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Health disparities are important determinants of outcome for children with solid tumor malignancies

Mary T. Austin[a,b,c,*], **Hoang Nguyen**[d], **Jan M. Eberth**[e], **Yuchia Chang**[d], **Andras Heczey**[f], **Dennis P. Hughes**[a], **Kevin P. Lally**[c], and **Linda S. Elting**[d]

[a]Department of Pediatrics, Children's Cancer Hospital at the University of Texas M.D. Anderson Cancer Center, Houston, Texas

[b]Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

[c]Department of Pediatric Surgery, The University of Texas Medical School at Houston, Houston, Texas

[d]Department of Health Services Research, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

[e]Department of Epidemiology and Biostatistics, The University of South Carolina, Columbia, South Carolina

[f]Department of Pediatrics, Baylor College of Medicine, Houston, Texas

Abstract

Purpose—The purpose of this study was to identify health disparities in children with non-CNS solid tumor malignancies and examine their impact on disease presentation and outcome.

Methods—We examined the records of all children (age ≤ 18 years) diagnosed with a non-CNS solid tumor malignancy and enrolled in the Texas Cancer Registry between 1995 and 2009 (n = 4603). The primary outcome measures were disease stage and overall survival (OS). Covariates included gender, age, race/ethnicity, year of diagnosis, socioeconomic status (SES), and driving distance to the nearest pediatric cancer treatment facility. Statistical analyses included life table methods, logistic, and Cox regression. Statistical significance was defined as $p < 0.05$.

Results—Children with advanced-stage disease were more likely to be male, <10 years old, and Hispanic or non-Hispanic Blacks (all $p < 0.05$). Distance to treatment and SES did not impact stage of disease at presentation. However, Hispanic and non-Hispanic Blacks and patients in the lowest SES quartile had the worst 1- and 5-year survival (all $p < 0.05$). The adjusted OS differed by age, race, and stage, but not SES or distance to the nearest treatment facility.

Conclusions—Race/ethnicity plays an important role in survival for children with non-CNS solid tumor malignancies. Future work should better define these differences to establish mechanisms to decrease their impact.

[*]Corresponding author at: The University of Texas M. D. Anderson Cancer Center, 1400 Pressler, Unit 1406, Houston, TX 77030–1439. Tel.: +1 713 794 4408; fax: +1 713 794 5720. MAustin@mdanderson.org. .

Keywords

Pediatric cancer; Solid tumors; Health disparities; Survival

Disparities in cancer burden and access to cancer care are well described in adults. However, these disparities are much less defined in the pediatric population especially in the United States. Very few studies exist and most were conducted outside the United States in countries with nationalized health care systems. United States based studies focus much of their attention on racial and ethnic disparities with little regard for environment and socioeconomic factors.

Bhatia [1] recently published a comprehensive review of the literature on how racial and ethnic disparities impact outcome of childhood cancers. Most studies focused on racial/ethnic variability in hematologic malignancies [2–6]. In general, minority groups had worse overall and event free survival compared to their White counterparts even after controlling for important determinants of survival such as disease type and stage at presentation. However, most of these studies failed to account for environmental and socioeconomic differences between the groups. Only a few studies evaluated patients with solid tumors [7,8] and even fewer studies examined the impact of SES or access to care on pediatric cancer burden and outcome [3,9–12].

The impact of racial/ethnic, socioeconomic and geographic factors remains unclear especially for children with non-CNS solid tumor malignancies. The purpose of this study was to identify health disparities within a large cohort of children with non-CNS solid tumor malignancies from the Texas Cancer Registry (TCR) and examine their impact on disease presentation and survival.

1. Methods

1.1. Study population

We performed a retrospective case-only analysis of the records for all patients less than 19 years old diagnosed with a non-CNS solid tumor malignancy and enrolled in the TCR between January 1, 1995 and December 31, 2009. The TCR, a state-wide population based registry, is a part of the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) with standardized data collection and quality control protocols [13]. The TCR is gold certified by the North American Association of Central Cancer Registries (NAACCR) and meets the CDC's high quality data standards [14]. Data are abstracted from medical and laboratory records by trained tumor registrars and include patient demographics, primary tumor site, stage, first course of treatment, tumor morphology, cause of death, and survival. Tumor site and histology are coded according to the World Health Organization's criteria in the third edition of the International Classification of Diseases for Oncology (ICD-O-3) [15]. Non-CNS solid tumor malignancies were defined by morphology codes 8041 through 9270, 9310, 9365, 9370–9372, 9490, 9500, 9522, 9540, 9560, 9561, and 9581. Retinoblastoma, melanoma and other skin cancers were excluded.

The dataset for this study included patient demographics (date of birth, gender, race/ethnicity, and home address), date of diagnosis, SEER-defined category of stage, date of last follow-up and status, and date of death. Patients were grouped according to self-defined race/ethnicity as non-Hispanic White, Hispanic, non-Hispanic Black or other. Patients with in situ disease were excluded from analyses. Patients were categorized as having regional disease if the SEER-defined category of stage included any of the following: regional by direct extension, regional to lymph nodes, regional by direct extension and to lymph nodes, regional NOS. Patients were categorized as having advanced disease if they had either regional disease or distant metastases.

Data on pediatric cancer treatment centers were collected and mapped in ArcGIS (version 10.0, ESRI, Redlands, CA). We geocoded the location of each treatment center to a street road network available in the accompanying ArcGIS version 10.0 data and maps CD (ArcGIS Version 10.0, Redlands, CA). This information was then used to calculate the driving distance between a patient's home address and the nearest pediatric cancer treatment center. Pediatric cancer treatment centers were identified as either Children's Oncology Group members in Texas or bordering states (New Mexico, Oklahoma, Arkansas and Louisiana) or any Texas institution with greater than 100 discharges per year in patients less than 18 years old and a primary diagnosis of cancer. The Texas Department of State Health Services (DSHS) Discharge Data File was queried to identify the hospitals with greater than 100 discharges per year in children with a primary diagnosis of cancer. The driving distance was then categorized into 0–25 miles, 26–50 miles and > 50 miles for each patient.

The SES index used in this study was determined using the 2007–2011 US Census block group data and the following formula developed and validated by the Agency for Healthcare Research and Quality (AHRQ) [16]:

$$\begin{aligned}\text{SES Index Score} = {} & 50 + (-0.07^{*}\text{crowded}) + (0.08^{*}\text{prop100}) \\ & + (-0.10^{*}\text{pct\_ poverty}) + (0.11^{*}\text{hhinc100}) + (0.10^{*}\text{high\_ educ}) \\ & + (-0.11^{*}\text{low\_ educ}) + (-0.08^{*}\text{pct\_ unemp})\end{aligned}$$

The 7 components of the index are provided by the U.S. Census Bureau and are available at the block group level. The components include the percentage of households containing one or more person per room (crowded), the median home value standardized to range from 0 to 100 (prop100), the percentage of persons below the federally defined poverty level (pct_poverty), the median household income standardized to 0–100 (hhinc100), the percentage of persons aged ≥ 25 years with at least 4 years of college (high_educ), the percentage of persons aged ≥ 25 years with less than a 12th grade education (low_educ), and the percentage of persons aged 16 years or older in the labor force who are unemployed and actively seeking work (pct_unemp). We used each patient's geocoded residential address and linked it to the 2010 US census data to calculate a SES index score. Each patient was assigned an SES quartile based on the SES index distribution of the study population.

Institutional review board approval was obtained from both UT MD Anderson Cancer Center (Protocol PA12-0059) and the Texas Department of State and Health Services (DSHS) (IRB# 12–023).

1.2. Statistical analyses

Overall survival was defined as the time from the date of diagnosis and the date of death from any cause or patients were censored at the last follow-up date. Overall survival was estimated by Kaplan–Meier methods and survival curves were compared using the log-rank test. One- and 5-year survival probabilities were determined using the life table method. Multivariate Cox regression was used to determine the independent predictors of OS. Covariates included sex, age, race/ethnicity, year of diagnosis, stage, travel distance and SES quartile. Results are reported as hazard ratios with 95% confidence intervals. To determine variables associated with advanced disease, defined as either regional or distant metastases, we used univariate and multivariate logistic regression to estimate odds ratio (OR) and associated 95% confidence intervals. The multivariate model was adjusted for gender, age, race/ethnicity, year of diagnosis, travel distance and SES quartile at the time of diagnosis. All analyses were performed with SAS version 9.3 (SAS institute, Cary, NC). Statistical comparisons were two sided and were considered significant at the P level < .05.

2. Results

A total of 6352 pediatric patients were diagnosed with a non-CNS solid tumor in the dataset. After excluding 1300 for unknown stage, 34 benign or borderline histology, 6 diagnosed at death, 407 melanoma or other skin cancer and 2 without geocoded information on their home address, the final sample size was 4630 patients. The median age was 11 years (range 0–18 years). Patient demographics, tumor types and stage distribution are shown in Table 1. The median driving distance from a patient's home to the nearest pediatric cancer treatment center was 19 miles (range less than 1–239 miles). The majority of patients lived less than or equal to 25 miles from a pediatric cancer treatment center (n = 2734, 59%). However, nearly 25% (n = 1116) lived more than 50 miles from the nearest pediatric cancer treatment center and the majority of these counties are classified as noncore or micropolitan according to the U.S. Census. All centers that met the definition of a pediatric cancer treatment center were COG members.

The socioeconomic characteristics of the study population are shown in Table 2. The median SES index score was 57 (range 20–78). There was a great deal of variability within the study population for each component of the SES index. For example, the mean unemployment rate was 7% but ranged from 0 to 78%.

Fifty percent presented with local disease, 25% with regional and 25% with distant metastasis. The results of the univariate and multivariate analyses to evaluate the impact of the covariates on the odds of presenting with advanced stage (either regional or distant metastasis) are shown in Table 3. Patients with advanced stage non-CNS solid tumor malignancies are more likely to be male, less than 10 years old, and Hispanic or non-Hispanic Blacks (all $p < 0.05$). There is a trend toward increased odds of patients in the lowest SES quartile of presenting with advanced stage disease ($p = 0.05$); however, this was

not significant in the multivariate analysis. The driving distance to the nearest pediatric cancer treatment center did not impact the stage of disease at presentation.

Hispanic and non-Hispanic Blacks and patients in the lowest SES quartile had the worst 1- and 5-year OS (all $p < 0.05$). Figs. 1 and 2 are the Kaplan–Meier survival curves stratified by race/ethnicity and SES quartile, respectively. The results of the multivariate analysis to determine the independent effects of each covariate on OS are shown in Table 4. Socioeconomic status is highly associated with race/ethnicity. There are a greater proportion of Hispanics and non-Hispanic Blacks populating the lower SES quartiles ($p < 0.0001$). The distribution of race/ethnicity by SES quartile is shown in Fig. 3. Thus, the adjusted OS differed by age, race/ethnicity, year of diagnosis, and stage but not by SES or driving distance to the nearest pediatric cancer treatment center. Non-Hispanic Blacks had a significantly worse OS compared to Non-Hispanic Whites (HR 1.6, 95% CI 1.3–1.9), and patients classified as ‘other’ had improved survival compared to non-Hispanic Whites (HR 0.6, 95% CI 0.4–1.0).

3. Discussion

These data show that racial and ethnic differences play an important role in both disease presentation and survival for children with non-CNS solid tumor malignancies. Hispanics and non-Hispanic Blacks are more likely to present with regional or metastatic disease compared to non-Hispanic Whites. Furthermore, Hispanics, non-Hispanic Blacks and patients in the lowest socioeconomic quartile have the worst 1- and 5-year survival probability. Thus, socioeconomic factors contribute but do not fully explain the differences in survival observed between different racial and ethnic groups.

Several prior studies noted similar racial and ethnic disparities in survival for children and adolescents with hematological malignancies [2–6]. However, very few studies have evaluated the impact of racial and ethnic disparities for children with nonhematological solid tumor malignancies. Baker and colleagues [7] conducted a retrospective cohort analysis of patients treated on Intergroup Rhabdomyosarcoma Study Group (IRSG) protocols between 1984 and 1997. They found that although ethnic minority groups were more likely to present with advanced disease, there was no statistically significant difference in 5-year disease-free survival. In a similar cooperative group study, Henderson and colleagues [8] evaluated racial and ethnic differences in clinical and biological risk factors and survival for neuroblastoma patients enrolled in COG trials between 2001 and 2009. Although Blacks and Native Americans had a higher prevalence of high-risk disease and worse disease-free survival compared to Whites, this difference was not evident after adjustment for risk group. Although cooperative group studies provide valuable clinical and therapeutic details, a potential limitation is selection bias which may be more pronounced in studies that evaluate racial/ethnic disparities. It is well established that racial/ethnic minorities are significantly less likely to enroll in cooperative group cancer trials compared to Whites [17]. Lund and colleagues [18] evaluated the observed expected enrollment of US children in COG trials and found that Blacks and Hispanics were underrepresented in clinical trials. Although our study has limited ability to control for clinical and therapeutic risk factors, it is the first

population-based study to identify racial/ethnic differences in survival for nonhematologic solid tumors.

Other groups have evaluated treating institution volume and COG membership on outcomes for patients with neuroblastoma and Wilms tumor [19–21]. Axt and colleagues [19] [19] used data from the health care utilization project kids' inpatient database to determine volume-outcome effects for children undergoing resection of renal malignancies. They found that the number of complications, total charges and length of stay did not differ among high-, medium- and low-operative volume hospitals but were unable to assess oncologic outcomes owing to limitations in the dataset. In 2009, Gutierrez and colleagues published a population-based study using Florida Cancer Data Systems data to determine the effect of hospital surgical volume on survival for pediatric neuroblastoma and Wilms tumor [20]. They found that hospital surgical volume and patient race did not impact survival; however, non-Hispanic ethnicity was associated with an increased risk of death in patients with Wilms tumor. In a subsequent analysis using the same dataset, the authors evaluated the impact of COG membership on survival for neuroblastoma and Wilms tumor [21]. They found that children treated at both high-volume and low-volume COG centers in Florida had a higher overall use of chemotherapy as well as significantly improved survival for patients with Wilms tumor compared to patients treated at low-volume non-COG institutions. These results suggest that protocol-driven treatment rather than increased surgical volume may result in better outcomes for patients. Although our results demonstrated that children in the lowest socioeconomic quartile had the worst OS, adjustment for other covariates including race/ethnicity abrogated this difference. There is considerable debate as to whether racial and ethnic differences are mitigated primarily by social or biologic effects [1]. In our study, SES was highly associated with race/ethnicity with a predominance of Hispanics and non-Hispanic Blacks in the lowest SES quartile. In the unadjusted model, SES was significant; however, in the adjusted model, SES was no longer significant showing that race/ethnicity is a stronger predictor of survival for our study population. In contrast to the population-based studies and cooperative group trials, many previous single-center studies failed to show an association between race/ethnicity for pediatric cancer [22–24]. This suggests that in populations with equivalent access to care, racial disparities may have less impact and supports the idea that SES factors play an important role in survival differences between racial/ethnic groups.

A recent systematic review examined the impact of SES on multiple outcome measures for pediatric cancer [25]. In the 36 articles included in the review, they found that socioeconomic disadvantage was uniformly associated with decreased survival for children living in low- and middle-income countries and frequently associated with decreased survival for those children living in high-income countries. There was considerable heterogeneity in the selected studies which limited their ability to compare magnitudes of associations across studies. Based on our results and previous studies, it is likely that SES plays a role in determining outcome for pediatric cancer. However, SES is multifaceted and the impact of each SES component will most certainly vary between patient populations and malignancies. Future studies must integrate reliable measures of patient-level SES into analyses that account for other important patient-, treatment- and disease-based confounders.

We did not identify a relationship between the driving distance from the patient's home residence to the nearest pediatric cancer treatment facility and stage of disease at presentation or OS. Although a number of adult studies have shown a significant association between the distance cancer patients travel for treatment and either stage of disease at presentation and/or survival [26,27], very few studies have evaluated the impact of geography on outcome for pediatric cancer. In a population-based study using the Surveillance, Epidemiology and End Results (SEER) database, Hsieh and colleagues [28] found that mortality for pediatric neuroblastoma was higher in patients living in nonmetropolitan counties versus metropolitan counties. Similarly, Youlden and colleagues [10] found that children with cancer from remote/very remote areas in Australia had a significantly lower survival rate than their counterparts in major cities.

In our cohort, the majority of patients lived less than 50 miles from the nearest pediatric cancer treatment center which may have limited our ability to detect a difference. In addition, other geographic factors such as access to primary care or emergency/acute care services may have greater impact than a patient's travel distance to his/her cancer treatment center. We could not evaluate these factors using our current dataset. It is important to note that we chose to evaluate the distance from the patient's address of residence to the nearest potential treatment facility as our goal was to evaluate access to care. In future work, we plan to evaluate the impact that the distance traveled by patients to receive care (actualized access) has on outcome measures such as adherence and completion of therapy, follow-up surveillance and survival.

It is clear from our work and others that disparities exist in outcomes for pediatric cancer and are especially pronounced for Hispanics and non-Hispanic Blacks. The underlying causes for such disparities are most certainly multifactorial and diverse. Future work should seek to identify population- and disease-specific causes of disparities and thereby lay the foundation to develop evidence-based interventions and strategies to alleviate health disparities for children with cancer.

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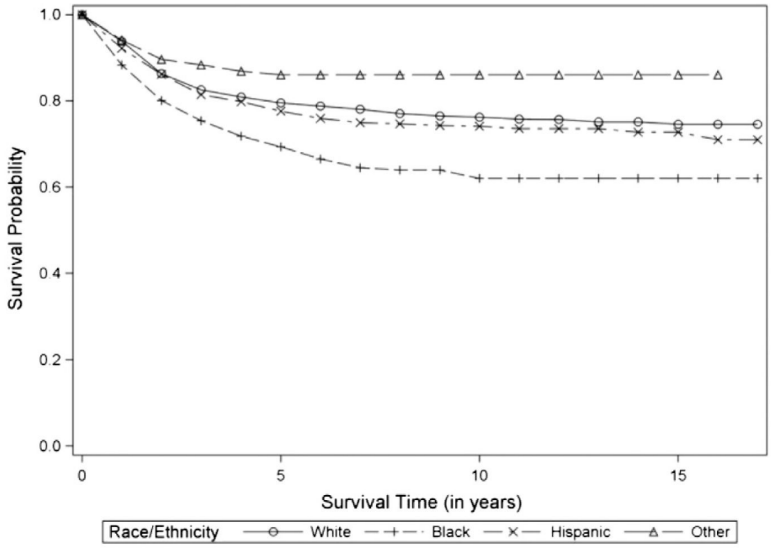

Fig. 1.
Kaplan–Meier survival curve for OS by race/ethnicity.

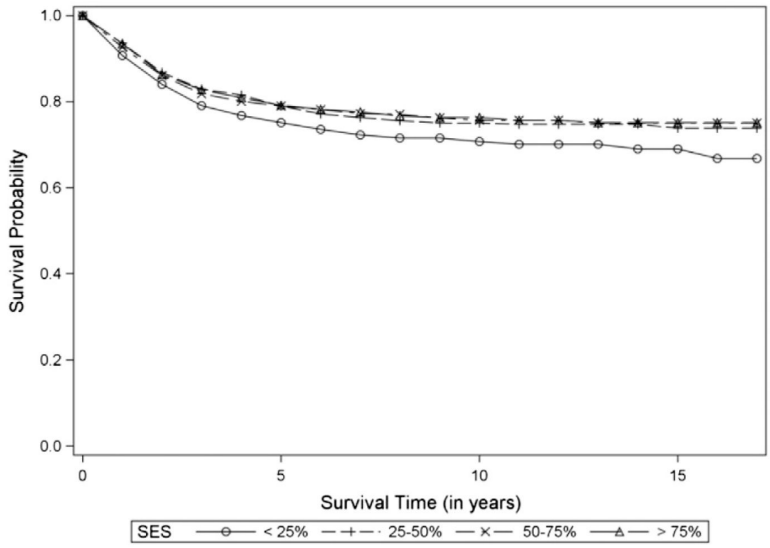

Fig. 2.
Kaplan–Meier survival curve for OS by socioeconomic quartile.

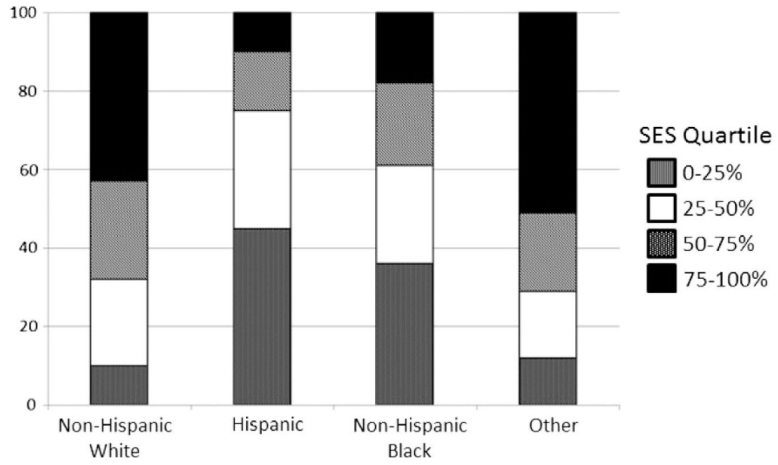

Fig. 3.
The distribution of SES quartiles within each racial/ethnic group.

Table 1

Demographics of the study population.

	Number of patients (%)
Sex	
Male	2384 (52)
Female	2219 (48)
Age group	
<1 year	572 (12)
1–10 years	1716 (37)
>10 years	2315 (50)
Race	
Non-Hispanic White	2120 (46)
Hispanic	1831 (40)
Non-Hispanic Black	466 (10)
Other	186 (4)
Year of diagnosis	
1995–2002	2132 (46)
2003–2009	2471 (54)
Diagnosis	
Germ cell tumor	797 (17)
Soft tissue sarcoma	788 (17)
Bone sarcoma	772 (17)
Neuroblastoma	672 (14)
Renal tumor	584 (13)
Endocrine tumor	492 (11)
Liver or bile duct tumor	177 (4)
Other	321 (7)
Stage	
Local	2277 (50)
Regional	1172 (25)
Distant	1154 (25)

Table 2

Socioeconomic characteristics of the study population at the block group level.

	Median	Mean (SD)	Min	Max
SES score (median, mean & range)	57	57.1 (10.2)	20	78
Percent of housing units in crowded living quarters	3	5.6 (7.4)	0	59
Ranking based on median house value (0–100%)	52	51.3 (28.3)	0	100
Percent living below poverty level	13	17.8 (16.0)	0	100
Ranking based on median household income (0–100%)	53	51.9 (29.5)	0	100
Percent with low education level (no high school graduation)	18	22.1 (18.3)	0	96
Percent with high education level (college graduation)	18	24.0 (20.3)	0	100
Percent unemployed	6	7.4 (6.1)	0	78

Table 3

Unadjusted and adjusted odds for presenting with advanced stage disease*.

	Univariate analysis			Multivariate analysis		
	OR	**CI**	**p**	**OR**	**CI**	**p**
Sex						
Male	1.1	0.9–1.2	NS	1.0	0.9–1.2	NS
Female	Reference	–	–	Reference	–	–
Age						
<1 year	1.1	0.9–1.3	NS	1.1	0.9–1.3	NS
1–10 years	1.6	1.4–1.8	<.0001	1.6	1.4–1.8	<.0001
>10 years	Reference	–	–	Reference	–	–
Race						
Non-Hispanic White	Reference	–	–	Reference	–	–
Hispanic	1.2	1.0–1.3	.02	1.2	1.0–1.3	NS
Non-Hispanic Black	1.3	1.1–1.6	.01	1.3	1.0–1.6	.03
Other	0.8	0.6–1.1	NS	0.8	0.6–1.1	NS
Year of diagnosis						
1995–2002	Reference	–	–	Reference	–	–
2003–2009	1.0	0.9–1.1	NS	1.0	0.9–1.1	NS
Travel distance-road network						
<25 miles	Reference	–	–	Reference	–	–
25–50 miles	1.1	0.9–1.2	NS	1.1	0.9–1.3	NS
>50 miles	1.0	0.9–1.1	NS	1.0	0.9–1.2	NS
SES quartile						
<25%	1.2	1.0–1.4	.05	1.1	0.9–1.3	NS
25–50%	1.0	0.8–1.1	NS	0.9	0.8–1.1	NS
50–75%	1.0	0.8–1.2	NS	0.9	0.8–1.1	NS
>75%	Reference	–	–	Reference	–	–

Table 4

Multivariate Cox regression to determine independent predictors for OS.

	HR	CI	P
Sex			
Male	Reference	–	–
Female	0.9	0.8–1.0	NS
Age			
<1 year	0.8	0.6–0.9	.01
1–10 years	0.9	0.8–1.0	.03
>10 years	Reference	–	–
Race			
Non-Hispanic White	Reference	–	–
Hispanic	1.0	0.8–1.1	NS
Non-Hispanic Black	1.6	1.3–1.9	<.0001
Other	0.6	0.4–1.0	.03
Year of diagnosis			
1995–2002	Reference	–	–
2003–2009	0.8	0.7–0.9	<.0001
Stage			
Local	Reference	–	–
Regional	1.9	1.6–2.3	<.0001
Distant	5.6	4.8–6.7	<.0001
Travel distance-road network			
<25 miles	Reference	–	–
25–50 miles	1.1	1.0–1.3	NS
>50 miles	1.1	1.0–1.3	NS
SES quartile			
<25%	1.1	0.9–1.3	NS
25–50%	1.0	0.8–1.2	NS
50–75%	1.0	0.8–1.2	NS
>75%	Reference	–	–