Treatment of pediatric Grade II spinal ependymomas: a population-based study

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OBJECT Grade II spinal cord ependymomas occurring in pediatric patients are exceptionally rare neoplasms. In this paper the authors use a national cancer database to determine patient demographics, treatment patterns, and associated outcomes of this cohort.

METHODS The Surveillance Epidemiology and End Results (SEER) database was used to analyze subjects younger than 18 years with histologically confirmed diagnoses of Grade II spinal cord ependymoma from the years 1973 to 2008. Descriptive data on the demographic characteristics of this cohort and the associated treatment patterns are shown. The Kaplan-Meier method was used to estimate overall survival at 1, 2, 5, and 10 years.

RESULTS This cohort comprised 64 pediatric subjects with Grade II spinal ependymoma. The median age was 13 years, nearly half of the patients were male, and most were white (84%). The median follow-up was 9.2 years. Overall survival at 5 and 10 years was 86% and 83%, respectively. Gross-total resection was achieved in 57% of subjects, and radiation therapy was administered to 36%. Radiation therapy was administered to 78% of subjects after subtotal resection but only to 19% of patients after gross-total resection; this difference was significant ($p < 0.001$). In a multivariate regression model analyzing sex, age at diagnosis, year of diagnosis, radiotherapy, and extent of resection, female sex was found to be an independent predictor of decreased mortality (HR 0.15 [95% CI 0.02–0.94], $p = 0.04$).

CONCLUSIONS These data show long-term outcomes for pediatric patients with Grade II spinal ependymoma. Radiotherapy was more likely to be administered in cases of subtotal resection than in cases of gross-total resection. Female sex is associated with decreased mortality, while other demographic or treatment modalities are not.

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KEY WORDS spinal cord tumor; ependymoma; pediatric; SEER; children; spinal cord ependymoma; oncology; spine

PEDIATRIC primary spinal cord neoplasms are rare tumors, with reported estimated incidences of 0.9–2.6 per 100,000 person-years.^{32,61} Among these, astrocytomas are the most common subtype, accounting for an estimated 60%–80% of pediatric spinal cord tumors, with ependymoma making up most of the remaining tumors.^{29,33,34,39,42,44} The reverse pattern is true in adult populations.^{31,32,42,44} The WHO categorizes spinal ependymomas into 3 histological subtypes: Grade I myxopapillary ependymoma; Grade II ependymoma, which includes the cellular, clear cell, tanycytic, and papillary subtypes; and finally Grade III anaplastic ependymoma.⁴³

Pediatric Grade II spinal ependymomas are generally intramedullary tumors that occur in the proximal spinal cord.^{7,42} They are slow-growing, indolent tumors with a benign course; in the literature, rates of both overall survival (OS) and progression-free survival (PFS) at 5 years have

been reported at 90%–100%.^{7,42,62} Maximal resection is generally agreed to be the cornerstone of treatment for pediatric spinal ependymomas;^{2,7,8,34,42,47,50} however, the addition of adjuvant radiation therapy after surgery is the subject of more debate.^{2,7,8,48} While there are many studies on spinal ependymomas in adults,^{11,12,16–18,21,24,25,38,41,45,51,56,57,61,65} there are few papers on these tumors in children, and those that do exist tend to be small, single-institution retrospective studies that are not powered for statistical analysis stratified by tumor grade.^{2,8,13,22,27,42,47,53}

The goal of this paper is to use the nationally representative Surveillance Epidemiology and End Results (SEER) database to offer a population-based perspective on pediatric Grade II spinal ependymomas. Specifically, this study provides data on the demographics and treatment patterns in this cohort, as well as the impact of those factors on survival outcomes.

ABBREVIATIONS GTR = gross-total resection; ICD-O-3 = *The International Classification of Diseases for Oncology, Third Edition*; NOS = not otherwise specified; OS = overall survival; PFS = progression-free survival; SEER = Surveillance Epidemiology and End Results; STR = subtotal resection.

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Methods

Study Population

Data for this analysis were obtained from the SEER program (1973–2008) of the National Cancer Institute. This cancer registry includes data from 17 geographic areas in the US and represents approximately 26% of the US population. For the purposes of the present analysis, cases from Louisiana were not used as suggested by SEER due to noncontinuous reporting of data from the impact of Hurricanes Katrina and Rita in the Gulf Coast region. Site and histology codes of *The International Classification of Diseases for Oncology, Third Edition* (ICD-O-3) were used to identify cases. Patients younger than 18 years old classified as having histopathologically confirmed ependymoma including cellular, clear cell, tanycytic, and ependymoma not otherwise specified (NOS) (ICD-O-3 Code 9391) and papillary ependymoma (ICD-O-3 Code 9393) in a location classified as spinal cord (C72.0) or cauda equina (C72.1) were included in this study. We included only individuals for whom the ependymoma was their only or first primary tumor. Myxopapillary ependymoma (ICD-O-3 Code 9394) was not included. Subsequent tumors or recurrences were not considered for this analysis. Patients with a survival time of 0 months ($n = 3$) had their survival time changed to 0.5 months to avoid any bias that could result from the exclusion of these subjects. SEER data are publicly available, and exempt status as non-human subjects research was granted by our institutional review board.

Surgical Procedure Data

In the SEER database, surgical procedure codes were extracted by trained coders to determine the extent of resection. The SEER program has a standardized methodology for coders to look in detail at operative reports, surgeon intraoperative assessment, radiology reports, pathology reports, and medical record notes, and to enter the data according to the FORDS (Facility Oncology Registry Data Standards) manual established by the Commission on Cancer with the American College of Surgeons. We cannot independently confirm the coding assignments. The variable containing surgery codes for the cases diagnosed between 1998 and 2007 was named “RX Summ-Surg Prim Site (1998+)” and was based on the American College of Surgeons Commission on Cancer’s Facility Oncology Registry Data Standards.⁵⁵ Field codes for patients diagnosed between 1983 and 1997 were included in the “Site Specific surgery (1983-1997)” variable. Any case diagnosed prior to 1983 was coded using a nonspecific scheme (yes/no/unknown). To create a new variable for analysis that includes cases from all time periods, we recoded the surgical procedures for all years into 6 previously established categories.¹ Briefly, these categories included: no surgery (pre-1998 codes 00, 01, 03, 04, and 07; for 1998+, code 00); biopsy (pre-1998 code 02; for 1998+, code 20); partial resection (pre-1998 codes 20 and 40; for 1998+, code 40); gross-total resection (GTR) (pre-1998 codes 30, 50, 60; for 1998, code 55); surgery NOS (pre-1998 codes 10 and 90; for 1998+, codes 10 and 90); and surgery status unknown (pre-1998 codes 05, 06, 09, and 80; for 1998+, code 99).^{39,68}

Covariates

Age at diagnosis, sex, race (white, black, American Indian, Asian/Pacific Islander, and other/unknown), Hispanic ethnicity (yes/no), surgery (no surgery/biopsy/partial resection/GTR/surgery not otherwise specified/unknown), radiation therapy (yes/no/unknown), were evaluated in this analysis. For the surgery variable, “no surgery,” “biopsy,” and “surgery NOS” were collapsed into “no resection,” partial resection was “subtotal resection” (STR), and GTR remained as is; unknown status retained its own category but was excluded from most statistical analyses. Detailed patient and treatment-related factors such as chemotherapeutic regimens, radiotherapy technique, radiation dose, and comorbid conditions were unaccounted for in the SEER database and are therefore not evaluated in the present analysis.

Statistical Analysis

Descriptive analyses were conducted to evaluate the distribution of patient and tumor-related characteristics. The Kaplan-Meier method was used to estimate 10-year, 5-year, 2-year, and 1-year survival; log-rank analyses were conducted to evaluate differences in survival curves. Multivariate Cox proportional hazards models for tumor subsets were conducted to estimate the hazard function using variables identified for analysis based on a priori assumptions of associations with survival. A reverse Kaplan-Meier estimator (using censorship as the event of interest) was used to calculate median follow-up times.¹⁵ Chi-square tests were used to compare categorical variables; unpaired t-tests were used to compare continuous variables. Statistical significance was defined as $p \leq 0.05$. The statistical analyses were carried out using STATA version 12 (Stata Corp.).

Results

Overall, this cohort comprised 64 pediatric patients with Grade II spinal ependymoma. The median age was 13 years, nearly half of the patients were male, and most were white (84%). Among those who underwent surgery, GTR was attained in 57% and STR was attained in 43%. Only about one-third of the cohort (36%) received radiation therapy. Adjuvant radiotherapy was statistically significantly more likely to be administered in cases of STR than in cases of GTR ($p < 0.001$). After STR, 11 (79%) of 14 patients received radiation treatment, while after GTR, only 4 (19%) of 21 patients did. This pattern has not significantly varied over the 3.5 decades examined in the study cohort (Table 1).

Of the 64 subjects, 55 were alive after a median follow-up of 9.2 years (95% CI 6.9–12.7 years), and 9 died after a median of 15 months (range 0–96 months). The survival curve is shown in Fig. 1. Overall survival was 94% at 1 year, 92% at 2 years, 86% at 5 years, and 83% at 10 years. Survival at 10 years was 93% for females and 74% for males; this difference was nearly significant by log-rank testing ($p = 0.059$) (Fig. 2). Overall, chi-square analysis found that females were statistically significantly less likely to die than males ($p = 0.045$). Multivariate regression analyses adjusted for age, year of diagnosis, radiotherapy, and extent of resection found a significant association be-

TABLE 1. Characteristics in 64 patients with Grade II spinal ependymoma

Variable	Value*
Sex	
Male	30 (46.9)
Female	34 (53.1)
Age at diagnosis in yrs	
Mean $\pm$ SD	11.9 $\pm$ 4.7
Median	13
0–5	9 (14.1)
6–11	14 (21.9)
12–17	41 (64.1)
Race	
White	54 (84.4)
Black	5 (7.8)
Asian/Pacific Islander	3 (4.7)
Unknown	2 (3.1)
Hispanic Ethnicity	
No	55 (85.9)
Yes	9 (14.1)
Period of diagnosis	
1973–2000	33
2001–2008	31
Tumor location	
Spinal cord	62 (96.9)
Cauda equina	2 (3.1)
Received radiotherapy	
No	37 (57.8)
Yes	23 (35.9)
Unknown	4 (6.2)
Extent of resection	
No resection	23 (35.9)
STR	16 (25)
GTR	21 (32.8)
Unknown	4 (6.2)
Follow-up in yrs	
Median	9.2
95% CI	6.9–12.7
Survival (95% CI)	
1 yr	93.6% (83.8–97.5%)
2 yrs	92% (81.7–96.6%)
5 yrs	86% (73.7–92.8%)
10 yrs	83.2% (69.8–91.1%)

* Values are number of patients (%) unless stated otherwise.

tween female sex and decreased mortality at 10 years (HR 0.15 [95% CI 0.02–0.94], $p = 0.04$). This study found no statistically significant association between OS and age, race/ethnicity, diagnosis year, radiation treatment status, or extent of resection in chi-square, t-test, log-rank, or multivariate regression analyses.

The Kaplan-Meier survival estimate at 10 years for

FIG. 1. Kaplan-Meier graph depicting the 10-year survival curve for patients with Grade II ependymoma. Figure is available in color online only.

those who underwent STR was 87.5% and for those those who underwent GTR it was 93.8%; this difference was not statistically significant. However, among the patients who did not survive, the survival time for the patient who received a GTR was 55 months, and for the 2 patients who received an STR it was 8 and 15 months. The Kaplan-Meier survival estimate at 10 years for those who underwent radiation therapy was 87.4%, and for those who did not, it was 75.1%; this difference was not statistically significant (Tables 2 and 3).

Discussion

To our knowledge, this is the largest published series of pediatric Grade II spinal ependymoma cases to date, with 64 subjects overall. The median follow-up was 9.2 years. Overall survival was 86% at 5 years and 83% at 10 years. Adjuvant radiation therapy was much more likely to be used in cases of STR than in cases of GTR. Females were significantly more likely to survive than males. Neither extent of resection nor adjuvant radiotherapy significantly affected OS.

FIG. 2. Kaplan-Meier graph of 10-year survival of pediatric spinal ependymoma patients stratified by sex. Figure is available in color online only.

TABLE 2. Patient characteristics and survival outcome*

Variable	Survived (n = 55)	Died (n = 9)	p Value
Sex			0.05†
Male	23	7	
Female	32	2	
Age at diagnosis in yrs			
Mean ± SD	11.8 ± 4.8	12.3 ± 4.3	0.75
Median	13	13	
10th–90th percentile	3–17	4–17	
0–5	8	1	0.66
6–11	11	3	
12–17	36	5	
Race‡			0.69
White	47	7	
Black	4	1	
Asian/Pacific Islander	2	1	
Hispanic ethnicity			0.78
No	47	8	
Yes	8	1	
Period of diagnosis			0.79
1973–2000	28	5	
2001–2008	27	4	
Received radiation‡			0.25
No	33	4	
Yes	18	5	
Surgery type‡			0.61
No resection	20	3	
STR	14	2	
GTR	20	1	
Time to death in mos			
Mean		30.4	
Median		15	
Range		0–98	

* Values are presented as the number of patients unless stated otherwise.

† Statistically significant.

‡ Unknowns are not shown.

Characteristics and Demographics

Grade II ependymomas, including cellular, clear cell, tanycytic, papillary, and ependymoma NOS, are slow-growing, indolent tumors.^{7,42} Our study found 5- and 10-year OS to be 86% and 83%, respectively, which is consistent with the reported literature. In a 2010 retrospective study using the Hirntumor (HIT) database (n = 17 Grade II ependymomas), Benesch et al. reported 100% OS and 94% PFS after 4 years of follow-up.⁸ In a 2012 retrospective single-institution study (n = 11 Grade II ependymomas), Stephen et al. reported 100% PFS and OS after a mean of 51 months of follow-up.⁶² In a 2013 literature review of more than 30 series (n = 43 Grade II ependymomas), Safaee et al. reported a 5-year OS of greater than 90% and a PFS of approximately 80%.⁵⁹

This study found that females were much more likely to survive than males among pediatric subjects with Grade

TABLE 3. Multivariate analysis of risk factors for 10-year mortality

Variable	HR	95% CI	p Value
Sex			
Male	1.000	Reference	
Female	0.151	0.024–0.940	0.043*
Age at diagnosis	0.892	0.737–1.080	0.241
Year of diagnosis			
1973–2000	1.000	Reference	
2001–2008	5.615	0.853–36.969	0.073
Received radiation†			
No	1.000	Reference	
Yes	2.35805	0.486–11.440	0.287
Extent of resection†			
No resection	1.000	Reference	
STR	0.896	0.125–6.417	0.913
GTR	0.571	0.053–6.166	0.645

* Statistically significant.

† Unknowns are not shown.

II spinal ependymoma. To the best of our knowledge, such a finding in this neoplasm subgroup has not been previously reported. Published studies on this topic have not been powered for analysis stratified by grade. However, an association between male sex and mortality has been reported among intracranial ependymomas in adult populations.^{45,57} Further prospective studies are warranted to elucidate the possible role of sex in the prognosis of pediatric spinal Grade II ependymoma. The data in our study are observational and cannot provide explanations for this sex-related disparity in survival outcomes. Our results are in keeping with reports in the literature. The higher incidence and worse outcomes of parenchymal CNS tumors in male versus female patients, independent of age, race, tumor histology (including gliomas, ependymomas, and medulloblastomas), and country of residence/origin, has been reported in the literature.^{3,30,35,37,46,52,58,63,70} Sun et al., in a review examining this disparity, postulated that it may be due to sexually dimorphic biology, specifically sex chromosome–based mechanisms of growth regulation.⁶³ Male embryos are larger, contain more cells, and show differential expression of genes important for glucose metabolism (*G6PD* and *HPRT1*), cellular growth (*XIAP*), and gene regulation (*DMNT3A* and *DMNT3B*); these differences are evident at the blastocyst stage, before gonadal differentiation at 8 weeks.^{9,10,36,60,67} These differences are reported to have physiologically relevant manifestations; male embryos display increased glucose and pyruvate uptake and lactate production, while female embryos display greater *G6PD* activity and increased activity through the pentose phosphate pathway.^{9,10,23,49} The Warburg effect describes the observation that tumor cells prefer anaerobic glycolysis as an energy source, and thus would be expected to have increased uptake of glucose and production of lactate. These metabolic differences may affect the probability, rate, or severity of oncogenic transformation in the CNS. Alternate explanations include sex-based differen-

tial activation of the MAPK pathway, differential sensitivity to estradiol-mediated suppression of the MAPK pathway (correlating with differential rates of proliferation and apoptosis), and differential regulation of CREB, a growth-regulating transcription factor.^{5,19,28,64,69} In an intracranial xenograft model of glioblastoma, estradiol induced tumor cell apoptosis and promoted survival.⁶ Although SEER data cannot provide further explanation for disparity in outcome based on sex, there is ongoing work reported in the literature to gain understanding of these differences.

This cohort had no significant association between age or race/ethnicity and outcomes in Grade II ependymoma. With regard to spinal ependymoma in general, Safaee et al. (n = 80) found a significant association between age and mortality,⁵⁹ while Benesch et al. (n = 29) did not.⁸ However, neither paper provides outcome analysis stratified by tumor grade.

Surgery and Adjuvant Radiation Therapy

Maximally safe resection is the cornerstone of care in the management of pediatric Grade II spinal ependymomas.^{7,42,50} In this cohort, GTR was attained in 57% of subjects who underwent resection, which is on par with published accounts of 50%–100% in the pediatric literature.^{8,59,62} Our study did not find a statistically significant relationship between extent of resection and OS; data on tumor progression were not available. Of note, among the 3 patients in our study who underwent resection and eventually died, the patient who achieved GTR survived 55 months, while the 2 patients with STR survived 8 and 13 months. While this small number is not amenable for statistical analysis, this finding is consistent with the widely reported connection between GTR and outcomes listed in the literature. An association between GTR and increased OS and PFS in cases of spinal ependymoma has been well documented in the adult literature and in a handful of pediatric studies; however, few studies provide analysis stratified by grade.^{11,12,14,16,17,59,62} Safaee et al. reported that among 43 Grade II ependymomas, GTR was associated with increased PFS.⁵⁹ Benesch et al. (n = 29) did not find a statistically significant relationship between extent of resection and OS; however, they found that GTR trended toward an association with increased PFS (p = 0.088).⁸

The role of adjuvant radiation therapy in the treatment of pediatric spinal ependymomas has historically been a subject of debate, as the rarity of these neoplasms has led to a paucity of data. Our study shows that in practice, about one-third of this cohort received radiation therapy, which is slightly lower than previously reported rates of 49%–58%.^{8,59,62} Our data also found that radiation therapy is statistically significantly more likely to be administered in conjunction with STR as opposed to GTR (p < 0.001). Benesch et al. reported a similar pattern in their 2010 study; however, it did not reach statistical significance.⁸ This study did not find a significant relationship between radiation treatment and OS. It should be noted that, given the limited nature of the data regarding radiation therapy in SEER, it is difficult to draw conclusions regarding the impact of radiation therapy on outcomes in this study cohort. These findings are consistent with what has been published before in the literature. Safaee et al. (n = 43 Grade II ependymomas,

total n = 80) found no significant association between radiotherapy and PFS in multivariate analyses pooling Grade I, II, and III spinal ependymoma.⁵⁹ Lonjon et al. published a cohort (n = 17 Grade II ependymomas, total n = 20) that achieved 90% 10-year OS rates and 70% 10-year PFS rates without the use of additional adjuvant radiation therapy.⁴² Neither study provided statistical analyses stratified by tumor grade. In the adult literature, the role of adjuvant radiation in the management of spinal ependymomas is also a matter of debate: some studies recommend postoperative radiation therapy in cases of STR but not GTR,^{18,40,41,65,66} others advocate for postoperative radiation therapy after GTR,³⁸ and some maintain that radiation is not indicated regardless of degree of resection.^{20,26,42} Further studies are needed to determine the optimal management of these rare tumors.

Limitations

There are limitations to this study, many of which are related to the nature of the underlying data set. There is a lack of data about the focality, location, clinical symptoms, and functional status of the patients, which other studies have shown to be important prognostic indicators of outcome.^{54,59} The outcome available for examination is survival; there are no data about tumor progression or recurrence. This limits the ability to calculate PFS, which other studies have shown to be more influenced by treatment modalities than OS.^{8,59} There are no data regarding functional status preoperatively or postoperatively, which are highly clinically relevant. SEER does not contain information regarding the type, dose, field, timing, or duration of radiation therapy, rendering it difficult to derive conclusions about the impact of radiation treatment in this study cohort. There is also a lack of data on chemotherapeutic regimens in SEER; however, chemotherapy is not typically used in the treatment of Grade II spinal ependymomas.^{4,7,42,47,50} For each case, to what extent the “extent of resection” was coded based on operative reports/surgeon estimates versus postoperative imaging cannot be known from SEER. We do not have access to primary imaging data, and an independent comparison of pre- and postoperative scans to confirm the extent of resection was not possible. Likewise, while tumor histology is coded according to standardized methodology by coders with access to pathology reports, histological data were not available to us for independent verification and review. There are also no data about comorbid conditions that may have influenced the management or outcomes of the subjects in this cohort. The longitudinal nature of the database reflects the evolution of diagnostic and surgical care over the decades of observation. Changes in the histological classification criteria of Grade II spinal ependymomas over the time period examined in this study may lead to heterogeneity within the data. MRI was not developed until 1973, and mainstream incorporation of diagnostic MRI followed over the next 2 decades. This could result in heterogeneity within the “extent of resection” variable; specifically, it may be difficult to interpret “gross-total resection” in pre-MRI era patients, as they may have been classified as “subtotal resection” in the post-MRI era. Finally, as with all population-based studies, these data are observational in nature and cannot

be used to deduce causality or to influence clinical decision making.

Conclusions

This study examined 64 cases of pediatric Grade II spinal ependymoma with a median of 9.2 years of follow-up and reported the demographic characteristics, treatment trends, and outcomes. Overall survival at 5 and 10 years was 86% and 83%, respectively. Subjects were significantly more likely to undergo radiation therapy after STR than GTR. Female sex was associated with increased survival; other demographic factors, extent of resection, and radiation treatment were not.

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Conception and design: Lam. Acquisition of data: Lam, Melkonian. Analysis and interpretation of data: Lam, Lin, Melkonian. Drafting the article: Lin. 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: Lam. Statistical analysis: Lin, Melkonian. Administrative/technical/material support: Lam, Jea. Study supervision: Lam.

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