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Clinical Study

Treatment and survival of supratentorial and posterior fossa ependymomas in adults

Miriam Nuño *, Jeffrey J. Yu, Kunal Varshneya, Julia Alexander, Debraj Mukherjee, Keith L. Black, Chirag G. Patil

Center for Neurosurgical Outcomes Research, Maxine Dunitz Neurosurgical Institute, Department of Neurosurgery, Cedars-Sinai Medical Center, Advanced Health Sciences Pavilion, 127 S. San Vicente Boulevard, Suite A6229, Los Angeles, CA 90048, USA

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ABSTRACT

Ependymoma is a rare primary brain or spinal cord tumor that arises from the ependyma, a tissue of the central nervous system. This study analyzed a large cohort of adult supratentorial and posterior fossa ependymoma tumors in order to elucidate factors associated with overall survival. We utilized the USA National Cancer Database to study adult World Health Organization grade II/III supratentorial and posterior fossa ependymoma patients treated between 1998 and 2011. Overall survival was estimated by the Kaplan–Meier method and factors associated with survival were determined using a multivariate Cox proportional hazards model. Among 1318 patients, 1055 (80.0%) had grade II and 263 (20.0%) anaplastic tumors located in the posterior fossa (64.3%) and supratentorial region (35.7%). Overall average age was 44.3 years, 48.0% of patients were female, 86.5% were Caucasian, and 36.8% underwent near/gross total surgical resection. Radiotherapy was given to 662 patients (50.8%) and 75 (5.9%) received chemotherapy. Older age at diagnosis (hazard ratio [HR] 1.51, $p < 0.0001$), high tumor grade (HR 1.82, $p = 0.005$), and large tumor size (HR 1.66, $p = 0.008$) were associated with poor survival. Females compared to males (HR 0.67, $p = 0.03$) and patients with posterior fossa tumors *versus* supratentorial (HR 0.64, $p = 0.04$) had a survival advantage. Our study showed that older patients, with supratentorial tumors, and high histological grade had an increased risk of mortality. A survival benefit was captured in females and patients with posterior fossa tumors. Adjuvant radiotherapy and chemotherapy did not confer a survival benefit among all patients, even after stratification by tumor grade or anatomical location.

1. Introduction

Ependymoma tumors are rare, accounting for 1.9–3.5% of all primary brain and central nervous system (CNS) tumors [1]. Ependymomas are found throughout the CNS in the supratentorial, posterior fossa and spinal compartments. Nearly 40% of adult ependymoma tumors are intracranial but most occur in the spinal cord. They make up about 5% of adult intracranial gliomas of the CNS [1–4]. The World Health Organization (WHO) classifies ependymoma into grade III anaplastic, grade II, and grade I (myxopapillary occurring in the spine, and subependymoma occurring across all compartments). Numerous studies have illustrated several limitations with WHO histological classification for ependymomas, particularly among grade II and III [5–7]. Distinct genetic, epigenetic alterations, and transcriptional programs have been documented for histologically similar variants of ependymomas [3,8–15]. While benign ependymomas are characterized by small size, slow growth and location, anaplastic tumors develop with a much higher proliferative rate and often spread to other locations in the intracranial hemisphere through cerebrospinal fluid [16]. Presenting symptoms include morning headaches, drowsiness and irritability [13,17]. Treatment for ependymomas includes maximal safe surgical resection, followed by focal radiotherapy, however standard of care remains actively debated [18–21]. Postoperative adjuvant therapy with radiation and chemotherapy is often utilized to treat patients diagnosed with high grade ependymoma. But no evidence supports this approach as a first line of treatment [22].

Recent studies have analyzed incidence, optimal treatments, and survival rates of grade II and III ependymoma tumors [14,17,23–25]. However, due to the scarcity of ependymoma cases, comparative analysis which aimed to evaluate associations between patient, tumor, and treatment characteristics and overall survival have yielded little success. Most importantly, however, these studies neglect recent evidence that supports the superiority

* Corresponding author. Tel.: +1 310 423 8506; fax: +1 310 423 8400.
E-mail address: miriam.nuno@cshs.org (M. Nuño).

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of molecular subgrouping for risk stratification in patients diagnosed with ependymal tumors [15]. Due to these challenges, optimum management of adult patients diagnosed with ependymoma tumors remains controversial [20]. Utilizing a large cohort of adult supratentorial and posterior fossa patients, this study aimed to evaluate the role of patient baseline factors, tumor characteristics, and adjuvant therapies on overall survival.

2. Data and methods

2.1. Study population

The National Cancer Database (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society containing outcomes data from more than 1500 cancer programs in the USA and Puerto Rico. Grade II and III ependymoma tumor cases were identified according to the *International Classification of Disease for Oncology, Third Edition* (ICD-O-3) histology codes 9391 (ependymoma-WHO grade II) and 9392 (anaplastic ependymoma-WHO grade III), and 9393 (papillary ependymoma-WHO grade II). Adult patients (18 years and older) with a WHO histologically confirmed primary ependymoma that underwent surgical resection were included in this study. Patients diagnosed with grade I myxopapillary or subependymoma tumors (ICD-O-3 codes 9394) were excluded. Collaborative stage site-specific factor 1 and grade variables were utilized to discern grade II and III tumors in this study. Only patients with brain tumors located in the posterior fossa and supratentorial region were included. In light of recent evidence supporting strong correlation between ependymoma subcategories and survival, this study considered a cohort that is mostly consistent with the subgroups ependymoma-posterior fossa type B (PFB) and ependymoma-supratentorial (RELA) previously identified in the landmark study by Pajtler et al. (Table 1) [15].

2.2. Variables

Patient baseline information included age at diagnosis in years, sex, race, median household income, tumor site and size, comorbidities, and hospital type. Extent of surgical resection, adjuvant radiotherapy and chemotherapy were described in detail; therapies were prescribed as a first course of treatment following surgery. Tumor size was dichotomized into clinically relevant categories. Due to low frequencies of patients in the non-Caucasian cohorts, we categorized rate into Caucasian *versus* non-Caucasian. Overall survival was estimated as the time from diagnosis to the date of death or last known contact with patients. Survival data was available in 799 (60.6%) patients of our original cohort (N = 1318).

Table 1
Molecular subclassification of ependymal tumors by anatomical site, histology, grade and age as previously derived by Pajtler et al. [15] Grey-shaded regions correspond to cohorts that are consistent with the current study

	Posterior fossa tumors			Supratentorial tumors		
Patient characteristics	SE	EPN-PFA	EPN-PFB	SE	EPN-YAP	EPN-RELA
Patients, n	33	240	51	21	113	88
Age in years						
<4	0 (0)	131 (58)	0 (0)	0 (0)	8 (62)	20 (24)
4–18	0 (0)	93 (41)	9 (19)	0 (0)	4 (30)	44 (52)
>18	29 (100)	2 (1)	38 (81)	13 (100)	1 (8)	20 (24)
Histologic grade						
I	21 (66)	0 (0)	0 (0)	14 (67)	0 (0)	0 (0)
II	10 (31)	69 (30)	29 (59)	7 (33)	5 (42)	20 (23)
III	1 (3)	160 (70)	20 (41)	0 (0)	7 (58)	66 (77)

Subgroups EPN-PFB and EPN-RELA described in shaded areas reflect age and tumor histologies (age 18+, histological grade II/III) that are generally consistent with the cohort of patients analyzed in the present study.
Data are presented as number (%) unless otherwise stated.
EPN = ependymoma, PFA = posterior fossa type A, PFB = posterior fossa type B, SE = subependymoma, RELA = expressing the *C11orf95–RELA* fusion protein, ST = supratentorial, YAP = yes-associated protein.

2.3. Statistical methods

Descriptive statistics were reported for all patients as well as by subgroups according to anatomical site, tumor grade, and extent of surgical resection. Continuous variables were described by means, medians, and interquartile ranges; categorical variables were reported in frequencies. Differences in patient characteristics and treatment by tumor grade were evaluated with the chi-square and Student's t-tests; non-parametric tests were utilized when applicable. Survival was estimated by the Kaplan–Meier method and a multivariate Cox proportional hazards model was used to evaluate associations between patient, tumor, and treatment factors and overall survival. Hazard ratio (HR), 95% confidence intervals (CI) and p values are reported throughout. Multivariate analysis was utilized to account for known confounders such as patient age, tumor size, tumor location, and extent of surgical resection. Tumor size was imputed in the Cox proportional hazards model and did not impact all other estimates adjusted in the multivariate model. A p value cut-off of 0.05 was considered statistically significant. All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline demographics

A total of 1318 patients met the inclusion criteria. Of these, 1055 (80.0%) harbored grade II ependymoma tumors and 263 (20.0%) anaplastic tumors (Table 2). Overall, the median age at diagnosis was 43 years, 86.5% of patients were Caucasian, and tumors were mainly located in the posterior fossa (64.3%) and supratentorial region (35.7%). Tumors $\geqslant$4 cm were documented in 46.9% of patients and most patients did not report any comorbidities (83.3%). Most cases were treated at academic (52.7%) and comprehensive community (41.7%) hospitals. Univariate differences between grade II and anaplastic cohorts were captured by tumor location and size (Table 2). More grade II tumors were located in the posterior fossa than anaplastic (74.7% *versus* 22.8%, $p < 0.0001$). The fraction of patients with large tumors ($\geqslant$4 cm) was higher in the anaplastic cohort than grade II (65.9% *versus* 41.8%, $p < 0.0001$).

3.2. Treatment utilization

Near/gross total surgical resection was achieved in 36.8% of patients (Table 3). Six hundred sixty-two patients (50.8%) received radiotherapy and only 75 (5.9%) were treated with chemotherapy as a first course of treatment. Most patients received external beam (46.8%), photon (24.6%), and intensity modulated radiation therapy (24.0%) modalities of radiotherapy. The average time from diagnosis to radiation was 63.9 days, and 51.0 days for chemotherapy. A greater fraction of patients with anaplastic ependymomas received radiation (76.4% *versus* 44.3%, $p < 0.0001$) and chemotherapy (21.1% *versus* 2.1%, $p < 0.0001$) than grade II. The median time to