Prognostic Factors for Recurrent Glioma: A Population-Based Analysis

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ABSTRACT

BACKGROUND: The overall survival (OS) for patients with recurrent glioma is meager. Also, the effect of radionecrosis and prognostic factors for recurrent glioma remains controversial. In this regard, developing effective predictive models and guiding clinical care is crucial for these patients.

METHODS: We screened patients with recurrent glioma after radiotherapy and those who received surgery between August 1, 2013, and December 31, 2020. Univariate and multivariate Cox regression analyses determined the independent prognostic factors affecting the prognosis of recurrent glioma. Moreover, nomograms were constructed to predict recurrent glioma risk and prognosis. Statistical methods were used to determine the prediction accuracy and discriminability of the nomogram prediction model based on the area under the curve (AUC), the C-index, the decision curve analysis (DCA), and the calibration curve. In order to distinguish high-risk and low-risk groups for OS, the X-Tile and Kaplan-Meier (K-M) survival curves were employed, and the nomogram prediction model was further validated by the X-Tile and K-M survival curves.

RESULTS: According to a Cox regression analysis, independent prognostic factors of recurrent glioma after radiotherapy with radionecrosis were World Health Organization (WHO) grade and gliosis percentage. We utilized a nomogram prediction model to analyze results visually. The C-index was 0.682 (95% CI: 0.616–0.748). According to receiver operating characteristic (ROC) analysis, calibration plots, and DCA, the nomogram prediction model was found to have a high-performance ability, and all patients were divided into low-risk and high-risk groups based on OS ($P < .001$).

CONCLUSION: WHO grade and gliosis percentage are prognostic factors for recurrent glioma with radionecrosis, and a nomogram prediction model was established based on these two variables. Patients could be divided into high- and low-risk groups with different OS by this model, and it will provide individualized clinical decisions for future treatment.

KEYWORDS: Recurrent glioma, radionecrosis, nomogram, prognosis, overall survival, gliosis

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Introduction

Among adults, glioma is the most common malignancy of the central nervous system.[1] The age-adjusted annual incidence of glioma is 5 to 8 per 100,000 people in China, and about 50% is glioblastoma (GBM).[2] The standard treatment includes surgical resection with adjuvant radiotherapy and chemotherapy.[3] Despite the emergence of several new therapeutic modalities, such as tumor treatment fields (TTFields), the long-term survival of glioma patients remains poor due to high recurrence rates. For example, the median survival time is 14.6 months, and the 5-year overall survival (OS) rate is 6.8% for GBM.[4]

Radiation therapy is a commonly used modality in the treatment of glioma, but the survival rate varies considerably across different patients.[5] The factors affecting prognosis are still poorly understood, especially in patients with radionecrosis. For example, in some studies, radionecrosis affects the long-term prognosis of these patients, but this is controversial in another study.[6,7] Moreover, there needs to be more clarity regarding the relationship between radionecrosis and prognosis in recurrent glioma.

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The principal objective of this project was to investigate the potential prognostic factors of OS in patients with recurrent glioma and radionecrosis. A cohort of patients with recurrent glioma underwent surgery in our hospital and were included in this study. We investigated the influence of possible prognostic factors on these patients. As a result, we want to construct a prediction nomogram model based on these prognostic factors and use it to guide future therapies.

Materials and Methods

Data collection

This retrospective cohort study was conducted between August 1, 2013, and December 31, 2020, at Shanghai Huashan Hospital. Criteria for inclusion were (1) patients with recurrent glioma who received a second surgery and radiation therapy, and (2) histology indicates radionecrosis. Patients with incomplete data were excluded, including medical records, radiological data, and pathology information.

Patient outcome measurements

The pathological classification was based on the WHO 2016 classification of tumors.[8] Radionecrosis was detected after pathological examination (Figure 1). The following variables were included: gender, age, survival status, OS time, radionecrosis percentage (RF-PCT), tumor cell percentage (tumor cell PCT), gliosis percentage (Gliosis PCT), the degree of tumor resection, the location of tumor, lateral of tumor, location relative to the tentorium, WHO grade, MIB-1/Ki67, chemotherapy, tumor size, Ki-67 index, IDH1 mutation status, O6-methylguanine-DNA methyltransferase (MGMT) methylation status, and Alpha thalassemia/mental retardation (ATRX) status. The RF-PCT, tumor cell PCT, and Gliosis PCT were identified by immunohistochemical staining. A magnetic resonance imaging (MRI) or computed tomography (CT) scan is routinely obtained within 24 hours after surgery to establish the degree of tumor resection. All patients were followed up for at least 2 years. Based on the last follow-up or death, OS was defined as the interval between surgery and death.

Statistical analysis

Continuous variables were summarized by mean, median, and standard deviations, and the categorical variable was described by constituent ratio. The Kolmogorov–Smirnov test was used for regular distribution testing; student *t*-tests were used for comparison between groups, and categorical data were tested using the chi-square test. An individual's OS refers to the time between the date of surgery and death or the last follow-up. All analyses were performed using R and RStudio (version 1.0.143). Optimal cutoffs for each variable were determined using X-Tile. Statistical significance was set at $P < .05$; all tests were 2-tailed.

Results

Baseline characteristics of patients

A total of 126 patients with recurrent glioma and radionecrosis were included in the study. According to Table 1, the study population had the following demographic, clinical, histological, and radiological characteristics at baseline.

Selected prognostic factors for OS

The univariate Cox regression model further examined the cohort's basic demographics, histopathological examination, and imaging examination for mortality prediction. Variables, including Gliosis PCT, WHO grade, Ki67 index, and MIB-1/Ki67, were potential predictors of mortality in the univariate analysis ($P < .1$). Those factors were entered into the multivariable Cox proportional hazard model, and two prognostic factors, WHO grade and Gliosis PCT, were added to the final prediction model (each $P < .05$); the extent of tumor resection ($P = 1$) and different radionecrosis PCT ($P = .26$) do not affect OS of these patients. Patients could be divided into low- and high-risk groups by Gliosis PCT ($P < .0001$) and WHO grade ($P < .0001$) separately; the cutoff value is 17% and WHO grade 3 (Table 2, Figure 2).

Prognostic nomogram for OS

Using the nomogram scoring system, the positive variables from the multivariable analysis were assigned a point value on the scale (Figure 3). The estimated probability of OS was calculated by counting the scores and locating them on the total point scale. The C-index of the nomogram was 0.682 (95% CI: 0.616–0.748).

Performance evaluation of the prognostic nomogram model

Based on the area under the curve (AUC), the prediction model had a predictive capacity of 0.728 (95% CI: 0.635–0.82) in a 2-year follow-up and 0.786 (95% CI: 0.679–0.893) in a 3-year follow-up (Figure 4). According to the calibration plot, the nomogram model adequately predicted survival in both cohorts, which is consistent with the Kaplan-Meier estimates (Figure 5). Based on our decision curve analysis, we found net benefits from applying our nomogram with threshold probabilities of 0.472 (Figure 6).

The nomogram score was classified into two levels of low (−1.75 to 1.93 points) and high (>1.93 points) risk based on the Cox risk score using X-Tile software (Figure 7), corresponding to two subgroups of patients with good and poor prognosis, respectively. A Kaplan-Meier survival curve analysis showed that the low-risk group had a significantly better OS than the high-risk group ($P < .0001$).

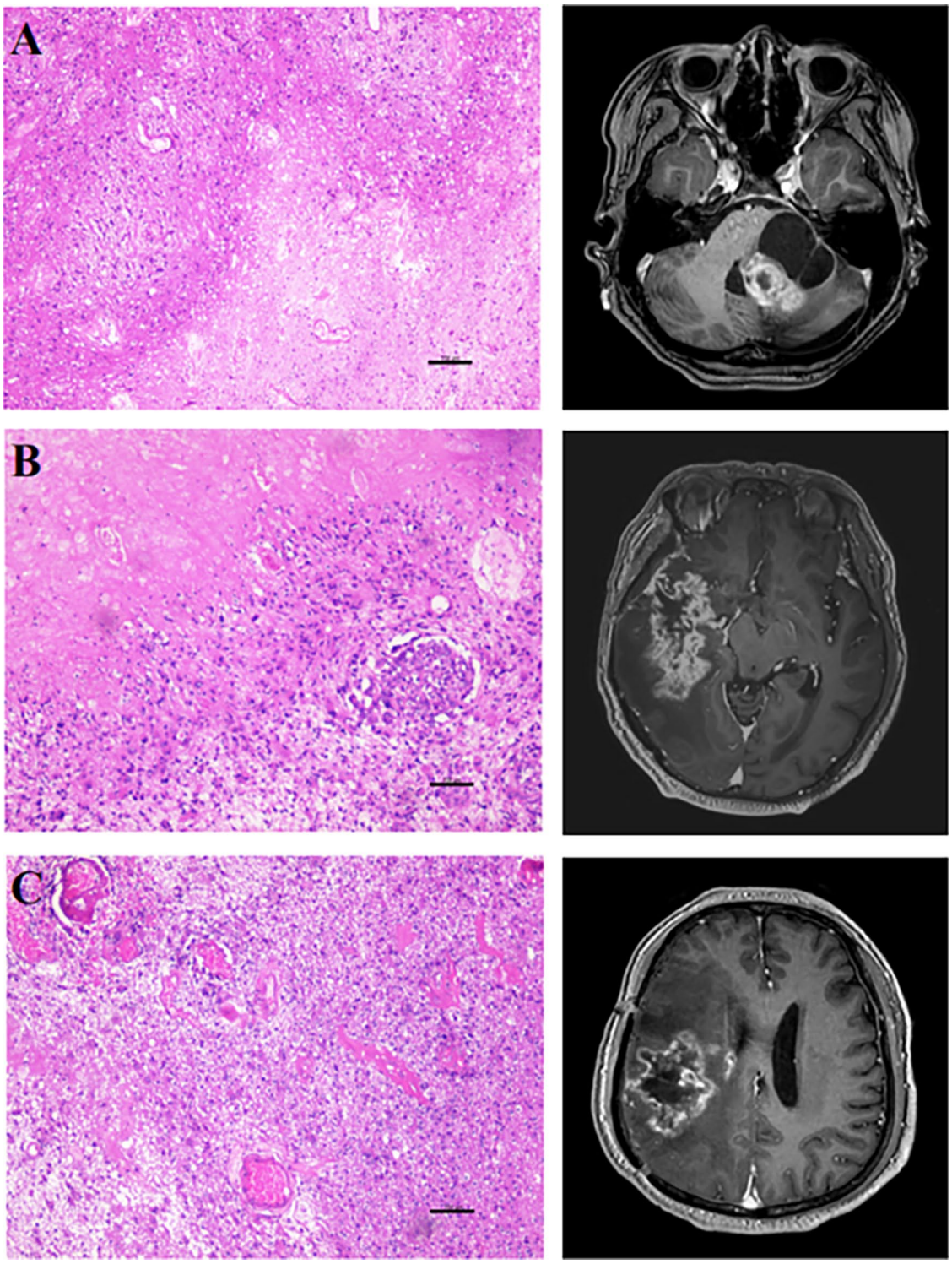

Figure 1. T1-enhanced MRI and corresponding H&E-stained sections of brain tissue from patients with glioma treated with radiotherapy. (A) The section shows recurrent glioma with 20% of radionecrosis and 80% of WHO grade I tumor cell (100×). The right panel is the corresponding T1-enhanced MRI image. (B) The section shows recurrent glioma with 50% of radionecrosis and 50% of WHO grade IV tumor cell (100×). The right panel is the corresponding T1-enhanced MRI image. (C) The section shows recurrent glioma with 90% of radionecrosis and 10% of WHO grade II glioma (100×). The right panel is the corresponding T1-enhanced MRI image, scale bar 100 μm.

Discussion

Glioma is a primary brain tumor originating from glial cells.[9] Maximum safe resection and adjuvant chemoradiotherapy have improved the survival rate of patients with glioma.[10] However, the prognosis of glioma is still poor. The prognostic factors for patients with recurrent glioma who underwent secondary surgery remain unclear.[11] As previously stated, few reports have described the risk factors for recurrent glioma

Table 1. Baseline clinical features of recurrent glioma patients.

CHARACTERISTICS	RECURRENT GLIOMA PATIENTS (N = 126)
Gender Female Male	51 (40.5%) 75 (59.5%)
Age	
<60 years old >60 years old	99 (78.6%) 27 (21.4%)
Tumor proportion ($\bar{x} \pm SD$)	0.29 (0.28)
Gliosis proportion ($\bar{x} \pm SD$)	0.16 (0.25)
Radionecrosis proportion ($\bar{x} \pm SD$)	0.55 (0.27)
RF-PCT <60% >60%	75 (59.5%) 51 (40.5%)
Total resection No Yes	35 (27.8%) 91 (72.2%)
Location Left frontal Right frontal Left temporal Right temporal Basal ganglia region Cerebellum Brainstem Multiple tumors Others: mesolobus, paracele, thalamus, conarium	25 (19.8%) 22 (17.5%) 5 (4.0%) 14 (11.1%) 1 (0.8%) 2 (1.6%) 3 (2.4%) 30 (23.8%) 24 (19.0%)
Side Left Right Both	48 (38.1%) 65 (51.6%) 13 (10.3%)
Tentorium Supra-tentorial Sub-tentorial	119 (94.4%) 7 (5.6%)
WHO grade Grade I Grade II Grade III Grade IV N/A	5 (4%) 24 (19%) 21 (16.7%) 68 (54%) 8 (6.3%)
Chemotherapy No Yes N/A	18 (14.3%) 76 (60.3%) 32 (25.4%)
Lesion size ($\bar{x} \pm SD$) >4 cm <4 cm	4.62 (1.59) 59 (46.8%) 67 (53.2%)
Ki67 ($\bar{x} \pm SD$) >15% <15% N/A	6.67 (8.52) 91 (72.2%) 21 (16.7%) 14 (11.1%)
IDH1 mutation Wild type Mutated N/A	97 (77%) 19 (15%) 10 (8%)
MGMT promoter methylation Unmethylated Methylated N/A	1 (0.8%) 8 (6.3%) 117 (92.9%)
ATRX mutation Wild type Mutated N/A	97 (77%) 7 (5.5%) 22 (17.5)
OS days ($\bar{x} \pm SD$)	838.36 (780.05)
Overall survival status Death	72 (57.1%)

(Continued)

Table 1. (Continued)

with radionecrosis. The current study investigated prognostic factors of patients with recurrent glioma. This is the first retrospective study that constructs nomogram models to predict the prognosis and risk of recurrent gliomas with radionecrosis. In this study, the population was characterized by patients of a relatively young age (median 49.27 years), and 14 factors were included.

According to this study, grade and Gliosis PCT were established as prognostic factors for patients with recurrent glioma and radionecrosis, and a nomogram prediction model was constructed based on these two variables. The nomogram model has a high degree of differentiation and specificity. Patients with recurrent glioma and radionecrosis could be divided into low- and high-risk subgroups for OS based on our nomogram prediction model, and the 2- and 3-year survival probability could be predicted by this model with high accuracy. However, the other variables, such as RF-PCT, have no relation to these patients' OS.

All these patients had radionecrosis confirmed by pathologic evaluations. Radionecrosis is a common complication of radiotherapy, which occurs months to years after radiotherapy or 6–24 months after chemotherapy, with an incidence ranging from 5% to 40%.[12] However, our study found that radionecrosis was not correlated with OS. The result was consistent with previous studies; a low Gliosis PCT combined with a high WHO grade portended the worst OS, indicating the beneficial role of both Gliosis PCT and WHO grade as markers in stratifying patients with glioma. The mechanism of radionecrosis includes increased permeability and edema associated with vascular endothelial cell damage, white matter damage, and immune mechanism, which has been mentioned in previous studies.[13] Patients with radionecrosis usually present with ring-like enhancement and central hypointensity with peripheral hyperintensity due to edema.[14] When radionecrosis occurs, surgery, bevacizumab, steroids, and laser interstitial thermal therapy (LITT) are essential treatments.[15] Several studies have tried to identify the association between radionecrosis and glioma recurrence.

Table 2. Univariable and multivariable Cox regression analyses of overall survival (n = 126).

UNIVARIATE MODEL				MULTIVARIATE MODEL		
VARIABLES	HR	95% CI	*P*-VALUE	HR	95% CI	*P*-VALUE
Gliosis PCT	0.070	0.017– 0.286	<.0001	0.081	0.017–0.385	.002
WHO grade	2.173	1.525–3.095	<.0001	1.954	1.351–2.826	<.0001
Ki67c	1.043	1.019–1.068	<.0001			.101
MIB/Ki67	63.121	6.412–621.33	<.0001			.235

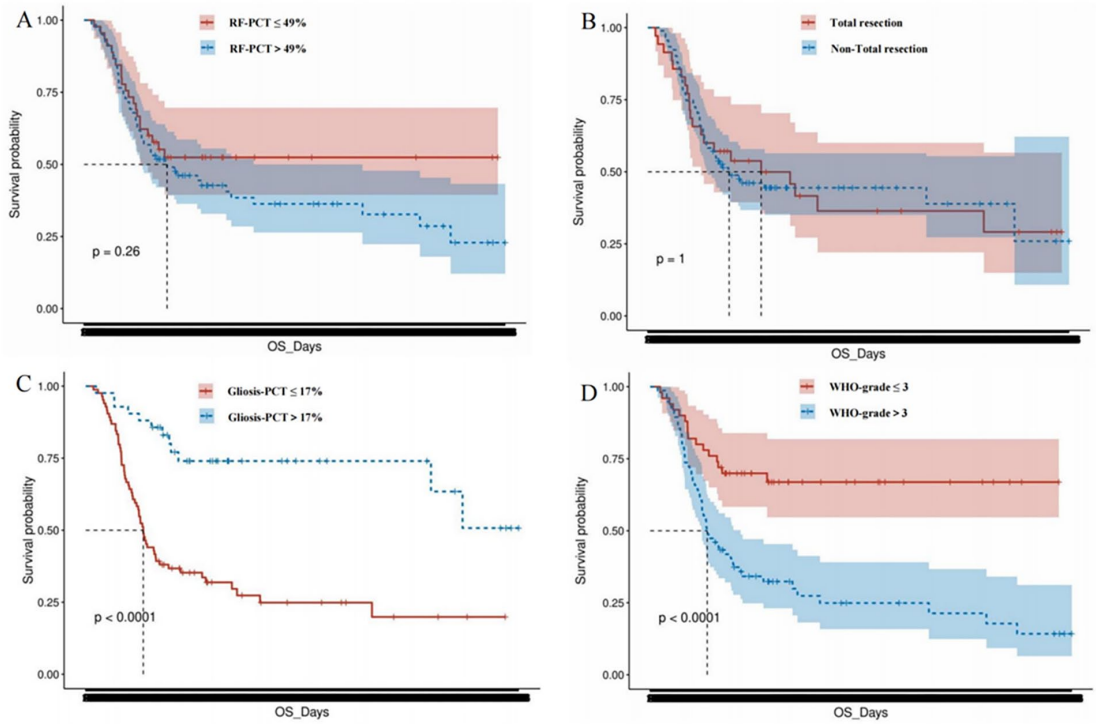

Figure 2. OS in recurrent glioma stratified according to different prognosis factors. (A) OS in recurrent glioma stratified according to radionecrosis percent (RF-PCT) (*P* = .26). (B) OS in recurrent glioma stratified according to total resection (*P* = 1). (C) OS in recurrent glioma stratified according to gliosis percent (Gliosis PCT; *P* < .0001). (D) OS stratified according to WHO grade (*P* < .0001). OS, overall survival; RF-PCT, radionecrosis percent; Gliosis PCT, gliosis percent.

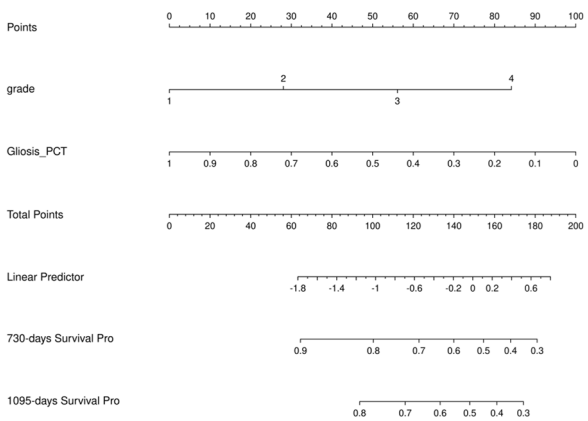

Figure 3. Nomogram for predicting 2-year and 3-year overall survival.

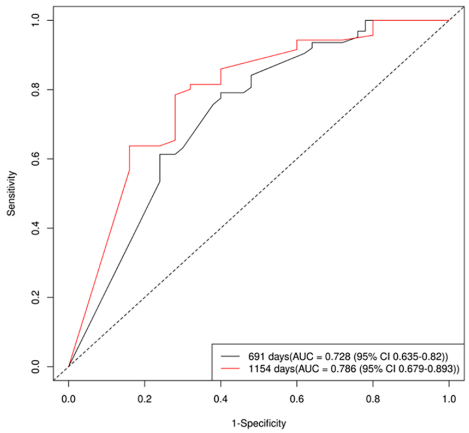

Figure 4. The ROC curve to predict 2-year and 3-year overall survival (OS) in the cohort.

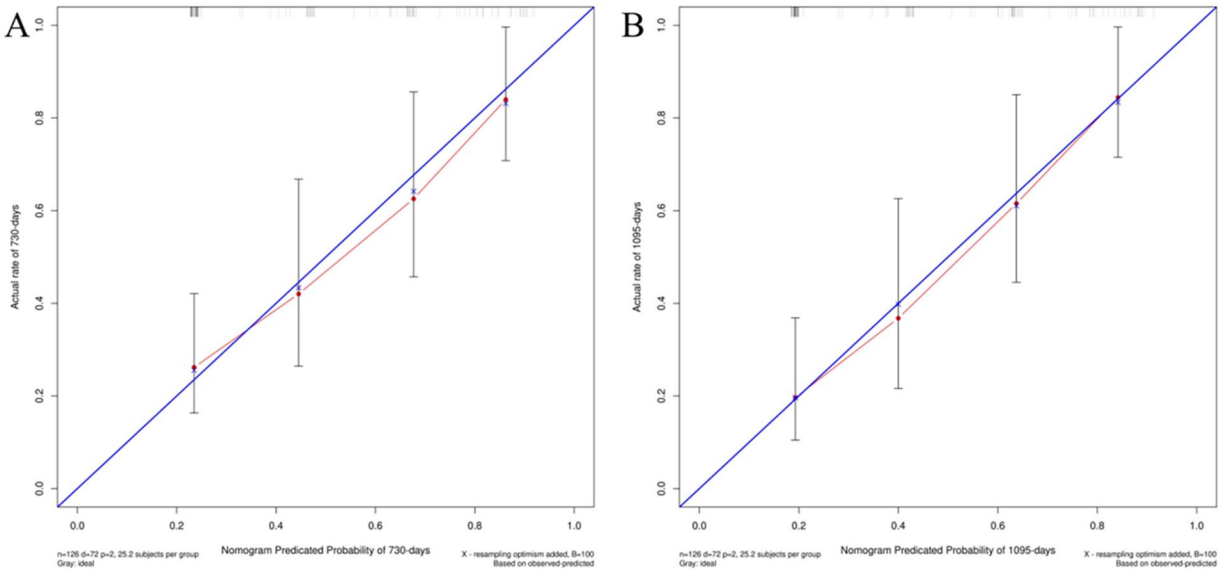

Figure 5. The calibration curve to predict 2-year (A) and 3-year (B) overall survival (OS) in the cohort.

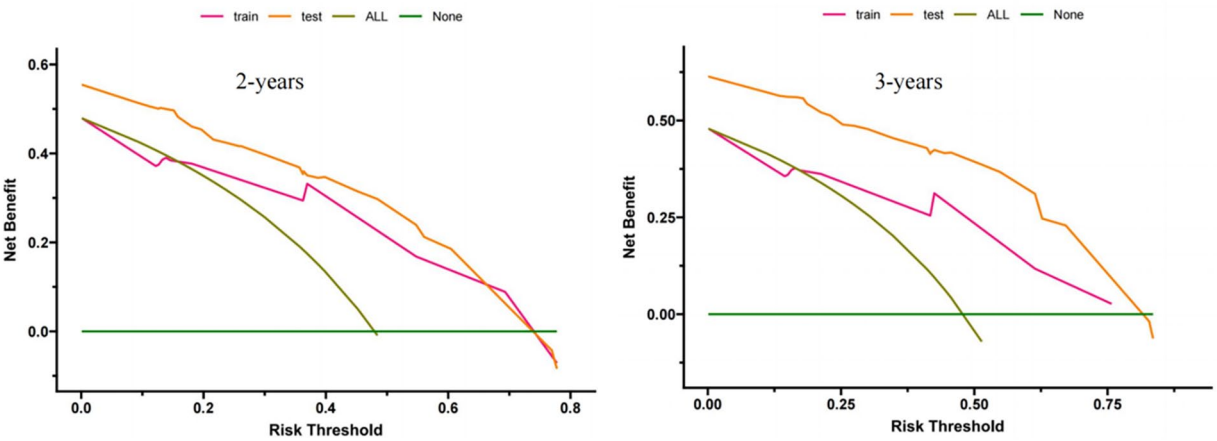

Figure 6. Decision curve analysis of the nomogram for survival prediction at 2 years and 3 years in patients with recurrent glioma.

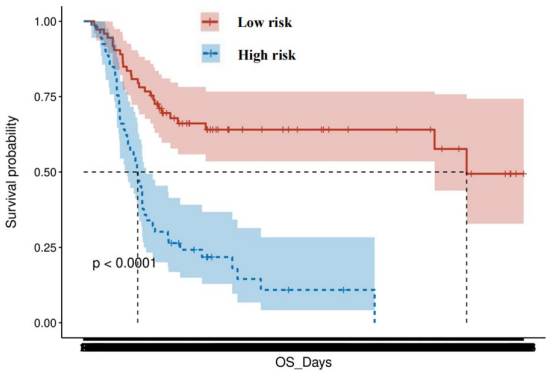

Figure 7. OS in recurrent glioma between low- and high-risk groups ($P < .0001$).

In recurrent glioma, however, the prognostic value of radionecrosis remains controversial.[16,17] Stereotactic biopsy was valuable for distinguishing radionecrosis from tumor recurrence. In 2005, research conducted by Tihan et al[6] noted that the histopathology of postoperative specimens did not help guide treatment and prognosis prediction. Other studies also showed that radionecrosis does not affect OS.[18] Our research shows that the proportion of radiation necrosis was not associated with OS in patients with recurrent glioma, which is consistent with previous studies.

In this study, the cutoff value of WHO grade is grade 3. It is well known that high-grade glioma, including WHO grade 3 and grade 4, accounts for 70% of all glioma patients in this cohort. Despite aggressive therapeutic strategies, such as surgical resection, radiotherapy, and chemotherapy, the prognosis for these patients remains poor. This is mainly because glioma cells strongly infiltrate brain parenchyma, and complete lesion removal is difficult. Research reveals that patients with high-grade glioma had worse OS than those with low-grade glioma (hazard ratio [HR] 0.61, 95% CI: 0.36–0.96).[19] Kim et al[20] found that tumor size and WHO grade could predict GBM

recurrence and OS in patients with recurrent GBM. In this research, we found that WHO grade with an OR of 2.946 and patients could be divided into low- and high-risk subgroups with different OS by WHO grade, which shows it is the most important predictor of recurrent glioma.

In addition, the Gliosis PCT has been associated with OS, consistent with previous findings.[21] Gliosis is a reactive change of glial cells in the central nervous system in response to tissue damage. Both surgery and radiotherapy can cause damage to brain tissues, which causes reactive gliosis, primarily astrocytes.[22] Although numerous studies have distinguished reactive gliosis from recurrent glioma, few have examined the association of reactive gliosis with glioma recurrence. Reactive gliosis has generally been reported to be associated with poor prognosis.[23] Astrogliosis is an essential feature of the epileptic foci that cause epilepsy. The Gliosis PCT was negatively correlated with glioma recurrence in the present study. Gliosis is indistinguishable from histopathology with glioma recurrence; even a pathological examination is needed. Gliosis also shares a standard molecular biological process with glioma recurrence. Therefore, we speculate whether gliosis has a competing relationship with glioma and whether gliosis inhibits glioma recurrence, but it remains to be confirmed.

O6-methylguanine-DNA methyltransferase is a DNA repair enzyme mainly distributed in the cytoplasm.[24] MGMT promoter methylation results in an altered chromatin structure, which prevents transcription factors from binding, resulting in the silencing of genes and, thus, loss of function, i.e., DNA repair.[25] The probability of MGMT promoter methylation was different in recurrent and primary glioma cases, and the incidence of MGMT promoter methylation was higher in patients with recurrent glioma than in those with the new-onset disease.[26] The incidence of pseudoprogression is significantly higher in those with MGMT methylation than in those without methylation, while the presence of pseudoprogression suggests a better prognosis. Patients with glioma and MGMT promoter methylation are sensitive to chemotherapy and radiotherapy and have more prolonged survival, so it is recommended that such patients should be treated with more standardized chemotherapy, which generally helps to improve survival.[27] MGMT promoter methylation is reportedly a prognostic and predictive factor for glioma.[28] However, in this research, MGMT promoter methylation is negative in the prediction of OS. The proportion of vivacious MGMT promoter methylation is 88.9%; this means MGMT promoter methylation is homogeneous for most patients with recurrent glioma and thus makes it not a vital prognosis factor.

Surgery remains the primary therapy for recurrent glioma and has shown clinically beneficial effects. The extent of resection at recurrence predicts OS in glioma, and long-term survival may be achieved with total resection.[29] In our study, 72.2% of patients received total resection; this may explain why the extent of resection does not affect the prognosis of recurrent glioma. However, whether it is suitable for patients with recurrent glioma to receive total resection is still debated. It is important to note that a more radical surgery approach must be balanced against neurological function. Therefore, maximal safe resection is recommended rather than total resection. In our study, the extent of reoperation was not correlated with OS, which suggests that preservation of neurological function may be a better choice.

To summarize, it will enable doctors to determine the best treatment strategy for patients with this tool, making it easier to use in clinical practice.

Limitations and Future Perspectives

Several limitations also mark our study. It is a retrospective study and thus may present some potential selection bias, concluding that it appears more suitable for patients with high-grade glioma. Moreover, most patients received total resection so that the cohort may have selection bias. Moreover, future research with larger sample sizes is still needed.

Conclusion

In summary, patients with recurrent glioma and radionecrosis, whose WHO grade is $\leqslant 3$ and Gliosis PCT is $>17\%$, have a better prognosis, and a nomogram prediction model with reasonable specificity and discrimination ability was established based on these two variables. Patients could be distinguished into low-risk and high-risk subgroups based on this nomogram model, which may guide future treatment.

Author Contributions

All authors contributed to the study's conception and design. PF, JS, and ZZ performed data collection and analysis. The first draft of the manuscript was written by PF, JS, MX, and HX, and all authors commented on previous versions. All authors read and approved the final manuscript.

Availability of Supporting Data

All data generated or analyzed during this study are included in this published article.

Ethical Approval and Consent to participate

The institutional review board of Huashan Hospital, Fudan University, approved the study protocol (KY2020-670). Patients' personal information was strictly protected by the ethics committee. Patient consent was waived due to the nature of a retrospective study.

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