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Does Race Influence Health-related Quality of Life and Toxicity Following Proton Therapy for Prostate Cancer?

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Objective: This matched-paired analysis explores disparities in health-related quality of life (QOL) and common toxicities between African American (AA) and white patients following proton therapy for prostate cancer at our institution.

Materials and Methods: A total of 1536 men with clinically localized prostate cancer were treated from 2006 to 2009 with definitive proton therapy to a median dose of 78 Gy +/− androgen deprivation therapy. A cohort of 92 consecutively treated AA men was matched to a cohort of 92 white men on the basis of National Comprehensive Cancer Network risk category and age. The 2 groups were compared with regard to comorbidities, demographics, and treatment regimen. Differences in genitourinary and gastrointestinal (GI) toxicity according to the Common Terminology Criteria for Adverse Events scale and QOL data from the Expanded Prostate Index Composite 26-question questionnaire were reported.

Results: Median follow-up was 2.1 years. Baseline patient and treatment characteristics were similar between the 2 groups with the exception of prostate-specific antigen ≥ 10 (32% for AAs vs. 20% for whites; $P = 0.068$) and use of androgen deprivation therapy (26% for AAs vs. 21% for whites; $P = 0.38$). No difference in Expanded Prostate Index Composite 26-question sexual summary, urinary incontinence, urinary obstruction, or bowel summary scores was detected between the 2 groups, nor was there a difference in grade 2 or higher GI toxicity ($P = 0.45$). AAs had a statistically nonsignificant higher absolute incidence of late grade 3 genitourinary toxicity (4.4% vs. 0%; $P = 0.12$).

Conclusions: After 2 years, there were no disparities in health-related QOL, physician-reported Common Terminology Criteria for Adverse Events GI toxicity, or biochemical relapse. Longer follow-up is needed to confirm these findings.

Key Words: particle Therapy, proton therapy, race, toxicity, quality of life

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Evaluating patients' health-related quality of life (QOL) and toxicity following treatment for prostate cancer provides valuable information for patients and physicians. Various predictors for genitourinary (GU), gastrointestinal (GI), and sexual decline following treatment for prostate cancer have been reported. Pretreatment GI and GU symptoms, prostate volume, previous transurethral radical prostatectomy (TURP), androgen deprivation therapy (ADT), radiation dose, and radiation technique have all been shown to predict toxicity following radiation therapy.[1,2] Obesity, patient age, and surgical technique have also been shown to influence toxicity following prostatectomy for patients with prostate cancer.[3,4]

Whether race independently influences health-related QOL and toxicity following treatment for prostate cancer is a subject of ongoing debate. Some studies have shown worse patient-reported health-related QOL among African American (AA) men following surgery and radiation, especially in the domain of urinary function.[2,5,6] Conversely, other studies indicate that AA race predicts for better erectile function following external-beam radiation therapy.[7,8]

Overall, studies comparing treatment outcomes between AA men and white men have focused on QOL following prostatectomy, brachytherapy, or photon radiotherapy.[5,6,9–12] To date, no published series has compared health-related QOL or treatment-related toxicity of AA and white patients treated with proton-based radiation therapy. Proton therapy (PT) has been used for several years with encouraging results and an excellent side effect profile among prostate cancer survivors,[13–16] but no reports of PT focus on outcomes for AA patients.[17] The purpose of our study was to determine whether race influenced treatment response in terms of toxicity and health-related QOL following definitive PT.

MATERIALS AND METHODS

This study was approved by our institution's Institutional Review Board (IRB) and included men treated at our institution definitively for prostate cancer between 2006 and 2010. The charts of 1536 men were reviewed. Each patient was treated on an IRB-approved outcome tracking protocol and each may also have been enrolled on 1 of 3 prospective IRB-approved treatment protocols between August 2006 and January 2010. The 3 protocols included PR01 for low-risk prostate cancer, on which patients received 78 cobalt gray equivalent (CGE) to the prostate at 2 CGE per fraction; PR02 for intermediate-risk prostate cancer patients, a radiation dose-escalation trial on which patients received 78 to 82 CGE to the prostate and proximal seminal vesicles depending on normal-tissue constraints; and PR03 on which patients received 78 CGE to the prostate and seminal vesicles with concomitant weekly docetaxel (20 mg/m^2) followed by 6 months of androgen deprivation.

All patients had a pathology-confirmed diagnosis based on biopsy of a minimum of 10 prostate zones as well as a bone scan, chest x-rays within 6 months of enrollment, computed tomography (CT) scans, magnetic resonance imaging (MRI) of

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the pelvis, and a prostate-specific antigen (PSA) test. Every patient received PT with or without ADT. The decision to receive ADT was based on individual physician and patient choice but most patients with National Comprehensive Cancer Network (NCCN) high-risk disease were encouraged to receive ADT.

Ninety-two consecutively treated men who self-identified themselves as AA were the subject of the analysis. A comparative cohort was created by matching each AA patient to a white patient treated contemporaneously for prostate cancer at our institution with the same NCCN risk category and with a similar age, using age bins spanning 5 years.

Patient-reported QOL parameters were assessed before PT and at 6- to 12-month intervals using the following standard tools: the Expanded Prostate Cancer Index Composite (EPIC) and the International Prostate Symptom Score (IPSS). Physician-determined treatment toxicities using the Common Terminology Criteria for Adverse Events version 3.0 were recorded weekly throughout treatment and at 6-month intervals after completing treatment. PSA was assessed before treatment, at the end of treatment, and at 3-month intervals after completing treatment.

Patient histories were extracted for prior treatment of urinary retentive and obstructive symptoms, prostatitis, and rectal bleeding as well as factors that might affect tolerance of radiation therapy, such as smoking history, anticoagulation, diabetes mellitus (DM), hypertension, blood disease, cardiovascular disease, and chronic obstructive pulmonary disease. Pretreatment TURP, use of α-blockers, and prostate volume were recorded for each patient. These factors were compared between the 2 cohorts of patients because of their impact on health-related QOL, toxicity, and overall survival for patients following PT.

Simulation, Planning, and Treatment

The University of Florida Proton Therapy Institute simulation, planning, and treatment guidelines for prostate cancer have previously been published.[16] In brief, all patients underwent CT simulation with fiducial markers in place. Thirty minutes before simulation, patients drank 15 ounces of water. Patients were simulated while supine and in a vac-locked body mold. Saline was instilled into the rectum or a rectal balloon was used to stabilize the prostate position.

Immediately after CT simulation, an MRI scan was obtained and the CT and MRI images were fused. The prostate, seminal vesicles, penile bulb, bladder, rectum, bowel, and femoral heads were contoured. A planning target volume (PTV) was constructed from the prostate and/or seminal vesicles with margins of 4 mm in the anteroposterior and lateral directions, and 6 mm in the superior-inferior direction. Dosimetric specifications required that 95% of the PTV receive 100% of the prescribed dose and 100% of the PTV receive at least 95% of the prescribed dose. Patients were treated with double-scatter PT with right and left lateral (or slightly oblique) field arrangements with customized brass apertures and compensators. Image-guided treatment was performed by using orthogonal kilovolt imaging for fiducial localization. Depending on the protocol, patients were treated either with 2 CGE per fraction to a total dose of 76 to 82 CGE or at 2.5 CGE per fraction to a total dose of 70 to 72.5 CGE.

Statistical Analysis

All statistical analyses were performed with SAS and JMP software (SAS Institute, Cary, NC). For individual EPIC question endpoints, data were first regrouped as binary levels and Fisher exact test was used to test for ethnicity response differences. Summary scores were analyzed as continuous variables. Baseline summary score between ethnicities was assessed with Wilcoxon rank sum test. Univariate tests of each posttreatment timepoint were then assessed between ethnicity groups by constructing a regression model that also included baseline score as a controlling variable. Posttreatment summary scores were then analyzed using repeated-measures analysis of variance (ANOVA). Ethnicity was the main prognostic factor of interest, but the repeated-measures ANOVA was also set up as a multiple regression that controlled for pretreatment hormone and diabetes status as well as baseline score.

RESULTS

Patient and Tumor Characteristics

Characteristics of the AA patients and matched white patients are listed in Table 1. For both the groups, the median age at presentation was 65 years. The median time of follow-up was 2.1 years for the entire group. Specifically, it was 2.1 years for AA patients and 2.2 years for white patients. As expected, there was no difference between the groups in the percentage of patients presenting with NCCN-designated low-risk, intermediate-risk, or high-risk disease, which were 31%, 44%, and 25%, respectively, for both the groups. Despite matching for risk category, 32% of AAs presented with pretreatment PSAs of >10 compared with 20% for the matched white patients, a difference that approached statistical significance ($P = 0.0675$).

As described in Table 2, AAs and white patients used α-blockers for urinary obstructive symptoms as well as

TABLE 1. Racial Differences in Demographic, Clinical, and Treatment Characteristics (n = 184)

Characteristics	African American Patients	White Patients	*P*
Total patients	92	92	
NCCN risk category (%)			
Low	31	31	
Intermediate	44	44	
High	25	25	
Median age (y)	65	65	
Median prostate size (range)	34.9 (9.82-130)	32.75 (13.1-111)	0.38
T stage (%)			0.51
T1	74	70	
T2	23	29	
T3	2	1	
Gleason score (%)			0.99
≤6	37	38	
7	46	45	
≥8	17	17	
Pretreatment PSA (%)			0.07
<10	67	80	
10-19	21	10	
≥20	11	10	
Median dose (range) (Gy)	78 (58-82)	78 (70-82)	
Androgen deprivation therapy (%)	26	21	0.38
Concurrent chemotherapy (docetaxel) (%)	9	4	0.23

NCCN indicates National Cooperative Cancer Network; PSA, prostate-specific antigen

TABLE 2. Medication Use and Comorbidities (n = 184)

	African American Patients	White Patients	*P*
Total patients	92	92	
Pretreatment TURP (%)	4.3	6.5	0.75
Statin use (%)	35.9	38.0	0.88
α-blocker use (%)	17.4	15.2	0.84
5-α reductase inhibitor (%)	3.3	10.9	0.08
Phosphodiesterase inhibitor use (%)	17.4	14.1	0.69
DM (%)	27.2	10.9	< 0.01
Cardiac disease (%)	10.9	15.2	0.51
No cardiac disease or DM (%)	65.2	75.0	0.20

DM indicates diabetes mellitus; TURP, transurethral radical prostatectomy.

phosphodiesterase inhibitors for erectile dysfunction, and had TURP for benign prostatic hypertrophy (BPH) at similar rates before receiving radiation therapy. White patients received 5-α reductase inhibitors more often for BPH than AA patients (10% vs. 3%; $P = 0.08$), but the difference was not statistically significant. At presentation, rates of heart disease were similar between both the groups, but rates of DM were much higher among AAs. DM was present in 27% of AAs versus 10% for white patients ($P < 0.01$).

Treatment Characteristics

All patients were treated with primary proton radiotherapy. The median dose for both the AA and the white cohort was 78 CGE. More AAs were treated with ADT (27% vs. 21%) compared with white patients, but the difference was not significant ($P = 0.38$). In the intermediate-risk group, ADT was given to 5 of 40 patients (13%) AAs versus 2 of 40 (5%) white patients. For high-risk patients, ADT was given to 17 of 23 (74%) AAs versus 15 of 23 (65%) white patients. Neoadjuvant ADT was given to 15% of AAs versus 11% of white patients. Adjuvant ADT was given to 13% of AAs versus 12% of white patients. Concurrent ADT was given to 5.4% of patients in each group.

Race and Posttreatment QOL

A total of 94%, 86%, 87%, and 72% of patients answered the EPIC-26 questionnaire at baseline, 6 months, 1 year, and 2 years. There was no difference between the percentages of AA and white patients who responded. Summary scores for urinary irritative and obstructive symptoms, bowel function, sexual function, and urinary incontinence are depicted in Figures 1A to D. The only >5-point decline from baseline in median score at 2 years following treatment was in urinary irritative/obstructive symptom among AAs, which declined from a median of 93.8 to 87.5. No statistically significant difference was observed between the 2 cohorts during the 2 years of follow-up for bowel summary, urinary irritative/obstructive, urinary incontinence, or sexual summary scores. When patients who did not receive ADT were analyzed separately, a difference was seen in the rate of erectile dysfunction, with lower rates among AAs, but the difference was not statistically significant.

As Table 3 demonstrates, AA and white patients initially had minor differences in IPSS score after PT but after 2 years, patient IPSS scores did not differ significantly between the 2 cohorts. The percentage of patients requiring medications for urinary obstructive symptoms was similar between the groups.

Race and Posttreatment Adverse Effects

By 2 years, 23% of AA patients had developed a late grade 2+ GI toxicity compared with 29% of whites, and the difference was not statistically significant ($P = 0.45$). The majority of GI toxicities in the AA (89%; 16/18) and white (79%; 19/24) cohorts were rectal bleeding that required medications only. The median time to late grade 2+ toxicities was 11 months for AAs and 12 months among white patients. Importantly, only 2% of AAs required cautery for rectal bleeding compared with 4.3% of white patients. AAs had a higher absolute risk of late grade 3 GU toxicity (4.4% vs. 0%; $P = 0.12$), which included urinary obstruction requiring a temporary catheter, hematuria, and radiation cystitis. Among AAs, the median time to grade 3 GU toxicity was 22 months. No patient receiving chemotherapy experienced a grade 3 GU toxicity.

DISCUSSION

This study assesses health-related QOL and treatment toxicity of AAs compared with white men treated for prostate cancer with definitive PT. This is the first study to attempt to compare outcomes for AA men and white men following PT.

The value of PT in the management of prostate cancer has recently been questioned. In particular, results from a recent Surveillance, Epidemiology, and End Results and Medicare-linked report suggest that rectal toxicity is worse for patients treated with PT for prostate cancer compared with patients treated with intensity-modulated radiation therapy (IMRT).[17] Our study was not specifically designed to counter this argument; however, we found overall low rates (< 5%) of grade 3 GU toxicity and our patients experienced rectal toxicity rates that were similar to commonly reported rates after IMRT and 3D conformal radiation therapy in prospective trials.[15,18,19] We also found that race did not affect the likelihood of toxicity and had no effect on QOL following PT. Specifically, our study demonstrates no differences in EPIC QOL 2 years after treatment between the AA and the white cohort. Urinary irritative/obstruction, urinary incontinence, and bowel function were similar between both the groups. Sexual function was not statistically different between the groups, despite higher rates of diabetes and more ADT use among AA patients. Both factors are known to contribute to the development of erectile dysfunction following radiation therapy.[2,7,13]

AAs had a higher incidence of late GU toxicity than white patients (4.4% vs. 0%) but the difference was not statistically significant ($P = 0.12$). AAs had similar prostate volumes, IPSS scores, and use of medications for BPH before treatment. The number of patients on medications for urinary symptoms after treatment was also similar between the 2 groups, as were radiation doses and techniques. The small difference seen in GU toxicity may be related to the higher use of ADT in AAs compared with white patients (27% vs. 21%, $P = 0.38$). Others have found that ADT may be a risk factor for the development of urinary obstructive symptoms following radiation therapy.[7]Alternatively, the small difference in GU toxicity may point to racial differences in mucosal sensitivity of the urethra or bladder to high-dose radiation. More likely, the difference is a chance outcome, considering none of the white patients developed grade 3 GU toxicities. We know from other studies at our institution that the rate of Common Terminology Criteria for Adverse Events version 3.0 grade 3 GU toxicity

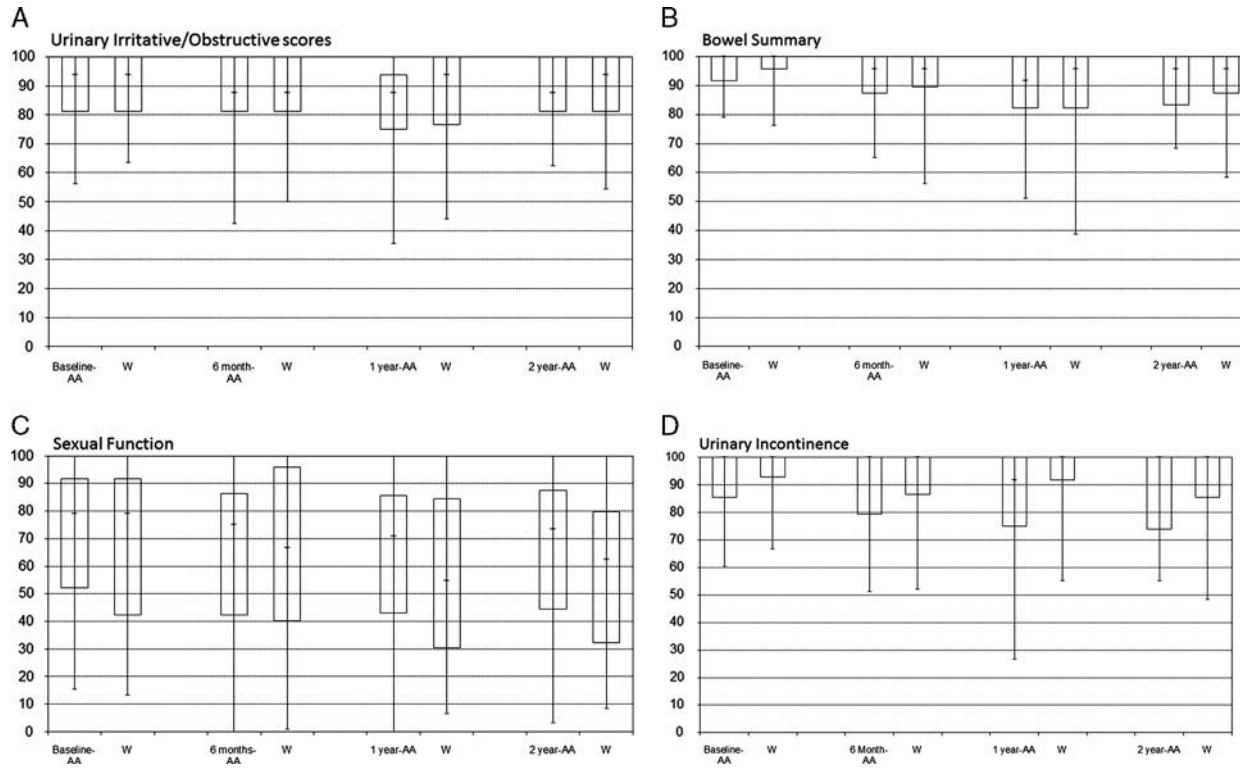

FIGURE 1. Expanded Prostate Cancer Index Composite (EPIC) summary scores overtime for men treated with intensity-modulated radiotherapy or proton therapy for prostate cancer. Bar and whisker graphs at baseline and 6 months, 1 year, and 2 years after proton therapy or intensity-modulated radiotherapy for (A) urinary irritative/obstructive score; (B) bowel summary score; (C) sexual summary score; and (D) urinary incontinence score (no androgen deprivation therapy). The bottom whisker represents the cut-off for the score of the lowest 5%, the bottom bar represents the cut-off score for the lowest quartile, the dash represents the median score, the top of the bar represents the cut-off for the top quartile, and the top of the whisker represents the cut-off for the score of the top 5%.

among the overall population of white patients is approximately 5% following PT, so the white cohort in this study may not have been entirely representative of the entire white population of patients treated with PT at our institution.[20]

Previous analyses have reported mixed results when exploring differences in QOL and/or toxicity between AAs compared with whites following treatment for prostate cancer. Shah and colleagues found that AA men did not have worse physician-reported toxicity or QOL following brachytherapy or external-beam radiotherapy. AA men were actually less likely to develop urinary incontinence following external-beam radiotherapy compared with white men. No differences were noted between groups in the rates of urinary retention, frequency, rectal pain, or bleeding.[21]

Rice and colleagues analyzed health-related QOL for AAs and whites following prostatectomy and/or external-beam radiotherapy for prostate cancer. The patients were treated at an equal-access military multidisciplinary prostate cancer clinic. Using the EPIC questionnaire to assess health-related QOL, AAs had a greater risk for a decline in urinary function following therapy than whites regardless of treatment choice. The difference persisted on multivariate analysis.[6]

A large prospective trial reported by Sanda et al[2] in 2008 on a total of over 1200 patients included 114 AA patients treated with external-beam radiation, brachytherapy, or prostatectomy. Health-related QOL was evaluated for patients treated with each modality. Urinary incontinence following prostatectomy was significantly worse among AAs than white patients. Despite similar care settings, AAs were also less likely to achieve satisfaction with the overall outcome in terms of health-related QOL.

Unlike several other studies, our study did not show a difference in health-related QOL or toxicity between AA and white patients following definitive treatment for prostate cancer. The potential reasons include the possibility that AAs in our study may not be biologically, economically, or culturally similar to AAs treated at other centers around the United States. Our

TABLE 3. Median Change in IPSS Score at 6-Month Intervals

	African American Patients	White Patients
Median pre-RT IPSS score (range)	6 (0-30)	6 (0-25)
Change of IPSS score at 6 mo	+1 (−13 to +19)	0 (−18 to +25)
Change of IPSS score at 12 mo	+2 (−9 to +24)	+0.5 (−16 to +21)
Change of IPSS score at 18 mo	+1 (−13 to +19)	0 (−11 to +21)
Change of IPSS score at 24 mo	+1 (−14 to +13)	+1 (−11 to +14)

IPSS indicates International Prostate Symptom Score.

patient sample could have presented with differences in pretreatment obesity rates, comorbidities, prostate size, or a combination of those differences, which could affect the likelihood of toxicity or changes in QOL following radiation therapy. Conversely, the reason could relate to the radiation technique used for treatment. PT has been shown to deliver more conformal radiation therapy for localized prostate cancer than 3D conformal radiation or IMRT.[22] It is possible that because PT delivers less radiation to the rectum and bladder it also minimizes the chance of racial disparities in QOL and toxicity.

The limitations of our study include, first, that it was a matched-paired analysis instead of a review of all patients treated with PT at our institution. Although all AA patients treated for prostate cancer at our institution were included, only a cohort of matched white patients was included in the analysis. Second, this is a single-institution study and the men who present to our institution may not represent most AAs and whites with respect to socioeconomic factors or disease characteristics. Third, defining QOL in terms of sexual, bowel, and urinary function is subjective. Although no difference was found between AAs and white patients on the EPIC scale, because median EPIC scores are reported and analyzed, subtle but relevant differences between the 2 groups may be obscured.

CONCLUSIONS

When matched, on the basis of age and NCCN risk category, AAs and whites did not demonstrate a significant difference in health-related QOL or toxicity following PT, although a nonsignificantly higher incidence of late GU toxicity following PT was observed among AA men.

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