Pediatric Low-Grade Ganglioglioma: Epidemiology, Treatments, and Outcome Analysis on 348 Children From the Surveillance, Epidemiology, and End Results Database

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BACKGROUND: Low-grade gangliogliomas/gangliocytomas (GGs) are rare tumors of the central nervous system that occur mostly in young people. Because of their rarity, large-scale, population-based studies focusing on epidemiology and outcomes are lacking.

OBJECTIVE: To use the Surveillance, Epidemiology, and End Results (SEER) data sets of the National Cancer Institute to study demographics, tumor location, initial treatment, and outcome data on low-grade GGs in children.

METHODS: SEER-STAT v8.1.2 identified all patients aged 0 to 19 years in the SEER data sets with low-grade GGs. Using the Kaplan-Meier method and Cox proportional hazard regression, we examined associations between these characteristics and survival.

RESULTS: There were 348 children with low-grade GGs diagnosed from 2004 to 2010, with a median follow-up of 37 months. Tumors were more prevalent in males (n = 208, 59.8%) than females (n = 140, 40.2%) ($P < .001$). Almost 63% occurred in children >10 years, whereas only 3.5% were found in those <1 year old. Approximately 50% were located in the temporal lobes, and only 3.7% and 3.5% were located in the brainstem and spinal cord, respectively. Surgery was performed on 91.6% of cases, with gross total resection achieved in 68.3%. Radiation was used in 3.2%. Young age (<1 year) and brainstem location were associated with worse overall survival.

CONCLUSION: This study shows that low-grade GGs occur in older children with a male preference. Gross total resection is achieved in the majority of cases, and radiation is rarely used. Although the majority of patients have an excellent prognosis, infants and patients with brainstem tumors have worse survival rates.

KEY WORDS: Demographics, Low-grade ganglioglioma/gangliocytoma, Outcomes, SEER, Treatment

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Low-grade gangliogliomas/gangliocytomas (GGs) are rare, well-differentiated, glial-neural tumors that account for only 0.5% of all central nervous system (CNS) tumors, and 1% to 5% of all pediatric CNS tumors.[1-4] Indeed, they are thought to be tumors of young people, with most studies reporting mean or median ages anywhere from 8 to 26 years.[1] Although the majority occur in the temporal lobes, causing epilepsy,[5] they occur throughout the CNS, including the brainstem and spinal cord.[1,2,6-10] These latter lesions may present with varied neurological signs/symptoms, including cranial nerve deficits, focal weakness, and hydrocephalus.[7,8,11,12] In general, supratentorial low-grade GGs are thought to be very benign lesions, with good prognosis being associated with temporal location, epilepsy, and gross total resection (GTR).[6,9,10,13] Owing to their rarity, the epidemiology and factors affecting outcome are poorly understood.

The US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data sets represent approximately 28% of the US

ABBREVIATIONS: GG, ganglioglioma/gangliocytoma; **GTR,** gross total resection; **NOS,** not otherwise specified; **PFS,** progression-free survival; **SEER,** Surveillance, Epidemiology, and End Results; **STR,** subtotal resection

population[14] and include data on patient demographics, primary tumor site, treatment information, as well as patient survival data,[14] thereby making them a useful resource for studying rare tumors.[15] We used SEER to study low-grade GG in patients aged 0 to 19 years and, in particular, to investigate associations between patient and treatment characteristics and survival. We hypothesized that demographic and treatment factors affect survival for children with low-grade GGs, and, based on our clinical experience, that brainstem tumors would have a worse outcome than other GGs.

METHODS

The sample frame was identified from the most recent SEER data sets (Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2012 Sub [1973-2010 varying]).[14] We included patients with age <20 years and *International Classification of Diseases for Oncology, Third Edition* diagnosis codes 9505/0 (ganglioglioma) and 9492/0 (gangliocytoma), diagnosed from January 1, 2004 to December 31, 2010. Anaplastic ganglioglioma (9505/3) and desmoplastic infantile astrocytoma/ganglioglioma (9412/1) were excluded from this study. The primary outcome was overall survival (OS), defined as the number of months from the date of diagnosis to the date of last follow-up or death. Cause-specific survival was also examined. Data collected for each subject included sex, race, age at diagnosis, anatomic location, extent of surgical resection, use of radiation therapy, OS, and cause-specific survival. SEER does not contain data regarding treatment with chemotherapy.[16]

For most analyses we categorized age as <1, 1 to 4, 5 to 9, 10 to 14, and 15 to 19 years. Owing to the small numbers, we dichotomized age into <1 vs "other age" to examine cause-specific survival. Race was dichotomized as "white" and "nonwhite." Tumor location was recorded in SEER in 14 categories corresponding to the various lobes of the brain, as well as cerebrum, cerebellum, brainstem, spinal cord, cerebral meninges, ventricles, optic nerves, brain-not otherwise specified (NOS), and overlapping lesion of the brain. The extent of surgical resection was divided into 3 groups: subtotal resection (STR), gross total resection (GTR), and no surgery (none), based on SEER site-specific coding guidelines.[17] The STR group included patients with surgical codes 20 (local excision of tumor, lesion, or mass, excisional biopsy, or stereotactic biopsy of the brain), 21 (subtotal resection of tumor, lesion or mass, NOS), 22 (partial resection of tumor, lesion, or mass), and 27 (excisional biopsy), whereas the GTR group included patients with surgical codes 30 (radical, total, gross resection of tumor, lesion or mass in brain), 40 (partial resection of lobe of brain, when the surgery cannot be coded as 20-30), and 55 (GTR of lobe of brain [lobectomy]).[17] These definitions have been used by us and others previously for SEER data set analysis.[18,19] Two cases with surgical codes 90 (surgery, NOS) and 99 (unknown if cancer-directed surgery performed; death certificate only), respectively, were excluded from the analysis.

For survival analysis, overall and cause-specific survival curves were estimated by using the Kaplan-Meier method and compared by using the log-rank test. For the purpose of univariate survival analysis, we categorized location as "brainstem," "spinal cord," and "other." For variables found to be associated with survival, we also performed 5-year relative survival analysis. Proportional hazards ratios were estimated by using Cox regression analysis. The assumption of proportionality was visually assessed by using log-log survival plots and by testing the statistical significance of time-dependent covariates. Relative survival was calculated by using the actuarial method. Finally, we compared survival of brainstem GGs with other GGs in terms of age at diagnosis, sex, use of radiation, and extent of resection. SEER*STAT v8.1.2 was used to extract case-level data.[20] SAS v9.2 and SEER*STAT v8.1.2 were used for data analyses. $P < .05$ was considered statistically significant.

Findings from SEER were compared with the previously published literature. Relevant reports were found through a review of the English language articles in the PubMed database by using the search terms "low-grade ganglioglioma," "ganglioglioma," or "gangliocytoma" in combination with one or more of the following search terms: "treatment," "clinical outcomes," "demographics," and "pediatric." The first author screened all abstracts and selected articles for full review. The references for each article were further reviewed to identify other relevant articles.

RESULTS

We identified 348 children who were diagnosed with low-grade GG between 2004 and 2010. Of the total population, 59.8% (208/348) were male, producing a male-to-female ratio of almost 1.5:1.0 (Table 1). Eighty-three percent (282/341) were "white." The mean and median ages at diagnosis were 10.9 and 12.0 years, respectively, with 62.9% (219/348) being older than 10 years of age, and 3.5% (12/348) younger than 1 year of age (Table 1, Figure 1). Regarding anatomic location, 47.4% (165/348) of patients had temporal lobe tumors (Table 2). The next most frequent locations were the frontal lobe, parietal lobe, and cerebellum at 10.3% (36/348), 8.9% (31/348), and 6.3%

TABLE 1. Univariate Analysis of Demographics and Treatments of Pediatric Patients With Low-Grade Gangliogliomas/Gangliocytomas, 2004 to 2010 (n = 348)[a]

Characteristic	n	%
Sex		
Male	208	59.8
Female	140	40.2
Age, y		
0	12	3.5
1-4	49	14.1
5-9	68	19.5
10-14	110	31.6
15-19	109	31.3
Race (n = 341)		
White	282	82.7
Other	59	17.3
Extent of resection (n = 344)		
GTR	235	68.3
STR	80	23.3
No surgery	29	8.4
Radiation treatment (n = 345)		
No radiation	334	96.8
Beam radiation	11	3.2
Vital status		
Alive	339	97.4
Dead	9	2.6

[a]GTR, gross total resection; STR, subtotal resection.

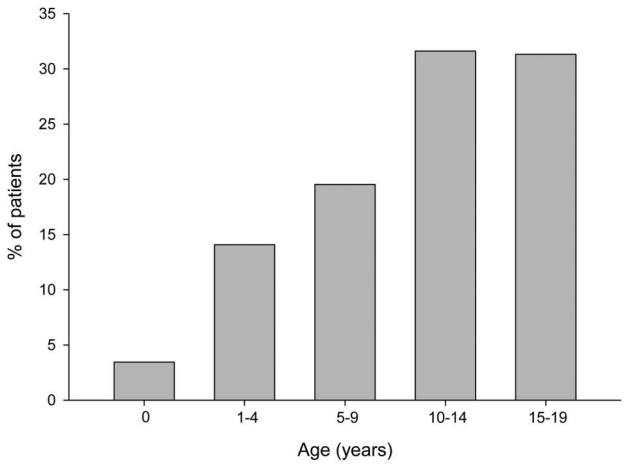

FIGURE 1. *Age distribution of 348 children with low-grade gangliogliomas/gangliocytomas from the SEER data sets (2004-2010). SEER, Surveillance, Epidemiology, and End Results.*

(22/348), respectively. Brainstem and spinal cord tumors occurred in 3.7% (13/348) and 3.5% (12/348) of patients, respectively. The least common locations were the cerebral meninges and pituitary gland, with only 1 such tumor (0.3%) found in each of these sites. GTR was achieved in 68.3% (235/344) of patients, STR was achieved in 23.3% (80/334) of patients, and 8.4% (29/344) of patients did not have surgery. Those patients who did not have surgery were diagnosed by imaging alone or at autopsy. Radiation treatment was used in 3.2% (11/345) of patients.

Very young age at diagnosis (<1 year) and brainstem location were associated with worse OS ($P \leq .01$ for both) (Table 3). These findings were confirmed by proportional hazard ratio estimated using Cox regression analysis (hazard ratio [HR], 31.4; 95% confidence interval [CI], 2.8-351.4 and HR, 8.2; 95% CI, 1.7-39.5, respectively). No such association was found for sex, race, the use of radiation, the use of surgery, or extent of surgical resection. Only age group was associated with cause-specific survival, with patients <1 year of age faring worse than older patients (log-rank $P = .009$, HR = 10.4; 95% CI, 1.2-91.0; data not shown).

Because of the survival associations found for age at diagnosis and anatomic location, we performed 5-year relative survival analysis for these 2 variables. For age at diagnosis, the 5-year relative survival was >92% for all age groups tested (1-4, 5-9, 10-14, and 15-19 years), except for children diagnosed at less than 1 year of age, for whom 5-year survival was 43.2% (Figure 2). This survival difference could not be explained by differences in anatomic location, extent of resection, or radiation treatment (Table 4), although it should be noted that no patient under 1 year old was treated with radiation, vs a 3.3% radiation use in older patients. There was, however, a statistically significant difference in male-to-female ratio with only 25% (3/12) males in patients <1 year old vs 61% males (205/336) in the older patients.

TABLE 2. Anatomic Location of Pediatric Low-Grade Gangliogliomas/Gangliocytomas, 2004 to 2010 (n = 348)[a]

	Frequency	%
Temporal lobe	165	47.41
Frontal lobe	36	10.34
Parietal lobe	31	8.91
Cerebellum, NOS	22	6.32
Overlapping lesion of brain	15	4.31
Occipital lobe	15	4.31
Brainstem	13	3.74
Ventricle, NOS	13	3.74
Brain, NOS	12	3.45
Spinal cord	12	3.45
Cerebrum	10	2.87
Optic nerve	2	0.57
Cerebral meninges	1	0.29
Pituitary gland	1	0.29
Total	348	100

[a]NOS, not otherwise specified.

TABLE 3. Log Rank Test *P* Values and Crude Hazard Ratios for Mortality Among Cases of Low-Grade Pediatric Gangliogliomas/Gangliocytomas, 2004 to 2010 (n = 348)[a]

	P Value[b]	HR	95% CI
Age, y	.001		
0		31.4	2.8-351.4
1-4		2.2	0.1-35.5
5-9		5.4	0.6-52.4
10-14		2.0	0.2-21.7
15-19		ref	
Sex	.35		
Female		1.9	0.5-6.9
Male		ref	
Race (n = 341)	.23		
White		ref	
Not white		2.3	0.6-9.1
Extent of resection (n = 343)	.84		
GTR		ref	
STR		0.6	0.1-4.9
No surgery		1.3	0.2-10.8
Radiation treatment (n = 345)	.16		
No radiation		ref	
Beam radiation		4.0	0.5-31.8
Location	.01		
Brainstem		8.2	1.7-39.5
Spinal cord[c]		N/A	
Other site		ref	

[a]CI, confidence interval; GTR, gross total resection; HR, hazard ratio; STR, subtotal resection.
[b]Overall survival curves were calculated by using the Kaplan-Meier method and compared with the log-rank test.
[c]Zero deaths in patients with spinal cord tumors.

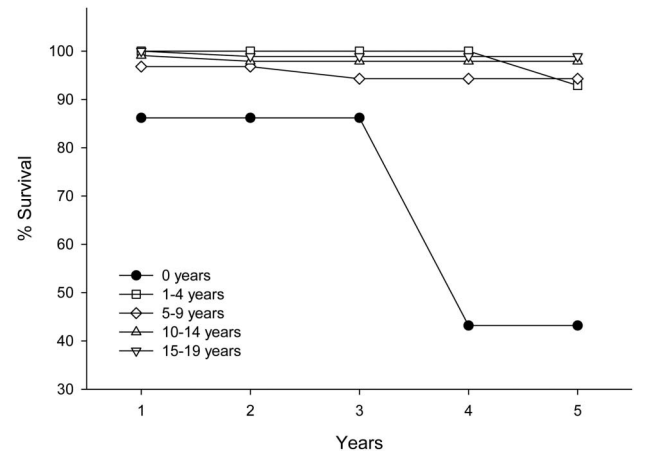

FIGURE 2. *Five-year relative survival analysis of different age groups of patients with low-grade gangliogliomas/gangliocytomas from the SEER data sets (2004-2010). SEER, Surveillance, Epidemiology, and End Results.*

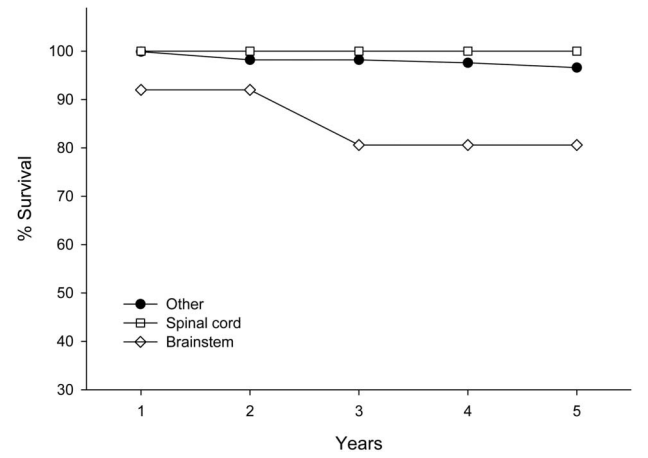

FIGURE 3. *Five-year relative survival analysis of patients with gangliogliomas/gangliocytomas of the brainstem, spinal cord, and other locations, from the SEER data sets (2004-2010). SEER, Surveillance, Epidemiology, and End Results.*

The 5-year relative survival for patients with low-grade GGs in locations other than the brainstem was 96.6%, whereas the 5-year relative survival for patients with brainstem tumors was 80.6% (Figure 3). This difference could not be explained by differences in age, sex, use of radiation, or extent of surgical resection (Table 5). Radiation was used in 1/13 (7.7%) brainstem tumors and 10/332 (3.0%) tumors in other sites. Patients with brainstem tumors had GTR less than patients with tumors at other sites (58.3% and 68.7%, respectively). The GTR percentage for spinal cord tumors alone and other tumors alone was 83.3% and 68.1%, respectively (data not shown). The percentage of brainstem tumors not operated on was double that of other locations (2/12, 16.7% vs 27/332, 8.1%, respectively). Despite the above-described male predisposition in the overall population, there were 7 males (53.9%) to 6 females (46.2%) in the brainstem group. These trends did not achieve statistical significance.

TABLE 4. Comparison of Demographic and Treatment Factors by Age Group Among Pediatric Patients With Low-Grade Gangliogliomas/Gangliocytomas, 2004 to 2010 (n = 348)[a]

	<1 year, n (%)	1-19 years, n (%)	*P* Value[b]
Tumor location			.37
Brainstem	1 (8.3)	12 (3.6)	
Other	11 (91.7)	324 (96.4)	
Sex			.02
Male	3 (25.0)	205 (61.0)	
Female	9 (75.0)	131 (39.0)	
Extent of resection (n = 344)			.63
None	1 (8.3)	28 (8.4)	
STR	4 (33.3)	76 (22.9)	
GTR	7 (58.3)	228 (68.7)	
Radiation (n = 345)			1.00
Yes	0 (0.0)	11 (3.3)	
No	12 (100.0)	322 (96.7)	

[a]GTR, gross total resection; STR, subtotal resection.
[b]Fisher exact test.

TABLE 5. Comparison of Demographic and Treatment Factors by Anatomic Location Among Pediatric Patients With Low-Grade Gangliogliomas/Gangliocytomas, 2004 to 1020 (n = 348)[a]

	Other, n (%)	Brainstem, n (%)	*P* Value[b]
Age, y			.56
0	11 (3.3)	1 (7.7)	
1-4	48 (14.3)	1 (7.7)	
5-9	64 (19.1)	4 (30.8)	
10-14	107 (31.9)	3 (23.1)	
15-19	105 (31.3)	4 (30.8)	
Sex			.66
Male	201 (60.0)	7 (53.9)	
Female	134 (40.0)	6 (46.2)	
Extent of resection (n = 344)			.38
None	27 (8.1)	2 (16.7)	
STR	77 (23.2)	3 (25.0)	
GTR	228 (68.7)	7 (58.3)	
Radiation (n = 345)			.35
Yes	10 (3.0)	1 (7.7)	
No	322 (97.0)	12 (92.3)	

[a]GTR, gross total resection; STR, subtotal resection.
[b]Pearson χ^2 or Fisher exact test.

DISCUSSION

Most reports of low-grade GGs include a limited number of patients with mostly tumors of the cerebral hemispheres.[2,5-7,10-13,21,22] A 30-year review of all age groups from the Mayo Clinic included 88 patients.[10] The largest study to date included 184 patients, but focused exclusively on supratentorial GGs, and included both high-grade and low-grade tumors.[6] Reports regarding brainstem and spinal cord GGs are exceedingly rare, with only 3 previous case series in the literature.[7-9] Only one of these, which included 58 patients of all ages, attempted to compare outcomes of cerebral, spinal cord, and brainstem tumors.[9] Few case series have focused specifically on children.[2,5,7,11-13,21-24] To our knowledge, this report, which includes 348 pediatric low-grade GGs, is the largest study of its kind, and is the only study to compare brainstem and spinal cord GGs with tumors in other locations with a large number of children. Inclusion of such a large number of rare tumors in children alone was only made possible by the use of the SEER data sets.

This study confirmed several previously described epidemiological phenomena regarding low-grade GGs. First, within the pediatric age groups, these are thought to be tumors of older children and young teenagers. In 7 studies focusing specifically on children, the mean age ranged from 5.6 to 15.6 years, but the average of all mean ages from those 7 studies, including 232 children, was 10.5 years.[2,5,7,11-13,21] In our study, with 348 children, the mean and median ages at diagnosis were 10.9 and 12.0 years, respectively. Indeed, the majority of patients (62.9%) were older than 10 years of age, but only 3.5% were less than 1 year of age. Second, the majority of studies describe an increased male-to-female ratio of 1.5 to 1.9:1 for GGs in all locations,[6,9,11,13,23] but a study of only infratentorial GGs found a male-to-female ratio of 1:1.[13] Likewise, in our study, the male-to-female ratio was 1.5:1 for nonbrainstem tumors, but closer to 1:1 for brainstem tumors, with 7 males to 6 females. Finally, most studies describe the temporal lobes as the predominant location for low-grade GGs, making these tumors the number 1 neoplastic entity leading to long-term epilepsy.[1,5] Some studies report that 43% to 79% of GGs occur in the temporal lobes.[2,6,10,23] Here, we found a 47.4% occurrence in the temporal lobes. However, the SEER data sets also included 3 nonspecific codes for "cerebrum," "overlapping region of the brain," and "brain, not otherwise specified."[14] Together these coding categories contained 37 GGs, some of which might represent temporal GGs.

We found that GTR was achieved in 68.3% of children, in keeping with other studies, which report a rate of GTR ranging from 45% to 79%.[5,9,10,12,13,21-24] At least part of this variability reflects differences in tumor location. Mickle[11] described a 100% GTR rate for supratentorial tumors, and 0% GTR for infratentorial tumors. In the only study looking specifically at brainstem GGs, none underwent GTR.[8] On the contrary, Lang et al[9] described 97% GTR for spinal cord GGs, 33% for those of the brainstem, and 63% for those of the cerebral hemispheres. Similarly, we found a higher GTR percentage for spinal cord tumors (83.3%) than brainstem tumors (58.3%), and the percentage of GTR for other GGs (ie, mostly supratentorial and cerebellar) was in the middle (68.1%) (data not shown). The fact that our study reveals a higher GTR rate for brainstem tumors cannot be explained by more modern techniques or surgical approaches, because some of the above-described series were also very recent.

There appears to be a trend toward less use of radiotherapy for GGs over the past 30 years. Between 1983 and 1997, there were 5 studies that described a rate of radiation use that ranged from 20% to 40%.[9,11,12,21,22] However, since 2004, 4 studies have reported rates of radiation between 2% and 10%.[6,7,10,13] The realization that these are generally very benign tumors, and an increased understanding of the detrimental effects of radiation, are likely the main factors responsible for this trend. In our study, which included patients added to the SEER data sets between 2004 and 2010, radiation treatment was used in only 11/345 (3.2%) children.

GGs, in general, are thought to be very benign lesions. In a report regarding supratentorial lesions, Luyken et al[6] reported a 7.5-year recurrence-free survival of 97%, and a 7.5-year OS of 98%. These authors found that low-grade lesions, temporal location, epilepsy, and complete resection were associated with better progression-free survival (PFS). Compton et al[10] studied only low-grade GGs and found 15-year OS of 94%, with a median PFS of 5.6 years and a 10-year PFS of 37%. PFS was dramatically associated with the extent of resection. This study included supra- and infratentorial tumors, but only 5/88 tumors were located in the brainstem and spinal cord. Specifically looking at children and including 7/38 brainstem/spinal cord tumors, Khashab et al[13] found the 5-year PFS rate to be 81.2%. Prolonged PFS was associated with initial presentation with seizures, cerebral hemisphere location, and complete resection. In a rare study that may have been biased toward brainstem/spinal cord tumors (39/58), Lang et al[9] described worse operative morbidity rates (35% vs 5%), worse 5-year relative survival rates (78.5% vs 93%), and worse event-free survival rates (44.5% vs 95%) for brainstem/spinal cord GGs vs cerebral tumors. Tumor location was the only factor associated with outcome, with spinal cord/brainstem tumors having a 3.5- and 5-fold increased risk of recurrence. Most recently, Haydon et al[23] reported on 53 low-grade GGs in children, including 6 infratentorial tumors, and found a 5-year recurrence-free survival rate of 70.5% and OS rate of 98%. These authors found that older age, supratentorial location, seizure history, and complete resection were associated with prolonged recurrence-free survival, but only complete resection retained significance in multivariate analysis.

The SEER data sets do not allow us to study PFS, but we found that brainstem location was significantly associated with worse OS. This must be interpreted with caution because only 9 patients (2 brainstem and 7 other) died in our study. Furthermore, although the hazard ratio for mortality is elevated, the wide confidence intervals (1.7-39.5) reflect the small sample number of patients with tumors located in the brainstem (n = 13). We also found 5-year relative survival to be $\geq$97% for nonbrainstem tumors, but 80.6% for brainstem tumors. The only other factor that was negatively associated with survival was young age (ie, $<$1 year),

which is similar to the findings of Haydon et al[23] above. When we performed 5-year relative survival analysis on the patients of different age groups, we found that all patients older than 1 year of age had 5-year survival of greater than 92%, whereas patients <1 year of age had a 5-year OS rate of only 43%. Unlike the recent study of Haydon et al,[23] and other previous studies,[6,10,13] we did not identify an association between extent of resection and survival. Of note, for both 5-year relative survival analyses of different age groups and different anatomic locations, there was a delayed separation of the survival curves that became most obvious at 3 to 4 years after diagnosis. This likely reflects the amount of time it takes for recurrence/progression and subsequent patient demise for such a histologically benign and slow-growing tumor, and reinforces the need for long-term follow-up studies for such tumors. Unfortunately, because of the limitations of the SEER data sets, we cannot say whether the patients experienced morbidity related to the initial tumor resection, and/or repeated procedures to treat delayed recurrences. At present, it is unclear why very young patients would do so much worse. This could not be explained by differences in age, extent of resection, or radiation use. There was a statistically significant difference in male-to-female ratio with much fewer males in children <1 year of age, but how this might relate to survival is unclear. Unlike other pediatric brain tumors, where such a relationship might be attributed to the lack of radiation therapy use in the very young children, radiation therapy was only used in 3.4% of pediatric patients of all ages in SEER. However, although we did not find a statistically significant difference between these very young patients and older patients in terms of radiation use, it should be noted that not a single patient <1 year of age was treated with radiation. In addition, GTR was achieved in a smaller percentage of patients <1 year old. Because the small numbers of patients in this subgroup precluded us from studying interactions between GTR and radiation use, at this point, we cannot fully dismiss the possibility that these infants have worse survival because they are left with greater residual tumor, without an option for adjuvant radiation postoperatively.

Likewise, it is unclear why outcome is worse for low-grade GGs in the brainstem. It is intuitive that tumors in this location would be more difficult to resect, and, indeed, we found a trend toward less GTR for these tumors. However, this did not achieve statistical significance. Furthermore, there was no statistically significant difference in age, sex, or radiation use. This leaves us to speculate that these tumors are inherently different because of genetic or molecular characteristics. Rush and colleagues[24,25] noted that brainstem GGs are difficult to treat despite their low-grade pathological characteristics and suggested that this might be related to activating mutations in the BRAF gene. To our knowledge, genetic differences between brainstem GGs and those in other locations have not been described, but molecular signatures, such as BRAF mutations, or other yet-to-be-defined genetic alterations, might provide insight into the survival trends observed in SEER.

Limitations

We have previously described various limitations inherent in the use of SEER data sets as a means of studying epidemiology and outcomes, particularly for benign tumors.[18] In brief, because benign tumors, such as GGs, were added to the SEER data sets in 2004, there is a relatively short period of follow-up, which limits the conclusions that can be drawn from survival statistics. Also, the small number of outcome events (ie, deaths) limits our ability to detect survival relationships. In particular, we were not able to perform multivariate analysis owing to the small number of deaths. PFS is perhaps more relevant for such tumors, but the SEER data sets do not provide information regarding this outcome measure. Furthermore, SEER offers no data regarding quality of life, such as control of seizures or cranial nerve dysfunction. In addition, SEER does not include data on other factors affecting survival, such as the use of chemotherapy, socioeconomic status, and the biological profiles of tumors. Also, as we and others have done previously, we defined "extent of resection" based on the surgical codes provided by SEER that are most in keeping with GTR and STR. However, SEER does not offer a standardized means of defining these variables, which leaves our definition open to criticism. Furthermore, retrospective database analysis with the use of the SEER data sets is not conducive to pathology re-review, which can be a concern when basing conclusions on small numbers of tumors within subgroups. For instance, here we report that very young patients (<1 year old) had the worse survival, but this is based on only 12 cases. Although the individual institutions, SEER delegates, as well as independent examiners review the cases entered into the SEER data set, without 2014 pathology re-review we cannot say with 100% certainty that all cases were truly low-grade GGs. Finally, this study is subject to all the potential biases of a retrospective, registry-based study, including selection and reporting bias. For instance, it is possible that some patients with brainstem, or spinal cord, or supratentorial tumors in eloquent regions of the brain were not treated, and therefore possibly not reported as well.

CONCLUSION

Analysis of 348 low-grade GGs from the SEER data sets defines these as tumors of older children and young teenagers, with a male predominance, and a predilection to the temporal lobes. GTR is achieved in the majority of these tumors, and radiation therapy is only rarely used. Survival rates for patients with low-grade GGs are high, with 96% 5-year relative survival. Worse OS is associated with young age and brainstem location, but, at present, this cannot be explained by age, sex, extent of resection, or the use of radiation treatment. We did not find an association between extent of resection and survival. Analysis of a larger group of low-grade pediatric GG cases would permit a more robust evaluation of demographic and treatment factors associated with mortality in this patient population. Further work is needed to confirm these findings and to improve outcomes for the more vulnerable subgroups.

Disclosures

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COMMENT

The authors used SEER data sets to report survival outcome in 331 patients less than 20 years of age who were diagnosed of ganglioglioma between 2004 and 2010. The limitations of SEER database are well-known to this same group of authors who had referenced their own publication in the article. Some of the limitations that are relevant in this case:

1. SEER data set only provides survival analysis and no other measurements. Patients with ganglioglioma often present with first-time seizure, and whether or not the patient achieves seizure freedom is most clinically relevant and is often the focal point of institutional series. There is no information on seizure status (or morbidity or quality of life) in SEER.
2. SEER data set is not very useful for benign lesions with low mortality rates. Some clinical series had documented 10-year survival rate greater than 90% in ganglioglioma. The follow-up period here is between 2 and 8 years. As the authors pointed out, there were only 8 mortalities among the 331 patients, which explained the wide confidence interval in the statistical analysis.
3. SEER data set is not immune from reporting bias. Although 27 of 331 patients were diagnosed by imaging alone (which is disputable) or at autopsy, it is conceivable that patients with spinal cord lesions, compared with those with supratentorial lesions, are less likely to undergo surgery and therefore are underreported.

As the authors pointed out, when the SEER database is queried, there are only a limited number of data fields that could be extracted: sex, race, age at diagnosis, anatomic location, extent of surgical resection, use of radiation therapy (yes/no), overall survival and cause-specific survival. Although age- and sex-specific trends can sometimes be identified and are certainly interesting, other important clinical features are lacking. The shortcomings are especially accentuated in benign lesions such as ganglioglioma.

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CME QUESTIONS:

1. What is the most common presentation of pediatric gangliogliomas?
   a. Hydrocephalus
   b. Incidental finding
   c. Headaches
   d. Seizures
   e. Hemiparesis

2. What is the most common anatomic location of pediatric gangliogliomas?
   a. Frontal lobe
   b. Parietal lobe
   c. Temporal lobe
   d. Brainstem
   e. Spinal cord

3. What treatment modality is associated with the highest rates of progression free survival in pediatric patients with gangliogliomas?
   a. Gross total resection + radiatiotherapy
   b. Gross total resection + chemotherapy
   c. Gross total resection alone
   d. Stereotactic radiosurgery
   e. Gross total resection + chemotherapy + radiotherapy