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Research article

The impact of the subventricular zone invasion types and MGMT methylation status on tumor recurrence and prognosis in glioblastoma

Zhiying Shao [a,b,1], Hao Yan [b,c,d,1], Min Zhu [b,c,d,1], Zhengyang Liu [b,c,d], Ziqin Chen [b,c,d], Weiqi Li [b,c,d], Chenyang Wang [b,c,d], Longzhen Zhang [b,c,**], Junnian Zheng [c,d,*]

[a] Department of Clinical Trial, Zhejiang Cancer Hospital, Hangzhou Institute of Medicine (HIM), Chinese Academy of Sciences, Hangzhou, Zhejiang, 310022, China
[b] Cancer Institute, Xuzhou Medical University, 209 Tongshan Road, Xuzhou, Jiangsu, 221004, China
[c] Center of Clinical Oncology, The Affiliated Hospital of Xuzhou Medical University, 99 West Huaihai Road, Xuzhou, Jiangsu, 221002, China
[d] Jiangsu Center for the Collaboration and Innovation of Cancer Biotherapy, Xuzhou Medical University, 209 Tongshan Road, Xuzhou, Jiangsu, 221004, China

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ABSTRACT

Purpose: The prognosis of isocitrate dehydrogenase (IDH) wild-type glioblastoma (GBM) with the subventricular zone (SVZ) invasion is extremely unfavorable but the underlying mechanism remains unclear. We aimed to conduct a retrospective study to mainly investigate the prognostic value of SVZ invasion and MGMT status, and developed a novel clinical prediction model based on our findings.

Methods: 139 patients with IDH wild-type GBM were retrospectively studied. They were categorized into four types, taking into consideration of the spatial positional relationship between tumor, SVZ and the cerebral cortex (Ctx) on the preoperative T1-weighted contrast-enhanced images (T1WI + C). Survival analysis was conducted to identify significant variables, which were then included in a clinical model to predict patient survival outcomes.

Results: Among the included patients, 41 (29.5 %) were type I, 23 (16.5 %) were type II, 59 (42.4 %) were type III, and 16 (11.5 %) were type IV. In Cox regression analysis, partial surgical resection, SVZ invasion, MGMT unmethylation, short adjuvant chemotherapy cycles, and distant recurrence were identified as independent risk factors of prognosis. A clinical prediction model based on these factors was developed to accurately predicted the survival outcome at 6, 12, and 18 months.

Abbreviations: CI, confidence interval; GBM, glioblastoma; EGFR, epidermal growth factor receptor; Ctx, cerebral cortex; HR, hazard ratio; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Score; MGMT, O-6-methylguanine-DNA-methyltransferase; mOS, median overall survival; MRI, magnetic resonance imaging; NSCs, neural stem cells; OS, overall survival; PFS, progression-free survival; SVZ, subventricular zone; TMZ, temozolomide; TTFields, tumor treating fields; T1WI + C, T1-weighted contrast-enhanced images.

* Corresponding author. Jiangsu Center for the Collaboration and Innovation of Cancer Biotherapy, Xuzhou Medical University, 209 Tongshan Road, Xuzhou, Jiangsu, 221004, China.

** Corresponding author. Department of Radiation Oncology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, 221004, China.

E-mail addresses: jsxyfyzlz@126.com (L. Zhang), jnzheng@xzhmu.edu.cn (J. Zheng).

[1] These authors contributed equally to this work.

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Conclusion: Both SVZ invasion and MGMT unmethylation negatively influenced the prognosis of patients with IDH wild-type GBM. The clinical model developed in this study accurately predicts the survival outcome, providing a basis and reference for clinical practice.

1. Introduction

Glioblastoma (GBM) is a prevalent and highly malignant primary brain tumor of the central nervous system [1]. It is well-known for its aggressive growth and high angiogenesis, which contribute to its early recurrence and poor prognosis [2]. The current standard treatment involves a maximum safe resection, along with concurrent chemoradiotherapy and adjuvant chemotherapy using temozolomide (TMZ) [3], which extends the median overall survival (mOS) of patients from 12.1 months to 14.6 months [4,5].

O-6-methylguanine-DNA-methyltransferase (MGMT) is a DNA repair enzyme predominantly located in the cytoplasm, responsible for repairing DNA damage caused by alkylating agents like TMZ to uphold genome stability within cells [6]. Methylation of the MGMT promoter induces alterations in chromatin structure, hindering the binding of transcription factors, resulting in gene silencing and subsequent loss of function, specifically the loss of DNA repair capability. Therefore, MGMT promoter methylation has been identified as a reliable predictor for determining the effectiveness of TMZ in GBM patients. Nevertheless, TMZ shows limited benefits in glioblastoma patients with unmethylated MGMT, which is the case for the majority of GBM [7,8].

The subventricular zone (SVZ) is a 3–5 mm thick area located adjacent to the lateral ventricle. It contains a high concentration of neural stem cells (NSCs) throughout adulthood [9]. The human SVZ is composed of an ependymal layer, a low cell space layer, a stellate cell band and a transition zone [10]. Recent research has increasingly supported the SVZ as a possible source of brain tumors. Several clinical studies have shown that invasion of the SVZ at the initial diagnosis is an independent risk factor for the prognosis of GBM, regardless of other prognostic factors such as age, degree of resection, MGMT status and recurrence pattern [11–14]. Lee et al. conducted experiments on human brain tumors, which demonstrated that GBM originates from SVZ cells with low-level drive mutations [10]. In clinical practice, magnetic resonance imaging (MRI) is predominantly used to identify the contact relationship between SVZ and the tumor [13]. However, there is a lack of objective criteria for observers to determine whether the tumors originate from SVZ or invade towards SVZ, which hampers the reliability of image-based classification [15]. Therefore, integrating imaging phenotypes with molecular features may allow for a more comprehensive assessment of patient conditions.

Clinical prediction models are typically constructed combining patients' clinical features, imaging characteristics, and molecular features. For example, Gittleman et al. established a predictive model using NRG Oncology RTOG 0525 and 0825 data, allowing for personalized prognosis assessment in newly diagnosed GBM based on their clinical characteristics and MGMT status [16]. Zheng et al. identified eosinophil infiltration as an independent prognostic factor impacting progression-free survival (PFS) in GBM, with their prognostic model achieving a concordance index of 0.629 [17]. Additionally, some researchers have developed molecular feature-based models to anticipate treatment response and recurrence in GBM patients [18–20]. These prediction models are established to attempt in assisting healthcare professionals in the diagnosis, treatment, and monitoring of GBM. The patient populations exhibit significant heterogeneity, yet few prediction models have thoroughly examined potential prognostic factors across various aspects.

This study applied an innovative approach by integrating imaging classification with molecular expression to analyze the recurrence and prognosis of GBM. The researchers developed a new clinical prediction model that accurately predicts the prognosis of patients. These findings have significant implications in clinical practice.

2. Materials and methods

2.1. Patients

This study retrospectively analyzed a total of 139 patients with IDH wild-type GBM who were treated at the Affiliated Hospital of Xuzhou Medical University from January 2015 to January 2023. Ethical approval was granted by the Ethics Committee of the affiliated hospital of Xuzhou Medical University (June 23, 2022/No. XYFY2022-KL198). The inclusion criteria for the study were as follows: confirmation of IDH wild-type GBM through pathology, undergoing surgery and chemoradiotherapy, no prior antitumor treatment before surgery, and availability of complete follow-up data. Patients under 18 years old at the time of diagnosis, those with a history of low-grade glioma or other tumors, presence of other serious diseases, and those with irregular treatment were excluded.

The study collected basic information of patients, including gender, age at diagnosis and postoperative Karnofsky Performance Score (KPS) from medical electronic records. The degree of surgical resection was categorized as either total resection or partial resection based on the presence of residual contrast-enhanced lesions. Tumor progression was evaluated according to RANO criteria by three experienced radiologists and radiation oncologists. PFS was defined as the duration from surgery to the date of progression assessed by imaging or death. OS was defined as the duration from surgery to the date of death or the last follow-up. All patients were diagnosed, treated and followed up at our hospital. The patients were then divided into two groups: the short cycle group (<6 cycles) and the long cycle group (≥ 6 cycles).

2.2. Imaging and molecular detection

The criterion refers to the proximity of the patient's preoperative magnetic resonance contrast-enhanced lesions to SVZ should be less than 5 mm. GBM are classified into four types based on the Lim classification [13]. Type I refers to the invasion of both SVZ and Ctx (SVZ+/Ctx+), type II refers to the invasion of only SVZ (SVZ+/Ctx-), type III refers to the invasion of only Ctx (SVZ-/Ctx+), and type IV refers to the invasion of neither SVZ nor Ctx (SVZ-/Ctx-) (Fig. 1a–d). The maximum diameter of the tumor was measured on the sagittal, coronal and axial views of the preoperative contrast-enhanced sequence. Recurrence patterns were assessed based on the following criteria: (a) The number of recurrent lesions categorized patients into single lesion or multiple lesions. (b) The relationship between the recurrent lesion and the tumor bed determined if it was a local recurrence or distant recurrence. (c) The distance between the recurrent lesion and the tumor bed categorized it as in situ recurrence, peripheral recurrence or extended recurrence ($<$2 cm, 2–4 cm, and $>$ 4 cm, respectively). MGMT promoter status was determined using real-time fluorescence quantitative PCR, with a positive criterion of $\Delta Ct \leq 9$. Ki-67 (%) was assessed through immunohistochemistry analysis. IDH, TP53, and EGFR status were determined using second-generation sequencing. All samples tested met the qualification criteria.

2.3. Risk factor screening and predictive model construction

Through univariate and multivariate Cox regression analysis, independent risk factors influencing prognosis were identified. Subsequently, relevant data was organized and pre-processed to address missing values, outliers, data conversion, and standardization. The data was randomly grouped using the internal random grouping package in R to create a training set and a test set. The predictive model was developed by training the model with the training set data.

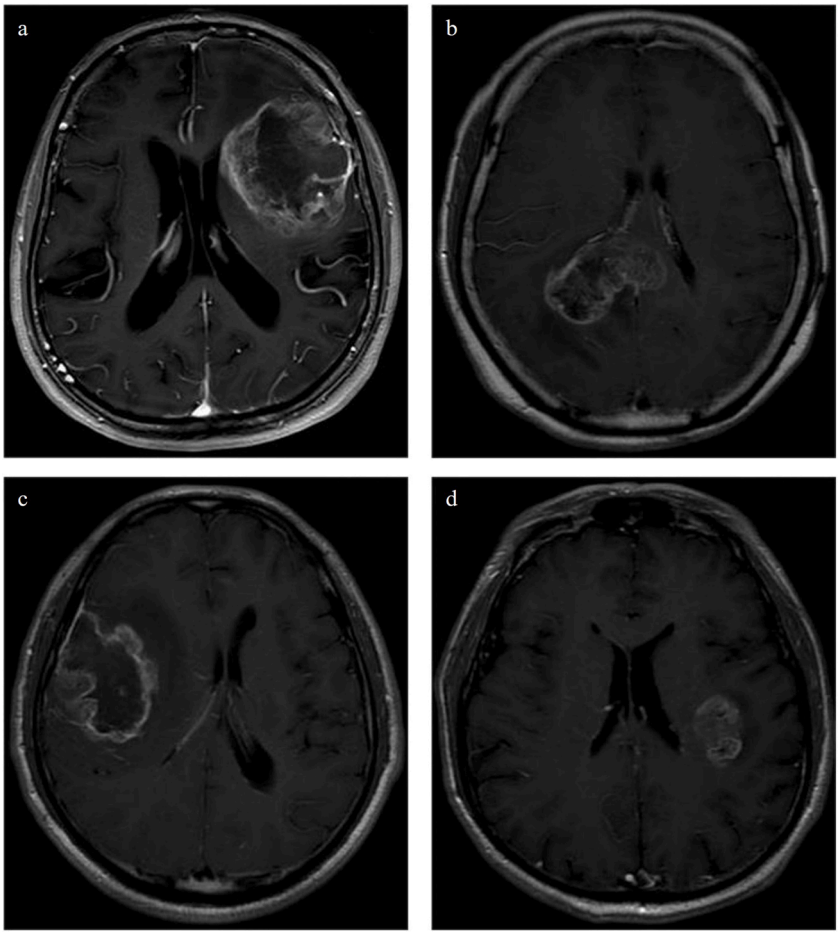

Fig. 1. Classification of GBM into four types based on preoperative MRI T1 enhancement. Type I, tumors invaded both SVZ and Ctx (a); Type II, tumors invaded only SVZ (b); Type III, tumors invaded only Ctx (c); Type IV, tumors did not invade SVZ or Ctx (d).

2.4. Statistical analysis

The proportion and difference of categorical variables in each group were compared using either the Chi-square test or Fisher's exact test. Numerical variables were analyzed using either one-way analysis of variance or independent sample *t*-test. Kaplan-Meier survival curves were generated to analyze PFS and OS, with the log-rank test used to compare between groups. Hazard ratios were calculated using the univariate Cox regression model, and the multivariate Cox regression model was used to account for confounding factors in survival analysis. Statistical analysis and mapping were performed using SPSS (v26, IBM, USA) and GraphPad Prism (9.0, GraphPad Software, USA). Clinical prediction modeling was conducted using R (R 4.3.1, New Zealand). A two-tailed test was employed, and statistical significance was defined as $P < 0.05$.

3. Results

A total of 266 patients diagnosed with GBM underwent surgery. However, 127 patients were excluded duo to incomplete imaging data (52 cases), lost to follow-up (15 cases), existence of IDH mutation (11 cases) and unconventional treatment as either stereotactic body radiation therapy or no radiotherapy (49 cases). Consequently, we included a total of 139 patients. Among the included patients, 41 (29.5 %) were classified as type I, 23 (16.5 %) as type II, 59 (42.4 %) as type III, and 16 (11.5 %) as type IV. Throughout the follow-up period, 132 patients experienced recurrence and 132 patients passed away. Patients with the invasion of both SVZ and Ctx (type I) had the worst PFS and OS rates (Fig. 2a and b).

In terms of surgical methods, patients with type I and II (SVZ+) had a lower proportion of total resection compared to patients with type III and IV (SVZ-), and their tumor size was significantly larger. Regarding recurrence pattern, patients with SVZ invasion had a significantly higher proportion of multifocal and distant recurrence compared to patients without SVZ invasion. Gender, age, post-operative KPS, and molecular expression did not show statistically significant differences among four types (Table 1).

Univariate Cox regression analysis revealed significant associations between patient prognosis and several factors, including the extent of surgical resection, tumor size, SVZ invasion, MGMT status, adjuvant chemotherapy cycle, and recurrence pattern (Table 2). SVZ invasion was associated with both PFS (SVZ+ 3 months vs. SVZ- 8 months; $P < 0.001$) and OS (SVZ+ 11 months vs. SVZ- 19 months; $P < 0.001$) (Fig. 3a and b). MGMT unmethylation was linked to poor PFS (MGMTm 6 months vs. MGMTu 2 months; $P < 0.001$) and OS (MGMTm 17 months vs. MGMTu 11 months; $P < 0.001$) (Fig. 3e and f). Tumor size, adjuvant chemotherapy cycle and recurrence pattern were also identified as important prognostic factors (all $P < 0.05$). However, tumor location, Ctx invasion and Ki-67 (%)failed to show significant associations with patient survival.

Although Ctx invasion did not have significant effect on the prognosis of GBM in univariate analysis (Fig. 3c and d), we further divided the 139 patients into two subgroups: the SVZ-invaded group (SVZ+, Type I + II) and the SVZ-uninvaded group (SVZ-, Type III + IV). Compared with the SVZ-uninvaded group, the SVZ-invaded group had a greater proportion of MGMT unmethylation, multifocal recurrence, and distant recurrence (Fig. 4a–c).

Multivariate Cox regression analysis was performed to investigate the factors contributing to prognosis in the univariate analysis. The results revealed that several variables, including partial resection, SVZ invasion, MGMT unmethylation, short cycles of adjuvant chemotherapy, multifocal recurrence, and recurrence 2 cm away from the tumor bed, were recognized as independent risk factors of poor prognosis (Table 3).

A total of 139 GBM patients were randomly allocated and divided into a training set and a test set at a 7:3 ratio, with 98 cases in the training set and 41 cases in the test set. There were no significant differences in the composition of the five independent risk factors between the two data sets ($P = 0.734$). The length of the line segment in the nomogram represents the contribution of each factor to the prognosis, with scores calculated accordingly. The total score, obtained by summing the scores of the five factors, corresponds to the probability of death. The ROC curve and the area under the curve (AUC) (0.945, 0.840, and 0.854 for 6-month, 12-month, and 18-month survival outcomes, respectively) demonstrated high predictive accuracy (Fig. 4d and e). The calibration curve shows good alignment between predicted and observed probabilities (Fig. 5a–c).

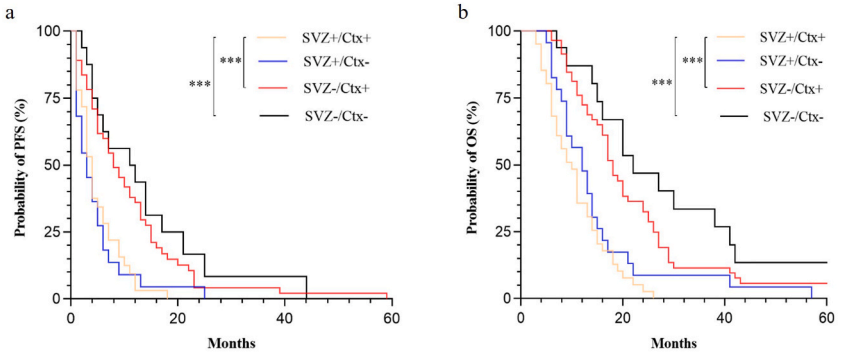

Fig. 2. Kaplan-Meier curves for progression-free survival (a) and overall survival (b) according to four types of GBM (Type I-IV). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 1
Patient Characteristics of the IDH wild-type Cohort.

Parameter; n (%)	Type I	Type II	Type III	Type IV	All people	P-value
	41 (29.5)	23 (16.5)	59 (42.4)	16 (11.5)	139 (100)	
Age (years)						0.673
< 55	17 (41.5)	13 (56.5)	30 (50.8)	8 (50.0)	68 (48.9)	
≥ 55	24 (58.5)	10 (43.5)	29 (49.2)	8 (50.0)	71 (51.1)	
Sex; n (male/female)	26/15	10/13	31/28	9/7	76/63	0.466
Extent of resection						<0.001
Total	14 (34.1)	7 (30.4)	47 (79.7)	12 (75.0)	80 (57.6)	
Partial	27 (65.9)	16 (69.6)	12 (20.3)	4 (25.0)	59 (42.4)	
Postoperative KPS						0.851
< 80	6 (14.6)	5 (21.7)	9 (15.3)	2 (12.5)	22 (15.8)	
≥ 80	35 (85.4)	18 (78.3)	50 (84.7)	14 (87.5)	117 (84.2)	
Tumor location						0.018
Frontal	14 (34.1)	12 (52.2)	20 (33.9)	6 (37.5)	52 (37.4)	
Temporal	17 (41.5)	4 (17.4)	23 (39.0)	3 (18.8)	47 (33.8)	
Parietal	4 (9.8)	1 (4.3)	10 (16.9)	2 (12.5)	17 (12.2)	
Occipital	6 (14.6)	4 (17.4)	6 (10.2)	2 (12.5)	18 (12.9)	
Others	0 (0.0)	2 (8.7)	0 (0.0)	3 (18.8)	5 (3.6)	
Tumor largest diameter (cm)						0.003
< 5.0	13 (31.7)	13 (56.5)	36 (61.0)	13 (81.3)	75 (54.0)	
≥ 5.0	28 (68.3)	10 (43.5)	23 (39.0)	3 (18.7)	64 (46.0)	
MGMT status						0.246
Unmethylated	22 (53.7)	12 (52.2)	21 (35.6)	6 (37.5)	61 (43.9)	
Methylated	19 (46.3)	11 (47.8)	38 (64.4)	10 (62.5)	78 (56.1)	
Ki-67 (%)						0.194
< 30	16 (39.0)	10 (43.5)	23 (39.0)	2 (12.5)	51 (36.7)	
≥ 30	25 (61.0)	13 (56.5)	36 (61.0)	14 (87.5)	88 (63.3)	
TP53 status						0.715
Mutation	18 (43.9)	9 (39.1)	26 (44.1)	5 (31.3)	58 (41.7)	
Wildtype	21 (51.2)	14 (60.9)	31 (52.5)	11 (68.7)	77 (55.4)	
Unkonw	2 (4.9)	0 (0.0)	2 (3.4)	0 (0.0)	4 (2.9)	
EGFR status						0.395
Mutation	26 (63.4)	13 (56.5)	36 (61)	11 (68.8)	86 (61.9)	
Wildtype	7 (17.1)	6 (26.1)	15 (25.4)	1 (6.2)	29 (20.9)	
Unkonw	8 (19.5)	4 (17.4)	8 (13.6)	4 (25.0)	24 (17.3)	
Recurrence Characteristic						0.019
Unifocal	18 (46.2)	12 (54.5)	43 (76.8)	9 (60.0)	82 (62.1)	
Multifocal	21 (53.8)	10 (45.5)	13 (23.2)	6 (40.0)	50 (37.9)	
Recurrence pattern						0.088
Local	20 (51.3)	17 (77.3)	41 (73.2)	9 (60.0)	87 (65.9)	
Distant	19 (48.7)	5 (22.7)	15 (26.8)	6 (40.0)	45 (34.1)	
Site of progression (cm)						0.004
< 2	8 (20.5)	5 (22.7)	30 (53.6)	8 (53.3)	51 (38.6)	
2-4	11 (28.2)	10 (45.5)	12 (21.4)	1 (6.7)	34 (25.8)	
> 4	20 (51.3)	7 (31.8)	14 (25.0)	6 (40.0)	47 (35.6)	

KPS: Kanofsky Performance Score; MGMT: O-6-methylguanin-DNA-methyltransferase; EGFR: Epidermal Growth Factor Receptor.

4. Discussion

This study has confirmed that partial resection, SVZ invasion, MGMT unmethylation, short adjuvant chemotherapy cycles, and recurrence pattern are independent risk factors for the prognosis of GBM. Gender, age, postoperative KPS, tumor location, and Ctx invasion had no significant effect on the prognosis of patients. The clinical prediction model established in this study, based on the identified prognostic factors, can effectively predict the survival status of patients. This model addresses the limitations of previous clinical studies and provides valuable insights and assistance for clinical diagnosis and treatment.

Clinical studies have shown that patients with the SVZ invasion have a worse prognosis [15]. Furthermore, tumors with SVZ invasion were more prone to early and distant recurrence, signifying a potential origin from malignant mutations of NSCs in SVZ [13]. Jafri et al. discovered that when tumors invaded SVZ, patients experienced faster disease progression and shorter survival time regardless of the involvement of Ctx. This highlights the significant impact of SVZ invasion on PFS and OS [14]. In line with this, Mistry et al. found that SVZ invasion was associated with decreased survival, as well as with hydrocephalus and leptomeningeal dissemination after treatment [21]. The deep sequencing on three pairs of matched tissues from patients with IDH wild-type GBM (normal SVZ tissue distant from the tumor, tumor tissue, and normal brain tissue) revealed that GBM originates from cells in SVZ with low-level driver mutations [10]. Therefore, it is crucial to prioritize further investigation in this area to potentially discover breakthroughs in overcoming the formidable nature of GBM and improving patient survival rates.

Combined with clinical and basic research, the invasion of SVZ has been identified as a significant risk factor that greatly affects the survival of GBM [22–24]. Given the poorer prognosis associated with SVZ invasion, it is imperative to consider more aggressive

Table 2
Univariate analysis of progression-free survival and overall survival for the complete IDH wild-type cohort.

Parameter	Progression-free survival			Overall survival		
	Median (m)	HR (95 % CI)	P-value	Median (m)	HR (95 % CI)	P-value
Age (years)			1.000			0.164
< 55	4	1.00 (0.709–1.410)		16	0.783 (0.554–1.105)	
≥ 55	5	1 (ref.)		13		
Extent of resection			<0.001			<0.001
Total	9	0.249 (0.166–0.374)		19	0.33 (0.227–0.480)	
Partial	2	1 (ref.)		10		
Postoperative KPS			0.080			0.058
< 80	3	1.515 (0.951–2.413)		12	1.578 (0.984–2.531)	
≥ 80	5	1 (ref.)		15		
Tumor location			0.683			0.593
Frontal	5	0.581 (0.230–1.467)		15	0.491 (0.195–1.239)	
Temporal	5	0.551 (0.216–1.403)		16	0.457 (0.179–1.164)	
Parietal	4	0.721 (0.265–1.964)		12	0.535 (0.196–1.458)	
Occipital	5	0.556 (0.202–1.525)		13	0.498 (0.180–1.378)	
Others	3	1 (ref.)		7		
Tumor largest diameter (cm)			0.575			0.038
< 5.0	5	0.906 (0.641–1.280)		17	0.691 (0.487–0.980)	
≥ 5.0	4	1 (ref.)		13		
SVZ invaded			<0.001			<0.001
No	8	0.437 (0.304–0.629)		19	0.398 (0.278–0.571)	
Yes	3	1 (ref.)		11		
Cortex invaded			0.699			0.473
No	5	0.927 (0.632–1.359)		15	0.870 (0.594–1.274)	
Yes	5	1 (ref.)		14		
MGMT status			<0.001			<0.001
Unmethylated	2	2.081 (1.454–2.978)		11	1.916 (1.337–2.746)	
Methylated	6	1 (ref.)		17		
Ki-67 (%)			0.927			0.519
< 30	4	1.017 (0.713–1.450)		17	0.887 (0.615–1.278)	
≥ 30	5	1 (ref.)		14		
TP53 status			0.922			0.953
Mutation	4	1.018 (0.716–1.446)		16	0.989 (0.696–1.407)	
Wildtype	5	1 (ref.)		14		
EGFR status			0.462			0.593
Mutation	4	0.847 (0.545–1.318)		14	0.890 (0.580–1.366)	
Wildtype	5	1 (ref.)		14		
Adjuvant chemotherapy cycle			0.001			<0.001
< 6	4	1.895 (1.315–2.731)		11	2.380 (1.644–3.446)	
≥ 6	9	1 (ref.)		19		
Characteristics at Recurrence			0.035			0.002
Uinfocal	6	0.678 (0.473–0.972)		17	0.567 (0.393–0.819)	
Multifocal	3	1 (ref.)		13		
Recurrence pattern			0.005			<0.001
Local	6	0.583 (0.401–0.849)		16	0.505 (0.344–0.741)	
Distant	3	1 (ref.)		10		
Site of progression (cm)			0.009			<0.001
< 2	8	0.531 (0.353–0.800)		20	0.422 (0.276–0.645)	
2-4	3	0.781 (0.493–1.235)		11	0.757 (0.479–1.196)	
> 4	4	1 (ref.)		13		

SVZ: subventricular zone; KPS: Kanofsky Performance Score; MGMT: O-6-methylguanin-DNA-methyltransferase; IDH: Isocitrate Dehydrogenase; EGFR: Epidermal Growth Factor Receptor; HR: hazard ratio; CI: confidence interval.

treatment strategies, such as intensified radiotherapy in conjunction with concurrent chemotherapy. Evers et al. found that the bilateral SVZ irradiation with dose exceeding 43Gy could significantly improve PFS of patients with high grade glioma [25]. In an analysis of 173 GBM patients, a significant improvement in PFS was detected in patients received the high-dose irradiation (>59.4 Gy) compared with low-dose irradiation to the ipsilateral SVZ [26]. Distant recurrence is a crucial negative prognostic factor [13,27–29]. In line with this, our study showed that patients with in situ recurrence had a significantly better prognosis than those with peripheral recurrence. Therefore, it is imperative to conduct further clinical prospective studies to explore the optimal design of postoperative radiotherapy and the potential benefits of increasing the local dose to control distant recurrence, especially in patients with SVZ invasion. Additionally, our study found that administrating more than 6 cycles of adjuvant chemotherapy significantly improved survival, aligns with the notion that prolonging the adjuvant chemotherapy cycle can be beneficial for survival [30–32]. However, the question of whether increasing the individual dose of chemotherapy can enhance survival remains a topic of debate [33,34].

The conclusion regarding the proportion of MGMT methylation in patients with SVZ invasion being significantly lower than those without SVZ invasion remains contradictory. A meta-analysis of GBM found no significant difference in the constituent ratio between

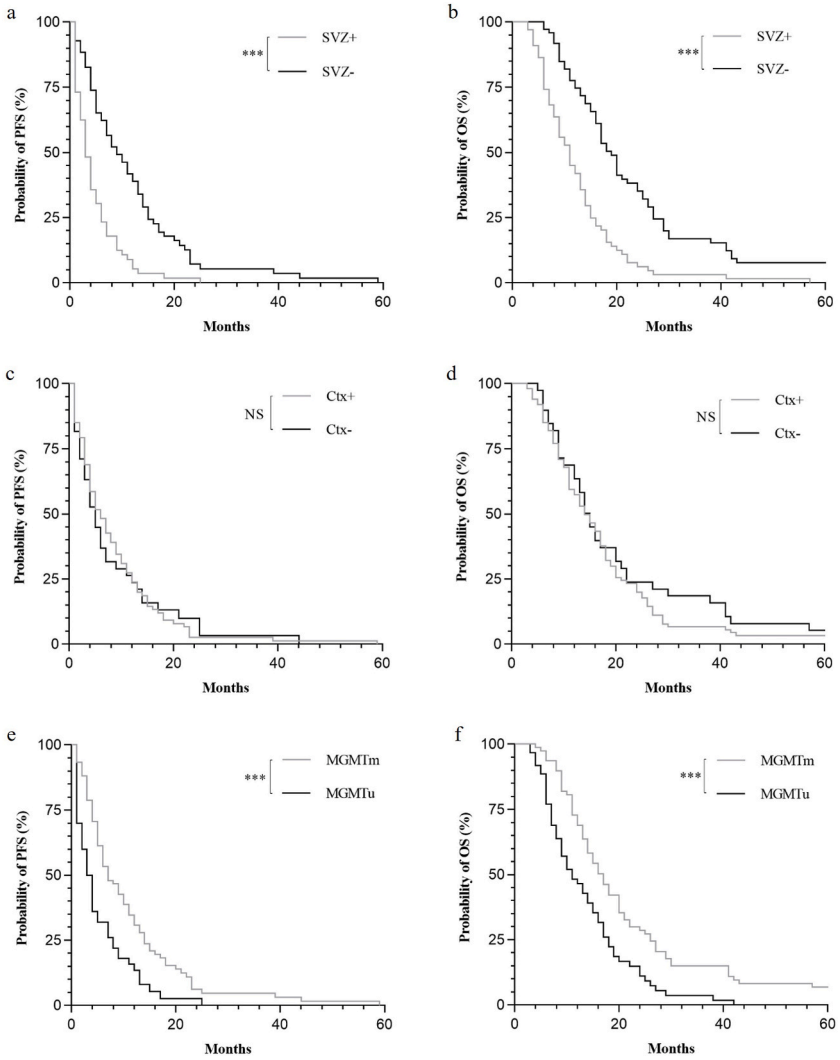

Fig. 3. Kaplan-Meier curves of progression-free survival (a) and overall survival (b) in the SVZ invaded group (Type I + II) versus the SVZ uninvaded group (Type III + IV). Kaplan-Meier curves for progression-free survival (c) and overall survival (d) in the Ctx-invaded group (Type I + III) versus the Ctx-uninvaded (Type II + IV) group. Kaplan-Meier curves of progression-free survival (e) and overall survival (f) for MGMT methylation (MGMTm) versus MGMT unmethylation (MGMTu). *P < 0.05, **P < 0.01, ***P < 0.001, NS, not significant.

the two groups [35]. Similar findings were reported by Van Dijken et al. [36]. On the other hand, Some studies found that the proportion of MGMT methylation in patients with SVZ invasion was significantly lower [15,37]. Han et al. obtained similar results in predicting MGMT methylation status based on preoperative MR Imaging [38]. It is important to note that patients with MGMT unmethylation have decreased sensitivity to chemotherapy, leading to a worse prognosis. This study identified a notable increase in the proportion of MGMT unmethylation among patients with SVZ invasion. Further investigation is needed to determine if this is associated with decreased responsiveness to radiotherapy and chemotherapy, as well as its impact on prognosis.

The prediction models of GBM in previous studies mainly focused on some basic influencing factors like gender, age, KPS, and treatment methods [16,17]. There is a pressing need for more precise and innovative prediction models to forecast patient prognosis. In this study, we established a model that incorporates five novel factors: extent of resection, SVZ invasion, MGMT status, adjuvant chemotherapy cycle and recurrence pattern. The result showed that the model exhibits a high predictive value for prognosis, which holds significant clinical implications.

This study has several limitations, with the most significant being the selection bias inherent in the retrospective study design. Meanwhile, there were variations in patient treatment after disease recurrence or progression. Model validation was constrained by the absence of a large-scale external validation, which should be considered in further study. In terms of model validation, we lack a large-scale external validation. The number of samples included in this study needs to be further increased. Despite these limitations, adherence to new guidelines resulted in the exclusion of patients with IDH-mutant, reducing potential interference. Furthermore, the model incorporated molecular information and imaging classification, culminating in the development of a novel prediction model

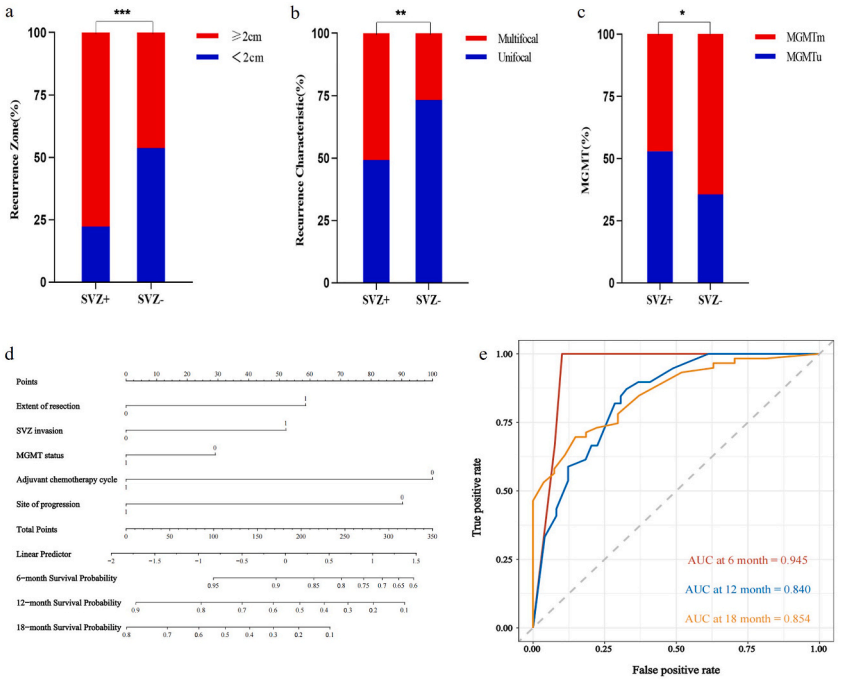

Fig. 4. Proportions and Differences of local and distant recurrence (a), single-lesion and multi-lesion recurrence (b), MGMT methylation (MGMTm) and unmethylation (MGMTu) (c) in the SVZ invaded group versus the SVZ uninvaded group. A prediction model for survival status of GBM patients at 6, 12, and 18 months (d). ROC curve and area under curve of prognostic model for GBM in training set (e). *P < 0.05, **P < 0.01, ***P < 0.001.

Table 3
Multivariate analysis of progression-free survival and overall survival for the complete IDH wild-type cohort.

Parameter	Progression-free survival		Overall survival	
	HR (95 % CI)	P-value	HR (95 % CI)	P-value
Extent of resection	0.331 (0.206–0.531)	<0.001	0.571 (0.364–0.895)	0.014
Tumor largest diameter (cm)	1.378 (0.933–2.035)	0.107	0.967 (0.659–1.421)	0.866
SVZ invaded	0.525 (0.348–0.793)	0.002	0.592 (0.382–0.917)	0.019
MGMT status	1.556 (1.059–2.284)	0.024	1.723 (1.168–2.541)	0.006
Adjuvant chemotherapy cycle	1.587 (1.065–2.364)	0.023	2.707 (1.825–4.015)	<0.001
Characteristics at Recurrence	1.243 (0.701–2.205)	0.456	1.239 (0.679–2.264)	0.485
Site of progression (cm)				
<2 vs.2-4	0.507 (0.267–0.962)	0.038	0.372 (0.193–0.719)	0.003
2-4 vs. > 4	0.658 (0.372–1.164)	0.151	0.582 (0.325–1.042)	0.069

SVZ: subventricular zone; MGMT: O-6methylguanin-DNA-methyltransferase; HR: hazard ratio; CI: confidence interval.

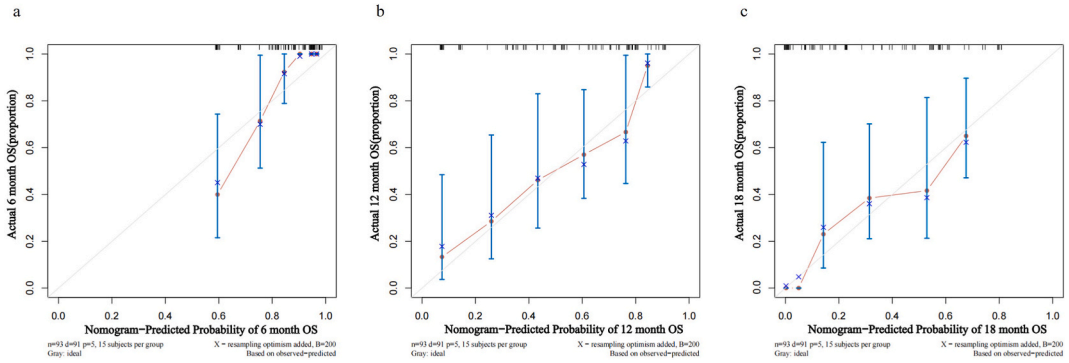

Fig. 5. The calibration curves to assess the alignment between predicted and observed probabilities at 6 months (a), 12 months (b) and 18 months (c).

with substantial clinical value. This model serves as a crucial basis for clinical diagnosis, treatment decisions, and prognosis determination.

5. Conclusions

In recent years, significant investment has been made in the research related to the treatment of GBM, including targeted therapy, immunotherapy and radiotherapy. However, the outcomes of these treatments are unsatisfactory. SVZ invasion is identified as an independent risk factor for prognosis, and patients with SVZ invasion have a significantly higher proportion of MGMT unmethylation. Therefore, SVZ is expected to be a potential target for the treatment of GBM. The novel clinical prediction model established in this study can accurately predict the survival outcome of patients, which has important guiding significance for clinical practice.

CRediT authorship contribution statement

Zhiying Shao: Writing – review & editing, Writing – original draft, Project administration, Conceptualization. **Hao Yan:** Writing – original draft, Software, Project administration, Conceptualization. **Min Zhu:** Resources, Project administration, Formal analysis. **Zhengyang Liu:** Investigation, Data curation. **Ziqin Chen:** Software, Methodology. **Weiqi Li:** Validation, Methodology, Conceptualization. **Chenyang Wang:** Visualization, Conceptualization. **Longzhen Zhang:** Supervision, Funding acquisition, Conceptualization. **Junnian Zheng:** Supervision, Conceptualization.

Ethics approval statement

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the affiliated hospital of Xuzhou Medical University (June 23, 2022/No. XYFY2022-KL198). Informed consent was obtained to publish clinical data of the patient(s) in the study.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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