Race Does Not Affect Survival in Patients With Prostate Cancer Treated With Radiation Therapy

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Abstract. *Background/Aim: Recent evidence has shown that African American men with prostate cancer may have more radiosensitive disease with greater overall survival (OS) with radiotherapy compared to Caucasian men. We compared OS in African American and Caucasian men receiving radiotherapy utilizing the National Cancer Database. Patients and Methods: African American or Caucasian men with N0M0 prostate adenocarcinoma diagnosed between 2004 and 2013 were selected and grouped into favorable and unfavorable risk based on clinical T-stage, clinical Gleason score, and prostate-specific antigen. Patients with favorable risk received brachytherapy or dose-escalated external beam radiation (EBRT); those with unfavorable risk received EBRT plus anti-androgen therapy with/without brachytherapy. African American and Caucasian men in each subgroup were propensity score-matched and analyzed for survival. Sensitivity analysis used treatment–race and age–race interaction terms. Results: 27,150 patients met the inclusion criteria, with a median age of 68 (range=38-90) years and median follow-up of 59.93 (range=48-142.62) months. OS was equivalent between African American and Caucasian race in favorable risk [log-rank p=0.82; hazard ratio (HR)=0.928; 95% confidence intervaI (CI)=0.583-1.477, p=0.753] and unfavorable-risk subgroups (log-rank p=0.87, HR=1.078, 95% CI=0.843-1.379, p=0.550). No significant interaction existed between treatment and race for either cohort but there was a significant interaction between race and age in those with unfavorable risk (HR=1.046, 95% CI=1.009-1.084, p=0.015), with greater OS in those of Caucasian race ≤60 years (HR=0.320, 95% CI=0.137-0.752, p=0.009).*

Conclusion: African American and Caucasian men have similar survival when treated with risk-appropriate definitive radiotherapy. However, younger (age ≤60 years) African American men with unfavorable risk have poorer survival than their Caucasian counterparts and may harbor a significantly different biology of disease.

It is commonly held that African American men have more aggressive prostate cancer, with several series demonstrating that African American men were more likely to require treatment from active surveillance compared to Caucasian men (1, 2). However, it is debatable whether differences in presentation and disease progression are largely socioeconomically or biologically driven (3).

Notably, significant variations in disease presentation, progression and morbidity between African American and Caucasian men may in part be explained by key genetic differences. Several distinct high-risk chromosomal variations associated with African American men with prostate cancer have been observed in 8q24, 17q21, 17α-hydroxy/17,20-lyase (CYP17), and ten-eleven translocation-2 (TET2) (4-7). Hence, it has been hypothesized that such differences in biology may portend different responses to therapy.

In particular, recent evidence using The Cancer Genome Atlas (TCGA) and tissue samples from four Radiation Therapy Oncology Group (RTOG) trials demonstrated African Americans with prostate cancer have more radiosensitive disease with better distant metastasis and biochemical recurrence-free survival when treated with radiation therapy (8). We investigated whether such a difference in overall survival (OS) exists in a national database between African American and Caucasian men receiving risk-appropriate definitive radiotherapy.

Patients and Methods

The National Cancer Database was queried for African American or Caucasian men, as defined by the primary race assignment, with prostate adenocarcinoma diagnosed between 2004 and 2013. Patients were excluded if they had node-positive, metastatic or noninvasive disease. A minimum of 4 years of follow-up, measured from the date of diagnosis to death or last follow-up was required.

Since the only survival endpoint in the database was OS, measured from the date of diagnosis to death from any cause, early events are likely not attributed to prostate cancer given the prolonged natural history of the disease.

Patients were grouped into favorable and unfavorable-risk cohorts based on National Comprehensive Cancer Network risk stratification derived from clinical T-stage, clinical Gleason score, and PSA (9). All analyzed patients had to have received risk-appropriate definitive radiation therapy: Those with favorable risk received brachytherapy (BT) or dose-escalated external beam radiation (EBRT), while those with unfavorable risk received EBRT plus antiandrogen therapy (ADT) with/without BT. Patients receiving EBRT or EBRT plus ADT were to have received at least 7,560 cGy. The cutoff of 7,560 cGy was chosen given the randomized data demonstrating superiority of radiation dose escalation for prostate cancer (10), which is now the standard of care. Patients receiving salvage or adjuvant radiotherapy were excluded.

Statistical considerations. Propensity score analysis was carried out in order to balance confounding covariates including treatment, facility type, facility location, insurance status, income, comorbidities (derived from Charleson–Deyo score) (11), age group, risk group, clinical T-stage, clinical Gleason score, prostate-specific antigen (prostate-specific antigen), and whether treatment started within 90 days.

Two groups were then created based on risk (favorable or unfavorable). African American and Caucasian men in each group were matched using calculated propensity scores. Multivariate analysis was carried out on both unmatched and matched cohorts, and subgroup analysis on the matched cohorts. Covariates in the multivariate analysis were selected a priori and included clinically and socioeconomically meaningful variables including radiation treatment modality, race, facility type, facility location, insurance status, income, comorbidities, age, treatment start time, risk group, clinical T-score, clinical Gleason score, and PSA.

In order to analyze whether BT-containing therapy had a different impact on survival based on race, sensitivity analysis was conducted using a treatment–race interaction term. Additionally, a second sensitivity analysis was performed using an age–race interaction term given the strong evidence that earlier onset prostate cancer is a significantly different disease entity from older onset prostate cancer (12), and hence may show a differential response to radiation.

Survival analysis consisted of Kaplan–Meier statistics and Cox proportional hazard regression models. All propensity score-matched (PSM) models were well balanced with covariate standardized mean differences <10%, and all Cox multivariate models were evaluated for the proportional hazards assumption using Schoenfeld residuals. Two-sided p-values were utilized using a significance level of 0.05. Statistical analysis was completed using R version 3.5.1.

Results

Of 1,294,126 patients identified, 27,150 met the inclusion criteria (Figure 1), with a median age of 68 (range=38-90) years and median follow-up of 59.93 (range=48-142.62) months.

In the unmatched favorable-risk group (n=13,870), no significant survival difference was seen between African American and Caucasian race (Figure 2A). A total of 2,688 cases were matched (Table I). Seventy percent (n=1878) of

patients were at low risk, with nearly all having PSA <10 ng/ml (n=2,655; 99%) and most having clinical Gleason score ≤6 (n=1,900; 71%). There was no significant difference in OS between African American and Caucasian men in this matched cohort (HR=0.928, 95% CI=0.583-1.477, *p*=0.753). Subgroup analysis based on clinical or pathological variables demonstrated no significant survival differences (Figure 3). Sensitivity analysis revealed no significant interactions between race and treatment (Table II) or race and age (Table IV).

Among the patients of the unfavorable-risk group (n=13,280), no significant survival difference was seen between African American and Caucasian race (Figure 2B). A total of 1,468 cases were matched (Table III). Most were at high risk (n=1,317; 90%) with PSA>20 ng/ml (n=1,141; 78%). African American and Caucasian men had no significant difference in OS (hazard ratio=0.972, 95% confidence interval=0.765-1.236, *p*=0.819). Subgroup analysis demonstrated Caucasian race was a predictor for greater OS in the cohort aged ≤60 years (HR=0.320, 95% CI=0.137-0.752, *p*=0.009) (Figure 4). Sensitivity analysis demonstrated no significant interaction between race and treatment (Table II), but did demonstrate a significant interaction between race and age (HR=1.046, 95% CI=1.009-1.084, p=0.015) (Table IV).

Discussion

No survival difference was observed between African American and Caucasian men in both the favorable risk cohort receiving radiation (BT or EBRT) and the unfavorable risk cohort receiving radiation (EBRT plus ADT or EBRT plus BT and ADT). BT-containing therapy, either BT monotherapy for favorable risk or BT boost in unfavorable risk, did not significantly differ in race-specific survival. In the favorable-risk group, multivariate analysis demonstrated that radiation modality did not significantly influence survival, while EBRT plus BT and ADT conferred a significant survival advantage, regardless of race (Table II).

The lack of survival difference between African American and Caucasian men in our study is consistent with several smaller retrospective studies (13-17). One series of 2,301 patients (270 African Americans) receiving BT-containing therapy across all risk groups demonstrated no significant difference in OS between African American and Caucasian race, with comparable biochemical disease-free survival in the intermediate- and high-risk groups (11). Similarly, in a series from Memorial Sloan Kettering of 1,081 patients (246 African Americans) receiving BT-containing therapy, no significant difference in biochemical disease-free survival was observed at 5 years between African American and Caucasian men in risk- matched cohorts (14). In a retrospective study of four randomized trials from 1975 to 1992, which included 191 African Americans, no OS or disease-specific survival differences were seen between African American and
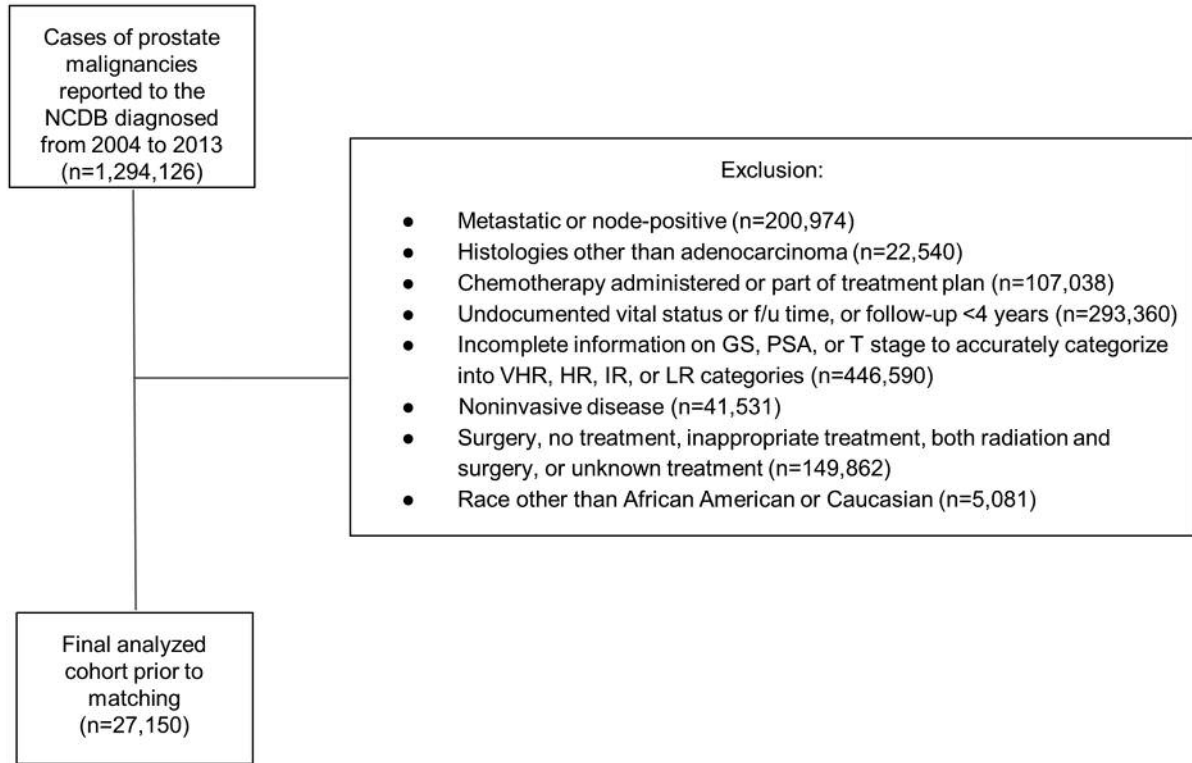
Figure 1. *CONSORT diagram. GS: Gleason score; HR: high risk; LR: low risk; NCDB: National Cancer Database; PSA: prostate-specific antigen; IR: intermediate risk; RT: radiation therapy; VHR: very high risk.*
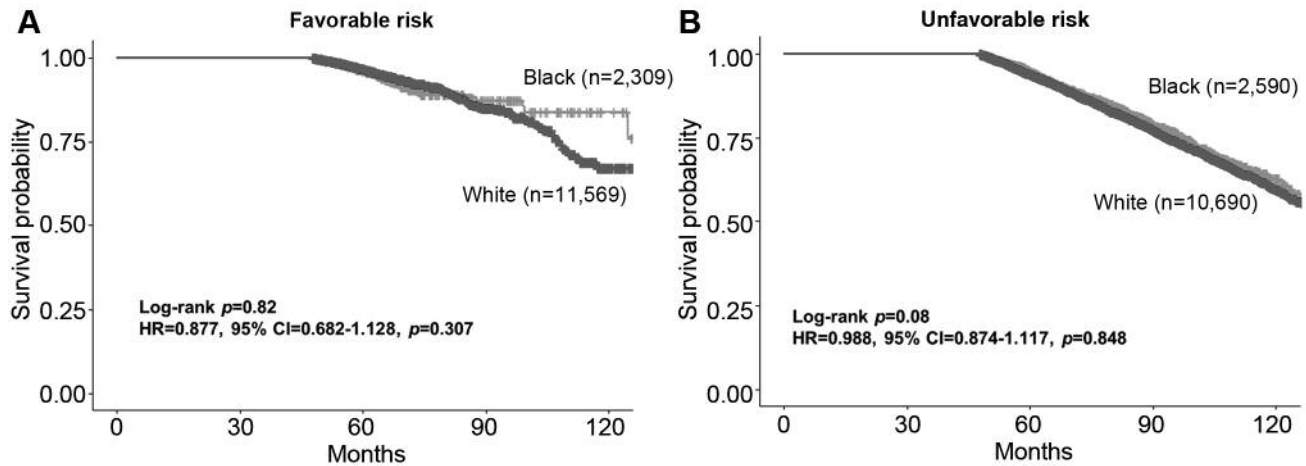
Figure 2. *Kaplan-Meier curves comparing survival between African Americans (AfAs) and Caucasians (Ccs) in favorable (A) and unfavorable (B) risk cohorts. HR: Hazard ratio; CI: confidence interval.*

Caucasian men receiving EBRT with/without ADT (12). In contrast to many of the aforementioned studies, a significant strength of our study is the large number of African Americans (n=4,818) in the database that were investigated, as well as the inclusion of only modern treatment regimens, particularly excluding any patient that did not receive dose-escalated EBRT (at least 7,560 cGy), and excluding those high-risk patients who did not receive ADT with EBRT.

Table I. *Patient baseline characteristics in the matched, favorable-risk cohort according to race.*

		Race, n (%)			
		African American N=1344	Caucasian N=1344	*p*-Value	SMD
Age, years	Mean±SD	64.55±6.73	64.77±6.80	0.386	0.033
Treatment	BT	757 (52.3)	706 (52.5)	0.053	0.076
	EBRT	587 (43.7)	638 (47.5)		
Facility type	Academic	620 (46.1)	569 (42.3)	0.052	0.076
	Community	724 (53.9)	775 (57.7)		
Facility location	Midwest	220 (16.4)	238 (17.7)	0.225	0.081
	Northeast	243 (18.1)	217 (16.1)		
	South	813 (60.5)	836 (62.2)		
	West	68 (5.1)	53 (3.9)		
Diagnosis to treatment start	0-90 Days	655 (48.7)	660 (49.1)	0.709	0.032
	>90 Days	675 (50.2)	674 (50.1)		
	Unknown	14 (1.0)	10 (0.7)		
Insurance status	Insured	1339 (99.6)	1340 (99.7)	1.000	0.013
	Uninsured	5 (0.4)	4 (0.3)		
Median income	<38,000 $	317 (23.6)	321 (23.9)	0.598	0.039
	≥38,000 $	1026 (76.3)	1023 (76.1)		
	Unknown	1 (0.1)	0 (0.0)		
Comorbidities	Absent	1206 (89.7)	1222 (90.9)	0.328	0.040
	Present	138 (10.3)	122 (9.1)		
Risk group	Low	946 (70.4)	932 (69.3)	0.585	0.023
	Favorable intermediate	398 (29.6)	412 (30.7)		
PSA, ngl/ml*	≤10	1329 (98.9)	1326 (98.7)	0.726	0.020
	10-20	15 (1.1)	18 (1.3)		
Gleason score[†]	≤6	957 (71.2)	943 (70.2)	0.582	0.023
	7 (3+4)	387 (28.8)	401 (29.8)		
T-Stage	T1	1240 (92.3)	1222 (90.9)	0.237	0.048
	T2	104 (7.7)	122 (9.1)		

BT: Brachytherapy; EBRT: external beam radiation therapy; ADT: androgen deprivation therapy; SMD: standardized mean difference; CI: confidence interval; [†]combined score.

Table II. *Hazard ratios (HR) and confidence intervals (CI) for death in propensity score-matched favorable- and unfavorable-risk cohorts according to race and treatment, with treatment modality interaction term*.*

	Favorable risk			Unfavorable risk		
Variable		HR (95% CI)	*p*-Value		HR (95% CI)	*p*-Value
Race	African American	Reference		African American	Reference	
	Caucasian	0.636 (0.309-1.311)	0.22	Caucasian	0.9545 (0.742-1.227)	0.714
Treatment	BT	Reference		EBRT+ADT	Reference	
	EBRT	1.136 (0.580-2.224)	0.711	EBRT+BT+ADT	0.491 (0.255-0.944)	0.033
Race × Treatment		1.983 (0.755-5.209)	0.165		1.246 (0.525-2.956)	0.618

BT: Brachytherapy; EBRT: external beam radiation therapy; ADT: androgen deprivation therapy. *Controlled for socioeconomic factors, age, comorbidity, risk, clinical Gleason, prostate-specific antigen, clinical T-stage, and treatment delay.

A notable finding of our study is the significant interaction of race with age for the unfavorable-risk group (Table IV). Subgroup analysis of the younger (age ≤60 years) unfavorable risk cohort demonstrated that Caucasian race was a significant predictor for improved OS. Our findings suggest that young African American men with unfavorable-risk prostate cancer may have a significantly more aggressive disease entity portending a worse OS than that of Caucasian men in the same age category, which is not seen in the older cohort, nor in those with favorable risk disease. Furthermore,

Table III. *Patient baseline characteristics in the matched, unfavorable-risk cohort according to race.*

Race		Race, n (%)			
		African American N=734	Caucasian N=734	*p*-Value	SMD
Age, years	Mean±SD	68.02±6.88	68.03±6.88	0.984	0.001
Treatment	EBRT+ADT	651 (98.7)	646 (88)	0.745	0.021
	EBRT+BT+ADT	83 (11.3)	88 (12.0)		
	Academic	275 (37.5)	279 (38.0)	0.872	0.011
	Community	459 (62.5)	455 (62.0)		
Facility Location	Midwest	136 (18.5)	135 (18.4)	0.999	0.007
	Northeast	161 (21.9)	163 (22.2)		
	South	391 (53.3)	390 (53.1)		
	West	46 (6.3)	46 (6.3)		
Diagnosis to treatment start	0-90 Days	660 (89.9)	657 (89.5)	0.967	0.013
	>90 Days	49 (6.7)	51 (6.9)		
	Unknown	25 (3.4)	26 (3.5)		
Insurance status	Insured	733 (99.9)	733 (99.9)	>0.999	<0.001
	Uninsured	1 (0.1)	1 (0.1)		
Median income	<38,000 $	147 (20.0)	147 (20.0)	0.846	0.030
	≥38,000 $	586 (79.8)	585 (79.7)		
	Unknown	1 (0.1)	2 (0.3)		
Comorbidities	Absent	702 (95.6)	699 (95.2)	0.802	0.020
	Present	32 (4.4)	35 (4.8)		
Risk group	Unfavorable intermediate	44 (6.0)	44 (6.0)	0.992	0.007
	High	659 (89.8)	658 (89.6)		
	Very high	31 (4.2)	32 (4.4)		
PSA, ngl/ml	<10	115 (15.7)	120 (16.3)	0.710	0.061
	10-20	48 (6.5)	43 (5.9)		
	>20	571 (77.8)	570 (77.7)		
Gleason score†	≤6	4 (0.5)	5 (0.7)	0.999	0.025
	7	72 (9.8)	74 (10.1)		
	8	72 (9.8)	73 (9.9)		
	9	24 (3.3)	22 (3.0)		
	10	1 (0.1)	1 (0.1)		
	Unknown	561 (76.4)	559 (76.2)		
T-Stage	T1	387 (52.7)	384 (52.3)	0.837	0.063
	T2	264 (36.0)	263 (35.8)		
	T3	81 (11.0)	85 (11.6)		
	T4	2 (0.3)	1 (0.1)		
	Tx	0 (0.0)	1 (0.1)		

BT: Brachytherapy; EBRT: external beam radiation therapy; ADT: androgen deprivation therapy; SMD: standardized mean difference; CI: confidence interval; †combined score.

this finding is consistent with prior evidence showing that prostate cancer of younger patients is a biologically different entity with greater likelihood for genetic etiology (10).

Although African American men may have more aggressive prostate cancer compared to their Caucasian counterparts, their similar survival on treatment with definitive radiotherapy may be due to a different gene-expression profile compared to that of Caucasian men, making their disease more sensitive to radiation (7-9, 18-21). Significant differences in genomic expression have already been established, including CYP17 polymorphisms, high risk TET2 variants, 8q24 variants, and 17q21 variants (4, 7, 21). One study created four prognostic genomic subgroups (gain of chromosome 7, deletion of 8p/gain of 8q, loss of 8p and 16q, and quiet genome) which successfully stratified outcomes of patients undergoing definitive surgery or radiation therapy (19). Another study of cases from two randomized trials found that specific markers for tumor hypoxia and angiogenesis, particularly expression of vascular endothelial growth factor and hypoxia-inducible-factor-alpha, were negative prognosticators in those undergoing radiation or surgery, but osteopontin expression was a negative prognosticator for those undergoing surgery but not radiation, thus highlighting different responses to treatment modalities based on the biology of the disease (20).

Recent evidence has shown that African American men may even do better than Caucasian men with radiation therapy.
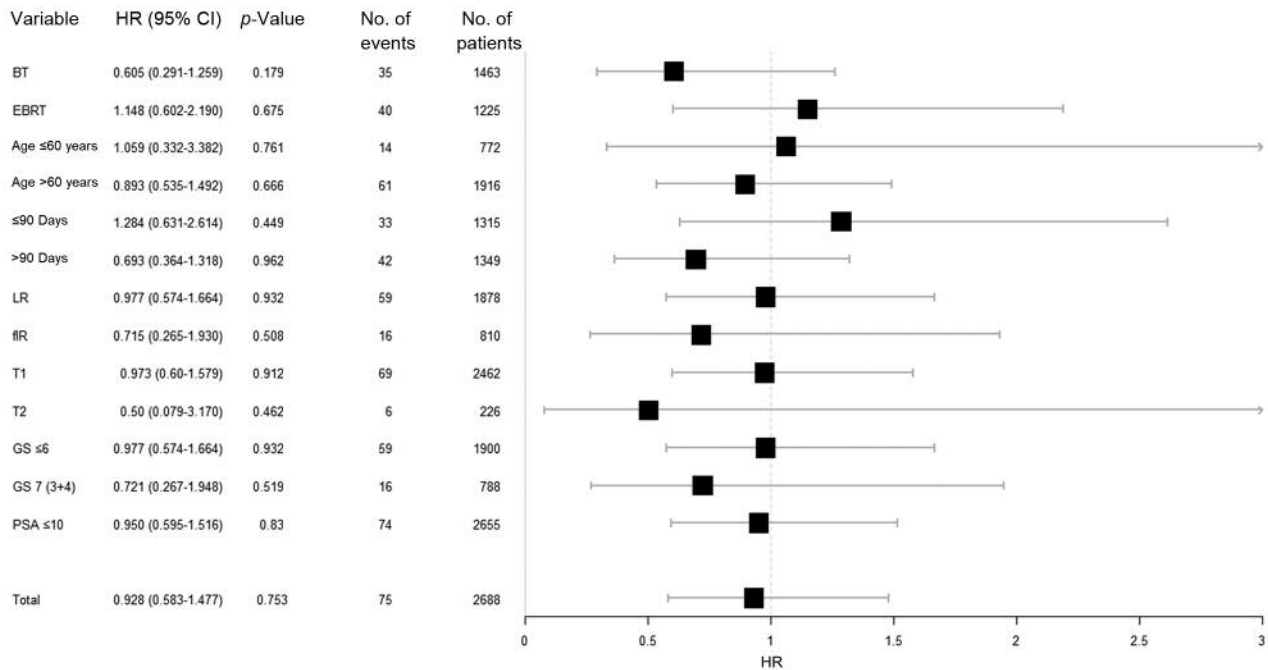
Variable	HR (95% CI)	*p*-Value	No. of events	No. of patients
BT	0.605 (0.291-1.259)	0.179	35	1463
EBRT	1.148 (0.602-2.190)	0.675	40	1225
Age ≤60 years	1.059 (0.332-3.382)	0.761	14	772
Age >60 years	0.893 (0.535-1.492)	0.666	61	1916
≤90 Days	1.284 (0.631-2.614)	0.449	33	1315
>90 Days	0.693 (0.364-1.318)	0.962	42	1349
LR	0.977 (0.574-1.664)	0.932	59	1878
fIR	0.715 (0.265-1.930)	0.508	16	810
T1	0.973 (0.60-1.579)	0.912	69	2462
T2	0.50 (0.079-3.170)	0.462	6	226
GS ≤6	0.977 (0.574-1.664)	0.932	59	1900
GS 7 (3+4)	0.721 (0.267-1.948)	0.519	16	788
PSA ≤10	0.950 (0.595-1.516)	0.83	74	2655
Total	0.928 (0.583-1.477)	0.753	75	2688

Figure 3. *Subgroup analysis forest plot of hazard ratios (HR) and confidence intervals (CI) in African Americans (AfAs) and Caucasians (Ccs) with favorable risk. HR greater than 1 favors African American race. BT: Brachytherapy; EBRT: external beam radiotherapy; LR: low risk; fIR: favorable intermediate risk; GS: Gleason score; PSA: prostate-specific antigen.*
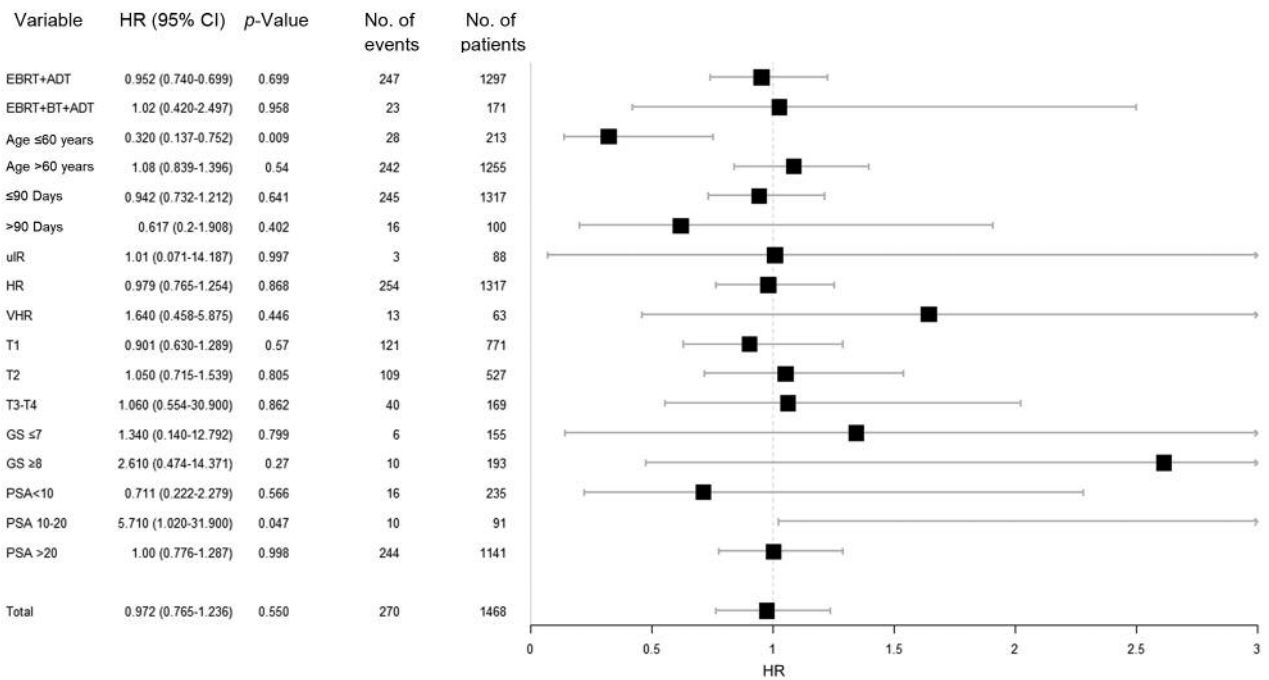
Variable	HR (95% CI)	*p*-Value	No. of events	No. of patients
EBRT+ADT	0.952 (0.740-0.699)	0.699	247	1297
EBRT+BT+ADT	1.02 (0.420-2.497)	0.958	23	171
Age ≤60 years	0.320 (0.137-0.752)	0.009	28	213
Age >60 years	1.08 (0.839-1.396)	0.54	242	1255
≤90 Days	0.942 (0.732-1.212)	0.641	245	1317
>90 Days	0.617 (0.2-1.908)	0.402	16	100
uIR	1.01 (0.071-14.187)	0.997	3	88
HR	0.979 (0.765-1.254)	0.868	254	1317
VHR	1.640 (0.458-5.875)	0.446	13	63
T1	0.901 (0.630-1.289)	0.57	121	771
T2	1.050 (0.715-1.539)	0.805	109	527
T3-T4	1.060 (0.554-30.900)	0.862	40	169
GS ≤7	1.340 (0.140-12.792)	0.799	6	155
GS ≥8	2.610 (0.474-14.371)	0.27	10	193
PSA<10	0.711 (0.222-2.279)	0.566	16	235
PSA 10-20	5.710 (1.020-31.900)	0.047	10	91
PSA >20	1.00 (0.776-1.287)	0.998	244	1141
Total	0.972 (0.765-1.236)	0.550	270	1468

Figure 4. *Subgroup analysis forest plot of hazard ratios (HR) and confidence intervals (CI) in African Americans (AfAs) and Caucasians (Ccs) with unfavorable risk. HR greater than 1 favors African American race. BT: Brachytherapy; EBRT: external beam radiotherapy; uIR: unfavorable intermediate risk; HR: high risk; VHR: very high risk; GS: Gleason score; PSA: prostate-specific antigen.*

Table IV. *Hazard ratios (HR) and confidence intervals (CIs) for death in propensity score-matched favorable- and unfavorable-risk cohorts according to race and age, with age interaction term*.*

		Favorable risk		Unfavorable risk	
Variable		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Race	African American	Reference		Reference	
	Caucasian	1.031 (0.630-1.687)	0.905	0.917 (0.716-1.174)	0.493
Age		1.032 (0.978-1.088)	0.248	1.015 (0.989-1.041)	0.258
Race × Age		0.956 (0.975-1.121)	0.208	1.046 (1.009-1.084)	0.015

*Controlled for socioeconomic factors, comorbidity, risk, clinical Gleason, prostate-specific antigen, clinical T-stage, and treatment delay.

Using a scale to predict radiotherapy response called the PORTOS (a 24-gene Post-Operative Radiation Therapy Outcomes Score) (18), Spratt et al. demonstrated that African American men had a higher PORTOS score than Caucasian men, which was clinically validated using patients receiving radiation from four RTOG trials (18.5% African American race); PSM multivariate analysis demonstrated African American race predicted improved biochemical recurrence (HR=0.82, 95% CI=0.74-0.92, *p*<0.001) and DM rates (HR=0.7, 95% CI=0.57-0.86, *p*<0.001) (8). Genomic risk stratification of prostate cancer appears to have great potential compared to the current NCCN risk stratification and may allow for better tailoring of treatment options. Unfortunately, many of the large genomic studies under-represented African Americans and over-represented Caucasians, consequently having inadequate power to detect mutational frequency rates in African Americans with prostate cancer, hence making it difficult to stratify risk better and prognosticate their disease compared to that of Caucasians (22, 23).

Our major limitation is due to the retrospective nature of our study. We attempted to control selection bias and influential covariates by using PSM analysis. However, without randomization, there will always be undefined covariates that may explain the absence of survival differences. In addition, the database is limited to OS data only, yet there may be a significant influence of competing risks which may play a significant role in the observed survival rates. Additionally, PSM analysis inherently selects a subgroup of the total population in an attempt to reduce confounding. However, in doing so, the selected sample may not accurately represent the general population; although all matched cohorts were well-balanced in all selected covariates, the majority of matched patients had no comorbidities, were insured and had income ≥38,000 $.

Conclusion

No difference in survival was observed between African American and Caucasian men when treated with risk-appropriate definitive radiotherapy. However, younger (age ≤60 years) African American men with unfavorable risk have poorer survival than their Caucasian counterparts and may harbor a significantly different biology of disease.

Conflicts of Interest

All Authors listed contributed sufficiently to the project to be included as authors, and all those who are qualified to be authors are listed in the author byline. To the best of our knowledge, no conflict of interest, financial or other, exists. No specific funding was received for this work.

Authors' Contributions

Joyson Kodiyan: Writing, methodology, statistical design, reviewing, editing. Mark Ashamalla: reviewing, editing. Adel Guirguis: data acquisition, statistical design. Hani Ashamalla: supervision, conceptualization, methodology, reviewing, editing.

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