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Increased Incidence of Pathologically Nonorgan Confined Prostate Cancer in African-American Men Eligible for Active Surveillance

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Abstract

OBJECTIVE—To compare the clinicopathologic findings of African-American (AA) and White-American (WA) men with prostate cancer (PCa) who were candidates for active surveillance (AS) and underwent radical prostatectomy (RP).

METHODS—Prospectively maintained database of men who underwent RP from 2 academic centers were analyzed retrospectively. Postoperative pathologic characteristics of patients who met the AS inclusion criteria of the University of California, San Francisco (UCSF) and National Comprehensive Cancer Network (NCCN) were evaluated. After RP, the rate of pathological upstaging and Gleason upgrading were compared between AA and WA men.

RESULTS—In the AA cohort, 196 and 124 men met the UCSF and NCCN criteria for AS, respectively. With respect to WA patients, 191 and 148 fulfilled the AS criteria for UCSF and NCCN, respectively. AA men had a higher percentage of maximum biopsy core than WA men (15.3%–20.4% vs 11.5%–15.0%, $P < .05$, respectively) in both cohorts. In addition, a greater proportion of AA men had multiple positive biopsy cores compared to WA men (45.2% vs 33.1%, $P = .046$) under the NCCN criteria. A higher proportion of AA men were upstaged (pT3) compared to WA men (19.4% vs 10.1%, $P = .037$). A multivariate regression test revealed that age, preoperative PSA, and number of positive cores were independent predictors of more advanced disease (upstaging and/or upgrading) in AA men.

CONCLUSION—AA men who were candidates for AS criteria had worse clinicopathological features on final surgical pathology than WA men. These results suggest that a more stringent AS criteria should be considered in AA men with prostate cancer.

African-American (AA) men have a relatively higher risk of developing prostate cancer (PCa) and dying of PCa compared to White-American (WA) men.^{1–4} Between 2004 and 2008, in the United States, the annual PCa incidence and mortality rates for AA men were 230.8 and 54.9 (per 100,000), respectively; whereas the respective rates for WA men were

142.8 and 22.4 (per 100, 000), respectively.⁵ Although the precise reason for this racial disparity is uncertain, higher tumor grade at initial diagnosis, more aggressive tumor behavior, and poorer access to care in AA men have been suggested to contribute to these differences.^{1,3,6,7}

Active surveillance (AS) is an acceptable treatment option for men with low risk PCa. However, there is reluctance among health care providers and patients in accepting AS as a viable treatment option for PCa because of the inaccuracy of clinical staging.⁸ In this regard, it has been reported that in men who are eligible for AS, the risk of nonorgan-confined disease (pathological upstaging) at radical prostatectomy (RP) ranges from 5%–13.7%.^{9–12} Because AA men tend to have a more aggressive disease at diagnosis compared to WA men,^{13,14} it is unclear whether the same AS criteria should be applied to AA men. For example, Iremashvili et al¹⁵ recently reported that AA patients on AS have a significantly higher risk of progression than their WA counterparts. In contrast, Cullen et al¹⁶ reported that there was no racial disparity in overall survival among the AS cohort. In this study, we compared the rates of upstaging and upgrading after RP between AA and WA men with very low-risk PCa that met the inclusion criteria for AS using the guidelines from the University of California, San Francisco (UCSF) and National Comprehensive Cancer Network (NCCN).

MATERIAL AND METHODS

Patients

After obtaining the Institutional Review Board approval, a retrospective analysis of a prospectively maintained database of men who underwent RP at the Johns Hopkins Medical Institutions (Baltimore, MD) and the Cancer Institute of New Jersey (New Brunswick, NJ) between 1997 and 2011 was carried out. All patients had transrectal ultrasound-guided prostate biopsy. All biopsy and radical prostatectomy specimens were reviewed by a genitourinary pathologist. Those with the total number of biopsy cores less than 12 were excluded from this study. Pathological characteristics of patients who fulfilled the inclusion criteria under the UCSF or NCCN AS criteria were examined.

UCSF criteria includes prostate-specific antigen (PSA) <10 ng/mL, biopsy Gleason sum ≤ 6 with no pattern 4 or 5, cancer involvement of $\leq 33\%$ of biopsy cores, and clinical stage T1/T2a tumor.¹⁷ NCCN criteria includes (1) life expectancy <10 years with PSA <10 ng/mL, clinical stage $\leq$ T2a, Gleason sum ≤ 6 ; or (2) life expectancy up to 20 years with PSA <10 ng/mL, clinical stage $\leq$ T2a, Gleason score ≤ 6 , fewer than 3 biopsy cores, $\leq 50\%$ positive core.¹⁸ Upstaging of PCa was defined as pathologically nonorgan-confined disease ($\geq$ pT3) and upgrading as pathologic Gleason score ≥ 7 in RP. The specimen slides were reviewed by more than 1 pathologist who specialized in uropathology in a blinded fashion.

Initial analysis of the database from the 2 institutions revealed 1536 AA men who underwent RP consecutively. Of these, 196 and 124 men met the eligibility criteria for AS based on the UCSF and NCCN criteria, respectively. For comparison to a similar number of WA patients, the data of 608 WA men who chose RP from the same time period were reviewed. This identified 191 and 143 WA men who were eligible for AS based on the UCSF and NCCN criteria, respectively.

Statistical Analysis

Differences in continuous variables were assessed using *t* test and categorical variables were compared with the chi-square test. Univariate and multivariate logistic regression was used to assess the relationship of more advanced disease after RP with preoperative parameters in

AA men. Statistical analysis was completed using SPSS version 18.0 (SPSS Inc., Chicago, IL). Any P values $<.05$ were considered significant.

RESULTS

Baseline characteristics of these patients based on the AS protocol are listed in Table 1. Under the UCSF criteria, AA men were younger than WA men (56.0 vs 59.0 , $P <.001$). In addition, the percentage of maximum positive core was significantly higher in AA men (15.3 ± 8.7 vs 11.5 ± 8.4 , $P <.001$). There was a trend for higher rate of multiple positive cores in AA men, but this did not reach statistical significance ($P = .065$). Applying the NCI criteria, AA men had a higher prevalence of multiple positive biopsy cores than WA men ($P = .046$). Simultaneously, AA men had a significantly higher percentage of maximum positive core (20.4 ± 14.6 vs 15.0 ± 13.2 , $P = .001$).

The rates of upstaging and upgrading stratified by the 2 racial groups are shown in Table 2. Among 196 AA men who met the UCSF AS criteria, 73 patients (37.2%) had advanced disease; advanced disease was defined as being upstaged and/or upgraded. The rates of upstaging and upgrading were 15.8% and 32.7%, respectively. Of the 191 WA men who met the UCSF AS criteria, 64 (33.5%) experienced upstaging and/or upgrading (upstaging 9.4%, upgrading 30.4%). Although both the rates of upstaging and upgrading using the UCSF guideline were not significantly different between AA and WA men, there was a trend for increased incidence nonorgan-confined disease in AA men ($P = .067$). Using the NCCN AS criteria, the frequency of advanced disease was 46.0% (upstaging 19.4%, upgrading 39.5%) in 124 AA patients. On the other hand, in WA patients, 39.2% had advanced disease (upstaging 10.1%, upgrading 34.5%). The incidence of upstaging was significantly higher in AA men ($P = .037$).

Table 3 shows the results of the univariate and multivariate logistic regression test in patients eligible for the UCSF AS criteria among AA men. The following 3 parameters were significantly associated with advanced disease after RP in both univariate and multivariate analyses: age, preoperative PSA, and number of positive cores. High PSA (odds ratio [OR] 1.247) and multiple positive cores at biopsy (OR 1.883) were independent predictors of advanced cancer in these AA men with a very low-risk PCa. In patients eligible for the NCCN AS protocol, only preoperative PSA was marginally related to more advanced cancer at the time of RP in univariate analysis (OR 1.171, $P = .072$). Among WA patients, positive cores (OR 2.024) in the UCSF criteria and age (OR 1.086) in the NCCN criteria were significantly associated with advanced disease (Table 4).

COMMENTS

In this study, the rate of advanced disease in AA men with very low-risk PCa based on the UCSF and NCCN guidelines ranged from 37.2%–46.0%. This overall rate of advanced disease was slightly higher but not significantly different than that of WA men (33.5%–39.2%). When the rates of upstaging and upgrading were compared separately, AA men had a significantly higher risk of having a nonorgan-confined disease (15.8%–19.4% vs 9.4%–10.1%). Further analysis revealed that AA men were more likely to have a higher percent maximum core and greater proportion of multiple cores than WA men.

Previously, it has been reported that the overall risk of nonorgan-confined disease at RP in men who met AS criteria ranged 5%–13.7%.^{9–12} This range of risk is not significantly different than the present study's observed rate of upstaging of 9.4%–10.1% in WA patients. In contrast, the rate of nonorgan-confined PCa (15.8%–19.4%) in AA men was significantly

higher. This increased rate of upstaging seen in AA men at RP who are candidates for AS is consistent with the available body of literature on PCa racial disparity.

Iremashvili et al¹⁵ reported a significantly higher progression risk in black patients with PCa on AS when compared to white patients. During a median follow-up of 2.9 years with a mean of 2.3 surveillance biopsies, the risk of progression was significantly higher in AA men (hazard ratio 3.87–4.12).

Sanchez-Ortiz et al⁶ compared the post-RP pathologic characteristics of 37 AA men and 35 white men with clinical stage T1c PCa who were matched for age, clinical stage, PSA level, year of surgery, prostate weight, and prostate biopsy strategy. The results demonstrated that Gleason score and mean tumor volume were significantly higher among AA men and had 2.8 times more tumor per ng/mL of PSA.

More importantly, AA men with PCa have 2–3 times higher mortality rate compared to white men.³ Powell et al¹ evaluated subclinical PCa characteristics on autopsy from 1056 black men and white men who died of causes other than PCa. They also reviewed prostate pathology data from their database and from the Detroit Surveillance, Epidemiology, and End Results database. The results demonstrated that tumor volume and Gleason score were higher in black men than white men. Advanced or metastatic PCa was also more common in AA men (4:1). Another study examined prostate biopsies from AA men and found that their tumors expressed higher levels of aggressive disease biomarkers than tumors from WA men.¹⁹ Given this, the results of the present study suggest that the commonly used AS strategies have a significant risk of cancer misclassification and AS may not be as safe a treatment modality for many AA patients with PCa. Therefore, more stringent criteria for AS should be developed for AA men.

As an initial attempt to tailor the AS criteria for AA men, the present study carried out a multivariate logistic regression analysis. This revealed that a higher preoperative PSA level and multiple positive biopsy cores were significantly associated with an increased likelihood of advanced disease in AA men based on the UCSF protocol. In addition to PSA, multiple positive cores on biopsy were associated with advanced disease. This is consistent with the recent report that the total number of positive cores in the diagnostic and first surveillance biopsies provide important information about the risk of PCa progression in AS patients,²⁰ whereas another group suggested that the number of positive cores on initial biopsy predicted unfavorable pathology at RP.²¹

Our study has several limitations. First, the data was collected prospectively but the analysis was carried out retrospectively. Second, the preoperative prostate volume was not available in many patients. As a result, PSA density could not be determined. Third, preoperative PSA kinetics were not available for analysis in this study. Fourth, the follow-up for most patients was not sufficiently long enough to evaluate the rate of postoperative biochemical recurrence or disease progression. Last, all men were treated at National Cancer Institute-designated Comprehensive Cancer Centers that have a special interest in PCa, which might limit the generalizability of our findings. Despite these shortcomings, the results of the present study suggest that a more restricted AS criteria should be considered in AA men with PCa.

CONCLUSIONS

AS in AA men with PCa carries a higher risk of advanced cancer compared to the WA population. The results of this study suggest that more stringent AS entrance criteria may be necessary for AA men. Because the preoperative PSA level and number of positive cores were associated with increased risk of more advanced cancer at RP, we recommend a lower

PSA cutoff and single positive core be considered as inclusion criteria for AS in AA men with PCa. These findings and the most effective PSA cutoff point will need to be determined with a larger prospective study.

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Table 1
Preoperative baseline characteristics of enrolled patients according to active surveillance protocol stratified by race/ethnicity

Variables	UCSF Criteria			NCCN Criteria		
	WA Men (N = 196)	AA Men (N = 191)	P Value	WA Men (N = 124)	AA Men (N = 148)	P Value
Median age (range)	56.0 (36–74)	59.0 (36–77)	<.001	60.0 (55–74)	60.0 (55–77)	.494
BMI (kg/m ²)	26.9 ± 3.2	26.4 ± 3.8	.222	26.3 ± 3.0	26.2 ± 3.9	.832
PSA (ng/mL)	4.97 ± 1.90	4.80 ± 2.05	.405	5.23 ± 2.00	5.08 ± 1.94	.524
Biopsy Gleason score	6	6	1	6	6	1
Clinical stage (%)			.496			.473
T1c	179 (91.3)	170 (89.0)		110 (88.7)	126 (85.1)	
T2a	17 (8.7)	21 (11.0)		14 (11.3)	22 (14.9)	
Positive cores (%)			.065			.046
Single	101 (51.5)	117 (61.3)		68 (54.8)	99 (66.9)	
Multiple	95 (48.5)	74 (38.7)		56 (45.2)	49 (33.1)	
Percentage of maximum core	15.3 ± 8.7	11.5 ± 8.4	<.001	20.4 ± 14.6	15.0 ± 13.2	.001

AA, African-American; BMI, body mass index; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; UCSF, University of California San Francisco; WA, White-American.

Table 2

Rate of upstaging and upgrade according to active surveillance protocol stratified by race/ethnicity

Variables	Upstaging (%)	P Value	Upgrading (%)	P Value	Upstaging and/or Upgrading (%)	P Value
USCF criteria		.067		.662		.458
AA men (N = 196)	31 (15.8)		64 (32.7)		73 (37.2)	
WA men (N = 191)	18 (9.4)		58 (30.4)		64 (33.5)	
NCCN criteria		.037		.449		.27
AA men (N = 124)	24 (19.4)		49 (39.5)		57 (46.0)	
WA men (N = 148)	15 (10.1)		51 (34.5)		58 (39.2)	

Abbreviations as in Table 1.

Table 3

Univariate and multivariate logistic regression analysis for prediction of advanced disease (upstaging and/or upgrading) at the time of prostatectomy in eligible patients for the criteria of UCSF among AA men

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.005 (1.009–1.103)	.019	1.055 (1.006–1.106)	.027
Clinical stage (T1c vs T2a)	1.597 (0.587–4.343)	.359		
Preoperative PSA	1.270 (1.080–1.494)	.004	1.247 (1.057–1.471)	.009
Positive cores (single vs multiple)	1.875 (1.041–3.378)	.036	1.883 (1.022–3.468)	.011
Percentage of maximum core	1.006 (0.973–1.039)	.745		

CI, confidence interval; OR, odds ratio; other abbreviations as in Table 1.

Table 4

Univariate logistic regression analysis for prediction of advanced disease (upstaging and/or upgrading) at the time of prostatectomy in eligible patients for active surveillance among WA men

Variables	USCF Criteria		NCCN Criteria	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age	1.039 (0.991–1.090)	.116	1.086 (1.006–1.171)	.034
Clinical stage (T1c vs T2a)	1.953 (0.782–4.877)	.152	1.681 (0.676–4.177)	.264
Preoperative PSA	1.008 (0.871–1.167)	.916	1.074 (0.906–1.274)	.412
Positive cores (single vs multiple)	2.024 (1.095–3.739)	.024	1.618 (0.806–3.245)	.176
Percentage of maximum core	1.008 (0.972–1.044)	.670	1.012 (0.987–1.037)	.361

Abbreviations as in Tables 1 and 3.