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ORIGINAL ARTICLE

Association between race and oncologic outcome following radical prostatectomy for clinically organ-confined prostate cancer: a long-term follow-up study

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Abstract

Purpose Few studies have evaluated prostate cancer oncologic outcomes in different ethnic groups following radical prostatectomy for clinically organ-confined disease. Existing studies lack long-term outcome data. We conducted this study to assess the impact of racial differences on risk profile and oncologic outcomes in a large cohort of patients with prostate cancer who underwent radical prostatectomy.

Methods Using our institutional review board-approved prostate cancer database, we retrospectively reviewed the records of 3437 patients who underwent radical prostatectomy with curative intent in our institution between 1987 and 2009. Based on ethnicity, patients were divided into Asian Americans ($n=133$), African Americans ($n=155$) and Caucasians ($n=3149$). Baseline characteristics and oncologic outcomes including biochemical recurrence free, clinical recurrence free and overall survival were compared between the study groups.

Results A total of 3437 patients with a mean age of 63 ± 9.8 years and median follow-up period of 8.7 (range 0.1–24.1) years were included in the analysis. Pathologic stage and the frequency of poorly differentiated cancer were higher in Asian Americans; however, margin status did not differ significantly. Moreover, oncologic outcomes were comparable between different ethnic groups. In multivariate analysis, both pathologic stage and grade were independent predictors of oncologic outcomes, but race was not.

Conclusions In this large, ethnically diverse long-term follow-up study, we noted that Asian Americans compared to African Americans and Caucasians are more likely to have high risk prostate cancer; however, race was not an independent predictor of oncologic outcome following radical prostatectomy with curative intent.

Keywords Ethnic groups · Prostatic neoplasms · Race · Recurrence · Survival

Introduction

Prostate cancer is one of the leading causes of cancer death in men and based on the American Society of Cancer estimates, 26,730 prostate cancer deaths are anticipated in the United States in 2017 [1]. The incidence and mortality of prostate cancer varies significantly between different races [2]. Racial disparities observed in patients with prostate cancer may be a consequence of genetic predisposition and environmental factors [3]. Some epidemiologic studies have shown that Asian and African American men may present with advanced disease [4, 5]; however, unfavorable risk profile in these ethnic groups may be related to screening behavior and/or delayed diagnosis and it is not clear whether racial differences persist on a stage-specific basis. Few reports have evaluated the impact of race on oncologic outcomes in patients with localized prostate cancer and existing studies lack long-term post-treatment follow-up data [6, 7]. Considering the indolent nature of disease, studies with long-term follow-up are imperative to see if poorer risk profile translates to worse oncologic outcome and higher mortality. In addition, studies addressing racial disparities in prostate cancer comprise patients from different centers

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and countries that make comparison difficult as radical prostatectomy is profoundly influenced by surgeon's experience and surgeon can have a substantial impact on oncologic outcomes [8]. To overcome the current limitations in the literature, we conducted a long-term single institutional study to assess the impact of racial differences on oncological outcomes in a large, ethnically diverse cohort of patients with clinically localized prostate cancer who underwent radical prostatectomy.

Materials and methods

Using our institutional review board-approved prostate cancer database, we retrospectively reviewed the records of all patients who underwent open radical prostatectomy with curative intent in our institution between 1987 and 2009. Patients with missing data of interest as well as those who underwent salvage radical prostatectomy after radiation therapy were excluded from enrollment. The final cohort consisted of 3437 patients. Based on ethnicity, patients were divided into three groups comprising Asian Americans, African Americans and Caucasians. Baseline characteristics including age and diagnostic serum prostate specific antigen (PSA) level were compared between different ethnic groups. Furthermore, to investigate the impact of racial variations on pathologic outcome after radical prostatectomy, we compared pathologic stage, Gleason score and surgical margin status across the three race groups. To ensure accurate histopathological assessment and precise staging, all radical prostatectomy specimens were embedded totally and inked up after being sent to the laboratory and read by expert GU pathologists. Following surgery, patients were followed every 4 months in the first year, every 6 months up to 5 years and annually thereafter.

Our oncologic outcomes of interest were biochemical recurrence-free survival (BCRFS), clinical recurrence-free survival (CRFS) and overall survival (OS). Patients with a rise in serum PSA level above 0.2 ng/mL threshold were considered to have biochemical recurrence. Clinical recurrence was defined as imaging and/or biopsy-proven local or systemic recurrence of disease. OS was defined as the time from the surgery to death (any cause). In the absence of an event, we censored BCRFS, CRFS and OS to the last follow-up.

Statistical analysis

Independent characteristics were compared between the study groups using frequency tables and Pearson's Chi-square or Fisher's exact test for categorical variables and analyses of variance for continuous variables. In not normally distributed variables, Wilcoxon rank sum test was used to assess differences. Kaplan–Meier plots were used to estimate the probabilities of OS and recurrence-free survivals. Cox proportional hazard models, through stepwise selection, were utilized to evaluate the independent prognostic factors for oncologic outcomes in multivariable setting. SAS, Version 9.3 (SAS Institute Inc., Cary, NC, USA) was applied to all the analyses in this study. All p values reported are two-sided and $p < 0.05$ is considered statistically significant.

Result

A total of 3437 patients with a mean age of 63 ± 9.8 years and median follow-up period of 8.7 (range 0.1–24.1) years following radical prostatectomy were eligible for analysis in this study. The study population was divided into three different ethnic groups including 133 (3.9%) Asian Americans, 155 (4.5%) African Americans and 3149 (91.6%) Caucasians. Prostate cancer was diagnosed at an older age in Asian Americans (66.1 ± 7.1) and median diagnostic PSA value was higher in this ethnic subgroup (7, IQR: 5.1–12) compared to Caucasian (6.1, IQR: 4.5–9.4) or African American patients (6.4, IQR: 4.7–12.1) ($p = 0.002$). Features of high risk prostate cancer including higher serum PSA level, poorly differentiated cancer (pathologic grade) and advanced disease (pathologic stage) were seen more frequently in Asian Americans. A higher proportion of Asian Americans revealed poorly differentiated (GS 8–10) and advanced stage disease in radical prostatectomy specimens; however, margin status and oncologic outcomes of interest did not differ significantly between the study subgroups (Table 1). Figure 1 shows Kaplan–Meier curve estimation of BCRFS, CRFS and OS stratified by race.

On multivariable analysis using Cox's regression model, different independent variables including ethnicity, age at the time of radical prostatectomy, diagnostic serum PSA level, pathological stage and Gleason score as well as adjuvant treatments were included. All variables with significant univariable test were selected for multivariable analysis. As shown in Table 2, both pathological stage and GS were independent predictors of BCRFS, CRFS and OS. Adjuvant radiation therapy was associated with higher likelihood of clinical recurrence (HR = 1.648; 95% CI 1.178–2.306), whereas adjuvant androgen deprivation therapy decreased the probability of biochemical recurrence. Baseline serum PSA level was also an independent predictor of BCRFS with no significant impact on CRFS and OS. Although Asian Americans were more likely to be diagnosed with high risk prostate cancer, race was not an independent predictor of long-term oncologic outcomes.

Table 1 Baseline patient characteristics and oncologic outcomes stratified by race

Patient characteristics	Whites ($n=3149$)	African Americans ($n=155$)	Asian Americans ($n=133$)	p value
Age (mean ± SD), year	63.0 ± 7.6	60.6 ± 7.8	66.1 ± 7.1	<0.001[a]
Diagnostic PSA level *n* (%)				
≤10	2452 (77.9)	112 (72.3)	92 (69.2)	0.004[b]
10–20	461 (14.6)	26 (16.8)	20 (15.0)	
>20	236 (7.5)	17 (10.9)	21 (15.8)	
Neoadjuvant hormone therapy	554 (17.6)	32 (20.6)	36 (27.1)	0.015[c]
Pathologic stage, *n* (%)				
≤pT2, N0	2185 (69.4)	108 (69.7)	78 (58.6)	0.040[d]
≥pT3, N0	731 (23.2)	31 (20)	44 (33.1)	
pN+	233 (7.4)	16 (10.3)	11 (8.3)	
Pathologic Gleason score, *n* (%)				
≤6	1281 (40.9)	50 (32.3)	43 (32.6)	0.001[e]
3+4	1046 (33.4)	51 (32.9)	39 (29.5)	
4+3	356 (11.4)	30 (19.3)	17 (12.9)	
8	254 (8.1)	13 (8.4)	14 (10.6)	
9–10	193 (6.2)	11 (7.1)	19 (14.4)	
Positive margins, *n* (%)	813 (25.8)	45 (29.0)	31 (23.3)	0.530
Adjuvant hormone therapy	120 (3.8)	16 (10.32)	10 (7.52)	<0.001[f]
Adjuvant radiation therapy	611 (19.4)	24 (15.5)	27 (20.3)	0.459
10-year biochemical recurrence-free survival (SE) (%)	82.6 (0.7)	84.1 (3.5)	77.0 (4.3)	0.241
10-year clinical recurrence-free survival (SE) (%)	93.4 (0.5)	91.0 (3.5)	96.3 (2.3)	0.766
10-year overall survival (SE) (%)	83.5 (0.8)	76.8 (5.3)	85.2 (4.1)	0.481

[a]Whites vs. African Americans ($p=0.004$), Whites vs. Asian Americans ($p<0.001$), Asians vs. African Americans ($p<0.001$)

[b]Whites vs. African Americans ($p=0.184$), Whites vs. Asian Americans ($p=0.002$), Asians vs. African Americans ($p=0.747$)

[c]Whites vs. African Americans ($p=0.331$), Whites vs. Asian Americans ($p=0.005$), Asians vs. African Americans ($p=0.201$)

[d]Whites vs. African Americans ($p=0.311$), Whites vs. Asian Americans ($p=0.023$), Asians vs. African Americans ($p=0.041$)

[e]Whites vs. African Americans ($p=0.027$), Whites vs. Asian Americans ($p=0.002$), Asians vs. African Americans ($p=0.193$)

[f]Whites vs. African Americans ($p<0.001$), Whites vs. Asian Americans ($p=0.032$), Asians vs. African Americans ($p=0.408$)

Discussion

In the present study, despite higher likelihood of poor risk and more advanced prostate cancer in Asian Americans, we noted comparable long-term oncologic outcome in different ethnic groups. In multivariate analysis, pathologic stage and grade were independently associated with oncologic outcomes, whereas race was not. Studies describing racial differences in outcomes after radical prostatectomy are conflicting; however, several studies addressing racial disparities in prostate cancer have shown differences in the incidence, pathologic features and oncologic outcomes [9, 6]. Both genetic predisposition and environmental factors are assumed to contribute to racial disparities in patients with prostate cancer [3, 10]. Variation in testosterone metabolism has been postulated as a potential explanation for racial disparities in prostate cancer incidence and mortality. Circulating total testosterone has been shown to be 71% higher in older Dutch whites compared to Japanese men [11]. Moreover, several studies have shown lower 5α-reductase activity in Asian population [12, 13]. In contrast, the level of circulating androgen has been shown to be higher in young healthy black men compared to whites [14]. Increased androgen level and higher proportion of susceptibility alleles in testosterone metabolism [15] may contribute to greater disease burden in African American men. However, androgen level is not the sole contributing factor as several studies including our study have shown higher frequency of poor pathological features in Asian population despite having lower androgen level. Takahashi et al. compared pathological outcomes between 159 men from United States and 211 men from Japan who underwent radical prostatectomy between 2010 and 2012 [16]. In their study, Japanese men had significantly higher Gleason scores and more advanced disease compared to US men. Lymph node metastases were also observed in 1.3% of American compared to 7.4% Japanese patients. However, there was no data on long-term oncologic outcomes in this study and comparison was

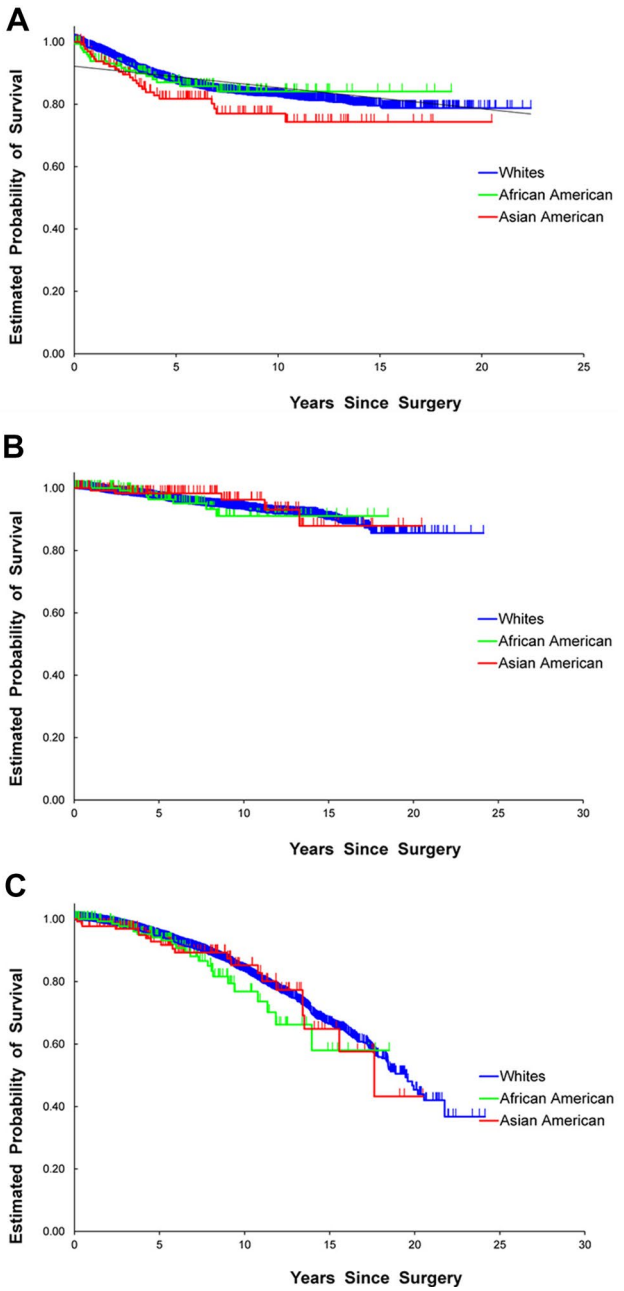

Fig. 1 Kaplan–Meier curve estimation of BCRFS (**a**), CRFS (**b**) and OS (**c**) stratified by race following radical prostatectomy

performed between two institutions from different countries. Oncologic and pathological outcomes following radical prostatectomy are highly dependent on surgical experience. In addition, pathological evaluation of radical prostatectomy specimens is associated with significant inter-observer variability; therefore, racial variations in outcomes from multicenter studies could more likely to be influenced by the center where surgery is carried out rather than ethnic background. More advanced disease in certain races might also reflect variations in screening behavior. In Takahashi et al. study, Japanese men were older by the average of 6 years compared to American patients. The observed difference in age and pathological findings could be secondary to lower prevalence of prostate cancer screening in Japan. Similarly, in a study on 90,845 men with prostate cancer using data from the California cancer registry, the authors noted that both foreign and the US born Asians as well as non-Hispanic black population were more likely to have a high risk disease compared to non-Hispanic whites [5]. This unfavorable risk profile in different subgroups of Asian American men may be related to less PSA screening in this population and consequent delayed diagnosis and does not necessarily corresponds to worse long-term oncologic outcomes and poorer survival. Even some studies have shown better survival in Asians compared to whites. In a population-based study from Surveillance, Epidemiology and End Results (SEER) program, Asians were shown to have better prostate cancer survival compared to non-Hispanic whites [17]. Robbins et al. also compared survival between White and Asian men with prostate cancer in California and showed that nearly all Asian subgroups have better survival compared to whites despite having more advanced disease and greater frequency of high grade tumors [9].

African Americans are hypothesized to suffer from more advanced and more aggressive prostate cancer with poorer oncologic outcomes and it has been mainly linked to disparities in socioeconomic status and late stage cancer diagnosis. In a population-based study, Du et al. assessed a cohort of 61,228 men with prostate cancer and showed that socioeconomic status and strong social support determine the treatment patterns and influence outcomes [18] and some studies reported comparable outcomes between African Americans and Caucasians in setting of equal access to health care [19]. However, Sundi et al. assessing 1801 men with very low risk prostate cancer showed that the disease might be more aggressive in African Americans even when diagnosed at an early stage; however, in their study, baseline characteristics including percent of positive cores and percent cancer per core differed significantly between African Americans and whites, and there was no report on long-term oncologic outcome [6]. In a similar study, Jalloh et al. assessed the impact of race on the risk of upgrading, upstaging and positive surgical margins among men eligible for active surveillance who underwent radical prostatectomy, the authors showed higher likelihood of positive surgical margins in African Americans (31%) compared to Caucasians (21%). Of note, most African American men had less comprehensive insurance coverage and were treated in community based centers. Therefore, the higher rate of positive surgical margin in African American men may be influenced by the surgeon and surgical technique rather than ethnic background. In another study from university of Pennsylvania, authors

Table 2 Cox proportional hazards of factors associated with BCRFS, CRFS and OS after radical prostatectomy

Prognostic factors	BCRFS		CRFS		OS	
	HR [95% CI]	*p* value	HR [95% CI]	*p* value	HR [95% CI]	*p* value
Race						
Caucasian	Referent		Referent		Referent	
African American	0.934 [0.589–1.482]	0.773	0.939 [0.438–2.012]	0.871	1.443 [0.939–2.218]	0.094
Asian American	1.006 [0.668–1.517]	0.976	0.567 [0.231–1.390]	0.215	0.804 [0.513–1.258]	0.339
Age						
< 65	Referent		Referent		Referent	
≥ 65	1.004 [0.843–1.196]	0.963	1.028 [0.778–1.359]	0.845	2.577 [2.167–3.065]	*< 0.001*
Diagnostic PSA						
≤ 10	Referent		Referent		Referent	
10–20	1.382 [1.106–1.728]	*0.004*	1.077 [0.746–1.555]	0.693	0.964 [0.780–1.192]	0.737
> 20	1.692 [1.308–2.190]	*< 0.001*	1.224 [0.833–1.800]	0.303	1.068 [0.836–1.365]	0.599
Pathologic Gleason score						
6	Referent		Referent		Referent	
3 + 4	1.788 [1.392–2.297]	*< 0.001*	2.446 [1.517–3.945]	*< 0.001*	1.152 [0.936–1.418]	0.183
4 + 3	1.895 [1.386–2.590]	*< 0.001*	2.295 [1.264–4.167]	*0.006*	1.023 [0.752–1.393]	0.884
8	2.241 [1.633–3.076]	*< 0.001*	4.372 [2.590–7.383]	*< 0.001*	1.451 [1.109–1.899]	*0.007*
9–10	3.294 [2.377–4.565]	*< 0.001*	5.254 [3.048–9.055]	*< 0.001*	1.895 [1.409–2.547]	*< 0.001*
Pathologic stage						
T2N0	Referent		Referent		Referent	
T3N0	2.336 [1.857–2.938]	*< 0.001*	2.015 [1.334–3.044]	*0.001*	1.258 [1.015–1.559]	*0.036*
N1	3.674 [2.729–4.947]	*< 0.001*	4.517 [2.849–7.163]	*< 0.001*	1.661 [1.243–2.221]	*0.001*
Adjuvant radiation therapy						
Not received	Referent		Referent		Referent	
Received	1.117 [0.903–1.381]	0.308	1.648 [1.178–2.306]	*0.003*	1.205 [0.982–1.478]	0.0748
Adjuvant androgen deprivation therapy						
Not received	Referent		Referent		Referent	
Received	0.555 [0.383–0.805]	*0.002*	1.056 [0.654–1.706]	0.824	1.186 [0.801–1.758]	0.394

BCRFS biochemical recurrence-free survival, *CRFS* clinical recurrence-free survival, *OS* overall survival

evaluated African American men with low risk prostate cancer and eligible for active surveillance who underwent radical prostatectomy and did not report worse outcomes in terms of positive surgical margin, disease upstaging/upgrading and biochemical recurrence compared to white patients [20]. It seems that in low risk (localized) disease, biology is comparable between different ethnic groups and observed differences might be limited to more aggressive forms of disease presenting as locally advanced or metastatic disease initially. Moreover, multimodal treatment in patients with high-risk disease has the potential to mask differences in outcomes between different ethnic groups. Interestingly, receiving adjuvant radiation therapy in addition to pathologic stage and Gleason grade was an independent predictor of clinical recurrence in our study. Selecting patients for adjuvant radiation therapy may be based on the presence of several poor prognostic features and patient conditions. Patients who receive adjuvant radiation therapies harbor more aggressive disease and a higher risk of clinical recurrence even after multimodal treatment; however, receiving adjuvant radiation therapy was not an independent predictor of OS.

Powell et al. assessing 848 consecutive patients after radical prostatectomy, found no difference in biochemical recurrence between African American and white men after a mean follow-up of 34 months. In the present study, we also did not find more aggressive disease in black men, and both CRFS and OS were comparable between African American men and other races. Although in most studies with long-term follow-up race has not been an independent factor for oncologic outcome, the controversy continues and in a recent study from Johns Hopkins University comparing radical prostatectomy outcomes in 15,993 white and 1634 African American, authors showed that race is an independent predictor of biochemical recurrence in patients with low-risk prostate cancer. After a median follow-up of 4 years, biochemical recurrence occurred more frequently among African Americans. However, they did not compare

clinical recurrence and OS between the study groups [21]. Some investigators, assessing different genes associated with prostate cancer have also shown the potential for prostate cancer molecular differences between African American and white men [22].

In the present study, we found that race did not have any impact on outcome of patients with prostate cancer treated with radical prostatectomy. The major limitation of our study was related to the small percentage of African American and Asian American population available for analysis. Moreover, pathology specimens were not re-reviewed for the purpose of this study and pathology standards changed during the time of the study as the International Society of Urological Pathology (ISUP) modified the definition of Gleason grading system in 2005. However, it should be considered that all specimens were evaluated by a few expert uropathologists from a single institution and accrual of different ethnic groups did not differ before and after 2005. Therefore, modification of Gleason grading affected all groups similarly. Older age in Asian American population could also be a confounding factor. Furthermore, results of the present study might be associated with referral bias as most of our patients were insured and presumably from high socioeconomic status with screened cancers. This could also be the strength of the study, showing that racial disparities seen in most other studies could be a consequence of socioeconomic inequalities. In addition, this study represents one of the largest cohorts of African and Asian American men who underwent homogenous surgery by a limited number of expert urologic oncologists with curative intent and a centralized pathology review. Although longer follow-up may be necessary to show differences in OS, median follow-up period of 8.7 years (up to 24 years) is the longest to date among studies addressing racial disparities in prostate cancer outcome.

Conclusions

Despite all assumed racial differences in prostate cancer aggressiveness, our results showed that patients from different ethnic groups have similar oncologic outcomes after radical prostatectomy for clinically localized prostate cancer. Although extensive studies have evaluated racial variations in prostate cancer, the exact mechanism explaining variations in the incidence and mortality is not fully understood. This is a hypothesis generating observation and undoubtedly more investigation is warranted.

Authors' contribution EA, TCP, JC and HD were involved in project development and statistical analysis. EA, GL, SD and HD were involved in manuscript writing/editing. EA, TCP, JC, GL, SD and HD were involved in data management.

Compliance with ethical standards

Conflict of interest Nothing to disclose.

Ethical approval All patients included in this study had provided informed consent.

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