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Racial disparities in brachytherapy administration and survival in women with locally advanced cervical cancer

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HIGHLIGHTS

- Black women with locally advanced cervical cancer are less likely to receive brachytherapy compared to non-black women.
- Black women have worse all-cause mortality compared to non-black women.
- Brachytherapy use mediates survival differences by race in the inverse probability treatment weighting interaction model.
- Survival among black women with cervical cancer may be improved by increasing access to brachytherapy services.

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ABSTRACT

Objective. Black women have the highest incidence and mortality from cervical cancer in the United States. This study evaluated whether racial disparities in the receipt of brachytherapy (BT) for locally advanced cervical cancer mediate survival differences by race using the National Cancer Database.

Methods. A retrospective cohort study was performed using 16,116 women with stage IB2-IVA cervical cancer treated from 2004 to 2014. Women who did not receive external beam radiation therapy, those with unknown survival data or stage, and those status post hysterectomy or pelvic exenteration were excluded. Multivariate logistic regression was performed to evaluate factors associated with BT use. Using a propensity score adjusted model with inverse probability treatment weighting, adjusted hazard ratios for overall survival were calculated, including an interaction term between BT and race.

Results. Of 16,116 patients, 19.2% were black and 55.8% received BT. Black women were significantly less likely to receive BT (AOR 0.87, 95% confidence interval [CI] 0.79–0.96, $p = 0.007$) and had worse all-cause mortality (median survival 3.9 years [95% CI 3.6–4.6] versus 5.2 years [95% CI 4.9–5.5] for non-black women, $p < 0.001$). In the adjusted model, black patients had an increased risk of death compared to non-black patients (AHR 1.14, 95% CI 1.05–1.24; $p = 0.002$) among women who did not receive BT. However, there was no difference in survival by race when both groups received BT (AHR 1.04, 95% CI 0.95–1.13, $p = 0.42$; p-interaction $= 0.005$).

Conclusions. Black women with locally advanced cervical cancer are less likely to receive brachytherapy, which mediates survival differences by race. Improving access to brachytherapy may improve overall survival.

1. Introduction

Cervical cancer is the fourth most common cancer among women worldwide, with an estimated 12,820 new diagnoses in the United States in 2017 [1]. The National Comprehensive Cancer Network (NCCN) recommends that primary therapy for locally advanced cervical cancer (stage IB2, IIA2, IIB to stage IVA) consist of external beam radiation therapy (EBRT) with concurrent chemotherapy, followed by intracavitary/interstitial brachytherapy (BT) completed in <8 weeks [2]. Specifically, use of BT has been associated with improved patient outcomes including cancer-specific and overall survival [3–5].

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African American, Hispanic, and American Indian women have the highest incidences of cervical cancer in the United States [1,6,7]. Importantly, mortality is worse for black patients diagnosed with cervical cancer [7,8]. Hispanic and Asian women have similar to improved survival outcomes compared to white women, and thus racial disparities in cervical cancer mortality predominate among black women [9,10]. A health disparity is defined as a health difference that is closely linked with social, economic, and/or environmental disadvantage [11]. Multiple factors have been implicated as drivers of racial disparities in cervical cancer care, including differences in pap smear screening [12,13] and variation in stage at diagnosis. Black women are more likely to present with regional or distant disease and less likely to have local disease at time of presentation [7,12,14].

Treatment differences may also play a role in racial disparities in cervical cancer. Black women are less likely to receive a radical hysterectomy for early stage disease [15]. In the setting of locally advanced disease, studies have reached varying conclusions on the impact of race on brachytherapy (BT) utilization [8,16,17]. Two large population studies involving Survival, Epidemiology, and End Results (SEER) and National Cancer Database (NCDB) data did not find any association between BT use and race, although these studies were not specifically designed to examine this question [3,18]. In a third study utilizing NCDB data, Robin, et al. found that black women with cervical cancer were less likely to receive the standard of care for radiation; however, they did not specifically examine the interaction between radiation, race, and survival [19]. The present study sought to determine whether racial differences in the receipt of BT mediate racial disparities in overall survival.

2. Methods

A retrospective cohort study was performed using the NCDB. This database collects information from approximately 1500 cancer programs accredited by the American College of Surgeons' Commission on Cancer. Approximately 70% of all patients newly diagnosed with cancer in the United States are captured by the NCDB [20]. While the SEER database uses regional cancer registries, the NCDB registry is hospital-based. Compared with SEER data, the NCDB reports more information regarding radiotherapy modality and timing, chemotherapy use, and comorbidities (using the Charlson/Deyo comorbidity index) [20,21].

Women diagnosed with stage IB2, IIA2, IIB to IVA cervical cancer who received treatment at a reporting facility from January 1, 2004 to December 31, 2014 were included. All histologies were included and categories of squamous cell histology and non-squamous cell histology were used. Squamous cell histology was defined as codes 8070, 8071, 8072, 8073, 8074, 8075, 8076 in the database. In the NCDB, stage is entered into the database using the American Joint Committee on Cancer staging manual edition that was in use during the year in which the case was diagnosed. Women with missing stage were excluded from the analysis. Women were also excluded from the study if they had unknown survival data, did not receive EBRT, or if they underwent hysterectomy or pelvic exenteration.

Statistical analyses were performed using R, version 3.5.0. A p-value of 0.05 was set as the threshold for statistical significance. To identify factors associated with BT use, multivariate logistic regression was used. The following baseline variables were included in the model: race (black versus non-black), age (41–50, 51–60, 61–70, >70), Charlson/Deyo score (0, 1, 2 or more), stage (IB2, II, III, IVA), histology (squamous versus non-squamous), facility location (Northeast, Midwest, South, West), facility type (academic versus non-academic hospital), education (percent of people in patient's area of residence who completed high school, divided into quartiles), income (divided into quartiles), insurance status (private, government, not insured/unknown), facility distance, patient's living setting (metropolitan, urban, rural, other/missing), clinical nodal status (positive versus negative/not available), and year of diagnosis (2004–2009 versus 2010–2014). Race was defined as black or non-black race given previous data has shown similar and even increased survival rates for Hispanic and Asian-American patients compared to white patients, and this study was designed to focus on disparities among black women [9,10]. Boost modality was defined as BT boost or no BT boost (encompassing both patients who received EBRT boost and no boost modality). For facility type, academic hospitals were defined as facilities listed as Academic/Research Program in the NCDB, and non-academic centers were defined as all other facility types (Comprehensive Community Cancer Program, Community Cancer Program, and Integrated Network Cancer Program).

Propensity score adjustment with inverse probability treatment weighting (IPTW) was performed in order to balance baseline covariates between women who did and did not receive BT [22]. A generalized boosting method was used to create the IPTW-adjusted synthetic populations with matched baseline covariates [23]. The standardized difference was used to assess covariate balance between groups, and a value <10% (0.1) was defined as a negligible difference. Variables included in the IPTW model included race, age, Charlson/Deyo score, stage, histology, facility location, facility type, education, income, insurance status, facility distance, living setting, clinical nodal status, and year of diagnosis, given these are factors that may affect treatment received.

To evaluate overall survival by race, IPTW-adjusted Kaplan-Meier curves of women stratified by BT boost and race were obtained. An IPTW-adjusted multivariate Cox proportional hazards model was then used to evaluate the influence of the following variables on overall survival: time to treatment initiation (months), boost modality, and

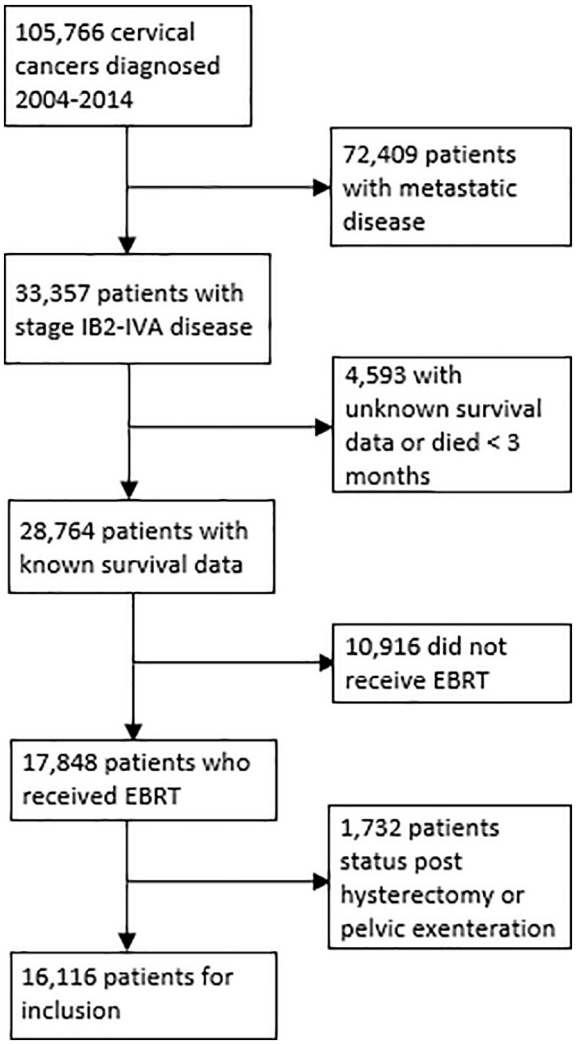

Fig. 1. Flowchart of application of inclusion/exclusion criteria.

Table 1
Demographic and treatment characteristics of the study population and chi square comparison by race.

Characteristic	N	%	Black ($N = 3099$)	Non-Black ($N = 13,017$)	p
Boost modality					
BT boost	8993	55.8%	1558 (50.3%)	7435 (57.1%)	<0.001
No BT boost	7123	44.2%	1541 (49.7%)	5582 (42.9%)	
Chemotherapy					
Yes	13,871	86.1%	2568 (82.9%)	11,303 (86.8%)	<0.001
No	2245	13.9%	531 (17.1%)	1714 (13.2%)	
Age					
≤ 40	2521	15.6%	514 (16.6%)	2007 (15.4%)	0.09
41–50	3990	24.8%	752 (24.3%)	3238 (24.9%)	
51–60	4193	26.0%	796 (25.7%)	3397 (26.1%)	
61–70	2757	17.1%	495 (16.0%)	2262 (17.4%)	
> 70	2655	16.5%	542 (17.5%)	2113 (16.2%)	
Insurance Type					
Private	5535	34.3%	835 (26.9%)	4700 (36.1%)	<0.001
Government	8231	51.1%	1783 (57.5%)	6448 (49.5%)	
Not insured/Unknown	2350	14.6%	481 (15.5%)	1869 (14.4%)	
Income					
< $38,000	4438	27.5%	1528 (49.3%)	2910 (22.4%)	<0.001
$38,000 - $47,999	4259	26.4%	675 (21.8%)	3584 (28.0%)	
$48,000 - $62,999	3940	24.4%	537 (17.3%)	3403 (26.1%)	
$63,000+	3274	20.3%	328 (10.6%)	2946 (22.6%)	
Stage					
IB2	1439	8.9%	238 (7.7%)	1201 (9.2%)	<0.001
II	7182	44.6%	1308 (42.2%)	5874 (45.1%)	
III	6289	39.0%	1336 (43.1%)	4953 (38.1%)	
IVA	1206	7.5%	217 (7.0%)	989 (7.6%)	
Histology					
Squamous cell	13,093	81.2%	2631 (84.9%)	10,462 (80.4%)	<0.001
Non-squamous cell	3023	18.8%	468 (15.1%)	2555 (19.6%)	
Facility Type					
Academic	6564	40.7%	1462 (47.2%)	5102 (39.2%)	<0.001
Non-Academic	7031	43.6%	1123 (36.2%)	5908 (45.4%)	
Unknown	2521	15.6%	514 (16.6%)	2007 (15.4%)	
Facility Location					
Northeast	2850	17.7%	566 (18.3%)	2284 (17.5%)	<0.001
Midwest	3145	19.5%	486 (15.7%)	2659 (20.4%)	
South	5181	32.2%	1408 (45.4%)	3773 (29.0%)	
West	2419	15.0%	125 (4.0%)	2294 (17.6%)	
Unknown	2521	15.6%	514 (16.6%)	2007 (15.4%)	
Facility Distance					
< 5 miles	4431	27.5%	1227 (39.6%)	3204 (24.6%)	<0.001
5.1–10 miles	3438	21.3%	783 (25.3%)	2655 (20.4%)	
10.1–30 miles	4548	28.2%	641 (20.7%)	3907 (30.0%)	
> 30 miles	3486	21.6%	412 (13.3%)	3074 (23.6%)	
Education (% who did not graduate high school)					
≥ 21%	4678	29.0%	1300 (41.9%)	3378 (26.0%)	<0.001
13–20.9%	4813	29.9%	1111 (35.9%)	3702 (28.4%)	
7–12.9%	4330	26.9%	520 (16.8%)	3810 (29.3%)	
< 7%	2092	13.0%	138 (4.5%)	1954 (15.0%)	
Urban or Rural					
Metropolitan	12,977	80.5%	2694 (86.9%)	10,283 (79.0%)	<0.001
Urban	2350	14.6%	311 (10.0%)	2039 (15.7%)	
Rural	296	1.8%	33 (1.1%)	263 (2.0%)	
Other/missing	493	3.1%	61 (2.0%)	432 (3.3%)	
Charlson/Deyo Score					
0	13,702	85.0%	2538 (81.9%)	11,164 (85.8%)	<0.001
1	1863	11.6%	412 (13.3%)	1451 (11.1%)	
2 or more	551	3.4%	149 (4.8%)	402 (3.1%)	
Clinical Nodal Status					
Negative	11,823	73.4%	2271 (73.3%)	9552 (73.4%)	0.93
Positive	4293	26.6%	828 (26.7%)	3465 (26.6%)	
Year of Diagnosis					
2004–2009	7503	46.6%	1496 (48.3%)	6007 (46.1%)	0.04
2010–2014	8613	53.4%	1603 (51.7%)	7010 (53.9%)	

chemotherapy use. Time to radiation initiation was included as a time-dependent covariate. An interaction term between race and boost modality was included to determine whether receipt of BT mediated differences in overall survival between black and non-black patients. Finally, chi squared anaysis was used to determine whether there were racial differences in time to completion of radiation by race among women who received BT (≤8 weeks versus >8 weeks).

3. Results

After exclusion criteria were applied, 16,116 women with stage IB2 to IVA cervical cancer who received primary treatment with EBRT were identified during the study period (Fig. 1). Of these women, 8993 women (55.8%) received a BT boost, and 7123 women (44.2%) did not. A total of 13,017 patients (80.8%) were non-black and 3099

Table 2
Results of multivariate logistic regression for factors associated with brachytherapy use.

Characteristic	OR brachytherapy	95% CI	p
Race			
Non-Black	1.0	Reference	
Black	0.87	0.79–0.96	0.007*
Age			
41-50[a]	1.0	Reference	
51-60	0.91	0.83–1.00	0.06
61–70	0.83	0.75–0.93	<0.001*
> 70	0.54	0.48–0.60	<0.001*
Insurance Type			
Private	1.0	Reference	
Government	0.84	0.77–0.92	<0.001*
Not insured/Unknown	0.70	0.63–0.79	<0.001*
Income			
< $38,000	1.0	Reference	
$38,000 - $47,999	1.08	0.97–1.20	0.15
$48,000 - $62,999	1.06	0.94–1.20	0.32
$63,000+	1.09	0.94–1.26	0.28
Stage			
IB2	1.0	Reference	
II	0.89	0.77–1.04	0.15
III	0.47	0.41–0.55	<0.001*
IVA	0.20	0.17–0.25	<0.001*
Histology			
Squamous cell	1.0	Reference	
Non-squamous cell	0.89	0.81–0.97	0.01*
Facility Type			
Academic/Research Program	1.0	Reference	
Non-Academic	0.78	0.73–0.84	<0.001*
Facility Location			
Northeast	1.0	Reference	
Midwest	0.95	0.85–1.07	0.40
South	0.70	0.63–0.77	<0.001*
West	0.88	0.78-0.99	0.04*
Facility Distance			
≤5 miles	1.0	Reference	
5.1–10 miles	1.05	0.95–1.17	0.33
10.1–30 miles	1.09	0.99–1.21	0.08
>30 miles	1.38	1.22–1.57	<0.001*
Education (% who did not graduate high school)			
≥ 21%	1.0	Reference	
13–20.9%	1.04	0.94–1.15	0.41
7–12.9%	1.09	0.97–1.23	0.16
< 7%	1.02	0.87–1.19	0.82
Urban or Rural			
Metropolitan	1.0	Reference	
Urban	0.81	0.61–1.07	0.14
Rural	0.97	0.86–1.10	0.63
Charlson/Deyo Score			
0	1.0	Reference	
1	1.04	0.93–1.16	0.50
2 or more	0.75	0.62–0.90	0.003*
Clinical Nodal Status			
Negative	1.0	Reference	
Positive	0.94	0.86–1.02	0.12
Year of Diagnosis			
2004–2009	1.0	Reference	
2010–2014	1.31	1.21–1.41	<0.001

OR = odds ratios. CI = confidence interval.
* Statistically significant ($p \le 0.05$).
[a] Reference of age 41–50 was set given no facility location or facility type listed for all patients under age 40.

women were black (19.2%). The mean age was 54.3 ± 14.5 for non-black women versus 54.3 ± 15.0 for black women, ($p = 0.92$). Of non-black patients, 11,764 (90.4%) were white. Black women were more likely to be enrolled in governmental insurance, to be in the lowest income quartile, and were less likely to have graduated high school. Regional differences were also noted by race, with black women predominantly receiving treatment in the South (45.4% of black versus 29.0% of non-black women). Table 1 lists these and other demographic data, comparing by race using chi square.

Multivariate logistic regression revealed that black women were significantly less likely to receive BT compared to non-black women (OR 0.87, 95% confidence interval [CI] 0.79–0.96, $p = 0.007$). Fifty-seven percent of non-black women received a BT boost, compared to 50.3% of black women. Additionally, 29.2% of black women compared to 24.2% of non-black women received no boost modality, and 20.6% of black women versus 18.7% of non-black women received EBRT boost ($\chi 2 = 50.21$, $p < 0.001$). Women >age 60 were significantly less likely to receive BT compared to younger women. Additionally, women had a lower likelihood of receiving BT if they had governmental insurance (Medicare or Medicaid), were uninsured or with unknown insurance status, had stage III-IVA disease, had non-squamous cell histology, received care from a non-academic center, were treated in the South and West of the United States, or had a Charlson/Deyo score of 2 or more (see Table 2).

Black race was associated with a shorter median survival (3.9 years, 95% CI 3.6–4.6) compared to non-black race (5.2 years, 95% CI 4.9–5.5, $p < 0.001$) on Kaplan Meier analysis. IPTW-adjustment showed appropriate baseline covariate balance between patients who did and did not receive a BT boost (see balance table in Supplemental material). In the IPTW-adjusted multivariate model, black women were noted to have a significantly higher risk of death compared to non-black women among patients who did not receive BT (AHR 1.14; 95% CI 1.05–1.24; $p = 0.002$). However, black women were noted to have similar survival to non-black women among patients who received BT (AHR 1.04; 95% CI 0.95–1.13, $p = 0.42$). The interaction term was statistically significant ($p = 0.005$, see Table 3), and highlights the convergence of the black/BT and non-black/BT curves shown in the IPTW-adjusted Kaplan Meier curves in Fig. 2. In sensitivity analysis, when the model was repeated for patients who received chemotherapy ($N = 13{,}871$), the hazard ratio for black women who did and did not receive BT were 1.07 (95% CI 0.97–1.18, $p = 0.16$) and 1.19 (95% CI 1.08–1.30, $p = 0.001$). The interaction term remained significant ($p = 0.001$).

Regarding time to completion of radiation therapy among women who received BT, black women were significantly less likely to complete radiation therapy in the recommended ≤8 weeks compared to non-black women (48.1% of non-black women versus 43.5% of black women, $p < 0.001$).

4. Discussion

The present study shows that black women with cervical cancer in the United States receive different treatment compared to women of other races. Black women in our study were significantly less likely to receive BT compared to non-black women. Consistent with prior data [7,8,24], we found that black women had a significant decrease in overall survival compared to non-black women. Furthermore, we determined that survival differences by race were mediated by BT use based on the interaction model, which was statistically significant.

Prior studies support our findings of differences in BT utilization by race [16,17]. In one study of 2034 women in Maryland, black women were significantly more likely to receive EBRT without BT compared to white women [17]. In another study which included 316 African American and 94 Caucasian cervical cancer patients, Mundt, et al [16], found a trend toward less frequent BT use among African American patients, although this did not reach statistical significance. In a recent study of California women, Mayadev, et al [8], examined 4783 women and found that black and Hispanic women trended toward lower utilization of boost therapy compared to white women. Finally, Robin, et al, similarly found that black women were less likely to receive a BT boost in their survival analysis of receipt of standard of care treatment using NCDB data [19].

Contrary to our results, Han, et al [3], found a difference in patterns of BT use by race using SEER data but did not find that race predicted BT use in their multivariable regression analysis. Our results may have been different from the Han, et al, study due to the larger number of

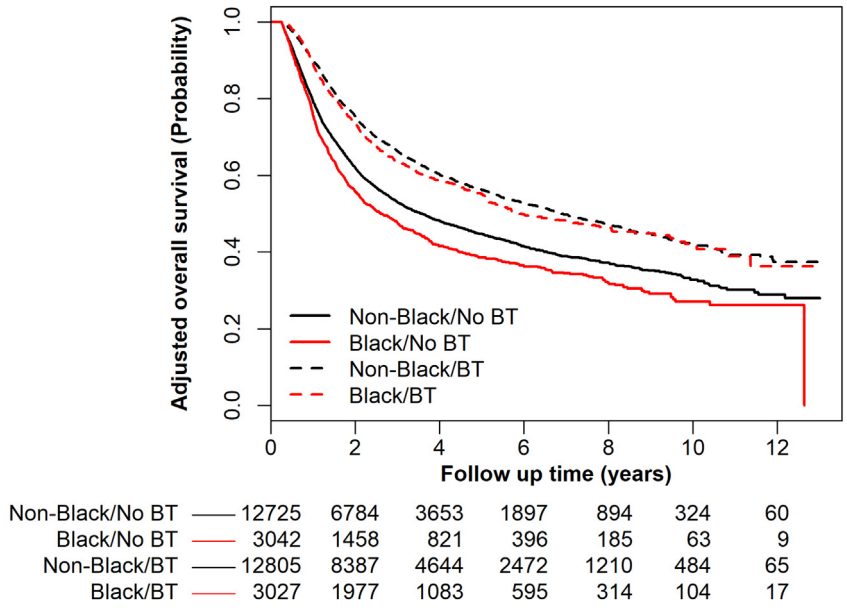

Fig. 2. Results of inverse probability treatment weighting-adjusted Kaplan-Meier analysis of non-black and black survival curves with and without brachytherapy use.

patients included in the NCDB versus the SEER database. Previous data suggests that the SEER database underreports radiation therapy use [25], while the NCDB records many details concerning radiotherapy (such as total dose, number of fractions, modality, region of body treated, and reason for no radiotherapy). Similarly, Gill, et al, found no difference in BT versus stereotactic body radiation therapy (SBRT)/intensity-modulated radiation therapy (IMRT) use by race using the NCDB [18]. However, their patient population specifically excluded patients who did not receive any boost modality, unlike our study.

There are several reasons why black women may be less likely to receive BT. While not directly tested in the present study, the most likely hypothesis is that black patients have poorer access to BT services. Supporting this, we found that women in the South and West of the United States were also less likely to receive BT, and 45.4% of black women in our cohort lived in the South. It is plausible that a paucity of treatment centers and trained physicians in the South of the United States contributes to difficulty in receiving BT. Prior data suggest a cumulative effect of living in the South and black race on survival in cervical cancer [26], and access to BT may in part explain this effect. Further study is needed to determine how access to BT plays a role in its underutilization in black women with cervical cancer.

Table 3
Results of inverse probability treatment weighting-adjusted multivariate Cox proportional hazards model for overall survival.

Clinical factor	Adjusted hazard ratio	95% CI	p
Time to treatment initiation (months)	1.26	1.10–1.44	0.001
Chemotherapy			
No	1.0	Reference	
Yes	0.56	0.53–0.60	<0.001
Brachytherapy boost			
No brachytherapy	1.0	Reference	
Brachytherapy	0.70	0.66–0.74	<0.001
Brachytherapy boost × race interaction	**Adjusted hazard ratio**	**95% CI**	**p**
Brachytherapy not administered			
Non-Black	1.0	Reference	
Black	1.14	1.05–1.24	0.002
Brachytherapy administered			
Non-Black	1.0	Reference	
Black	1.04	0.95–1.13	0.42

We found that BT mediates an increase in all-cause mortality in black individuals. Among patients who did not receive BT, black women had a higher risk of death compared with non-black women. However, black women had the same risk of dying compared to non-black women if they received BT. This analysis was performed with a propensity-adjusted model that balanced baseline covariates and accounted for other factors including chemotherapy, time to treatment, location, and time to completion of therapy. This highlights the importance of receiving BT and its impact on survival rates. This is the first study to our knowledge to show such an interaction between race and survival being mediated by one particular treatment modality. These results suggest that reducing racial disparities in survival is possible by increasing access to BT for black patients. This has important implications from a public health standpoint, and well-designed epidemiologic studies are needed to delineate the best ways to increase access for black patients. Notably, as alternative boost modalities such as IMRT and SBRT are increasingly used, radiation oncologists may become less familiar with BT techniques [18]. Our study highlights the importance of ensuring sufficient training in this treatment modality.

The significance of the finding that BT mediates differential racial survival curves is many-fold. It is plausible that blacks may have more radiosensitive tumors than non-black women, and BT may be more effective in black women. A recent meta-analysis examining men with prostate cancer suggested that black patients responded better to radiation than white patients [27]. In our dataset, black women were more likely to have squamous cell histology compared to white women, and previous research has shown increased radiosensitivity of HPV positive cervical cancers and squamous cell cancers compared to adenocarcinomas [28,29]. Additionally, black women who did not receive BT in our population were more likely to receive no boost rather than EBRT boost in chi square analysis. Thus, black women who did not receive BT likely also had poorer survival because they were undertreated compared to white women who did not receive BT. Further study is needed to delineate the significance of this finding.

Regarding timing of radiotherapy, we found that black women who received BT in our study were less likely to finish radiation in ≤8 weeks compared to white women, similar to previous work performed using the NCDB [30]. According to the NCCN Cervical Cancer Guidelines, radiation should be completed within 8 weeks of starting radiation therapy, which is used as a quality measure in the treatment of cervical cancer

[2]. Our study suggests that black women are less likely to receive this standard of care.

The strengths of this study include the large sample size utilizing the NCDB, which encompasses 70% of all cancer diagnoses in the United States. In comparison to the SEER database, the NCDB includes more patients, has more detailed information regarding radiation therapy, and includes comorbidity data, further strengthening our study. The propensity-adjusted nature of our analysis also allowed us to control for covariates that predict receiving BT. Additionally, prior studies have examined the differences between patients of several different races, whereas in our study we focused on black versus non-black patients. This comparison is more relevant in the discussion of racial disparities in cervical cancer since black women have the worst overall survival and women of other minorities tend to have similar or improved survival compared with white women [9,10].

A limitation of this study is the retrospective nature of data collection. While using a large database allows for a large sample size, there may also be errors in data input into the database and missing data. There may also be regional differences in treatment protocols, which would be difficult to detect. Additionally, the NCDB does not include cause-specific survival, only overall survival data. However, in cervical cancer, there is a strong correlation between cause-specific survival and overall survival [31]. Finally, while we did find an increased risk of all-cause mortality for black women who did not receive BT in our population, our relatively small effect sizes should be interpreted with caution [32]. However, despite our relatively small hazard ratios, our large sample makes it less likely that a Type I error occurred. As with all large database studies, there is also the potential that unmeasured confounding factors that may have affected our results.

In summary, our data suggest that black women with locally advanced cervical cancer in the U.S. receive different treatment compared to non-black women. Survival differences by race in our analysis were mediated by brachytherapy boost administration. More study is needed regarding ways to improve access to brachytherapy and timely administration of radiation for black patients.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.06.022.

Author contributions

Stephanie Alimena, MD: This author performed conceptualization, investigation, methodology, formal analysis, and writing – original draft, and writing – review and editing.

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Declaration of Competing Interest

There are no conflicts of interest for any of the authors.

References

[1] American Cancer Society, Cancer Facts & Figures 2017, American Cancer Society, Atlanta, 2017.

[2] The National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines v1.2019, cervical cancer, http://www.nccn.org/professionals/physician_gls/f_guidelines.asp, Accessed date: 15 August 2018.

[3] K. Han, M. Milosevic, A. Fyles, M. Pintilie, A.N. Viswanathan, Trends in the utilization of brachytherapy in cervical cancer in the United States, Int. J. Radiat. Oncol. Biol. Phys. 87 (1) (2013) 111–119, https://doi.org/10.1016/j.ijrobp.2013.05.033.

[4] G.E. Hanks, D.F. Herring, S. Kramer, Patterns of care outcome studies. Results of the national practice in cancer of the cervix, Cancer 51 (5) (1983) 959–967.

[5] M.D. Logsdon, P.J. Eifel, FIGO IIIB squamous cell carcinoma of the cervix: an analysis of prognostic factors emphasizing the balance between external beam and intracavitary radiation therapy, Int. J. Radiat. Oncol. Biol. Phys. 43 (4) (1999) 763–775 (doi: S0360-3016(98)00482-9 [pii]).

[6] J. Weragoda, A. Azuero, S. Badiga, W.C. Bell, R. Matthews, C. Piyathilake, An examination of racial differences in 5-year survival of cervical cancer among African American and white American women in the southeastern US from 1985 to 2010, Cancer Med 5 (8) (2016) 2126–2135, https://doi.org/10.1002/cam4.765.

[7] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2018, CA Cancer J. Clin. 68 (1) (2018) 7–30, https://doi.org/10.3322/caac.21442.

[8] J. Mayadev, A. Klapheke, C. Yashar, et al., Underutilization of brachytherapy and disparities in survival for patients with cervical cancer in California, Gynecol. Oncol. 150 (1) (2018) 73–78, https://doi.org/10.1016/j.ygyno.2018.04.563.

[9] Patel DA, Barnholtz-Sloan JS, Patel MK, Malone JM, Jr, Chuba PJ, Schwartz K. A population-based study of racial and ethnic differences in survival among women with invasive cervical cancer: analysis of surveillance, epidemiology, and end results data. Gynecol. Oncol. 2005;97(2):550–558. (doi: S0090-8258(05)00111-3 [pii]).

[10] V.T. Nghiem, K.R. Davies, W. Chan, Z.D. Mulla, S.B. Cantor, Disparities in cervical cancer survival among Asian-American women, Ann. Epidemiol. 26 (1) (2016) 28–35, https://doi.org/10.1016/j.annepidem.2015.10.004.

[11] Healthy People, Foundation health measures: disparities, https://www.healthypeople.gov/2020/about/foundation-health-measures/Disparities 2020, Accessed date: 2 October 2018.

[12] E.I. Garner, Cervical cancer: disparities in screening, treatment, and survival, Cancer Epidemiol. Biomark. Prev. 12 (3) (2003) 242s–247s.

[13] J.F. Wharam, F. Zhang, X. Xu, B.E. Landon, D. Ross-Degnan, National trends and disparities in cervical cancer screening among commercially insured women, 2001-2010, Cancer Epidemiol. Biomark. Prev. 23 (11) (2014) 2366–2373, https://doi.org/10.1158/1055-9965.EPI-13-1202.

[14] E.P. Simard, D. Naishadham, D. Saslow, A. Jemal, Age-specific trends in black-white disparities in cervical cancer incidence in the United States: 1975-2009, Gynecol. Oncol. 127 (3) (2012) 611–615, https://doi.org/10.1016/j.ygyno.2012.08.021.

[15] M.G. del Carmen, F.J. Montz, R.E. Bristow, A. Bovicelli, T. Cornelison, E. Trimble, Ethnic differences in patterns of care of stage 1A(1) and stage 1A(2) cervical cancer: a SEER database study, Gynecol. Oncol. 75 (1) (1999) 113–117, https://doi.org/10.1006/gyno.1999.5543.

[16] A.J. Mundt, P.P. Connell, T. Campbell, J.H. Hwang, J. Rotmensch, S. Waggoner, Race and clinical outcome in patients with carcinoma of the uterine cervix treated with radiation therapy, Gynecol. Oncol. 71 (2) (1998) 151–158 (doi: S0090-8258(98)95203-9 [pii]).

[17] S. Fleming, N.H. Schluterman, J.K. Tracy, S.M. Temkin, Black and white women in Maryland receive different treatment for cervical cancer, PLoS One 9 (8) (2014), e104344. https://doi.org/10.1371/journal.pone.0104344.

[18] B.S. Gill, J.F. Lin, T.C. Krivak, et al., National cancer data base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements, Int. J. Radiat. Oncol. Biol. Phys. 90 (5) (2014) 1083–1090, https://doi.org/10.1016/j.ijrobp.2014.07.017.

[19] Robin TP, Amini A, Schefter TE, Behbakht K, Fisher CM. Disparities in standard of care treatment and associated survival decrement in patients with locally advanced cervical cancer. Gynecol. Oncol.. 2016;143(2):319–325. doi: S0090-8258(16)31412-3 [pii].

[20] K.Y. Bilimoria, A.K. Stewart, D.P. Winchester, C.Y. Ko, The National Cancer Database: a powerful initiative to improve cancer care in the United States, Ann. Surg. Oncol. 15 (3) (2008) 683–690, https://doi.org/10.1245/s10434-007-9747-3.

[21] D.J. Boffa, J.E. Rosen, K. Mallin, et al., Using the National Cancer Database for outcomes research: a review, JAMA Oncol 3 (12) (2017) 1722–1728, https://doi.org/10.1001/jamaoncol.2016.6905.

[22] P.C. Austin, The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments, Stat. Med. 33 (7) (2014) 1242–1258.

[23] G. Ridgeway, D.F. McCaffrey, A. Morral, B.A. Griffin, L.F. Burgette, Twang: Toolkit for Weighting and Analysis of Nonequivalent Groups, 2017.

[24] B.A. Quinn, X. Deng, A. Colton, D. Bandyopadhyay, J. Carter, E. Fields, Increasing age predicts poor cervical cancer prognosis with subsequent effect on treatment and overall survival, Int. J. Radiat. Oncol. Biol. Phys. 99 (2) (2017) E308.

[25] R. Jagsi, P. Abrahamse, S.T. Hawley, J.J. Graff, A.S. Hamilton, S.J. Katz, Underascertainment of radiotherapy receipt in surveillance, epidemiology, and end results registry data, Cancer 118 (2) (2012) 333–341, https://doi.org/10.1002/cncr.26295.

[26] W. Yoo, S. Kim, W.K. Huh, et al., Recent trends in racial and regional disparities in cervical cancer incidence and mortality in United States, PLoS One 12 (2) (2017), e0172548. https://doi.org/10.1371/journal.pone.0172548.

[27] D.E. Spratt, R.T. Dess, H.E. Hartman, et al., Androgen receptor activity and radiotherapeutic sensitivity in African-American men with prostate cancer: a large

scale gene expression analysis and meta-analysis of RTOG trials, Int. J. Radiat. Oncol. Biol. Phys. 102 (3) (2018) S3.
[28] N.R. Datta, S. Singh, P. Kumar, D. Gupta, Human papillomavirus confers radiosensitivity in cancer cervix: a hypothesis toward a possible restoration of apoptotic pathways based on clinical outcomes, Future Oncol. 11 (9) (2015) 1363–1371, https://doi.org/10.2217/fon.15.53.
[29] M. Zhang, S. Cai, D. Shi, The comparison of radiosensitivity between uterine cervical squamous carcinoma and adenocarcinoma, Zhonghua Fu Chan Ke Za Zhi 33 (10) (1998) 611–613.
[30] A.I. Tergas, A.I. Neugut, L. Chen, W.M. Burke, D.L. Hershman, J.D. Wright, Radiation duration in women with cervical cancer treated with primary chemoradiation: a population-based analysis, Cancer Investig. 34 (3) (2016) 137–147, https://doi.org/10.3109/07357907.2015.1131291.
[31] A. Diaz, P.D. Baade, P.C. Valery, et al., Comorbidity and cervical cancer survival of indigenous and non-indigenous Australian women: a semi-national registry-based cohort study (2003−2012), PLoS One 13 (5) (2018), e0196764. https://doi.org/10.1371/journal.pone.0196764.
[32] D.A. Grimes, K.F. Schulz, False alarms and pseudo-epidemics: the limitations of observational epidemiology, Obstet. Gynecol. 120 (4) (2012) 920–927, https://doi.org/10.1097/AOG.0b013e31826af61a.