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CLINICAL ARTICLE

A comprehensive epidemiological review of spinal astrocytomas in the United States

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OBJECTIVE Spinal cord astrocytoma (SCA) is a rare tumor whose epidemiology has not been well defined. The authors utilized the Central Brain Tumor Registry of the United States (CBTRUS) to provide comprehensive up-to-date epidemiological data for this disease.

METHODS The CBTRUS was queried for SCAs on ICD-O-3 (*International Classification of Diseases for Oncology*, 3rd edition) histological and topographical codes. The age-adjusted incidence (AAI) per 100,000 persons was calculated and stratified by race, sex, age, and ethnicity. Joinpoint was used to calculate the annual percentage change (APC) in incidence.

RESULTS Two thousand nine hundred sixty-nine SCAs were diagnosed in the US between 1995 and 2016, resulting in an average of approximately 136 SCAs annually. The overall AAI was 0.047 (95% CI 0.045–0.049), and there was a statistically significant increase from 0.051 in 1995 to 0.043 in 2016. The peak incidence of 0.064 (95% CI 0.060–0.067) was found in the 0- to 19-year age group. The incidence in males was 0.053 (95% CI 0.050–0.055), which was significantly greater than the incidence in females (0.041, 95% CI 0.039–0.044). SCA incidence was significantly lower both in patients of Asian/Pacific Islander race (AAI = 0.034, 95% CI 0.028–0.042, p = 0.00015) and in patients of Hispanic ethnicity (AAI = 0.035, 95% CI 0.031–0.039, p < 0.001). The incidence of WHO grade I SCAs was significantly higher than those of WHO grade II, III, or IV SCAs (p < 0.001).

CONCLUSIONS The overall AAI of SCA from 1995 to 2016 was 0.047 per 100,000. The incidence peaked early in life for both sexes, reached a nadir between 20 and 34 years of age for males and between 35 and 44 years of age for females, and then slowly increased throughout adulthood, with a greater incidence in males. Pilocytic astrocytomas were the most common SCA in the study cohort. This study presents the most comprehensive epidemiological study of SCA incidence in the US to date.

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KEYWORDS spinal cord astrocytoma; SCA; epidemiology; intradural tumor; incidence; spinal tumor; oncology

Gliomas account for approximately 26.5% of primary brain tumors, and astrocytomas represent the majority (75.5%) of these cases.[1] Astrocytomas comprise a wide variety of subtypes, ranging from low-grade pilocytic astrocytomas to high-grade glioblastomas.[2,3] While astrocytomas are known to develop throughout the CNS, astrocytomas of the spinal cord are rare, with limited published epidemiological information.[3–10]

While the vast majority of astrocytomas arise in the brain, 3% of these cases occur as intramedullary spinal cord tumors, most of which are either pilocytic (WHO grade I) or diffuse (WHO grade II).[7] However, high-

ABBREVIATIONS AAI = age-adjusted incidence; APC = annual percentage change; CBTRUS = Central Brain Tumor Registry of the United States; CI = confidence interval; ICD-O-3 = *International Classification of Diseases for Oncology*, 3rd edition; IRR = incidence rate ratio; NOS = not otherwise specified; SCA = spinal cord astrocytoma; SEER = Surveillance, Epidemiology, and End Results.

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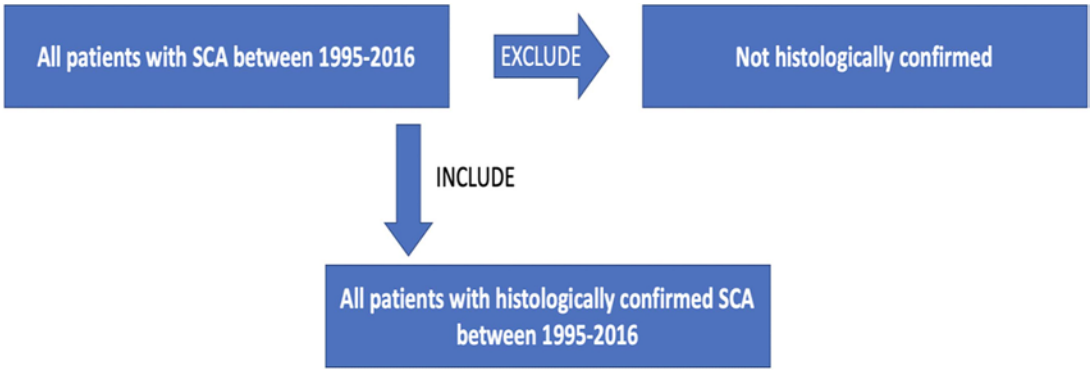

FIG. 1. Inclusion and exclusion criteria. Only histologically confirmed cases were included in the study. Figure is available in color online only.

grade spinal cord astrocytomas (SCAs) do occur and are associated with a high rate of recurrence and overall poor prognosis.[7,11] Infiltrating astrocytomas (grades III and IV) account for 10%–20% of intramedullary spinal cord tumors.[11] Histologically, pilocytic astrocytomas are most common in the pediatric population, while diffuse astrocytomas are most commonly found in adults.[5,8,12–14] While SCAs are rare in the general population, they have a much higher incidence in patients with neurofibromatosis type 1, a phenomenon believed to be due to the increased replication of nonmyelinating Schwann cells in these patients.[15]

SCAs are generally diagnosed using MRI, and there are no current guidelines or consensus on the best management course.[4–6,11] Asymptomatic patients are followed with serial imaging, and surgery may be performed for patients with progressive symptoms or tumor growth, with the extent of resection dependent on tumor grade.[4–6,11] Other treatment modalities include postoperative radiotherapy and chemotherapy for tumors that recur after surgery and radiotherapy.[11,14,16–19] Early detection and appropriate treatment are of paramount importance in these tumors, a challenging task given our limited understanding of their epidemiology and clinical profiles, both of which require significant elucidation. To this end, the authors performed a large-scale epidemiological review of SCA patients utilizing the Central Brain Tumor Registry of the United States (CBTRUS), which contains population-based incidence data for benign CNS tumors. The vast coverage of this registry, accounting for 99% of the US population between 1995 and 2016, renders it an ideal source for our study.[1] Utilizing CBTRUS, we present the most comprehensive epidemiological description of SCAs in the US to date, thereby filling a current gap in the literature by expanding our knowledge of trends in SCA incidence between 1995 and 2016.

Methods

The CBTRUS database was queried for astrocytoma and spinal cord lesions from the years 1995–2016. Histological and topographical codes from the *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3), were used to query the database. CBTRUS accounts for 99% of the US population and also contains information about all newly diagnosed primary CNS tumors. Additionally, demographic information including patient age, race, sex, and ethnicity was also collected from the CBTRUS database. Population data from the US Census Bureau from the year 2000 were used to calculate age-adjusted incidence (AAI) rates, and the 95% confidence intervals (CIs) were acquired from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Figure 1 shows the inclusion/exclusion criteria.

Histological and Topographical ICD-O-3 Codes

The following ICD-O-3 histological codes were utilized to query the database: 9421/1 (pilocytic astrocytoma), 9400/3 (astrocytoma, NOS [not otherwise specified]), 9401/3 (astrocytoma, anaplastic), 9420/3 (fibrillary astrocytoma), 9424/3 (pleomorphic xanthoastrocytoma), 9410/3 (protoplasmic astrocytoma), 9412/1 (desmoplastic infantile astrocytoma), 9382/3 (mixed glioma), 9425/3 (pilomyxoid astrocytoma), and 9440/3 (glioblastoma).

The following ICD-O-3 topographical codes of spinal cord locations were utilized to query the database: C72.0 (spinal cord), C41.2 (vertebral column), C70.1 (spinal cord meninges), and C72.1 (cauda equina). Cases that were diagnosed via radiograph only were excluded; only cases confirmed histologically were included in the final analysis. Table 1 shows a detailed description of the cohort.

Statistical Analysis

AAI per 100,000 persons was calculated with SEER*Stat (version 8.3.4, National Cancer Institute) with a 95% CI. In addition to overall incidence, AAI was also calculated with respect to patient demographic variables, such as age and sex, as well as with respect to histology and grade. The authors used the WHO grading system to categorize the SCAs into grades I–IV. The Joinpoint Regression Program (version 4.5.0.1, National Cancer Institute) was used to calculate the annual percentage change (APC) in incidence to allow evaluation of trends over time. Of note, CBTRUS is not permitted to report counts of less than 16.

TABLE 1. Description of cohort demographics

Characteristic	AAI*	No. of Patients (%)	IRR	p Value
Histology				
Pilocytic astrocytoma	0.017	1036 (34.9)	1.000	Reference
Mixed glioma	0.001	54 (1.8)	0.052	<0.001
Astrocytoma NOS	0.016	994 (33.5)	0.942	0.18
Anaplastic astrocytoma	0.004	271 (9.1)	0.254	<0.001
Fibrillary astrocytoma	0.003	171 (5.8)	0.162	<0.001
Glioblastoma NOS	0.007	416 (14.0)	0.392	<0.001
Undocumented	0.0004	27 (0.9)	0.026	<0.001
Race				
White	0.048	2430 (81.8)	1.000	Reference
American Indian/Alaska Native	0.025	20 (0.7)	0.529	0.003
Asian or Pacific Islander	0.034	106 (3.6)	0.728	0.001
Black	0.044	374 (12.6)	0.915	0.11
Undocumented	0.150	39 (1.3)	3.158	<0.001
Ethnicity				
Spanish-Hispanic-Latino	0.035	334 (11.2)	1.000	Reference
Non–Spanish-Hispanic-Latino	0.050	2635 (88.8)	1.315	<0.001
Sex				
Male	0.053	1646 (55.4)	1.000	Reference
Female	0.041	1323 (44.6)	0.778	<0.001
WHO grade				
I	0.017	1036 (34.9)	1.000	Reference
II	0.003	171 (5.8)	0.165	<0.001
III	0.004	271 (9.1)	0.261	<0.001
IV	0.007	416 (14.0)	0.400	<0.001
Undocumented	0.017	1075 (36.2)	1.008	0.86

* Rate per 100,000.

Results

A total of 2969 SCAs were diagnosed and confirmed histologically from 1995 to 2016 in the US. There was a statistically significant decrease in AAI from 0.051 in 1995 to 0.043 in 2016 (Fig. 2). The overall incidence during the study period was 0.047 (95% CI 0.045–0.049), translating into an average of approximately 136 SCAs diagnosed annually.

Incidence With Respect to Demographics

The peak AAI of 0.064 (95% CI 0.060–0.067) was observed in the 0- to 19-year age group, while the lowest AAI of 0.015 (95% CI 0.034–0.040) was observed in the 20- to 34-year age group (Fig. 3). The AAI steadily rose with older age, hitting a second peak with the 75- to 84-year age group (AAI = 0.047, 95% CI 0.039–0.056) before reaching a nadir in the ≥ 85-year age group (AAI = 0.015, 95% CI 0.0086–0.024). The AAI of the 0- to 19-year age group was significantly higher than the AAI of the rest of the age groups ($p < 0.001$). With respect to patient sex, the mean AAI in males of 0.053 (95% CI 0.050–0.055) was significantly greater than the mean AAI in females (0.041, 95% CI 0.039–0.044), with an incidence rate ratio (IRR) of 0.78 ($p < 0.001$). The trends of AAI with respect to age groups for both males and females are shown in Fig. 3. It is important to note that there were insufficient numbers of both male and female patients in the 75- to 84-year age group and ≥ 85-year age group, and thus no data were reported for these age groups relative to AAI with respect to sex.

The AAI for the White population was 0.048 (95% CI 0.045–0.049), which was similar to the AAI for the Black population (0.044, 95% CI 0.039–0.048, $p = 0.280$). Compared to the White population, the AAI was significantly lower for the American Indian/Alaskan Native population (0.025, 95% CI 0.015–0.039) and the Asian or Pacific Islander population (0.034, 95% CI 0.028–0.042). There was a significantly lower incidence in patients of Hispanic ethnicity (0.035, 95% CI 0.031–0.039) compared to patients not of Hispanic ethnicity (0.050, 95% CI 0.048–0.052, $p < 0.001$).

Incidence With Respect to Grade and Histology

Of the 2969 cases of SCA diagnosed during 1995–2016, pilocytic astrocytoma was the most prevalent histological subtype of SCA in all age groups ($p < 0.001$ in all groups). Patients ≥ 65 years of age had significantly higher incidences of anaplastic astrocytomas and astrocytoma not

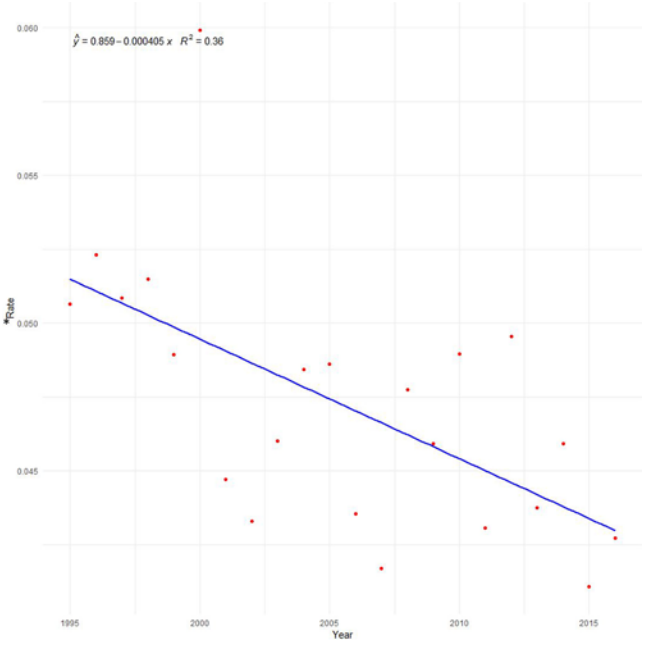

FIG. 2. AAI of SCAs over the study period (1995–2016). There is a steady decrease in SCA AAI from 0.051 to 0.043 over the study period. *Rates are per 100,000 and age-adjusted to the 2000 US population. Figure is available in color online only.

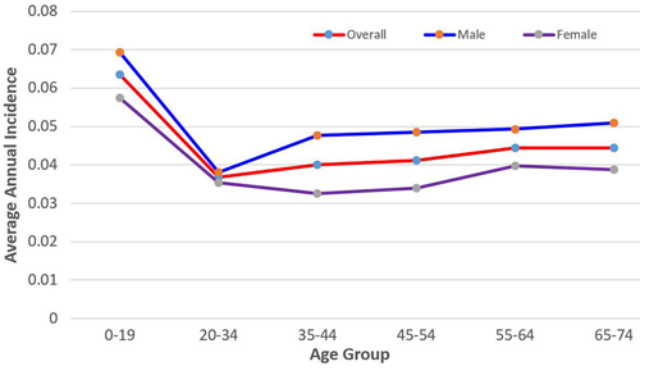

FIG. 3. Rate of SCA by age group for both sexes. AAI peaks in the 0- to 19-year age group in both sexes and is higher in males across all age groups. Figure is available in color online only.

otherwise specified (NOS) compared to the 0- to 19-year age group ($p = 0.01$ and $p = 0.013$, respectively). There were insufficient data to perform a histology-age analysis for the mixed glioma subtype (Fig. 4). The WHO grade was available for 1894 patients (63.9%): 1036 (34.9%) were categorized as WHO grade I, 171 (5.8%) as WHO grade II, 271 (9.1%) as WHO grade III, 416 (14.0%) as WHO grade IV, and 1075 (36.2%) did not have documented grades.

To further examine the epidemiological relationship between grade and age of diagnosis, we stratified patients by age and comparatively examined incidences of each histological subtype in each age group. Of note, patients were separated into three primary age groups: 0–19, 20–64, and ≥ 65 years. We report a significantly higher incidence of both pilocytic astrocytoma and fibrillary astrocytoma in the 0- to 19-year age group ($p = 0.0316$ and $p = 0.0043$, respectively; Table 2). There was a significantly higher incidence of anaplastic astrocytoma and astrocytoma NOS in the ≥ 65-year age group ($p = 0.01$ and $p = 0.013$, respectively).

Discussion

This study provides the most comprehensive epidemiological description of SCAs to date, as it queried for all SCAs documented in the CBTRUS database, which encompasses approximately 99% of the US population.[1] Previously, our epidemiological understanding of SCAs stemmed largely from two large-scale studies: a review utilizing the SEER database accounting for 664 patients with SCA, and a retrospective study of all primary SCAs seen at the Mayo Clinic over 40 years.[5,7,8,17,20] However, the SEER database only covers approximately 28% of the US population and is a subset of the CBTRUS database.[21] In contrast, CBTRUS contains data on incidence from more than 50 cancer registries and is recognized as the largest data bank of population-based incidence data on CNS tumors in the country.[1] As such, our study is subject to less selection bias than those that utilize less comprehensive databases.

A comparison between our results and those from the SEER study conducted by Milano and colleagues reveals important similarities and distinctions.[20] Comparable results included age at diagnosis: in our cohort, 37.3% of patients diagnosed with SCA fell into the 0- to 19-year age group, which also had the highest incidence of SCA compared to the other age groups. Similarly, the SEER analysis found that 36% of patients diagnosed with SCA were between the ages of 0 and 19 years.[20] Our results on SCA WHO grade differed from those of the SEER study, which found the following WHO grade breakdown: 27% WHO grade I, 23% WHO grade II, 18% WHO grade III, and 12% WHO grade IV, with 20% of patients having an unknown WHO grade.[20] In contrast, we found a greater proportion of WHO grade I SCAs, accounting for 34.9% of the cohort, and a markedly lower proportion of WHO grade II (5.8%) and III (9.1%) SCAs, with a comparable proportion of WHO grade IV SCAs (14.0%). Significant results in our cohort also include a higher incidence in males compared to females, a finding that is consistent with previous reports, and the downward trend in AAI of SCA in the US during the study period, from 0.051 in 1995 to 0.043 in 2016. One potential explanation for this decreasing incidence could be changes in management as the natural history of SCA becomes better understood. Specifically, an increase in observation and careful monitoring may have replaced biopsy and surgery at first discovery. This, in turn, would increase the incidence of SCAs that are diagnosed radiographically without histological confirmation.

Patient Demographics Versus Outcomes

The peak incidence of SCAs in both males and females occurred in the 0- to 19-year age group (male: AAI = 0.069, 95% CI 0.064–0.075; female: AAI = 0.057, 95% CI

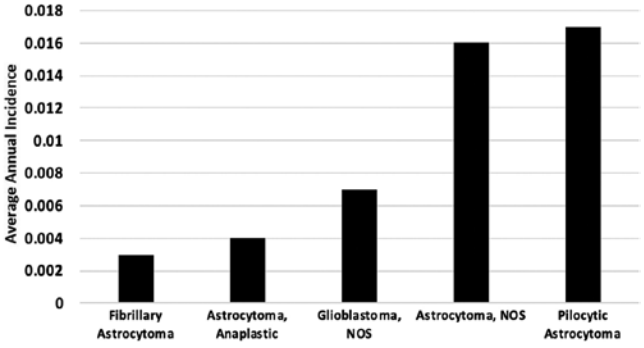

FIG. 4. Rate of SCAs by histological type. Rates are per 100,000 and age-adjusted to the 2000 US population.

0.053–0.063). Previous studies have identified age as a significant prognostic factor in patients; specifically, increasing age has been associated with decreased survival and worse outcomes.[8,18,19,22] Sandler et al. reported that patients with SCA recurrence were significantly older than those without recurrence (average age of 38 vs 19 years, respectively).[23] Furthermore, Lee et al. found that older age had adverse effects on local control in addition to overall survival and progression-free survival.[25] A large multicenter study of pediatric patients with SCAs found that younger age, defined as less than 7 years, correlated with better patient outcomes, such that the 10-year overall survival for younger patients was 76% compared to 38% for the older patient cohort (age > 7 years, $p = 0.04$).[6] While there have been studies that failed to find a significant relationship between these two variables, the majority of reports have identified increasing age as a poor prognostic factor.[5,7,8,13,14,16,18,23–25] The association between age of diagnosis and survival both informs our understanding of the disease course for patients and facilitates the development of individualized treatment and follow-up plans.

An important gap in our knowledge is an understanding of the factors responsible for the correlation between age and prognosis. Our cohort analysis reveals a significantly higher AAI of WHO grades I and II in the 0- to 19-year age group compared to the 20- to 64-year and ≥ 65-year age groups ($p < 0.001$ for both). In contrast, the AAI of WHO grade III SCA was highest in the ≥ 65-year age group ($p = 0.01$). These results suggest that one possible explanation for the association between age at diagnosis and prognosis could be the increased incidence of higher-grade SCAs in older individuals.

Study Limitations

Despite the completeness of this study, it does have important limitations. First, 36.2% of WHO grade data were missing, and as such, the corresponding results may not represent the entire population of SCA patients. Additionally, CBTRUS only provides data on a limited number of variables. Because a comprehensive understanding of SCAs—including associated neurological deficits, functional outcomes, and preoperative comorbidities—is necessary for informing survival and optimizing patient outcomes, it will be important to analyze these factors in a future study. Furthermore, because only histologically confirmed cases were included in our analysis, it is possible that our data slightly underestimate the true SCA incidence during the study period. However, given the tumor's sensitive location, it is unlikely to have a significant number of asymptomatic SCAs. One important limitation is the underreporting of data from the Veterans Health Administration facilities. Thus, the data here may underrepresent the incidence of SCA during the study period. However, assuming that the underreporting was consistent throughout the study period, this may have less of an impact on the trends in SCA incidence over time than it does on the absolute SCA incidence at specific time points. Nonetheless, it is important to note that this underreporting of data may lead to an important underrepresentation of the true SCA incidence during the study period. Additionally, another key limitation is the possible delay in reporting tumors by facilities, which may artificially inflate the SCA incidence in more recent years, depending on the length of the delay. One area in which this could introduce bias, however, is in the incidence of SCAs in the ≥ 85-year age group. Specifically, in this patient population it is likely that diagnosis was made radiographically without biopsy; thus, these patients would not be included in our cohort restricted to pathol-

TABLE 2. SCA incidence stratified by histology

Histology, Age Group (yrs)	AAI*	No. of Patients	IRR	p Value
Astrocytoma NOS				
0–19	0.0158	275	1.0000	Reference
20–64	0.0149	563	0.9437	0.433678
65+	0.0204	149	1.2930	**0.012789**
Anaplastic astrocytoma				
0–19	0.00379	66	1.0000	Reference
20–64	0.00412	156	1.0855	0.575165
65+	0.00627	46	1.6589	**0.009951**
Fibrillary astrocytoma				
0–19	0.00430	75	1	Reference
20–64	0.00194	74	0.45135	**<0.001**
65+	NR	NR	NR	
Pilocytic astrocytoma				
0–19	0.0316	551	1	Reference
20–64	0.0113	428	0.357681	**<0.001**
65+	0.0075	55	0.237663	**<0.001**
Glioblastoma NOS				
0–19	0.00637	111	1	
20–64	0.00643	244	1.007486	0.948069
65+	0.00787	57	1.236016	0.199372
Mixed glioma				
0–19	0.00138	24	NR	NR
20–64	NR	NR	NR	NR
65+	NR	NR	NR	NR

NR = counts were less than 16 and thus figures were not reported in CBTRUS.
Boldface type indicates statistical significance.
* Rate per 100,000.

ogy confirmation and would artificially lower the reported SCA incidence in this age group. Last, because CBTRUS does not allow reporting of counts less than 16, some available data could not be reported in this study. For instance, although we queried the database for locations in addition to the spinal cord—such as cauda equina, spinal meninges, and vertebral column to account for any erroneously coded SCAs—we found that the number of cases were fewer than 16 for each location, and thus these cases were not reportable. This study presents a comprehensive description of the longitudinal epidemiological trends in SCA between 1995 and 2016, and thus has the potential to inform clinicians in their management of patients with SCA. Because the nature of this study is descriptive, the exact manner in which our results can clinically inform management is outside the scope of the current endeavor but would serve as an important question for future investigations.

Conclusions

The annual AAI of SCAs decreased significantly between 1995 and 2016. The peak incidence for both males and females occurred in the 0- to 19-year age group, with males having a significantly higher incidence of SCAs relative to females. SCA incidence was significantly lower in patients of Asian/Pacific Islander race compared to patients identified as White. Similarly, patients of Hispanic ethnicity had a significantly lower SCA incidence than patients not of Hispanic ethnicity. The incidence of WHO grade I SCAs was significantly higher than those of grade II, III, or IV. This study provides the most comprehensive report on the incidences of SCA to date.

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Disclosures

Dr. Kshettry reports being a consultant to Integra.

Author Contributions

Conception and design: Recinos, Jones, Kshettry. Acquisition of data: Shao, Jones, Cioffi, Patil, Ostrom, Kruchko, Barnholtz-Sloan. Analysis and interpretation of data: Recinos, Shao, Jones, Cioffi, Patil, Kruchko, Barnholtz-Sloan, Kshettry. Drafting the article: Shao. Critically revising the article: Recinos, Shao, Jones, Habboub, Kruchko, Kshettry. Reviewed submitted version of manuscript: Recinos, Shao, Jones, Habboub, Ostrom, Barnholtz-Sloan, Kshettry. Approved the final version of the manuscript on behalf of all authors: Recinos. Statistical analysis: Ellsworth. Study supervision: Recinos, Kshettry.

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