Subependymal Giant Cell Astrocytoma: A Surveillance, Epidemiology, and End Results Program—Based Analysis from 2004 to 2013

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- **BACKGROUND:** Subependymal giant cell astrocytoma (SEGA) is a rare, benign neoplasm predominantly associated with tuberous sclerosis complex. Clinical outcomes have largely been conveyed via small- and medium-sized case series.

- **METHODS:** With the Surveillance, Epidemiology, and End Results Program (SEER)–18 registry database, information from all patients diagnosed with SEGA from 2004 to 2013 was obtained (age, sex, race, marital status, tumor size, tumor location, occurrence of surgery, receipt of radiation, and follow-up data). Age-adjusted incidence rates and overall survival (OS) were determined. Cox proportional hazards model was used for both univariate and multivariate analyses.

- **RESULTS:** The overall incidence of SEGA within the SEER-18 database is 0.027 per 100,000 person-years (95% confidence interval, 0.024–0.031). A total of 226 cases were identified. For OS, univariate analysis revealed age younger than 18 years (hazard ratio [HR], 0.214; \( P = 0.004 \)) and occurrence of surgery (HR, 0.328; \( P = 0.039 \)) were significant positive prognostic factors. Sex, marital status, race, tumor size, tumor location, and receipt of radiation did not exhibit significant relationships. Interestingly, subanalysis for extent of resection to gross total resection did not show benefit. Multivariate analysis revealed that both age younger than 18 years (HR, 0.193; \( P = 0.002 \)) and occurrence of surgery (HR, 0.286; \( P = 0.021 \)) remained significant.

- **CONCLUSIONS:** Based on our analysis, younger age and occurrence of surgery are significant independent factors associated with better OS. There was no support for radiation.

**INTRODUCTION**

Subependymal giant cell astrocytoma (SEGA) is a rare, benign (World Health Organization grade I) neoplasm that constitutes approximately 1%–2% of all intracranial pediatric tumors.1 Nearly all cases have occurred in patients with tuberous sclerosis complex (TSC).1,2 SEGAs frequently arise near the foramen of Monro.3 Presentations vary from obstructive hydrocephalus, neurologic deficits, and seizures4 to intracranial hemorrhage5 and sudden death.6,7 Current treatment options include surgical resection, cerebrospinal fluid diversion, and/or mechanistic target of rapamycin (mTOR) inhibitors.1,7-9 Prior literature has been largely restricted to small- and medium-sized case series, with reserved input regarding the epidemiology and outcomes for patients with SEGAs.2,10-14 Consequently, we mined the Surveillance, Epidemiology, and End Results Program (SEER)–18 registry to assess the pathology across a large subset (approximately 28%) of the U.S. population.15
METHODS

Following the footstrokes of previous analyses, we vetted the SEER-18 registry (including Hurricane Katrina–impacted Louisiana) for patients with SEGA (International Classification of Diseases for Oncology—3rd edition histology codes C71.8/1 and C71.8/3) diagnosed from 2004 to 2013. The minimum year was set as such because 2004 was the first year that required the report of benign brain tumors. Patients with prior malignancies were permitted into the search results. Age, sex, race, marital status, occurrence of surgery, tumor size, tumor location, receipt of radiation, and follow-up data were acquired.

With the SEER*Stat Software, we performed the following calculations analogous to other colleagues: 1) age-adjusted incidence rates were determined as the number of SEGA cases per 100,000 person-years; 2) incidence rate ratios (IRRs) were determined based on age, sex, and race with a significance threshold at \( P = 0.05 \); and 3) overall survival (OS) was determined using the Kaplan-Meier method. Causes of death coded as brain and other nervous system; in situ, benign, or unknown behavior; neoplasm; and miscellaneous malignant cancer were all attributed to SEGA, akin to recent SEER investigations. Categorical data are conveyed through frequency counts and percentages.

Age was dichotomized with a cutoff at 18 years. Sex was dichotomized to men and women. Marital status was dichotomized to single (coded as single, never married; separated; divorced; widowed; or unmarried or domestic partner) and married (coded as married, including common law). Race was dichotomized to white (coded as white) or nonwhite (coded as black, American Indian/Alaska Native, or Asian or Pacific Islander). Tumor was dichotomized with a threshold of 2.5 cm. Location was dichotomized to ventricles (coded as ventricle not otherwise specified [NOS] [C71.5]) or not ventricles (all other codes except brain NOS [C71.9] and overlapping lesion of brain [C71.8]—2 codes considered as unknown/not specified). Any case with an unknown value for a specific variable was excluded from the analysis of that specific variable.

Occurrence of surgery was defined as follows: no surgery (those coded as no surgery [00]) or surgery (those coded as local tumor destruction NOS [10], biopsy [20], surgery NOS [90], partial resection NOS [40], and subtotal resection [21], gross total resection [GTR] [55], or radical, total, GTR [30]). Of those who underwent surgery, the extent of primary surgery was defined as follows, similar to that previously described: no GTR (those coded as local tumor destruction NOS [10], biopsy [20], partial resection NOS [40], and subtotal resection [21] or GTR (those coded as GTR [55] or radical, total, GTR [30]). Surgery status unknown (those coded as surgery, unknown [99] and surgery NOS [90]) was not included in the extent of resection analysis.

Receipt of radiation was defined as follows: no radiation (those coded as none [0] and patient or patient’s guardian refused radiation therapy [7]) or radiation (those coded as beam radiation [1], radioactive implants [2], radioisotopes [3], combination of beam radiation with radioactive implants or radioisotopes [4], and radiation NOS [5]); unknown status of radiation was not included in the relevant analysis. IBM SPSS 22 (IBM, Armonk, New York, USA) was used for statistical analysis. For univariate analysis, relationships between various demographic/clinical/treatment variables and OS were determined using the Cox proportional hazards model. Those that exhibited \( P < 0.1 \) were incorporated into a backward conditional multivariate analysis that also used the Cox proportional hazards model. All \( P \) values reported represent 2-sided statistical tests. \( P < 0.05 \) was considered statistically significant.

RESULTS

Epidemiology

The overall incidence of SEGA within the SEER-18 database is 0.027 per 100,000 person-years (95% confidence interval [CI], 0.024–0.031). As shown in Figure 1, incidences ranged from 0.022 to 0.035 per 100,000 person-years from 2004 to 2013.

The mean age at diagnosis was 16.61 ± 0.93 years. As shown in Figure 2, the incidence of SEGA peaks for age younger than 1 year (0.095 per 100,000 person-years; 95% CI, 0.048–0.17) and steadily diminishes with increasing age groups. From age group 20–24 years onward, the incidences are significantly lower than the incidence for age younger than 1 year (\( P < 0.05 \)).

The incidences for men and women are 0.031 (95% CI, 0.026–0.037) and 0.023 (95% CI, 0.019–0.029), respectively. There is a decreased incidence among women compared with men (IRR, 0.7489; 95% CI, 0.5686–0.9822; \( P = 0.0362 \)).

Compared with whites, the IRR for blacks is 1.0992 (95% CI, 0.7211–1.6154; \( P = 0.6762 \), for American Indians/Alaska Natives is 0.2352 (95% CI, 0.0059–1.8456; \( P = 0.3411 \), and for Asian or Pacific Islanders is 0.9163 (95% CI, 0.545–1.4629; \( P = 0.8209 \)).

Univariate Analysis

In the same vein of earlier studies, only cases with actively followed/known age/within research database were considered; death certificate only/autopsy only/alive with no survival time were excluded. A total of 226 cases were identified in the SEER-18 database. Table 1 summarizes patient characteristics.

Multivariate Analysis

From univariate analysis for OS, variables with \( P < 0.1 \) (age and occurrence of surgery) were incorporated in a multivariate analysis. The regression revealed that both younger age (HR, 0.193; 95% CI, 0.067–0.553; \( P = 0.002 \)) and occurrence of surgery (HR, 0.286; 95% CI, 0.099–0.827; \( P = 0.021 \)) remained significant when accounting for each other.
DISCUSSION
This study represents the largest group of people diagnosed with SEGA. The findings fuel the current literature with respect to overall incidence and incidence relative to age group, sex, and race. Figure 1 depicts that the incidence has remained largely steady from 2004 to 2013. Figure 2 shows that incidence is significantly higher in the pediatric age groups, which agrees with prior literature. The mean age of this SEER cohort at
diagnosis was 16.61 years, within the pediatric ages like most other studies; however, a few studies mention mean ages up to 31 years. Overall, approximately 36% of new diagnoses in this SEER cohort were at least 18 years of age (Table 1). There is a significantly lower incidence of SEGA in women than men, with an IRR of 0.7489; the underlying explanation remains unclear to the authors. No differences in incidences were noted among race. Neither tumor size nor location (regarding involvement of ventricles) demonstrated a significant relationship with OS in the SEER cohort. No studies have examined these specific relationships, but tumor size has been implicated with surgical complications/morbidity. In 2014, Kotulska et al. reported 57 patients who received surgeries for 64 SEGAs. For tumors less than 2 cm, no complications were noted; for those between 2 and 3 cm, the complication rate rose to 46%; for tumors larger than 3 cm, rates skyrocketed to more than 80%. The most frequent morbidities were hemiparesis, hydrocephalus, hematoma, and cognitive decline.

From our regression, younger age portended a better OS. The literature has explored the association with age and surgical risk/complications but has been quiet regarding OS. Kotulska et al. noted that for those who underwent surgery, children less than 3 years of age demonstrated significant risk for surgery. On the other hand, Goh et al. observed higher rates of long-term complications after tumor resection when patients were age 11 years or older compared with those younger than 11 years; this was attributed to less frequent surveillance in the older patients, which amounted to larger, more vascular tumors. Tsai et al. found that SEGA exhibited a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total*</th>
<th>Number of Patients (%)</th>
<th>5-Year OS (months)</th>
<th>Univariate HR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P Value</th>
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<td>&lt;18 years</td>
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<td>Male</td>
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<td>Not married</td>
<td>209 (93.72)</td>
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<td>96.73</td>
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<td>0.114</td>
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<td>No</td>
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<td>62 (53.91)</td>
<td>96.52</td>
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</table>

OS, overall survival; CI, confidence interval; GTR, gross total resection.

*Value reflects the total number of cases where data were available for the specific variable.
significantly faster growth rate in children than adults, advocating for more routine surveillance in younger patients.

From our regression, the occurrence of surgery was associated with improved OS. Interestingly, the analysis for extent of resection (to GTR) did not reveal significance. Prior literature supports improved outcomes with surgery, especially with complete resection compared with subtotal resection. In 2007, de Ribaupierre et al. observed no obvious recurrence after GTR when they reviewed the prior literature (15 cases) and assessed their own 19 patients, where 15 obtained GTR, with a mean follow-up of 77 months. Overall, rates of GTR have ranged from 43% to 88%. More recently, Jiang et al. reported 17 patients with 18 SEGAs (1 patient with 2 tumors); surgery occurred in 17 SEGAs, and 15 achieved GTR and subsequently exhibited no recurrence, with a mean follow-up of 46 months. Moreover, Amin et al. described 16 surgical patients, and 13 had GTR with no recurrence. Nevertheless, subtotal resection has been associated with long-term stability; there is a general conviction that SEGAs halt growth with adulthood. However, authors have reported recurrence from as early as 3 months to as late as 22 years after subtotal resection.

Our analysis reveals no support for radiation therapy regarding OS. There is some anxiety regarding this treatment modality and the possibility of malignant degeneration because patients with SEGAs largely possess a mutation for TSC tumour suppressor genes (either TSC1 or TSC2). In 2011, Park et al. reported 6 patients over a 20-year period who underwent gamma knife surgery for SEGAs, with a median follow-up of 73 months. Local tumor control was evident in 4 patients, 1 patient received more gamma knife surgery with subsequent tumor regression, and the last patient exhibited growth and received surgical resection.

Like prior SEER-based analyses, this study has noted limitations. Information regarding radiation (dosage, fields, or fractionation) was incomplete. As previously noted, gamma knife may induce local tumor control. Additionally, details about chemotherapy were not collected. With TSC, mTOR inhibitors, such as everolimus, are a key component in treatment regimens. Moreover, pertinent surgical details were not offered. Information regarding extent of resection resorted to primitive codes, which dilutes the interpretation of resection. There was no mention of surgical adjuncts, which may influence survival based on recent literature, such as intraoperative magnetic resonance imaging, endoscopy, and stereotactic laser ablation. There were no reports of surgical complications, which can be up to 48.9% based on recent articles. There was incomplete information regarding surgical pathology; although rare, SEGAs have been associated with atypical histologic features and spinal metastasis. Features worrisome for aggressive clinical course. Importantly, status of TSC was not revealed. It has been shown that in patient with TSC2 mutation, SEGAs develops at a younger age, arises more frequently, and grows more rapidly in comparison with TSC1 mutation. Overall, the median OS was not attained and the median follow-up was 53 months. The latter is less than some of the prior cases series. Longer-term follow-up would be favorable for survival analysis. Finally, the diagnosis of TSC/SEGAs significantly alters quality of life and functional status for the patient and their families, outcome factors not available within the SEER database. In addition to SEGAs, 60% of patients or more also suffer from skin lesions, seizures, and impairment of cognition; moreover, close to 40% require a visit to an emergency department and/or a hospital admission. Side effects from mTOR inhibitors can cause stomatitis, noninfectious pneumonitis, rash, metabolic abnormalities, and infections. The psychologic factors can be prominent, where caregivers face real emotions regarding the experience of losing control because of unexpected disease manifestations and the feeling of loneliness and abandon from health care.

CONCLUSIONS

Based on our analysis, younger age and occurrence of surgery are significant independent factors associated with better OS. There was no support for radiation. Although SEER-based analyses have noted limitations, we think the findings offer new contributions and reinforce current views surrounding SEGAs.

REFERENCES


Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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