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Patient and treatment factors associated with survival among pediatric glioblastoma patients: A Surveillance, Epidemiology, and End Results study

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ABSTRACT

Glioblastoma (GBM) is a rare malignancy in children. The United States Surveillance, Epidemiology, and End Results (SEER) database allows large-scale analyses of clinical characteristics and prognostic features. We used it to study patients aged <20 years with histologically confirmed GBM (2000–2010) and examined the relationship between patient demographics, tumor characteristics, patterns of treatment, and outcomes. The primary outcome was disease-specific survival. 302 subjects were identified, with median age 11 years. Median follow-up was 32 months (95% CI 27–39). 34.4% had gross total resection (GTR). 61% underwent radiation after surgery (17% of subjects <3 years, 67% of those aged 4–19 years). Median survival and 2-year survival rates were 20 months and 46.9%, respectively. In multivariate analyses, age, tumor location, extent of resection, and year of diagnosis were significantly associated with the primary outcome. Compared to those aged 0–4 years, subjects aged 5–9 years and 10–14 years had higher risk of mortality. Infratentorial tumor location (HR 2.0, 95% CI 1.2–3.3, $p = 0.007$) and subtotal resection (HR 2.04, 95% CI 1.4–3.0, $p < 0.001$) were associated with increased mortality. Later year of diagnosis was significantly associated with decreased risk of death (HR 0.93, 95% CI 0.9–0.99, $p = 0.031$). There was no association between sex, race, region, or tumor size and the primary outcome. Repeat analyses examining all-cause mortality identified the same risk factors as for CNS cancer–specific mortality. Younger age, supratentorial location, GTR, and later year of diagnosis were associated with improved survival.

1. Introduction

Percival Bailey and Harvey Cushing described glioblastoma (GBM) in the early 1900 s as a tumor derived from the primitive precursors of glial cells (glioblasts) with a highly variable appearance due to necrosis, hemorrhage, and cysts (multiform). Evolving understanding over time revealed that GBM cells have high mitotic activity (as quantitated by Ki-67) and form ambiguous tumor margins that are locally infiltrative, typically alongside deep white matter tracts such as the corpus callosum, anterior commissure, fornix, internal capsule, and perivascular spaces [1–3].

Unlike in adults, high-grade gliomas are rare tumors in the pediatric population. Data from the European Union and Central Brain Tumor Registry of the United States (CBTRUS) show that GBM accounts for less than 3% of all primary central nervous system (CNS) tumors among children, with an estimated incidence of 1.4 per 1,000,000 [4,5]. In children, signs and symptoms of high-grade gliomas can include headaches, seizures, visual changes, and focal neurological deficits [6]. In infants, symptoms, such as irritability and change in feeding patterns, may be manifest. Heightened suspicion for GBM is warranted in children with certain genetic syndromes such as neurofibromatosis Type 1, Turcot syndrome, and Li–Fraumeni syndrome [7].

Due to the rarity of these neoplasms, the number of available studies has been limited. Published studies indicate GBM in children may not behave the same as that in adults [6,8–10]. For example, pediatric GBM has a distinct and more favorable natural history [9], expresses different oncogenic mutations [11–14], and does not always respond to the same chemotherapeutic treatments as adult GBM [7,15–20].

Most publications on pediatric GBM to date are single-center studies with relatively small cohorts drawn from over decades

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[6,8,9,21,22]. The goal of this study was to examine a large nationally representative cohort of patients from the recent decade to evaluate the impact of demographics, tumor characteristics, and modern treatment patterns on survival outcomes. The present study is based on data from the United States Surveillance, Epidemiology and End Results (SEER) program between the years 2000 and 2010.

2. Methods

2.1. Data source and study cohort

The SEER database, a program of the United States National Cancer Institute, collects cancer incidence and survival data from 18 population-based cancer registries covering approximately 28% of the U.S. population [23]. Our study population consisted of pediatric patients less than 20 years of age with a first-time diagnosis of GBM, defined using the International Classification of Diseases for Oncology Version 3 (ICD-O-3) histology codes 9440–9442, diagnosed between the years 2000 and 2010. Data was available through December 31, 2010, to allow for a minimum of 12 months' follow-up. The study cohort had their first and primary diagnosis of cancer as GBM in a SEER registry and did not have any other cancer diagnoses. We aimed to examine the effects of treatment in our cohort, so patients who carried only a postmortem diagnosis of GBM (i.e. in death certificate or autopsy only) were excluded. Surgical intervention was classified as no surgery, biopsy, partial resection, or gross total resection (GTR); patients with unknown surgery type were excluded. SEER data is publicly available, and non-human subjects research exempt status was obtained from the Baylor College of Medicine Institutional Review Board.

2.2. Patient and tumor characteristics

Variables of interest from the SEER database were examined, including subjects' age at diagnosis, gender, race, and geographic registry. Age was further categorized into four groups: 0–4, 5–9, 10–14, and 15–19 years. Race was categorized as white, black, and Asian/others. Subjects' residential states were converted into four geographical regions defined by the U.S. Census: Northeast, Midwest, South, and West.

Tumor topographic sites were identified through the ICD-O-3 codes as follows: supratentorial included cerebrum, frontal, temporal, parietal, and occipital (C71.0, C71.1–C71.4); infratentorial included cerebellum and brain stem (C71.6, C71.7); and not otherwise specified (NOS, C71.5, C71.8, and C71.9). Laterality (left, right, bilateral/NOS) and tumor size (0–3 cm, 3–6 cm, >6 cm, unknown) were also included in the analysis model. Since advances in treatment paradigms might be correlated with improved patient outcomes, year of diagnosis was also included as a study variable. Medical comorbidities, functional performance status, and quality of life data are not available in the SEER database; these are known limitations with the SEER program.

2.3. Treatment and outcomes

Patients were grouped by radiation status: "radiation after surgery" and "other." The SEER variable "RX Summ-Surg Prim Site" was used to determine the extent of resection (biopsy only, partial resection, and GTR) [24,25]. First treatment is recorded; subsequent surgeries cannot be elucidated in SEER. No chemotherapy or biologic treatment information is available in the SEER database.

Disease-specific survival is the primary outcome in this study and was defined using the SEER cause of death recode "31010" to identify cancer cause of death by brain and other nervous system [26]. To specifically identify factors leading to GBM-related death, other causes of death were treated as "censored" and counted as survival events.

2.4. Statistical analysis

Descriptive analyses were used to describe patient demographic and clinical characteristics. Number of cases and percentages are shown. We reported median overall survival (OS) time by months, 2-year OS (2YSR), and 95% confidence intervals (CI) for each subgroup, as well as for the entire cohort using the Kaplan-Meier method [27]. Log-rank tests were used to compare survival between subgroups; p-values were reported. P-values of <0.05 were considered statistically significant.

The Cox proportional hazards method was used for multivariate analysis. All variables (age, race, region, tumor location, laterality, tumor size, radiation, type of surgery, and year at diagnosis) were included in the final multivariate model based on *a priori* identification. We also performed sensitivity analyses to evaluate the robustness of study findings with or without Louisiana registry data due to the possibility of noncontinuous reporting secondary to the effects of Hurricane Katrina. Similar methods have been described elsewhere [25,28]. Data management and statistical analyses were conducted using STATA 12 software (Stata Corp., College Station, TX).

3. Results

302 pediatric glioblastoma patients met inclusion criteria for the study (Fig. 1). Median follow-up was 32 months (95% CI 27–39). The median age was 11 years, (range 0–19 years), and

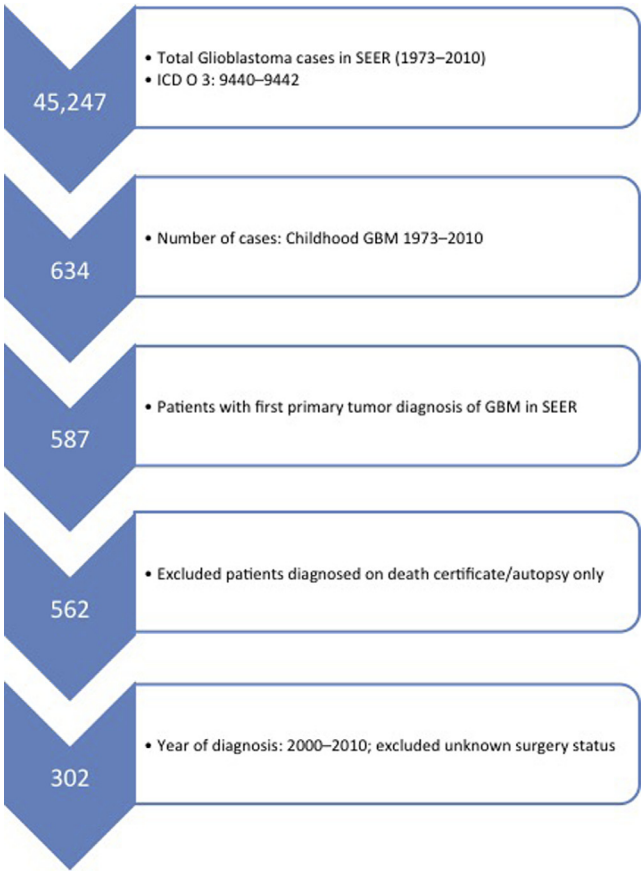

Fig. 1. Data selection flowchart.

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