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Prognostic Factors for Ependymoma Survival: A Retrospective Study

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Abstract

Background: Ependymoma is a rare primary brain tumor that arises from the ependymal cells of the intra-ventricular central nervous system.

Methods: Thirty-two clinical cases of ependymoma were obtained from the tumor registry of the Scott & White Integrated Healthcare System from 1976 to 2013. We investigated the effects of gender, age, race, tumor grade, surgical method, recurrence, radiation therapy (RT), chemotherapy (CT), and mortality of patients.

Results: Fifty percent of patients had RT and 12.5% had CT. Tumor recurrence was observed in only 4 (12.5%) cases and all were diagnosed with grade II tumors. Sixteen patients (50.0%) underwent subtotal resection, 11 (34.4%) gross total, and 5 (15.6%) underwent no surgical procedures. Twenty-two patients (68.8%) are still living and 10 (31.3%) were deceased at time of analysis. Forty percent of deceased were under 18 year of age. The median overall survival time for all patients was 15.2 years (182.5 months), with a 5-year survival rate of 80.0%. Patients with primary tumor sites in the brain stem, frontal, and parietal lobes had survival rates of 87.5%, 100%, and 100%, respectively, with no reported tumor recurrence (0.0% each).

Conclusion: Surgical treatment with attempted gross total resection was the most successful method of ependymoma treatment. Primary tumor site is another important prognostic value for evaluation of short and long-term outcomes of ependymoma diagnosed patients.

Impact: This study aims to identify novel prognostic factors for survival and to describe effective treatments and outcomes of ependymoma diagnosed patients.

Keywords: Ependymoma; Prognostic factors; Survival; Outcomes; Epidemiology

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Introduction

Ependymoma is a primary brain tumor that arises from the ependymal cells of the intraventricular central nervous system (CNS) parenchyma. It is distinguishable from other CNS neoplasms by its rarity and its propensity to afflict children [1].

Ependymomas account for 6-10% of pediatric intracranial tumors and represent 2-6% of adult intracranial tumors [2-7]. Among pediatric cohorts, supratentorial ependymomas are more common than infratentorial tumors and make up one-third of all ependymomas, whereas infratentorial tumors are more common in adults [5,8-11]. Currently, the 5-year survival rates from time of diagnosis for adults and children with ependymoma are 55-90% and 40-65%, respectively [3,5,6,12,13]. Several studies have analyzed survival rates of patients less than or equal to 3 years of age and these findings demonstrate that young children often have less favorable prognoses than adult or older pediatric patients [9,13]. This disparity can most likely be attributed to the fact that young children are often diagnosed when their disease has already progressed to a more advanced stage, thereby imparting a less favorable prognosis as compared to a patient whose ailment had been promptly observed and treated [4]. The World Health Organization (WHO)

data classify ependymomas into 3 groups by histopathology: grade I (subependymoma or myxopapillary ependymoma), grade II (classic ependymoma with cellular, papillary, clear cell, and tanycytic variants), and grade III (anaplastic) [14]. Ependymomas of the anaplastic variety are the most aggressive [15,16]. Some studies have concluded that prospective research should be continued on ependymomas before the anaplastic and classic varieties are more clearly delineated [13,15,16]. However, patients presenting with subependymomas or classic ependymomas can still display bleak prognoses before treatment. With respect to subependymomas, the size and location of the tumor is most helpful in determining prognosis [2-5,17-21]. Few instances of extracranial metastases have been recorded, but intraventricular metastases are relatively common with grade II and grade III tumor variants. Although the current gold standard of care for ependymoma treatment is gross total resection (GTR) with concurrent radiation therapy (RT), studies have been done comparing the relative efficacy of GTR against subtotal resection (STR) in children and adults, depending on the location of their ependymomas (infratentorial vs. supratentorial) [2,3,5,12,13,15-17,22,23]. The most recurrences following treatment are local, but RT decreases the probability of recurrence. The existence of relatively few ependymoma cases precludes the ability to reach any unassailable conclusions concerning appropriate treatment regimens. However, most physicians agree that chemotherapy is relatively ineffective in enhancing progression-free survival (PFS) for ependymoma patients [8,13,16,24-27].

This study aims to evaluate the prognostic value of various factors which could be utilized to generate more accurate predictions regarding patient survival in individuals diagnosed with ependymoma, including short and long-term outcomes. Further studies will be needed to elucidate detailed analyses of tumor locations in different regions of the brain with associated prognostic values of disease.

Materials and Methods

Sources of data and study population

All human investigations were performed after approval by an institutional review board and in accordance with an assurance filed with and approved by the US Department of Health and Human Services.

Thirty-two total clinical cases of ependymoma were obtained from the tumor registry of the Scott & White Integrated Healthcare System from 1976 to 2013. There were no exclusion criteria and all cases diagnosed with ependymoma were selected for this study. Age was categorized into two groups: children (less than or equal to 18 years) and adults (over 18). Race was categorized as white, Hispanic, black non-Hispanic, and other/unknown, with white vs. non-white also examined. Our categorization of ependymoma tumor grade fell into 3 groups as determined by histopathological studies: grade I, grade II, and grade III. Data describing surgical method, RT, chemotherapy (CT), tumor recurrence, and time to follow-up were also included in data analyses. Surgical methods were described as STR, GTR, or no surgical procedure (NSP). RT and CT were described as either administered or not administered.

Data analysis

The data were incorporated from an Excel file into SAS, v9.2 (Cary, NC), and R, v2.15.1 (*The R Foundation for Statistical Computing*) to be analyzed for a number of variables. Descriptive statistics, including frequencies and percentages, were calculated to describe patient characteristics, tumor location, and mortality among ependymoma cases. Comparisons for mortality among locations were examined, overall and pairwise, using two-sample proportion tests. A type I error of α=0.10 was assumed throughout given the smaller size of 32 for the sample. Kaplan-Meier curves were drawn for overall statistics by gender, pediatric vs. adult, and white vs. other comparisons. Log-rank tests were used to compare mortality across groups. Quartile estimates of median survival time were carried out with difficulty due to the small sample sizes in use. Several of those median survival times lacked a lower or an upper 95% Confidence Interval (CI) as a result.

Table 1: Overall demographic characteristics of ependymoma patients (N=32). Table shows descriptive values of overall occurrence of ependymoma by age, race, gender, treatment modalities, tumor grades, recurrence of disease, median overall survival time and 5 years survival rates, including time to follow up.

Characteristics	Study Sample (N=32) N (%)
Age	
Adult (age > 18 years)	21 (65.6)
Pediatric (age ≤ 18 years)	11 (34.4)
Female	13 (40.6)
Race	
White	23 (71.9)
Hispanic	5 (15.6)
Black	2 (6.3)
Other/Unknown	2 (6.3)
Treatment	
Surgery	27 (84.4)
Gross total resection	11 (34.4)
Subtotal resection	16 (50.0)
No Surgery	5 (15.6)
Radiation therapy	16 (50.0)
Chemotherapy	4 (12.5)
WHO grade	
Grade I	8 (25.0)
Grade II	21 (65.6)
Grade III	3 (9.4)
Recurrence	4 (12.5)
Survival	
Median overall time	15.2 years (182.5 months)
Pediatric 5-years survival rate	65.6% (95% CI 40.2-100)
Adult 5-years survival rate	78.4% (95% CI 57.9-100)
Median time to follow-up	
Survived	60.2 months
Deceased	74.6 months

Results

Twenty-one (65.6%) patients were adults, and the remaining 11 (34.4%) were under or equal to 18 years of age. Twenty-three patients (71.9%) were white, 5 (15.6%) Hispanic, 2 (6.3%) black and 2 (6.3%) other/unknown ethnicity. The majority of patients were male (59.4%). Three patients (9.4%) presented with grade III anaplastic ependymoma, 21 (65.6%) with grade II ependymoma, and the remaining 8 (25.0%) had grade I subependymoma. Sixteen

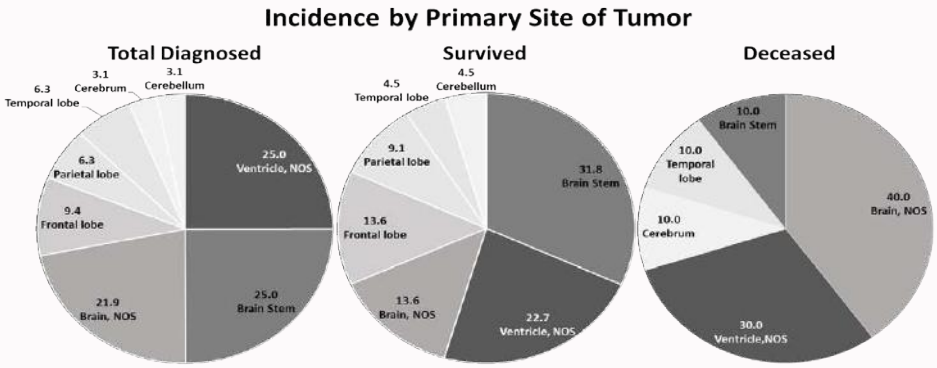

Figure 1: Comparative analysis of primary tumor sites in ependymoma total diagnosed patients vs. survived vs. deceased patients at the time of data analysis. Total number of 32 cases were analyzed using R, ver. 2.15.1. Ependymoma was located in the ventricle NOS (25.0% vs. 22.7%, p=0.660), in brain stem (25.0% vs. 31.8%, p=0.186), in brain, NOS (21.9% vs. 13.6%, p=0.094), in frontal lobe (9.4% vs. 13.6%, p=0.220), in parietal lobe (6.3% vs. 9.1%, p=0.325), in temporal lobe (6.3% vs. 4.5%, p=0.555), in cerebrum (3.1% vs. 0.0%, p=0.132), and in cerebellum (3.1% vs. 4.5%, p=0.493), respectively.

Table 2: Mortality rate overall and by location. Overall average for survivors was 68.8% of the sample. Among survivors, brain stem (32.0%) and ventricle, NOS (23.0%) were most prevalent locations. Overall average for deceased patients was 31.3%. Among the deceased, mortality was greater for brain, NOS (57.1%), temporal lobe (50.0%), and ventricle, NOS (37.5%). Cerebrum location (1 case) resulted in death. Lower rates of mortality were observed for the brain stem, frontal lobe, and parietal lobe with a single case for cerebellum surviving. A significant difference in mortality was observed for brain, NOS versus other locations (57.1% vs. 24.0%, p=0.094).

Location	Total (N=32) N (%)	Alive (N=22, 68.8%) N (%)	Dead (N=10, 31.3%) N (%)	Mortality Rate %	P-value
Brain stem	8 (25.0)	7 (31.8)	1 (10.0)	12.5	0.186
Brain, NOS	7 (21.9)	3 (13.6)	4 (40.0)	57.1	0.094
Cerebellum, NOS	1 (3.1)	1 (4.5)	0 (0.0)	0.0	0.493
Cerebrum	1 (3.1)	0 (0.0)	1 (10.0)	100	0.132
Frontal lobe	3 (9.4)	3 (13.6)	0 (0.0)	0.0	0.220
Parietal lobe	2 (6.3)	2 (9.1)	0 (0.0)	0.0	0.325
Temporal lobe	2 (6.3)	1 (4.5)	1 (10.0)	50.0	0.555
Ventricle, NOS	8 (25.0)	5 (22.7)	3 (30.0)	37.5	0.660

patients (50.0%) underwent STR, 11 (34.4%) GTR, and 5 (15.6%) underwent NSP (Table 1). Among total 10 deceased patients, 8 (80.0%) underwent STR rather than GTR. RT was administered in 50% of all cases and CT in only 12.5%.

Eight patients (25.0% overall) became disease-free with no recurrence at the time of analysis. Two of them (25.0%) were treated only surgically. The remaining 6 (75.0%) were treated with a combination of surgery and RT and/or CT. Among them, 5 were administered RT and 1 had a combination of RT and CT. These efforts resulted in 5 being alive (62.5%) at time of analysis.

Nine patients (28.1%) overall did not have remission of disease after treatment. Seven surviving patients in this group received surgical treatments. Four of them underwent surgery alone. Two were treated with RT and CT, and one received RT in addition to surgical resection. Two deceased patients (22.2%) underwent surgery and CT alone, respectively.

Tumor recurrence was reported in only 4 cases (12.5% overall), and all were grade II tumors, with 1 (25.0%) deceased. Data on tumor recurrence were unavailable for 11 patients. Among patients with unknown recurrence, 7 patients were diagnosed with grade II tumors, 3 with grade I tumors, and 1 with grade III tumor. Four (36.4%) were deceased by the time of data analysis.

Forty percent of deceased patients were under the age of 18. Our pediatric 5-year survival rate was 65.6% (95% CI 40.2-100%). The adult 5-year survival rate was 78.4% (95% CI 57.9-100%). The median overall survival time for 32 reported cases was 15.2 years (182.5 months), and the 5-year survival rate was 80.0%. The median time to follow-up for those patients who are still living was 60.2 months, and the median time to follow-up for the deceased patients was 74.6 months (Table 1).

Mortality by tumor location

We compared the incidence rates of the primary tumor sites between the total ependymoma diagnosed population, the subsistent treated, and deceased population to elucidate possible survival trends. A side-by-side comparison is shown in Figure 1. These data suggest a survival rate of 87.5% observed with primary tumor sites located in the brain stem versus 62.5% elsewhere (p=0.186; Table 2). Survival with tumors located in the frontal lobe was 100% versus 65.5% in other locations (p= 0.220), with 100% survival for parietal lobe (p=0.325).

Among patients who died, accounting for 31.3% of all cases (Table 2), and the most prevalent location was brain, NOS (40.0%), followed by ventricle, NOS (30.0%). Among survivors, accounting for the remaining 69.0% of the sample, brain stem (32.0%) and ventricle, NOS (23.0%) were most prevalent locations. Mortality was greater for brain, NOS (57.1%), temporal lobe (50.0%), and ventricle, NOS (37.5%) compared to the overall average of 31.3%. There was one case involving the cerebrum, which resulted in death. Lower rates were observed for the brain stem, frontal lobe, and parietal lobe with a single case for cerebellum surviving. A significant difference in mortality was observed for brain, NOS versus other locations (57.1% vs. 24.0%, p=0.094).

Table 3: Pairwise comparisons of mortality rates among locations. Test represents significantly lower mortality rate for brain stem compared to brain, NOS (12.5% vs. 57.1%, p=0.067), to cerebrum (12.5% vs. 100%, p=0.047), respectively. Greater mortality of brain, NOS was significant compared to locations in frontal lobe (57.1% vs. 0.0%, p=0.091). Cerebrum showed significantly greater rates of mortality compared to frontal lobe (100% vs. 0.0%, p=0.046) and to temporal lobe (100% vs. 0.0%, p=0.083), respectively.

Pairwise P-values	Brain stem n=8	Brain NOS n=7	Cerebellum NOS n=1	Cerebrum n=1	Frontal lobe n=3	Parietal lobe n=2	Temporal lobe n=2	Ventricle NOS n=8
Mortality:	**12.5%**	**57.1%**	**0.0%**	**100%**	**0.0%**	**0.0%**	**50.0%**	**37.5%**
Location n, Mortality								
Brain stem n=8, **12.5%**	---	0.067	0.708	0.047	0.521	0.598	0.236	0.248
Brain, NOS n=7, **57.1%**		---	0.285	0.408	0.091	0.151	0.858	0.447
Cerebellum, NOS n=1, **0.0%**			---	0.157	NA	NA	0.386	0.453
Cerebrum n=1, **100%**				---	0.046	0.083	0.386	0.236
Frontal lobe n=3, **0.0%**					---	NA	0.171	0.214
Parietal lobe n=2, **0.0%**						---	0.248	0.301
Temporal lobe n=2, **50.0%**							---	0.747
Ventricle, NOS n=8, **37.5%**								---

Pairwise comparisons among tumor locations (Table 3) revealed a significantly lower mortality rate for brain stem compared to brain, NOS (12.5% vs. 57.1%, p=0.067), and to cerebrum (12.5% vs. 100%, p=0.047). Tumors located in the brain, NOS also resulted in greater mortality than in frontal lobe (57.1% vs. 0.0%, p=0.091). Cerebral tumors had higher rates of mortality if compared with both frontal and parietal lobes (100% vs. 0.0% for both, p=0.046 and p=0.083), respectively.

Discussion

Physicians are currently trying to discern the most effective treatments for ependymoma patients and identify associated prognostic factors to better evaluate outcomes. Due to their rarity, researchers must rely on a paucity of information that can only be retrospectively analyzed.

Tumor site

Our data for a total diagnosed ependymoma population were analyzed based on tumor primary site in living and deceased patients who underwent treatments. It was found that treatment of ependymoma located in the brain stem, frontal lobe, and parietal lobe had significantly greater survival and recurrence-free outcomes than tumors in other regions of the brain: cerebrum, cerebellum, temporal lobe, brain NOS, or ventricles. These findings were supported by McGuire et al. where cranial variants of ependymoma have a less favorable outcome than primary spinal cord ependymomas [11]. It has been reported that location within the spinal cord may also affect outcome, with tumors in the lower portion of the spinal cord having a worse prognosis [28].

Treatment modality and recurrence

Surgical excision with attempted GTR is the current gold standard for ependymoma treatment. The administration of concurrent RT is contingent upon the extent of resection, tumor grade, patient age, and the presence or absence of tumor dissemination, which would most commonly occur through the cerebrospinal fluid [12,29-34]. Since 80% of our patients who died underwent STR rather than GTR, GTR could perhaps have been attempted on some of our diagnosed patients. As was reported by other clinicians, STR is sometimes preferred over GTR if the physician wishes to decrease the risk of debilitating morbidity to the patient [8,28,35,36]. STR excises less tissue and is therefore less likely to cause comorbidities. Based on our observations, there seems to be a correlation between mortality and surgery type in that GTR confers better prognosis.

Among the 8 patients who became disease-free with no recurrence after treatment, 3 are now deceased. All three underwent a combination of surgery with RT treatment and were diagnosed with grade II tumors located in the brain stem (1 patient) and brain, NOS (2 patients). Among the 5 living, 2 were diagnosed with grade II tumors and underwent a combination of surgery and RT treatment. In living individuals, the primary tumor sites were in the frontal lobes (2 patients) and the brain, NOS (1 patient).

In this study, recurrence data were not reported for 11 patients, but it is not unusual for patients whose symptoms have dissipated to neglect contact with the healthcare system. Recurrence was seen/reported in only 4 (12.5%) of our patients.

It has been reported that recurrence is relatively common in grade III ependymomas and it is not uncommon with grade II tumors [37]. Subependymomas are generally well-circumscribed and well-differentiated, thus surgical resection with or without concurrent radiotherapy is usually very effective in conferring a favorable long-term prognosis [2,37,38]. It is known that survival rates for subependymoma are generally higher than those of grade II or grade III [10,39,40]. On the other hand, anaplastic ependymomas most likely metastasize, recur, and diminish overall survival. Studies published by several groups have shown anywhere from 42% to 100% recurrence in grade III ependymoma [39,41-44]. In our observations, 3 patients with anaplastic ependymomas were still alive at the time of analysis and had no recurrence. It is known that subependymomas usually carry very different prognoses dependent on location and age [18-21,45]. Therefore, we hypothesize that location and age might contribute more to prognosis than histopathological qualities of the tumor.

RT was administered in 50% of our ependymoma cases and was excluded from treatment regimens of the pediatric group, but CT was administered in only 12.5% of all cases. This approach corresponds well with the current standard of ependymoma treatment and has been reported in several other studies [26,45]. CT has not been found to decrease instance of tumor recurrence and potentially even

exacerbates progression of the tumor by conferring natural selection, and thereby resistant qualities upon the tumor cells [46,47]. Some studies have shown that CT can delay progression and provide palliative relief to patients with ependymoma, but it has not been found to increase survival [25-27,41]. According to our findings, RT also does not seem to significantly improve survival.

Age

Age associated observations in our study show that 65.6% of the patients were adults and only 34.4% were children. Forty percent of deceased patients were under 18 years of age and a survival curve estimated a 65.6% of pediatric 5-year survival rate. These findings corresponded with 5-year survival rates published by the American Cancer Society (ACS) which demonstrate that ependymoma has the 4th worst rate among child brain tumors with a value of 75% (with a pediatric qualifier of 19 years or younger) [48]. Our adult group showed a 5-year survival rate of 78.4%. This may illustrate the recent advances in cancer treatment.

Gender

The influence of gender has not been thoroughly investigated in ependymoma studies because it almost equally afflicts men and women and progresses similarly in both. However, in our study, 59.4% of all diagnosed patients were men and 40.6% were women.

Race

Another neglected survival relationship is ependymoma outcome by race. Our study showed that despite the similarity in mortality between white and other races, a correlation might exist between ethnicity and ependymoma development since 71.9% of all patients was white. However, all of the patients in our study were from Central Texas. Thus, considering the local demographics (whites are less predominant than Hispanics), the fact that more whites were afflicted than any other race possibly denotes to genetic correlation, although no genetic markers have been discovered as of yet.

Limitations and Conclusion

The purpose of this study is to add obtained knowledge to currently available ependymoma literature. It is expected that the field will benefit from additional information in this area to better understand ependymoma associated prognostication. Although the epidemiologic literature on brain tumors is inconclusive in many areas, there is a pressing need for more researchers to study ependymoma epidemiology.

The present study has several limitations: Even though this study covers 37-year time frame which resulted in change of guidelines, diagnostics, and treatment of disease, this study does not account for the impact of time in respect to treatment of documented ependymoma cases. This study has a limited sample size available from the Scott & White Brain Tumor Registry. Despite the institutional reliability and accuracy, all retrospective and exploratory investigations are inherent to limitations including variability of diagnostic criteria and tools, lack of diagnosis confirmation, and loss to follow up. We did not include tumor grade/stage in our analysis which may possibly be a confounder or effect modifier. However, since CNS tumor grading and staging is continuously subject to change over time, age, race and location of the primary tumor are likely to be more important prognostic indicators in current consideration. Finally, the ethnical diversity of the Central Texas population should be taken into account as it may not be representative of the overall US population.

In conclusion, our study suggests that one of the major factors that can be used to evaluate prognosis of ependymoma patients is primary site of the tumor. Tumor locations in the brain stem, frontal lobe, and parietal lobe seem to have greater survival outcomes and lower recurrence of disease when treated surgically at the very least, when compared to other regions of the brain. There also seems to be a genetic correlation of ependymoma development with white ethnicity, and male sex.

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