Nomograms for predicting the overall survival of patients with cerebellar glioma: An analysis of the SEER (Surveillance Epidemiology and End Results) database

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Nomograms for predicting the overall survival of patients with cerebellar glioma: An analysis of the SEER (Surveillance Epidemiology and End Results) database

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Abstract

Purpose: At present, our understanding of cerebellar glioma is still not enough. This study collected information on patients in the seer database to determine the predictive factors patients with cerebellar glioma.

Patients and Methods: The data of patients with cerebellar glioma diagnosed from 1975 to 2018 were retrieved from the Surveillance Epidemiology and End Results Database. We randomly divide the data into a training group and a validation group, establish a nomogram based on the training group, and use the validation group data to verify the clinical value of the model.

Results: A total of 508 patients were included in this study. Multivariate analysis was performed based on the data before randomization, and the results showed that the patient's age, the tumor's WHO grade, histological type, and extension are significantly correlated with the survival rate. The c index of OS nomograms of the training cohort was 0.909 (95% CI,(0.880-0.938)) and 0.932(95% CI, (0.889-0.975)) in validation group. The calibration curve of OS for 3 and 5 years show that there was a good consistency between the actual survival probability and the predicted survival probability.

Conclusion: For patients with cerebellar glioma, the age of the patient at the time of diagnosis, WHO grade of the glioma, histological type, and extension are the four most prominent factors that affect the overall survival outcomes. Furthermore, our model may be a useful tool for predicting OS in these patients.

Key words: Cerebellum glioma, Nomogram, Overall survival, SEER database

Introduction

Gliomas are common intracranial tumors, but gliomas that occur in the cerebellum are very rare, especially in adults¹. Because of its rarity, there had few previous studies on this area, so it is necessary to conduct research in this field. AS we known, regardless of the patient's age, histology, or pathology, cerebellar gliomas are serious neurological tumors, usually manifested as life-threatening complications such as compression of the cerebellum and adjacent brainstem or obstruction of the cerebrospinal fluid circulation pathway, resulting in increased intracranial pressure, which leads to serious consequences and even threatens the life of the patient. Some researcher have reported that patients with cerebellar glioblastoma have a poor prognosis, with a survival period of three to seven months^{2,3}, while others had observed that cerebellar glioblastoma and brain glioblastoma are similar in survival time^{4,5}. In this article, we collected information on patients with cerebellar glioma from the seer database, explored the factors that affect the overall survival time of cerebellar glioma, and constructed a clinical prognostic model of cerebellar glioma to provide risk assessment for clinical patients.

Methods

Study Population

The data of patients with cerebellar glioma diagnosed from 1975 to 2018 were retrieved from the Surveillance Epidemiology and End Results Database. The Surveillance Epidemiology and End Results Database collects *information* about patients' baseline *characteristics*, and the information of tumor such as histological characteristics, WHO grade, surgery, and patients' vital status in 9 registries within the United States. By using SEER*Stat software (Version 8.3.9), we retrieved 65369 cases in total. The inclusion criteria included 1) first primary cerebellar glioma; 2) The ICD-O-3 site codes were limited to Cerebrum (C71.6); 3) The detailed information on sex, race, and tumor size, WHO grade, surgery information, histological characteristics, pathological diagnosis, and patients' vital status. The exclusion criteria include 1) Patients without histological confirmed glioma; 2) Patients with unknown information such as tumor size, extension, reason for death and surgery status **Figure 1**.

Figure1

Figure 1. Flowchart of cerebellum glioma patient selection.

Covariates Included

The data included for analysis were: age (≤ 20 years old were defined as pediatric group, and > 20 years old were defined as adult group), race (white, black and other) and sex. The cerebellar glioma characteristics data obtained for analysis were: Tumor size (size ≤ 3.0 cm, size > 3.0 cm), tumor extension (cerebellum, brainstem, ventricular and other). Histological characteristics (Pilocytic astrocytoma, anaplastic astrocytoma, ependymoma, glioblastoma, and other). WHO grade (WHO grade III and IV were assigned to high grade, WHO grade I and II were assigned to low grade). The extent of tumor resection (Local excision/biopsy, STR, GTR, and resection lobe of brain).

Statistical Analyses

The variables associated with OS in this study including age, race, sex, year at diagnosis, WHO grade, tumor size, histological type, and extent of surgery. *We use the Kaplan-Meier method to assess overall survival rate, using the log-rank test to evaluate the differences between survival curves. Then we use the univariate and multivariate analyses to determine the effect prognostic factors on OS, both multivariate and univariate cox proportional hazard models were used to calculate HRs (hazard ratios) and the 95% CIs (confidence intervals), If $P < 0.05$ was considered statistically significant. Randomly dividing the population into validation group ($n = 152$) and training group ($n = 356$). Then we use using the package of RMS in R version 4.1.0 (<http://www.r-project.org/>) building a nomogram model to calculate*

risk score according to the formula. Calibration curve and Harrell's concordance index (C-index) were used to estimate the accuracy and consistency of nomogram between the predicted and actual OS rate.

RESULTS

Patient Population and Baseline Characteristics

A total of 508 patients were included in this study. Demographic information, surgery information and tumor characteristics were described in Table 1.

TABLE 1 | Patient demographics, tumor characteristics and treatment of 508 patients with histologically confirmed cerebellar gliomas

Characteristics	ALL	Local excision/biopsy	STR	GTR	Resection lobe of brain	P-value
POPULATION SIZE	508	24(4.7%)	152(29.9%)	174(34.3%)	158(31.1%)	
AGE						<0.001
<20	290(57.1%)	5 (20.8%)	66 (43.4%)	121 (69.5%)	98 (62.0%)	
20-60	151(29.7%)	4 (16.7%)	62 (40.8%)	39 (22.4%)	46 (29.1%)	
>60	67(13.2%)	15 (62.5%)	24 (15.8%)	14 (8.0%)	14 (8.9%)	
RACE						0.221
White	396(78.0%)	17 (70.8%)	122 (80.3%)	131 (75.3%)	126 (79.7%)	
Black	58(11.4%)	1 (4.2%)	15 (9.9%)	25 (14.4%)	17 (10.8%)	
Other	54(10.6%)	6 (25.0%)	15 (9.9%)	18 (10.3%)	15 (9.5%)	
SEX						0.346
Female	252(49.6%)	13 (54.2%)	83 (54.6%)	78 (44.8%)	78 (49.4%)	
Male	256(50.4%)	11 (45.8%)	69 (45.4%)	96 (55.2%)	80 (50.6%)	
YEAR						<0.001
2011-2015	252(49.6%)	16 (66.7%)	91 (59.9%)	142 (81.6%)	3 (1.9%)	
2004-2010	256(50.4%)	8 (33.3%)	61 (40.1%)	32 (18.4%)	155 (98.1%)	
HIST						<0.001
Glioblastoma	67(13.2%)	3 (12.5%)	31 (20.4%)	17 (9.8%)	16 (10.1%)	
Ependymoma	36(7.1%)	1 (4.2%)	9 (5.9%)	15 (8.6%)	11 (7.0%)	
Anaplastic ast	29(5.7%)	9 (37.5%)	10 (6.6%)	6 (3.4%)	4 (2.5%)	
Pilocytic ast	325(64.0%)	4 (16.7%)	86 (56.6%)	129 (74.1%)	106 (67.1%)	
Other	51(10.0%)	7 (29.2%)	16 (10.5%)	7 (4.0%)	21 (13.3%)	
WHO GRADE						<0.001
Low	52(10.2%)	1 (4.2%)	16 (10.5%)	7 (4.0%)	28 (17.7%)	
High	67(13,2%)	11 (45.8%)	25 (16.4%)	18 (10.3%)	13 (8.2%)	
Unknow	389(76.6%)	12 (50.0%)	111 (73.0%)	149 (85.6%)	117 (74.1%)	
EXTENSION						0.213
Cerebellum	381(75.0%)	17 (70.8%)	105 (69.1%)	137 (78.7%)	122 (77.2%)	
Brainstem	59(11.6%)	4 (16.7%)	20 (13.2%)	16 (9.2%)	19 (12.0%)	
Ventricular	31(6.1%)	1 (4.2%)	9 (5.9%)	9 (5.2%)	12 (7.6%)	
Other	37(7.3%)	2 (8.3%)	18 (11.8%)	12 (6.9%)	5 (3.2%)	
TUMOR SIZE						<0.001
<3cm	161(31.7%)	16 (66.7%)	55 (36.2%)	42 (24.1%)	48 (30.4%)	

>3cm	347(68.3%)	8 (33.3%)	97 (63.8%)	132 (75.9%)	110 (69.6%)	<0.001
VITAL STATUS						
Alive	129(25.4%)	8 (33.3%)	103 (67.8%)	143 (82.2%)	125 (79.1%)	
Dead	379(74.6%)	16 (66.7%)	49 (32.2%)	31 (17.8%)	33 (20.9%)	

GTR: gross total resection STR: Subtotal resection HIST: Histologic type
 Anaplastic ast :Anaplastic astrocytoma Pilocytic ast: Pilocytic astrocytoma

The average age of our study is 25.5year old, and the average survival time of patients is 73.8 months. In our study, most people were white, it accounts for78.0% of population, whereas 58(11.4%) were black, and 54(10.6%) were define as other group. Patients diagnosed during 2011–2015 is almost unchanged compared to 2004–2010 ($n = 252(49.6\%)$, vs $n = 256(50.4\%)$). From the perspective of tumor histology, majority of tumor were pilocytic astrocytoma 325(64.0%). 67(13.2%) were glioblastoma, 29(5.7%) were anaplastic astrocytoma, whereas 36(7.1%) were ependymoma, and 51(10.0%) were defined as others group. In terms of tumor's WHO grade, 52(10.2%) were assigned to low group, and 67(13,2%) were assigned to high group, whereas 389(76.6%) defined as other group according to the most recent CBTRUS. 75.0% of tumors were confined to the cerebellum, 59(11.6%) were extended to brainstem, and 31(6.1%) were extended to the ventricular. Among them, 24(4.7%) patients were received Local excision /biopsy only, 152(29.9%) patients treated with received STR (subtotal resection) ,174(34.3%) patients received underwent GTR (gross total resection), and 158(31.1%)patients underwent resection lobe of brain .The overall survival rate of GTR group was also the highest ($P<0.001$).

Prognostic Factors of OS

The univariate analysis was used to identify significant characteristics in Table2.

Table 2 Univariate and Multivariate Analysis of Overall Survival

Characteristics	Univariate Analysis HR (95%CI)	P	Multivariate Analysis HR (95%CI)	P
AGE				
<20	0.03(0.02-0.06)	<0.001	0.25(0.13-0.49)	<0.001
20-60	0.21(0.15-0.31)	<0.001	0.35(0.23-0.53)	<0.001
>60	Reference		Reference	
RACE				
White	1.11(0.62-1.99)	0.72	0.76(0.41-1.41)	0.39
Black	Reference		Reference	
Other	2.22(1.12-4.40)	0.02	1.01(0.47-2.16)	0.97
SEX				
Female	Reference			
Male	1.16(0.82-1.64)	0.40		
YEAR				
2004-2010	0.96(0.68-1.36)	0.80		
2011-2015	Reference			

HIST				
Glioblastoma	1.93(1.19-3.12)	0.007	4.92(2.55-9.46)	<0.001
Ependymoma	0.23(0.11-0.47)	<0.001	0.78 (0.33-1.84)	0.57
Anaplastic astrocytoma	Reference		Reference	
Pilocytic astrocytoma	0.02(0.01- 0.04)	<0.001	0.119 (0.04-0.29)	<0.001
Other	0.34(0.19 -0.62)	<0.001	1.06 (0.50-2.24)	0.87
WHO GRADE				
Low	0.08(0.03-0.19)	<0.001	0.30(0.12-0.79)	0.015
High	Reference		Reference	
Unknow	0.14(0.09-0.20)	<0.001	0.43(0.27-0.68)	<0.001
EXTENSION				
Cerebellum	0.45(0.28-0.71)	<0.001	0.60(0.37-0.97)	0.04
Brainstem	Reference		Reference	
Ventricular	0.78(0.37-1.65)	0.52	1.19(0.57-2.58)	0.66
Other	1.40(0.76-2.57)	0.28	1.00(0.53-1.91)	0.99
TUMOR SIZE				
<3cm	Reference			
>3cm	0.78(0.55-1.12)	0.18		
SURGERY				
Local excision/biopsy	6.23 (3.40 -11.41)	<0.001	2.18(1.10-4.29)	0.02
STR	2.02 (1.28-3.16)	0.002	1.10(0.68-1.77)	0.70
GTR	Reference		Reference	
Resection lobe of brain	1.13 (0.69 -1.84)	0.64	1.05(0.63-1.77)	0.84

including age, race, histologic type, tumor WHO grade, tumor extension, and surgery. Kaplan–Meier curves were painted to compare the overall survival cerebellar glioma by different variates as showed in Figure2.

Figure2

Figure 2. Kaplan–Meier curves for patients with cerebellum glioma by different variates. **(A)** Age, **(B)** Histology, **(C)** WHO Grade, **(D)**Extension, **(E)** Surgery.

The result showed that age ($P < 0.001$), histology type ($P < 0.001$), WHO grade ($P < 0.001$), surgery ($P < 0.001$), these factors are related to the overall survival of the patients. Next, the nomograms model was build based on the five characteristics: age, race, extension, tumor grade, histological type, and surgery as showed in Figure 3.

Figure 3

Figure 3. Nomogram for overall survival rate

The 3-year and 5-year overall survival rate were evaluated by nomogram to compute the corresponding score. Then, we randomly divide the data into Validation group and training group. Among them, there are 356 people in the training group and 152 people in the validation group. There has no significant statistical difference between the two groups (Table 3).

Table 3 Training and validation of cerebellum glioma patient.

Characteristics	All <i>n</i> (%)	Training <i>n</i> (%)	Validation <i>n</i> (%)	<i>p</i>
AGE				0.586
<20	290(57.1%)	198	92	
20-60	151(29.7%)	109	42	
>60	67(13.2%)	49	18	
RACE				0.405
White	396(78.0%)	273	123	
Black	58(11.4%)	45	13	
Other	54(10.6%)	38	16	
SEX				0.373
Female	252(49.6%)	172	80	
Male	256(50.4%)	184	72	
YEAR				0.615
2004-2010	252(49.6%)	182	74	

2011-2015	256(50.4%)	174	78	
HIST				0.396
Glioblastoma	67(13.2%)	50	17	
Ependymoma	36(7.1%)	27	9	
Anaplastic astrocytoma	29(5.7%)	17	12	
Pilocytic astrocytoma	325(64.0%)	225	100	
other	51(10.0%)	37	14	
WHO GRADE				0.206
Low	52(10.2%)	42	10	
High	67(13.2%)	46	21	
Unknown	389(76.6%)	268	121	0.300
EXTENSION				
Cerebellum	381(75.0%)	268	113	
Brainstem	59(11.6%)	41	18	
Ventricular	31(6.1%)	25	6	
Other	37(7.3%)	22	15	
TUMOR SIZE				0.651
<3cm	161(31.7%)	115	46	
>3cm	347(68.3%)	241	106	
SURGERY				0.957
Local excision/biopsy	24(4.7%)	17	7	
STR	152(29.9%)	109	43	
GTR	174(34.3%)	120	54	
Resection lobe of brain	158(31.1%)	110	48	
STATUS				0.563
Alive	129(25.4%)	263	116	
Dead	379(74.6%)	93	36	

C-index (receiver operating curve) and internal calibration curve were plotted to verify the accuracy and discriminative of the model. The C-index of overall survival rate prediction was 0.909 (95% CI, (0.880-0.938)) and 0.932 (95% CI, (0.889-0.975)), respectively. The ROC (receiver operating curve) and AUC (area under curve) were plotted. The area under curve values of the 3 year- and 5-year overall survival rates in the training group were 0.935 and 0.941, and in the validation group were 0.966 and 0.949 (Figure 4), which suggested that the predictive model was effective and accurate. The calibration curve of overall survival rate at 3 year- and 5-year shows that there was an excellent consistency between the predicted survival probability and the actual survival probability (Figure 5).

Figure 4. Time-dependent ROC curve and areas under ROC curve. Areas under ROC curve of 3-year overall survival rates in training group **(A)** and validation group **(B)**. Areas under ROC curve of 5-year overall survival rates in training group **(C)** and validation group **(D)**.

Figure 5

Figure 5. Internal calibration plots of 3-year overall survival rates in training group (A) and validation group (B). Internal calibration plots of 5-year overall survival rates in training group (C) and validation group (D)

Discussion

CNS (Central nervous system) tumors comprise a majority of malignant and benign neoplasms prevalent across the entire age spectrum⁶. Although the incidence of central nervous system tumors is higher in adults, it is also the main cause of death in children⁷. The cerebellar glioma is a common type of central nervous system tumor in children but relatively rare in adults¹. Since the incidence of cerebellar glioma is not high, there are not many studies focus on this area. Central nervous system tumors, especially tumors of the cerebellum and brainstem causing the greatest proportion of deaths (37.9% and 16.6%, respectively)⁸. Patients with cerebellar glioma often present with the symptom of intracranial hypertension, and some cerebellar symptoms for example ataxia in walking, unstable standing, dizziness, mental disorders and other symptoms that seriously affect the quality of daily life^{2,9-13}. Our analysis of patients with cerebellar glioma demonstrated that the the younger the patient with cerebellar glioma, the better the prognosis, and age is an important factor affecting the prognosis. The difference in the prognosis of children and adults may be

caused by differences in the molecular mechanism of tumors, but our study did not include the study of molecular mechanisms, because there is no relevant information about molecular mechanisms in the seed database. Ranjith Babu et al found that: Patients older than 40 years has poor outcomes, and age over 65 years had worst survival rate (4 versus 12 months, $p < 0.0001$) compared to the younger patients¹⁴. Our study found that the prognosis of patients with cerebellar glioma is independent of gender. In terms of races, univariate analysis shows that there has no difference in the prognosis of whites and blacks, and the prognosis of the rest of the population is worse, but the difference was disappeared after multivariate analysis. *Zhuoyi Liu* reported that whether in univariate analysis or multivariate analysis: the prognosis of tumors has nothing to do with gender and race¹⁵. Our study found that cerebellar glioblastoma had the worst prognosis, followed by anaplastic astrocytoma, and pilocytic astrocytoma had the best prognosis. These differences were statistically significant regardless of univariate analysis or multivariate analysis. Glioblastoma has a high degree of malignancy, its growth rate is blocky, the boundary is not clear, and the operation is difficult to complete, which is the main reason for the poor prognosis. Xingwang Zhou et al demonstrates that oligodendroglioma, anaplastic glioma and glioblastoma were risk factors of early mortality for children, and pointed out that glioblastoma increases early childhood mortality¹⁶. Ankush Chandra et al found a very meaningful study: tumor >40 mm were associated with decreased survival for patients with supratentorial glioblastoma¹⁷. But in our study, the prognosis of cerebellar glioma has little to do with the size of the tumor. This may be because there is no obvious correlation between the size and the degree of malignancy of the tumor. In this study, we found that the higher the WHO grade of the tumor, the worse the prognosis, the lower the patient's median survival time and overall survival rate. Adams et al found that the prognosis of high-grade gliomas was much worse than that of low-grade gliomas¹⁸. Some scholars found that the higher the grade of glioma, the higher the activity level and the higher the tumor angiogenesis¹⁹. Also, malignant high-grade gliomas are diffuse and infiltrating lesions that often infiltrate some important peripheral functional areas, which seriously affect the quality of life of patients²⁰. In terms of the extension of the tumor, tumors confined to the cerebellum have the best prognosis, and the prognosis is poor after expansion to the brainstem. It may be that after the tumor has expanded to the brainstem, it is difficult to completely removed, because the brainstem is the core part of the brain. Weber et al found that extent of surgery and brainstem involvement were associated with poorer survival¹⁴. The conclusion is roughly the same as ours. As for extent of tumor resection, univariate analysis showed that patients with total tumor resection had the best prognosis and the highest overall survival rate. Univariate analysis showed that patients with total tumor resection had the best prognosis and the highest overall survival rate. However, in a multivariate analysis, the overall survival rate of the patient has little to do with the degree of tumor resection. Our research also has many limitations. First of all, the data available in SEER is observational. The allocation of subjects is arbitrary and lacks randomization. Secondly, we do not have the authority to obtain information about radiotherapy and chemotherapy. Currently, chemotherapy is considered to be

the standard treatment for patients with the following diseases: high-grade glioma in the United States. In addition, other important factors are not easily available in the SEER database, which includes the patient's preoperative symptoms, imaging data, family financial status, postoperative neurological function, and the patient's postoperative quality of life. Our research is a retrospective clinical study, with the general limitations of retrospective studies. Therefore, it is necessary to conduct high-quality prospective studies to verify our conclusions.

Conclusion

Our study is a large-scale population-based study of cerebellar glioma. It directly compares factors such as age, gender, tumor size, histological type, grade, and resection, founding that young age, pilocytic astrocytoma, low-grade, and confined tumor, can significantly prolong the survival time of patients with cerebellar glioma while cerebellar glioblastoma can significantly reduce the survival time of the patients. Our study provides very useful information for further research on cerebellar glioma.

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