Involvement of subventricular zone shortened the survival of pediatric glioblastoma

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Abstract

PURPOSE

Glioblastoma involved with subventricular zone (SVZ) predicted a worse outcome in adult, but we know less about it based on children population due to the rarity of pediatric glioblastoma (pGBM). We performed this study to probe into the clinical and prognostic features of glioblastoma involved with SVZ in children.

METHODS

We selected thirty-one patients diagnosed with pediatric supratentorial glioblastoma at our department between January 2015 and January 2020. Clinical data and prognostic results were reviewed retrospectively.

RESULTS

Involvement of SVZ was associated with larger tumor volume ($p = 0.007$), lower edema index (EI) ($p = 0.010$), passive adjuvant therapy ($p = 0.029$), worse progression-free survival (PFS) ($p = 0.001$) and overall survival (OS) ($p < 0.001$), it didn't correlate to age, sex, preoperative KPS, extent of resection (EOR), tumor side, Ki-67, expression of P53 and ATRX and mutation of IDH1 and IDH2 genes. Independent of EOR and adjuvant therapies, involvement of SVZ was a prognostic factor of PFS and OS in pGBM.

CONCLUSION

Involvement of SVZ was an independent prognostic factor of PFS and OS in pGBM, and it associated with large volume, mild edema and passive adjuvant therapy. More research should be developed to optimize the treatment strategy of pGBM involved with SVZ.

Introduction

Glioblastoma (GBM) is a rare malignant tumor of the central nervous system in children. According to statistics, the annual incidence rate is 1.4/ million, accounting for 3% of the primary tumors of the central nervous system in children [1, 2]. Several studies had demonstrated that maximum safe resection of tumor and postoperative radiotherapy (RT) and chemotherapy (CT) were effective treatment for pediatric glioblastoma (pGBM) [3–7]. However, the median overall survival (OS) was still between one and two years after active treatment [5, 8, 9].

Subventricular zone (SVZ) is a neurogenic area which harbors neural stem cells. In recent research, glioma stem cells were found in SVZ, which play a critical role in the occurrence and progression of

glioma [10–12]. It has been proved that adult GBM involved with SVZ predict an adverse prognosis and tend to present a multifocal tumor phenotype in many studies [13–16].

Because of the rarity of pGBM, the clinical features and prognostic outcomes about pGBM involved with SVZ had never been described before. To better comprehend its clinical features and provided basis for judgment of prognosis preoperatively, we retrospectively analyzed the institutional database for 31 patients with pediatric supratentorial GBM diagnosed and treated at our hospital during 2015–2020.

Materials And Methods

Ethical statement

The implementation of this study had been approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. The use of data for analysis had been agreed by all patients. No personal information was disclosed in this article.

Patient selection

Thirty-one patients with histopathologically confirmed diagnosis of GBM at our hospital between January 2015 and January 2020 were selected for review. All patients were newly diagnosed with primary supratentorial GBM and were under 18 years at the time of diagnosis. In addition, cases with incomplete clinical data or not treated according to the Stupp protocol were excluded.

Data collection

Data collection included age of diagnosis, sex, preoperative KPS, tumor side, adjuvant therapy, tumor volume, edema index (EI), extent of resection (EOR), involvement of SVZ, immunohistochemistry indexes (ATRX, Ki-67, P53), genetic testing (IDH1 and IDH2), overall survival (OS) and progression-free survival (PFS). Evaluating of KPS was routinely completed by the neurosurgeon before operation. Postoperative radiotherapy was given at 2gy per day, 5 days per week, with a total dose of 50-60gy. Temozolomide was prescribed for chemotherapy according to Stupp 5/28 regime [3]. Tumor volume was measured with a preoperative T1-weighted MR images after injection of gadolinium. Peritumoral brain edema (PTBE) was evaluated on T2-weighted images. The maximum perpendicular diameters (A and B) of the tumor and the PTBE were measured on the axial images, and the diameter in the coronal direction (C) was measured on the coronal or sagittal image, the formula used to calculate tumor and PTBE volume was $V = 4/3\pi \times A/2 \times B/2 \times C/2$. To reduce artificial bias, tumor and PTBE volume were measured by three neurosurgeons and the mean value was recorded. Severity of edema was evaluated by edema index (EI), it was calculated by the formula: $EI = (V_{\text{tumor}} + V_{\text{edema}})/V_{\text{tumor}}$ [17]. The extent of resection was verified by comparing preoperative MRI with that performed within 72 hours after surgery. GTR was defined as no residual enhancement on postoperative enhanced MRI and STR was defined while any residual enhancement was observed. Typical images of involvement with SVZ are shown in Fig. 1. The neurosurgeons who completed the collection of imaging data knew nothing about the clinical

characteristics and outcomes of the patients. OS was defined as time between the initial treatment and death or the last follow-up. PFS was defined as time between the initial treatment and diagnosis of tumor recurrence. Follow-up was performed for all patients by making phone call once every two months or outpatient review on a timely basis.

Statistical analysis

Age, tumor volume, EI, Ki-67, PFS and OS were analyzed as continuous variables, whereas gender, tumor side, immunohistochemistry indexes (positive or negative), genetic testing (mutant or wild-type), KPS (≥ 80 or <80), EOR (GTR or STR), adjuvant therapy (Radiotherapy combined with chemotherapy; Other: incomplete adjuvant therapies including chemotherapy only, radiotherapy only and none) and involvement with SVZ were analyzed as a categorical variables. Mann Whitney U test was used to evaluate the distribution of continuous variables and Fisher's exact test was employed to evaluate the distribution of categorical variables. Kaplan–Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). Variables analyzed in univariate Cox regression model analysis included the variables that may affect the survival including age, sex, tumor volume, EI, preoperative KPS, EOR, adjuvant therapy, Ki67 and SVZ involvement. Log-rank test was employed to compare survival distribution. Multivariate Cox proportional hazard model analysis included all variables with $P < 0.05$ in univariate analysis. $P < 0.05$ was defined as statistically significant. All statistical analyses were performed using IBM SPSS 22.0 software. Box plots and survival curves were completed by Graph Pad Prism 9.

Results

Involvement of SVZ relates to large tumor volume, mild edema, passive treatment and poor prognosis.

The distributions of continuous variables and categorical variables with statistical analysis results were summarized in Table 1 and Table 2 respectively. Box graphs showing the distribution of continuous variables were presented in Fig. 2. No gender or side predominance was found for tumor involved with SVZ. Age, Ki-67, EI, EOR and preoperative KPS didn't differ in patients who had a tumor involved with SVZ. However, patients who had a tumor involve with SVZ were more likely to receive passive adjuvant therapy ($p = 0.029$). There were no differences in the results of ATRX and p53 immunohistochemistry between patients with SVZ involvement and patients without SVZ involvement. The tumor volume was significantly larger when SVZ was involved ($p = 0.007$), but it tended to have a mild PTBE ($p = 0.010$). We observed a decline on PFS ($p = 0.001$) and OS ($p < 0.001$) in subset of tumor involve with SVZ.

Involvement of SVZ is an independent prognostic factor for pGBM.

The median follow-up was 12 months (range 2 to 48 months). Median PFS and OS were respectively 6 and 10.5 months. Half-year, 1-year and 2-year PFS rates were 80.6%, 48.4% and 12.9%, respectively, vs. OS counterparts of 58.1%, 19.4% and 6.5%, respectively. Involvement of SVZ ($p = 0.001$ for PFS; $p < 0.001$ for OS), EOR ($p = 0.003$ for PFS; $p = 0.003$ for OS), adjuvant therapy ($p = 0.007$ of PFS; $p = 0.007$ for OS)

were identified as prognostic factor for PFS and OS on univariate analysis, patients with tumor involve SVZ, STR or incomplete adjuvant therapy predicted a worse PFS and OS (Table 3, Fig. 3, Fig. 4). Multivariate analysis showed patients with tumor involve SVZ (HR = 2.888; 95%CI, 1.096–7.630; $p = 0.032$ for PFS and HR = 6.033; 95%CI, 1.789–20.343, $p = 0.004$ for OS), STR (HR = 3.490; 95%CI, 1.381–8.819; $p = 0.008$ for PFS and HR = 3.305; 95%CI, 1.366–7.995, $p = 0.008$ for OS) or incomplete adjuvant therapy (HR = 3.405; 95%CI, 1.348–8.600; $p = 0.010$ for PFS and HR = 2.587; 95%CI, 1.093–6.124, $p = 0.031$ for OS) were independent risk factor for bad PFS and OS.

Discussion

Involvement of SVZ had been proved to be a prognostic factor for adult GBM in many researches [14–16, 18–21]. The clinical significance of this finding was to help us judge the prognosis of patients before surgery. On the one hand, several studies have reported the discovery of glioma stem cell in SVZ, where provides a protective environment and increase resistance to irradiation and chemotherapy [22–29]. On the other hand, tumor cells could shed into the lateral ventricle and spread with cerebrospinal fluid, resulting in poor progression free survival and overall survival. However, due to the rarity of pediatric glioblastoma, nearly all of the reports about SVZ were based on adult population in the past. The only report containing some cases of high-grade glioma in children found a poor prognosis for high-grade glioma patients with involvement of SVZ, suggesting that the prognosis of high-grade glioma patients with involvement of SVZ in children may be as poor as that of adults [15]. We are the first to research on the impact of tumor involved with SVZ on survival in children population. Our results indicated that involvement of SVZ is a prognostic factor for PFS and OS in pGBM independent of EOR and adjuvant therapy.

Researchers held different opinions on the relationship between SVZ involvement and total resection rate in the past reports [14, 21]. In order to avoid the risk of communicating hydrocephalus and the spread of tumor with cerebrospinal fluid caused by ventriculotomy, many neurosurgeons tend not to remove the entire tumor which involved lateral ventricle [30]. However, it had also been reported that surgical incision of lateral ventricle to achieve complete resection of supratentorial GBM has a better prognosis [31]. Our results confirmed that there was no relationship between GTR and involvement of SVZ, however, since GTR could prolong the survival of pGBM in our study, we advise to realize GTR with the application of microsurgical technology and intraoperative neuronavigation as far as possible even facing tumor involved with SVZ.

Adult GBM with no SVZ involvement were more likely to receive active adjuvant therapy in the literature [14], they attributed this difference to raised suspicion for treatment given by mild symptoms (higher KPS) of patients, we also found active treatment were given to patients with no SVZ in pGBM cases, but our patients didn't represent a serious condition when SVZ was involved.

Harat M et al. showed SVZ infiltration of GBM by O-(2-[^{18}F] fluoroethyl)-L-tyrosine (FET) PET scan, they found SVZ infiltration was correlated to larger tumor volumes [32]. Our results also showed that

supratentorial GBM with SVZ infiltration were larger in children. To some extent, tumor itself may not originated from SVZ, but invaded SVZ with its growth. This view was supported by the theory that tumor stem cells migrate along the CXCL12 / CXCR axis or pleiotrophin-driven axis to SVZ [33, 34]. According to our results, we could speculate that the same mechanism of glioma stem cell migration also exists in children.

Although it has been reported that the degree of PTBE is not related to tumor volume [35], however, surprisingly, we found that pGBM exposed to SVZ had lower edema index (EI), which may be related to the expression of aquaporins and tumor microenvironment, we hope the specific mechanism can be studied in future. Meanwhile, mild PTBE suggests that patients with SVZ involvement may needn't to use steroids or mannitol before surgery to reduce tumor edema.

Status of IDH gene has been tested routinely in our center. Because of the low incidence of IDH gene mutation, relationship between IDH gene mutation and SVZ involvement cannot be analyzed properly. In consideration of it had been reported that IDH gene mutation is not associated with SVZ infiltration in adults GBM [25, 36], we need a larger sample size to confirm the result in pGBM. In addition, we found that there was no difference in the expression of ATRX and p53 between SVZ contact subset and no SVZ contact subset, which indicated that the poor prognosis caused by SVZ exposure was not related to these pathological prognostic indicators.

At present, no particular treatment was applied on GBM with SVZ involvement. In the retrospective analysis, whether patients can benefit from radiotherapy for SVZ is still controversial [37, 38]. A prospective study found that patients with radiation necrosis in SVZ have a longer survival time [39]. Several drug treatments are being studied, it had been reported that CXCL12 inhibitors can improve radiosensitivity and reduce tumor cell proliferation in animal models [33]. Besides, administration of drugs, vectors or cells in the lateral ventricles, which can bypass the blood-brain barrier, have been considered as a more effective treatment in theory, and obtained positive results in animal models [40–43]. Our study shows that RT + CT is still an effective therapy of pGBM, but the treatment of pGBM with SVZ infiltration needs further study in the future.

Conclusion

We have proved that SVZ involvement is an independent prognostic factor in this study, and we found it also associate with large tumor volume, mild PTBE and passive adjuvant therapy. Even though there weren't any available specific treatment for GBM with SVZ involvement, some possible therapies have been proved to be effective in animal models. We hope more research could be developed to optimize the treatment strategy of GBM involved with SVZ.

Abbreviations

SVZ, subventricular zone

pGBM, pediatric glioblastoma

GBM, glioblastoma

EI, edema index

PTBE, peritumoral brain edema

PFS, progression-free survival

OS, overall survival

EOR, extent of resection

RT, radiotherapy

CT, chemotherapy

Declarations

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Conflicts of interest

Neither I nor my spouse/partner has a commercial interest, financial interest, and/or other relationship with manufacturers of pharmaceuticals, laboratory supplies, and/or medical devices or with commercial providers of medically related services.

Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable

Authors' contributions

Yang Jiao: Conceptualization, Data Curation, Writing-Original Draft Preparation.

Meng Wang: Writing-Reviewing and Editing

Xueyou Liu: Writing-Reviewing and Editing

Junkuan Wang: Writing-Reviewing and Editing

Wenzheng Luo: Writing-Reviewing and Editing

Yang Yu: Writing-Reviewing and Editing

Hongwei Sun: Supervision, Writing-Reviewing and Editing

Ethics approval

The implementation of this study has been approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University. The use of data for analysis has been agreed by all patients. No personal information will be disclosed in this article.

Consent to participate

Consent to participate in our study had been obtained from parents of every patient.

Consent for publication

Written informed consent for publication was obtained from all participants.

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Tables

Table 1
Comparisons of categorical variables and statistical results based on SVZ involvement.

	SVZ contact	No SVZ contact	Fisher exact test (Two-side)
Gender	6	10	P = 0.722
Male	7	8	
Female			
KPS	5	10	P = 0.473
≥80	8	8	
<80			
EOR	4	11	P = 0.149
GTR	9	7	
STR			
Side	5	6	P > 0.999
Left	8	12	
Right			
Adjuvant therapy	3	12	P = 0.029
RT + CT	10	6	
Other			
ATRX	10	13	P = 0.999
Positive	3	5	
Negative			
P53	10	14	P = 0.999
Positive	3	4	
Negative			
IDH1	1	1	P = 0.999
Mutant	12	17	
Wild-type			

EOR, extent of resection; GTR, gross total resection; STR, sub-total resection; RT, radiotherapy; CT, chemotherapy.

	SVZ contact	No SVZ contact	Fisher exact test (Two-side)
IDH2	0	0	Unavailable
Mutant	13	18	
Wild-type			
EOR, extent of resection; GTR, gross total resection; STR, sub-total resection; RT, radiotherapy; CT, chemotherapy.			

Table 2
Comparisons of continuous variables and statistical results based on SVZ involvement.

	SVZ contact (mean $\pm$ SD)	No SVZ contact (mean $\pm$ SD)	Mann Whitney U test (Two side)
Age (years)	11.5 $\pm$ 5.1	13.2 $\pm$ 4.1	p = 0.409
Volume (cm ³)	52.1 $\pm$ 32.9	20.6 $\pm$ 15.4	P = 0.007
Ki-67 (%)	41.9 $\pm$ 21.6	43.8 $\pm$ 18.7	P = 0.929
EI	1.8 $\pm$ 0.8	4.2 $\pm$ 3.7	P = 0.010
OS (months)	7.6 $\pm$ 4.1	19.4 $\pm$ 9.9	P < 0.001
PFS (months)	5.4 $\pm$ 3.0	13.6 $\pm$ 10.5	P = 0.001
EI, edema index; OS, overall survival; PFS, progression-free survival			

Table 3
Univariate and multivariate analysis of prognostic factors for PFS and OS.

Prognostic Factors	Univariate analysis		Multivariate analysis	
	PFS	OS	PFS	OS
Age				
HR	0.970	0.936		
95%CI	0.890–1.058	0.856–1.024		
P Value	0.498	0.150		
Sex				
HR	1.297	1.352		
95%CI	0.615–2.734	0.633–2.888		
P Value	0.494	0.436		
Volume				
HR	1.005	1.105		
95%CI	0.989–1.022	0.998–1.032		
P Value	0.504	0.083		
EI				
HR	0.979	0.926		
95%CI	0.827–1.158	0.773–1.110		
P Value	0.803	0.406		
KPS				
HR	1.951	2.101		
95%CI	0.877–4.343	0.976–4.522		

PFS, progression-free survival; OS, overall survival; EI, edema index; EOR, extent of resection; HR, hazard ratio; SVZ, subventricular zone.

Prognostic Factors	Univariate analysis				Multivariate analysis			
P Value	0.102		0.058					
Ki-67	1.001		1.005					
HR	0.980–1.021		0.984–1.027					
95%CI	0.970		0.636					
P Value	4.023		8.829		2.888		6.033	
SVZ contact	1.744–9.279		2.982–26.14		1.093–7.630		1.789–20.343	
HR	0.001		0.000		0.032		0.004	
95%CI								
P Value								
EOR								
HR	3.384		3.451		3.490		3.305	
95%CI	1.500-7.634		1.538–7.743		1.381–8.819		1.366–7.995	
P Value	0.003		0.003		0.008		0.008	
Adjuvant therapy	3.056		2.888		3.405		2.587	
HR	1.358–6.879		1.344–6.204		1.348-8.600		1.093–6.124	
95%CI	0.007		0.007		0.010		0.031	
P Value								
PFS, progression-free survival; OS, overall survival; EI, edema index; EOR, extent of resection; HR, hazard ratio; SVZ, subventricular zone.								

Figures

Figure 1

GTR was defined as no residual enhancement on postoperative enhanced MRI and STR was defined while any residual enhancement was observed. Typical images of involvement with SVZ are shown in Fig1.

Figure 2

Box graphs showing the distribution of continuous variables were presented in Fig2.

Figure 3

OS counterparts of 58.1%, 19.4% and 6.5%, respectively. Involvement of SVZ ($p=0.001$ for PFS; $p<0.001$ for OS), EOR ($p=0.003$ for PFS; $p=0.003$ for OS), adjuvant therapy ($p=0.007$ of PFS; $p=0.007$ for OS) were identified as prognostic factor for PFS and OS on univariate analysis, patients with tumor involve SVZ, STR or incomplete adjuvant therapy predicted a worse PFS and OS (Table 3, Fig 3, Fig4).

Figure 4

OS counterparts of 58.1%, 19.4% and 6.5%, respectively. Involvement of SVZ ($p=0.001$ for PFS; $p<0.001$ for OS), EOR ($p=0.003$ for PFS; $p=0.003$ for OS), adjuvant therapy ($p=0.007$ of PFS; $p=0.007$ for OS) were identified as prognostic factor for PFS and OS on univariate analysis, patients with tumor involve SVZ, STR or incomplete adjuvant therapy predicted a worse PFS and OS (Table 3, Fig 3, Fig4).