Active Surveillance for Low-risk Prostate Cancer in African American Men: A Multi-institutional Experience

Brian D. Odom, M. C. Mir, Scott Hughes, Cedric Senechal, Alexis Santy, Remi Eyraud, Andrew J. Stephenson, Kelly Ylitalo, and Ranko Miocinovic

OBJECTIVE To compare the outcomes of active surveillance (AS) series between African American men (AAM) and non-AAM diagnosed with low-risk prostate cancer at 3 medical centers.

METHODS Between 2005 and 2012, 214 men accepted AS on the basis of favorable clinical features and parameters after initial and repeat biopsy. Failure was defined as increase in Gleason score >6, total positive cores >33%, maximum cancer volume in any core >50%, or a prostate-specific antigen >10 ng/mL. Disease progression and overall AS failure were compared between the 2 groups.

RESULTS Of 214 men, 75 were excluded, leaving 67 AAM and 72 non-AAM on AS. Median age at diagnosis was 64 and 67 years for AAM and non-AAM, respectively, and median follow-up was 34 and 46 months, respectively. During this time, 44 AAM (66%) remained on AS, and 23 (34%) underwent treatment, of whom 6 (26%) were treated by patient choice and 17 (74%) because of disease progression. In the non-AAM group, 59 (82%) men remained on AS, and 13 (18%) underwent treatment, 8 (62%) were treated by patient choice and 5 (38%) because of disease progression. The 3-year freedom from overall treatment was 74% and did not differ by race ($P = .06$). The 3-year freedom from disease progression was 85%, where AAM were at significantly higher risk of disease progression (hazard ratio = 3.8; 95% confidence interval: 1.4-10.4; $P = .01$).

CONCLUSION Our study suggests a higher disease progression rate in AAM who choose AS for low-risk prostate cancer compared with non-AAM, signifying a potential need for closer follow-up and more stringent enrollment criteria in AAM. UROLOGY 83: 364–368, 2014. © 2014 Elsevier Inc.

Estimates from the European Randomized Screening Trial for Prostate Cancer and the US Surveillance, Epidemiology and End Results registry indicate that 25%-50% of cancers detected through screening represent over-diagnosis, defined as tumors that would have gone undiagnosed over a man's lifetime in the absence of screening.[1,2] Thus, the challenge in localized prostate cancer is to distinguish patients with significant cancer from those who will not benefit from active treatment. The long-term favorable outcomes for men with low-risk prostate cancer (PCa) undergoing active surveillance (AS) have evolved as a reasonable strategy.[3] Van den Bergh et al[4] performed a multicenter review and found 10-year PCa-specific mortality (PCSM) rate of 0%. Similarly, Klotz et al[3] reported a slightly higher 10-year PCSM of 3%, but 17% of this cohort also included intermediate-risk patients. Similar findings have been reproduced in other short and medium-term prospective series.[5,6] These rates are similar to other treatment modalities, but with an advantage of potentially avoiding significant side effects associated with active treatment.[7-11]

Although multiple studies have demonstrated the effectiveness and safety of AS, seldom have they included significant numbers of African American men (AAM) in the protocols.[3,4,12-20] PCa is known to be more common and more aggressive in AAM.[21-26] The reasons behind those differences are still uncertain. Some experts in the field lean toward biologic reasons, whereas others state that differences are based on the lack of access to health care for that specific population. Ha et al[22] recently showed that AAM who underwent radical prostatectomy for very low-risk PCa had a significantly higher rate of nonorgan-confined disease when compared with white men. We endeavored to report the early outcomes of an AAM AS series.

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From the Detroit Medical Center, Michigan State University College of Osteopathic Medicine, Detroit, MI; the Cleveland Clinic, Cleveland, OH; the Centre Hospitalier Universitaire, Pointe-á-Pitre, Guadeloupe, France; and the Department of Epidemiology and Internal Medicine, University of Michigan, Ann Arbor, MI

Reprint requests: Ranko Miocinovic, M.D., Detroit Medical Center, Harper Hospital, Harper Professional Building, 4160 John R. Suite 1017, Detroit, MI 48201. E-mail: rmiocinovic@gmail.com

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MATERIALS AND METHODS

Patient Population

After an institutional review board committee approval, a retrospective evaluation of prospectively collected data for patients with low-risk PCa undergoing AS at 3 medical centers, including Cleveland Clinic (CC), Detroit Medical Center, and Centre Hospitalier Universitaire (CHU) in Guadeloupe, was conducted. Between July 2005 and October 2012, a total of 214 men were enrolled in an AS protocol (CC n = 133, Detroit Medical Center n = 24, and CHU n = 57). Eligibility criteria were based on favorable clinical features and parameters after initial biopsy. Favorable clinical features included Gleason score (GS) 3 + 3 = 6, total number of cores positive for cancer ≤33%, each core containing ≤50% volume of disease, and prostate-specific antigen (PSA) ≤10 ng/mL. For the purposes of this study, only patients with a repeat biopsy confirming favorable features within 1 year of diagnosis were included. Thus, 75 patients (33 AAM and 42 non-AAM) were excluded.

The initial and confirmatory patient biopsies were based on a minimum of 12-cores transrectal ultrasound-guided prostate biopsy. The trigger for repeat prostate biopsy was physician dependent, and a decision for a saturation biopsy was seldom performed and was based on individual physician recommendation.

The AS protocol consisted of clinical assessment with digital rectal examination and serum PSA levels at 6-12 month intervals for the first 2 years and then annually. Surveillance biopsy was performed every 1-2 years or sooner depending on adverse clinical or PSA parameters or patient preference. Radical treatment was recommended in the event of GS progression to ≥7, increase in total number of biopsy cores to ≥33%, or increase in tumor volume to ≥50% per core. The primary endpoints of this study were freedom from overall treatment (FOT) (patient choice and/or disease progression) and freedom from disease progression.

Statistical Analysis

Chi-square tests were used to compare the proportions of overall failure and disease progression between the AAM and non-AAM. Logistic regression analysis was used to calculate the log odds of AS failure given race. Kaplan Meier estimates (proc lifetest) were used to assess the time on AS, separately for overall failure and disease progression, and log-rank tests were used to compare the AS experience between the AAM and non-AAM. Finally, Cox proportional hazards models were used to compare the rates of AS failure between AAM and non-AAM, after correcting for patient age. Statistical tests were 2-sided, with the level of significance defined as $P < .05$. SAS version 9.3 (SAS Institute, Inc., Cary, NC) was used for all statistical analyses.

RESULTS

Between July 2005 and October 2012, of 214 men with low-risk prostate cancer included in the AS protocol, 75 were excluded because of upstaging of disease on repeat biopsy or because of repeat biopsy period longer than 1 year, leaving 67 AAM and 72 non-AAM for analysis (Table 1). Median age at diagnosis was 64 years (interquartile range [IQR] 59-69) and 67 years (IQR 62-70) for AAM and non-AAM ($P = .02$), respectively, and median follow-up was 34 months (IQR 21-58) and 46 months (IQR 15-64), respectively ($P = .3$; Table 1).

Table 1. Clinical/pathologic features of African American men and non-African American men

Variables	AAM (%)	Non-AAM (%)	P
Patients	67 (48)	72 (52)	
Median age, y (IQR)	64 (59-69)	67 (62-70)	.02
Failure	23 (34)	13 (18)	.03
"True"	17 (74)	5 (38)	.07
"Patient choice"	6 (26)	8 (62)	
Median f/u, mo (IQR)	34 (21-58)	46 (15-64)	.3
Median time AS, mo (IQR)	29 (19-46)	31 (15-58)	.5
Median PSA, ng/mL (IQR)	5 (4.2-6.4)	5 (3.7-7.1)	.7
≤4 ng/mL	13 (19)	20 (27)	.2
4-10 ng/mL	50 (75)	46 (61)	
>10 ng/mL	4 (6)	5 (7)	
No initial PSA	0 (0)	4 (5)	
Treatment	23 (34)	13 (18)	
Surgery	16 (70)	6 (46)	.2
Radiation	6 (26)	7 (54)	
Cryo	1 (4)	0 (0)	
Reason for AS failure			
Patient choice	6 (26)	8 (62)	
Gleason score ≥7	7 (30)	3 (23)	
Total positive cores >33%	6 (26)	2 (15)	
Core cancer volume >50%	6 (26)	3 (23)	
PSA >10	1 (4)	0 (0)	
Unknown	2 (9)	1 (8)	

AAM, African American men; AS, active surveillance; IQR, interquartile range; PSA, prostate-specific antigen.

Of the 139 men included, a total of 36 (26%) men had treatment, and 22 (16%) experienced disease progression. In the AAM cohort, 44 (66%) men remained on AS, and 23 (34%) underwent treatment, including 16 (70%) radical prostatectomy, 6 (26%) radiation, and 1 (4%) cryotherapy, of whom 6 (26%) were treated by patient choice and 17 (74%) because of disease progression (Table 1). In the non-AAM cohort, 59 (82%) men remained on AS, and 13 (18%) underwent treatment, including 6 (46%) radical prostatectomy and 7 (54%) radiation, of whom 8 (62%) were treated by patient choice and 5 (38%) because of disease progression (Table 1). Compared with non-AAM, AAM were more likely to experience overall failure (OR = 2.4; 95% confidence interval [CI]: 1.1-5.2; $P = .03$) and disease progression (OR = 4.6; 95% CI; 1.6-13.2; $P = .01$). After adjusting for age, AAM still had twice the odds of overall failure (OR = 2.29; 95% CI: 1.03-5.08; $P = .04$) and 4 times the odds of disease progression (OR = 4.46; 95% CI: 1.52-13.10; $P = .01$) compared with non-AAM. Median time to treatment was 29 months (IQR 19-39) and 21 months (IQR 17-30) for AAM and non-AAM, respectively ($P = .5$), and median time to disease progression was 36 months (IQR 24-39) and 30 months (IQR 22-44) for AAM and non-AAM, respectively ($P = .9$).

Of the 16 AAM who underwent radical prostatectomy, no patient demonstrated high-grade disease (GS ≥8) or

Table 2. Final pathology for patients that underwent a radical prostatectomy

Final Pathology	AAM (%)	Non-AAM (%)	*P*
Stage			
≤pT2C	16 (100)	5 (83)	.3
pT3a	0	1 (17)	
Nodes			
N0	1 (6)	3 (50)	
NX	15 (94)	3 (50)	
Surgical margins			
Pos	3 (19)	4 (67)	.1
Neg	12 (81)	2 (33)	
Gleason score			
≤3 + 3	8 (50)	2 (33)	.8
3 + 4	5 (31)	3 (50)	
4 + 3	3 (19)	1 (17)	

N0, zero lymph nodes were positive for metastatic disease after having node dissection; NX, the number of nodes for metastatic disease is unknown since dissection was not done at all; other abbreviation as in Table 1.

extraprostatic extension on final pathology (Table 2). Although 3 (19%) AAM had positive surgical margins, none has undergone adjuvant radiation therapy. Similarly, of the 6 non-AAM who underwent radical prostatectomy, 1 had missing data, and the remaining 5 did not show high grade (GS ≥8) or extraprostatic disease on final pathology. Positive surgical margins were observed in 3 (60%) patients, of whom 2 underwent subsequent adjuvant radiation therapy.

The 3-year FOT was 74% (95% CI: 64-82) and did not differ between AAM vs non-AAM ($P = .06$; Fig. 1). The 3-year freedom from disease progression was 85% (95% CI: 75-91) and differed by race ($P = .01$; Fig. 2). AAM were at significantly higher risk of disease progression (hazard ratio = 3.8; 95% CI: 1.4-10.4; $P = .01$) compared with non-AAM. After adjusting for age, AAM still had higher rate for true disease progression compared with that of non-AAM (hazard ratio = 3.85; 95% CI: 1.39-10.63; $P = .03$).

COMMENT

Throughout the last decade, AS has become an increasingly adopted treatment option for men with low-risk PCa, with reported 5-year FOT and freedom from PCSM in the range of 70%-75% and 99%-100%, respectively.[3,6,19] However, these findings are based on studies composed mainly of Caucasian-based population. We evaluated potential outcome differences between the AAM and non-AAM who accepted AS as a treatment option at 3 different centers. Our findings demonstrate that AAM were more likely to experience both overall failure (34% vs 18%) and disease progression (25% vs 7%) in comparison with non-AAM. Radical prostatectomy specimen analysis showed no worsening of disease in our series; however, the number of patients undergoing that treatment option was low to account for final conclusions. This is particularly important because AAM have a tendency to be diagnosed with PCa at a younger age, thus the potential progression of disease might lead to an incurable outcome.

Although most studies have demonstrated a more aggressive natural history of PCa in AAM when compared with non-AAM,[21-26] some have observed that these racial disparities tend to disappear once the socioeconomic factors and treatment methods are taken into account.[27,28] For example, Powell et al[25] found that AAM had twice the risk of disease progression after radical prostatectomy in comparison with Caucasian men. Ritch et al[26] described similar findings in AAM and Caribbean African men who had an approximately 6 times greater risk of biochemical recurrence after radical prostatectomy. However, after controlling for multiple factors, Moses et al[28] reported that the only significant difference between the AAM and non-AAM receiving treatment for PCa was the primary modality of therapy, mainly AAM were more likely to receive nonsurgical therapy, but the adjusted overall and PCa-specific mortality were similar. Similarly, Schwartz et al[27] evaluated Detroit Surveillance, Epidemiology, and End Results registry data and found that lower socioeconomic status and nonsurgical treatment modality were responsible for the differences in PCa survival rates between the 2 groups.

The effect of race on AS has not been extensively studied. Recently, Abern et al[21] carefully compared AS outcomes at their institution between AAM and non-AAM after controlling for socioeconomic and health insurance factors. Interestingly, black race remained a significant predictor for overall and disease-specific discontinuation of AS, although AAM were less likely to opt-out in comparison with non-AAM.[21] The authors concluded that AAM on AS experienced a faster disease progression rate likely because of a biologically different entity. Iremashvili et al[23] also confirmed a 4 times higher risk of disease progression in AAM compared with non-AAM. Although both these studies included small numbers of AAM in their cohorts (22% and 9.6%, respectively), they suggest a more aggressive disease in this population of men which might require more stringent follow-up and selection criteria.

Our findings are consistent with the reported different outcomes between AAM and non-AAM undergoing AS.[21,23] After a median 36 months follow-up, only 66% of AAM remained on AS compared with 82% of non-AAM. AAM were twice as likely to experience overall treatment (OR = 2.4) and 4 times more likely to have disease progression (OR = 4.6) in comparison with non-AAM. However, there were no adverse features (GS ≥8, nonorgan-confined disease) observed on final pathology for men who underwent radical prostatectomy after disease progression in both groups. This latter observation differs from recent studies. For example, in the largest multi-institutional study up to date, the Prostate Cancer Research International Active Surveillance, 19% of the

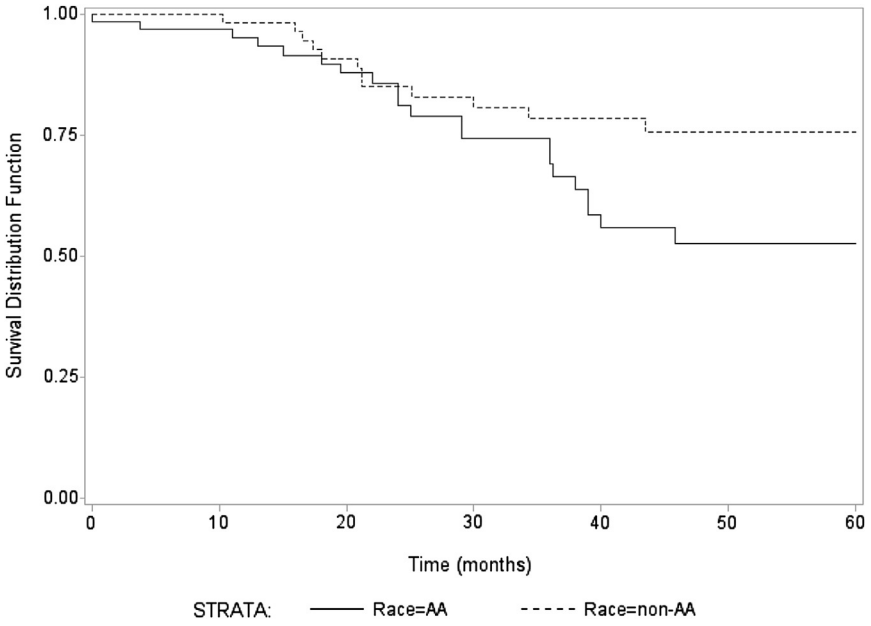

Figure 1. Three-year freedom from overall treatment among 139 patients on active surveillance.

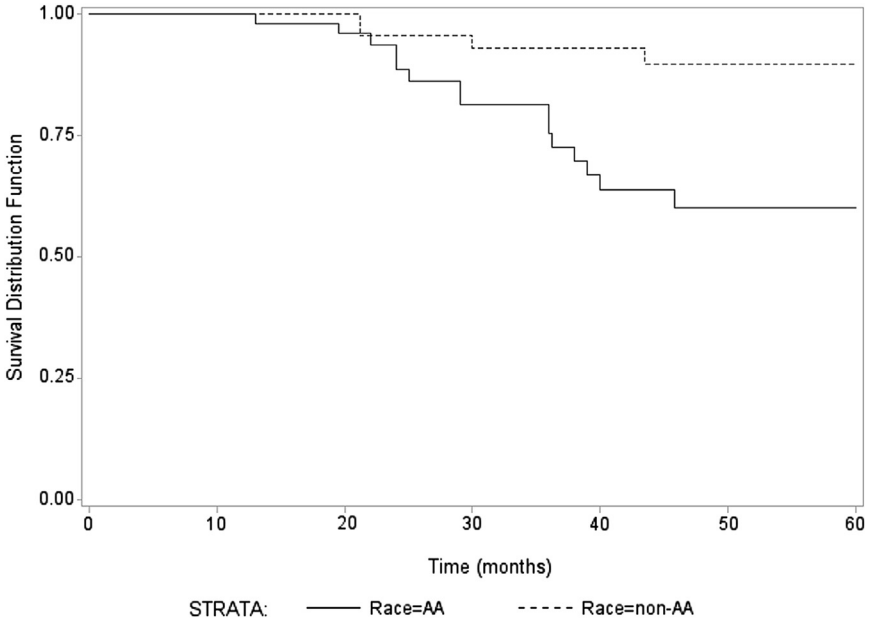

Figure 2. Three-year freedom from disease progression among 139 patients on active surveillance.

167 men who underwent radical prostatectomy after progression on AS had pT3a disease, and 25% had positive surgical margins.[29] Similarly, Duffield et al[30] reported a 35% nonorgan-confined disease rate in 48 men who previously failed AS at Johns Hopkins. Ha et al[22] pointed out AAM had a higher risk of having nonorgan-confined disease (16%-19% vs 9%-10%) and upgrading rates (33%-40% vs 30%-35%) when compared with White American men, respectively, in patients with low-risk disease who could otherwise be considered as candidates for AS on the basis of initial biopsy. Our findings might be explained by a relatively small number of patients included in the present study and short follow-up.

There are several limitations to our study. First, this was a retrospective review of prospectively collected data with a relatively short follow-up and small cohort of patients. Second, nearly all the non-AAM included in this study were from CC, and most AAM from CHU. The different socioeconomic and geographic states between these groups were not accounted for. As our study patients were a heterogeneous group from different

institutions, the criteria for proceeding to treatment were different because they were based on each institution's standards. In addition, final pathology data for some individuals who underwent radical prostatectomy were missing. Nevertheless, our multi-institutional study demonstrates that the short-term outcomes of AAM on AS for low-risk PCa differ from non-AAM and suggests that prospective trials are desperately needed in this area.

CONCLUSION

The present study suggests a higher disease progression rate in AAM who choose AS for initially diagnosed low-risk PCa when compared with non-AAM. Although the increasing acceptance and safety of AS has been demonstrated, the natural history of PCa in AAM might require closer follow-up and more stringent criteria to avoid a missed opportunity for cure.

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