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

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Abbreviations and Acronyms

AA = black
AS = active surveillance
BMI = body mass index
GS = Gleason score
MRI = magnetic resonance imaging
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = PSA density
RP = radical prostatectomy

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Purpose: Of men with very low risk prostate cancer at biopsy recent evidence shows that black American men are at greater risk for adverse oncologic outcomes after radical prostatectomy. We studied radical prostatectomy specimens from black and white men at very low risk to determine whether there are systematic pathological differences.

Materials and Methods: Radical prostatectomy specimens were evaluated in men with National Comprehensive Cancer Network® (NCCN) very low risk prostate cancer. At diagnosis all men underwent extended biopsy sampling (10 or more cores) and were treated in the modern Gleason grade era. We analyzed tumor volume, grade and location in 87 black and 89 white men. For each specimen the dominant nodule was defined as the largest tumor with the highest grade.

Results: Compared to white men, black men were more likely to have significant prostate cancer (61% vs 29%), Gleason 7 or greater (37% vs 11%, each $p < 0.001$) and a volume of greater than 0.5 cm^3 (45% vs 21%, $p = 0.001$). Dominant nodules in black men were larger (median 0.28 vs 0.13 cm^3, $p = 0.002$) and more often anterior (51% vs 29%, $p = 0.003$). In men who underwent pathological upgrading the dominant nodule was also more frequently anterior in black than in white men (59% vs 0%, $p = 0.001$).

Conclusions: Black men with very low risk prostate cancer at diagnosis have a significantly higher prevalence of anterior cancer foci that are of higher grade and larger volume. Enhanced imaging or anterior zone sampling may detect these significant anterior tumors, improving the outcome in black men considering active surveillance.

Key Words: prostate, prostatic neoplasms, African Americans, risk, neoplasm grading

Active surveillance is a treatment option recommended by the NCCN for men with very low risk PCa.[1] As described by Epstein et al, very low risk criteria select men predicted to have insignificant tumors based on small pathological volume and low GS.[2] These criteria, which were adopted by the NCCN, include clinical stage T1c, GS 6 or less, PSA less than 10 ng/ml, PSAD 0.15 ng/ml/gm or less, 2 or fewer positive cores and 50% or less cancer involvement per core.[2,3]

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In men who meet the criteria of Epstein et al[2] and are enrolled in our AS program outcomes are generally excellent with 0.08% PCa specific mortality and a 12.6% rate of upgrading on followup biopsies (median followup 2.7 years).[4,5] However, evidence indicates that AS is not equally safe for all race groups.[6] In particular, AA men with favorable risk cancers may have surprisingly adverse outcomes. In separate AS cohorts of 24 to 32 men at the University of Miami[7] and Duke Prostate Center[8] those who were AA were at higher risk for progression at biopsy and treatment, respectively. In the AS program at our institution AA men are at especially higher risk for progression by grade (unpublished data). Furthermore, analysis of a large, NCCN very low risk cohort in which RP was done showed that AA men have markedly adverse pathological outcomes compared to white men.[9]

In light of emerging evidence revealing significant racial disparities in PCa outcomes even among men with very low risk disease we determined whether any underlying pathological differences could explain these findings. Therefore, we identified men with NCCN very low risk PCa who were candidates for AS but underwent RP. We performed detailed pathological examination of surgical specimens, noting the volume, location, stage and grade of all tumor nodules.

MATERIALS AND METHODS

We analyzed the institutional review board approved RP database at our institution, which includes 19,142 men from the PSA era. After excluding 833 men who received neoadjuvant hormonal therapy we identified 1,801 who met all NCCN very low risk criteria, including PSA less than 10 ng/ml, PSAD 0.15 ng/ml/gm or less, 2 or fewer positive cores, 50% or less cancer involvement per core and GS less than 6.[1] Also, to reflect standard clinical practice and minimize sampling heterogeneity among study subjects all men had to have been diagnosed by extended core biopsy, defined as 10 or more cores. Only men who underwent treatment since 2004 were included in analysis since that is when the modern Gleason grading system was adopted at our institution. The International Society of Urological Pathology consensus scheme assigns poorly formed glands with poorly defined lumina, glomeruloid patterns and cribriform structures to pattern 4 instead of pattern 3.[10]

Of NCCN men at very low risk who were diagnosed by extended biopsy sampling and underwent treatment in the modern Gleason era (2004 to 2012) 221 were white and 100 were AA. To establish symmetrical comparison groups for detailed prospective pathological examination we randomly selected 100 white men. In these 2 select cohorts of 100 white and 100 AA men, respectively, 24 RP specimens were not available for review. The final analysis cohort consisted of 89 white and 87 AA men with corresponding prostatectomy specimens.

Each surgical specimen was surface coated with india ink and fixed in 10% buffered formalin for 18 to 24 hours. The gland was step sectioned at 3 mm intervals along the coronal plane and the resulting sections were halved or quartered to fit the tissue cassette. Tissue sections were embedded in paraffin blocks, from which 4.0 μm sections were prepared and stained with hematoxylin and eosin for routine histological analysis.

Two genitourinary pathologists (ONK and JIE) examined each prostatectomy specimen and prospectively recorded the number of tumor nodules, Gleason patterns in each nodule, and stage, volume and location/extent of each nodule in the prostate. All tumor nodules were mapped on slides to calculate tumor volume and distinguish separate lesions. Tumor volume was calculated as previously described.[11] Tumor nodules were considered spatially separate if they were 3 mm or more apart in a plane of a section or 4 mm or more on adjacent sections.[12]

We used adverse pathological findings, as defined by specific findings at prostatectomy, including 1) pT2 and GS 4 + 3 or greater, 2) pT3a and GS 3 + 3 with positive surgical margins, 3) pT3a and GS 3 + 4 or greater, or 4) pT3b or greater, to designate men predicted to have a 25% or greater 10-year probability of biochemical recurrence.[13] Unfavorable pathological findings at RP were also quantified by the Cancer of the Prostate Risk Assessment (CAPRA) Post-Surgical (CAPRA-S) score, a validated risk assessment with a range of 0 to 12 points that is derived from margin status, extraprostatic disease site, Gleason pattern and PSA. CAPRA-S 3 or greater is associated with a 27% or greater 5-year probability of biochemical recurrence.[14] Significant tumors were defined as those with a pathological Gleason sum of 7 or greater and those with a dominant nodule volume of 0.5 cm^3 or greater.

Means were compared by the Student t-test. Medians of nonnormally distributed variables were compared by the Wilcoxon rank sum test. Proportions were compared by the chi-square test. Statistical significance was predefined at 2-tailed 0.05. Analysis was done using Stata®, version 11.0.

RESULTS

In all men NCCN very low risk disease was diagnosed by extended biopsy sampling in the modern Gleason grading era. AA and white men were similar in age, PSA, PSAD, BMI, number of cores, percent core involvement and CAPRA score at diagnosis (supplementary table 1, http://jurology.com/). There was no difference in the mean or median interval between biopsy and RP. Notably, AA men had higher Charlson comorbidity scores (supplementary table 1, http://jurology.com/). Preoperative characteristics were also similar in men whose RP specimens were not available for review, although excluded AA men were younger (53.1 vs 59.5 years, $p = 0.015$, table 1). At prostatectomy AA men had significantly higher rates of nonorgan confined disease (14.9% vs 3.4%, $p = 0.008$), positive surgical margins (19.8% vs 5.6%, $p = 0.002$) and