Published in final edited form as:

J Clin Neurosci. 2014 December ; 21(12): 2096–2101. doi:10.1016/j.jocn.2014.05.011.

Prognosis by tumor location in adults with intracranial ependymomas

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Abstract

Intracranial ependymomas are rare tumors in adults. Thus, factors affecting prognosis are poorly understood. We performed a study to investigate whether tumor location is an important prognostic factor in adults who undergo surgery for intracranial ependymomas. PubMed was searched to identify studies that reported clinical outcomes in adult patients with intracranial ependymoma. Data were extracted for patient and tumor characteristics, extent of resection, progression-free survival (PFS), and overall survival (OS). Tumors were categorized as supratentorial or infratentorial and extraventricular or intraventricular. Presenting clinical features and tumor characteristics were tabulated. Kaplan–Meier and multivariate Cox regression survival analyses were performed to determine PFS and OS by tumor location. Extent of resection was also analyzed by tumor location. A total of 183 patients were included in the metaanalysis. Patients presented at a mean of 8.2 months with a myriad of clinical features. The mean tumor size was 3.38 cm, and 19.3% of tumors were cystic. Supratentorial tumors were most commonly located in the frontal and parietal lobes, and infratentorial tumors in the fourth ventricle. Supratentorial tumors demonstrated significantly poorer PFS ($p < 0.001$) and OS ($p = 0.003$) than infratentorial tumors, despite a higher rate of gross total resection (GTR) for the supratentorial tumors (72.6% *versus* 42.1%). Extraventricular ependymomas displayed significantly poorer PFS than intraventricular ependymomas ($p = 0.009$). In summary, supratentorial ependymomas have significantly poorer PFS and OS than their infratentorial counterparts, despite being more conducive to GTR, suggesting increased clinical aggressiveness. Extraventricular location is also associated with significantly poorer PFS than intraventricular location.

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Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Keywords

Adults; Ependymoma; Intracranial; Prognosis; Survival; Tumor location

1. Introduction

Ependymomas are rare, unencapsulated glial tumors that arise from ependymal cells lining the ventricular system of the brain or the central canal of the spinal cord. They comprise 3% of all primary central nervous system (CNS) tumors diagnosed annually in the USA [1]. Only one-quarter of ependymomas involve the brain in adults, in contrast to 90% in children [2]. Thus, prognostic factors relating to intracranial tumors in adults have not well described. Infratentorial ependymomas are twice as common as their supratentorial counterparts [3, 4]. Ependymomas are classified as being World Health Organization (WHO) grade I (myxopapillary or subependymoma), II (tanycytic, papillary, or classic), or III (anaplastic or malignant). Broadly speaking, they are indolent and compressive rather than infiltrative in nature, often leading to delayed diagnosis at 1 month to 2 years after symptom onset [5, 6]. In other respects, the natural history of this tumor has been inadequately characterized.

It is unclear whether ependymoma comprises a diverse set of pathologic entities with heterogeneous natural histories or one disease with multiple disease courses [7]. Unfortunately, the study of this neoplasm is limited by its low incidence and the 2007 revision of histopathologic criteria for the WHO classification scheme, complicating interpretation of the historical literature. Indeed, these tumors significantly differ in their histology, gross characteristics, location, and molecular make-up [8, 9], which in turn affects the prognosis [10]. Intracranial and spinal ependymomas of the same grade in adults can behave much differently and display striking genetic disparity [8, 11, 12]. Furthermore, biomarkers of clinical aggressiveness in other CNS tumors, such as Ki67, mitotic index, and cellular density, appear less useful in ependymoma [6, 8].

Intracranial ependymomas present with an array of nonspecific clinical features, including nausea and vomiting, headache, focal neurologic deficits, seizures, ataxia, memory or behavioral changes, and lethargy [13]. Brainstem signs and hydrocephalus typify infratentorial lesions, which are preferentially intraventricular [4, 13]. Compared with spinal ependymomas, intracranial lesions are associated with greater clinical aggressiveness and poorer overall survival (OS) [14]. Disease progression in grade I and II ependymomas is characterized by local recurrence rather than leptomeningeal spread [8, 15, 16]. Mortality in these patients is often due to disease-related complications and neurological deficits, such as immobility, deep venous thrombosis, and infections, rather than disease recurrence [10].

Reported prognostic factors in adult ependymoma include age [17], tumor location [17], tumor grade [1, 14, 18], tumor size [19], duration of symptoms [20], metastatic spread [21], preoperative neurological status [22], extent of resection [23–28], and use of adjuvant radiotherapy [16, 19, 29–32]. In general, progression-free survival (PFS) varies with WHO grade [8]. High-grade intracranial ependymomas [33] may disseminate either locally or into the cerebrospinal fluid, especially the basal cisterns and cauda equina, and usually within 5 years of diagnosis [34]. It is not clear whether delayed dissemination in ependymoma is a

function of this tumor's natural history or of postoperative radiotherapy administration, or whether such late recurrences actually represent a second tumor developing in patients with a predisposition to develop ependymomas [34]. The tumor bed is the main site of failure [3], and metastasis is uncommon [35]. Long-term development of secondary neoplasms has been observed in this patient population [8, 36, 37].

Given the rarity of this tumor type in adults, individual patient data from multiple studies were aggregated in order to characterize its natural history and assess the prognostic significance of tumor location. We specifically analyzed all reported cases of adult intracranial ependymomas.

2. Materials and methods

2.1. Article selection

The English-language literature was reviewed for studies that reported clinical outcomes for intracranial ependymomas in adults. Articles were identified via PubMed search using the keyword “ependymoma,” which resulted in 3765 articles published from 1965 to 2011. These articles were then individually reviewed. Articles were included if they contained disaggregated outcome data for adult patients surgically treated for intracranial ependymoma. All available data for individual patients were extracted from the included articles. Aggregated data sets, wherein individual patient data were grouped, were excluded from this analysis, as the goal of the study was to analyze individual patient data with long-term follow-up periods to allow analysis of PFS and OS using Kaplan–Meier and multivariate Cox regression survival analyses. Weighted metaanalysis (such as 5 and 10 year PFS and OS) could not be performed, as these data were not consistently reported by studies.

2.2. Data extraction

The following data items were extracted from institutional series and case reports whenever they were available for individual patients: patient demographics, follow-up interval, tumor location, tumor size, tumor composition (cystic *versus* solid), presenting clinical features, time to presentation, extent of resection (gross total resection [GTR] *versus* subtotal resection [STR]), rate of recurrence or progression as radiologically defined or confirmed at repeat surgery, time to recurrence or progression, rate of mortality, and time to death. Tumors were categorized as (1) supratentorial or infratentorial and (2) extraventricular or intraventricular. Only adults (18 years of age and older) were included in the meta-analysis.

2.3. Statistical analysis

PFS and OS were analyzed by constructing Kaplan–Meier curves, and differences between groups were assessed using the log-rank test or, when the survival curves crossed each other, the Tarone–Ware test. Cox proportional hazards analysis by backward stepwise model selection was subsequently performed to account for potential confounding variables: age, sex, tumor grade, cystic pattern, intraventricular location, extent of resection (GTR *versus* STR), and administration of adjuvant therapy. Hazard ratios (HR) were estimated. The standard error of the mean and/or the 95% confidence interval (CI) was used to convey

variance about the mean. Continuous variables were analyzed using the *t*-test or analysis of variance with *post hoc* Tukey test, and categorical variables were analyzed using the Pearson's chi-squared test. Statistical significance was defined by $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

A total of 56 articles containing 183 patients were included in the meta-analysis (Table 1). The mean follow-up interval was 53.6 months (range, 0–288 months). The mean age was 42.2 years (range, 18–89 years), and there were more males (52.5%) than females (47.5%). Supratentorial location (84 of 138; 60.9%) was more common than infratentorial location (54 of 138; 39.1%). Tumor location was not significantly associated with sex ($p = 0.682$).

3.2. Tumor characteristics

Seventeen of 88 (19.3%) ependymomas were cystic and 71 (80.7%) were solid. The mean tumor size was 3.38 cm (standard error of the mean, 0.26 cm; range, 0.5–6.0 cm), including 3.30 cm for supratentorial and 3.53 cm for infratentorial ependymomas. Tumor location was not significantly associated with cystic pattern ($p = 0.995$) or tumor size ($p = 0.672$). Supratentorial ependymomas were most likely to be located in the frontal (22 of 106; 20.8%), parietal (14 of 106; 13.2%), or temporal (nine of 106; 8.5%) lobes (Table 2). Extraventricular location (80 of 118; 67.8%) was more common than intraventricular location (38 of 118; 32.2%) in this subgroup. Two supratentorial ependymomas were disseminated on presentation. Infratentorial ependymomas were located in the fourth ventricle (25 of 79; 31.6%), cerebellum (eight of 79; 10.1%), or cerebellopontine angle (six of 79; 7.6%).

3.3. Presenting clinical features and time to presentation

Presenting symptoms were reported for 93 patients (Table 3). The most common presenting signs and symptoms for intracranial ependymomas were, in order of decreasing frequency, headache (37.6%), intracranial hypertension (21.5%), seizure (17.2%), vertigo or dizziness (15.1%), visual deficit (15.1%), cranial nerve paresis (14.0%), nausea or vomiting (11.8%), limb weakness (9.7%), altered mental status (6.5%), abnormal gait (5.4%), paresthesia or dysesthesia (4.3%), and bowel, bladder, or sexual dysfunction (2.2%). Less common symptoms included blepharospasm, torticollis, and back pain. Deficits involving every cranial nerve except for I and XI were reported. Intracranial ependymomas presented, on average, at 8.2 months (range, acute to 48 months).

3.4. Extent of resection by tumor location

Infratentorial ependymomas were less amenable to GTR (25 of 68; 36.8%) than STR (43 of 68; 63.2%) relative to supratentorial ependymomas ($p < 0.001$), for which GTR (69 of 101; 68.3%) was more frequently achieved than STR (32 of 101; 31.7%). Overall for intracranial ependymomas, GTR (94 of 169; 55.6%) was achieved more often than STR (75 of 169; 44.4%).

3.5. Supratentorial location is associated with poorer PFS and OS

Supratentorial ependymomas had a median PFS of 24.0 months (95% CI 7.4–40.6 months), which was significantly lower than 144.0 months (95% CI 89.4–198.6 months) for infratentorial tumors ($p < 0.001$) (Table 4) (Fig. 1a). Supratentorial tumors had significantly poorer OS with median survival of 61.0 months (95% CI 15.0–107.0 months) compared to infratentorial tumors ($p = 0.003$) (median survival could not be calculated for infratentorial tumors as mortality did not reach 50%) (Fig. 1b). Overall for intracranial ependymomas, the median PFS and OS were 87.0 months (95% CI 29.7–144.3 months) (Fig. 2a) and 180 months (95% CI not calculable; mortality did not reach 50%) (Fig. 2b), respectively. Multivariate Cox regression analysis was performed to account for potential confounding variables. The reduced PFS in the supratentorial group remained significant in multivariate Cox regression analysis (HR = 3.89; 95% CI 1.12–13.50; $p = 0.033$), while accounting for potential confounding variables, including age, sex, tumor grade, cystic pattern, intraventricular location, extent of resection, and adjuvant therapy. As with PFS, the reduced OS of supratentorial tumors remained significant in the analysis (HR = 49.48; 95% CI 8.91–274.83; $p < 0.001$).

3.6. Extraventricular location is associated with poorer PFS

Extraventricular ependymomas were associated with a significantly poorer PFS with median PFS of 19.0 months (95% CI 9.4–28.6 months) compared to intraventricular tumors with median PFS of 108.0 months (95% CI 4.5–221.5 months) ($p = 0.009$) (Fig. 3a). Extraventricular location was also associated with a strong trend toward decreased OS ($p = 0.054$) (Fig. 3b). As intraventricular tumors did not reach 50% survival in the latter analysis, comparison of the two groups was limited.

4. Discussion

Intracranial ependymomas are rare CNS tumors whose natural history in adults is poorly defined. The incidence of these tumors in the general population is very low, and the existing literature is largely limited to small case series from single or few institutions. Therefore, we comprehensively reviewed the literature in order to perform an integrative analysis. A multi-institutional database was constructed through pooling of previously reported individual cases. The intent of this study was to assess the impact of tumor location upon the extent of resection, specifically focusing on prognostic differences between supratentorial *versus* infratentorial and extraventricular *versus* intraventricular ependymomas.

We found that adult intracranial ependymomas present with a gamut of clinical symptoms including, most frequently, headache, intracranial hypertension, seizure, and vertigo or dizziness. Notably, intracranial ependymomas presented earlier than we have previously reported for adult spinal ependymomas (8.2 *versus* 25.9 months) [38]. Traditionally, ependymomas are stratified by histopathologic factors including cellular pleomorphism, mitotic activity, cellular density, and extent of infiltration into the brain parenchyma. Until recently, prognostic factors have been poorly characterized in ependymomas. Intracranial ependymomas in adults display significantly reduced PFS relative to those in the spinal cord

[14]. Our research group has previously reported, in parallel, on the prognostic significance of tumor location in adult spinal ependymomas using the same methodology and aggregated data [38]. However, the prognostic significance of tumor location, particularly in intracranial ependymomas, has been debated [39]. We found in the present study that the tumor location of intracranial ependymomas has significant prognostic consequences, as infratentorial location is a more favorable location than supratentorial with respect to PFS and OS in adults.

A striking finding of our analysis was that supratentorial ependymomas, despite being significantly more amenable to GTR than infratentorial, displayed significantly poorer PFS and OS. This is in spite of the fact that the extent of resection is positively correlated with the prognosis of adult intracranial ependymoma [3, 40–44]. Supratentorial ependymomas in adults tend to be of higher grade and larger size [45, 46], and tend to recur more aggressively, including with craniospinal seeding [2, 4, 45, 47], which occurs in 8.7% of high-grade and 5% of low-grade ependymomas [48]. The opposite pattern, with supratentorial location conferring a more favorable prognosis, has been demonstrated for pediatric intracranial ependymomas [49]. Previous studies have reported conflicting findings as to the attainability of GTR for supratentorial *versus* infratentorial location [39, 50, 51], two of which suggested that supratentorial ependymomas may possess a more disseminative phenotype that precludes GTR from involved brain parenchyma. In children, supratentorial ependymomas have a higher mitotic activity than infratentorial types [52]. Alternatively, it has been suggested that infratentorial ependymomas involving the posterior fossa may be more challenging to cleanly dissect due to invasion of the brainstem, floor of the fourth ventricle, cerebellopontine angle, and cranial nerves [51]. It was further demonstrated in this study that extraventricular location is associated with significantly poorer PFS and a trend toward poorer OS relative to intraventricular location. A series of adult ependymoma patients previously showed decreased OS and recurrence-free survival in third ventricular *versus* hemispheric tumors, although the sample size was too small for statistical comparison [53]. It is unclear whether differential rates of GTR and/or anaplastic histology within the cerebral hemispheres and ventricular system underlie this phenomenon [53]. The latter pattern has been demonstrated in pediatric intracranial ependymomas [54].

As our findings were obtained through meta-analysis of data, there are inherent limitations to our study. The literature is subject to publication bias such that favorable results may be preferentially reported. As a result of our exclusion of aggregated patient data, which group together individual patient data, our findings could have been biased by individual case reports or smaller case series from institutions with less experience treating patients with intracranial ependymomas. Additional, such level IV evidence is susceptible to numerous biases, including selection and detection biases. While our study included several publications containing sizable cohorts treated at large referral centers, which possess extensive experience with this tumor entity, our aggregate sample may actually depict some medium between their actual experience and that of smaller, less experienced institutions. While Cox multivariate regression analysis was performed to test for seven potential confounding factors, it was not possible to analyze Karnofsky Performance Status because few studies reported this parameter. Lastly, our sample had a relative preponderance of

supratentorial to infratentorial tumors, which discords with their reported epidemiology [3, 4], and thus our description of presenting clinical features may be accordingly skewed toward supratentorial tumors.

5. Conclusion

The findings of this study describe the clinical outcomes of surgically treated intracranial ependymomas in adults based on tumor location, which has historically been inadequately characterized. These patients present to clinical attention through a myriad of diverse symptoms and signs, which are nonspecific and require added vigilance by the practitioner. Tumor location above *versus* below the tentorium cerebelli was found to dramatically alter the patient prognosis. A substantial finding of the analysis is that supratentorial ependymomas, despite being significantly more amenable to GTR, have significantly poorer PFS and OS than their infratentorial counterparts. This suggests that the tumor phenotype widely varies according to the tumor location, underscoring the importance of close follow-up following surgery and ongoing research to characterize the genetic and molecular characteristics of ependymomas.

Acknowledgements

This work was supported by grants from the National Research Service Award from the National Institutes of Health (F32NS073326-01) (MCO), the Howard Hughes Medical Institute (ETS), the Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery at UCSF (ATP), and the Michael J. Marchese Professor and Chair at Northwestern University (ATP).

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Fig. 1.
Kaplan–Meier survival analysis of (a) progression-free survival and (b) overall survival for supratentorial *versus* infratentorial tumor location.

Fig. 2.
Kaplan–Meier survival analysis of progression-free survival and (b) overall survival for intracranial ependymomas.

Fig. 3. Kaplan-Meier survival analysis of progression-free survival and (b) overall survival for extraventricular *versus* intraventricular tumor locations.

Table 1

Patient demographics and tumor characteristics of the included subjects

	Overall	Supratentorial	Infratentorial
Follow-up interval, months	53.6 (range 0–288)	–	–
Age, years	42.2 (range 18–89)	41.7	43.2
Male, %	52.5	53.6	50.0
Tumor size, cm	3.38 [95%CI 2.85–3.91]	3.30 [95%CI 2.50–4.10]	3.53 [95%CI 2.90–4.17]
Cystic, %	19.3	19.3	19.4
Location, %	–	60.9	39.1
Extraventricular vs. intraventricular location	–	67.8 / 32.2	–

CI = confidence interval, vs. = *versus*.

Table 2

Distribution of supratentorial and infratentorial ependymomas according to tumor location

Supratentorial	
Frontal	22
Parietal	14
Temporal	9
Occipital	2
Fronto-temporal	1
Fronto-parietal	2
Temporo-parietal	3
Temporo-occipital	1
Parieto-occipital	2
Sella turcica	3
Tectum	2
Corpus callosum	1
Trigeminal ganglion	1
Pineal region	1
Lateral ventricle	8
Third ventricle	5
Unspecified	29
Total:	106
Intraventricular	38
Extraventricular	80
Disseminated on presentation	2
Infratentorial	
Cerebellum	8
Cerebellopontine angle	6
Medulla oblongata	2
Fourth ventricle	25
Unspecified	38
Total:	79

Table 3

Summary of the common presenting clinical features

Clinical features	n	%
Headache	35	37.6
Intracranial hypertension	20	21.5
Seizure	16	17.2
Vertigo/dizziness	14	15.1
Visual deficit	14	15.1
Cranial nerve paresis ^a	13	14.0
Nausea/vomiting	11	11.8
Limb weakness	9	9.7
Altered mental status	6	6.5
Abnormal gait	5	5.4
Paresthesia/dysesthesia	4	4.3
Bowel/bladder/sexual dysfunction	2	2.2
Others	3	3.2

^a Cranial nerve deficits involved cranial nerve II, III, IV, V, VI, VII, VIII, IX, X, and XI.

Table 4

Overview of resection status and median survival outcomes associated with supratentorial *versus* infratentorial location

	Intracranial (Overall)	Supratentorial	Infratentorial
GTR	93/152 (61.2%)	69/95 (72.6%)	24/57 (42.1%)
STR	59/152 (38.9%)	26/95 (27.4%)	33/57 (57.9%)
Median PFS	123.1 months	80.2 months	155.6 months
Median OS	161.9 months	127.5 months	207.7 months

GTR = gross total resection, OS = overall survival, PFS = progression-free survival, STR = subtotal resection.