk PCa patients. Nevertheless, the racial differences seemed to be more pronounced between White and Black patients, which was consistent with the study constructed by Stolzenbach et al. [5]. Some previous studies [19, 20] have already explored the relationship between older age and Gleason grade upgrading, and they reflected that an inherently more aggressive biology in older patients. Moreover, larger number of positive cores may indicate that this was a sporadic, multi-focus tumor, and the tumor stage of PCa was tightly associated with the location and extent of the lesion. In addition, many clinical variables have been explored to be risk factors of upgrading or upstaging, while the specific mechanism remains to be studied in depth. Moreover, some other variables have also been reported to be independent risk factors of upgrading after RP in low-risk PCa patients, including perineural invasion [21], prostate volume [22], PSA density [23] and so on. In Asian patients, Japanese race had a significant higher risk of upgrading than other races. However, race seemed to have no significant impact on upstaging.

In recent years, the imaging technique of PCa detection has undergone tremendous changes, mainly including transrectal ultrasound (TRUS), multi-parameter magnetic resonance imaging (mpMRI) and prostate specific membrane antigen (PSMA). It was well-known that significant discrepancies were observed in results among different imaging techniques, which were used to guide the biopsy. Wegelin et al. [24] found that MRI-guided biopsy had increased detection rates of clinically significant PCa (csPCa) than TRUS-guided biopsy. Emmett et al. [25] discovered that the combination of MRI and PSMA could reduce the false negatives for csPCa when compared with MRI alone, and reduce the number of biopsy cores required to diagnose csPCa. However, there was no data on imaging technique for biopsy in the SEER database, which was likely to lead to unavoidable selection bias. In the latest clinical guidelines, the

selection strategy of appropriate AS patient is still based on the patient's Gleason score, PSA, clinical T stage, and so on. Although there is a lack of relevant data on mpMRI in the SEER database, it does not mean that patients have not undergone mpMRI. mpMRI may also play a potentially important role in the evaluation of clinical TNM stage. However, in subsequent analyses, especially in the multivariate regression analysis, we should include relevant data of mpMRI, including the prostate imaging reporting and data system (PI-RADS) score of suspicious lesions, the location of the tumor (peripheral, transitional zone, central zone, etc.), and the effects of these factors. Inclusion could improve the accuracy of the prediction model.

To our best knowledge, there has not been any study to evaluate the role of Asian race in the upgrading and upstaging of low-risk PCa patients who fulfilled the AS strategy. Most previous studies were single-center, small sample studies, and only focused on Black and White patients. However, our study had some limitations that should not be ignored. Firstly, it was a retrospective and population-based study, and further prospective and well-designed studies are needed to validate our results. Then, some important variables are missing in the SEER database, including prostate volume, PI-RADS score, medication history, percentage of cancer in each fragment/core, and pathological data of RP (seminal vesicle invasion, extra-prostatic extension, nerve invasion and positive surgical margin). Why did the patient change from AS to active treatment? Where was the tumor located, peripheral zone, central zone or transition zone, left or right, apex or base? Moreover, our study did not explore the effect of upgrading/upstaging on biochemical recurrence or PCa-specific mortality, which might help clinicians better understand the clinical significance of upgrading.

Lastly, we have been thinking about whether Asian-American patients can represent the Asian population, this was also one of the major flaws in this study. Although these people are Asians, due to long-term living in the United States, environmental factors, living habits, and related policies (medical insurance, etc.) would have an important impact on patients. Despite this, many high-quality studies still used the SEER database to explore the race/ethnicity disparities of survival outcomes and incidence rates of cancer patients. Lim et al. [26] compared the survival differences in Chinese and White women with breast cancer in the United States using the SEER database. Stolzenbach et al. [5] discussed the grade and stage misclassification of low-risk PCa patients in Blacks and Whites. Although environmental factors affect the diagnosis and treatment of PCa, many ethnic-specific factors will always affect the characteristics of patients' tumors. For example, Asian patients have a higher tumor stage than European and American patients at the initial diagnosis. Many large-scale prospective studies in Europe and the United States also stratify analysis based on race, including many Asian patients living in Europe and the United States.

Conclusion

Patients with low-risk PCa had a high risk of misclassification regardless of race. Asian-American patients had a significantly higher rate of upgrading to ISUP 3-5 diseases than White and Black patients. Moreover, Asian-American patients were more likely to upgrade to diseases with higher ISUP grades. In

addition, Japanese patients had the highest risk of upgrading among Asian patients. Further risk assessment before clinical decision for these patients with the help of significant clinical variables is required.

Declarations

Data availability statement

Publicly available datasets were analysed in this study. This data can be found in the SEER database (<https://seer.cancer.gov/>).

Conflicts of Interest

The authors declare that there are no competing interests related to this work.

Authors' Contributions

Study design and concepts: Zicheng Xu

Data acquisition: Feng Qi and Xiao Li

Quality control of data and algorithms: Zicheng Xu and Feng Qi

Data analysis and interpretation: Wenbo Xu, Xiao Li and Qing Zou

Statistical analysis: Feng Qi and Wenbo Xu

Manuscript preparation: Feng Qi

Manuscript editing: Wenbo Xu, Zicheng Xu and Qing Zou

Manuscript review: Zicheng Xu

All authors read and approved the final manuscript and the corresponding author had final responsibility for the decision to submit for publication.

Feng Qi, Wenbo Xu and Xiao Li contributed equally to this work.

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Supplementary Materials

Table S1: Basic characteristics of Asian patients with low risk prostate cancer in the SEER database; **Table S2:** Rate of upgrading, upstaging and upgrading and/or upstaging in Asian patients; **Table S3:** Uni- and multivariate logistic regression analyses to explore risk factors of upgrading in Asian patients with low risk prostate cancer; **Table S4:** Uni- and multivariate logistic regression analyses to explore risk factors of upstaging in Asian patients with low risk prostate cancer

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Tables

Table 1: The recommended criteria of AS in prostate cancer patients

	EAU	NCCN
	Low risk PSA < 10 ng/ml	Very low risk PSA < 10 ng/ml
T stage	cT1-2a	T1c
Gleason score	Gleason score ≤6	Gleason score ≤6
Restrictions	-	<3 positive cores, ≤50% cancer in each core; PSAD <0.15 ng/ml/g
Recommendation for AS	Preferred	Preferred

AS=active surveillance; EAU=European association of Urology; NCCN=National Comprehensive Cancer Network; PSA=prostate specific-antigen; PSAD=prostate specific-antigen density.

Table 2: Basic characteristics of patients with low risk prostate cancer in the SEER database

	Race				P1	P2
	Total	White	Black	Asian		
	20,993	17,475	2,679	839		
Age at RP, y	60.0 (55-65)	60.0 (55-65)	57.0 (52-62)	62.0 (57-66)	<0.001	<0.001
Median (IQR), y	5.1 (4.2-6.4)	5.0 (4.1-6.3)	5.2 (4.3-6.5)	5.5 (4.6-6.9)	<0.001	<0.001
Initial T stage, n (%)					0.847	<0.001
	19,479 (92.79)	16,132 (92.31)	2,574 (96.08)	773 (92.13)		
	1,514 (7.21)	1,343 (7.69)	105 (3.92)	66 (7.87)		
Initial N stage, n (%)					<0.001	0.076
Grade 1	11,392 (54.27)	9,580 (54.82)	1,403 (52.37)	409 (48.75)		
Grade 2	8,283 (39.46)	6,834 (39.11)	1,096 (40.91)	353 (42.07)		
Grade 3	1,021 (4.86)	828 (4.74)	138 (5.15)	55 (6.56)		
Grade 4	203 (0.97)	150 (0.86)	35 (1.31)	18 (2.15)		
Grade 5	94 (0.45)	83 (0.47)	7 (0.26)	4 (0.48)		
Initial T stage, n					0.962	0.508
	18,851 (89.80)	15,673 (89.69)	2,424 (90.48)	754 (89.87)		
	2,039 (9.71)	1,718 (9.83)	238 (8.88)	83 (9.89)		
	22 (0.10)	17 (0.10)	5 (0.19)	0 (0.00)		
	81 (0.39)	67 (0.38)	12 (0.45)	2 (0.24)		
Initial N stage, n					0.924	0.973
	7,254 (34.55)	6,031 (34.51)	933 (34.83)	290 (34.56)		
	50 (0.24)	39 (0.22)	9 (0.34)	2 (0.24)		
	13,689 (65.21)	11,405 (65.26)	1,737 (64.84)	547 (65.20)		

Data were n (%) or median (IQR).

y=year; SEER=Surveillance, Epidemiology, and End Results; IQR=interquartile range; PSA=prostate specific antigen; ISUP=International society of urological pathology; RP=radical prostatectomy. P1: comparisons between White and Asian race; P2: comparisons between Black and Asian race.

Table 3: Rate of upgrading, upstaging and upgrading and/or upstaging

Characteristic	Race			P1	P2
	White	Black	Asian		
Total patients	17,475	2,679	839		
Upgraded	7,895 (45.18)	1,276 (47.63)	430 (51.25)	0.001	0.067
Upstaged	1,749 (10.01)	249 (9.29)	84 (10.01)	0.997	0.536
Upgraded to ISUP grade 3-5	1,061 (6.07)	180 (6.72)	77 (9.18)	<0.001	<0.001
Upgraded and/or upstaged	8,331 (47.67)	1,352 (50.47)	445 (53.04)	0.002	0.193
Type of upgrading					
To ISUP grade 2	6,834 (86.56)	1,096 (85.89)	353 (82.09)	0.010	0.105
To ISUP grade 3	828 (10.49)	138 (10.82)	55 (12.79)		
To ISUP grade 4-5	233 (2.95)	42 (3.29)	22 (5.12)		
Upgraded					
Total	7,895	1,276	430		
Without upstaging	6,582 (83.37)	1,103 (86.44)	361 (83.95)	0.751	0.201
With upstaging	1,313 (16.63)	173 (13.56)	69 (16.05)		
Upgraded to ISUP grade 2					
Total	6,834	1,096	353		
Without upstaging	5,826 (85.25)	959 (87.50)	309 (87.54)	0.236	0.986
With upstaging	1,008 (14.75)	137 (12.50)	44 (12.46)		
Upgraded to ISUP grade 3,4,5					
Total	1,061	180	77		
Without upstaging	756 (71.25)	144 (80.00)	52 (67.53)	0.487	0.031
With upstaging	305 (28.75)	36 (20.00)	25 (32.47)		
Upstaged					
Total	1,749	249	84		
Without upgrading	436 (24.93)	76 (30.52)	15 (17.86)	0.142	0.024
With upgrading	1,313 (75.07)	173 (69.48)	69 (82.14)		

Data were n (%), unless otherwise specified.

ISUP=International society of urological pathology

P1: comparison between White and Asian race; P2: comparison between Black and Asian race.

Table 4: Multivariate logistic regression models to investigate the effect of Asian Race on upgrading and/or upstaging in patients with low risk prostate cancer

	Upgrading		Upstaging		Upgrading and/or Upstaging	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
		0.015		0.677		0.015
	Reference		Reference		Reference	
	1.134 (1.019-1.262)	0.021	0.925 (0.773-1.108)	0.399	1.145 (1.028-1.274)	0.014
	1.195 (0.996-1.435)	0.055	1.030 (0.767-1.384)	0.843	1.173 (0.977-1.409)	0.088
	1.029 (1.024-1.035)	<0.001	1.029 (1.020-1.038)	<0.001	1.031 (1.025-1.036)	<0.001
	1.101 (1.079-1.124)	<0.001	1.158 (1.121-1.198)	<0.001	1.108 (1.086-1.131)	<0.001
Age	0.916 (0.798-1.053)	0.217	1.297 (1.047-1.608)	0.017	0.900 (0.784-1.034)	0.137
Free biopsy	0.979 (0.965-0.992)	0.002	0.953 (0.927-0.980)	0.001	0.974 (0.961-0.987)	<0.001
PSA positive	1.109 (1.073-1.147)	<0.001	1.190 (1.125-1.259)	<0.001	1.134 (1.096-1.173)	<0.001
	1.330 (0.917-1.930)	0.133	0.959 (0.501-1.835)	0.899	1.346 (0.923-1.964)	0.123

OR: odds ratio, CI: confidence interval, PSA: prostate specific antigen

Abbreviations

RP: radical prostatectomy; SEER: Surveillance, Epidemiological and End Results; PCa: prostate cancer; ISUP: International Society of Urological Pathology

Figures

Figure 1

Flowchart of patient selection

Figure 2

The rate of upgrading (A), upstaging (B) and upgrading and/or upstaging (C) in patients with low-risk prostate cancer

A

B

Figure 3

Temporal trends of upgrading (A) and upstaging (B) rates in patients with low-risk prostate cancer

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.doc](#)
- [TableS2.doc](#)
- [TableS3.docx](#)
- [TableS4.docx](#)