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Head and Neck Cancer Survival Disparities by Race and Rural–Urban Context

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ABSTRACT

Background: This study aims to examine the relationship between race and rural–urban context in head and neck cancer (HNC) survival and determine factors that potentially drive this disparity.

Methods: Using the National Cancer Database from 2004 to 2015, we identified a retrospective cohort of 146,256 patients with HNC. Kaplan–Meier survival curves and the Cox proportional hazards regression were used to calculate adjusted HRs.

Results: Median survival by patient subgroup was as follows: White urban [67 months; 95% confidence interval (CI), 66.0–67.9], White rural (59.1 months; 95% CI, 57.2–60), Black urban (43.1 months; 95% CI, 41.1–44.5), and Black rural (35.1 months; 95% CI, 31.9–39.0). The difference in 5-year survival, stratified by rural–urban context, was greater among Black patients [Δ restricted mean survival time (ΔRMST) 0.18; 95% CI, 0.10–0.27] than White patients (ΔRMST 0.08; 95% CI, 0.06–0.11). In the univariate Cox proportional hazards analysis with White urban patients as reference group, Black rural patients had the worst survival (HR, 1.45; 95% CI, 1.43–1.48; $P < 0.001$), followed by Black urban patients (HR, 1.29; 95% CI, 1.28–1.30; $P < 0.001$), and White rural patients (HR, 1.08; 95% CI, 1.07–1.09; $P < 0.001$). This disparity persisted when controlling for demographic, socioeconomic, and clinical factors.

Conclusions: Black patients with HNC, specifically those living in rural areas, have decreased survival. Survival differences by rural–urban status are greater among Black patients than White patients.

Impact: We have shown that race and rural–urban status impact HNC survival outcomes. Our findings will help future researchers to better frame approaches to address this disparity.

Introduction

Head and neck cancer (HNC) encompasses cancers of the oral cavity, oropharynx, hypopharynx, larynx, paranasal sinuses, and nasal cavity. In 2020, the American Cancer Society estimates 53,260 new diagnoses of HNC and 10,750 HNC-related deaths (1). According to the Surveillance, Epidemiology, and End Results database, the overall incidence rate of HNC between 1992 and 2014 was 14.3 per 100,000 Black patients compared with 12.2 per 100,000 White patients (2). In addition, the mean 5-year survival among Black patients with HNC has been reported between 29% and 31% compared with 55%–59% in Whites (3). Factors contributing to racial outcome disparities among patients with HNC have been debated in the literature.

In addition to race, the geographic location of the patient's residence (rural–urban context) is another important factor that has been shown to influence patient outcomes. Prior research has demonstrated associations between rural–urban context and survival outcomes in breast, lung, and colorectal cancers (4). In patients with HNC, rural context has been associated with advanced disease stage at diagnosis and worse survival as compared with urban (2). Differences by rural–urban context are often attributed to travel barriers and decreased access to care among rural patients (5, 6). However, previous findings have not been consistent with respect to the impact of rural–urban status on survival (5, 7–9).

Although the impacts of race and rural–urban context in HNC survival have been addressed separately, there has not been adequate research into the combined effect of these factors (10–12). We aimed to examine the relationship between race and residential rural–urban context and its impact on overall survival in patients with HNC. We hypothesized that the combined impact of both race and rural–urban status in nonoropharyngeal HNC would disproportionately influence Black rural patients.

Materials and Methods

Study population

The National Cancer Database (NCDB) is maintained by the American College of Surgeons and American Cancer Society. It was established in 1989 and includes 34 million records from cancer registries of more than 1,500 participating hospitals. The database contains more than 70% of newly diagnosed cancer cases nationwide (13). The NCDB includes data on baseline patient demographics, staging, and survival.

We evaluated HNC cases from 2004 to 2015, filtering the data for adult patients with International Classification of Diseases for Oncology, 3rd edition (ICD-O-3) codes for cancers of the oral cavity, larynx, or hypopharynx (**Table 1**). We excluded nonsquamous cell cases, palliative care patients, cases missing variables, and those diagnosed after the reference date. Patients with oropharyngeal cancer were excluded because of the association between human papillomavirus (HPV) and improved survival, and because of unequal distribution by race and geographic location (14, 15). In addition, we only included non-Hispanic Black and White patients due to small sample size of other races/ethnicities. After applying inclusion and exclusion criteria, our study cohort consisted of 146,256 patients with cancers involving hypopharynx, larynx, and oral cavity subsites (**Fig. 1**).

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Table 1. ICO-0-3 codes used for site classification.

Category	ICD-O-3 codes
Oral cavity	C02.0–C02.3, C02.8, C03.0–C03.9, C04.0–C04.9, C05.0, C05.2, C05.8, C06.0–C06.8
Larynx	C32.0–C32.9
Hypopharynx	C12.9-C13.9
Squamous cell histology	8052, 8083, 8078–8070

Exposure and outcome assessment

Our primary exposures were race and rural–urban context. We defined rural–urban context using Rural-Urban Continuum Codes (RUCC) published by the U.S. Department of Agriculture Economic Research Service to distinguish counties by population size, adjacency to metropolitan areas, and degree of urbanization (16). RUCCs were

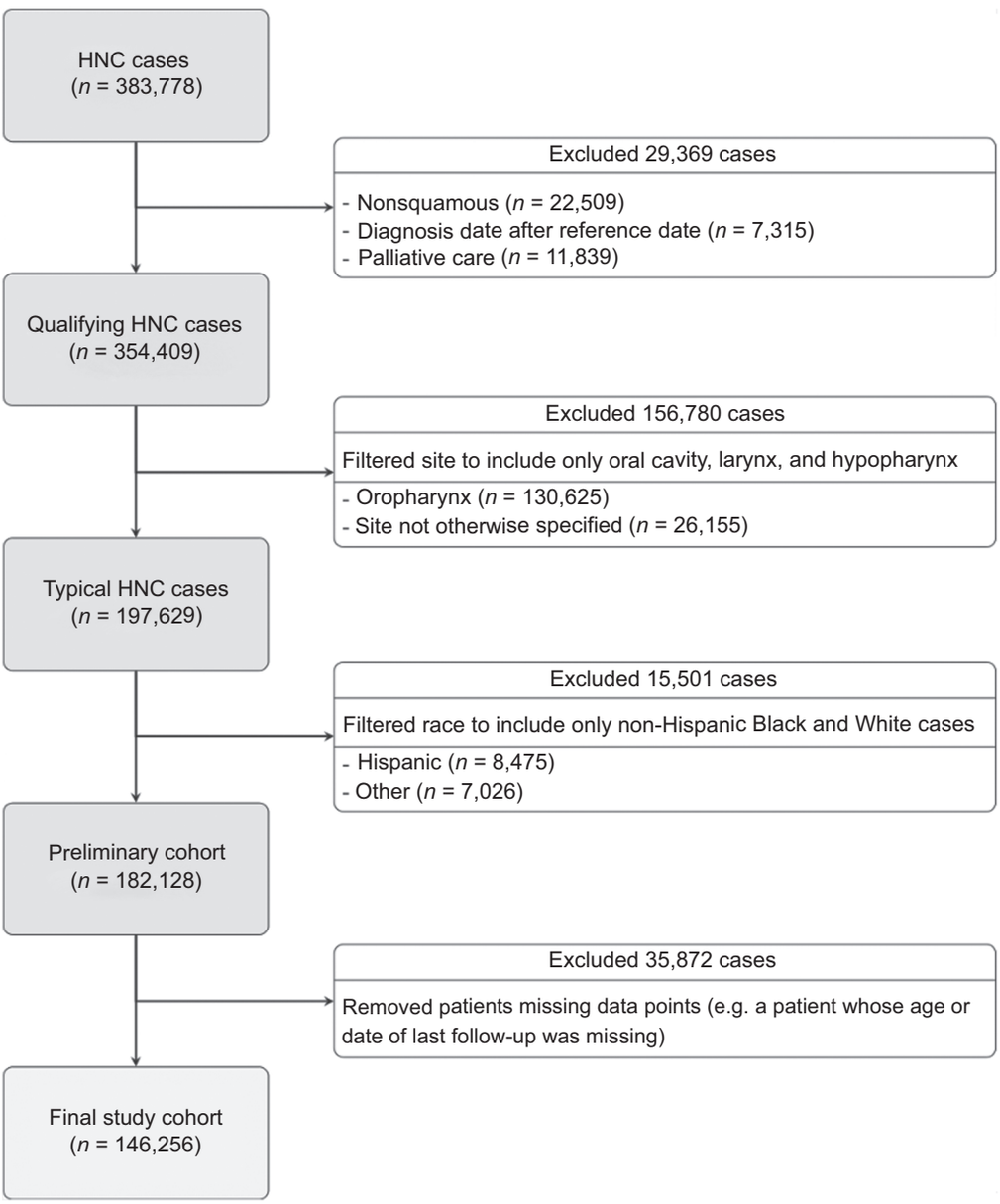

Figure 1.
Exclusion criterion for NCDB cohort. This figure depicts our exclusion criteria for filtering the original 383,778 patients found in the NCDB to our final cohort of 146,256.

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determined on the basis of patient county of residence recorded at diagnosis. We used RUCCs from 2003 to classify patients into urban (RUCC 1–3) and rural subgroups (RUCC 4–9). To study the interaction between race and rural–urban context, patients were further grouped as Black urban, Black rural, White urban, and White rural patients.

Death was our primary outcome and was ascertained using the NCDB participant user file vital status variable. All patients alive after the study ended in 2015 were censored in our analysis.

Covariates

Covariates were classified into demographic (age and gender), socioeconomic (insurance status and distance traveled to primary treatment center), and clinical (primary tumor site and stage) factors. Age was treated as a continuous variable. The NCDB categorizes the patient's primary insurance carrier at the time of diagnosis and treatment into the following groups: not insured, private insurance, Medicaid, Medicare, and other government funding entities. Distance traveled was reported in the NCDB as crowfly. This variable was calculated by measuring the longitudinal distance between the center of the patient's zip code (the center of the patient's city was used when zip code was unavailable) and the address of the facility where they received treatment. We categorized the crowfly variable into quartiles 1 (<4.8 miles), 2 (4.8–11.4 miles), 3 (11.5–28.7 miles), and 4 (>28.8 miles). Stage was classified using the pathologic stage of the patient. Clinical stage was used where pathologic stage was not available. The Commission on Cancer Accreditation program categorizes cancer treatment facilities into the following types: Community Cancer Program, Comprehensive Community Cancer Program, Academic/Research Program, Integrated Network Cancer Program, and Other or unknown type of cancer program. Each case was assigned a facility type based on the facility where it was first reported.

Statistical analysis

The descriptive analysis compared covariates across race and rural–urban context and was tested by two-sided Pearson χ^2 tests for categorical variables. For continuous variables, means and SDs were calculated and t tests were conducted for normally distributed variables. Kaplan–Meier overall survival curves were constructed and log-rank P values were calculated. Cox proportional hazards regressions were used to estimate both unadjusted HR and adjusted HRs (aHR). The proportional hazards and linearity assumptions were tested and satisfied. We also estimated restricted mean survival time (RMST) and differences in RMST. RMST is the area under the Kaplan–Meier curve and is interpreted as the "life expectancy" between diagnosis and 5 years. We also conducted exploratory analyses to investigate changes in rural–urban disparities over time and within each treatment facility for each subgroup (Black urban, Black rural, White urban, and White rural). To increase the sample size, we used only two groups: cases diagnosed between 2004–2007 and cases diagnosed between 2008–2011. All statistical analyses were implemented using the R studio version 3.5.1 using the survival, survminer, and survRM2 packages (17–20).

Results

Descriptive statistics

Our cohort comprised of 80.1% (n = 117,081) urban patients and 19.9% (n = 29,175) rural patients (**Table 2**). Most of our cohort was made up of White patients. There was a modest increase in private insurance in urban compared with rural areas. The urban and rural cohorts had comparable numbers in each stage. Approximately 9.8% (n = 14,320) of patients had cancer of the hypopharynx, 54.6% (n = 79,902) of the larynx, and 35.6% (n = 52,034) of the oral cavity.

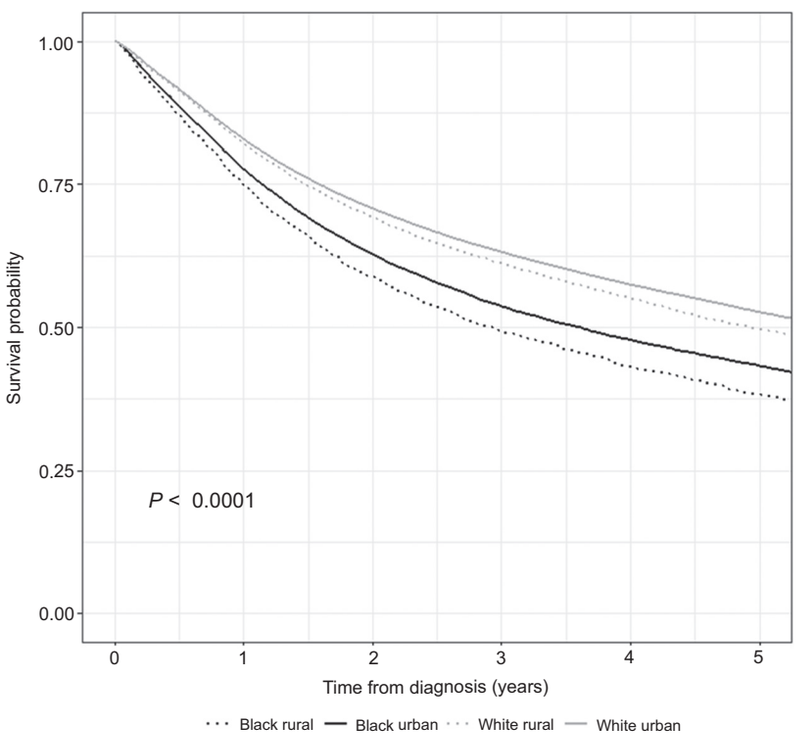

Figure 2.
Kaplan–Meier curve stratified by race and rural–urban status. This figure depicts survival probability over 5 years from the original date of diagnosis. Black rural patients are depicted by a dotted black line (n = 2,272), Black urban patients by a solid black line (n = 16,053), White rural by a dotted gray line (n = 101,028), and White urban by a solid gray line (n = 26,903).

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Table 2. Descriptive statistics of population.

	Black rural (n = 2,272)	Black urban (n = 16,053)	White urban (n = 101,028)	White rural (n = 26,903)	P	Overall (N = 146,256)
Gender						
Female	465 (20.5%)	4,003 (24.9%)	29,743 (29.4%)	7,429 (27.6%)	<0.001	41,640 (28.5%)
Male	1,807 (79.5%)	12,050 (75.1%)	71,285 (70.6%)	19,474 (72.4%)		104,616 (71.5%)
Age						
Mean (SD)	61.2 (10.6)	62.1 (10.7)	64.8 (12.2)	64.2 (11.7)	<0.001	64.4 (11.9)
Median (min, max)	60.0 (21.0, 90.0)	61.0 (18.0, 90.0)	65.0 (18.0, 90.0)	64.0 (18.0, 90.0)		64.0 (18.0, 90.0)
Insurance						
Medicaid	524 (23.1%)	3,485 (21.7%)	8,033 (8.0%)	2,802 (10.4%)	<0.001	14,844 (10.1%)
Medicare	984 (43.3%)	6,784 (42.3%)	49,515 (49.0%)	14,117 (52.5%)		71,400 (48.8%)
Other government	46 (2.0%)	356 (2.2%)	1,816 (1.8%)	728 (2.7%)		2,946 (2.0%)
Private	414 (18.2%)	4,051 (25.2%)	37,288 (36.9%)	7,834 (29.1%)		49,587 (33.9%)
Uninsured	304 (13.4%)	1,377 (8.6%)	4,376 (4.3%)	1,422 (5.3%)		7,479 (5.1%)
Stage						
0	60 (2.6%)	538 (3.4%)	5,307 (5.3%)	1,012 (3.8%)	<0.001	6,917 (4.7%)
1	391 (17.2%)	3,145 (19.6%)	32,252 (31.9%)	7,795 (29.0%)		43,583 (29.8%)
2	298 (13.1%)	2,234 (13.9%)	15,720 (15.6%)	4,625 (17.2%)		22,877 (15.6%)
3	432 (19.0%)	2,892 (18.0%)	15,295 (15.1%)	4,450 (16.5%)		23,069 (15.8%)
4	1,091 (48.0%)	7,244 (45.1%)	32,454 (32.1%)	9,021 (33.5%)		49,810 (34.1%)
Site						
Hypopharynx	302 (13.3%)	2,154 (13.4%)	9,570 (9.5%)	2,294 (8.5%)	<0.001	14,320 (9.8%)
Larynx	1,466 (64.5%)	10,450 (65.1%)	53,037 (52.5%)	14,949 (55.6%)		79,902 (54.6%)
Oral cavity	504 (22.2%)	3,449 (21.5%)	38,421 (38.0%)	9,660 (35.9%)		52,034 (35.6%)

Univariate survival analysis

Survival was assessed through Kaplan–Meier survival curves and 5-year overall survival. The highest median survival time was observed in White urban patients [67.0 months; 95% confidence interval (CI), 66.0–67.9], followed by White rural (59.1 months; 95% CI, 57.2–60.8), Black urban (43.1 months; 95% CI, 41.1–44.5), and Black rural (35.1 months; 95% CI, 31.9–39.0; **Fig. 2**; **Table 3**). Five-year survival differences by rural–urban context were greater among Black patients (ΔRMST 0.18; 95% CI, 0.10–0.27) than White patients (ΔRMST 0.08; 95% CI, 0.06–0.11).

In our univariate Cox proportional hazard regression model, using White urban patients as the reference group, Black rural patients (HR, 1.5; 95% CI, 1.43–1.48; $P < 0.001$) had the worst survival, followed by Black urban (HR, 1.29; 95% CI, 1.28–1.30; $P < 0.001$), and White rural (HR, 1.08; 95% CI, 1.07–1.09; $P < 0.001$; **Table 4**).

Multivariate survival analysis

With demographic, socioeconomic, and clinical factors included in the Cox regression model, a significant difference in survival outcome was observed between racial and geographic groups (**Table 4**). Using White urban patients as the reference group, Black rural patients had the highest risk of mortality (aHR, 1.30; 95% CI, 1.27–1.33) followed by Black urban (aHR, 1.11; 95% CI, 1.10–1.12) and White rural patients (aHR, 1.04; 95% CI, 1.10–1.12; **Table 4**). However, the interaction between race and rural–urban context was not statistically significant ($P = 0.18$).

Year of diagnosis analyses

There were no significant differences observed by year of diagnosis in any of the subgroups (Supplementary Fig. S1; Supplementary Table S1). However, Black urban, White urban, and White rural patients diagnosed from 2008–2011 trended toward increased survival compared with 2004–2007.

Facility type analyses

In our next survival analysis, we grouped patients by facility type (Supplementary Table S1; Supplementary Fig. S2). In all subgroups, except for Black rural, community hospitals had the lowest survival. However, the 95% CI of median survival in months of all facility types overlapped in both the Black rural and Black urban subgroups. Among both urban and rural White patients, patients treated in academic facilities had the longest medial survival.

Table 3. Cumulative deaths.

	Time from diagnosis (years)					
Subgroup	0	1	2	3	4	5
Black rural	0	556	899	1,076	1,181	1,248
Black urban	1	3,538	5,779	6,997	7,689	8,143
White rural	7	4,724	7,962	9,776	10,951	11,835
White urban	28	16,968	28,518	34,877	39,171	42,145

Table 4. Unadjusted and adjusted HRs.

Variable	HR (95% CI)	aHR[a] (95% CI)
Subgroup		
White urban	Reference	Reference
White rural	1.08 (1.07–1.09)	1.11 (1.10–1.12)
Black urban	1.29 (1.28–1.30)	1.11 (1.10–1.12)
Black rural	1.45 (1.43–1.48)	1.30 (1.27–1.33)

[a]HR adjusted for demographic, socioeconomic, and clinical factors.

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Discussion

Our analysis demonstrates differences in survival of patients with HNC according to racial–geographic status, with worse overall survival in the Black rural population. This disparity persists after adjusting for potential mediating covariates in a multivariate model. In addition, when comparing rural–urban disparities by race, we found that the effect of rural–urban context is greater among Black patients compared with White patients. Interestingly, we found that there is no synergistic interaction between race and rural–urban context.

Studies reporting HNC survival differences according to rural–urban context have shown inconsistent results (6, 7). Similar to our study, a prior Canadian study limited to patients with oral cavity cancer showed improved disease-free survival in patients living in urban compared with rural geographic locations (7). A more recent Canadian study by Kim and colleagues showed no association between rural–urban context and survival, however, their study included patients with oropharyngeal cancer which is closely associated with HPV (5). HPV-positive oropharyngeal cancer represents a biologically distinct disease with improved prognosis over HPV-negative HNC. While HPV-positive disease has become more prevalent, Black Americans bear a disproportionate burden of HPV-negative HNC (2). Indeed, a recent meta-analysis showed that oropharyngeal survival disparities by race disappear after controlling for HPV status (12). Therefore, HNC racial disparity research that has traditionally included oropharyngeal cases has been obscured by HPV status. To avoid this, our current study did not include oropharyngeal cases. In the future, we plan to perform an additional analysis addressing the differences in the impact of rural–urban status and race on oropharyngeal cancer. Contrary to the before mentioned studies, we used a U.S. data source, which may have different factors driving disparity than the Canadian data sources used in the other studies. In addition, our study used rural–urban definitions based on the U.S. RUCC, which differ from the definitions used by these previous studies. The Zhang and colleagues' study defined rural as any community smaller than 10,000 people. The Kim and colleagues' study classified urban–rural status based on postal code into four categories: rural (<1,000 residents), small urban centers (1,000–29,999 residents), medium urban centers (30,000–99,999 residents), and large urban centers (100,000+ residents). In contrast, the RUCC used by our study classify population centers into metro urban counties (RUCC 1–3), nonmetro urban counties (RUCC 4–6), and nonmetro completely rural counties (RUCC 7–9). Because there were relatively few cases in rural areas alone (8,164 cases; 5.58%), we included all nonmetro areas in our rural subgroup (29,175 cases; 20%). We believe this cut-off point is more relevant and helped our study to better identify trends that were missed in the Kim and colleagues' article, which only had a total sample size of 3,036 patients.

Several factors associated with rural residence may contribute to our findings. Rural residents have less access to tertiary care centers, specialized medical professionals, and public transportation, all of which can cause significant delays in diagnosis and treatment (21). One study highlighted the importance of timely care by demonstrating that even a 2-month delay in treatment contributes to a higher hazard of death in pharyngeal cancers (22). To address these disparities, researchers should focus on geographic distribution of treatment services, as well as potential solutions to increase access and transportation in rural areas.

Our findings are consistent with many previous studies that have suggested a difference in survival between Black and White patients with HNC (3, 23–25). Recent studies show that Black patients are more likely to distrust health care professionals, which may stem from a fear of discrimination or from misinformation about health-related procedures (26, 27). Black patients are also more likely to be underinsured, have lower income, and have lower medical literacy (28, 29). These barriers may decrease their number of clinical visits and cancer screenings. Ultimately, these racial disparities result in later HNC diagnosis and worse survival outcomes (3).

Previous studies have found that rural, racial minority cancer patients have more difficulty accessing care (30). Our study highlights this problem, showing a greater difference in survival between Black rural and urban patients than between White rural and urban groups. Survival disparities by race and rural–urban context may also be influenced by differences in smoking rates. People living in rural communities have a higher prevalence of cigarette smoking, and their health is also negatively impacted more than patients living in urban areas (31). In addition, there are known differences in smoking levels by race (32). In fact, it has been shown that minority patients experiencing racial discrimination have higher risk for smoking (33). In addition to smoking, rural areas have higher rates of obesity and physical inactivity (34). Although we did not find a statistical interaction between race and rural–urban context, these factors clearly increase the risk of death among rural Black patients with HNC (35).

Both of our analyses showed no statistical significance by date of diagnosis when groups were subclassified by rural–urban status. This indicates that racial–geographic disparities did not significantly change from 2004 to 2011. However, survival in all groups except Black rural patients trended toward increased survival. The lack of trend in the Black rural group is likely due to a smaller sample size and insufficient power.

In our survival analysis by facility type, our results showed that academic hospitals had the highest median survival time followed by comprehensive, integrated network, and community hospitals. When further classifying by race and rural–urban status, community-treated patients trended toward having the lowest survival in all subgroups except Black rural. In addition, White patients treated at academic facilities had improved survival over all other facilities. This finding matches previous studies suggesting that patients at nonteaching hospitals had lower survival outcomes (36). These outcome differences by facility type may be attributed, in part, to case volume at different centers. Academic centers have a higher case volume compared with other cancer centers, which is strongly associated with improved survival (37). However, this difference was not observed among Black patients. Black rural patients had their best outcomes when treated at integrated network facilities, and Black urban patients survived longest when treated at comprehensive facilities.

There are several limitations to this study. Although the NCDB is comprehensive for oncologic variables and outcomes, large database studies have some inherent limitations. Because of the nature of this database, there may be some errors present in coding. Furthermore, the data are retrospective and incomplete in some areas. The NCDB does not capture smoking status and alcohol consumption and, therefore, we were unable to control for these known risk factors. Another limitation is our inability to estimate true distances traveled to receive care because the crowfly variable in NCDB represents a straight line. Future prospective studies should incorporate smoking and alcohol consumption, as well as true distance traveled to better evaluate the effects of race and rural–urban context on HNC patient outcomes.

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We used the NCDB database, which allows for a large, generalizable study with a diverse population. With this large sample size, we can study the cross-classification of rural–urban context with race. Our results demonstrate a disparity in survival in the context of rural–urban status and race, with Black rural patients exhibiting the worst survival followed by Black urban, White rural, and White urban patients. To enhance survival among burdened patients with HNC, further studies should be performed in small community settings to determine effective and specific solutions.

Disclosure of Potential Conflicts of Interest

J.P. Zevallos reports other from Summit Biolabs, Inc. (equity stock, chief medical officer) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

J.A. Clarke: Conceptualization, data curation, formal analysis, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **A.M. Despotis:** Conceptualization, data curation, writing–original draft, writing–review and editing. **R.J. Ramirez:** Methodology, writing–review and editing. **J.P. Zevallos:** Conceptualization, resources, supervision, funding acquisition, methodology, project administration, writing–review and editing. **A.L. Mazul:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, methodology, writing–original draft, project administration, writing–review and editing.

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