Racial and Ethnic Disparities in Survival of Children with Brain and Central Nervous Tumors in the United States

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Abstract

BACKGROUND Despite improvements in overall survival for pediatric cancers, treatment disparities remain for racial/ethnic minorities compared to non-Hispanic white; however, the impact of race on treatment outcomes for pediatric brain and central nervous system (CNS) tumors in the United States is not well known. METHODS We included 8713 children aged 0 – 19 years with newly diagnosed primary brain and CNS tumors between 2000 – 2015 from the Census Tract-level SES and Rurality Database developed by Surveillance, Epidemiology and End Results Program. We used Chi-square tests to assess differences in sociodemographic, cancer, and treatment characteristics by race/ethnicity and Kaplan–Meier curves and Cox proportional hazards models to examine differences in 10-year survival, adjusting for these characteristics. RESULTS Among 8,713 patients, 56.75% were non-Hispanic white, 9.59% non-Hispanic black, 25.46% Hispanic, and 8.19% from "other" racial/ethnic groups. Median unadjusted survival for all pediatric brain tumors was 53 months but varied significantly by race/ethnicity with a median survival of 62 months for Non-Hispanic whites, 41 months for Non-Hispanic blacks, and 40 months for Hispanic and Other. Multivariable analyses demonstrated minority racial groups still had significantly higher hazard of death than non-Hispanic whites; Hispanic [aHR 1.25 (1.18 - 1.31)]; non-Hispanic black [aHR 1.12(1.04 - 1.21)]; Other [aHR 1.22(1.12 - 1.32)]. Results were consistent when stratified by tumor histology. CONCLUSION We identified disparities in survival among racial/ethnic minorities with pediatric brain and CNS tumors, with Hispanic patients having the highest risk of mortality. Eliminating these disparities requires commitment towards promoting heath equity and personalized cancer treatment.

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Key words: brain, central nervous system, tumor, race, ethnicity, survival

Abbreviations

SEER	Surveillance Epidemiology and End Results
CNS	Central nervous system
NCI	National Cancer Institute
(ICD-O-3)	International Classification of Diseases for Oncology, 3rd Edition
SES	Socioeconomic Status
NOS	Not Otherwise Specified
SAS	Statistical Analysis System
aHR	Adjusted Hazard Ratio

Data Availability Statement

The data that support the findings of this study are available from the Surveillance Epidemiology and End Results Program (*https://seer.cancer.gov/seerstat/databases/census-tract/index.html*) Restrictions apply to the availability of these data. Data are available with permission and approval.

ABSTRACT

BACKGROUND

Despite improvements in overall survival for pediatric cancers, treatment disparities remain for racial/ethnic minorities compared to non-Hispanic white; however, the impact of race on treatment outcomes for pediatric brain and central nervous system (CNS) tumors in the United States are not well known.

METHODS

We included 8713 children aged 0 – 19 years with newly diagnosed primary brain and CNS tumors between 2000 – 2015 from the Census Tract-level SES and Rurality Database developed by Surveillance, Epidemiology and End Results (SEER) Program. We used Chi-square tests to assess differences in sociodemographic,

cancer, and treatment characteristics by race/ethnicity and Kaplan–Meier curves and Cox proportional hazards models to examine differences in 10-year survival, adjusting for these characteristics.

RESULTS

Among 8,713 patients, 56.75% were non-Hispanic white, 9.59% non-Hispanic black, 25.46% Hispanic, and 8.19% from "other" racial/ethnic groups. Median unadjusted survival for all pediatric brain tumors was 53 months but varied significantly by race/ethnicity with a median survival of 62 months for Non-Hispanic whites, 41 months for Non-Hispanic blacks, and 40 months for Hispanic and Other. Multivariable analyses demonstrated minority racial groups still had significantly higher hazard of death than non-Hispanic whites; Hispanic [aHR 1.25 (1.18 - 1.31)]; non-Hispanic black [aHR 1.12(1.04 - 1.21)]; Other [aHR 1.22(1.12 - 1.32)]. Results were consistent when stratified by tumor histology.

CONCLUSION

We identified disparities in survival among racial/ethnic minorities with pediatric brain and CNS tumors, with Hispanic patients having the highest risk of mortality. Eliminating these disparities requires commitment towards promoting heath equity and personalized cancer treatment.

INTRODUCTION

While pediatric cancers represent less than 1% of the cancer burden in the United States, cancer remains the major cause of non-injury related mortality among children.[1,2,3,4] Brain and central nervous system (CNS) tumors are the most common type of pediatric cancer in the US after leukemia and have the highest mortality rates among all cancers affecting children.[5,6,7,8,9,10] While the incidence and mortality of pediatric brain and CNS tumors remains high, previous research has identified significant differences across racial and ethnic groups in both diagnosis and treatment in this population.[6,11,12] Several studies have identified a significantly higher incidence of brain and CNS tumors in non-Hispanic white children relative to those in racial/ethnic minorites.[7,8,9,13] While scientific breakthroughs in cancer treatment have improved cancer survival, leading to a one-third decrease in overall pediatric cancer mortality from 1990-2016, these advances have not benefited all racial/ethnic groups equally.[1,14] Specifically, despite the observed improvement in overall survival for pediatric cancers, disparities are evident in access to and use of guideline-recommended treatment and outcomes across racial/ethnic groups. [6,15,16,17] Prior research has demonstrated that minority populations including African Americans, American Indian, Native populations, and Hispanics have worse pediatric cancer survival compared to non-Hispanic whites.[7,17,18,19,20,21,] These studies have identified significant opportunities to reduce racial/ethnic disparities to improve both detection and survival in pediatric cancer patients.

Prior research also demonstrates significant gaps in our understanding of racial/ethnic disparities in pediatric brain and CNS tumors. Two previous studies have shown that socioeconomic status (SES) does not influence the relationship between race/ethnicity and survival for solid tumors including pediatric brain and CNS tumors,[6,22]but limited work has been done to evaluate the mechanisms by which race/ethnicity influences survival outcomes independent of SES. Based on the existing knowledge gap, the purpose of this study is to explore if racial/ethnic disparities in survival for pediatric brain and CNS tumors can be partially explained by sociodemographic and treatment differences across these populations.

METHODS

In this retrospective, population-based cohort study, we included children between the ages of 0-19 years newly diagnosed with primary CNS tumors between 2000 - 2015 in the Surveillance, Epidemiology, and End Results (SEER) Program sponsored by the National Cancer Institute (NCI). These population-based cancer registries include all incident cancer from 18 geographical locations in the US representing more than 28% of the US population.[23] SEER collects demographic, clinical, treatment and survival information on all incident cancers (excluding non-melanoma skin cancer). Tumor histology is classified using International Classification of Diseases for Oncology (ICD-O-3) codes.[24] We additionally received special permission to access the Specialized Census Tract-level SES and Rurality Database developed by SEER. In these data,

socioeconomic status for patients represented by Yost quintile reflects the SES group for the patients' census tract of residence at the time of disease (see below for measure definition). [25,26] The SES Yost quintile classification of census tracts is based on a time dependent composite score of the social and economic stratification of the area in which a patient resides at the time of diagnosis.[26]

Cancers diagnosed only by direct visualization or clinical impression without any imaging or laboratory confirmation were excluded from the study (n=73). Cases diagnosed by autopsy or death certificate only were also excluded (n=41), as were cases without information on their SES (n=151). Patients who had the optic nerve as the primary site of tumor were also excluded (n=723) from the data set due to its association with neurofibromatosis and complex natural history and therapy.[27] Our final sample included 8,713 children aged 0-19 at diagnosis.

Measures

The independent variables measured were age at the time of diagnosis, race, gender, Yost quintile, stage of cancer at diagnosis, histological type of tumor, tumor grade, and treatment received: radiotherapy, chemotherapy, and surgery. Study subjects were categorized into four age groups: 01-04 years, 05-09 years, 10-14 years, and 15-19 years. Race/ethnicity was categorized as non-Hispanic white, Hispanic, African American, with Asian or Pacific Islander/ American Indian/Unknown race all grouped together as "Other" due to the small numbers in these groups. Yost quintile is categorized into five groups with Group 1 having the lowest SES (<20th percentile) and Group 5 having the highest SES (>80th percentile).[25]

Tumor grade was reclassified as low grade (Well differentiated: Grade I and Moderately differentiated: Grade II) and high grade (Poorly differentiated: Grade III and Undifferentiated anaplastic Grade IV) tumor. Based on the treatment received, chemotherapy and radiotherapy were simply grouped as "yes" and "no". Patients were classified as yes if they received the various types of radiotherapy: beam radiation, radioactive implants, radioisotopes, combination of beam with implants or isotopes, or radiation not otherwise specified (NOS). Surgery status was classified as local excision/excisional biopsy, subtotal tumor resection, gross total tumor resection, partial lobectomy, total lobectomy (includes 86 cases who had unspecified surgery), or surgery not done/unknown.

Due to small sample sizes, histological tumor types were grouped as diffuse astrocytoma (protoplasma, fibrillary) and mixed glioma, anaplastic astrocytoma and glioblastoma, pilocytic astrocytoma, astrocytoma NOS and unique variants, ependymoma/anaplastic ependymoma/ependymoma variants, embryonal/primitive/medulloblastoma, glioma NOS.

Our dependent variable was overall survival. Survival was defined as the time from diagnosis until death of a study subject or the end of the follow-up period (November 2018).

Statistical Analysis

Chi-square tests were used to assess differences in the independent variables of interest across the four racial groups. Kaplan-Meier curves were used to estimate the unadjusted overall survival by race. The log rank test was used to estimate the differences in survival among the racial groups. Multivariable Cox proportional hazards models were used to determine the differences in overall risk of mortality in the study sample based on the independent variables including race, age at diagnosis, Yost Quintile, stage, tumor grade, histology, radiation, chemotherapy, and surgery.. All Chi-square tests and survival analyses were conducted using SAS version 9.4 statistical software, with p-values <0.05 considered significant.

RESULTS

We identified 8713 cases newly diagnosed with brain and CNS tumor from 2000-2015. 56.75% were non-Hispanic whites, 9.59% were non-Hispanic black, 25.46% were Hispanic, and 8.19% belong to "Other" race (Table 1). The majority of cancer diagnoses were children aged 0-4 years (31.49%). The age at diagnosis differed significantly by race/ethnicity ($p<0.0001$). 53.81% of children diagnosed with brain tumor were males and 46.19% were females. We identified no significant differences in the distribution of patients by gender

among the four racial groups (p=0.0660). Yost quintile was significantly different by race (p<0.0001). Non-Hispanic blacks had the largest proportion (35.05%) belonging to Yost quintile Group 1, with non-Hispanic whites having the largest proportion (19.82%) in Group 3, and Other with the largest proportion (32.07%) in Group 5.

Pilocytic astrocytoma was the most common histological type of tumor (30.08%) and diffuse astrocytoma (protoplasma, fibrillary). The histological type of tumor differed significantly by racial group (p<.0001). Non-Hispanic Whites had the highest proportion of pilocytic astrocytoma and diffuse astrocytoma (protoplasma, fibrillary) and mixed glioma tumor types, Hispanics had the largest proportion of ependymoma/anaplastic ependymoma/ependymoma variants and embryonal/primitive/ medulloblastoma tumor types, and non-Hispanic blacks had the largest proportion of astrocytoma NOS and unique variants and glioma NOS tumor types.

By tumor stage, the majority (78.56%) were localized, with a lesser proportion of tumors being regional (11.61%), distant (6.09%), or unknown/unstaged (3.73%). The racial groups differed by tumor stage (p=0.0003). The grade of the majority (68.72%) of tumors was not described as CNS tumor grade is inferred by name, 16.93% of tumors were described as high grade, and 14.35%, low grade tumors. Significant differences (p=0.0043) were also noted across racial/ethnic groups by tumor grade.

Regarding cancer therapy, among the cases with information on treatment received, we observed a larger proportion of patients having surgery (76.85%) than chemotherapy (41.54%) or radiation (39.60%). We noted significant differences (p<0.0001) in cancer therapy received by the racial/ethnic groups for all three treatment modalities. Hispanics had the largest proportion of patients receiving chemotherapy or radiation therapy with non-Hispanic whites having large proportions of patient not receiving chemotherapy or radiation therapy / status unknown. Non-Hispanic blacks had the largest proportion of patients who received no form of surgical therapy/ surgery status unknown.

Survival

Plotted survival curves (Figure 1) for pediatric brain tumors showed disparities in survival across racial/ethnic groups (p<0.001). Overall median survival for all pediatric brain and CNS tumors (Fig. 1A) was 53 months (95% CI, 50-55). Non-Hispanic whites had better survival (Fig. 1B) with a median of 62 months (95% CI, 59-65). The remaining three racial groups had a worse survival with non-Hispanic blacks having a median survival of 41 months (95% CI, 34-47) and Hispanics and "Other" racial/ethnic groups both experiencing a median survival of 40 months (Table 2). When stratified by histology, anaplastic astrocytoma and Glioblastomas had the worst survival (Fig. 1C) with an overall median survival of 14 months (95% CI, 13-15). There were statistically significant differences in survival by race/ethnicity within these histologic sub-types (p=0.0001) with Hispanics and non-Hispanic blacks having a worse survival than non-Hispanic whites and Other. Children diagnosed with diffuse astrocytoma (protoplasma, fibrillary) and Mixed glioma (Fig. 1D), had a good prognosis with an overall median survival of 89 months (95% CI, 80-98) with no statistically significant differences across racial/ethnic groups (p=0.2908).

Multivariate adjustment of the model also revealed non-Hispanic black [adjusted Hazard Ratio (aHR) 1.12(1.04-1.21)], Hispanic [aHR 1.25(1.18- 1.31)], and Other [aHR 1.22(1.12- 1.32)] racial groups had a significantly increased hazard of death as compared to non-Hispanic whites (Table 3). Hispanics and "Other" had a slightly increased hazard of death than was found in the unadjusted model while non-Hispanic blacks had a significantly decreased 10-year hazard of death in the adjusted model as compared to the unadjusted model.

There was no statistical difference between each Yost quintile groups and the reference group with the 10-year hazard of death for each group being approximately the same as that of the reference group. Controlling for all other variables decreased the hazard of death associated with the tumor type except for anaplastic astrocytoma and glioblastoma tumor types which still had a significantly high hazard of death [aHR, 2.13(1.83-2.48)].

Sensitivity Analyses

We re-analyzed our survival models evaluating the relationship between race/ethnicity and survival to evaluate whether the relationship varied when limited to 5-year hazard of death. The Cox proportional hazard model to determine the 5-year hazard of death (Supplemental Table S1) showed only Hispanic patients having a significantly higher hazard of death than non-Hispanic white patients in both the unadjusted model ($p<0.0001$) and the adjusted model ($p=0.0003$). To a large extent, 5- year hazard of death associated with histology type and surgery modality did not differ significantly within each group while significant differences were largely noted in the remaining covariates in both the unadjusted and adjusted models except for hazard of death associated with radiation, which was also non-significant. Additionally, we found no significant interaction between race and histology type in the survival model, indicating there is no differential impact of race on survival by histology type.

DISCUSSION

Overall, non-Hispanic whites had the highest 10-year survival, with non-Hispanic blacks, Hispanics, and Other having a worse survival. Considering histologic types, anaplastic astrocytoma and glioblastoma had the lowest survival and diffuse astrocytoma (protoplasma, fibrillary) and mixed glioma had the highest survival. This is consistent with findings from previous studies.[8,28,29,30,31,32] This study differs from other studies of pediatric brain and CNS tumor survival because it assesses the racial disparities in brain and CNS tumor survival using recent national specialized census tract data that provide information on both SES and cancer treatment received by patients.

The largest group of minority patients were Hispanics, which is not surprising because Hispanics are currently the largest racial minority and one of the fastest growing racial minority groups in the US.[33] Similar to what was found in other studies[6,11,12] there was a male predominance in diagnosed cases and the majority of cases were diagnosed before age ten. Pilocytic astrocytoma was found to be the most common tumor type in children, with non-Hispanic whites having the highest proportion of cases. This concurs with findings from other studies.[6,12] It was also previously shown that non-Hispanic blacks had the highest burden of medulloblastoma,[34] however, similar to the findings of Cooney, et al. and Barnholtz-Sloan et al.,[7,11] our study showed Hispanics had the highest burden of both medulloblastoma and ependymoma. "Other" race/ethnicities had the highest proportion of anaplastic astrocytoma and glioblastoma histology types. Studies that examined these histologies separately found that non-Hispanic whites had an increased proportion of glioblastoma tumors[8] while non-Hispanic blacks had an increased proportion of anaplastic astrocytoma.[11]

Even though our study showed a strong association between race and SES, similar to Austin and Kehm's findings,[6,22] SES was not significantly associated with adverse cancer outcomes in the univariate and multivariate models for both 5-year and 10-year risk of death. Accounting for SES in the multivariate model reduced the risk of death across all racial groups. This supports findings from previous studies on the relationship between SES and solid tumor outcomes demonstrating that low SES is not associated with poor survival outcomes.[6,22] Results from our study suggest that factors other than SES mediate the racial survival disparities observed in brain and CNS tumors.

Examining the multivariate analysis, we found that the 10-year hazard of death was significantly increased for all three minority racial groups as compared to non-Hispanic whites, with Hispanics having the highest risk of death. Survival reaches a plateau for most tumors quite late with the exception of high-grade gliomas and medulloblastoma.[35,36,37] It is thus not surprising that in our study, the racial/ethnic survival disparities were more pronounced in the 10-year models. Late mortality could also occur in 5-year survivors, attributable to multiple causes including late treatment effects, tumor recurrence or progression which could be influenced by quality of initial therapy.[38,39,40] It will be informative to look at the cause-specific mortality for cases.

The relatively poor 5-year survival seen among Hispanics could be due to multiple factors. Based on the study results, Hispanics have the highest proportion of patients undergoing partial lobectomy. This procedure was associated with an increased 5-year risk of death based on the study results. Similar to finding from other

studies[6,41], our results showed that Hispanics have a slighter higher burden of cases reporting with advanced cancer compared to the other racial groups. It may stem from the fact that the affected individuals may be uninsured/underinsured which is influenced by several factors including parents' immigration status and healthy families who choose to forgo insurance.[42,43]

In our study, we found significant differences in treatment modality by race/ethnicity, which may partially explain the increased risk of death seen in minority racial groups. Similar treatment differences were noted in a study which addressed the disparities in brain tumor treatment.[13] Considering that treatment received is known to impact survival,[19] patients who receive inadequate treatment or poor quality treatment have less chances of survival. Minority populations as compared to non-Hispanic whites often receive treatment from low volume hospitals which are less equipped to handle such cases rather than high volume hospitals or specialized cancer centers where they can receive adequate and quality care from a multidisciplinary clinical team for both initial therapy and follow up care for survivors.[10,13,38] Furthermore, there is evidence to suggest that racial discrimination on the part of healthcare providers, minority patients being less likely to be enrolled in clinical trials, and patients declining treatment options due to mistrust of the health system contribute to disparities in treatment.[13,20,44,45,46,47,48] There could also be racial differences in the response to chemotherapeutics due to potential differences in pharmacogenomics and tumor molecular markers across the racial/ethnic groups.[49,50] However, there doesn't appear to be a documentation of raced-based biological differences in these factors and the extent to which they impact treatment outcomes.[37] Future studies should specifically explore host and tumor genetic factors and its influence on treatment response across racial groups.

Challenges with patient provider communication especially when it involves patients with limited English proficiency (LEP), the majority of which are from minority racial groups[51] could negatively impact delivery of optimum health care, patients' compliance to therapy, follow up care and ultimately treatment outcomes. Few studies done to evaluate the impact of language barrier on cancer treatment outcomes indicate that there is limited information shared between providers and patients even when interpreters are engaged due to difficulties in direct communication between the two parties.[52,53,54] The impact of patient and provider communication and the role of medical interpreters in cancer treatment and outcomes need to be explored further in future studies.

The study has several limitations. Data for this study were obtained from SEER and the supplementary Specialized Census Tract-level SES and Rurality Database which provides information on the overall SES of the census tract of residence of a patient and not the SES of the patient.[25,26] Only information on the insurance status of patients diagnosed from 2007 – 2015 was available, hence the influence of insurance on treatment outcome was not assessed in this study. Additionally, Asians, American Indians, and cases without racial identity were grouped together due to their small sample sizes, which does not allow for good representation of the independent survival outcomes of Asians and American Indians. Treatment information in SEER is incomplete with no clear differentiation between cases who did not receive treatment and those whose treatment information is missing, making it difficult to infer real differences in treatment among the racial groups. SEER does not have information on molecular tumor markers or genomic ancestry which may influence the racial disparities in outcome.[55,56,57] Finally, the data do not include patients' choice in the treatment.

CONCLUSION

Overall, we identify significant racial/ethnic disparities in survival among those diagnosed with pediatric brain and CNS tumors, with Hispanic patients having the highest risk of mortality, even after accounting for stage of diagnosis, tumor grade, and SES. The observed differences in survival become more pronounced with increasing follow up time. Eliminating these disparities requires commitment towards promoting equity in healthcare delivery. Future studies aimed at delineating how differences in host and tumor genetic factors impact treatment response could help optimize treatment for patients including offering personalized cancer treatment.

CONFLICTS OF INTEREST :

There are no financial disclosures or conflicts of interest to report.

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FIGURE LEGEND

Figure 1. Kaplan–Meier survival curves for children diagnosed with pediatric primary brain and CNS tumor 2000-2015.

Figure 1A. Kaplan Meier curve for overall 10-year tumor survival

Figure 1B. Kaplan Meier curve for 10-year tumor survival by race

Figure 1C. Kaplan Meier curve for 10-year survival by race for Anaplastic astrocytoma and Glioblastoma histology group

Figure 1D. Kaplan Meier curve for 10-year survival by race for Diffuse astrocytoma (protoplasma, fibrillary) and Mixed glioma histology group.

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