Active Surveillance for African-American Men With Prostate Cancer: Of Course!

Of course we should offer active surveillance (AS) to African-American men with localized prostate cancer! We simply need to do it selec- tively and in a smarter way—and we need to be aware of some of the potential pitfalls.

Prostate cancer in African-American men has been a crit-
ically important issue for many years. We know prostate can- cer is more common in African-American men; whether it is more aggressive has been debated for some time. We also know African-American men are at higher risk for prostate cancer, and are at risk for developing the disease at a younger age. In 1994,1 led the US Army medical team that showed that African-American men, in general, had higher prostate-spe- cific antigen (PSA) values, even with careful multivariable analysis, even including careful tumor volume assessment. [1] This study also showed, for the first time, that within clinical stage categories (Tic, for example), carefully measured tumor volumes were higher for black men than for white men; this partially accounted for the higher PSA values we observed. We then went on to develop specific guidelines to help fine- tune PSA testing and screening in this high-risk group.[2] What we are talking about now is fine-tuning AS, not aban- doning it! Our US Army team also examined a large US mili- tary hospital radical prostatectomy series and showed that African-American men have worse disease-free survival than Caucasian men.[3]

Since our data were published, many other studies from multiple healthcare settings have generally confirmed these findings, although the cause of these racial differences remains elusive. Causation is highly likely to be multifactorial, including socioeconomic, behavioral, and biologic factors; however, sorting out the proportional contribution of the various factors remains challenging. For example, some in the field are convinced of an underlying biologic basis, while oth- ers feel that societal issues (lack of access, lack of insurance, etc) are the main culprits for the observed disparity. [4]

AS as an accepted treatment strategy for clinically localized prostate cancer has grown in use and popularity over the last 5 years. High-profile patient series from Canada, the United States, and Europe now have longer follow-up and support the concept. [5,6] AS has now been endorsed by prominent organi- zations, such as the National Comprehensive Cancer Network

^*Duke Prostate Center, Duke Cancer Institute, Duke University, Durham, North Carolina*

(NCCN), and its use has been fueled by the recognition that we are overtreating many low-risk and/or elderly men.

Over the last several years, several groups have raised a red flag regarding AS in African-American men. Ha et al studied almost 400 patients matched by race who had undergone radical prostatectomy for low-/very-low-risk clinically local- ized prostate cancer and who also met either NCCN or the

"Now that we are facing a backlash against PSA testing as a result of the USPSTF and AUA guidelines . . . we are entering an era of fewer men being eligible for AS. However, for those men who *are* eligible for AS, we still should offer i t . . . but be more cautious and work up patients more carefully."

University of California at San Francisco (UCSF) criteria for being managed with AS. [7] The keyfindingwas that African- American men had a significantly higher rate of non-organ- confined disease (15.8% to 19.4%) compared with Caucasian men (9.4% to 10.1%). Furthermore, African-American men had more cancer-involved prostate biopsy cores and a higher percentage of prostate cancer core involvement preoperatively than did Caucasian men. Ha et al have voiced concern about using the same criteria to recommend AS in African-American men as are currently used in non-African-American men. Virtually all the current data collected on AS from the major world studies involve Caucasian men, so current entry criteria may not be applicable to African-American men.

In addition to Ha et al, a number of groups now have reported higher progression rates in African-American men on AS. Iremashvili et al from the University of Miami and Abern et al from my group at Duke University both reported in 2012 that African-American men did not fare as well in terms of the length of time they remained on AS. [8,9] Both of these studies were preliminary retrospective reviews and used the same currently accepted entry criteria for AS. Also of note, Drs. Sundi and Schaeffer of Johns Hopkins, my "opponents" in this Pro/Con, have recently reported some excellent work

PRO/continued

showing that African-American men who met the criteria for AS and who underwent radical prostatectomy had bigger and higher-grade tumors than did their Caucasians counterparts. [10,11] Unfortunately, we have no prospective randomized controlled trials of AS for any ethnic group, much less for African-American men.

I think we need to offer multidisciplinary education to all men—including all African-American men—with localized prostate cancer, and specifically discuss AS, radical prostatec- tomy, radiotherapy, and other treatment options with them. [12] However, for the African-American man with low-risk disease who is considering AS, we may want to be a little more cautious. We may want to consider multiparametric MRI, repeat confirmatory biopsy, genomic testing (such as Myriad s Prolaris test or the Oncotype DX Genomic Prostate Score), or more conservative follow-up intervals (for example, every 4 months rather than every 6 months).[13-15]

One problem that I am seeing more often in practice is inappropriate or ill-advised AS. A fairly typical example is the man who is not a good candidate for AS, but who insists on it for fear of treatment or treatment side effects. I have coined the term "dumb active surveillance" or "dumb AS" to charac- terize this phenomenon, and we are studying this further at my center. I think this is happening due to the uncertainty surrounding the PSA test and the news about overtreatment of some men with localized disease. I have seen this occur also in some African-American men, and in these men, the con- sequences could be grave. This phenomenon may be seen in African-American men because of underinsurance, lack of insurance, fear and mistrust of the predominantly white healthcare system, or fear of side effects (particularly erectile dysfunction resulting from active treatment). Whatever the cause or causes, we need to be cognizant of this and be espe- cially sensitive to the need to provide proper education and counseling.

I am also concerned that the latest controversy surround- ing use of the PSA test to screen for prostate cancer will erase the progress we have made in lessening the disparity in pros- tate cancer rates between African-American and Caucasian men and may further limit the number of African-American men in whom AS would be appropriate. I am worried that primary care doctors and providers will ignore the NCCN guidelines calling for a baseline PSA test at age 40. In my opinion, getting a baseline PSA level is especially important for African-American men, since they tend to get prostate cancer at younger ages than Caucasian men, and thus may have more to lose if the disease is not detected in an early cur- able state.

In 2012, the US Preventive Services Task Force (USPSTF) released guidelines stating that, based on the currently avail- able randomized trials, PSA screening did not reduce prostate cancer mortality and suggesting that physicians stop ordering
the PSA test. [16] This caused a firestorm, since many groups and individuals have disagreed with the Task Force and have re-emphasized the value of PSA testing. Unfortunately, the confusion itself may cause many doctors to stop recommend- ing PSA testing to their patients, with the result that even fewer African-American men may wind up getting tested. The American Urological Association (AUA) did not help, in my opinion, when they abandoned their support of popula- tion-based PSA screening and no longer recommended base- line PSA risk stratification at age 40. [17,18] The AUA now only recommends PSA testing every other year for men between the ages of 55 and 69. This maybe too little, too late for many African-American men and may further limit the ability to employ AS in this population, since few black men will present with disease in an early enough stage to be con- sidered for AS.

Now that we are facing a backlash against PSA testing as a result of the USPSTF and AUA guideHnes,[16-18] I am afraid but fairly confident that we will see a return to an era when up to a quarter of men presented with incurable bony metastatic prostate cancer and faced a much shortened life expectancy. For African-American men, who generally present at a young- er age, we may go from seeing men in their mid-40s to late 50s who have a mildly to moderately elevated PSA level and an early-detected, curable prostate cancer, to men who show up in their mid-to-late 50s to mid-60s with metastatic disease and a dismal prognosis. We are entering an era of fewer men being eligible for AS. However, for those men who are eligible for AS, we still should offer it in a multi-discipline context but be more cautious and work up patients more carefully to better ensure true low-volume, low-grade, and low-stage disease. O

Financial Disclosure: *Dr. Moul serves on the Speakers Bureau for Myriad Genetics (for Prolaris) and recently attended a Genomic Health advisory board meeting related to the Oncotype DX prostate cancer test.*

REFERENCES

1. Moul JW, Sesterhenn IA, Connelly RR, et al. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. JAMA. 1995:274:1277-81. 2. Morgan TO, Jacobsen SJ, McCarthy WF, et al. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med. 1996:335:304-10.
3. Moul JW, Douglas TH, McCarthy WF, McLeod DG. Black race is an adverse prog- nostic factor for prostate cancer recurrence following radical prostatectomy in an equal access health care setting. J Urol. 1996:155:1667-73.
4. Powell U. The precise role of ethnicity and family history on aggressive prostate cancer: a review analysis. Arch Esp Urol. 2011:64:711-9.
5. Dall'Era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate can- cer: a systematic review of the literature. Eur Urol. 2012:62:976-83.
6. Eggener SE, Mueller A, Berglund RK, et al. A multi-institutional evaluation of active surveillance for low risk prostate cancer. J Urol. 2013:189(1 Suppl):S19-25: discussion S25.
7. IHa YS, Salmasi A, Karellas M, et al. increased incidence of pathologically nonor- gan confined prostate cancer in African-American men eligible for active surveil- lance. Urology. 2013 Feb 25. [Epub ahead of print]
8. Iremashvili V, Manoharan M, Lokeshwar SD, et al. Comprehensive analysis of post-diagnostic prostate-specific antigen kinetics as predictor of a prostate cancer progression in active surveillance patients. BJU Int. 2013:111:396-403.
9. Abern MR, Bassett MR,Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer: results from the Duke Prostate

PRO/continued

Center. Prostate Cancer Prostatic Dis. 2013;16:85-90.
10. Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol. 2013;31:2991 -7. 11. Sundi D, Kryvenko ON, Carter HB, et al. Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men. J Urol. 2013 Jun 14. [Epub ahead of print]
12. Stewart SB, Bañez LL, Robertson CN, et al. Utilization trends at a multidisci- plinary prostate cancer clinic: initial 5-year experience from the Duke Prostate Center. J Urol. 2012:187:103-8.
13. Müller B, van den Bos W, Brausi M, et al. The role of multiparametric magnetic resonance imaging in focal therapy for prostate cancer: a Delphi Consensus project. BJU Int. 2013 Nov 1. [Epub ahead of print]
CONTINUED FROM PAGE 83

CON/continued

ta¨te gland, especially in tbe setting of high-grade disease. [15] This finding adds to the complexity of AS for African- American men, given that dominant tumor nodules are more likely to be in the anterior aspect of the prostate gland, a difficult location to sample with standard biopsy tecbnique (wbicb uses a posterior approach). It is not known whether prostate imaging performed in African-American men wbo are AS candidates will be able to detect large anterior tumor nodules in order to aid risk stratification, altbougb this ques-
tion merits prospective evaluation.

It is troubling tbat current risk-stratification tools are in-
accurate wben applied to African-American men. Men witb favorable-risk prostate cancer wbo enroll in AS programs generally bave acceptable oncologic outcomes, but African- American men bave a distinct, elevated risk profile, wbicb may be tied to innate differences in cancer biology and/or tumor location. Even among men wbo meet NCCN very- low-risk criteria, African-Americans are approximately two to three times more likely to harbor undetected high-grade disease and adverse pathologic features at surgery, and to demonstrate progression to bigb-grade disease on serial bi- opsy. Tbis is not to say tbat AS is contraindicated for African- American men. However, AS in African-Americans sbould be undertaken witb substantial caution and only after tbe patient is counseled about his elevated oncologic risks. O

14. Shore N, Concepción R, Saltzstein D, et al. Clinical utility of a biopsy-based cell cycle gene expression assay in localized prostate cancer. Curr Med Res Opin. 2013 Dec 10. [Epub ahead of print)
5S. Knezevic D, Goddard AD, Natraj N, et al. Analytical validation of the Oncotype DX prostate cancer assay—a clinical RT-PCR assay optimized for prostate needle biopsies. BMC Genomics. 2013,14:690.
16. Moyer VA: US Preventive Services Task Force. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med. 2012;157:120-34.
17. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline. J Urol. 2013:190:419-26.
18. Moul JW, Walsh PC, Rendell MS, et al. Re: Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA guideline (J Urol. 2013;190:419-26). J UroL 2013;190:1134-7.
2. WiltTJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2013;367:203-l 3.
3. Dall'era MA, Albertsen PC, Bangma C, et al. Active surveillance for prostate can- cer: a systematic review of the literature. Eur Urol. 2012;62:976-83.
4. Quinn M, Babb P Patterns and trends in prostate cancer incidence, survival, prev- alence and mortality. Part I: international comparisons. BJU Int. 2002:90:162-73.
5. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012:380:2095-128.
6. Rosen P, Pfister D, Young D, et al. Differences in frequency of ERG oncoprotein expression between index tumors of Caucasian and African American patients with prostate cancer. Urology. 2012;80:749-53.
7. Powell IJ, Dyson G, Land S, et al. Genes associated with prostate cancer are dif- ferentially expressed in African American and European American men. Cancer Epidemiol Biomarkers Prev 2013;22:891 -7.

8. Powell IJ, Bock CH, Ruterbusch JJ, Sakr W. Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity.
J Urol. 2010:183:1792-6.
9. Moul JW, Sesterhenn IA, Connelly RR, et al. Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men. JAMA. 1995:274:1277-81. 10. Chornokur G, Dalton K, Borysova ME, Kumar NB. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer Prostate. 2011:71:985-97.
11. Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M. Clinical and demo- graphic characteristics associated with prostate cancer progression in patients on active surveillance. J Urol. 2012:187:1594-9.
12. Abern MR, Bassett MR,Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer: results from the Duke Prostate Center Prostate Cancer Prostatic Dis. 2013:16:85-90.
13. Sundi D, Ross AD, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy: should active surveillance still be an option for them? J Clin Oncol. 2013;31:2991 -7. 14. Sanchez-Ortiz RF,Troncoso P, Babaian RJ, et al. African-American men with non- palpable prostate cancer exhibit greater tumor volume than matched white men.
Financial Disclosure: *The authors have no significant financial interest or*
Cancer. 2006:107:75-82.

other relationship with the manufacturers ofanyproducts orproviders ofany service mentioned in this article.

REFERENCES

1. Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N EngI J Med. 2012;366:981-90.
15. Sundi D, Kryvenko ON, Carter HB, et al. Pathological examination of radical pros- tatectomies in men with very low risk disease at biopsy reveals distinct zonal distri- bution of cancer in black American men. J Urol. 2013 Jun 14. [Epub ahead of print]