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Authors
Oh, Michael C
Sayegh, Eli T
Safaee, Michael
et al.

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Prognosis by tumor location for pediatric spinal cord ependymomas

Clinical article

Michael C. Oh, M.D., Ph.D.,[1] Eli T. Sayegh, B.S.,[4] Michael Safaee, B.S.,[1] Matthew Z. Sun, B.S.,[1] Gurvinder Kaur, B.S.,[1] Joseph M. Kim, B.A.,[1] Derick Aranda, M.D.,[1] Annette M. Molinaro, Ph.D.,[1,2] Nalin Gupta, M.D., Ph.D.,[1,3] and Andrew T. Parsa, M.D., Ph.D.[1]

Departments of [1]Neurological Surgery, [2]Epidemiology and Biostatistics, and [3]Pediatric Neurosurgery, University of California, San Francisco, California; and [4]Columbia University, New York, New York

Object. Ependymoma is a common CNS tumor in children, with spinal cord ependymomas making up 13.1% of all ependymomas in this age group. The clinical features that affect prognosis in pediatric spinal cord ependymomas are not well understood. A comprehensive literature review was performed to determine whether a tumor location along the spinal cord is prognostically significant in children undergoing surgery for spinal cord ependymomas.

Methods. A PubMed search was performed to identify all papers that contained data on patients with spinal cord ependymomas. Only pediatric patients (age < 18 years) who underwent resection with a clearly reported tumor location were included in the analysis. Myxopapillary tumors were excluded from study. Tumor location was subdivided into 6 regions: cervicomedullary, cervical, cervicothoracic, thoracic, thoracolumbar, and conus medullaris. Kaplan-Meier survival and Cox regression analyses were performed to determine the effects of tumor location on progression-free survival (PFS) and overall survival (OS).

Results. Fifty-eight patients who underwent resection of spinal cord ependymomas were identified. Ependymomas were located all along the spinal cord but occurred with the highest frequency in the cervical region (29.3%). Progression-free survival was significantly better in patients with tumors arising in the upper portion of the spinal cord ($p = 0.031$), which remained significant in the multivariate Cox regression analysis ($p < 0.05$). Moreover, OS was significantly better in patients with upper spinal cord ependymomas than in those harboring ependymomas in the lower spinal cord ($p = 0.048$).

Conclusions. Although more common in adults, spinal ependymomas can occur anywhere along the spinal cord in the pediatric population; however, tumors occurring in the lower half of the spinal cord carry a worse prognosis with shorter PFS and OS. By comparison, ependymomas in the upper spinal cord recur later and less frequently, with little or no mortality in this patient group.
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Key Words • **ependymoma** • **spine** • **recurrence** • **tumor location** • **pediatric** • **oncology**

Ependymoma arising in the brain or spinal cord is a common CNS tumor in children.[30] Spinal cord ependymoma constitutes only 13.1% of all pediatric ependymomas[24] and is the most common spinal cord tumor, followed by nerve sheath tumors and malignant neuronal/glial tumors.[24,37] Spinal cord ependymoma also demonstrates an older age distribution among children, as compared with tumors arising in a supratentorial or infratentorial location.[4] The WHO divides spinal cord ependymoma into 3 histological types: myxopapillary ependymomas and subependymomas (Grade I), classic ependymomas (Grade II), and anaplastic ependymomas (Grade III).[19] Although each subtype has an identified WHO grade, the factors affecting recurrence and survival following resection have not been clearly identified.

The relative scarcity of this tumor means that mostly case reports, small case series, and single-institution studies have been published, with limited outcome data obtained from their results.[9,11,20,27,31,32,34,35,38] It is recognized, however, that the prognosis in children is signifi-

Abbreviations used in this paper: GTR = gross-total resection; OS = overall survival; PFS = progression-free survival; STR = subtotal resection.

cantly worse than in adults (156 months vs 237 months, $p < 0.001$). Spinal cord ependymomas, in general, are associated with a significantly better 5-year survival rate than intracranial ependymomas.[15,28,38,42,43] Whereas children younger than 9 years of age respond best to radiation with improved survival, the disease's overall prognosis is poor, and even more so in children younger than 4 years.[34] In patients younger than 3 years, radiation may not improve survival.[7,13,20,32,34] The aggressive tumor behavior observed in younger patients may be attributable to more immature neural tissue and immunohistochemical findings more consistent with malignancy.[17,33] Although a WHO Grade III histology is associated with particularly aggressive disease and afflicts younger patients, as compared with WHO Grade II lesions, the specific pattern of genetic alterations may be a stronger determinant of tumor behavior.[17]

Aside from GTR, the prognostic factors that affect outcomes for ependymoma are not well defined.[1,5,8,39] While some studies suggest that tumor grade is a major prognostic factor,[21,26,29] others do not.[8,12,16,25,41] Tumor location may be more important in determining prognosis,[10] as it may affect clinical presentation and biological behavior.[4] For example, some data suggest that intracranial and spinal cord ependymomas can be distinguished by gene expression profiles.[6,18] Moreover, ependymoma behavior has been shown to vary with location, namely in intracranial versus spinal tumors,[2,3,14,23,24,27] but this factor has not been extensively studied along regions of the spinal cord. Elucidating tumor behavior at different locations along the spinal cord with respect to recurrence, morbidity, and OS, for example, could facilitate a more accurate prognosis, tailored management, and better patient counseling.

A few observations regarding tumor behavior as a function of location are already known. For example, WHO Grade I myxopapillary ependymomas occur more often in the cauda equina and filum terminale[27,40] and in males.[40] In addition, WHO Grade II classic ependymomas occur more frequently in the cervical and thoracic segments.[22] More detailed outcome data, such as recurrence rate, PFS, and OS, for different tumor locations in the spinal cord have not been provided. In this study, we performed an integrative analysis in which individual patient data from multiple studies were pooled and analyzed; published data on children who had undergone resection of spinal cord ependymomas were used to determine whether the tumor location along the spinal cord is a significant prognostic factor.

Methods

Article Selection

A comprehensive systematic review of the English-language literature was performed. Articles were identified via PubMed search using the key word "ependymoma," which revealed 3765 papers. These papers were then individually reviewed to search for data on patients who underwent resection. We found 31 articles containing outcomes data on pediatric spinal cord ependymoma for the years 1973–2011, from which 58 patients younger than 18 years of age were identified. Myxopapillary ependymomas were excluded from our review. Aggregated patient data were not included for analysis.

Data Extraction

Data from case reports and case series were extracted from the papers whenever the following information was available for individual patients: age, sex, tumor location, tumor grade, extent of resection (GTR or STR), morbidity, recurrence or progression of disease, time to recurrence or progression of disease, mortality, time to death, and follow-up duration. Presenting symptoms were not consistently reported, and thus this information was not analyzed. Tumor grades were categorized as WHO Grade II for benign ependymomas (including classic, cellular, papillary, clear cell, giant cell, and tanycytic subtypes) and WHO Grade III for anaplastic types.

Tumor locations were categorized into 6 different regions: cervicomedullary (extending both the cervical level and portions above the foramen magnum), cervical (C1–7), cervicothoracic (extending both cervical and thoracic levels), thoracic (T1–12), thoracolumbar (extending both thoracic and lumbar levels), and conus medullaris. Tumors listed as occurring in the cauda equina or filum terminale were excluded. For the purposes of this study the upper spinal cord region was made up of cervicomedullary, cervical, and cervicothoracic regions, whereas the lower spinal cord region was made up of thoracic, thoracolumbar, and conus medullaris regions. Patients with multiple tumors at more than 1 of the 6 locations listed above or those who underwent biopsy alone were excluded from study.

Statistical Analysis

Variables potentially associated with PFS and OS were first analyzed with Kaplan-Meier curves, and differences were assessed using the log-rank test. This analysis was followed by Cox proportional hazards analysis by backward stepwise model selection to adjust for confounding variables including age, sex, extent of resection, tumor grade, morbidity, and radiation treatment. Hazard ratios with 95% confidence intervals were estimated. Categorical values were tabulated with contingency tables and were analyzed using the Pearson chi-square test. The Fisher exact test was used if the expected cell count in a contingency table was less than 5. A $p < 0.05$ was considered statistically significant. Analyses were performed using the statistical software packages SPSS Statistics 20 (IBM, Inc.) and R (Comprehensive R Archive Network).

Results

Tumor Features by Location

This integrative analysis in which individual patient data from multiple studies were pooled and analyzed revealed a group of 58 patients who had undergone resection of a spinal cord ependymoma. The mean patient age was 12.3 years with a range of 3–17 years. The median follow-up period was 67 months (range 1–348 months).

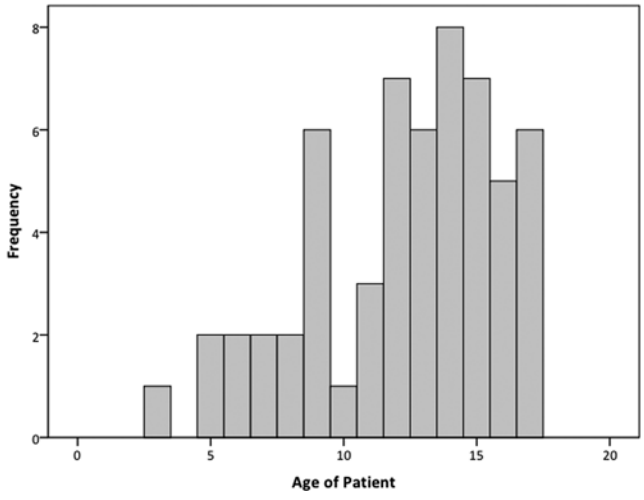

Fig. 1. Bar graph showing the distribution of spinal cord ependymomas by patient age. The frequency of spinal cord ependymomas rose with increasing age. The mean age of patients was 12.3 years (range 3–17 years). No patient in our study was younger than 3 years.

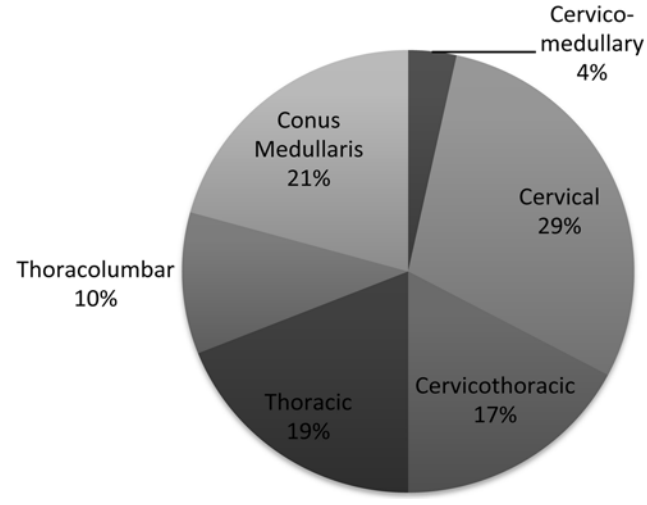

Fig. 2. Pie chart representing tumor distribution along the spinal axis. The cervical region had the greatest number of tumors, with 29.3% of all spinal cord ependymomas occurring at this location. Cervicomedullary junction ependymomas were the least frequent at 3.4%.

The frequency of spinal cord ependymomas continued to increase as age rose (Fig. 1). There were no patients younger than 3 years of age with spinal cord ependymoma in this study. Overall, an approximately equal number of males (29 [50.9%] of 57 patients) and females (28 [49.1%] of 57 patients; sex unknown for 1 patient) were affected, with no significant association between the 6 tumor locations and sex ($p = 0.558$; Table 1). Tumors most frequently occurred in the cervical region (17 [29.3%] of 58), followed by the conus medullaris (12 [20.7%] of 58), thoracic (11 [19.0%] of 58), and cervicothoracic regions (10 [17.2%] of 58; Fig. 2). The least frequent location was the cervicomedullary junction (2 [3.4%] of 58). We also divided patients into 2 groups according to broad regions of the spinal cord (upper vs lower), as our analysis revealed different outcomes for these 2 regions. Tumors were equally distributed between the upper and lower spinal cord, with 29 patients in each group (Table 2). There was not a significant difference in sex between the 2 spinal cord regions ($p = 0.689$).

We then analyzed the distribution of anaplastic ependymomas (WHO Grade III) by location. World Health Organization grades were available for 52 patients, 9 (17.3%) of whom had anaplastic tumors. Benign ependymomas (WHO Grade II) were more common in all regions except the thoracolumbar region, where 50% (3 of 6) of the tumors were anaplastic. There were no anaplastic ependymomas in the cervicomedullary region, although only 2 tumors occurred at this location overall. Despite these findings, the association between tumor location and tumor grade did not reach statistical significance ($p = 0.355$). By dividing tumor location according to upper and lower spinal cord regions, we found that anaplastic ependymomas were roughly twice as common in the lower spinal cord, although this was not statistically significant (upper spine 12%, lower spine 22.2%, $p = 0.469$; Table 2).

Treatment Paradigms and Tumor Location

Overall, GTR was achieved in 62.1% (36 of 58) of the patients. The highest GTR rate was achieved in the cervical and cervicothoracic regions at 76.5% and 80.0%, respectively (Table 1). Conus medullaris tumors had the

TABLE 1: Tumor location stratified by 6 spine regions*

Location	No. (%)						p Value†
	CM	C	CT	T	TL	Conus	
total lesions	2 (3.4)	17 (29.3)	10 (17.2)	11 (19.0)	6 (10.3)	12 (20.7)	
male sex	1/2 (50)	7/17 (41.2)	6/10 (60)	5/11 (45.5)	2/6 (33.3)	8/11‡ (72.7)	0.558
anaplastic subtype	0/2 (0)	2/14§ (14.3)	1/10 (10)	2/11 (18.2)	3/6 (50)	1/10¶ (10)	0.355
GTR	1/2 (50)	13/17 (76.5)	8/10 (80)	6/11 (54.5)	3/6 (50)	5/12 (41.7)	0.332
adjuvant radiotherapy	0/2 (0)	3/17 (17.6)	1/10 (10)	3/11 (27.3)	3/6 (50)	8/12 (66.7)	0.028

* C = cervical; CM = cervicomedullary; Conus = onus medullaris; CT = cervicothoracic; T = thoracic; TL = thoracolumbar.
† Fisher exact test.
‡ Sex not specified in 1 patient.
§ Grade not specified in 3 patients.
¶ Grade not specified in 2 patients.

TABLE 2: Tumor location broadly divided into upper and lower spinal cord regions

Location	No. (%)		p Value
	Upper Spinal Cord Ependymoma	Lower Spinal Cord Ependymoma	
total lesions	29/58 (50)	29/58 (50)	
male sex	14/29 (48.3)	15/28* (53.6)	0.689†
anaplastic subtype‡	3/25 (12)	6/27 (22.2)	0.469§
GTR	22/29 (75.9)	14/29 (48.3)	0.03†
adjuvant radiotherapy	4/29 (13.8)	14/29 (48.3)	0.01§

* Sex not specified in 1 patient.
† Chi-square test.
‡ Data available in 52 patients.
§ Fisher exact test.

lowest GTR rate (41.7%) despite having one of the lowest percentages of anaplastic ependymomas (10%). Extent of resection was not significantly related to the 6 spinal cord locations (p = 0.332). However, ependymomas in the lower spinal region had a significantly lower GTR rate (14 [48.3%] of 29) than tumors in the upper spinal region (22 [75.9%] of 29; p = 0.03; Table 2).

We then analyzed whether the number of patients treated with adjuvant radiotherapy is associated with tumor location. There were significant differences in the number of patients treated with adjuvant radiotherapy by tumor location (Tables 1 and 2). Thoracolumbar (3 [50%] of 6) and conus medullaris (8 [66.7%] of 12) tumors had the highest rate of adjuvant radiotherapy (p = 0.028), which resulted in a significantly higher rate of adjuvant radiotherapy for lower spinal cord tumors (lower: 14 [48.3%] of 29 vs upper: 4 [13.8%] of 29, p = 0.01).

Tumor Location and PFS and OS

We performed Kaplan-Meier analysis of PFS and OS for tumors at each of the 6 spinal regions to determine whether tumor location carries significant prognostic value for recurrence and mortality, respectively. There were significant differences in PFS for the 6 tumor locations (p = 0.015; Fig. 3 upper). Careful observation revealed that tumors in the lower spinal cord regions tended to recur more frequently than those in the upper regions. Thus, we repeated the Kaplan-Meier analysis after stratifying patients according to the 2 broad spine regions, which confirmed significantly worse PFS for those with lower spinal cord tumors (p = 0.031; Fig. 3 lower).

In a univariate Cox proportional hazards model, the hazard ratio for tumor location (upper vs lower spinal cord tumors) for PFS was 3.17 (95% CI 1.04–9.67, p = 0.042), again supporting higher recurrence rates for lower spinal cord ependymomas. We then fitted a multivariate Cox proportional hazards model by backward stepwise model selection to account for other confounding variables, including age, sex, extent of resection, tumor grade, morbidity, and radiation treatment. Location remained significant in the final multivariate model (HR 3.10, 95% CI 1.00–9.64, p < 0.05).

We next analyzed whether OS is also related to tumor location. There were significant differences in OS for the 6 tumor locations according to Kaplan-Meier analysis (data not shown, p = 0.004). Strikingly, there were no reported deaths in patients with upper spinal cord ependymomas. All 9 deaths among the 58 patients in this study occurred among those with lower spinal cord tumors. Stratifying

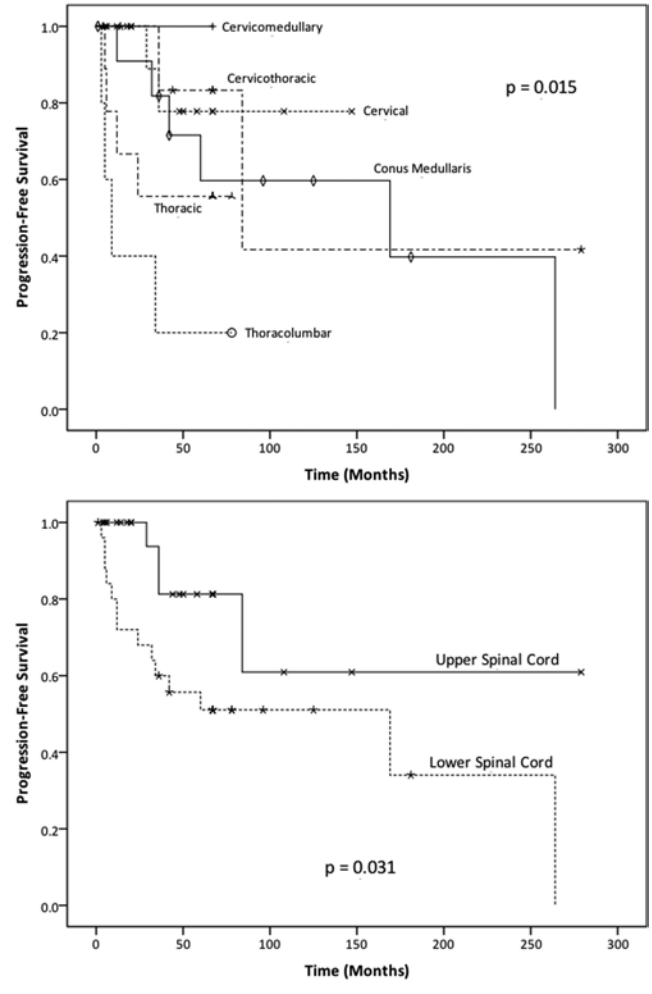

Fig. 3. Kaplan-Meier analysis curve showing PFS by tumor location. **Upper:** There were significant differences in PFS for the 6 tumor locations (p = 0.015). **Lower:** Tumors in the lower spinal cord regions tended to recur more frequently as compared with tumors in the upper regions (p = 0.031).

patients according to the 2 broad spine regions showed significantly worse OS in patients with lower spinal cord tumors than in those with upper spinal cord tumors (p = 0.048; Fig. 4). Multivariate analysis could not be performed for OS given the absence of events in the upper spinal cord group.

Discussion

Spinal cord ependymomas usually occur in adults,[10,27,36] and thus features important for prognosis in pediatric spinal ependymoma are limited. The main goal of this study was to determine whether the location of an ependymoma along the spinal cord could provide important prognostic information. It is the largest integrative analysis to date of children with spinal cord ependymoma.

The frequency of spinal ependymomas continued to increase with age in our study. Thus, as previously reported, spinal cord ependymomas mainly affect the young adult patient population.[14,24] In our pooled cohort of pediatric patients, there was a similar distribution of tumors for each sex (29 males [50.8%] among 57 patients, 28 females [49.1%] among 57 patients), with a slightly higher but not significant percentage of males with lower spinal cord tumors (15 [53.6%] of 29 lesions occurred in males and 13 [46.4%] of 29 lesions occurred in females; sex unknown in 1 patient). Previous studies have shown a higher male distribution for myxopapillary ependymomas in the cauda equina and filum terminale.[27,40] Our results suggest that sex distribution is equal across the different spinal cord locations for classic ependymomas.

Tumors were equally distributed between upper and lower spinal cord regions (Fig. 2). The most frequent location was cervical (17 [29.3%] of 58), followed by the conus medullaris (12 [20.7%] of 58), thoracic (11 [19.0%] of 58), and cervicothoracic regions (10 [17.2%] of 58). These results suggest that spinal cord ependymomas can occur along any portion of the spinal cord in children, although cervicomedullary tumors were rare (2 [3.4%] of 58). Although it is possible that cervicomedullary tumors behave like infratentorial ependymomas, we only considered tumors with components above and below the foramen magnum as cervicomedullary tumors for this study.

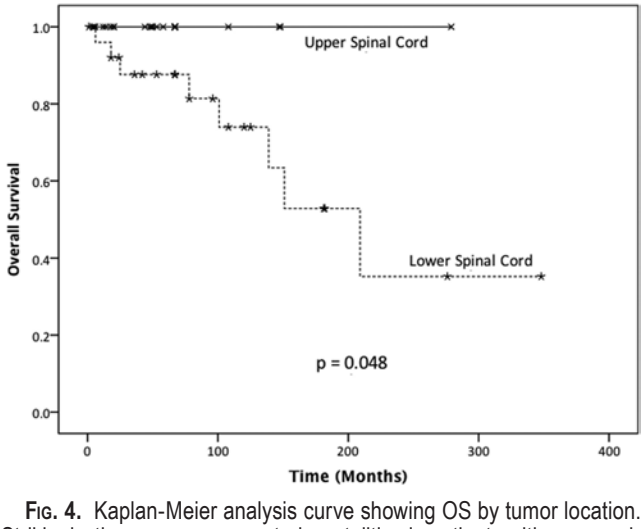

Fig. 4. Kaplan-Meier analysis curve showing OS by tumor location. Strikingly, there were no reported mortalities in patients with upper spinal cord ependymomas. All 9 deaths among the 58 patients occurred in those with lower spinal cord ependymomas. Kaplan-Meier analysis curve showing significantly shorter survival in patients with lower spinal cord ependymomas as compared with that in patients harboring upper spinal cord tumors (p = 0.048).

Our analysis revealed that anaplastic ependymomas (WHO Grade III) are more frequent in the lower spinal cord regions, although this was not statistically significant (Table 2). Because myxopapillary ependymomas (WHO Grade I) carry a histology and prognosis different from those of classic ependymomas, they were excluded from our study. However, the overall rate of anaplastic ependymomas was quite high in our study (data not shown). Overall, 17.3% of spinal cord ependymomas in children were anaplastic, which may be partly attributable to the more aggressive features of spinal cord ependymomas in children. Previous studies have also confirmed more aggressive behavior of spinal cord ependymomas in pediatric patients.[15,28]

Another possible reason for the more aggressive behavior of spinal ependymomas in pediatric patients may relate to extent of resection, although the overall rate in our study was 62.1%. Interestingly, the rate of GTR was significantly less for lower spinal cord tumors (48.3%) as compared with that for upper spinal cord tumors (75.9%; Table 2). While GTR should be the goal of every surgery, our results indicate that GTR is more difficult to achieve with lower spinal cord ependymomas.

The lower GTR rate for lower spinal cord tumors cannot be attributed to the higher WHO grade of tumors at this location, as the number of anaplastic ependymomas was not significantly different at the upper and lower spinal cord (Table 2). These results prove that tumor location does convey significant prognostic information regarding extent of resection. The reason for a lower GTR rate among lower spinal cord ependymomas is unknown, although the unique anatomical features of the lower spinal cord with potential areas for local spread, such as the cauda equina, filum terminale, and larger extramedullary compartment, could affect a surgeon's ability to achieve GTR in this region.

Clinical outcomes, in terms of PFS and OS, varied significantly by tumor location in the pediatric patients. Ependymomas in the lower spine region recurred more frequently and earlier than upper spine tumors (Fig. 3 lower). Furthermore, there were no deaths among patients with upper spinal tumors in our data set, which was pooled from individual patient data (Fig. 4). Interestingly, tumor location was an important variable for PFS after accounting for potential confounders in the multivariate Cox proportional hazards analysis. Moreover, we determined that adjuvant radiotherapy was used significantly more often for tumors in the lower spinal cord (48.3%) than for those in the upper spinal cord (13.8%). Despite this more frequent use of radiotherapy, lower spinal cord ependymomas recurred earlier and more often with shorter survival as compared with upper spinal cord tumors. Thus, broadly dividing tumor location into upper and lower spinal cord regions can provide a strong prognostic value for recurrence and survival.

It is unclear why lower spinal cord ependymomas clinically behave more aggressively with a lower GTR rate, higher adjuvant radiotherapy use, shorter PFS, and shorter OS, as compared with tumors in the upper spinal cord. Perhaps tumors in the lower spinal cord are histologically more aggressive with microsatellites of tumor invasion across the tumor capsule into the surrounding spinal cord or cauda equina, resulting in higher recurrence. This hypothesis remains untested in the current literature, however.

This is a retrospective integrative analysis of pediatric spinal ependymomas with a specific focus on patients who underwent resection. Thus, reported cases may not accurately reflect all patients with ependymomas as a whole, since only those with reported tumor location and extent of resection were included in our analyses. Because it is an analysis of studies from multiple institutions with different surgical experiences, the results do not take into account differences in clinical management at the various institutions, such as a surgeon's experience or technical skills, the likelihood of resecting a spinal ependymoma at a particular institution versus observation, or whether adjuvant radiotherapy was used.

Conclusions

Our results show that spinal cord ependymomas in the pediatric population have a distinct clinical course depending on tumor location. The extent of resection, use of adjuvant radiotherapy, PFS, and OS are related to the tumor location along the spinal cord. Specifically, ependymomas in the lower spinal cord recur earlier and at a higher frequency than tumors in the upper spinal cord. Death occurred only in those patients with lower spinal cord ependymomas. In summary, our results suggest that the location of a spinal cord ependymoma can provide important prognostic information for pediatric patients.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Parsa, Oh. Acquisition of data: Oh, Sayegh, Kim, Aranda. Analysis and interpretation of data: Parsa, Oh, Sayegh. Drafting the article: Oh, Sayegh. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Parsa. Statistical analysis: Oh, Safaee, Sun, Molinaro. Study supervision: Parsa, Oh.

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Address correspondence to: Andrew T. Parsa, M.D., Ph.D., Department of Neurological Surgery, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, California 94117. email: ParsaA@Neurosurg.UCSF.edu.