

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

Michael Safaee · Michael C. Oh · Joseph M. Kim ·  
Derick Aranda · Phiroz E. Tarapore · Tene A. Cage ·  
Nalin Gupta · Andrew T. Parsa

Received: 15 February 2013 / Accepted: 3 May 2013 / Published online: 16 May 2013  
© Springer-Verlag Berlin Heidelberg 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 (World 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

---

Michael Safaee and Michael C. Oh are contributed equally

M. Safaee · M. C. Oh · J. M. Kim · D. Aranda · P. E. Tarapore ·  
T. A. Cage · N. Gupta · A. T. Parsa (✉)  
Department of Neurological Surgery, University of California San  
Francisco, 505 Parnassus Ave,  
San Francisco, CA 94117, USA  
e-mail: Parsaa@neurosurg.ucsf.edu

N. Gupta  
Department of Pediatrics, University of California San Francisco,  
San Francisco, CA 94117, USA

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

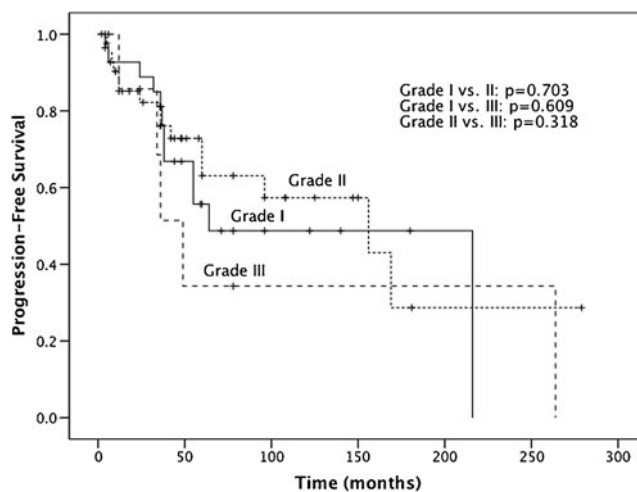
A comprehensive English-language PubMed search was performed using the keyword “ependymoma.” This query

**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,



**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

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.

**Table 2** Clinical characteristics

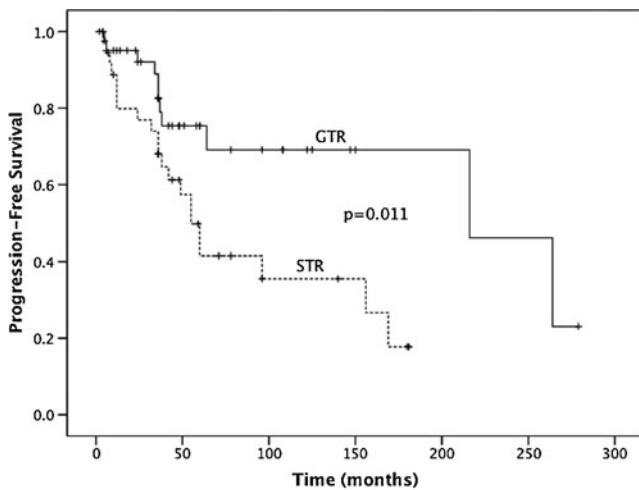
	WHO grade I (%)	WHO grade II (%)	WHO grade III (%)	Total (%)	Significance ( <i>p</i> value)
Number of patients	29 (36)	43 (54)	8 (10)	80 (100)	
Age (years)					
Mean	13.2±0.7	12.9±0.7	12.6±1.5	13.0±0.4	0.910 <sup>b</sup>
Median	13	14	14	13.5	
Gender					
Male	21 (75) <sup>a</sup>	19 (44)	5 (62.5)	45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

RT radiotherapy

<sup>a</sup> Unknown in one patient

<sup>b</sup> ANOVA

<sup>c</sup> 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,  $p=0.022$ )

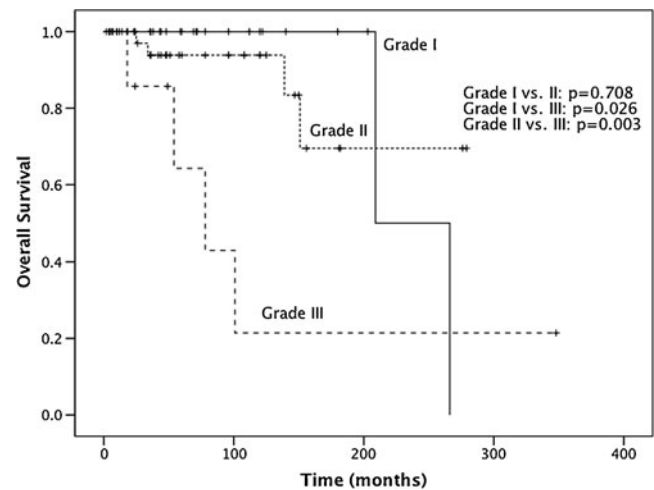
### Statistical analysis

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  $13.0\pm 0.4$  years with no significant difference across histologic grades ( $p=0.910$ ). Grade I tumors were more common in the lower spinal cord (97 %) compared



**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,  $p=0.008$ )

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.

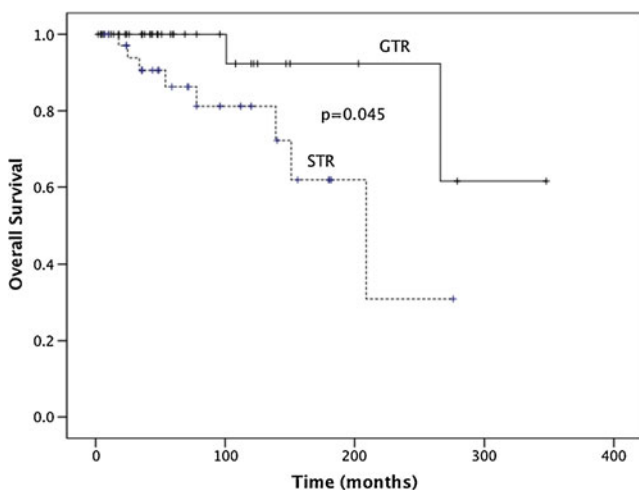
### Effect of tumor grade and extent of resection on PFS

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.

## References

1. Agbahiwe HC, Wharam M, Batra S, Cohen K, Terezakis SA (2013) Management of pediatric myxopapillary ependymoma: the role of adjuvant radiation. *Int J Radiat Oncol Biol Phys* 85:421–427
2. Aktug T, Hakguder G, Sarioglu S, Akgur FM, Olguner M, Pabuccuoglu U (2000) Sacrococcygeal extraspinal ependymomas: the role of coccygectomy. *J Pediatr Surg* 35:515–518
3. Akyurek S, Chang EL, Yu TK, Little D, Allen PK, McCutcheon I, Mahajan A, Maor MH, Woo SY (2006) Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at M.D. Anderson Cancer Center. *J Neurooncol* 80:177–183
4. Al-Halabi H, Montes JL, Atkinson J, Farmer JP, Freeman CR (2010) Adjuvant radiotherapy in the treatment of pediatric myxopapillary ependymomas. *Pediatr Blood Cancer* 55:639–643
5. Allen JC, Siffert J, Hukin J (1998) Clinical manifestations of childhood ependymoma: a multitude of syndromes. *Pediatr Neurosurg* 28:49–55
6. Amirian ES, Armstrong TS, Aldape KD, Gilbert MR, Scheurer ME (2012) Predictors of survival among pediatric and adult ependymoma cases: a study using surveillance, epidemiology, and end results data from 1973 to 2007. *Neuroepidemiology* 39:116–124
7. Armstrong TS, Vera-Bolanos E, Bekele BN, Aldape K, Gilbert MR (2010) Adult ependymal tumors: prognosis and the M. D. Anderson Cancer Center experience. *Neuro Oncol* 12:862–870
8. Bagley CA, Kothbauer KF, Wilson S, Bookland MJ, Epstein FJ, Jallo GI (2007) Resection of myxopapillary ependymomas in children. *J Neurosurg* 106:261–267
9. Bagley CA, Wilson S, Kothbauer KF, Bookland MJ, Epstein F, Jallo GI (2009) Long term outcomes following surgical resection of myxopapillary ependymomas. *Neurosurg Rev* 32:321–334, discussion 334
10. Benesch M, Weber-Mzell D, Gerber NU, von Hoff K, Deinlein F, Krauss J, Warmuth-Metz M, Kortmann RD, Pietsch T, Driever PH, Quehenberger F, Urban C, Rutkowski S (2010) Ependymoma of the spinal cord in children and adolescents: a retrospective series from the HIT database. *J Neurosurg Pediatr* 6:137–144
11. Cameron MM (1976) Surgical management of multiple neuraxial ependymomas. Case report. *Eur Neurol* 14:365–369

12. Cervoni L, Celli P, Fortuna A, Cantore G (1994) Recurrence of spinal ependymoma. Risk factors and long-term survival. *Spine (Phila Pa 1976)* 19:2838–2841
13. Chao ST, Kobayashi T, Benzel E, Reddy CA, Stevens GH, Prayson RA, Kalfas I, Schlenk R, Krishnaney A, Steinmetz MP, Bingaman W, Hahn J, Suh JH (2011) The role of adjuvant radiation therapy in the treatment of spinal myxopapillary ependymomas. *J Neurosurg Spine* 14:59–64
14. Cho JC, Miller A, Kettner NW (2009) Cervical ependymoma in a male adolescent with neck and back pain. *J Manip Physiol Ther* 32:695–700
15. Choi GH, Oh JK, Kim TY, You NK, Lee HS, Yoon do H, Ha Y, Yi S, Kim DS, Choi JU, Kim KN (2012) The clinical features and surgical outcomes of pediatric patients with primary spinal cord tumor. *Childs Nerv Syst* 28:897–904
16. Clover LL, Hazuka MB, Kinzie JJ (1993) Spinal cord ependymomas treated with surgery and radiation therapy. A review of 11 cases. *Am J Clin Oncol* 16:350–353
17. Conter C, Carrie C, Bernier V, Geoffray A, Pagnier A, Gentet JC, Lellouch-Tubiana A, Chabaud S, Frappaz D (2009) Intracranial ependymomas in children: society of pediatric oncology experience with postoperative hyperfractionated local radiotherapy. *Int J Radiat Oncol Biol Phys* 74:1536–1542
18. Di Marco A, Griso C, Pradella R, Camprostrini F, Garusi GF (1988) Postoperative management of primary spinal cord ependymomas. *Acta Oncol* 27:371–375
19. Dulai MS, Caccamo DV, Briley AL, Edwards MS, Fisher PG, Lehman NL (2010) Intramedullary papillary ependymoma with choroid plexus differentiation and cerebrospinal fluid dissemination to the brain. *J Neurosurg Pediatr* 5:511–517
20. Duong LM, McCarthy BJ, McLendon RE, Dolecek TA, Kruchko C, Douglas LL, Ajani UA (2012) Descriptive epidemiology of malignant and nonmalignant primary spinal cord, spinal meninges, and cauda equina tumors, United States, 2004–2007. *Cancer* 118:4220–4227
21. Engelhard HH, Villano JL, Porter KR, Stewart AK, Barua M, Barker FG, Newton HB (2010) Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equina. *J Neurosurg Spine* 13:67–77
22. Fischer G, Mansuy L (1980) Total removal of intramedullary ependymomas: follow-up study of 16 cases. *Surg Neurol* 14:243–249
23. Fujiyama K, Kishikawa M, Fujii H, Moriyama T, Fuchigami K, Iseki M, Shinkai K (1990) Anaplastic ependymoma of the spinal cord in childhood. A case report. *Acta Pathol Jpn* 40:376–382
24. Gilbert MR, Ruda R, Soffiatti R (2010) Ependymomas in adults. *Curr Neurol Neurosci Rep* 10:240–247
25. Gomez DR, Missett BT, Wara WM, Lamborn KR, Prados MD, Chang S, Berger MS, Haas-Kogan DA (2005) High failure rate in spinal ependymomas with long-term follow-up. *Neuro Oncol* 7:254–259
26. Goto T, Ohata K, Takami T, Nishikawa M, Nishio A, Morino M, Tsuyuguchi N, Hara M (2003) Prevention of postoperative posterior tethering of spinal cord after resection of ependymoma. *J Neurosurg* 99:181–187
27. Grill J, Le Deley MC, Gambarelli D, Raquin MA, Couanet D, Pierre-Kahn A, Habrand JL, Doz F, Frappaz D, Gentet JC, Edan C, Chastagner P, Kalifa C (2001) Postoperative chemotherapy without irradiation for ependymoma in children under 5 years of age: a multicenter trial of the French Society of Pediatric Oncology. *J Clin Oncol* 19:1288–1296
28. Hanbali F, Fourney DR, Marmor E, Suki D, Rhines LD, Weinberg JS, McCutcheon IE, Suk I, Gokaslan ZL (2002) Spinal cord ependymoma: radical surgical resection and outcome. *Neurosurgery* 51:1162–1172, discussion 1172–1164
29. Helseth A, Mork SJ (1989) Primary intraspinal neoplasms in Norway, 1955 to 1986. A population-based survey of 467 patients. *J Neurosurg* 71:842–845
30. Helseth E, Due-Tonnessen B, Lote K, Skullerud K, Storm-Mathisen I, Wesenberg F, Lundar T (2001) Ependymoma in children and young adults (0–19 years): report of 25 consecutive cases. *Childs Nerv Syst* 17:24–30
31. Horn B, Heideman R, Geyer R, Pollack I, Packer R, Goldwein J, Tomita T, Schomberg P, Ater J, Luchtman-Jones L, Rivlin K, Lamborn K, Prados M, Bollen A, Berger M, Dahl G, McNeil E, Patterson K, Shaw D, Kubalik M, Russo C (1999) A multi-institutional retrospective study of intracranial ependymoma in children: identification of risk factors. *J Pediatr Hematol Oncol* 21:203–211
32. Hoshimaru M, Koyama T, Hashimoto N, Kikuchi H (1999) Results of microsurgical treatment for intramedullary spinal cord ependymomas: analysis of 36 cases. *Neurosurgery* 44:264–269
33. Jaing TH, Wang HS, Tsay PK, Tseng CK, Jung SM, Lin KL, Lui TN (2004) Multivariate analysis of clinical prognostic factors in children with intracranial ependymomas. *J Neurooncol* 68:255–261
34. Jatana KR, Jacob A, Slone HW, Ray-Chaudhury A, Welling DB (2008) Spinal myxopapillary ependymoma metastatic to bilateral internal auditory canals. *Ann Otol Rhinol Laryngol* 117:98–102
35. Johnson JM, Jessurun J, Leonard A (1999) Sacrococcygeal ependymoma: case report and review of the literature. *J Pediatr Surg* 34:1405–1407
36. Johnson RA, Wright KD, Poppleton H, Mohankumar KM, Finkelstein D, Pounds SB, Rand V, Leary SE, White E, Eden C, Hogg T, Northcott P, Mack S, Neale G, Wang YD, Coyle B, Atkinson J, DeWire M, Kranenburg TA, Gillespie Y, Allen JC, Merchant T, Boop FA, Sanford RA, Gajjar A, Ellison DW, Taylor MD, Grundy RG, Gilbertson RJ (2010) Cross-species genomics matches driver mutations and cell compartments to model ependymoma. *Nature* 466:632–636
37. Kabler HA, Syska BE, Springer BL, Singer JI (2008) Ependymoma as a cause of low back pain in a young healthy athlete. *Pediatr Emerg Care* 24:685–687
38. Kaner T, Sasani M, Oktenoglu T, Solmaz B, Sarloglu AC, Ozer AF (2010) Clinical analysis of 21 cases of spinal cord ependymoma : positive clinical results of gross total resection. *J Korean Neurosurg Soc* 47:102–106
39. Kocak Z, Garipagaoglu M, Adli M, Uzal MC, Kurtman C (2004) Spinal cord ependymomas in adults: analysis of 15 cases. *J Exp Clin Cancer Res* 23:201–206
40. Lee TT, Gromelski EB, Green BA (1998) Surgical treatment of spinal ependymoma and post-operative radiotherapy. *Acta Neurochir (Wien)* 140:309–313
41. Lin YH, Huang CI, Wong TT, Chen MH, Shiau CY, Wang LW, Ming-Tak Ho D, Yen SH (2005) Treatment of spinal cord ependymomas by surgery with or without postoperative radiotherapy. *J Neurooncol* 71:205–210
42. Lonjon M, Goh KY, Epstein FJ (1998) Intramedullary spinal cord ependymomas in children: treatment, results and follow-up. *Pediatr Neurosurg* 29:178–183
43. Massimino M, Gandola L, Giangaspero F, Sandri A, Valagussa P, Perilongo G, Garre ML, Ricardi U, Forni M, Genitori L, Scarzello G, Spreafico F, Barra S, Mascarin M, Pollo B, Gardiman M, Cama A, Navarria P, Brisigotti M, Collini P, Balter R, Fidani P, Stefanelli M, Burnelli R, Potepan P, Podda M, Sotti G, Madon E (2004) Hyperfractionated radiotherapy and chemotherapy for childhood ependymoma: final results of the first prospective AIEOP (Associazione Italiana di Ematologia-Oncologia Pediatrica) study. *Int J Radiat Oncol Biol Phys* 58:1336–1345
44. Mavroudis C, Townsend JJ, Wilson CB (1977) A metastasizing ependymoma of the cauda equina. Case report. *J Neurosurg* 47:771–775
45. McGuire CS, Sainani KL, Fisher PG (2009) Both location and age predict survival in ependymoma: a SEER study. *Pediatr Blood Cancer* 52:65–69

46. McGuire CS, Sainani KL, Fisher PG (2009) Incidence patterns for ependymoma: a surveillance, epidemiology, and end results study. *J Neurosurg* 110:725–729
47. McLaughlin MP, Marcus RB Jr, Buatti JM, McCollough WM, Mickle JP, Kedar A, Maria BL, Million RR (1998) Ependymoma: results, prognostic factors and treatment recommendations. *Int J Radiat Oncol Biol Phys* 40:845–850
48. McLendon RE, Schiffer D, Rosenblum MK, Wiestler OD, Kros JM, Korshunov A, Ng H-K (2007) World Health Organization classification of tumors of the central nervous system. IARC Press, Lyon
49. Merchant TE, Kiehna EN, Thompson SJ, Heideman R, Sanford RA, Kun LE (2000) Pediatric low-grade and ependymal spinal cord tumors. *Pediatr Neurosurg* 32:30–36
50. Merchant TE, Jenkins JJ, Burger PC, Sanford RA, Sherwood SH, Jones-Wallace D, Heideman RL, Thompson SJ, Helton KJ, Kun LE (2002) Influence of tumor grade on time to progression after irradiation for localized ependymoma in children. *Int J Radiat Oncol Biol Phys* 53:52–57
51. Modena P, Lualdi E, Facchinetti F, Veltman J, Reid JF, Minardi S, Janssen I, Giangaspero F, Forni M, Finocchiaro G, Genitori L, Giordano F, Riccardi R, Schoenmakers EF, Massimino M, Sozzi G (2006) Identification of tumor-specific molecular signatures in intracranial ependymoma and association with clinical characteristics. *J Clin Oncol* 24:5223–5233
52. Moon K, Filis AK, Cohen AR (2010) Mobile spinal ependymoma. *J Neurosurg Pediatr* 5:85–88
53. Mork SJ, Loken AC (1977) Ependymoma: a follow-up study of 101 cases. *Cancer* 40:907–915
54. Mork SJ, Risberg G, Krogness K (1980) Case report. Anaplastic ependymoma of the spinal cord. *Neuropathol Appl Neurobiol* 6:307–311
55. Morris DM, Steinert HR, Wiernik PH (1983) Ineffectiveness of chemotherapy in patients with metastatic ependymoma of the cauda equina. *J Surg Oncol* 22:33–36
56. Mridha AR, Sharma MC, Sarkar C, Suri V, Rishi A, Garg A, Suri A (2007) Myxopapillary ependymoma of lumbosacral region with metastasis to both cerebellopontine angles: report of a rare case. *Childs Nerv Syst* 23:1209–1213
57. Nagasawa DT, Trang A, Choy W, Spasic M, Yew A, Zarinkhou G, Garcia HM, Yang I (2013) Genetic expression profiles of adult and pediatric ependymomas: molecular pathways, prognostic indicators, and therapeutic targets. *Clin Neurol Neurosurg* 115:388–399
58. Naidu MR, Dinakar I (1989) Intramedullary mass lesions of the spinal cord. *Clin Neurol Neurosurg* 91:135–138
59. Newton HB, Henson J, Walker RW (1992) Extraneural metastases in ependymoma. *J Neurooncol* 14:135–142
60. Nishio S, Morioka T, Fujii K, Inamura T, Fukui M (2000) Spinal cord gliomas: management and outcome with reference to adjuvant therapy. *J Clin Neurosci* 7:20–23
61. O'Sullivan C, Jenkin RD, Doherty MA, Hoffman HJ, Greenberg ML (1994) Spinal cord tumors in children: long-term results of combined surgical and radiation treatment. *J Neurosurg* 81:507–512
62. Oh MC, Sayegh ET, Safaee M, Sun MZ, Kaur G, Kim JM, Aranda D, Molinaro AM, Gupta N, Parsa AT (2013) Prognosis by tumor location for pediatric spinal cord ependymomas. *J Neurosurg Pediatr* 11:282–288
63. Ohata K, Takami T, Gotou T, El-Bahy K, Morino M, Maeda M, Inoue Y, Hakuba A (1999) Surgical outcome of intramedullary spinal cord ependymoma. *Acta Neurochir (Wien)* 141:341–346, discussion 346–347
64. Oya N, Shibamoto Y, Nagata Y, Negoro Y, Hiraoka M (2002) Postoperative radiotherapy for intracranial ependymoma: analysis of prognostic factors and patterns of failure. *J Neurooncol* 56:87–94
65. Payne NS 2nd, McDonald JV (1973) Rupture of spinal cord ependymoma. Case report. *J Neurosurg* 39:662–665
66. Peker S, Ozgen S, Ozek MM, Pamir MN (2004) Surgical treatment of intramedullary spinal cord ependymomas: can outcome be predicted by tumor parameters? *J Spinal Disord Tech* 17:516–521
67. Pica A, Miller R, Villa S, Kadish SP, Anacak Y, Abusaris H, Ozyigit G, Baumert BG, Zaucha R, Haller G, Weber DC (2009) The results of surgery, with or without radiotherapy, for primary spinal myxopapillary ependymoma: a retrospective study from the rare cancer network. *Int J Radiat Oncol Biol Phys* 74:1114–1120
68. Prayson RA (1999) Clinicopathologic study of 61 patients with ependymoma including MIB-1 immunohistochemistry. *Ann Diagn Pathol* 3:11–18
69. Preston-Martin S (1990) Descriptive epidemiology of primary tumors of the spinal cord and spinal meninges in Los Angeles County, 1972–1985. *Neuroepidemiology* 9:106–111
70. Puget S, Grill J, Valent A, Bieche I, Dantas-Barbosa C, Kauffmann A, Dessen P, Lacroix L, Geoerger B, Job B, Dirven C, Varlet P, Peyre M, Dirks PB, Sainte-Rose C, Vassal G (2009) Candidate genes on chromosome 9q33-34 involved in the progression of childhood ependymomas. *J Clin Oncol* 27:1884–1892
71. Schellinger KA, Propp JM, Villano JL, McCarthy BJ (2008) Descriptive epidemiology of primary spinal cord tumors. *J Neurooncol* 87:173–179
72. Schiffer D, Chio A, Giordana MT, Migheli A, Palma L, Pollo B, Soffietti R, Tribolo A (1991) Histologic prognostic factors in ependymoma. *Childs Nerv Syst* 7:177–182
73. Schiffer D (1997) Brain tumors: biology, pathology, and clinical references. Springer, Berlin
74. Scott M (1974) Infiltrating ependymomas of the cauda equina. Treatment by conservative surgery plus radiotherapy. *J Neurosurg* 41:446–448
75. Smyth MD, Horn BN, Russo C, Berger MS (2000) Intracranial ependymomas of childhood: current management strategies. *Pediatr Neurosurg* 33:138–150
76. Stephen JH, Sievert AJ, Madsen PJ, Judkins AR, Resnick AC, Storm PB, Rushing EJ, Santi M (2012) Spinal cord ependymomas and myxopapillary ependymomas in the first 2 decades of life: a clinicopathological and immunohistochemical characterization of 19 cases. *J Neurosurg Pediatr* 9:646–653
77. Taylor MD, Poppleton H, Fuller C, Su X, Liu Y, Jensen P, Magdaleno S, Dalton J, Calabrese C, Board J, Macdonald T, Rutka J, Guha A, Gajjar A, Curran T, Gilbertson RJ (2005) Radial glia cells are candidate stem cells of ependymoma. *Cancer Cell* 8:323–335
78. Timmermann B, Kortmann RD, Kuhl J, Meisner C, Slavc I, Pietsch T, Bamberg M (2000) Combined postoperative irradiation and chemotherapy for anaplastic ependymomas in childhood: results of the German prospective trials HIT 88/89 and HIT 91. *Int J Radiat Oncol Biol Phys* 46:287–295
79. Volpp PB, Han K, Kagan AR, Tome M (2007) Outcomes in treatment for intradural spinal cord ependymomas. *Int J Radiat Oncol Biol Phys* 69:1199–1204
80. Wahab SH, Simpson JR, Michalski JM, Mansur DB (2007) Long term outcome with post-operative radiation therapy for spinal canal ependymoma. *J Neurooncol* 83:85–89
81. Waldron JN, Laperriere NJ, Jaakkimainen L, Simpson WJ, Payne D, Milosevic M, Wong CS (1993) Spinal cord ependymomas: a retrospective analysis of 59 cases. *Int J Radiat Oncol Biol Phys* 27:223–229
82. Wen BC, Hussey DH, Hitchon PW, Schelper RL, Vigliotti AP, Doornbos JF, VanGilder JC (1991) The role of radiation therapy in the management of ependymomas of the spinal cord. *Int J Radiat Oncol Biol Phys* 20:781–786
83. Whitaker SJ, Bessell EM, Ashley SE, Bloom HJ, Bell BA, Brada M (1991) Postoperative radiotherapy in the management of spinal cord ependymoma. *J Neurosurg* 74:720–728
84. Yasui T, Hakuba A, Katsuyama J, Nishimura S (1988) Microsurgical removal of intramedullary spinal cord tumours: report of 22 cases. *Acta Neurochir Suppl (Wien)* 43:9–12