ORIGINAL ARTICLE doi: 10.2176/jns-nmc.2022-0027

Neurol Med Chir (Tokyo) 62, 322-327, 2022 Online May 10, 2022

Prognostic Factors and Histopathological Features of Pediatric Intracranial Ependymomas: Nationwide Brain Tumor Registry-based Study of Japan

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Abstract

To assess the clinicopathological features and prognostic factors of pediatric intracranial ependymomas and to explore the current diagnostic practice, we analyzed clinical data from the Brain Tumor Registry of Japan (BTRJ). Data of fifty children under 18 years of age diagnosed with intracranial ependymoma were extracted from the BTRJ database. Cases were reviewed for overall survival (OS) and progression-free survival (PFS), with attention to gender, preoperative Karnofsky performance status score, location of the tumor, the extent of resection, World Health Organization (WHO) histopathological grading, and adjuvant therapy. The median age at diagnosis was 6.1 years, ranging from 7 months to 17.6 years. Based on the WHO histopathological grading, 27 patients were classified under grade 2 (54%) and 23 patients were classified under grade 3 (46%). Gross total resection (GTR) was achieved in 30 patients (60%). The median follow-up time was 65 months. Five-year PFS and OS were 47.2 ± 7.3% and 73.3 ± 6.7%, respectively. GTR was associated with longer OS (P = 0.02). The histopathological grading was not an independent prognostic factor for the OS. Mitosis and microvascular proliferation were higher among patients with grade 3 than in those with grade 2, which aided in deciding the WHO grade. This nationwide study revealed the characteristics and outcomes of patients with childhood ependymomas. GTR was the factor most consistently associated with improved survival. In contrast, the histopathological grading in this cohort was not a significant prognostic factor. More reproducible and practical criteria for the diagnosis of intracranial ependymomas should be further pursued in future studies.

Keywords: pediatric ependymoma, histopathological grading, prognostic factors

Introduction

Ependymomas were traditionally thought to arise from ependymal cells of the ventricular lining of the brain and the spinal cord. However, there is now evidence that radial glial cells are candidate stem cells of ependymoma.[1)] In children, intracranial ependymoma is the third most common type of brain tumor, accounting for 5.2% of all intracranial tumors.[2)] Gross total resection (GTR) is the most important factor associated with improved survival.[3-6)] Besides that, postoperative conformal radiotherapy with doses up to 59.4 Gy is recommended for children older than 18 months in terms of local control and survival rates.[6)] Intracranial ependymomas are prone to relapse; however, the

Received January 31, 2022; Accepted March 17, 2022

prognosis is dismal.[4)]

According to the classification of central nervous system (CNS) tumors in 2016 by the WHO, ependymal tumors are classified into five subgroups: subependymoma (grade 1), myxopapillary ependymoma (grade 1), ependymoma (grade 2), RELA fusion-positive ependymoma (grade 2 or 3), and anaplastic ependymoma (grade 3).[7)] Accurate histopathological grading of ependymoma can be difficult, because clear consensus is not required for the diagnosis of anaplastic ependymoma.[8,9)] The role of histological grading of ependymoma for risk stratification has been controversial due to the difficulty in grading and tumor heterogeneity compared with most other CNS tumors.[8-10)] A recent molecular classification has distinguished nine subgroups of ependymal tumors that appear to reflect the prognosis more precisely than histopathology alone.[11,12)] However, these classifications have not yet become routinely available in clinical practice. To assess the clinicopathological features and prognostic factors of pediatric intracranial ependymomas, this study analyzes clinical data from the Brain Tumor Registry of Japan (BTRJ). An additional questionnaire survey was conducted to explore the current practice of histopathological grading in pediatric intracranial ependymomas.

Materials and Methods

Ethics

This study was carried out in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the institutional review boards of Wakayama Medical University (No. 1305) and the National Cancer Center Japan (No. 20-038). The requirement of written informed consent from the patients was waived by the above-mentioned boards owing to the use of retrospective anonymized data.

Patient cohort

This is a retrospective review of 57 patients under 18 years of age at the time of diagnosis of WHO grade 2 and grade 3 intracranial ependymoma from the BTRJ registry between 2001 and 2004. Seven patients who had less than six months of follow-up were excluded. Data obtained from the BTRJ database included patient demographics, preoperative Karnofsky performance status (KPS) score, the extent of resection (EOR), WHO histopathological grading, anatomical location, adjuvant radiation and chemotherapy regimens, progression-free survival (PFS) time, and overall survival (OS) time. EOR was classified as either ≥95% or <95% according to the surgeon's assessment. An additional survey was sent to the hospitals enrolled in the BTRJ: a questionnaire regarding the histopathological features including tissue architecture, the presence of necrosis, vascular proliferation, mitosis, and immunohistochemistry, and how the pathologist made the WHO grading.

Table 1 Patient demographic and clinical characteristics

	Mean	Range
Age at diagnosis (years)	6.1	0.7-17.8
	Frequency (*N*)	Percent (%)
Gender		
Male	31	62
Female	19	38
WHO grading		
2	27	54
3	23	46
Histology		
Ependymoma, NOS	23	46
Cellular	2	4
Tancytic	1	2
Myxopapillary	1	2
Anaplastic	23	46
Anatomical location		
Supratentorial	20	40
Infratentorial	30	60
Preoperative KPS score		
80-100	31	62
0-70	19	38
Extent of resection		
≥95%	30	60
<95%	18	36
Unknown	2	4
Adjuvant therapy		
Radiation	17	34
Chemotherapy	8	16
Radiation + chemotherapy	10	20
None	15	30

Statistical analysis

Statistical analysis was performed using the SAS package and JMP Pro version 14 (SAS Institute, Cary, NC, USA, 2021). Categorized data were compared between subgroups using the chi-squared test. The PFS and OS curves were obtained by the Kaplan-Meier method and compared with a log-rank test. Multivariate analyses of risk factors were performed using the Cox proportional hazards model. A P value of <0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

Fifty children with intracranial ependymoma were included in the study. The demographic and clinical characteristics of the institutional cohort are summarized in Table 1. The median age was 6.1 years (0.7-17.6 years), and the median KPS score was 80 (40-90). Overall, there were

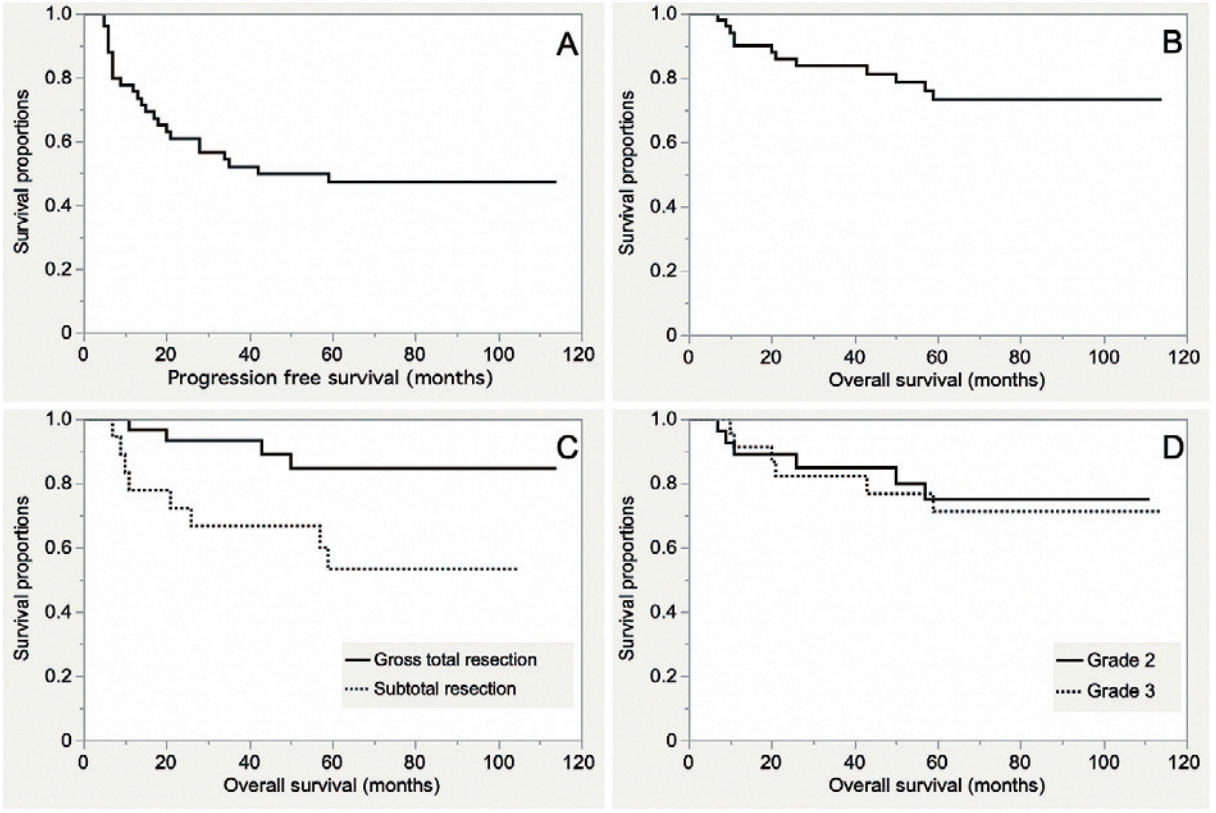

Fig. 1 Kaplan-Meier survival curves of pediatric intracranial ependymomas from the Brain Tumor Registry of Japan. A: Progression-free survival (PFS) of all cases. B: Overall survival (OS) of all cases. C: Gross total resection (GTR) was significantly associated with the OS (P = 0.02). D: There was no significant difference in survival between the WHO histopathological grades 2 and 3 (P = 0.78).

19 females (38%) and 31 males (62%). Twenty patients had supratentorial location (40%) and 30 had infratentorial location (60%). Patients with good preoperative KPS scores (80-100) accounted for 62% (31 patients). Based on the WHO histopathological grading, 27 patients were classified under grade 2 (54%) and 23 patients were classified under grade 3 (46%). The extent of surgery was as follows: 30 received GTR (60%), 18 received subtotal resection or biopsy (36%), and 2 had unknown surgical status (4%). Seventeen patients received radiation (34%), 8 received chemotherapy (16%), 10 received chemoradiation (20%), and 15 received no adjuvant therapy (30%).

Prognostic factors for survival outcomes

The median follow-up time was 65 months. Five-year PFS and OS were 47.2 ± 7.3% and 73.3 ± 6.7%, respectively (Fig. 1A and B). In univariate analysis, GTR was significantly associated with a longer OS (log-rank, P = 0.02, Fig. 1C). Males had a longer OS compared with female patients, but this failed to reach statistical significance (Table 2). No other clinical variables were associated with the outcomes in this cohort (Table 2 and Supplement Fig. 1, available online). The histopathological grading (WHO grade 2 vs. grade 3) was not a significant prognostic factor (log-rank, P = 0.78, Fig. 1D). On multivariate regression analysis, GTR was independently associated with longer survival (HR: 3.32, 95% CI: 1.03-12.64, P = 0.04, Table 3).

Questionnaire survey regarding histopathological features and decisions on the malignancy

Survey responses were collected from 30 institutions. Mitosis and microvascular proliferation (MVP) were significantly more likely to be seen in grade 3 than in grade 2 (mitosis; P = 0.048, MVP; P = 0.009, Table 4). The histopathological grading was determined based on the overall structure (13%), mitosis (13%), high cellularity (6.6%), atypia (3.3%), and high MIB-1 labeling index (10%, overlapping with other categories). However, 63% of participants did not provide a clear answer on the criteria for the discrimination of the grading.

Discussion

This report features data from 50 pediatric patients with ependymomas from the BTRJ. GTR was associated with significantly improved OS, as previously reported.[3-6] Males tended to have a longer OS compared with female patients, unlike a previous study.[13] On the other hand, tradi-

Table 2 Univariate prognostic factors of the progression-free survival (PFS) and overall survival (OS)

Demographic and clinical factors		Frequency (%)	5-year		5-year	
			PFS ± SE (%)	*P* values	OS ± SE (%)	*P* values
Age at diagnosis (years)	0-2	26	46.1 ± 13.8	0.74	57.1 ± 14.8	0.2
	3-17	74	47.9 ± 8.6		79.5 ± 7.0	
Gender	Male	62	52.6 ± 9.2	0.44	80.9 ± 7.8	0.08
	Female	38	38.9 ± 11.7		61.2 ± 11.7	
WHO grading	2	54	54.6 ± 9.8	0.35	74.9 ± 9.0	0.78
	3	46	44.5 ± 9.4		71.2 ± 10.1	
Anatomical location	Supratentorial	40	52.4 ± 11.6	0.46	84.0 ± 8.5	0.2
	Infratentorial	60	23.0 ± 2.2		65.5 ± 9.6	
Preoperative KPS score	80-100	62	55.8 ± 9.3	0.05	82.7 ± 7.1	0.13
	0-70	38	33.3 ± 11.1		59.0 ± 12.1	
Extent of resection	GTR (≥95%)	60	49.8 ± 9.1	0.53	84.5 ± 7.2	0.02
	STR (<95%)	36	37.4 ± 12.4		53.3 ± 12.3	
Adjuvant therapy	None	30	37.3 ± 13.2	0.23	68.9 ± 13.3	0.4
	Radiation therapy	34	62.7 ± 12.1		63.7 ± 11.9	
	Chemotherapy	16	57.1 ± 18.7		NA	
	Chemoradiation therapy	20	30.0 ± 14.5		78.8 ± 13.4	

Table 3 Multivariate prognostic factors of the overall survival (OS)

Demographic and clinical factors	Hazard ratio (95%Cl)	*P*-value
Gender (female)	2.32 (0.71-8.01)	0.15
Extent of resection (STR)	3.32 (1.02-12.6)	0.04

tional histopathological grading was not a prognostic factor in this cohort.

There has been a longstanding controversy over reproducibility and clinicopathological utility of the grading in ependymomas. The 2016 WHO classification distinguishes the anaplastic (grade 3) from the classic (grade 2) ependymoma based on high cellularity and mitotic activity accompanied by MVP and necrosis.[7] Distinction between grade 2 and grade 3 is often difficult, however, and interobserver reproducibility is poor. Expert neuropathologists reviewed the 130 samples from the Japan Pediatric Molecular Neuro-Oncology Group study; consensus regarding the diagnosis of ependymoma was 77% in supratentorial tumors diagnosed by local pathologists.[14] In addition, five expert neuropathologists reviewed the pathology from three European clinical trials, and the proportions of ependymomas allocated grade 2 and grade 3 ranged from 19% to 59% and 41% to 81% respectively.[8] Confirmed high proliferating activity of tumor cells including increased mitotic activity (at least 5/10 HPF) and/or high MIB-1 labeling index (>10%) was considered to be the most reproducible and reliable criteria for anaplastic ependymomas.[14] In the current study, mitosis and MVP were more prevalent in grade 3 than in grade 2, which contributed to the ease of diagnosis. Furthermore, while the role of histopathological grading in predicting survival has been controversial, our data also suggested that traditional histopathological classification did not provide a sufficient prognostic stratification.

In the 2021 WHO classification, ependymomas were classified according to a combination of histopathological and molecular features as well as anatomic sites including the supratentorial, infratentorial, and spinal compartments.[12,15] The term "anaplastic ependymoma" is no longer listed. A pathologist can assign either WHO grade 2 or 3 to an ependymoma, according to the histopathological features. Despite potential benefits in terms of prognostication and therapeutic decisions, molecular diagnoses have not yet become routinely available in current clinical practice. Several immunohistochemical markers have been reported to be effective surrogates for molecular diagnosis in ependymomas. In supratentorial ependymomas, both L1 CAM and NF-kB p65 could be useful surrogate diagnostic markers for ZFTA fusion-positive ependymoma.[13] H3K27-trimethylation immunostaining can also be used to distinguish between group A posterior fossa ependymoma and group B posterior fossa ependymoma.[16] More practical and accurate diagnostic markers are required for the routine diagnostics of pediatric ependymomas.

This study has a few limitations. First, owing to the multi-institutional retrospective design, there could be selection bias affecting the decision-making on the treatment strategy. Second, the comparatively small number of pa-

Table 4 Comparison of histological features in grade 2 and grade 3

Histological features		Grade 2		Grade 3		
		N	Frequency (%)	*N*	Frequency (%)	
Cellularity	Low	3	20.0	0	0.0	*P* = 0.068
	Moderate	9	60.0	5	41.7	
	High	3	20.0	7	58.3	
Mitosis	None	9	60.0	2	22.2	*P* = 0.048
	1-4/HPF	5	33.3	2	22.2	
	≥5/HPF	1	6.7	5	55.6	
Microvascular proliferation	Yes	2	12.5	7	70.0	*P* = 0.009
	No	14	87.5	3	30.0	
Necrosis	Yes	7	41.2	7	63.6	*P* = 0.44
	No	10	58.8	4	36.4	
MIB-1 labeling index	<5%	6	54.5	2	18.2	*P* = 0.08
	5-9%	2	18.2	2	18.2	
	10-19%	3	27.3	2	18.2	
	≥20%	0	0	5	45.5	

tients could explain the absence of statistical power to detect differences between groups. Third, there is a lack of information regarding molecular subtypes. Future studies should pursue a further prospective analysis of long-term outcomes within molecular subtypes to identify better overall patient care and to decrease all-cause mortality rates. Lastly, since a retrospective study of intracranial ependymomas from the BTRJ registry between 2005 and 2008 is in progress, this study analyzed data from the BTRJ registry between 2001 and 2004.

Conclusions

This nationwide study reveals the characteristics and outcomes of pediatric patients with intracranial ependymomas. GTR was the most consistent factor associated with improved survival. Histopathological grading was not a prognostic factor in this cohort, however, confirming the unreliability of the current histopathological grading. Future studies of intracranial ependymomas should pursue more reproducible diagnostic criteria.

Supplementary Material

https://doi.org/10.2176/jns-nmc.2022-0027

Acknowledgments

The authors thank all the BTRJ members for their continuous support in registering their data. We also thank Sasajima T (Akita University), Sonoda Y (Tohoku University), Sakurada K (Yamagata University), Saito K (Fukushima Medical University), Muragaki Y (Tokyo Women's Medical University), Sugo N (Toho University, Omori Medical Center), Tanioka D (Showa University), Sugawara T (Tokyo Medical and Dental University), Kobayashi K (Kyorin University), Miyajima Y (Kitasato University), Furura T (Kanazawa University), Sakata T (Nagoya City University), Osuka K (Aichi Medical University), Yano H (Gifu University), Nakagawa O (Kinki University), Fukami T (Shiga University of Medical Science), Kurozumi K (Okayama University), Yamasaki R (Nagasaki University), Takeishi G (University of Miyazaki), Miyakita Y (National Cancer Center Hospital), Ito T (Nakamura Memorial Hospital), Yamashita T (Yamaguchi Grand Medical Center), and Kawakami M (Ohta Nishinouchi Hospital) for their contributions to the secondary survey regarding the histopathological features. We acknowledge proofreading and editing by Benjamin Phillis at the Clinical Study Support Center at Wakayama Medical University.

Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest.

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