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Case study

Recursive partitioning analysis for disease progression in adult intracranial ependymoma patients

Sang Woo Song [a], Yun-Sik Dho [b], Jin Wook Kim [b], Yong Hwy Kim [b], Sun Ha Paek [b], Dong Gyu Kim [b], Hee-Won Jung [c], Sung-Hye Park [d], Seung Hong Choi [e], Tae Min Kim [f], Soon-Tae Lee [g], Il Han Kim [h], Sang Hyung Lee [c,*,1], Chul-Kee Park [b,*,1]

[a] Department of Neurosurgery, Konkuk University College of Medicine, Konkuk University Medical Center, Seoul, Republic of Korea
[b] Department of Neurosurgery, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[c] Department of Neurosurgery, Seoul National University College of Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea
[d] Department of Pathology, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[e] Department of Radiology, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[f] Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[g] Department of Neurology, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[h] Department of Radiation Oncology, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Republic of Korea

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ABSTRACT

Intracranial ependymomas are rare tumors in adults. Although recent advancements from demographic, clinical, and biological studies provide new perspectives on this rare tumor, they are not yet widely applied in clinical practice. Currently, most ependymoma patients are treated in the same way: via surgical resection with adjuvant radiation therapy. However, it is reasonable to apply more aggressive treatment for high-risk patients. From this point of view, we performed a study to investigate risk grouping for disease progression of intracranial ependymomas in adults. A total of 53 patients were included in this study. Data were extracted for patient and tumor characteristics, extent of resection, progression-free survival (PFS), and overall survival. Prognostic variables from univariate and multivariate survival analyses were included in a recursive partitioning analysis for the hierarchical risk grouping of the estimated PFS. Three risk groups were defined based on the clinical prognostic factors. Survival analysis showed significant differences in mean PFS between the different groups: 160.5 ± 22.1 months in the complete resection group, 100.4 ± 36.8 months in the incomplete-resection and intraventricular-location group, and 23.5 ± 6.9 months in the incomplete-resection and extraventricular-location group ($p < 0.001$). The risk of disease progression in adult intracranial ependymoma patients could be stratified by degree of resection and tumor location. In clinical practice, this result could provide useful information, such as when "second-look" surgery should be performed or whether small tumors invading the fourth ventricle floor should be resected at the expense of neurological deficit.

1. Introduction

Ependymal tumors are rare in the central nervous system (CNS), accounting for 1.9% of all primary CNS tumors [1]. The age-related incidence of ependymomas is greatly affected by location. Although ependymoma is the fourth most common primary CNS tumor in children younger than 4 years and the third most common histopathology among adult primary spinal tumors, adult intracranial ependymomas are relative very rare, accounting for less than 3% of all intracranial neuroepithelial tumors [1,2].

Many uncertainties in the natural course and overall survival of patients with ependymomas have recently been unearthed through extensive studies using population-based or online surveys, such as the Surveillance Epidemiology and End Results (SEER), Central Brain Tumor Registry of the United States (CBTRUS), and Adult Ependymoma Outcomes (AEO) projects [3–8]. Furthermore, there have been remarkable advancements in the molecular profiling of ependymomas in recent several years [9–12] and the

* Corresponding authors at: Department of Neurosurgery, Seoul National University College of Medicine, Seoul National University Boramae Medical Center, 20 Boramae-ro 5-gil, Dongjak-gu, Seoul, Republic of Korea (S.H. Lee). Department of Neurosurgery, Seoul National University College of Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Republic of Korea (C.-K. Park).

E-mail addresses: nslee@snu.ac.kr (S.H. Lee), nsckpark@snu.ac.kr (C.-K. Park).

[1] These authors contributed equally to this work.

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revised fourth edition of the World Health Classification (WHO) of Tumors of the CNS reflects some of these new perspectives [13]. There are two major areas of general consensus that have been established from these demographic and molecular data. First, molecular subgrouping is superior to histopathological grading in the prediction of clinical outcomes. Second, supratentorial (ST) ependymoma and posterior fossa (PF) ependymoma harbor separate genomic characteristics in spite of the same pathohistological findings [14]. However, all of this update knowledge has yet to be applied in routine clinical practice. The current management of intracranial ependymomas is still largely dependent on surgical resection with or without radiotherapy.

Ependymoma in adults differs from that in children in regard to its preferential location, clinical outcomes, and underlying molecular biology, and hence, phenomena observed in children may not necessarily apply to adults [2,15]. A considerable number of patients with adult intracranial ependymomas will eventually relapse. In the absence of established treatments for recurrent ependymomas, prevention of disease progression should be the core value of management in adult patients with intracranial ependymoma. Recently, a multi-institutional study from the Collaborative Ependymoma Research Network (CERN) including 282 adult ependymoma patients reported that ST tumor location, anaplastic histology, and incomplete tumor resection are associated with a shorter progression-free survival (PFS) [16]. This implies the significance of clinical variables for the prognosis of adult ependymoma patients. Taking a step forward from the previous data, we tried to stratify the risk groups for disease progression in adult intracranial ependymoma patients using recursive partitioning analysis (RPA). RPA, which was initially described by the Radiation Therapy Oncology Group, is a useful tool that can divide patients into homogenous groups based on the length of survival [17].

2. Materials and methods

This study was approved by the institutional review board. Based on prospectively collected brain tumor data from the adult neurosurgical clinic database of the Seoul National University Hospital, 65 consecutive patients were diagnosed as having intracranial ependymoma after surgical resection from August 1988 and January 2015. Among these patients, a total of 53 were included in this analysis; we excluded 4 patients younger than 18 years, 3 patients with a follow-up duration shorter than 24 months, 2 patients with neurofibromatosis, one patient without any available clinical radiological data, one patient with a previous history of brain irradiation, and one patient with intracranial metastasis from spinal myxopapillary ependymoma. Histological diagnoses were re-evaluated according to the WHO 2007 classification by a senior neuropathologist [18]. Pathologic findings known to be important diagnostic tools in neuro-glial tumors were also analyzed to establish their relationship with clinical outcomes in available patients.

Clinical data, such as age, sex, performance status, extent of resection and treatment modality, were retrospectively collected and are summarized in Table 1. The mean and median follow-up durations were 97.8 months and 59.1 months, respectively (range, 7.3–341.7 months). Twenty-two patients (41.5%) were male and 31 (58.5%) were female, with a median age of 38 years (range, 18–65 years). The patients' ages were dichotomized according to median age. Performance status was scored according to the Eastern Cooperative Oncology Group (ECOG) [19]. We analyzed the tumor location in two ways: infratentorial location vs supratentorial location and intraventricular location vs extraventricular location. An intraventricular location was defined when the tumor was located in any ventricular system, while tumors within brain parenchyma and extra-axial locations, such as the cerebellopontine angle, were considered extraventricular. The degree of resection was preferentially determined by a review of postoperative and follow-up MR imaging studies or CT scanning. Complete resection was defined when no residual tumor was seen on contrast T1-weighted or T2-weighted images or on contrast CT images; otherwise cases were defined as an incomplete resection. PFS was calculated from the date of initial surgery to the date of recurrence, progression, death or last radiologic follow-up, whereas overall survival (OS) was calculated from the date of surgery to the date of death. Data for patients who were alive were classified as censored at the time of the last follow-up.

Table 1
Correlations between Baseline characteristics according to histologic grade and locations in adult intracranial ependymomas patients.

	All	Histologic grade		p-value	Location 1		p-value	Location 2		p-value
		WHO grade II	WHO grade III		Infra-tentorial	Supra-tentorial		Intra-ventricular	Extra-ventricular	
Total, n	53	35	18		34	19		31	22	
Gender										
Male	22	13	9	0.368	13	9	0.570	12	10	0.778
Female	31	22	9		21	10		19	12	
Age										
<38 years-old	26	18	8	0.630	15	11	0.398	16	10	0.782
≥38 years-old	27	17	10		19	8		15	12	
ECOG										
ECOG grade 0 or 1	40	26	14	0.780	26	14	1.000	24	16	0.753
ECOG grade ≥2	13	9	4		8	5		7	6	
Histologic grade										
WHO grade 2	35	35	0		25	10	0.143	22	13	0.394
WHO grade 3	18	0	18		9	9		9	9	
Extent of resection										
Complete resection	29	16	13	0.066	18	11	0.780	18	11	0.588
Incomplete resection	24	19	5		16	8		13	11	
*Use of adjuvant radiation										
Yes	37	19	18	0.001	24	13	0.869	23	14	0.409
No	16	16	0		10	6		8	8	

Abbreviations: WHO, World Health Organization; ECOG, Eastern Cooperative Oncology Group.
* Adjuvant radiation includes external beam radiation and stereotactic radiosurgery.

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