Title

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Journal

Child's Nervous System, 29(11)

ISSN

0256-7040

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Publication Date

2013-11-01

DOI

10.1007/s00381-013-2149-x

Peer reviewed

Childs Nerv Syst
DOI 10.1007/s00381-013-2149-x

ORIGINAL PAPER

Histologic grade and extent of resection are associated with survival in pediatric spinal cord ependymomas

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Received: 15 February 2013 / Accepted: 3 May 2013

Abstract
Purpose Prognostic factors affecting outcomes in pediatric spinal cord ependymomas are limited. We sought to investigate potential associations between extent of resection and histologic grade on progression-free survival (PFS) and overall survival (OS).
Methods A comprehensive literature search was performed to identify pediatric patients who underwent surgical resection for spinal cord ependymomas. Only manuscripts with clearly defined age, tumor grade, extent of resection, and clinical follow-up were included.
Results A total of 80 patients were identified with a histologic distribution as follows: 36 % myxopapillary (grade I), 54 % classical (grade II), and 10 % anaplastic (grade III). There was no association between tumor grade and PFS. The only factor associated with improved PFS was gross total resection (GTR), which remained significant in a multivariate model (hazard ratio (HR)=0.248, p=0.022). Moreover, older age (HR=0.818, p=0.026), GTR (HR=0.042, p=0.013), and anaplastic grade (HR=19.847, p=0.008) demonstrated a significant association with OS in a multivariate model.
Conclusions Among pediatric patients with spinal cord ependymomas, PFS did not differ across histologic grades but was prolonged among patients who underwent GTR. Age, extent of resection, and tumor grade were all significantly associated with survival.

Keywords Ependymoma · Spine · Pediatric · Histologic grade · Recurrence · Survival

Introduction

Ependymomas are among the most common central nervous system tumors in children and young adults. They range from subependymomas (Word Health Organization (WHO) grade I) and myxopapillary ependymomas (WHO grade I) to more aggressive anaplastic ependymomas (WHO grade III). Classic ependymomas (WHO grade II) may vary in clinical behavior but are generally slow growing and found adjacent to the ventricular wall or within the spinal cord. There is a well-described relationship between the anatomic location of ependymomas and their histologic grade. Subependymomas are most commonly found in lateral or fourth ventricles [48], while myxopapillary ependymomas are almost exclusively limited to the conus medullaris, cauda equina, or filum terminale [48]. Classic ependymomas can occur at any point along the ventricular system or spinal canal but are most common in the fourth ventricle and spinal cord [68, 72]. More than half of anaplastic ependymomas occur in the ventricular system, with less than 10 % originating in the spinal cord [6].

Overall, ependymomas represent 21–29 % of spinal cord tumors and are among the most common primary tumors of the spine following meningiomas (24–33 %) and nerve sheath tumors (21–27 %) [20, 21, 71]. They are the most prevalent glial tumors and most common malignant tumors of the adult spinal cord [20, 69, 73]. The distribution of these tumors is age dependent; in adults, 55–64 % of ependymomas are found in the spinal cord, while in children, they occur more often in the brain with just 7–13 % occurring in the spinal cord [6, 46]. Aside from extent of resection, factors that affect outcomes for pediatric spinal cord ependymomas are not well defined [5, 17, 75]. Tumor

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Published online: 16 May 2013

location may be an important factor since it can determine clinical presentation and our group has shown that children with ependymomas of the upper spinal cord have more favorable progression-free survival (PFS) and overall survival (OS) [24, 62]. Location can also predict the tumor's biologic behavior, particularly when comparing intracranial and spinal cord ependymomas [7, 10, 29, 45, 46]. Tumor grade is an important prognostic factor in some studies [43, 50, 64] but not others [17, 27, 33, 47, 78]. It is well accepted that anaplastic ependymomas confer the worst prognosis, but the distinction between myxopapillary and classical ependymomas of the spinal cord is less clear, particularly within the pediatric population. In order to address some of these questions, we performed a systematic review of the literature to identify factors associated with outcomes, particularly PFS and OS.

Methods

Literature review and data aggregation

A comprehensive English-language PubMed search was performed using the keyword "ependymoma." This query

Table 1 Manuscript selection

Author	Year	Reference	Total number of patients in manuscript	Pediatric ependymoma patients included in present study
Payne et al.	1973	[65]	1	1
Scott	1974	[74]	3	1
Cameron	1976	[11]	1	1
Mavrouddis et al.	1977	[44]	1	1
Fischer and Mansuy	1980	[23]	16	1
Mørk et al.	1980	[54]	1	1
Morris et al.	1983	[55]	1	1
Yasui et al.	1988	[84]	22	1
Di Marco et al.	1988	[19]	11	1
Naidu et al.	1989	[58]	25	1
Fujiyama et al.	1990	[24]	1	1
Wen et al.	1991	[82]	20	1
Newton et al.	1992	[59]	5	2
Clover et al.	1993	[16]	11	3
Lonjon et al.	1998	[42]	20	7
Hoshimaru et al.	1999	[32]	36	6
Ohata et al.	1999	[63]	18	2
Johnson et al.	1999	[35]	1	1
Merchant et al.	2000	[49]	25	8
Nishio et al.	2000	[60]	19	1
Aktuğ et al.	2000	[2]	1	1
Hanbali et al.	2002	[28]	26	1
Goto et al.	2003	[26]	25	1
Peker et al.	2004	[66]	21	1
Kocak et al.	2004	[39]	15	2
Lin et al.	2005	[41]	20	1
Mridha et al.	2007	[56]	1	1
Jatana et al.	2008	[34]	1	1
Kabler et al.	2008	[37]	1	1
Cho et al.	2009	[14]	1	1
Kaner et al.	2010	[38]	21	1
Dulai et al.	2010	[20]	1	1
Moon et al.	2010	[52]	1	1
Al-Halabi et al.	2010	[4]	7	5
Stephen et al.	2012	[76]	21	19

yielded 3,675 manuscripts which were individually reviewed to identify those containing pediatric patients (defined as age less than 18 years at presentation) who underwent surgical resection for spinal cord ependymoma. Aggregated datasets and manuscripts lacking information on tumor location, extent of resection, histologic grade, and clinical follow-up were excluded. Patients with neurofibromatosis type 1 or 2 were also excluded. A weighted meta-analysis with 5- and 10-year PFS and OS, could not be performed since these statistics were not consistently reported in large aggregated studies. A total of 35 manuscripts, published between 1973 and 2012, containing data on 80 pediatric patients were identified [2, 4, 11, 14, 16, 18, 19, 22, 23, 26, 32, 34, 35, 37–39, 41, 42, 44, 49, 52, 54–56, 58–60, 63, 65, 66, 74, 76, 82, 84]. The manuscripts included in this study are summarized in Table 1.

The following data were extracted from each manuscript: age, gender, tumor location, histologic grade, extent of resection, use of radiotherapy, tumor recurrence, time to recurrence, mortality, time to death, and time to most recent follow-up. Based on the surgeon's report or postoperative imaging, the extent of resection was classified as gross total resection (GTR) or subtotal resection (STR). Histologic grade was classified according to the WHO grading system: grade I, myxopapillary ependymoma; grade II, classic ependymoma; and grade III, anaplastic ependymoma. Tumor location was defined as cervicomedullary, cervical, cervicothoracic, thoracic, thoracolumbar, or conus medullaris (including cauda equina and filum terminale). Location was dichotomized into upper (cervicomedullary, cervical, and cervicothoracic) or lower spinal cord (thoracic, thoracolumbar, or conus medullaris) for analysis.

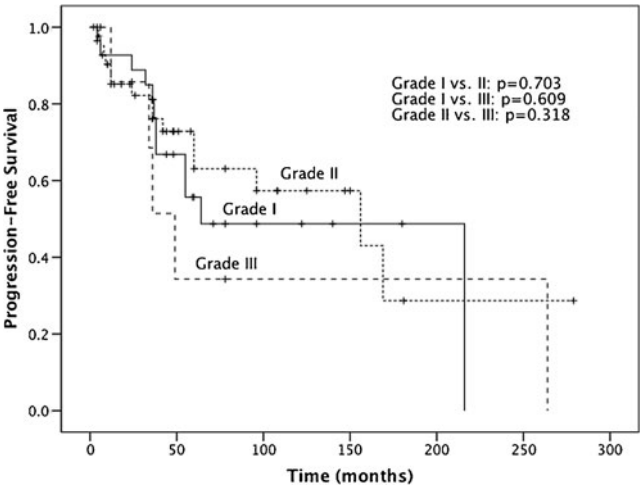

Fig. 1 Tumor grade is not associated with PFS in pediatric spinal cord ependymomas. There was no significant difference in PFS when comparing grade I to grade II (p=0.703), grade I to grade III (p=0.609), or grade II to grade III (p=0.318) tumors

Table 2 Clinical characteristics

	WHO grade I (%)	WHO grade II (%)	WHO grade III (%)	Total (%)	Significance (p value)
Number of patients	29 (36)	43 (54)	8 (10)	80 (100)	
Age (years)					
Mean	13.2±0.7	12.9±0.7	12.6±1.5	13.0±0.4	0.910[b]
Median	13	14	14	13.5	
Gender					
Male	21 (75)[a]	19 (44)	5 (62.5)	45 (57)[a]	0.035[c]
Female	7 (25)[a]	24 (56)	3 (37.5)	34 (43)[a]	
Location					
Upper spinal cord	1 (3)	17 (39.5)	2 (25)	20 (25)	0.002[c]
Lower spinal cord	28 (97)	26 (60.5)	6 (75)	60 (75)	
Extent of resection					
GTR	12 (41)	28 (65)	4 (50)	44 (55)	0.133[c]
STR	17 (59)	15 (35)	4 (50)	36 (45)	
Adjuvant RT	20 (71)[a]	21 (49)	4 (50)	45 (57)[a]	0.157[c]
Follow-up (months)					
Mean	81±12	79±10	85±39	80±8	0.975[b]
Median	60	48	52	53	

RT radiotherapy

[a] Unknown in one patient

[b] ANOVA

[c] Chi-square test

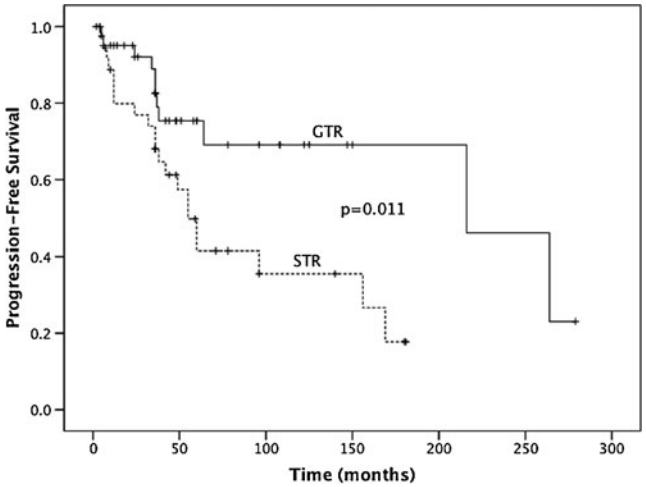

Fig. 2 Extent of resection is associated with PFS in pediatric spinal cord ependymomas. Patients who underwent GTR had significantly longer PFS compared with those who underwent STR (p=0.011), an association that remained significant in a multivariate model (HR= 0.248, p=0.022)

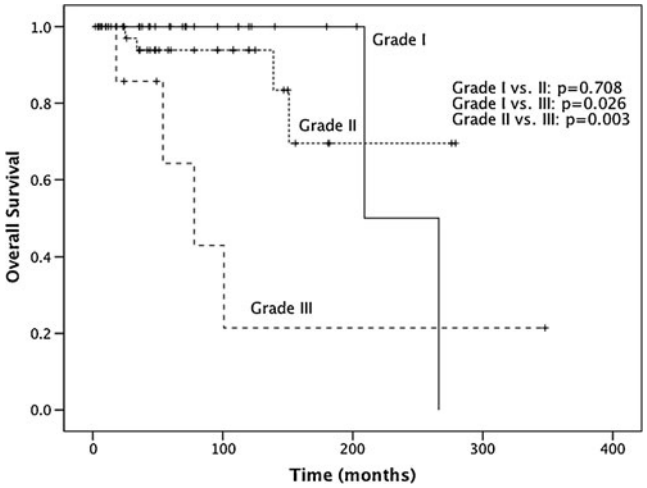

Fig. 3 Tumor grade is associated with survival in pediatric spinal cord ependymomas. Patients with grade III tumors had significantly shorter survival compared with those with grade I (p=0.026) or II (p=0.003) lesions, but there was no difference between patients with grades I and II tumors (p=0.708). The association between grade III histology and survival remained significant in a multivariate model (HR=19.847, p= 0.008)

Statistical analysis

Categorical variables were compared using the Chi-square or Fisher's exact test if cells contained less than 5 expected values. The independent samples' t test or analysis of variance (ANOVA) was used to compare continuous variables. Kaplan–Meier analysis was performed to identify variables associated with PFS or OS, with comparisons made using the log rank test. Multivariate Cox regression was performed to generate hazard ratios with 95 % confidence intervals. Statistical analysis performed using SPSS version 20 (IBM) with statistical significance was defined as $p<0.05$.

Results

Clinical characteristics

A total of 80 patients were identified from our literature review. The mean age was 13.0±0.4 years with no significant difference across histologic grades (p=0.910). Grade I tumors were more common in the lower spinal cord (97 %) compared with grades II (60 %) and III (75 %) tumors (p=0.002). Grade II tumors had a higher rate of GTR (65 %) compared with grades I (41 %) and III (50 %) lesions, but this difference was not significant (p=0.133). Grade I tumors had a higher rate of upfront radiotherapy at 71 %, compared with 49 % among grade II and 50 % among grade III lesions, but again this difference did not reach statistical significance (p=0.157). The median follow-up time for all patients was 53 months, and there was no difference in follow-up time across histologic grades. The clinical characteristics of our dataset are summarized in Table 2.

Effect of tumor grade and extent of resection on PFS

The effect of tumor grade on PFS was assessed by Kaplan–Meier analysis (Fig. 1). There was no difference in PFS when comparing grade I to grade II (p=0.703), grade I to grade III (0.609), or grade II to grade III tumors (0.318). We performed additional Kaplan–Meier analysis to determine the effect of extent of resection on PFS and found a

Table 3 Multivariate analysis of progression-free survival

Variable	Hazard ratio (95 % CI)	Significance (p value)
Age	0.934 (0.857–1.018)	0.121
Extent of resection (GTR)	0.248 (0.075–0.817)	0.022
Adjuvant RT	0.513 (0.153–1.718)	0.279
WHO grade I	1	–
WHO grade II	0.854 (0.382–1.910)	0.701
WHO grade III	1.009 (0.302–3.364)	0.989

CI confidence interval, *GTR* gross total resection, *RT* radiotherapy

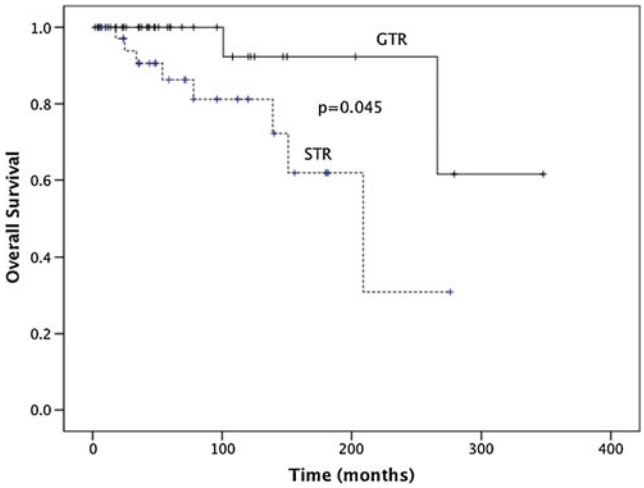

Fig. 4 Extent of resection is associated with survival in pediatric spinal cord ependymomas. Patients who underwent GTR had longer survival compared with those who underwent STR (p=0.045), an association that remained significant in a multivariate model (HR= 0.042, p=0.013)

significant increase (p=0.011) among patients who underwent GTR compared with STR (Fig. 2). To determine if this effect was conserved across grades, we repeated the analysis for each group. GTR was associated with increased PFS for patients with grade II (p=0.001) but not for grade I (p=0.730) or grade III (p=0.663) tumors. To control for all variables, we generated a multivariate model that included age, extent of resection, use of radiotherapy, and histologic grade. Only extent of resection was significantly associated with PFS (hazard ratio (HR)=0.248 (95 % confidence interval (95 % CI)), 0.075–0.817, p=0.022). The results of this analysis are summarized in Table 3.

Effect of tumor grade and extent of resection on OS

Although we were unable to detect an association between tumor grade and PFS, we sought to identify a potential relationship between tumor grade and OS. Kaplan–Meier analysis (Fig. 3) demonstrated a significant difference in OS when comparing grade I versus grade III tumors (p=0.026) and grade II versus grade III tumors (p=0.003), but no difference in OS between grades I and II lesions (p=0.708). Extent of resection was also a significant factor associated with OS (p= 0.045, Fig. 4). In a multivariate model, these relationships were preserved as we identified age (HR=0.818 (95 % CI, 0.685–0.976), p=0.026), GTR (HR=0.042 (95 % CI, 0.003–0.507), p=0.013), and anaplastic grade (HR= 19.847 (95% CI, 2.173–181.301), p=0.008) as factors significantly associated with OS. The results of this analysis are summarized in Table 4.

Discussion

Although spinal cord ependymomas are well studied in adults, prognostic factors associated with outcomes in children are limited. The goal of this study was to determine the prognostic factors affecting PFS and OS for pediatric spinal cord ependymoma patients, specifically focusing on extent of resection and histologic grade. In a large integrative analysis consisting of 80 patients, we show that GTR is associated with increased PFS, while younger age, grade III histology, and incomplete resection are associated with decreased OS. These results are similar to those reported by a multi-institutional study of pediatric patients with intracranial ependymomas, which found that young age, grade III histology, and incomplete resection were independently associated with poor outcomes [31].

Recent genomic analysis raises interesting questions with respect to the biology of spinal cord ependymomas across histologic grades [36, 51, 57, 70, 77]. If these tumors arise from distinct progenitor cells, then they likely exhibit unique to responses to adjuvant therapies. For example, the role of radiotherapy in the management of these lesions, particularly those of the myxopapillary subtype, is an area of active investigation. Several studies have demonstrated improved 5- and 10-year tumor control rates among patients who receive surgery plus radiotherapy compared with surgery alone, even in cases of complete resection [1, 3, 67]. Additionally, patients receiving high-dose radiotherapy had prolonged PFS compared with those receiving standard doses [67]. Since radiotherapy regimens and extent of resection are not standardized across manuscripts, it is difficult to draw more definitive conclusions from our data. Additional prospective studies are needed to determine the

Table 4 Multivariate analysis of overall survival

Variable	Hazard ratio (95 % CI)	Significance (p value)
Age	0.818 (0.685–0.976)	0.026
Extent of resection (GTR)	0.042 (0.003–0.507)	0.013
WHO grade I	1	–
WHO grade II	1.318 (0.219–7.931)	0.763
WHO grade III	19.847 (2.173–181.301)	0.008

CI confidence interval, *GTR* gross total resection

precise role of radiotherapy in the management of these tumors.

Although we were unable to identify an association between tumor grade and PFS, Waldron et al. showed that high-grade (poorly differentiated) tumors were associated with shorter PFS [81]. We did, however, find that extent of resection was an important factor associated with improved PFS, which is supported by other studies that demonstrate the protective effects of GTR and the association between extent of resection and improved tumor control [10, 12, 83]. Not surprisingly, tumor grade demonstrated a strong association with survival. Grade III histology conferred the worse prognosis, which has also been observed in patients with intracranial ependymomas [31]. Our findings support data from other large series, which also identifies age and extent of resection, along with histologic grade, as important factors associated with survival [15, 31, 53].

Surgical resection remains the first-line treatment for pediatric patients with spinal cord ependymomas [8, 9, 13, 25, 40, 79]. In a relatively large study of spinal cord ependymoma patients with good long-term follow-up, Gomez et al. found 10- and 15-year tumor control rates of 50 and 46 %, respectively, suggesting that treatment failure is not uncommon [25]. There are also reports suggesting that spinal cord ependymomas behave more aggressively in children than adults [30, 61]. In one of the few studies to investigate tumor size, Wahab et al. found improved tumor control with lesions less than or equal to 6 cm [80]. Given the strong associations between extent of resection and both PFS and OS, we recommend GTR whenever it is safely achievable without significant neurological deficits.

This study represents a retrospective integrative analysis of the published literature and is subject to certain limitations. The lack of reporting standards introduces the possibility that extent of resection, histology, and radiotherapy regimens may vary between studies. Furthermore, since these data were collected from multiple institutions, the results do not take into account variability in surgical expertise and clinical management. A minor limitation is the broad period over which data were collected (1973–2012); however, only ten patients (12 %) were treated before 1990. Despite these limitations, our results are significant given the relative paucity of spinal cord ependymomas in children.

Conclusions

Across pediatric spinal cord ependymomas, young age, STR, and grade III histology are associated with poor survival. There was no difference in survival between grades I and II tumors nor was tumor grade associated with PFS. The only factor associated with improved PFS was GTR, which remained significant in a multivariate model. Given the lack of data on prognostic factors in spinal cord ependymomas, future studies should focus on collaborative multi-institutional efforts. The incorporation of genetic analysis may help refine the current classification system and improve our ability to predict long-term tumor control and survival based on tumor biology.

Acknowledgments Mr. Safaee was supported by a grant from the Doris Duke Charitable Foundation. Dr. Oh was supported by the Neurosurgery Research and Education Foundation from the American Association of Neurological Surgeons. Dr. Parsa was partially funded by the Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery.

Conflict of interest The authors declare that they have no conflict of interest.

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