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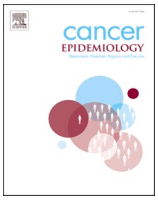

Associations between urbanicity and spinal cord astrocytoma management and outcomes

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ABSTRACT

Background: The management of spinal cord astrocytomas (SCAs) remains controversial and may include any combination of surgery, radiation, and chemotherapy. Factors such as urbanicity (metropolitan versus non-metropolitan residence) are shown to be associated with patterns of treatment and clinical outcomes in a variety of cancers, but the role urbanicity plays in SCA treatment remains unknown.

Methods: The Central Brain Tumor Registry of the United States (CBTRUS) analytic dataset, which combines data from CDC's National Program of Cancer Registries (NPCR) and NCI's Surveillance, Epidemiology, and End Results Programs, was used to identify individuals with SCAs between 2004 and 2019. Individuals' county of residence was classified as metropolitan or non-metropolitan. Multivariable logistic regression models were used to evaluate associations between urbanicity and SCA. Cox proportional hazard models were constructed to assess the effect of urbanicity on survival using the NPCR survival dataset (2004–2018).

Results: 1697 metropolitan and 268 non-metropolitan SCA cases were identified. The cohorts did not differ in age or gender composition. The populations had different racial/ethnic compositions, with a higher White non-Hispanic population in the non-metropolitan cohort (86 % vs 66 %, $p < 0.001$) and a greater Black non-Hispanic population in the metropolitan cohort (14 % vs 9.9 %, $p < 0.001$).

There were no significant differences in likelihood of receiving comprehensive treatment (OR=0.99, 95 % CI [0.56, 1.65], $p = >0.9$), or survival (hazard ratio [HR]=0.92, $p = 0.4$) when non-metropolitan and metropolitan cases were compared. In the metropolitan cohort, there were statistically significant differences in SCA treatment patterns when stratified by race/ethnicity ($p = 0.002$).

Conclusions: Urbanicity does not significantly impact SCA management or survival. Race/ethnicity may be associated with likelihood of receiving certain SCA treatments in metropolitan communities.

Importance of the study

Urbanicity is a social determinant of health of increasing interest shown to impact survival of cancer patients. In the field of neuro-oncology, specifically, rural patients are less likely to receive treatments such as surgery. Spinal cord astrocytomas are complex entities, and controversy surrounds their overall management. In this study, urbanicity did not impact survival in spinal cord astrocytoma patients, suggesting that the limiting factor in patient survival may be the current understanding of the disease, rather than resource availability. Furthermore, possible racial/ethnic disparities in treatment strategy were discovered. These warrant further investigation and are important

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to bring to the attention of the neuro-oncology community.

1. Introduction

Spinal cord astrocytomas (SCAs) are commonly highly infiltrative spinal cord tumors arising from astrocytic glial cells. SCAs are the second most common intramedullary spinal cord glioma, second only to spinal cord ependymomas [1,2]. Presenting symptoms can vary widely and may include weakness, pain, sensorimotor deficits, and proprioceptive deficits, with symptoms evolving with the progression of the disease [3]. The treatment of SCAs is not universally agreed upon, as the literature surrounding optimal management is quite limited [4]. Per some studies, one of the hallmarks of comprehensive care for SCA is surgery [1,5]. SCAs, however, can be highly infiltrative tumors, making gross total resection (GTR) unfeasible for many cases, particularly those with high grade [1]. Furthermore, attempted GTR can be associated with significant morbidity, and reduced neurologic function [6]. Radiotherapy, while not a highly effective treatment alone, is associated with improved outcomes as an adjunctive therapy to surgical management [7,8]. The treatment of SCAs is also clouded by the continued debate on the role of chemotherapy in overall management. While some studies demonstrate no obvious benefit of chemotherapy, others indicate that chemotherapeutic agents utilized in astrocytoma of the brain may also be used in refractory cases of SCAs [1,9,10].

These mixed findings in the current literature leave the management of SCAs as a challenging task, suggesting that well-experienced medical centers may be better equipped to treat such cases. Historically, patients living in non-metropolitan regions of the United States (US) can have decreased access to more experienced centers and thus, differences in treatment patterns and clinical outcomes can exist when compared to patients living in metropolitan centers [11]. This phenomenon is demonstrated in studies of glioblastoma (GBM), as GBM patients in non-metropolitan areas were found to be less likely to receive surgical treatment when compared to patients living in metropolitan centers [12]. Though studies examining the association of urbanicity and clinical outcomes in spinal cord trauma patients and intracranial astrocytic cancer patients have been conducted, no study, to the authors' knowledge, has investigated the association urbanicity in SCA treatment patterns and clinical outcomes.

Considering this gap in the literature, the authors aimed to investigate large, national databases to examine the association between urbanicity and the management of SCAs as well as the potential demographic disparities in SCA treatment in metropolitan and non-metropolitan case populations.

2. Materials and methods

Cases included in this study had at least one diagnosis of primary SCA tumor with a tumor primary site found in the International Classification of Diseases for Oncology, Third Edition (ICD-O-3), C72.0 (spinal cord) and C72.1 (cauda equina) and ICD-O-3 histopathology and behavior codes 9400/3, 9401/3, 9410/3, 9411/3, 9420/3, 9421/3, 9425/3, 9440/3, 9441/3, and 9445/3 diagnosed between January 1, 2004 and December 31, 2019.

Cases were identified within the Central Brain Tumor Registry of the United States (CBTRUS) database, which is a combined dataset from the Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. After excluding Nevada for years 2018–2019, Virginia for years 2017–2019, and Hawaii, Kansas, Connecticut, Minnesota, and New Mexico for all years due to a lack of available county-level data, it represents approximately 94 % of the US population for the period of diagnosis. Cases with invalid data values, unknown urbanicity, and those diagnosed via autopsy or death certificate were removed from all analyses [13–16]. De-identified case-level survival data were obtained from NPCR's Survival Analytical Database, containing data from 42 central cancer registries and covering approximately 82 % of the US population (excluding Kansas and Minnesota), for years 2004–2018.

Urbanicity status was determined using the United States Department of Agriculture (USDA) 2013 Rural-Urban Continuum (RUC) code definitions, which designate all counties in the US metropolitan and non-metropolitan groups by case residence at time of diagnosis [17]. RUC codes 1–3 are designated as metropolitan, while RUC codes 4–9 are designated as non-metropolitan.

Collected case demographics include urbanicity status, sex, race/ethnicity, survival time, and histopathologic findings. Race and ethnicity are combined and defined as White non-Hispanic, Black non-Hispanic, American Indian/Alaska Native (AIAN) non-Hispanic, Asian or Pacific Islander (API) non-Hispanic, and Hispanic (all races). Treatments included surgical type (gross total resection (GTR, site-specific surgery code of 22, 30, or 55), subtotal resection (STR, site-specific surgery code of 21 or 40), excisional biopsy (site-specific surgery code of 20), other surgery (site-specific surgery code 10 or 90), no surgery performed (site-specific surgery code of 0), and unknown), surgical treatment (yes, site-surgery codes 10–90; none, site-surgery codes 0; or unknown), radiation treatment (yes or none/unknown (unable to separate unknowns), and chemotherapy treatment (yes, none, or unknown). CNS World Health Organization (WHO) grade was determined by three variables: Collaborative Stage Site-Specific Factor 1 (cases diagnosed from 2011 to 2017), Site-Specific Data Items (SSDI) Grade Pathological, and SSDI Grade Clinical (both collected for cases diagnosed in 2018 or later). No grade information was collected prior to 2011. Primary outcomes of interest included survival and receiving comprehensive SCA treatment, which was defined as having received some degree of tumor excision and radiation. Survival was analyzed for all SCA cases, as well as malignant SCA cases, a sub-cohort that excluded cases with pilocytic astrocytomas (which despite their non-malignant behavior are defined as malignant tumors in US cancer registration). Secondary outcomes investigated included age at SCA diagnosis, extent of surgical treatment (no surgery, excisional biopsy, gross total resection, subtotal resection, other), whether the case received chemotherapy, method of diagnostic confirmation (microscopically-confirmed or none), and CNS WHO grade. Cases with unknown urbanicity, sex, race/ethnicity, or age at diagnosis were excluded from all analyses.

2.1. Statistical analysis

Individual demographic characteristics were evaluated overall and stratified by urbanicity, and urbanicity across treatment type (any surgery, any radiation, any chemotherapy, any treatment). Chi-square and t-tests were used to evaluate differences in proportions or means, respectively.

Individual multivariable logistic regression models were constructed for each treatment modality (any radiation, any surgery, any chemotherapy, chemotherapy and surgery only, radiation and surgery only [comprehensive treatment only], radiation and chemotherapy only, and received all three treatments) adjusting for age at diagnosis, sex, race/ethnicity, and urbanicity. Odds ratios (OR) with 95 % confidence intervals (95 % CI) are presented.

All-cause mortality was assessed using Cox proportional hazards ratios (HR) with corresponding 95 % CI and p-values to evaluate the effect of urbanicity on overall survival including 14 years of follow-up. Cox proportional hazards models adjusting for urbanicity, sex, race/ethnicity, and an interaction between ten-year age group at diagnosis and extent of surgical resection. Two additional sensitivity analyses were conducted restricting first to cases with malignant SCA only (excluding 9421/3: Pilocytic astrocytoma, malignant) and second restricting to only those who had microscopically-confirmed cases. Results were presented in adjusted survival curves. Statistical significance was assessed at alpha level 0.05. Analyses were conducted using R version 4.1.3 [18].

3. Results

3.1. Demographics

Overall, 1965 SCA cases with known urbanicity were identified within the study period. The metropolitan cohort contained 1697 cases, while the non-metropolitan cohort contained 268 cases. The two populations demonstrated no significant difference in sex composition or age. The two populations did, however, show a statistically significant difference in racial/ethnicity composition, with a greater proportion of individuals who were White, non-Hispanic individuals in the non-metropolitan cohort (86 % vs 66 %, $p < 0.001$) and a greater composition of individuals who were Black non-Hispanic in the metropolitan cohort (15 % vs 9.7 %, $p < 0.001$). Demographic data is further described in Table 1.

3.2. Nature and extent of treatment

There were no significant differences in extent of surgical treatment between non-metropolitan and metropolitan cases. When comparing non-metropolitan and metropolitan cases, there were no significant differences in likelihood of receiving comprehensive treatment (OR=0.99, 95 % CI [0.56, 1.65], p = >0.9), surgery (OR=0.94, 95 % CI [0.69, 1.31], $p = 0.7$), radiation (OR=0.89, 95 % CI [0.67, 1.19], $p = 0.3$) or chemotherapy (OR=0.74, 95 % CI [0.51, 1.07], $p = 0.11$) when adjusted for age, sex, and race/ethnicity (Table 2). Age at diagnosis, however, was found to be a significant predictor of the likelihood to receive certain treatments, with younger cases being more likely to receive surgery or surgery ($p < 0.001$) and chemotherapy ($p < 0.001$) (Table 2). Older cases were more likely to receive radiotherapy ($p < 0.001$), surgery and radiotherapy ($p < 0.001$), radiation and chemotherapy ($p < 0.001$), or surgery, radiation, and chemotherapy ($p < 0.006$) (Table 2). Additionally, differences in treatment strategy with respect to race and ethnicity were found, with individuals who were Hispanic (all races) and API non-Hispanic being more likely to receive certain treatment regimens. These findings are further described in Table 2.

3.3. Survival

Non-metropolitan cases were found to have no statistically significant difference in survival when compared to their metropolitan counterparts (HR=1.01, 95 % CI [0.79–1.28]), (Table 4), (Fig. 1). Median survival from time of diagnosis was 178 months for the metropolitan cohort. Median survival could not be calculated for the non-metropolitan cohort, as survival did not reach 50 % during the study period. When a sub-analysis of malignant astrocytomas only was performed, non-metropolitan cases were not found to have decreased survival when compared to their metropolitan counterparts (HR=0.98, 95 % CI [0.75, 1.27]) (Table 4). Median survival from time of diagnosis was 47 months (95 % CI [37–64]) for the metropolitan cohort, and 86 months (95 % CI [36−137]) in the non-metropolitan cohort. Compared to White non-Hispanic individuals, Hispanics had increased mortality for all spinal cord astrocytomas (HR=1.29, 95 % CI [1.02, 1.64] and microscopically-confirmed spinal cord astrocytomas (HR=1.30, 95 % CI [1.01, 1.66].

3.4. Age, tumor grade, and diagnostic confirmations at the time of diagnosis

Metropolitan and non-metropolitan cases did not demonstrate statistically significant differences in type of diagnostic confirmation (clinical, microscopic) ($p = 0.517$). The distribution of WHO grade, however, was statistically significantly different between groups ($p < 0.001$) with metropolitan cases possessing higher grade lesions. This is further depicted in Table 1.

Table 1
Cohort demographics by Urbanicity (Data from CBTRUS: US Cancer Statistics – NPCR and SEER, 2004–2019).

Characteristic	Overall n (%) N = 1965	Metropolitan n (%) N = 1697	Non-Metropolitan n (%) N = 268	p-value[1]
Median Age at Diagnosis[2]	30 (11, 52)	30 (12, 52)	28 (10, 51)	0.28
Sex				0.35
Female	909 (46 %)	778 (46 %)	131 (49 %)	
Male	1056 (54 %)	919 (54 %)	137 (51 %)	
Race/Ethnicity				**<0.001**
White non-Hispanic	1368 (69 %)	1133 (66 %)	235 (86 %)	
Black non-Hispanic	273 (14 %)	247 (15 %)	26 (9.7 %)	
AIAN non-Hispanic	<16 cases	<16 cases	<16 cases	
API non-Hispanic	66 (3.4)	–	<16 cases	
Hispanic (all races)	263 (13 %)	–	<16 cases	
WHO Grade				**<0.001**
Grade I	446 (23 %)	376 (22 %)	70 (26 %)	
Grade II	212 (11 %)	170 (10 %)	42 (16 %)	
Grade III	112 (5.7 %)	–	<16 cases	
Grade IV	223 (11 %)	–	<16 cases	
Unknown	972	841	131	
Extent of Surgical Treatment				0.67
Biopsy	304 (16 %)	257 (15 %)	47 (18 %)	
Gross Total	871 (45 %)	761 (45 %)	110 (41 %)	
None	435 (22 %)	375 (22 %)	60 (23 %)	
Other Surgery	–	–	<16 cases	
Subtotal	312 (16 %)	262 (16 %)	42 (16 %)	
Unknown	<16 cases	<16 cases	<16 cases	
Diagnostic Confirmation				0.84
None	160 (8.1 %)	139 (8.2 %	21 (7.8 %)	
Microscopically-confirmed	1805 (92 %)	1558 (92 %)	247 (92 %)	
Surgery Treatments Received				0.67
None	435 (22 %)	375 (22 %)	60 (23 %)	
Excisional biopsy	304 (16 %)	257 (15 %)	47 (18 %)	
Gross total resection	871 (45 %)	761 (45 %)	110 (41 %)	
Other surgery	–	–	<16 cases	
Subtotal resection	304 (16 %)_	–	–	
Unknown	<16 cases	<16 cases	<16 cases	
Any surgery received				0.91
None	–	–	–	
Yes	1517 (78 %)	1311 (78 %)	206 (77 %)	
Unknown	<16 cases	<16 cases	<16 cases	
Radiation Received				0.14
None/unknown	1256 (64 %)	1074 (63 %)	182 (68 %)	

(continued on next page)

Table 1 (*continued*)

Characteristic	Overall n (%) N = 1965	Metropolitan n (%) N = 1697	Non-Metropolitan n (%) N = 268	p-value[1]
Yes	709 (36 %)	623 (37 %)	86 (32 %)	
Chemotherapy Received				0.057
None	844 (67 %)	721 (66 %)	123 (73 %)	
Yes	420 (33 %)	375 (34 %)	45 (27 %)	
Unknown	701	601	100	

1 Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test for count data with simulated p-value (value based on 2000 replicates); Fisher's exact test.

2 Median (IQR).

3. CNS World Health Organization (WHO) grade was determined by three variables: Collaborative Stage Site-Specific Factor 1 (cases diagnosed from 2011-2017), Site-Specific Data Items (SSDI) Grade Pathological, and SSDI Grade Clinical (both collected for cases diagnosed in 2018 or later). No grade information was collected prior to 2011.

– Counts fewer than 16 or that can be back-calculated to a count less than 16 were suppressed.

Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results; AIAN, American Indian/Alaska Native; API, Asian or Pacific Islander; WHO, World Health Organization.

3.5. Disparities in treatment patterns

Likelihood to receive surgery was significantly related to age alone, with case sex, race/ethnicity, and urbanicity being insignificant predictors (Table 2). Neither the metropolitan nor the non-metropolitan populations displayed sex-based differences in the extent of surgical resection (Table 3). Likelihood to receive radiotherapy was significantly associated with age and race/ethnicity, with older cases and Hispanic (all races) cases being more likely to receive radiotherapy; sex was not a predictor of the likelihood to receive radiotherapy (Table 2). Age, race/ethnicity, and sex were not statistically significantly associated with the likelihood to receive chemotherapy (Table 2). When considering differences in overall SCA treatment patterns between sex, racial, and ethnic groups when stratified by urbanicity, there was a statistically significant difference when stratified by race/ethnicity only ($p = 0.002$). (Table 3).

4. Discussion

Management of SCAs remains controversial and challenging. SCAs can be highly invasive in nature, making GTR difficult and potentially associated with neurological morbidity [19]. There is a dearth of evidence suggesting overall survival is not improved by surgical resection alone, compared to a combination of surgery, radiation, and/or adjuvant chemotherapy [19]. In this sense, it is reasonable to hypothesize that the location of health care centers accessible to a patient may play an important role in the treatments they receive. Specifically, access to academic medical centers or university-adjacent community health centers, which are more commonly found in metropolitan locations could potentially play an important role in receiving optimal treatment. To our knowledge, this is the first study that investigates the role that urbanicity plays in SCA outcomes.

With respect to case demographics at time of diagnosis, there were no differences found in the average ages of the metropolitan and non-metropolitan SCA cases or in the sex composition of the cohorts. It was initially hypothesized that the reduced healthcare access associated with rural residence may result in a higher age of presentation, but this was not found to be the case. There was a statistically significant difference in the racial/ethnic composition of metropolitan and non-metropolitan SCA cases. As racial/ethnic diversity across the rural-urban continuum is well studied, it is a long held finding that metropolitan areas are historically more diverse than rural areas [20]. Interestingly, the individuals in the metropolitan and non-metropolitan areas did present with statistically significant differences in distribution of disease severity. Individuals from non-metropolitan areas, when compared to their metropolitan counterparts, presented with an increased incidence of low grade SCAs (WHO grades I-II) as opposed to high grade SCAs (WHO grades III-IV). This finding is limited by the low number of confirmed, high-grade gliomas in the non-metropolitan cohort.

Residential urbanicity is shown to impact survival in ovarian, colon, and lung cancer, with rural cases having reduced survival [21–23]. Furthermore, a recent systemic review demonstrated that metropolitan cancer cases, broadly, have improved survival when compared to non-metropolitan cases [23]. Interestingly, our study did not identify urbanicity as a statistically significant predictor of SCA case survival, even when analyzing only malignant lesions. A similar finding was observed in a neuro-oncology study, in which urbanicity had no significant impact on survival of glioblastoma patients, although socioeconomic status (SES) was significantly associated with survival [24]. Studies demonstrate that SES has the ability to modulate the relationship between a case's urbanicity status and access to academic medical centers. Another study by Bird et al. noted that GBM survival is impacted by distance traveled to treatment center and SES [25]. This study found that, when adjusted for income, distance traveled to treatment center had little impact on survival, however, in the absence of income adjustment, greater distance traveled was associated with increased survival. Presumably, this suggests that patients with the financial means traveled to health centers with better clinical outcomes. Treatment at an academic center was also found to be associated with increased survival in these cases. Overall, this suggests that treatment at an academic center improves survival, a fact that can be taken advantage of by high SES rural cases that may not experience the financial strain associated with travel. It is possible that, with more data, a relationship could arise showing reduced survival in low SES non-metropolitan cases.

With respect to patterns of treatment, urbanicity alone was not a statistically significant predictor for likelihood to receive surgery, radiation therapy, or chemotherapy. It is worth noting, however, that non-metropolitan status was associated with a reduced likelihood to receive radiation and chemotherapy although non-significant. In terms of neuro-oncology, this is in contrast to a previous analysis of the CBTRUS data demonstrating that non-metropolitan status was associated with a reduced likelihood to receive surgical treatment in cases with GBM [12]. Likelihood of receiving chemotherapy, in particular, was reduced in non-metropolitan cases, although non-significant. When performing multivariable analysis to assess the impacts of urbanicity, it was again revealed that there were no statistically significant relationships between urbanicity and treatment modality. It is also possible that the controversial nature of SCA treatment creates a situation in which urbanicity and/or resource availability are not the limiting factors. Rather, our limited understanding of the optimal treatment for this disease may result in comparable patterns of treatment in metropolitan and non-metropolitan cases, leading to similar survival rates in both cohorts.

Multivariable analysis revealed that age was a statistically significant predictor of treatment modality received, albeit with a minimal effect size. Advanced age (>= 65) was associated with a decreased likelihood of receiving surgery alone, or any treatment in both metropolitan and non-metropolitan cohorts. The general trend of age being inversely related to chances of receiving surgical treatment is consistent with the literature; elderly cancer cases are generally less like to receive surgery and are more likely to experience postoperative complications [26–30]. Multivariable analysis also revealed significant associations between

Table 2
Multivariable Logistic Regression with Accompanying 95 % Confidence Intervals and P-Values of Likelihood to Receive Specific Treatment Combinations (Data from CBTRUS: US Cancer Statistics – NPCR and SEER, 2004–2019).

Characteristic	Radiotherapy[1] Ref, None/ Unknown= 1256 Yes= 709		Surgery[1] Ref, None= 435 Yes= 1517		Chemotherapy[1] Ref, None = 844 Yes= 420		Surgery and Radiation[2] Ref, None/ Unknown= 1651 Yes= 132		Surgery and Chemotherapy[3] Ref, None/ Unknown= 1465 Yes= 126		Radiation and Chemotherapy[4] Ref, None/ Unknown= 1838 Yes= 65		Surgery, Radiation, and Chemotherapy[5] Ref, None/ Unknown= 1585 Yes= 197	
	Odds Ratio (95 % CI)	p-value[6]	Odds Ratio (95 % CI)	p-value[6]	Odds Ratio (95 % CI)	p-value[6]	Odds Ratio (95 % CI)	p-value[6]	Odds Ratio (95 % CI)	p-value[6]	Odds Ratio (95 % CI)	p-value[6]	Odds Ratio (95 % CI)	p-value[6]
Age at diagnosis	1.02 (1.02,1.03)	**<0.001**	0.98 (0.97,0.98)	**<0.001**	1.00 (0.99,1.00)	0.21	1.01 (1.01,1.02)	**<0.001**	0.97 (0.96,0.98)	**<0.001**	1.02 (1.01,1.03)	**<0.001**	1.01 (1.00,1.01)	**0.006**
Sex														
Female	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Male	1.18 (0.98,1.43)	0.088	0.97 (0.78,1.21)	0.77	1.11 (0.88,1.41)	0.38	1.08 (0.75,1.55)	0.68	0.84 (0.58,1.22)	0.4	1.18 (0.72,1.97)	0.52	1.29 (0.96,1.75)	0.1
Race/Ethnicity														
White non-Hispanic	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
AIAN non-Hispanic	<16 cases	–	<16 cases	–	<16 cases	–	<16 cases	–	<16 cases	–	<16 cases	–	<16 cases	–
API non-Hispanic	1.40 (0.82,2.34)	0.21	0.87 (0.48,1.64)	0.64	1.66 (0.91,3.01)	0.10	0.74 (0.18,2.08)	0.62	0.81 (0.24,2.08)	0.69	2.56 (0.85,6.27)	0.06	2.01 (0.96, 3.86)	0.047
Black non-Hispanic	1.07 (0.81,1.42)	0.62	0.81 (0.59,1.11)	0.18	0.97 (0.67,1.37)	0.85	1.16 (0.67,1.91)	0.58	0.88 (0.49,1.49)	0.64	0.74 (0.28,1.65)	0.50	1.01 (0.63,1.57)	0.95
Hispanic (all races)	1.50 (1.13,1.99)	**0.005**	1.07 (0.75,1.53)	0.72	1.33 (0.95,1.85)	0.10	1.52 (0.90,2.47)	0.11	1.01 (0.59,1.66)	0.98	1.39 (0.64,2.74)	0.37	1.69 (1.11,2.52)	**0.013**
Urbanicity														
Metropolitan	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Non-Metropolitan	0.89 (0.67,1.19)	0.44	0.94 (0.69,1.31)	0.72	0.74 (0.51,1.07)	0.11	0.99 (0.56,1.65)	0.97	1.00 (0.56,1.70)	>0.99	0.85 (0.34,1.79)	0.69	0.67 (0.39,1.09)	0.10

Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results; AIAN, American Indian/Alaska Native; API, Asian or Pacific Islander; WHO, 95 % CI, 95 % confidence interval.

[1] Group may include cases who received alternative treatment in addition to the treatment group being analyzed.

[2] Comprehensive treatment group contains only those who received any surgery and radiation and had a chemotherapy status of none; all other treatment combinations are included as the reference group none/unknown.

[3] Group contains only those who received surgery and chemotherapy and had a radiation status of none/unknown; all other treatment combinations are included as the reference group none/unknown.

[4] Group contains only those who received radiation and chemotherapy and had a surgical status of none; all other treatment combinations are included as the reference group none/unknown.

[5] Group contains only those who received all three treatments; all other treatment combinations are included as the reference group none/unknown.

[6] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test for count data with simulated p-value (value based on 2000 replicates); Fisher's exact test.

Table 3
Demographic Differences in Treatment Type, Stratified by Urbanicity (Data from CBTRUS: US Cancer Statistics – NPCR and SEER, 2004–2019).

Metropolitan												
Characteristic	Surgery (ever)			Radiotherapy (ever)			Chemotherapy (ever)			Any Treatment		
	None, N = 375[1]	Yes, N = 1311[1]	p-value[2]	None/ Unknown, N = 1074[1]	Yes, N = 623[1]	p-value[3]	None, N = 721[1]	Yes, N = 375[1]	p-value[3]	None/ Unknown, N = 103[1]	Yes, N = 1508[1]	p-value[3]
Age at diagnosis	45 (24, 62)	26 (10, 48)	**<0.001**	22 (8, 48)	41 (23, 56)	**<0.001**	30 (12, 53)	29 (12, 50)	0.36	45 (29, 67)	29 (11, 51)	**<0.001**
Age group at diagnosis			**<0.001**			0.18			0.085			**<0.001**
<65	296 (20 %)	1192 (80 %)		956 (64 %)	541 (36 %)		624 (65 %)	338 (35 %)		75 (5.3 %)	1348 (95 %)	
>=65	79 (40 %)	119 (60 %)		118 (59 %)	82 (41 %)		97 (72 %)	37 (28 %)		28 (15 %)	160 (85 %)	
Sex			0.61			0.093			0.72			>0.99
Female	176 (23 %)	596 (77 %)		509 (65 %)	269 (35 %)		339 (66 %)	172 (34 %)		47 (6.4 %)	689 (94 %)	
Male	199 (22 %)	715 (78 %)		565 (61 %)	354 (39 %)		382 (65 %)	203 (35 %)		56 (6.4 %)	819 (94 %)	
Race and Ethnicity			0.19			0.25			0.26			**0.002**
AIAN Non-Hispanic	<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases	
API Non-Hispanic	<16 cases	–		–	–		–	–		<16 cases	–	
Black Non-Hispanic	59 (24 %)	186 (76 %)		160 (65 %)	87 (35 %)		106 (68 %)	50 (32 %)		20 (8.5 %)	215 (91 %)	
Hispanic (All Races)	44 (17 %)	208 (83 %)		151 (59 %)	103 (41 %)		108 (61 %)	69 (39 %)		<16 cases	234 (96 %)	
White Non-Hispanic	253 (23 %)	860 (77 %)		715 (64 %)	405 (36 %)		475 (67 %)	233 (33 %)		63 (6.0 %)	995 (94 %)	

– counts fewer than 16 and those that can be calculated to those fewer than 16 were removed.
Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology, and End Results; AIAN, American Indian/Alaska Native; API, Asian or Pacific Islander; WHO, World Health Organization.
1Median (IQR); n (%).
2Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test; Fisher's Exact Test for Count Data with simulated p-value (based on 2000 replicates).
3Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's Exact Test for Count Data with simulated p-value (based on 2000 replicates); Fisher's exact test.

race/ethnicity and SCA treatment modality. Overall, Hispanic patients were found to have an increased likelihood of receiving radiation therapy, or a combination of all three major modality combinations when compared to White non-Hispanic patients. These findings are different from other cancer literature demonstrating Hispanic patients were less likely to receive treatment [31]. Conversely, studies in breast cancer cases have shown that Hispanic patients are more likely to receive chemotherapy, which was a non-significant trend observed in our study as well [32]. Greater understanding of these findings will likely require better insight of the impact of sociodemographic status and the settings and facilities in which these patients receive care [32].

4.1. Limitations

Our study presents with limitations. A primary limitation of this study is the reliance on cancer registry data. Central Cancer Registries (CCRs) do not conduct their own central pathology review and only report diagnoses as reported by the diagnosing pathologist at their treating institutions. During the study period, there have been revisions to the definitions of histopathology groupings and inclusion criteria. As a result, histopathology assignments may vary over time. This likely introduces errors in pathologic assignments. Additionally, treatment information is limited and lacks factors that may be more indicative of survival such as treatment pattern, treating facility type, and co-morbidities [33]. Furthermore, urbanicity was defined using a binary indicator based on the patient's residential county at diagnosis which does not capture the complexity of geographic and socioeconomic variability within counties. Finally, it has been found that survival data is less complete among Hispanic communities due to higher rates of loss to follow-up compared to non-Hispanic communities [34,35].

Altogether, the above findings demonstrate differences in the management of SCA cases based on urbanicity. When controlling for urbanicity, further differences in the treatment patterns of metropolitan SCA cases were found on the basis of race/ethnicity. While no statistically significant differences in the treatment patterns of individuals from non-metropolitan areas was found, race/ethnicity was statistically significantly associated with likelihood of receiving any SCA treatment in the metropolitan cohort. Unfortunately, due to the limited power when performing this analysis, multivariable logistic regression was not determined to be a reliable statistical method. With that said, our results suggest that race/ethnicity may be associated with likelihood of receiving SCA treatment for individuals in metropolitan areas. Further investigation is warranted as certain studies have demonstrated that differences in cancer treatment are more commonly observed in rural/non-metropolitan settings. For instance, Caldwell et al. showed that rural status gives additional health disadvantages to African American patients when compared to urban communities [36].

5. Conclusions

Urbanicity is not a significant predictor of SCA treatment patterns or survival overall. However, age and race/ethnicity are significant predictors of treatment strategies. Metropolitan and non-metropolitan cases presented at equivalent ages with similar diagnostic confirmations, but non-metropolitan case status was associated with lower tumor grade at presentation. Race/ethnicity may be associated with likelihood of receiving certain SCA treatments in metropolitan communities, but the nature of this relationship remains unclear and warrants further study.

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Non-Metropolitan										
Surgery (ever)			Radiotherapy (ever)			Chemotherapy (ever)			Any Treatment		
None, N = 60[1]	Yes, N = 206[1]	p-value[2]	None/ Unknown, N = 182[1]	Yes, N = 86[1]	p-value[2]	None, N = 123[1]	Yes, N = 45[1]	p-value[2]	None/ Unknown, N = 20[1]	Yes, N = 238[1]	p-value[3]
48 (31, 61)	22 (8, 44)	**<0.001**	18 (6, 46)	42 (22, 60)	**<0.001**	32 (14, 52)	13 (8, 50)	0.10	51 (35, 67)	26 (9, 48)	**<0.001**
		0.010			0.12			0.56			**0.013**
–	189 (80 %)		166 (69 %)	–		–	–		<16 cases	216 (94 %)	
<16 cases	17 (59 %)		16 (55 %)	<16 cases		<16 cases	<16 cases		<16 cases	22 (79 %)	
		0.12			0.44			0.23			0.079
24 (18 %)	106 (82 %)		86 (66 %)	45 (34 %)		62 (78 %)	18 (22 %)		<16 cases	120 (95 %)	
36 (26 %)	100 (74 %)		96 (70 %)	41 (30 %)		61 (69 %)	27 (31 %)		<16 cases	118 (89 %)	
		0.72			>0.99			0.40			0.78
<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases	
<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases	
<16 cases	20 (77 %)		18 (69 %)	<16 cases		<16 cases	<16 cases		<16 cases	23 (92 %)	
<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases		<16 cases	<16 cases	
51 (22 %)	177 (78 %)		156 (68 %)	74 (32 %)		105 (74 %)	36 (26 %)		17 (7.7 %)	204 (92 %)	

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CRediT authorship contribution statement

Original Drafting: **DS, RW.** Revisions: **DS, RW, NA-B, MP, TD, JS, EO, HH, BB, CK, JSB-S, ME, QO, RG**. Statistical Support: **MP, QO**. Table/Figure Creation: **MP, QO**. Database Support: **CK, JSB-S**. Supervision: **ME, QO, RG**.

Declaration of Competing Interest

JSB-S is a full-time employee of the NIH/NCI. GC and KAW are full-time contractors of the NIH/NCI. CRG received grants from the Robert Wood Johnson Harold Amos Medical Faculty Development Program, the Federal Food and Drug Administration, and is a Consultant for

Table 4
Multivariable Cox Proportional Hazards Ratios (HR) with 95 % Confidence Intervals (95% CI) and P-values for all Spinal Cord Astrocytoma, Malignant Spinal Cord Astrocytoma Only, and Microscopically-Confirmed Spinal Cord Astrocytoma Only (CBTRUS: NPCR, 2004–2018.

	All Spinal Cord Astrocytoma			Malignant Spinal Cord Astrocytoma only			Microscopically-confirmed Spinal Cord Astrocytoma only		
Characteristic	N	HR (95 % CI)	p-value	N	HR (95 % CI)	p-value	N	HR (95 % CI)	p-value
Urbanicity									
Metropolitan	1518	–	Ref	940	–	Ref	1391	–	Ref
Non-Metropolitan	230	1.01 (0.79, 1.28)	0.951	134	0.98 (0.75, 1.27)	0.864	212	0.96 (0.74, 1.23)	0.736
Sex									
Female	799	–	Ref	509	–	Ref	731	–	Ref
Male	949	1.24 (1.06, 1.45)	**0.007**	565	1.27 (1.08, 1.51)	**0.005**	872	1.25 (1.06, 1.48)	**0.007**
Race/ethnicity									
White Non-Hispanic	1190	–	Ref	725	–	Ref	1082	–	Ref
Black Non-Hispanic	241	1.22 (0.98, 1.53)	0.079	144	1.19 (0.93, 1.52)	0.172	226	1.19 (0.94, 1.50)	0.140
Hispanic (All Races)	233	1.29 (1.02, 1.64)	**0.035**	143	1.21 (0.93, 1.55)	0.150	220	1.30 (1.01, 1.66)	**0.038**
Other Non-Hispanic	84	1.01 (0.70, 1.47)	0.943	62	0.85 (0.58, 1.24)	0.396	75	1.05 (0.71, 1.55)	0.810
Age group at diagnosis									
(40,50]	217	–	Ref	155	–	Ref	196	–	Ref
[0,10]	402	0.29 (0.13, 0.63)	**0.002**	155	0.41 (0.17, 1.01)	0.052	395	0.28 (0.13, 0.63)	**0.002**
(10,20]	285	0.46 (0.22, 0.97)	**0.043**	144	0.71 (0.33, 1.53)	0.380	272	0.62 (0.29, 1.35)	0.232
(20,30]	200	1.27 (0.72, 2.26)	0.409	120	1.55 (0.86, 2.80)	0.145	187	1.79 (0.94, 3.42)	0.078
(30,40]	180	0.58 (0.31, 1.09)	0.088	119	0.60 (0.30, 1.21)	0.154	162	0.71 (0.35, 1.44)	0.341
(50,60]	200	1.01 (0.59, 1.75)	0.967	151	0.95 (0.54, 1.69)	0.865	175	1.56 (0.83, 2.91)	0.165
(60,70]	142	1.82 (1.11, 2.99)	**0.018**	123	1.86 (1.11, 3.11)	**0.018**	120	2.10 (1.19, 3.71)	**0.011**
(70,80]	88	3.13 (1.85, 5.30)	**<0.001**	75	3.06 (1.77, 5.29)	**<0.001**	72	5.74 (2.91, 11.3)	**<0.001**
(80,100]	34	4.16 (2.17, 7.96)	**<0.001**	32	4.10 (2.11, 7.96)	**<0.001**	24	6.09 (2.29, 16.2)	**<0.001**
Extent of surgery									
None	385	–	Ref	323	–	Ref	245	–	Ref
Excisional biopsy	281	0.90 (0.49, 1.65)	0.737	171	1.27 (0.67, 2.41)	0.470	280	0.78 (0.42, 1.48)	0.451
Gross Total	765	0.85 (0.52, 1.40)	0.526	387	1.25 (0.73, 2.14)	0.419	761	0.74 (0.44, 1.27)	0.276
Other Surgery	35	1.27 (0.44, 3.63)	0.655	23	1.59 (0.37, 6.72)	0.531	35	1.13 (0.39, 3.28)	0.824
Subtotal	282	1.66 (0.93, 2.95)	0.084	170	2.12 (1.17, 3.86)	**0.014**	282	1.44 (0.79, 2.65)	0.238

Abbreviations: CBTRUS, Central Brain Tumor Registry of the United States; NPCR, National Program of Cancer Registries; AIAN, American Indian/Alaska Native; API, Asian or Pacific Islander.

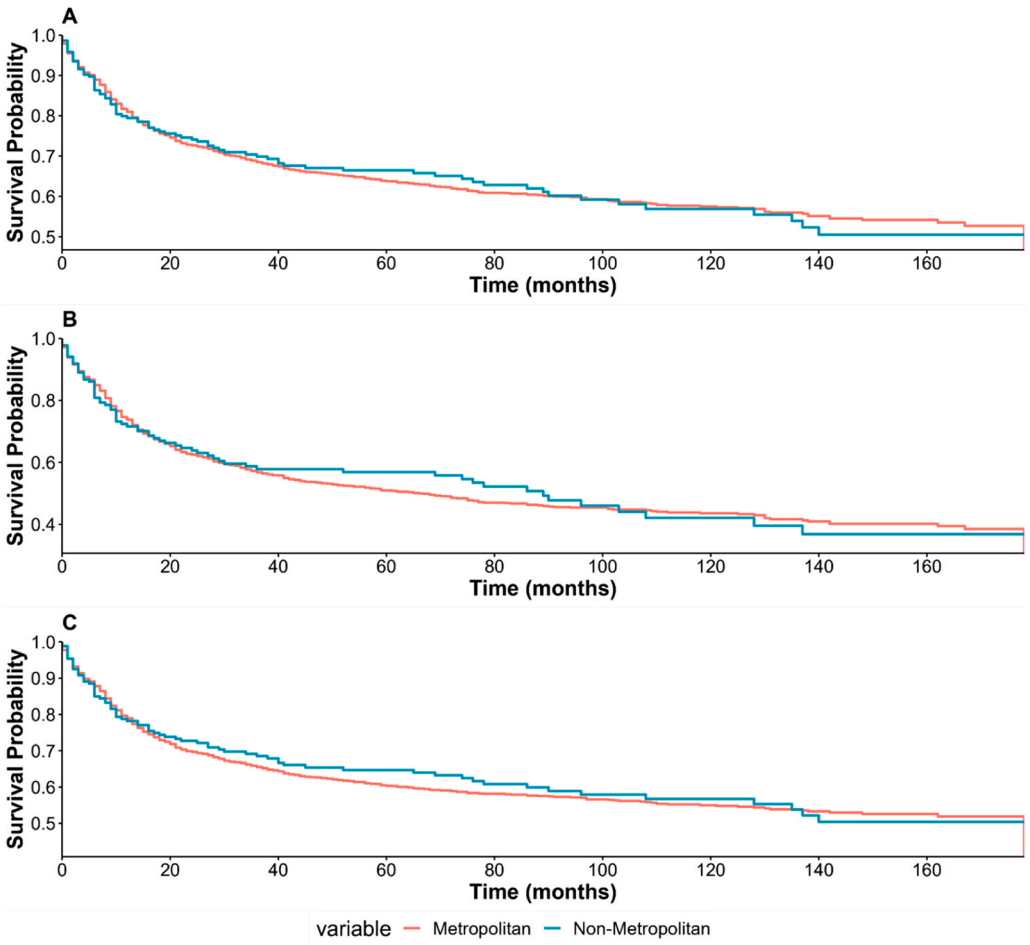

Fig. 1. Multivariable cox proportional hazards plots for overall survival of individuals with spinal cord astrocytoma (A), Malignant spinal cord astrocytoma only (B), and Individuals with microscopically-confirmed spinal cord astrocytoma only adjusted for sex, race/ethnicity, 10 year age group, extent of surgical resection, and urbanicity (Data from CBTRUS: US Cancer Statistics – NPCR, 2004–2018).

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