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365 Days of progress in neuro-oncology and neurosurgical oncology

Edited by
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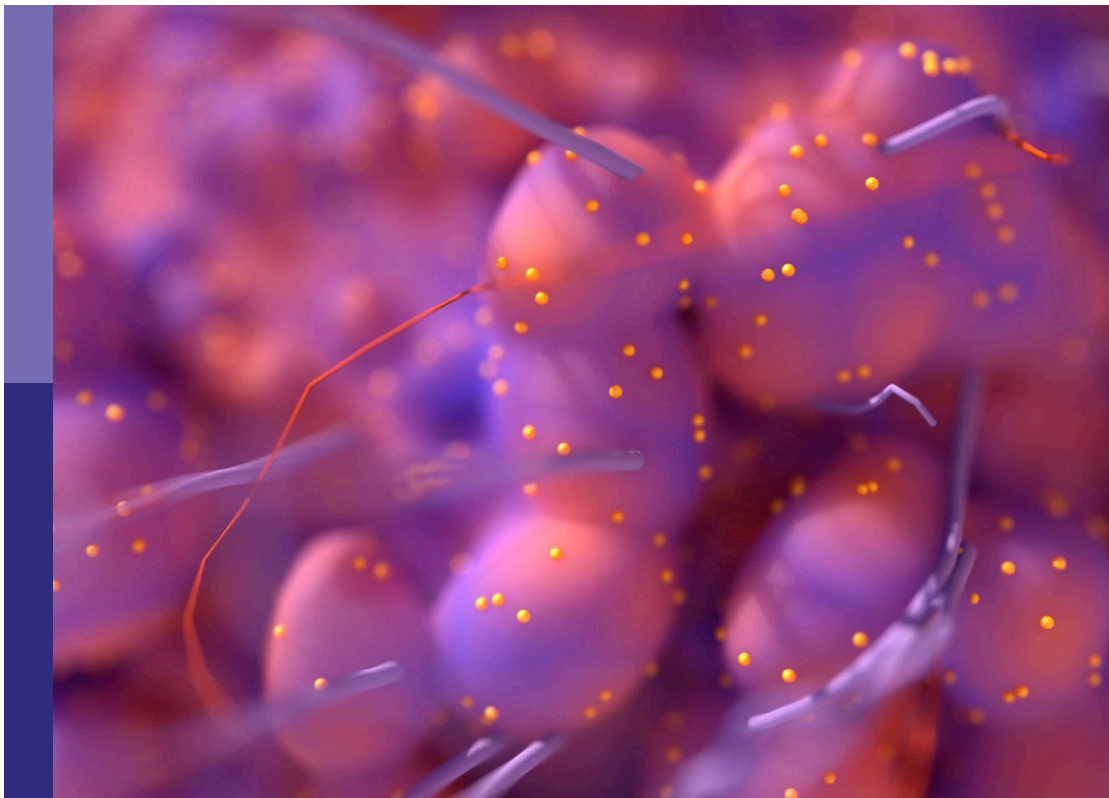

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365 Days of progress in neuro-oncology and neurosurgical oncology

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Editorial: 365 days of progress in neuro-oncology and neurosurgical oncology

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KEYWORDS

brain tumor, prognostic factor, biomarker, palliative care, tumor treating fields

Editorial on the Research Topic
365 days of progress in neuro-oncology and neurosurgical oncology

The Frontiers Research Topic titled *365 Days of Progress in Neuro-Oncology and Neurosurgical Oncology* published a collection of ten articles from August 2022 to March 2023. The topics contributed to the field of Neuro-Oncology on a variety of subjects focused on primary central nervous system (CNS) tumors as well as brain metastases, from tumor treating fields, palliative care for glioma patients and evaluation of clinical and/or biomarkers for risk or prognostic assessment for several CNS tumor entities.

Clinical prognostic factors for less common central nervous system tumors

The Surveillance, Epidemiology, and End Results (SEER) Program, funded by the USA-based National Cancer Institute (NCI), is a major cancer statistics database. Three separate analyses of the SEER population-based databases were submitted to this Research Topic. Zhang Z. et al. reviewed the SEER database for the relatively uncommon entity, *intracranial subependymoma*, from 2004-2016, and established a prognostic nomogram. Of 667 evaluable patients, 535 patients were assigned to the training cohort and 132 into the validation cohort. Of interest, only age and gender were independent prognostic factors for overall survival (OS); extent of resection, tumor location, grade, size and radiation treatment were not significant. Potential limitations of the study included exclusion of patients with acute deaths (i.e. survived less than a month), patient selection bias, and a median follow-up of 56 months. Validation in an independent cohort will be necessary. Zhang Z. et al. studied 413 patients with *central neurocytoma*, using the SEER database from 2003-2019, with specific attention to tumor size, the extent of resection and/or adjuvant radiation therapy (RT). The investigators demonstrated better outcomes for patients with smaller tumors (less than 4 cm), gross total resection (GTR) or for those who

did not receive RT, especially after a GTR. Outcomes after RT were worse for patients with extraventricular central neurocytoma. Similar to the other study, limitations included exclusion of patients with acute deaths. However, a major concern acknowledged by the authors was the change in diagnostic criteria for central neurocytoma during the study period, including revisions to the World Health Organization (WHO) CNS tumour classification in 2007, 2016 and most recently in 2021 (1). Validation in an independent clinical patient cohort with central neuropathology review using the WHO 2021 criteria are important next steps.

Liu et al retrospectively evaluated 18 cases of *secondary gliosarcoma* from their institution, diagnosed from 2013 to 2020 in patients with pre-existing gliomas. The authors also included 89 cases from 39 publications from the existing literature and applied PRISMA guidelines (2). As expected, patients who were less than 60 years or with a non-GBM initial diagnosis had longer periods of disease progression to secondary gliosarcoma. Ten of 107 patients had extracranial metastases (9.4%); the lungs were the most common site. Better outcomes were experienced by secondary gliosarcoma patients with a GTR and adjuvant chemoradiation. Study limitations also include changes in the diagnostic criteria for gliosarcoma for the institutional cases and those identified in the included published series.

Impact of patient and treatment-related factors on patient outcomes

Jin et al. also utilized the SEER database to evaluate factors contributing to cerebrovascular mortality in 72,916 patients diagnosed with a glioma from 2000 to 2018. The investigators applied the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (3).

In this retrospective, observational cohort study, surgery and chemotherapy had significantly decreased, whereas higher tumor grade (Grade 4 versus Grade 2) and larger tumors (greater than 3 cm) had significantly increased cerebrovascular mortality. Of particular interest for the field of CNS tumor survivorship was the association of radiotherapy with a higher risk of cerebrovascular mortality in those surviving 5 or more years from their cancer diagnosis. Study limitations include probable under-reporting of cerebrovascular events in patients with a glioma as well as the challenges of making a diagnosis of stroke in brain tumor patients, both clinically and neuroradiologically. Furthermore, the SEER database does not provide baseline cardiovascular risk factors which may impact both the incidence and outcomes of older patients with gliomas. However, this study identifies multiple avenues for future research.

Two reports examined patients with metastases to the brain and spine, respectively. Yu et al retrospectively studied the impact of smoking on the prognosis of 2,647 lung cancer patients with brain metastases from 2013 to 2021. Surprisingly, 67.1% declared no smoking history but this data was extracted from the electronic medical record and was not validated by patient self-report or by other means. Current and former smokers had an increased risk of death when compared to never smokers. Furthermore, quitting smoking did not correlate with better survival outcomes in this lung cancer patient cohort with established brain metastases. However, the authors suggest that increasing the accumulated smoking cessation time prior to a diagnosis of brain metastasis may improve patient survival. Validation of this study in other patient cohorts and from other countries is required. Hamed et al. retrospectively evaluated postoperative interventions and 30-day and 1 year mortality outcomes in 198 patients with spinal metastases treated surgically treated from 2015-2019 at a single institution. Postoperative mechanical ventilation (PMV) was considered prolonged if its duration was greater than 24 hours. Twenty patients (10%) had prolonged PMV; they experienced 70% and 100% mortality at 30-days and 1-year, respectively. PMV greater than 24 hr was the sole independent predictor for 30-days mortality. Given that the patient cohort with prolonged PMV was small, this report warrants further study in multiple centres.

Utility of clinical algorithms or biomarker-based signatures to predict patient outcomes

Biomarker discovery has been enhanced by the wider availability of RNA sequencing data that include microRNAs and long noncoding RNAs (lncRNAs), operationally defined as longer than 200 nt. Using the TCGA and GTEx databases, Song et al. focused their study on necroptosis-related lncRNAs in a cohort of patients with IDH-wild-type glioblastoma (GBM). The authors identified six necroptosis-related lncRNAs and then generated a prognostic lncRNA signature as well as investigated the associated immune-related tumor microenvironment. One lncRNA, RP11-131L12.4, was inversely correlated with OS in patients and the level of necroptosis *in vitro*. The authors suggest that targeting necroptosis-related ncRNAs may be a useful adjunct to current immunotherapy approaches under investigation for IDH-wild-type GBM.

El-Hajj et al. sought to assess the utility of the MAC-score to preoperatively predict an increased MIB-1 index (greater than 5%) in 108 spinal menigioma patients. The MIB-1 index is a semi-quantitative measurement of immunolabeling of Ki-67 of formalin-fixed paraffin embedded (FFPE) tissue sections. The MAC-score for spinal meningioma adds to the modified McCormick (mMC) scale that is in wide clinical use by adding 1 point for a preoperative mMC ≥ 2 (M), 1 point for age ≥ 65 years (A), and 2 points for the absence of calcification within the tumor (C). The authors were unable to externally validate the MAC-score and discuss potential methodological issues with the study by Wach et al. (4).

Real world experience with tumor-treating fields

Tumor-Treating Fields (TTFields) are an FDA-approved treatment for newly diagnosed and recurrent GBM. However,

evaluation of their use in many countries is ongoing. She et al retrospectively evaluated 52 newly diagnosed and 41 recurrent GBM patients from a single-center in China; 13 patients in each group received TTFields. The authors concluded that TTFields provided a clinical benefit in newly diagnosed but not in recurrent GBM, especially in patients who had a subtotal resection (STR). However, this is a small single-institution study and the authors advocate for further multi-institutional studies.

Bibliometric assessment of the role of palliative care in patients with glioma

Recently, there have been additions to meta-analyses and systematic reviews, including bibliometric analyses of publication databases, to provide a summary of current research and identify areas for future study. Xiao et al. used a type of bibliometry, known as scientometric analysis, on the topic of palliative care for glioma patients. The authors applied the PRISMA guidelines to this topic using the Web of Science database for the year of 2022 and selected the top-100 most cited papers from 2,542 articles. They identified a variety of palliative care needs for glioma patients as well as their caregivers. Furthermore, they observed few randomized controlled trials in palliative care in this patient group.

Concluding remarks

The selected topics included in this Research Topic in Neuro-Oncology and Neurosurgical Oncology provide a selected snapshot of current clinical and translational research activities. Of significance, many of these studies seek to identify clinical variables and/or biomarkers in various CNS tumor classes. Unfortunately, the established large databases have not incorporated revised molecular genetic criteria to confirm the neuropathological diagnostic entities listed in the updated 2021 WHO CNS tumor classification (1). Hence, some of the conclusions of the included manuscripts require validation in other patient cohorts whose diagnoses use the revised WHO CNS criteria. Although the use of the same database for both the identification and validation of prognostic factors, biomarkers and to establish nomograms is widely accepted, few if any novel observations from these types of study have been incorporated into clinical trials or the neuro-oncology clinic. Therefore, investigators in neuro-oncology are highly encouraged to validate these types of studies in another large patient database, confirm identified biomarkers in actual clinical samples and functionally validate them in relevant tumor cell line models and/or patient derived orthotopic xenotransplants as appropriate.

Author contributions

ES: Writing – review & editing. DE: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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Clinical independent prognostic factors and overall survival prognostic nomogram for intracranial subependymoma: A SEER population-based analysis 2004–2016

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Purpose: This study was launched to ascertain the independent prognostic factors influencing the overall survival (OS) prognosis of intracranial subependymoma and construct a prognostic model to predict OS time.

Materials and methods: We collected data from patients with intracranial subependymoma, including treatment data, follow-up data, and clinical and pathological characteristics from the SEER database within 2004 to 2016, and patients were randomly classified into training and validation cohorts. Univariate and multivariate analyses were applied to the training group through building a Cox proportional hazards model. According to the results of multivariate analysis, we established a nomogram to forecast the OS rate of the per-case patient graphically, then calculated the accuracy of verification in both training and validation cohorts by concordance index (C-index). Univariate and multivariate analyses were used for different subgroups of unoperated versus operated, gross total resection (GTR), subtotal resection (STR), and biopsy after using the propensity score matching (PSM) analyses.

Results: A total of 667 patients were enrolled, and we randomly assigned 535 patients (80.21%) into the training cohort and 132 patients (19.79%) into the validation cohort. Age [hazard ratio (HR) = 6.355; 95% confidence interval (CI), 2.240–18.029; p = 0.001] and sex (HR = 0.475; 95% CI, 0.232–0.974; p = 0.042) were the independent prognostic factors in the training cohort. On the basis of age and sex, the nomogram was established to predict the OS for every patient (C-index = 0.733 $\pm$ 0.065 in the training cohort and 0.850 $\pm$ 0.065 in the validation cohort), and calibration plots reflected the reliability of the nomogram. Age, gender, or laterality was the independent prognostic factor for OS in the different matched subgroups of unoperated versus operated, GTR, STR, and biopsy. Surgical treatment, race, year of diagnosis, insurance, tumor

location, tumor size, pathology, tumor grade, and radiation were not statistically significantly different in OS for subependymoma in our research.

Conclusion: Age and sex were the independent prognostic variables for OS in intracranial subependymoma. According to our research, we should not be more inclined to choose conservative or surgical treatment. Nonetheless, the information that we present might be useful to suggest potential hypotheses to be tested in the clinical research setting.

KEYWORDS

intracranial subependymoma, SEER, nomogram, surgery, prognosis

Introduction

Subependymoma is a neoplasm with a low incidence and low degree of malignancy (1–3).

Middle-aged and elderly men were the most affected age group by this type of cancer (4). The location of neoplasms was more likely to occur in the ventricle system than in the brain parenchyma or spinal cord (5). Generally speaking, surgical intervention has been recommended once symptoms occur, such as hydrocephalus (6), and conservative treatment has been used for incidental asymptomatic subependymoma. However, there is no detailed analysis of the different prognosis between conservative and surgical treatment including biopsy, STR, and GTR. Consequently, our study was launched to ascertain the independent factors influencing the OS prognosis of intracranial subependymoma and construct a prognostic model to predict OS time through exploring the SEER database.

Methods

Data

The data of 667 patients with intracranial subependymoma were investigated, including treatment and follow-up data, and clinical and pathological characteristics between 2004 and 2016 from the SEER (1975–2016 varying) database, by the SEER*Stat software (version 8.3.9.2).

This study's inclusion criteria included the following: (1) patient's ICD-O-3 histology codes in accordance with 9383/0 (subependymoma, benign), 9383/1 (subependymoma), or 9383/2(subependymoma, malignant); and (2) patients with definite information on the vital status and OS.

This study's exclusion criteria included the following: (1) patients with no specific survival time or with an OS time of less than 1 month; (2) tumor location involving pineal gland (C75.3), spinal cord (C72.0), or optic nerve (C72.3); and (3) the patient had no other specific information or unknown treatment, only a death certificate or an autopsy. The data on age, sex, race, year of diagnosis, insurance, marital status, primary site, tumor size, pathology, grade, laterality, primary site surgery, radiation, vital status, and OS were obtained. The method of retrieving data from the database is shown in Figure 1.

Endpoints

We used OS defined from the time of diagnosis to death or last investigation as the primary endpoint.

Statistical analysis

The whole sample was divided into a training and a validation cohort. Age, a continuous variable, was changed to an ordered classification variable. Disordered classification variables were analyzed by using the χ^2 test or Fisher's exact test, including sex, race, year of diagnosis, marital status, primary site, tumor size, grade, laterality, primary site surgery, and radiation. Ordered classification variables were analyzed by using the Mann-Whitney *U* test, including age, insurance, and pathology. Different survival rates of variables were graphically evaluated by using the Kaplan-Meier method.

The Cox proportional hazards model was used to perform univariate and multivariate analyses on the training group. According to clinical independent prognostic factors, a nomogram predicting survival probabilities at 3, 5, and 10 years for subependymoma patients was constructed through using the rms package in R (version 4.1.2) in the training group. The model's C-index, and 3 - and 5-year calibration curves in the training cohort were calculated. The nomogram was further validated by calculating C-index in the validation cohort.

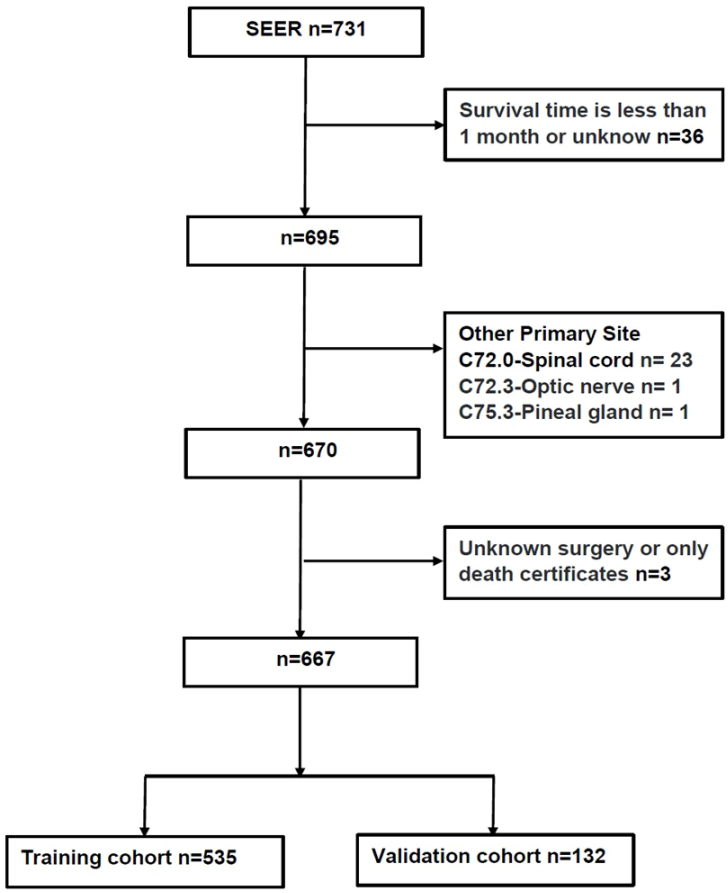

FIGURE 1
Method of retrieving data from the data base.

The Cox proportional hazards model method and PSM were used in different subgroups of 667 patients including unoperated versus operated, GTR, STR, and biopsy. A logistic regression model was constructed with operation status as the dependent variable for calculating the propensity scores. One-to-one matching without replacement was performed using the nearest-neighbor match on the logit of the propensity score for confounding factors (derived from age, sex, race, marital status, primary site, tumor size, pathology, grade, laterality, and radiation). The χ^2 test, Fisher's exact test, and Mann-Whitney *U* test were used to inspect the statistical differences of subgroups before and after matching. Cox proportional hazards model was used to perform univariate and multivariate analyses of various subgroups' data after PSM. Equilibrium of covariables between subgroups was indicated by $p > 0.05$.

Various statistical methods were finished in this paper by SPSS (SPSS 26.0, IBM, Inc., Armonk, NY, United States) and R software (R 4.1.2, Vienna, Austria). The *p*-value < 0.10 of the factor in the univariate analysis was included in the multivariate analysis. Two-tailed *p*-value < 0.05 was indicated statistically significant (7).

Results

Patient characteristics

Our study included 667 cases of intracranial subependymoma, which randomly assigned 535 patients (80.21%) into the training cohort and 132 patients (19.79%) into the validation cohort (Figure 1). The median OS for all of patients, training cohort, and validation cohort was 56 months [interquartile range (IQR), 24–93], 56 months (IQR, 22–93), and 57 months (IQR,25–90), respectively (Table 1).

The survival factors of the training cohort

The survival curves of age ($p < 0.0001$; Figure 2A) and sex ($p = 0.038$; Figure 2B) were compared using a log-rank test. The Cox proportional hazards model was used to perform univariate and multivariate analysis for the training cohort. As exhibited in Table 2, age ($p < 0.001$) and sex were ($p = 0.042$) independent

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TABLE 1 Details of patients with subependymoma.

Characteristics	Total n = 667	Training cohort N = 535	Validation cohort N = 132
Primary site surgery			
No surgery	243 (36.43%)	196 (36.64%)	47 (35.61%)
Surgery NOS or excisional biopsy	101 (15.14%)	86 (16.07%)	15 (11.36%)
STR	96 (14.39%)	77 (14.39%)	19 (14.39%)
GTR	227 (34.03%)	176 (32.90%)	51 (38.64%)
Age (years)			
0–39	126 (18.89%)	99 (18.50%)	27 (20.45%)
40–59	331 (49.63%)	266 (49.72%)	65 (49.24%)
≥60	210 (31.48%)	170 (31.78%)	40 (30.30%)
Sex			
Male	472 (70.76%)	375 (70.09%)	97 (73.48%)
Female	195 (29.23%)	160 (29.91%)	35 (26.52%)
Race			
White	584 (87.56%)	470 (87.85%)	114 (86.36%)
Black	37 (5.55%)	28 (5.23%)	9 (6.82%)
Others/Unknown	46 (6.90%)	37 (6.92%)	9 (6.82%)
Year of diagnosis			
4–9	230 (34.48%)	185 (34.58%)	45 (34.09%)
10–16	437 (65.52%)	350 (65.42%)	87 (65.91%)
Insurance			
Uninsured/unknown/blank	131 (19.64%)	102 (19.07%)	29 (21.97%)
Insured/no specifics	467 (70.01%)	376 (70.28%)	91 (68.94%)
Any Medicaid	69 (10.34%)	57 (10.65%)	12 (9.09%)
Marital status			
Married (including common law)	394 (59.07%)	185 (34.58%)	82 (62.12%)
Other	273 (40.93%)	350 (65.42%)	50 (37.88%)
Primary site			
Ventricle, NOS	347 (52.02%)	282 (52.71%)	65 (49.24%)
Brain stem	199 (29.84%)	153 (28.60%)	46 (34.85%)
Other	121 (18.14%)	100 (18.69%)	21 (15.91%)
Tumor size (cm)			
<2	216 (32.38%)	174 (32.52%)	42 (31.82%)
2–4	202 (30.28%)	155 (28.97%)	47 (35.61%)
≥4	62 (9.30%)	52 (9.72%)	10 (7.58%)
Unknown/blank	187 (28.04%)	154 (28.79%)	33 (25.00%)
Pathology			
Benign	6 (0.90%)	5 (0.93%)	1 (0.76%)
Subependymoma	656 (98.35%)	526 (98.32%)	130 (98.48%)
Malignant	5 (0.75%)	4 (0.75%)	1 (0.76%)
Grade			
Well differentiated	50 (7.50%)	41 (7.66%)	9 (6.82%)
Moderately differentiated	10 (1.50%)	9 (1.68%)	1 (0.76%)
Undifferentiated	1 (0.15%)	1 (0.19%)	0 (0.00%)
Unknown	606 (90.85%)	484 (90.47%)	122 (92.42%)
Laterality			
Left-origin of primary	77 (11.54%)	63 (11.78%)	14 (10.61%)
Right-origin of primary	86 (12.89%)	69 (12.90%)	17 (12.88%)
Not a paired site	484 (72.71%)	386 (72.15%)	98 (74.24%)
Paired or bilateral	20 (3.00%)	17 (3.18%)	3 (2.23%)

(Continued)

TABLE 1 Continued

Characteristics	Total n = 667	Training cohort N = 535	Validation cohort N = 132
Radiation			
None/Unknown	640 (95.95%)	513 (95.89%)	127 (96.21%)
Yes	27 (4.05%)	22 (4.11%)	5 (3.79%)
Vital status			
Alive	596 (89.36%)	478 (89.35%)	118 (89.39%)
Dead	71 (10.64%)	57 (10.65%)	14 (10.61%)
OS (M)	56 (24-93)	56 (22-93)	57 (25-90)

GTR, gross total resection; STR, subtotal resection; OS, overall survival.

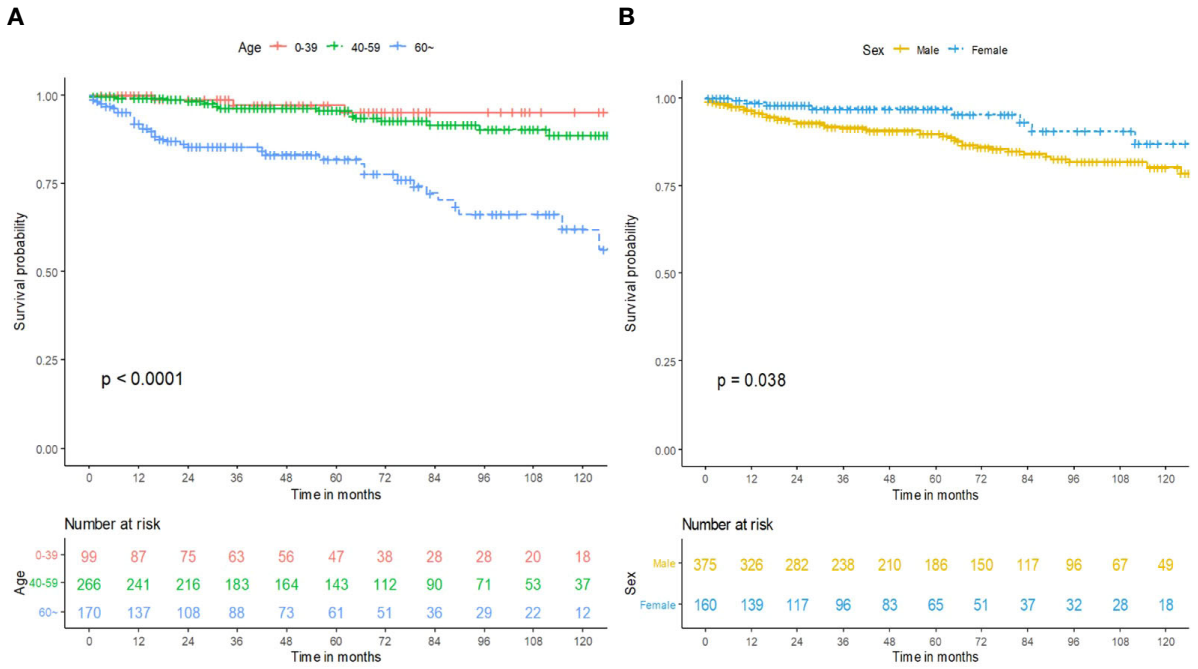

FIGURE 2
Prognosis of intracranial subependymoma for OS in the training cohort. **(A)** OS between the different age groups. **(B)** OS between the different sex groups. OS, overall survival.

prognostic predictors. Patients who were male or more than 60 years of age had less OS time compared with patients who were female or less than 60 years of age. Race, year of diagnosis, insurance, marital status, primary site, tumor size, pathology, grade, laterality, primary site surgery, and radiation had no statistically significant differences in OS for subependymoma in our research (Table 2).

Construction and validation of the nomogram

The Cox proportional hazards model uncovered two significant factors that were used to build the nomogram in the training cohort at last (Figure 3A). As exhibited in Figures 3B, C, calibration diagrams complement the internal validation of training queue. The C-index of the training cohort was 0.733 ± 0.065. The C-index and calibration plots confirmed the dependability of the nomograms. Then, the C-index of the validation cohort was 0.850 ± 0.065. Therefore, the 3-year, 5-year, and 10-year predictions of OS by the nomograms were reliable.

Different subgroups after COX regression analysis and PSM

We performed different subgroup analyses to determine whether surgery was an independent predictor for OS. After PSM of 667 patients

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TABLE 2 Training cohort characteristics.

Characteristics	Value N = 535	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Primary site surgery							
No surgery	196 (36.64%)	Reference			Reference		
Surgery NOS or excisional biopsy	86 (16.07%)	0.725	0.337–1.560	0.411	0.953	0.438–2.076	0.904
STR	77 (14.39%)	0.930	0.444–1.948	0.847	1.061	0.504–2.235	0.876
GTR	176 (32.90%)	0.566	0.292–1.096	0.091	0.799	0.405–1.574	0.516
Age (years)							
0–39	99 (18.50%)	Reference			Reference		
40–59	266 (49.72%)	1.570	0.528–4.672	0.417	1.484	0.496–4.442	0.481
≥60	170 (31.78%)	6.821	2.420–19.226	<0.001	6.355	2.240–18.029	0.001
Sex							
Male	375 (70.09%)	Reference			Reference		
Female	160 (29.91%)	0.478	0.235–0.975	0.043	0.475	0.232–0.974	0.042
Race							
White	470 (87.85%)	Reference					
Black	28 (5.23%)	0.986	0.308–3.159	0.981			
Others/Unknown	37 (6.92%)	0.210	0.029–1.522	0.123			
Year of diagnosis							
4–9	185 (34.58%)	Reference					
10–16	350 (65.42%)	1.174	0.639–2.156	0.606			
Insurance							
Uninsured/unknown/blank	102 (19.07%)	Reference					
Insured/no specifics	376 (70.28%)	1.484	0.755–2.914	0.252			
Any Medicaid	57 (10.65%)	1.641	0.606–4.441	0.330			
Marital status							
Married (including common law)	185 (34.58%)	Reference					
Other	350 (65.42%)	1.270	0.752–2.145	0.372			
Primary site							
Ventricle, NOS	282 (52.71%)	Reference					
Brain stem	153 (28.60%)	1.221	0.678–2.198	0.507			
Other	100 (18.69%)	1.058	0.515–2.172	0.879			
Tumor size (cm)							
<2	174 (32.52%)	Reference					
2–4	155 (28.97%)	0.907	0.462–1.781	0.778			
≥4	52 (9.72%)	0.921	0.342–2.481	0.870			
Unknown/blank	154 (28.79%)	1.208	0.627–2.328	0.573			
Pathology							
Benign	5 (0.93%)	Reference					
Subependymoma	526 (98.32%)	0.564	0.078–4.082	0.570			
Malignant	4 (0.75%)	0.801	0.050–12.861	0.876			
Grade							
Well differentiated	41 (7.66%)	Reference					
Moderately differentiated	9 (1.68%)	NA	NA	NA			
Undifferentiated	1 (0.19%)	NA	NA	NA			
Unknown	484 (90.47%)	0.734	0.315–1.711	0.474			
Laterality							
Left-origin of primary	63 (11.78%)	Reference					
Right-origin of primary	69 (12.90%)	0.622	0.216–1.797	0.381			

(Continued)

TABLE 2 Continued

Characteristics	Value N = 535	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Not a paired site	386 (72.15%)	0.684	0.320–1.463	0.328			
Paired or bilateral	17 (3.18%)	0.492	0.062–3.936	0.504			
Radiation							
None/unknown	513 (95.89%)	Reference					
Yes	22 (4.11%)	1.145	0.358–3.666	0.820			
Vital status							
Alive	478 (89.35%)						
Dead	57 (10.65%)						
OS (M)	56 (22-93)						

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; STR, subtotal resection; OS, overall survival; NA, not available.
The median OS time was 56 months (interquartile range, IQR 22–93). The Cox proportional hazards model was used to perform univariate and multivariate analyses on the training group.

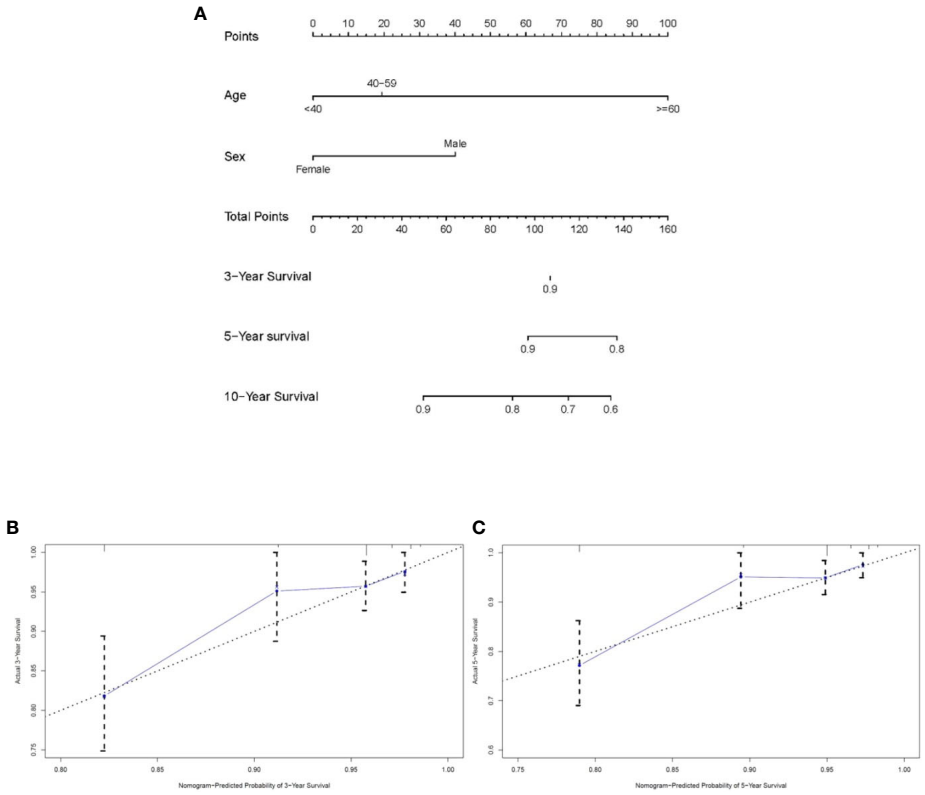

FIGURE 3
Nomogram analyses for patients with intracranial subependymoma. **(A)** A nomogram for predicting 3-, 5- and 10-year OS of patients. **(B)** Calibration curve of the nomogram predicting 3-year OS in training cohort. **(C)** Calibration curve of the nomogram predicting 5-year OS in training cohort. OS, overall survival.

in unoperated versus operated, 210 non-operative patients were matched with 210 surgical patients (Tables 3, S1). In the matched cohort, there was no significant difference in OS between the non-surgical and surgical groups (HR = 0.788; 95% CI, 0.457–1.359; p = 0.391; Table 3). In the multivariable regression analysis, age (HR = 8.870; 95% CI, 2.106–22.410; p = 0.001; Table 3) and sex (HR = 0.380; 95% CI, 0.170–0.846; p = 0.018; Table 3) were independent risk prognostic factors for OS.

TABLE 3 The characteristics of 420 patients from the 667 patients grouped according to no surgery and surgery after PSM.

Characteristics	Value N = 420	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Primary site surgery							
No surgery	210 (50.00%)	Reference					
Surgery	210 (50.00%)	0.788	0.457–1.359	0.391			
Age (years)							
0–39	77 (18.33%)	Reference			Reference		
40–59	199 (47.38%)	1.496	0.422–5.302	0.533	1.234	0.346–4.401	0.746
≥60	144 (34.29%)	8.040	2.477–26.099	0.001	6.870	2.106–22.410	0.001
Sex							
Male	295 (70.24%)	Reference			Reference		
Female	125 (29.77%)	0.358	0.162–0.795	0.012	0.380	0.170–0.846	0.018
Race							
White	361 (85.95%)	Reference					
Black	24 (5.71%)	1.620	0.643–4.082	0.306			
Others/unknown	35 (8.33%)	0.190	0.026–1.378	0.100			
Year of diagnosis							
4–9	135 (32.14%)	Reference					
10–16	285 (67.86%)	0.843	0.458–1.554	0.585			
Insurance							
Uninsured/unknown/blank	80 (19.05%)	Reference					
Insured/no specifics	297 (70.71%)	1.109	0.563–2.183	0.765			
Any Medicaid	43 (10.24%)	1.630	0.605–4.391	0.334			
Marital status							
Married (including common law)	243 (57.86%)	Reference					
Other	177 (42.14%)	1.095	0.631–1.899	0.747			
Primary site							
Ventricle, NOS	203 (48.33%)	Reference					
Brain stem	128 (30.48%)	0.819	0.422–1.588	0.555			
Other	89 (21.19%)	1.139	0.577–2.251	0.707			
Tumor size (cm)							
<2	173 (41.19%)	Reference					
2–4	110 (26.19%)	0.922	0.46–1.843	0.818			
≥4	33 (7.86%)	1.427	0.538–3.786	0.475			
Unknown/blank	104 (24.76%)	1.324	0.662–2.649	0.428			
Pathology							
Benign	5 (1.19%)	Reference					
Subependymoma	411 (97.86%)	0.623	0.086–4.517	0.639			
Malignant	4 (0.95%)	0.932	0.058–14.916	0.960			
Grade							
Well differentiated	7 (1.67%)	Reference					
Moderately differentiated	5 (1.19%)	NA	NA	NA			
Undifferentiated	1 (0.24%)	NA	NA	NA			
Unknown	407 (96.90%)	0.392	0.095–1.617	0.195			
Laterality							
Left-origin of primary	51 (12.14%)	Reference					
Right-origin of primary	57 (13.57%)	0.850	0.274–2.638	0.779			
Not a paired site	296 (70.48%)	1.003	0.424–2.372	0.994			
Paired or bilateral	16 (3.81%)	0.578	0.070–4.806	0.612			

(Continued)

TABLE 3 Continued

Characteristics	Value N = 420	Univariate analysis			Multivariate analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Radiation							
None/Unknown	406 (96.67%)	Reference					
Yes	14 (3.33%)	1.273	0.309–5.237	0.738			
Vital status							
Alive	368						
Dead	52						
OS (M)	48.50 (21–85)						

HR, hazard ratio; CI, confidence interval; OS, overall survival; NA, not available.
The median OS time was 51.5 months (IQR 17–89.75).

After PSM of 470 patients in unoperated versus GTR, 164 non-operative patients were matched with 164 GTR patients (Tables 4, S2). In the matched cohort, there was no significant difference in OS between the non-surgical and GTR groups (HR = 0.562; 95% CI, 0.299–1.054; p = 0.072; Table 4). In the multivariable regression analysis, sex (HR = 0.211; 95% CI, 0.065–0.684; p = 0.010; Table 4) was an independent risk prognostic factor for OS.

After PSM of 339 patients in unoperated versus STR, 92 non-operative patients were matched with 92 STR patients (Tables 5, S3). In the matched cohort, there was no significant difference in OS between the non-surgical and STR groups (HR = 0.765; 95% CI, 0.330–1.772; p = 0.532; Table 5). In the multivariable regression analysis, laterality (HR = 0.300; 95% CI, 0.106–0.847; p = 0.023; Table 5) was an independent risk prognostic factor for OS.

After PSM of 344 patients in unoperated versus surgery NOS or excisional biopsy, 87 non-operative patients were matched with 87 patients with surgery NOS or excisional biopsy (Tables 6, S4). In the matched cohort, there was no significant difference in OS between the non-surgical and surgery NOS or excisional biopsy groups (HR = 0.596; 95% CI, 0.258–1.377; p = 0.225; Table 6). In the multivariable regression analysis, age (HR = 10.758; 95% CI,2.377–48.693; p = 0.002; Table 6) was an independent risk prognostic factor for OS.

Discussion

Scheinker reported a case of a newly recognized tumor derived from the fourth subependymal zone in a 56-year-old man and firstly named subependymoma (8). To date, subependymoma was sporadically reported on case reports (4, 9–11) and accounted for 0.07%-0.7% of all brain tumors (9, 12). Subependymomas were brain neoplasms that tended to be benign, to be less aggressive, to grow slowly, and to be histologically classified as World Health Organization (WHO) grade 1 (13). D'Amico et al. reported a case that was diagnosed with subependymoma by pathological biopsy; CT and MRI confirmed no significant tumor progression after a 36-year follow-up, highlighting the extremely indolent nature of subependymoma (14). The pathogenesis of subependymoma may be related to potential precursor cells (13, 15). Zhiyong et al. reported that 43 patients with subependymoma were found in 60,000 cases of surgically intracranial tumors and the incidence of intracranial subependymoma was about 0.07%. The lesions were mostly located in lateral ventricles accounting for 65% of cases, followed by the fourth ventricle and third ventricle accounting for 19% and 7% of cases, respectively. Tumors were less common in the brain parenchyma and stem (2, 13). The occurrence of symptoms, such as initial clinical manifestations of increased intracranial pressure, was related to the disturbance of cerebrospinal fluid circulation caused by the tumor. Uncommon clinical symptoms including epilepsy, memory loss, ataxia, tremor, blurred vision, and subarachnoid hemorrhage have been reported in some cases (2, 7).

However, there is no prediction model for the OS of subependymoma and no large sample study about the impact of different surgical methods on patient prognosis.

We conducted a study for subependymoma based on the SEER database. The National Cancer Institute's SEER database collected cancer diagnosis, treatment, and survival data for approximately 30% of the U.S. population. SEER database is an important population-based resource that has become a unique research resource for oncology practice in the United States. The SEER database had the following advantages: representative and universal responses to disease in the United States population, long data collection time, large number of cases, and collection of specific cancer outcomes.

However, the SEER database had the following limitations: individual-level data on specific cancer risks and treatments are incomplete. The accuracy and completeness of raw data collected from the registry needed to be improved. SEER database could not evaluate the progression-free survival (PFS) of tumors.

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TABLE 4 The characteristics of 328 patients from the 470 patients grouped according to no surgery and GTR after PSM.

Characteristics	Value *N* = 328	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Primary site surgery							
No surgery	164 (50.00%)	Reference			Reference		
GTR	164 (50.00%)	0.549	0.292–1.030	0.062	0.562	0.299–1.054	0.072
Age (years)							
0–39	61 (18.60%)	Reference					
40–59	163 (49.70%)	NA	NA	NA			
≥60	104 (31.71%)	NA	NA	NA			
Sex							
Male	242 (73.78%)	Reference			Reference		
Female	86 (26.22%)	0.208	0.064–0.673	0.009	0.211	0.065–0.684	0.010
Race							
White	292 (89.02%)	Reference					
Black	16 (4.88%)	1.966	0.699–5.526	0.200			
Others/unknown	20 (6.10%)	NA	NA	NA			
Year of diagnosis							
4–9	110 (33.54%)	Reference					
10–16	218 (66.46%)	0.865	0.438–1.711	0.678			
Insurance							
Uninsured/unknown/blank	72 (21.95%)	Reference					
Insured/no specifics	228 (69.51%)	1.463	0.672–3.186	0.338			
Any Medicaid	28 (8.54%)	2.182	0.660–7.213	0.201			
Marital status							
Married (including common law)	186 (56.71%)	Reference					
Other	142 (43.29%)	1.124	0.606–2.083	0.711			
Primary site							
Ventricle, NOS	183 (55.79%)	Reference					
Brain stem	95 (28.98%)	1.237	0.608–2.516	0.557			
Other	50 (15.24%)	1.658	0.732–3.754	0.225			
Tumor size (cm)							
<2	121 (36.89%)	Reference					
2–4	81 (24.70%)	0.883	0.400–1.948	0.758			
≥4	25 (7.62%)	1.725	0.674–4.416	0.256			
Unknown/blank	101 (30.79%)	0.751	0.330–1.711	0.495			
Pathology							
Benign	5 (1.52%)	Reference					
Subependymoma	320 (97.56%)	0.626	0.086–4.567	0.644			
Malignant	3 (0.91%)	1.619	0.101–26.020	0.734			
Grade							
Well differentiated	6 (1.83%)	Reference					
Moderately differentiated	1 (0.30%)	NA	NA	NA			
Undifferentiated	0 (0.00%)	NA	NA	NA			
Unknown	321 (97.87%)	0.470	0.113–1.963	0.301			
Laterality							
Left-origin of primary	23 (7.01%)	Reference					
Right-origin of primary	41 (12.50%)	0.857	0.204–3.592	0.832			
Not a paired site	254 (77.44%)	0.900	0.275–2.941	0.861			
Paired or bilateral	10 (3.05%)	NA	NA	NA			

(Continued)

TABLE 4 Continued

Characteristics	Value *N* = 328	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Radiation							
None/unknown	317 (96.65%)	Reference					
Yes	11 (3.35%)	1.525	0.367–6.328	0.561			
Vital Status							
Alive	287 (87.50%)						
Dead	41 (12.50%)						
OS (M)	49 (17–89.75)						

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; OS, overall survival; NA, not available.
The median follow-up time was 49 months (IQR 20–91).

In this study, we combined the treatment data, follow-up data, and clinical and pathological data from 535 patients in the training group to construct a nomogram for the prediction of the OS of each patient.

Independent prognostic predictors and nomogram

Nguyen et al. drew a conclusion that age < 40 years, female sex, and location within ventricles or near brain stem were positive factors with OS by analyzing 466 cases of intracranial subependymomas from 2004 to 2013 in the SEER database (16). The authors suggest that surgery remains a mainstay treatment. Like prior studies, our study supported that age and sex were significant independent predictors of OS. After our statistical analysis, the prognostic model constructed by age and sex was in good agreement with the reality.

However, whether in the training or subgroup cohort, we revealed that surgery, tumor size, and location were not independent prognostic factors for OS. This seems to challenge the choice of surgical treatment.

D'Amico et al. found that the presence of early malignant lesions in subependymoma cannot be confirmed by early imaging examination and drew a conclusion that early resection was preferred by immunohistochemical analysis of 31 patients with pathologically proven subependymomas (9).

However, some scholars also proposed that conservative treatment was the main treatment for subependymoma. Kammer et al. reviewed 33 cases and showed that subependymomas were usually symptomless; 29 patients were discovered by chance. Subependymoma with no obvious growth tendency seldom led to decompensation of cerebrospinal fluid circulation by blocking the interventricular foramen or Magendie foramen.

In other words, hydrocephalus was relatively rare in subependymoma, which recommended expectant treatment or longer imaging follow-up than other lesions at the same location (10). With a retrospective analysis of 13 patients with intracranial WHO grade 1 subependymoma from 1990 to 2015, Varma revealed that occasional intraventricular subependymoma could be treated conservatively with MRI monitoring. Because there was no significant change in disease during a mean follow-up of 46 months, long-term follow-up was not necessary (14). The author further expounded that hydrocephalus was the main complication of surgical treatment of hydrocephalic subependymoma (2, 14). The appeal suggests that conservative treatment was also an appropriate approach. This may seem counterintuitive. Due to the low degree of malignancy, there were few reports of death caused by subependymoma in a short period. Patients are more likely to die from accidents or other factors.

We recognized that the established nomogram had some value in evaluating patient prognosis and were inclined to use models to predict the prognosis of the subependymoma.

Although nomograms had certain predictive accuracy in the training and validation groups in our study, the treatment strategy still needed to be further improved through subsequent studies, considering the inherent limitations of the SEER databases.

This may not mean that surgery was meaningless for subependymoma. We conducted a further subgroup analysis of the benefits of surgical treatment.

Subgroups analyses of different surgical methods

No large sample data analysis has reported the prognostic impact of different surgical methods for subependymoma.

Reviewing 466 patients with intracranial subependymoma, Nguyen et al. concluded that surgery was a significantly positive prognostic factor. However, the author further elaborated that GTR was not a significant prognostic factor and locations within

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TABLE 5 The characteristics of 184 patients from the 339 patients grouped according to no surgery and STR after PSM.

Characteristics	Value $N = 184$	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Primary site surgery							
No surgery	92 (50.00%)	Reference					
STR	92 (50.00%)	0.765	0.330–1.772	0.532			
Age (years)							
0–39	36 (19.57%)	Reference					
40–59	88 (47.83%)	NA	NA	NA			
≥60	60 (32.61%)	NA	NA	NA			
Sex							
Male	139 (75.54%)	Reference					
Female	45 (24.46%)	0.033	0.000–2.379	0.118			
Race							
White	154 (83.70%)	Reference					
Black	9 (4.89%)	0.740	0.099–5.520	0.769			
Others/unknown	21 (11.41%)	0.329	0.044–2.454	0.278			
Year of diagnosis							
4–9	63 (32.24%)	Reference					
10–16	121 (65.76%)	1.590	0.596–4.241	0.354			
Insurance							
Uninsured/unknown/blank	43 (23.37%)	Reference					
Insured/no specifics	113 (61.41%)	2.058	0.715–5.927	0.181			
Any Medicaid	28 (15.22%)	1.865	0.443–7.860	0.396			
Marital status							
Married (including common law)	103 (55.98%)	Reference					
Other	81 (44.02%)	0.652	0.266–1.602	0.352			
Primary site							
Ventricle, NOS	88 (47.83%)	Reference					
Brain stem	53 (28.80%)	1.168	0.423–3.225	0.764			
Other	43 (23.37%)	1.376	0.498–3.802	0.538			
Tumor size (cm)							
<2	47 (25.54%)	Reference					
2–4	46 (25.00%)	1.224	0.373–4.010	0.739			
≥4	21 (11.41%)	1.496	0.357–6.266	0.582			
Unknown/blank	70 (38.04%)	1.374	0.449–4.205	0.578			
Pathology							
Benign	2 (1.09%)	Reference					
Subependymoma	180 (97.83%)	NA	NA	NA			
Malignant	2 (1.09%)	NA	NA	NA			
Grade							
Well differentiated	2 (1.09%)	Reference					
Moderately differentiated	2 (1.09%)	NA	NA	NA			
Undifferentiated	0 (0.00%)						
Unknown	180 (97.83%)	0.222	0.030–1.666	0.143			
Laterality							
Left-origin of primary	20 (10.87%)	Reference			Reference		
Right-origin of primary	23 (12.50%)	0.372	0.089–1.564	0.177	0.372	0.089–1.564	0.177
Not a paired site	131 (71.20%)	0.300	0.106–0.847	0.023	0.300	0.106–0.847	0.023
Paired or bilateral	10 (5.43%)	0.371	0.043–3.180	0.366	0.371	0.043–3.180	0.366

(Continued)

TABLE 5 Continued

Characteristics	Value N = 184	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Radiation							
None/unknown	178 (96.74%)	Reference					
Yes	6 (3.26%)	0.048	0.000–9,009.212	0.624			
Vital status							
Alive	162 (88.04%)						
Dead	22 (11.96%)						
OS (M)	52.5 (16–93.75)						

HR, hazard ratio; CI, confidence interval; STR, subtotal resection; OS, overall survival; NA, not available.
The median follow-up time was 52.5 months (IQR 16–93.75).

"ventricles, NOS" or near "brain stem" were low-risk predictors factors for OS (16). Although there was the most extensive data analysis of intracranial subependymoma before 2017, the conclusion seemed to be counterintuitive.

Considering the importance of data quality, we screened the data of higher quality from the large sample and tried to make it equally comparable, through the application of statistical methods, such as eliminating incomplete data, univariate and multivariate analyses, PSM, and subgroup analysis.

To study the influence of different surgical methods on OS, we completed subgroup analyses through Cox regression analysis and PSM. Exhibited in Tables 3 and S1, patients matched after PSM had no significant difference in OS between the non-surgical and surgical groups. In the multivariable regression analysis, age and sex were significant prognostic variables for OS. The subgroup analysis of non-surgical versus surgical groups confirmed this finding in the training cohort.

Surgical treatment, race, year of diagnosis, insurance, tumor location, tumor size, pathology, tumor grade, and radiation had no statistically significant differences in OS for subependymoma in our research.

However, it was diacritical that age, sex, and laterality were the significant prognostic variables for OS in the different matched subgroups of unoperated versus GTR, STR, and biopsy. However, it did not mean that conservative treatment had a better prognosis.

The study of Nguyen et al. included fewer patients, lacking subgroup analyses, not clear prognostic factors of different treatment modalities, and the confounding factors were not matched. Improving deficiencies of previous studies, we should not be more inclined to choose conservative or surgical treatment.

Considering the rarity of the disease, our study is a retrospective analysis of the largest sample size of subependymoma to date, taking advantage of the SEER database's wide population coverage.

We predicted the 3-, 5-, and 10-year survival rates for subependymoma using a nomogram model based on age and sex as prognostic factors. Although the prognostic model performed well in the experimental and validation groups, the two prognostic factors might not be sufficient to clinical use.

Nonetheless, the information that we present might be useful to suggest potential hypotheses to be tested in the clinical research setting. Doctors needed to evaluate the indications, contraindications, and risks of surgery comprehensively, and then made recommendations based on the wishes of patients' families.

We suggested that the following measures needed to be adopted before the clinical implementation. Due to the extremely indolent nature of subependymoma, longer follow-up time was required to assess the outcome of the operative treatment. We need to expand the sample further and include more prognostic variables, such as immunohistochemical information. Prospective multicenter randomized controlled studies of subependymoma were needed to develop models with greater sensitivity and specificity.

Limitations

In our study, there was a particular patient selection bias based on the SEER database. Therefore, data quality is also a limitation of this study. Considering the rigor of the data, our study excluded patients with a survival time of less than 1 month, which might have skewed the results by excluding acute deaths from severe hydrocephalus without surgery. In addition, the median follow-up was only 56 months and the sample size was small after PSM. Longer follow-up and further multicenter studies with more sample sizes are needed.

Conclusion

Age and sex were the independent prognostic variables for OS in intracranial subependymoma. According to our research,

TABLE 6 The characteristics of 174 patients from the 344 patients grouped according to no surgery and surgery NOS or excisional biopsy after PSM.

Characteristics	Value *N* = 174	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Primary site surgery							
No surgery	87 (50.00%)	Reference					
Surgery NOS or excisional biopsy	87 (50.00%)	0.596	0.258–1.377	0.225			
Age (years)							
0–39	36 (20.69%)	Reference			Reference		
40–59	94 (54.02%)	0.677	0.124–3.697	0.652	0.938	0.166–5.310	0.942
≥60	44 (25.29%)	7.204	1.664–31.197	0.008	10.758	2.377–48.693	0.002
Sex							
Male	119 (68.39%)	Reference					
Female	55 (31.61%)	0.697	0.258–1.884	0.477			
Race							
White	154 (88.51%)	Reference					
Black	10 (5.75%)	2.602	0.769–8.802	0.124			
Others/unknown	10 (5.75%)	NA	NA	NA			
Year of diagnosis							
4–9	69 (39.66%)	Reference			Reference		
10–16	105 (60.34%)	2.364	0.890–6.280	0.084	2.654	0.862–8.170	0.089
Insurance							
Uninsured/unknown/blank	35 (20.11%)	Reference			Reference		
Insured/no specifics	119 (68.39%)	1.452	0.468–4.503	0.519	0.925	0.277–3.090	0.899
Any Medicaid	20 (11.49%)	4.454	1.152–17.224	0.030	3.358	0.828–13.619	0.090
Marital status							
Married (including common law)	98 (56.32%)	Reference					
Other	76 (43.68%)	1.579	0.695–3.588	0.275			
Primary site							
Ventricle, NOS	89 (51.15%)	Reference					
Brain stem	45 (25.86%)	1.461	0.556–3.842	0.442			
Other	40 (22.99%)	1.630	0.591–4.496	0.345			
Tumor size (cm)							
<2	48 (27.59%)	Reference					
2–4	51 (29.31%)	1.429	0.507–4.026	0.499			
≥4	16 (9.20%)	1.178	0.237–5.844	0.841			
Unknown/blank	59 (33.91%)	0.930	0.300–2.888	0.901			
Pathology							
Benign	3 (1.72%)	Reference					
Subependymoma	169 (97.13%)	0.471	0.063–3.531	0.464			
Malignant	2 (1.15%)	1.702	0.105–27.593	0.708			
Grade							
Well differentiated	5 (2.87%)	Reference			Reference		
Moderately differentiated	1 (0.75%)	NA	NA	0.983	NA	NA	NA
Undifferentiated	1 (0.75%)	NA	NA	0.986	NA	NA	NA
Unknown	167 (95.98%)	0.180	0.042–0.778	0.022	0.280	0.058–1.358	0.114
Laterality							
Left-origin of primary	23 (13.22%)	Reference					
Right-origin of primary	24 (13.79%)	0.361	0.070–1.864	0.224			
Not a paired site	121 (69.54%)	0.515	0.187–1.416	0.199			

(Continued)

TABLE 6 Continued

Characteristics	Value $N = 174$	Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*-value	HR	95% CI	*p*-value
Paired or bilateral	6 (3.45%)	NA	NA	NA			
Radiation							
None/unknown	166 (95.40%)	Reference					
Yes	8 (4.60%)	2.767	0.639–11.978	0.173			
Vital status							
Alive	151 (86.78%)						
Dead	23 (13.22%)						
OS (M)	56.50 (21.75–97.25)						

HR, hazard ratio; CI, confidence interval; OS, overall survival; NA, not available.
The median follow-up time was 56.50 months (IQR 21.75–97.25).

we should not be more inclined to choose conservative or surgical treatment. Nonetheless, the information that we present might be useful to suggest potential hypotheses to be tested in the clinical research setting.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

HC and ZZ: conception of the project. XP and YW: data reduction and screening. QL and HJ: statistical analysis and processing of data. ZZ, HC, and YW: writing and revising article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.939816/full#supplementary-material

SUPPLEMENTARY TABLE 1
The χ^2, Fisher's exact or Mann-Whitney U test was used to inspect the differences of the non-surgical and surgical groups before and after matching. Age, insurance and pathology were analyzed by using the Mann-Whitney U test. The grade was analyzed by using Fisher's exact test.

SUPPLEMENTARY TABLE 2
The χ^2, Fisher's exact or Mann-Whitney U test was used to inspect the differences of the no surgery and GTR before and after matching. Age, insurance and pathology were analyzed by using the Mann-Whitney Utest. The grade was analyzed by using Fisher's exact test.

SUPPLEMENTARY TABLE 3
The χ^2, Fisher's exact or Mann-Whitney U test was used to inspect the differences of the no surgery and STR in before and after matching. Age, insurance and pathology were analyzed by using the Mann-Whitney U test. The grade was analyzed by using Fisher's exact test.

SUPPLEMENTARY TABLE 4

The χ^2, Fisher's exact or Mann-Whitney U test was used to inspect the differences of the no surgery and Surgery NOS or excisional biopsy before and after matching. Age, insurance and pathology were analyzed by using the Mann-Whitney U test. The grade was analyzed by using Fisher's exact test.

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Postoperative prolonged mechanical ventilation correlates to poor survival in patients with surgically treated spinal metastasis

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Objective: Patients with spinal metastasis (SM) are at advanced stages of systemic cancer disease. Surgical therapy for SM is a common treatment modality enabling histopathological diagnosis and the prevention of severe neurological deficits. However, surgery for SM in this vulnerable patient cohort may require prolonged postoperative intensive care treatment, which could adversely affect the anticipated benefit of the surgery. We therefore assessed postoperative prolonged mechanical ventilation (PMV) as an indicator for intensive care treatment with regard to potential correlations with early postoperative mortality and overall survival (OS).

Methods: Between 2015 and 2019, 198 patients were surgically treated for SM at the author´s neurosurgical department. PMV was defined as postoperative mechanical ventilation of more than 24 hours. A multivariate analysis was performed to identify pre- and perioperative collectable predictors for 30 days mortality.

Results: Twenty out of 198 patients (10%) with SM suffered from postoperative PMV. Patients with PMV exhibited a median OS rate of 1 month compared to 12 months for patients without PMV ($p < 0.0001$). The 30 days mortality was 70% and after one year 100%. The multivariate analysis identified "PMV > 24 hrs" ($p < 0.001$, OR 0.3, 95% CI 0.02-0.4) as the only significant and independent predictor for 30 days mortality (Nagelkerke's R2 0.38).

Conclusions: Our data indicate postoperative PMV to significantly correlate to high early postoperative mortality rates as well as to poor OS in patients with surgically treated SM. These findings might encourage the initiation of further multicenter studies to comprehensively investigate PMV as a so far underestimated negative prognostic factor in the course of surgical treatment for SM.

KEYWORDS

prolonged mechanical ventilation (PMV), spinal metastasis treatment, spinal surgery, spinal surgery and complications, mortality

Introduction

Tumor disease with spinal metastases (SM) plays an increasing role in daily clinical practice (1) and surgery is a common treatment option for this highly affected patient cohort (2). Along with the lung and the liver, the skeletal system is among the most common locations of systemic metastasis (3, 4). Surgical treatment options comprise biopsy with vertebroplasty/kyphoplasty (5), decompression alone (6), or decompression in combination with percutaneous (7) or open instrumentation (8, 9). The goal of surgery is to minimize or prevent neurological deficits and to improve the patient's quality of life (10). The indication for surgery must be interdisciplinary, taking into account the urgency, the therapeutic objective, aspects of stability of spinal biomechanics and prognostic considerations of the underlying conditions (11, 12). Different score systems for estimating the prognosis and survival have limited capacity and can only be used as guide points (13, 14). Nevertheless, surgical treatment may require prolonged postoperative intensive care, which could adversely affect the anticipated benefits of the surgery. Postoperative prolonged mechanical ventilation (PMV) has recently been used as an indicator variable for intensive care treatment in several diseases (15–18). However, the impact of PMV in the field of surgery for SM has not been analyzed to date. In the present study we therefore assessed the prognostic impact of PMV regarding early postoperative mortality and overall survival (OS) in patients who had undergone surgery for SM.

Abbreviations: ASA, American Society of Anesthesiology; ASIA Score, American Spinal Injury Association; CCI, Charlson comorbidity index; CI, Confidence interval; CT, Computer tomography; HACs, Hospital-acquired conditions; IQR, Interquartile range; KPI, Karnofsky Performance Scale; MRI, Magnetic resonance imaging; OR, Odds ratio; OS, Overall survival; PMV, Prolonged mechanical ventilation; PSIs, Patient safety indicators; SM, Spinal metastasis; SSCs, Spinal surgery-related complications.

Methods

Patients and study design

All patients with SM aged > 18 years who had undergone primary posterior spinal canal decompression with or without instrumentation between 2015 and 2019 at the neurosurgical department of the University Hospital Bonn were entered into a computerized database (SPSS, version 25, IBM Corp., Armonk, NY). Follow-up checks were conducted after 3 and 12 months. Patients' clinical information including age, sex, primary tumor, location of SM, surgical procedure, number of affected vertebrae, ASA score, neurological and functional status (American Spinal Injury Association: ASIA Score (19)), and overall survival (OS) was recorded. The Karnofsky Performance Scale (KPS) was used to evaluate patients' preoperative functional status. We excluded all patients who were not classified as operable and those without complete data or follow-up information.

Indications for surgery as well as its extent were determined according to the Spinal Instability Neoplastic Score (SINS) (20, 21). Every patient received preoperative CT and MRI scans of the affected spinal level (22, 23). Patients with spine instability received posterior dorsal decompression with stabilization – because of pedicle system failure, pathological kyphosis of the spine, lytic bone lesions, or neurological deficits. Patients were treated by one of three neurosurgeons with many years' experience in spine surgery, all of whom used the same standardized workflow (including median posterior approach and navigation system) and the same instruments (Diplomat system, Signus Alzenau, Bavaria, Germany). Our standard surgical procedure consisted of the following steps: median posterior dorsal approach, open transpedicular screw implantation (we did not use a percutaneous system), spinal canal and nerve root decompression in combination with posterior bone fusion. We used Mastergraft Granules (Medtronic) rather than cages for the posterior fusion. During cervical and cervicothoracic instrumentation, we used only posterior fixation and dorsal fusion.

In cases of spine stability without pedicle failure or kyphosis and blastic bone lesions, the patients only received dorsal spinal canal and nerve root/spinal cord decompression *via* laminectomy of the affected segment(s) without stabilization. A biopsy from the tumor and bone was taken for histopathological analysis in each case, regardless of the surgical treatment. Patients with dorsal instrumentation received a CT scan immediately after the operation, which was used for comparison purposes in the follow-up checks. Patients who needed intensive medical monitoring were transferred to our intensive care unit, otherwise they received normal post-surgical care.

Once the results of the histopathological analysis were received, all cases were reviewed by our internal Neurooncological Tumor Board consisting of neurosurgeons, radiation therapists, neurooncologists and neuroradiologists. The recommendations for post-surgery management, such as further surgical treatment or other therapy options such as chemotherapy or radiation, were thus based on collective decision-making.

PMV was defined as an invasive ventilation period of > 24 hours after initial spinal surgery (16, 17, 24, 25). The comorbidity burden was measured using the Charlson comorbidity index (CCI) (26, 27).

Early postoperative complications were assessed using a publicly available list of adverse events introduced by the Agency for Healthcare Research and Quality and the Center for Medicare and Medicaid Services, and referred to as patient safety indicators (PSIs) and hospital-acquired conditions (HACs) (28–31). PSIs included acute myocardial infarction, pressure ulcers, iatrogenic pneumothorax, transfusion reactions, peri- and postoperative hemorrhage, pulmonary embolism, acute postoperative respiratory failure, deep vein thrombosis, postoperative sepsis, and wound dehiscence, as well as accidental puncture or laceration. Within the group of HACs, screening was performed for pneumonia, catheter-associated urinary tract infection, surgical site infection, blood incompatibility, crushing injury, manifestation of poor glycemic control (diabetic ketoacidosis, non-ketonic hyperosmolar coma, hyperglycemic coma), fall injury, and vascular catheter-associated infection. In addition, to assess complications specific to spinal surgery, postoperative records were screened for cerebrospinal fluid (CSF) leakage, postoperative meningitis, and implant failure, as well as postoperative new or worsened neurological deficits. These were classified as spinal surgery-related complications (SSCs). As described elsewhere, perioperative complications were defined as any postoperative adverse events, with or without further surgical intervention, occurring within 30 days of the initial surgery (32).

Overall survival (OS) was measured starting from the day of SM surgery until death or last observation. Patients for whom no further follow-up information was available (e.g. due to further treatment at external institutions) were excluded from further analysis. All parameters were compared in relation to OS.

This study was conducted in accordance with the 1964 Helsinki declaration and approved by the Ethics Committee of the University Hospital Bonn (protocol no. 067/21). Informed consent was not sought as a retrospective study design was used.

Weaning protocol

Patients with prolonged oral intubation and ventilation underwent swiftly tracheotomy. After tracheotomy, weaning phase begins on our intensive care unit, first for hours, then weaning depending on the patient's clinical condition. If patients continue to be ventilated, they will be transferd to a rehabilitation facility for further weaning, which has the option of combined rehabilitation and weaning. After the end of the weaning phase (3 weeks), patients were transferred to our clinic, for re-evaluation of clinical status. If they have recovered well, they will be treated further with chemotherapy and radiation therapy. If the clinical situation remains poor, they will be treated palliative.

Statistics

Data analyses were performed using SPSS (version 25, IBM Corp., Armonk, NY) and PRISM computer software packages. Categorical variables were analyzed in contingency tables using Fisher's exact test. The Mann-Whitney U test was chosen to compare continuous variables as the data were mostly not normally distributed, while non-parametric data are summarized by median values (first quartile – third quartile). Results with $p < 0.05$ were considered statistically significant. *Univariate analysis* (including following factors: primary tumor size, median age, gender, location and levels of disease, median CCI, perioperative neurological deficits, surgery, median duration of surgery, early postoperative complications, 30day/one year mortality and median OS) *was conducted using Fisher's exact test (two-sided) and the independent t-test. P values <0.05 were considered statistically significant.* In addition, in order to determine independent predictors of 30 days mortality in patients with surgically-treated spinal metastasis, a backward stepwise method was used to construct a multivariate analysis using a binary logistic regression, again with $p < 0.05$ being considered statistically significant. Additionally, we decided to add a Cox regression analysis in order to identify factors that are significantly associated with worsened OS. Under consideration of known prognostic parameters (patient age, tumor entity, ASIA classification score value, preoperative KPS, number of

affected spinal levels), a preoperative KPS > 70, lung cancer and PMV >24 hrs significantly correlated to shortened OS.

Results

Patient characteristics and demographic data

Between January 2015 and December 2019, 198 patients were surgically treated for SM at the authors' neurosurgical department. The median age was 66 years (range 57-74 years). The most common primary tumor site was the lung (23%), followed by the prostate (20%) and the breast (11%) (Table 1). The thoracic spine was the most commonly affected spinal section (56%). Single or dual-level disease was present in 120 of 198 patients (61%), whereas multilevel disease was present in 78 patients (39%). The majority of patients (63%) underwent decompression with additional dorsal instrumentation, while decompression alone was performed in 37% of cases. 126 of 198 patients (64%) presented with a preoperative KPS score of > 70.

TABLE 1 Patient characteristics*.

	n = 198
Median age (IQR) (in yrs)	66 (57–74)
Female sex	76 (38)
Primary tumor site	
Lung	46 (23)
Breast	22 (11)
Prostate	40 (20)
Other	90 (45)
Location of disease	
Cervical	20 (10)
Thoracic	111 (56)
Lumbar	33 (17)
Combined	34 (17)
Surgery	
Decompression	74 (37)
Stabilization	124 (63)
Levels of disease	
1-2	120 (61)
≥ 3	78 (39)
Median CCI (IQR)	8 (6-10)
ASA score ≥ 3	126 (64)
KPS ≥ 70	126 (64)
Pre-operative neurological deficit	46 (23)
Median OS (IQR) (in months)	11 (3-24)
Postoperative PMV	20 (10)

*Values represent the number of patients unless indicated otherwise (%).
ASA, American Society of Anesthesiology physical status classification system; ASIA, American Spinal Injury Association; CCI, Charlson comorbidity index; KPS Karnofsky Performance Scale; IQR, interquartile range; n, number of patients; OS, overall survival; PMV, prolonged mechanical ventilation; yrs, years.

Median OS for all patients with surgically treated SM was 11 months (interquartile range [IQR] 3-24). A total of 20 out of 198 patients (10%) underwent postoperative PMV. For further details of patients' and tumor-related characteristics see Table 1.

Patient-related and disease-related factors associated with postoperative PMV

Out of 20 patients with postoperative PMV, 10 (50%) exhibited tumor-related preoperative neurological morbidity (ASIA A-C) compared to 36 of 178 patients (20%) without PMV (p = 0.01) (Table 2). At 240 minutes (IQR 170-294), the median duration of surgery for these patients was significantly longer than 178 minutes (IQR 125-244) for those without postoperative PMV (p = *0.03).*

Two out of 19 patients (11%) with PMV exhibited postoperative pulmonary embolism, 2 patients (11%) suffered from postoperative hemorrhage with indication for revision surgery, 3 patients revealed postoperative pneumonia (15%) with respiratory failure. Furthermore, 8 of 19 patients (42%) with postoperative PMV suffered from lung carcinoma therefore exhibiting elevated risk profiles for postoperative PMV as well as prolonged time of weaning.

Age, primary tumor site, the number of affected spinal levels, preoperative CCI, and peri- and postoperative complications, among others, did not significantly differ between the two groups of patients with and without PMV (Table 2**).** The postoperative complications were postoperative hemorrhage (2%), Postoperative pulmonary embolism/deep vein thrombosis (5%), Wound dehiscence (1%), Pneumonia (3%), Catheter-associated urinary tract infection (2%), and CSF leakage (3%).

A total of 14 out of 20 patients (70%) with PMV died within 30 days of surgery compared to 5 of 178 patients (9%) without PMV (p < 0.0001). Patients with PMV exhibited a median OS of 1 month (IQR 0-7 months) compared to 12 months (IQR 4-26 months) for patients without PMV (p < 0.0001) (Table 2, Figure 1).

Multivariate analysis identifies PMV as an independent predictor of 30 days mortality

We conducted a multivariate analysis in order to identify independent pre- and perioperative predictors of 30 days mortality following surgery for spinal metastasis. The multivariate analysis identified "PMV > 24 hours" (p < 0.001, OR 0.3, 95% CI 0.02-0.4) as the only significant and independent predictor of 30 day mortality (Nagelkerke's R^2 0.38).

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TABLE 2 Factors associated with postoperative PMV following surgery for spinal metastasis*.

	Patients without PMV n = 178	Patients with PMV n = 20	p-value
Median age (yrs)	64 (56-76)	66 (57-74)	0.78
Female sex	68 (38)	8 (40)	1.0
Primary tumor site			
Lung	38 (21)	8 (42)	0.09
Breast	22 (12)	0 (0)	0.13
Prostate	39 (22)	1 (5)	0.08
Other	79 (44)	11 (55)	0.48
Location of disease			
Cervical	19 (11)	1 (5)	0.70
Thoracic	99 (56)	12 (60)	0.81
Lumbar	30 (17)	3 (15)	1.0
Combined	30 (17)	4 (20)	0.75
Levels of disease			0.15
1-2	111 (62)	9 (45)	
≥ 3	67 (38)	11 (55)	
Median CCI (IQR)	8.5 (7-10)	8 (6-10)	0.58
Preoperative neurological deficit (ASIA Score)			**0.0171**
A-B	23 (12.9)	7 (35)	
C-E	155 (87.1)	13 (65)	
Surgery			0.81
Decompression	66 (37)	8 (40)	
Stabilization	112 (63)	12 (60)	
Median duration of surgery (IQR)	178 (125-244)	240 (170-294)	**0.03**
Early postoperative complications			
PSIs	11 (6)	4 (20)	0.05
HACs	7 (4)	3 (15)	0.27
Specific SSCs	4 (2)	1 (5)	0.42
30 day mortality	9 (5)	14 (70)	**< 0.0001**
1 year mortality	85 (48)	20 (100)	**< 0.0001**
Median OS (IQR)	12 (4-26)	1 (0-7)	**< 0.0001**

*Values represent the number of patients unless indicated otherwise (%). Bold values means statistically significant.
CCI, Charlson comorbidity index; HAC, hospital-acquired conditions; IQR, interquartile range; OS, overall survival; PMV, prolonged mechanical ventilation; PSIs, patient safety indicators; SSCs, spinal surgery-related complications; yrs, years. Median (IQR).

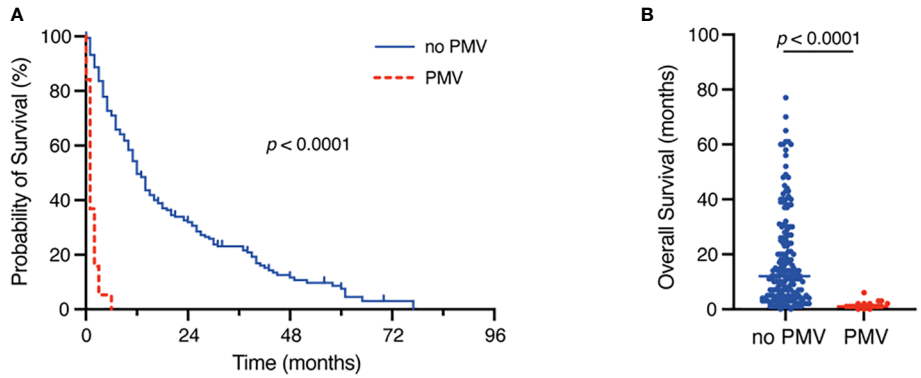

FIGURE 1
Kaplan-Meier survival analysis **(A)** and dot plots **(B)** dependent on the occurrence of postoperative PMV. PMV, prolonged mechanical ventilation.

Ten of 198 patients (5%) exhibited postoperative PMV with a ventilation time of > 48 hrs., 5 of 198 patients (3%) exhibited postoperative PMV with a ventilation time of > 72 hrs. Kaplan-Meier survival analysis revealed a mOS of 1 month for the 48 hrs. cut off-value of PMV ($p < 0.0001$) and a mOS of 0.5 months for the 72 hrs. cut-off value of PMV ($p < 0.0001$) (Figure 2).

Furthermore, Figure 2 was added depicting Kaplan-Meier survival analyses for the 48 hrs. and the 72 hrs. cut-off value for PMV

Cox regression analysis

"Cox regression analysis under consideration of patient age, tumor entity, ASIA classification score value, preoperative KPS, number of affected spinal levels as known prognostic relevant parameters identified a preoperative KPS < 70 (Hazard ratio (HR) 0.3, p<0.001, tumor entity lung (HR 0.6, p=0.03') and PMV >24 hrs (HR 0.15, p<0.001) as factors that were significantly associated with worsened OS".

Discussion

This study analyzes the prognostic impact of postoperative PMV in patients who had undergone surgical therapy for SM. We found that PMV was significantly correlated to high early postoperative mortality rates and poor OS.

Our results regarding the entity distributions reflect widely known study results (33–35). In our study, the thoracic spine was found to be the most frequently affected part of the spine in accordance with numerous studies (36, 37). A specific distribution pattern depending on the primary tumor, such as metastasis of lung cancer preferentially into the thoracic spine, could not be confirmed in some studies (38, 39). Contrary to this, other authors described bronchial carcinoma in the thoracic spine, prostate carcinoma as the most common primary in the lumbar spine (33). The literature describes multiple spinal metastasis up to 30% in the cases of SM, in our cohort we had 39% with multilevel SM (40). The gender distribution shows in our data as well as in the literature a male dominance (41, 42). One possible reason for this distribution may be that, prostate carcinoma is a common gender-specific tumor with high spinal metastasis tendency (43). Based on the KPI, the preoperative general condition of the patients was assessed, the score was 70% for the majority of our patients, in many studies the KPI varies between 50-70% (44, 45).

The optimal treatment of symptomatic SM is the focus of the therapy, and the aim of the several treatment options is usually limited to the maintenance or improvement of neurological function, reduction of pain, local tumor control, and improvement of the patient's general quality of life (41, 46). Recently, several patient-related and disease-related characteristics have been reviewed for their prognostic value and summarized in the form of prognostic systems and parameters. All these studies are seeking to predict life expectancy as accurately as possible, so as to be able to recommend the most appropriate treatment for the patient (20, 41, 47–50). However, surgery for SM in this patient cohort may require prolonged postoperative intensive care, which may adversely affect the anticipated benefit of the surgery.

PMV has previously been identified as a meaningful prognostic factor in patients suffering from several tumor diseases (16, 51). Recently, PMV of more than 48 hours has been reported to result in median OS of < 1 month in patients with surgically treated brain metastasis (16), therefore indicating that PMV constitutes a devastating prognostic factor in neurosurgical oncology. Similarly, PMV of more than 24 hours has been identified as an independent prognostic factor in patients undergoing surgery for glioblastoma, with a reported median OS of as low as 3 months (18). In an analysis of 5,138 cases, Shish et al. reported the 1 year survival rate in patients

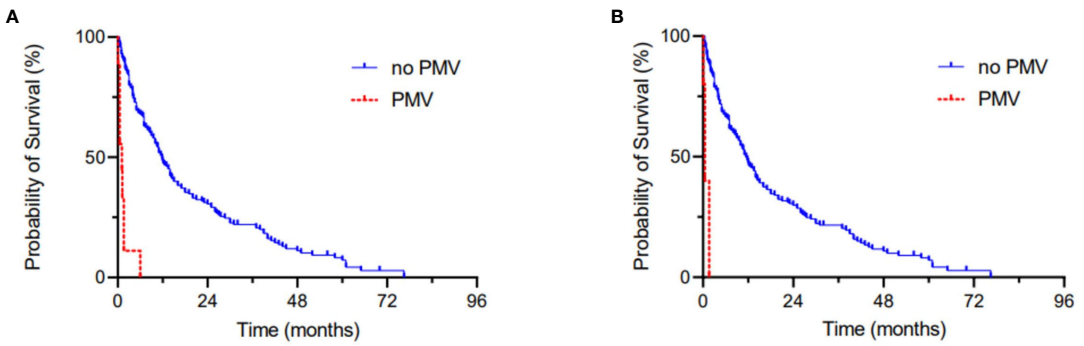

FIGURE 2
Kaplan-Meier survival analyses dependent on the occurrence of postoperative PMV > 48 hrs **(A)** and > 72 hrs **(B)**.

with malignancies and in need of PMV to be as low as 14% (24). There has been no analysis to date of the subgroup of patients with SM. This subgroup poses an additional challenge as it comprises critically ill patients at an advanced stage of metastatic cancer disease. Furthermore, unlike this study, most currently available data on PMV in the field of cancer treatment do not specifically focus on the subgroup of patients who underwent oncological surgery. Not all patients with SM are treated surgically: particularly in the case of small, non-space occupying tumors of the spinal canal or multiple asymptomatic findings, other treatment options are well established (52–56). Along these lines, the subgroup of patients with SM and additional surgical treatment are supposed be at a high risk of postoperative PMV. Regardless of the reason for surgical treatment, surgery induces a significant degree of surgical trauma (57, 58). Postoperative PMV in patients with surgically treated SM may be necessary not only because of the patient's weakness or a disease such as lung cancer, but also because of the localization of the SM surgery or because of associated postoperative complications (59–63). We found no correlation in our cohort between postoperative PMV and the primary tumor site, the spinal location affected, or the number of affected spinal levels. Instead, the group of PMV patients exhibited higher levels of preoperative neurological deficits and a significantly longer median surgery duration. These findings are in line with several reports linking postoperative PMV occurrence to elevated surgery duration and preoperative morbidity (64, 65). These findings point at recent efforts to use preoperative risk stratification to more comprehensively predict the course of early postoperative treatment (66). This study provides the only available data on PMV and prolonged intensive care in the field of surgery for SM. These data do not allow for preoperative risk assessment.

Furthermore, the unsatisfactory survival rates of patients with SM and postoperative PMV in the present study could also partly be attributed to a delay in postoperative adjuvant treatment and/or in further therapy for the underlying cancer disease (67, 68), the delay being caused by postoperative intensive care. Prolonged ICU observation of cancer patients and frequent communication with all clinical colleagues and with the patient or their authorized representative are important and indeed a basic aspect of interdisciplinary treatment. It is in the best interests of the patient for the neurosurgeons, neurooncologists and intensive care physicians to jointly determine the patient's ICU therapy and decide on the next stage of treatment (69). Oncological re-evaluation of the patient's prognosis after surgery and assessment of further treatment options can thus be complemented by the ICU physicians' knowledge of what is possible in the intensive care setting. Treatment providers should constantly check that continued treatment and an extended ICU stay are in accordance with the patient's wishes.

The findings of this study should raise awareness of the small subgroup of cancer patients with high early postoperative mortality and a poor overall prognosis – that is, the subgroup of patients with surgically-treated SM who need postoperative PMV for more than 24 hours. Early pre-surgical stratification may help to identify patients who are at a high risk of prolonged postoperative intensive care treatment. Preoperative identification of these patients is a major challenge for future scientific endeavors due to the limited data available. It is nevertheless worthwhile in order to predict the most appropriate course of postoperative treatment and to inform communication with patients about what can realistically be expected from the neurosurgical procedure.

Conclusions

Our data indicate postoperative PMV is significantly correlated to high early postoperative mortality rates as well as to poor OS in patients with surgically treated SM. The authors believe these findings justify further multicenter studies to comprehensively investigate PMV as an underestimated negative prognostic factor in the course of surgical treatment for SM.

Limitations

The present study has several limitations. Acquisition of data was retrospective; data are therefore subject to well-known and well-described types of bias. Patients were not randomized and their treatment was decided on by the neurosurgeon. Given the low incidence of postoperative PMV occurrence, the number of patients with PMV is quite small, which means the univariate and multivariate analyses may be subject to error. The authors intend to consider these data as a first estimation of a potential correlation between postoperative PMV and worsened survival in patients with surgery for SM. This may lead to further investigations structured to avoid the potential selection bias due to the limited group size in this study.

Additionally, in regard of the small patient cohort of 19 patients with PMV > 24 hrs, the present study did not allow for cut-off value determination in order to specifically identify the time of postoperative mechanical ventilation leading to an increase in early postopoerative mortality and reduced survival. Further multicenter studies will be needed in order to sufficiently address this issue.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

All of the procedures performed were in line with the ethical standards of our institutional and national research committee (Ethics committee of the Rheinische Friedrich Wilhelms University Bonn) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The local ethics committee at the University of Bonn approved this study (protocol no. 067/21).

Author contributions

Conceptualization, MH and MB. Methodology, MH and MB. Software, A-LP. Validation, MH, MS and MB. Formal analysis, MS and A-LP. Investigation, SB, SR, LE, CB, FS, AR, NS, UH, MK, FG, HV. Resources, HV. Data curation, SB, SR and MB. Writing—original draft preparation, MH, MS and MB. Writing—review and editing, all authors. Visualization, MH, MS and MB. Supervision, MB and MS. Project administration, MS, MB. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Unsuccessful external validation of the MAC-score for predicting increased MIB-1 index in patients with spinal meningiomas

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Objective: Recently, the MAC-spinal meningioma score (MAC-score) was proposed to preoperatively identify spinal meningioma patients with high MIB-1 indices. Risk factors were age ≥ 65 years, a modified McCormick score (mMCs) ≥ 2, and absence of tumor calcification. The aim of this study was to externally validate the MAC-score in an independent cohort.

Methods: Using the same inclusion and exclusion criteria as in the original study, we performed a retrospective, single-center, population-based, cohort study that included patients who had undergone surgical treatment for spinal meningiomas between 2005 – 2017. Data was collected from patient charts and radiographic images. Validation was performed by applying the MAC-score to our cohort and evaluating the area under the receiver operating characteristic curve (AUC).

Results: In total, 108 patients were included. Baseline and outcome data were comparable to the original development study. An increased MIB-1 index (≥5%) was observed in 56 (52%) patients. AUC of the MAC-score in our validation cohort was 0.61 (95% CI: 0.51 – 0.71), which corresponds to a poor discriminative ability.

Conclusion: The MAC-score showed poor discriminative ability for MIB-1 index prediction in patients with spinal meningiomas. Moreover, the MAC-score rests on a weak theoretical and statistical foundation. Consequently, we argue against its clinical implementation.

KEYWORDS

MIB-1 (Ki-67 labeling) index, score, spinal meningioma, proliferation, clinical implications, recurrence, external validation

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Introduction

Spinal meningiomas are intradural extramedullary tumors that originate from the arachnoid cap cells in the leptomeninges of the spinal canal. They are the most common adult primary spinal tumor, accounting for 25-45% of all spinal intradural tumors and occurring with an age-adjusted incidence of 0.33 per 100, 000 population (1).

Even though most spinal meningiomas are benign (World Health Organization (WHO) grade 1), (2) they can cause spinal cord compression and neurological deficits. (3) Surgery is the treatment of choice for symptomatic patients, (2) and often associated with improved neurological function. (4) The functional status in these patients is usually assessed using standardized methods, such as the modified McCormick scale (mMCS) (Table 1). (4–6) Tumor proliferation markers, like the MIB-1 index, are also often used to assess the growth fraction of the tumor cells. Although previous studies are scarce, spinal meningiomas tend to have low MIB-1 indices (7–9) and there is no consensus on a specific MIB-1 index cut-off value for the prediction of tumor progression or recurrence in spinal meningiomas.

Wach et al. recently developed a risk score to preoperatively predict a high MIB-1 Index (≥ 5%) in these patients. (10) The MAC-spinal meningioma score awards 1 point each for Age ≥ 65 and preoperative mMCs ≥ 2, and 2 points for the lack of intra-tumoral calcification. They reported an area under the receiver operating characteristic curve (AUC) of 0.83 (95% CI: 0.71 – 0.96) in their development cohort and concluded that the score could help support surgical decision making (10).

The performance of risk scores is typically overestimated in the datasets used to develop them. (11–14) They are often opportunistically produced to maximize the output from a study for which the tested predictors were not declared beforehand. Therefore, risk scores should always be subjected to external validation in an independent cohort. (13, 14) In the case of the MAC-score, it was developed from single-center data on 128 patients, with no internal validation or pre-published study protocol.

In light of the above, the aim of this study was to perform an external validation of the MAC-score in an independent cohort of adult patients who were surgically treated for a spinal meningioma.

TABLE 1 Modified McCormick scale.

Grade	Explanation
1	Intact neurologically, normal ambulation, minimal dysesthesia
2	Mild motor or sensory deficit, functional independence
3	Moderate deficit, limitation of function, independent w/external aid
4	Severe motor or sensory deficit, limited function, dependent
5	Paraplegia or quadriplegia, even w/flickering movement

Methods

Patient selection and study setting

The study cohort consisted of adult patients (≥18 years) who were surgically treated for a spinal meningioma at the study center between 2005 and 2017. Exclusion criteria were identical to those in the development study, (10) namely craniocervical meningiomas (foramen magnum, C1, C2), neurofibromatosis type 2 (NF2), recurrent meningiomas after radiotherapy, and those with missing MIB-1 index (Figure 1). The study center's routine for preoperative imaging, surgical technique, and follow-up has been described previously. (3, 4) The study was approved by the Regional and National Ethical Review Board who waived the need for informed consent (Dnr: 2016/1708-31/4 and 2020-00192).

Variables

Medical records and imaging data were retrospectively reviewed using the health record software TakeCare (CompuGroup Medical Sweden AB, Farsta, Sweden). Collected data included age, sex, preoperative modified McCormick Scale (mMCs), radiographic data (including tumor calcification and location), surgical data, MIB-1 index and World Health Organization (WHO) grade, as well as long-term tumor control and functional outcome.

In accordance with the study by Wach et al, (10) age was dichotomized into elderly (≥ 65 years) and non-elderly (18–64 years). Tumor calcification was assessed on preoperative CT and/or MRI images by two different reviewers. (9, 15) A tumor was deemed calcified when it was hyperintense on CT, reflecting a density close to that of adjacent bony structures, or when the tumor had decreased signal intensity on T1 and T2. (9, 16) Tumor growth was defined as the radiological growth of a tumor remnant following subtotal resection, while tumor recurrence was defined as the appearance of a new spinal meningioma following total resection. All histopathological analyses were performed at the Department of Pathology, Karolinska University Hospital, Stockholm, Sweden. The MIB-1 labeling index was determined using the anti-Ki67 antibody (product: "M7240, Ki-67 Antigen"; supplier: DAKO, Glostrup, Denmark). The MIB-1 labeling index was then analyzed by experienced pathologists at the authors' institution through manual counting of the number of Ki-67 positive cells (only nuclear staining) divided by the total amount of tumor cells in "hot-spot" regions, counting at least 2000 cells. Patients were classified according to WHO criteria from 2007. However, as no patients showed signs of spinal cord invasion, the grading is consistent with the 2016 WHO classification of meningiomas (17, 18).

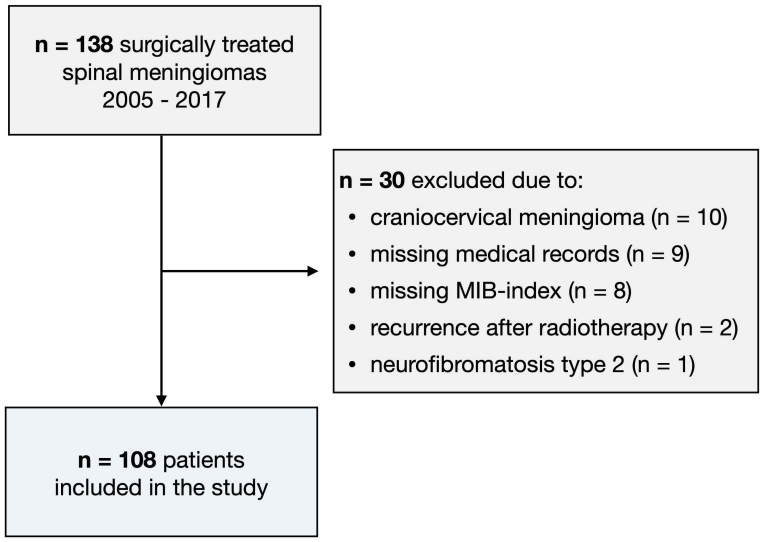

FIGURE 1
Flow-chart illustrating the patient inclusion process.

Statistical analysis

The Shapiro–Wilk test was used to evaluate the normality of the data. As all continuous data significantly deviated from a normal distribution pattern (Shapiro–Wilk test p-value < 0.05), it is presented using the median (interquartile range) and categorical data as numbers (proportion). Demographics, clinical data, and imaging data were stratified by MIB-1 index and compared using the chi-square test for categorical data and the Mann–Whitney U test for continuous variables. In addition, a uni- and multivariable logistic regression analysis was used with the MAC-score components as explanatory variables and MIB-1 index ≥ 5% as the binary outcome. Lastly, discrimination of the score was quantified by calculating the area under the receiver operating characteristics curve (AUC) statistic. Generally, an AUC value of 0.9 – 1.0 represents excellent, 0.8 – 0.9 good, 0.7 – 0.8 fair, and 0.6 – 0.7 poor discriminative ability. (19) The prognostic validity of the MAC-score was further investigated by calculating the sensitivity and specificity of each threshold. All statistical analyses were carried out in R (version 4.1.2). Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Of the 138 patients screened, 108 were included in the study (Figure 1). Complete data for all risk factors (mMCs ≥ 2, age ≥ 65 years, tumor calcification) were available in all included patients. The median age was 66 years (IQR 56 – 73) and 89 (82%) were female. Fifty-six patients (52%) had a MIB-1 index ≥ 5%. The median pre-operative mMCs was 2 (IQR 2 – 3), and the most common tumor location was the thoracic spine (n = 81, 75%). Fifteen (14%) of the tumors were calcified, and the median MIB-1 index was 5 (IQR 3 – 5). One-hundred and seven (99%) of the tumors were WHO grade 1, and one tumor was grade 2 (0.9%) (Table 2).

Association between MIB-1 index and clinical features

Univariable and multivariable associations between MIB-index ≥ 5% and baseline characteristics, imaging, and surgical data in the validation cohort, including the three components of the MAC-score, showed significant association only for tumor calcification (p = 0.008), but not for mMCs ≥ 2, age ≥ 65 years, sex, tumor level, tumor extent, anterior tumor location, or Simpson grade (Tables 3, 4).

External validation of the MAC-score

In our validation cohort, the AUC for the MAC-spinal meningioma score was 0.61 (95% CI: 0.51 – 0.71) (Figure 2). The cut-off points of 1, 2, 3 and 4 showed a sensitivity of 100%, 100%, 82%, and 45%, and a specificity of 2%, 12%, 35%, and 67%, respectively (Table 5). These results imply poor discriminative ability of the score in our cohort.

TABLE 2 Patient characteristics.

Variable	Patients (n = 108)
Age (years)	66 (56 – 73)
Female sex	89 (82%)
Pre-operative mMCs	2 (2 – 3)
Calcified tumor	15 (14%)
MIB-1 index	5.0 (3.0 – 5.0)
Tumor location	
Cervical	26 (24%)
Thoracic	81 (75%)
Lumbar	1 (0.9%)
Simpson grade	
Simpson grade II	78 (72%)
Simpson grade III & IV	30 (28%)
WHO grade	
WHO grade 1	107 (99%)
WHO grade 2	1 (0.9%)
Tumor growth or recurrence	4 (3.7%)

Data is presented as median (interquartile range) or number (proportion). mMCs, modified McCormick scale; WHO, World Health Organization.

Discussion

Principal findings

We sought to externally validate the recently proposed MAC-score for preoperative prediction of high MIB-1-index in patients with spinal meningiomas. (10) The score awards two points for the lack of calcification, and one point each for higher age (≥ 65) and poor preoperative mMCs (≥ 2). A higher MAC-score was suggested to indicate an increased risk of MIB-1 index of ≥5% and be able to discriminate between stable and growing spinal meningiomas. The original study also suggested a correlation between MAC-score and longer hospital stay as well as increased likelihood of improved postoperative mMCs. In our validation cohort, the AUC for the MAC-spinal meningioma score was 0.61 (95% CI: 0.51 – 0.71), as compared to 0.83 (95% CI: 0.71 – 0.96) in the original development cohort. Thus, the score showed poor discriminative ability for MIB-1 index prediction in this independent cohort. To further examine this failed validation of the MAC-score, its main parameters will be discussed below.

Effect of calcification

Tumor calcification was a significant predictor of low MIB-1 index in our study. This is in line with the study by Wach et al. and with the body of evidence regarding calcification as a marker of reduced growth potential of meningiomas. (20) This is also consistent with data from intracranial meningiomas. (20) The calcified appearance of spinal meningiomas on CT is thought to represent tightly packed psammoma bodies or the formation of metaplastic lamellar bone microscopically (17, 18). With varying definitions, calcified spinal meningiomas have been reported to make up 2.6 to 75% of the total. (5, 21, 22) While calcified spinal meningiomas may represent more quiescent tumors, they are associated with more surgical complications and a less favorable functional outcome after surgery, especially when ossification is found intraoperatively (23–27).

Effect of age

We could not verify the finding that older age was significantly associated with higher MIB-1 index. Previously published evidence rather seems to indicate that young age is associated with an increased risk of recurrence. (28–31) Notably, several studies have also failed to find any significant correlation between age and tumor recurrence. (5, 7, 21, 32) Previous studies also indicate that elderly patients benefit from surgery for spinal meningiomas and there are no significant differences regarding extent of surgery, complications, or recurrence. (4, 5, 7, 33, 34) Studies on the correlation between age and MIB-1-index in cranial meningiomas have failed to show significant results.

TABLE 3 Data comparison between patients with a normal (< 5%) and increased (≥ 5%) MIB-1 index.

Variable	MIB-1 < 5% (n = 52)	MIB-1 ≥ 5% (n = 56)	p-value
Age (years)	66 (55 – 74)	66 (58 – 72)	0.973
Female sex	41 (79%)	48 (86%)	0.349
Preoperative mMCs	2 (2 – 3)	2 (2 – 3)	0.479
Calcified tumor	12 (23%)	3 (5.4%)	**0.008**
Cervical tumor	14 (27%)	12 (21%)	0.434
Anterior tumor component	10 (19%)	14 (25%)	0.471
> 2 spinal segments	4 (7.7%)	5 (8.9%)	>0.999
Simpson grade III & IV	18 (35%)	12 (21%)	0.126

Bold text in the p-value column indicates a statistically significant correlation ($p < 0.05$). Data is presented as median (interquartile range) or number (proportion).mMCs, modified McCormick scale.

TABLE 4 Univariable and forced-entry multivariable logistic regression analysis predicting MIB-1 index ≥ 5%.

Variable	OR (95% CI)	Univariablep-value	Multivariable p-value
mMCs ≥ 2	1.23 (0.49 – 3.13)	0.663	0.721
Age ≥ 65 years	1.14 (0.53 – 2.45)	0.731	0.496
Absence of tumor calcification	5.30 (1.56 – 24)	**0.014**	**0.012**

mMCs, modified McCormick scale.
Bold text in the p-value column indicates a statistically significant correlation ($p < 0.05$).

A large study on 1372 patients found a nonsignificant trend towards higher MIB-1 index in older patients, (35) and another study on 385 patients, showed no differences in MIB-1 indices in relation to age. (36) Moreover, there is no evidence pointing towards spinal meningiomas having a more aggressive behavior in elderly patients. (4, 37).

Effect of preoperative mMCs

We found no association between a higher mMCs score and a higher MIB-1 index, thereby contradicting the findings by Wach et al. (10) Arguably, fast growing tumors may result in more severe neurological deficits and higher preoperative mMCs. However, there is currently no evidence to support the argument that a MIB-1 index ≥ 5% accelerates tumor growth sufficiently to negatively impact preoperative functional status. The vast majority of spinal meningiomas have indices lower than 4% (7, 37, 38) and further studies are needed to clarify the clinical utility of the MIB-1 index for the predominantly low-grade spinal meningiomas. Wach et al. also reported that patients with a higher MAC-score improved more than those with a lower score at three months follow-up. (10) Since the MAC-score partly rests on the mMCs data, and only patients with preoperative symptoms can improve, this finding becomes self-evident. In addition, two previously published studies found that the improvement in mMCs was correlated to the degree of spinal cord compression rather than MIB-1 index, (4, 6) and age,

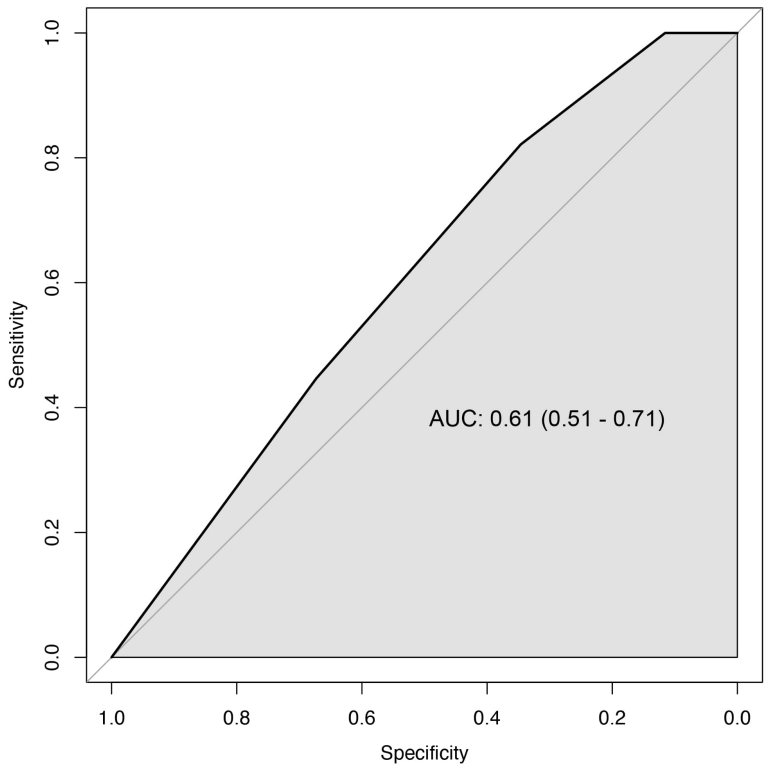

FIGURE 2
ROC curve of the MAC-scores ability to identify patients with high MIB-1 index (black line: AUC 0.61, 95% CI 0.51 – 0.71). The diagonal grey line indicates the model that has a completely random discrimination power.

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TABLE 5 Sensitivity and specificity for different MAC-score thresholds.

MAC-score threshold	Sensitivity	Specificity
MAC 1	100%	2%
MAC 2	100%	12%
MAC 3	82%	35%
MAC 4	45%	67%

sex, tumor location, and MIB-1 index all failed to significantly correlate with postoperative mMCs improvement. (4).

Hospital stay

Wach et al. also explored the association between MIB-1 index and length of hospital stay, suggesting that MIB-1 index ≥ 5% was associated with longer hospital stay. However, they present no hypothesis as to why meningioma patients with a MIB-1 index ≥ 5% would require a longer hospital stay. In our experience, length of hospital stay reflects local referral structures between surgical clinics and rehab centers as much as actual clinical aspects. Regarding the latter, more complex surgeries, complications, (16, 39) and the management of patients with comorbidities are likely to result in prolonged hospital stay. Conversely, as argued above, the evidence suggests that calcified tumors with a low MIB-1 index, rather than tumors with a high MIB-1 index, are associated with more surgical complications and longer hospital stays (22, 26, 27).

MIB-1 index

The same methodology was used to determine the MIB-1 index in this validation study and in the study performed by Wach et al, indicating negligible variability in the measurement of MIB-1 indices.

Regardless, inter-observer and inter-laboratory variabilities in the measurement of proliferation indices like the MIB-1 index have previously been reported. (40–43) However, the resulting errors are systematic rather than random and affect all measurements performed in a given laboratory and by a given pathologist in a similar manner. While the absolute numbers and averages would differ between analyses performed in different settings, (40) the relative distributions would not, as an element of proportionality should remain. This implies that associations with the MIB-1 index, when treated as a continuous variable, should be preserved in the presence of a big enough sample. However, when dichotomizing MIB-1 indices, as performed in the study by Wach et al, an absolute cut-off value determined at one laboratory may not be valid at another. In accordance, several studies have shown that MIB-1 cut-off values suggested for the prognostication of tumors have limited reproducibility between centers in a multi-center setting. (40, 41) This, in turn, limits the generalizability and usability of the MAC-score.

Methodological aspects

This validation study has several methodological strengths in relation to the development study by Wach et al. The same MIB-1 index determination technique, inclusion and exclusion criteria were used and the distribution of sex, age, tumor calcification, tumor location, pre-operative mMCs, MIB-1 indices, and the rate of tumor recurrence were similar. (4) The validation cohort was population-based, with few exclusions due to missing data thus minimizing selection biases.

It is likely that the unsuccessful validation of the MAC-score is partly due to type I errors in the original study. For instance, Wach et al. performed multiple comparisons on the same dependent variable without compensating for the number of inferences made. This could have been performed using a Bonferroni correction. Alternatively, the authors could have limited the events per variable (EVP), defined as the number of events divided by the number of predictor variables used. An EVP of 10 is often advocated as a minimal criterion in logistic regression analyses. (11) For the study by Wach et al. where 55 events and 19 predictors where identified, an EVP of 2.9 was calculated. This level is associated with considerable risk for type I errors. (44) Furthermore, as no pre-hoc statistical analysis plan was published, the steps leading to the choice of the evaluated parameters making up the MAC-score cannot be evaluated. In addition, the development study should ideally have randomly divided the cohort into a derivation and validation subset, allowing for internal validation to avoid overfitting. It should also be noted that the authors presented mMCs using means and standard deviations, even though it is an ordinal variable and should have been presented using medians or proportions at different cut-offs.

Clinical remarks

In the study by Wach et al, a higher MAC-score indicated an increased likelihood of elevated MIB-1 index. Because a higher MIB-1 index was significantly associated with a higher recurrence rate, the authors deduced that the MAC-score was also a predictor of tumor progression and recurrence rate. However, there were only four recurrences in the material and progression was not studied. Furthermore, the authors identified a correlation between MAC-score and the length of hospital stay without providing an explanatory theory for this. The authors concluded that the score may "support preoperative patient-surgeon consultation, surgical decision making and enable a tailored follow-up schedule". However, gross total resection is

the gold standard for treatment of spinal meningiomas, and we question the clinical usefulness of pre-operative prediction of MIB-1 index in surgical decision making, as compared to radiographic findings and clinical presentations. It has also been demonstrated that shorter time from diagnosis to surgery is a predictor of postoperative improvement, advising against a watch-and-wait strategy. (4) In the postoperative phase, it will be the extent of tumor resection, findings of the histopathological analysis, and clinical status of the patient that decide the management plan.

To assist clinicians in the management of spinal meningioma patients, a clinical score or biomarker needs the power to accurately predict outcomes or risk of tumor recurrence. For outcome prediction, the score should ideally be based on factors available before surgery to allow an informed decision regarding whether surgery should be performed or not. In addition, the score should rely on prognostic factors with an established mechanistic role in the disease. Poor preoperative status, longer time to surgery and reoperation are all predictors of unfavorable outcome. (2, 4) Similarly, known risk factors for tumor recurrence may for example include higher WHO grade and higher Simpson grade resection. (2, 45, 46) Hence, in our opinion, large multicentric datasets are needed to yield enough power for scores to directly predict outcomes of clinical interest (unfavorable neurologic status or recurrence) relying on well documented and logical predictors.

Conclusion

The MAC-spinal meningioma score showed poor discriminative ability when externally validated in an independent cohort. Gross total resection is the gold standard treatment of spinal meningiomas, and a pre-operative prediction of MIB-1 index will have little to no impact on surgical decision making. Based on these findings, clinical implementation of the MAC-spinal meningioma score is discouraged.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Regional and National Ethical Review Board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Data acquisition: VE-H, AF-S, JP-S and AE-T. Statistical analysis: AF-S. Data interpretation: VE-H, AF-S, JP-S, EE, and AE-T. Writing and creation of tables and figures: VE-H, AF-S, AE-T. Proof reading: EE. All authors approved of the final version prior to submission.

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Conflict of interest

AE-T was supported by Region Stockholm in a clinical research appointment.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Impact of tumour characteristics and cancer treatment on cerebrovascular mortality after glioma diagnosis: Evidence from a population-based cancer registry

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Objective: We aimed to examine brain tumour grade, a marker of biological aggressiveness, tumour size and cancer treatment are associated with cerebrovascular mortality among patients with malignant glioma, the most common and aggressive type of brain tumour.

Methods: We conducted a retrospective, observational cohort study using the US National Cancer Institute's state and regional population-based cancer registries. We identified adult patients with glioma in 2000 to 2018 (N=72,916). The primary outcome was death from cerebrovascular disease. Cox regression modelling was used to estimate the associations with cerebrovascular mortality of tumour grade, tumour size and treatment (surgery, radiotherapy, chemotherapy), calculating hazard ratios (HR) adjusted for these factors as well as for age, sex, race, marital status and calendar year.

Results: Higher grade (Grade IV vs Grade II: HR=2.47, 95% CI=1.69-3.61, p<0.001) and larger brain tumours (size 3 to <6 cm: HR=1.40, 95% CI=1.03 -1.89, p<0.05; size ≥ 6 cm: HR=1.47, 95% CI=1.02-2.13, p<0.05 compared to size < 3cm) were associated with increased cerebrovascular mortality. Cancer treatment was associated with decreased risk (surgery: HR= 0.60, p<0.001; chemotherapy: HR=0.42, p<0.001; radiation: HR= 0.69, p<0.05). However, among patents surviving five years or more from cancer diagnosis radiotherapy was associated with higher risk of cerebrovascular mortality (HR 2.73, 95% CI 1.49-4.99, p<0.01).

Conclusion: More aggressive tumour characteristics are associated with increased cerebrovascular mortality. Radiotherapy increased risk of cerebrovascular mortality five-year after cancer diagnosis. Further research is needed to better understand the long-term cardiovascular consequences of radiation therapy, and whether the consequent risk can be mitigated.

KEYWORDS

brain tumours, cerebrovascular mortality, risk factors, tumour aggressiveness, cancer treatment, radiotherapy, epidemiologyAbstract (250)

Introduction

Cerebrovascular diseases, including stroke, are the commonest life threatening and disabling neurological disorders. Higher mortality rates from stroke have been reported for cancer patients compared with the general population (1), particularly for brain tumour patients who have over 7 times higher risk of fatal stroke than that of the general population, one of the highest relative risk among all cancer types (2). The mechanisms of stroke in cancer patients are complex. They include cancer-mediated hypercoagulability that increases the risk of thromboembolic events as well as cancer treatment-associated thrombosis (1, 3, 4). Previous studies have reported late-occurring stroke associated with radiotherapy in childhood cancer survivors and in head and neck cancer patients (5, 6). In patients with brain tumour specifically, the increased risk of stroke may result from tumour-related factors including systemic effects of the underlying tumour, direct tumour compression or infiltration, or cancer therapies, including cranial surgery related complications and radiation-induced vasculopathy (1, 3, 6–9). In a study of patients with childhood brain tumour, over half of subsequent strokes occurred 5 years or longer from their diagnosis (8).

Many brain tumours are associated with significant morbidity and mortality. The high cerebrovascular mortality rate in patients with brain tumours, including both benign and malignant tumours, should therefore prompt consideration of preventive intervention. This could improve survival outcomes, particularly in the subset of longer-term survivors (10), but also maximise the quality of life of many other patients. In some brain tumour patients, cerebrovascular disease that results in a significant neurological deficit curtails access to chemotherapy, which might otherwise be effective in extending patient survival.

Despite the high risk for fatal stroke outcome, it remains largely unknown which tumour and treatment factors are associated with cerebrovascular mortality in patients with brain tumours. Although cancer treatment associated cardiovascular toxic effects, particularly radiation -induced cerebrovascular mortality has been well established in the long-term survivors of childhood brain tumours (11), cerebrovascular mortality risk among adult-onset brain tumours has not been well characterised. There is a lack of long-term safety data regarding cerebrovascular mortality in adults with brain tumours, particularly in those with low-grade tumour with a more favourable oncologic outcome. Most previous studies were limited to childhood cancer survivors, clinical case series or examining single factors with small sample sizes (6, 12–14). A better understanding of tumour- and treatment-related factors associated with cerebrovascular mortality should provide important insights for identification of high-risk groups and improved medical management.

With a focus on glioma, the most common adult primary brain tumour, we aimed to examine to what extent brain tumour grade, a marker of biological aggressiveness, tumour size and treatment are each associated with cerebrovascular mortality using population-based data from the US. We also examined the effect of tumour treatment on cerebrovascular mortality during different time periods after diagnosis.

Methods

Study design and data source

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (15). We used data from state and regional population-based cancer registries from the Surveillance, Epidemiology, and End Results (SEER) database (SEER 18 registry) (16). Approval to access the SEER data was granted by the US National Cancer Institute (NCI). In brief, SEER is a population-based incident tumour registries from geographically distinct regions in the USA, covering 28% of the US population, including incidence, survival, and treatment data. The SEER database is representative of the population of the US, and this has been

validated by external studies (17). The SEER registry incudes socio-demographic information such as sex, age at diagnosis, race/ethnicity, marital status, and year of diagnosis, tumour characteristics including stage of disease, grade, size, cancer treatment (surgery, chemotherapy, radiotherapy), and survival status.

Study population

We identified adults (≥18 years) diagnosed with glioma between 2000 and 2018 from SEER. Gliomas were classified based on histological and molecular type (18). We classified patients with glioma using International Classification of Diseases 10th revision (ICD-10) codes C700-C729. We used the International Classification of Diseases for Oncology third edition (ICD-O-3) codes to group gliomas following the definitions from the Central Brain Tumour Registry of the United States (CBTRUS) (19). Inclusion criteria required cases to have been actively followed up, not previously diagnosed with a primary cancer, and to have pathologic confirmation of the glioma diagnosis.

Exposures

The primary exposures include tumour grade, tumour size and treatments. Based on World Health Organisation (WHO) criteria, glioma is classified into four grades, with higher grade indicating increasing tumour aggressiveness (20): Grade I incudes pilocytic astrocytoma, Grade II includes low grade diffuse astrocytoma, Grade III includes anaplastic astrocytoma and Grade IV includes the most aggressive and malignant glioblastoma (GBM). Histology codes follow the definitions from the Central Brain Tumour Registry of the United States (CBTRUS) (16). Although pilocytic astrocytoma (Grade I) is classified as a non-malignant tumour by the WHO, this histology has been historically classified as malignant for mandatory US cancer registry reporting (21). Tumour sizes were grouped as <3cm, 3 to <6 cm and ≥6cm. Treatment variables included surgery intervention (having surgery or not having surgery/unknown); radiation therapy (radiation given/no radiation given (no/unknown/refused/recommended, unknown if administered) and chemotherapy (yes and no/unknown).

Outcome

The outcome of interest was primary cause of death from cerebrovascular disease using ICD-10 codes (I60-69), including the following subtypes: non-traumatic intracranial haemorrhage, cerebral infarction, occlusion and stenosis of cerebral of precerebral vessels without infarction, other cerebrovascular diseases, and sequelae of cerebrovascular disease (late effect) (16).

Covariates

We included the following covariates in our analysis: age at diagnosis, sex (male, female), race/ethnicity (non-Hispanic white, Hispanic, non-Hispanic Black, Asian/Pacific Island/ American Indian/other), marital status (married/having partner, single/separated/divorced, unknown) and calendar years, diagnostic confirmation by microscopy or not.

Statistical analysis

We performed descriptive analyses of baseline characteristics of patients with glioma, overall and according to glioma grade, summarising categorical variables as numbers and percentages per category. The Pearson's Chi-squared test was used for comparison across glioma grades. We compared continuous variables across glioma grade subgroups using analysis of variance for normally distributed variables (summarized as means and standard deviations [SD]) or the Kruskal–Wallis test for non-normally distributed variables (summarized as medians and interquartile ranges). Deaths from other causes were censored at the time of death. Survival time from the date of diagnosis until date of death or last contact (December 31, 2018) were computed. We used multiple imputation with chained equations to impute missing values for tumour size. The imputation model included all variables in the Table 1. Kaplan-Meier methods with log-rank tests were used to assess the differences in cerebrovascular mortality in gliomas patients, comparing cerebrovascular cause-specific mortality between groups by the log-rank test. Cause-specific multivariable Cox regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between cerebrovascular mortality and tumour grade (II-IV) were used, tumour size (<3cm, 3 to <6 cm, ≥6cm), and treatment status (surgery yes/no, radiation therapy yes/no, chemotherapy yes/no). We also calculated HRs for the association between cancer treatment and cerebrovascular mortality stratified by different survival periods (<1, 1 to 5 & ≥5 years) after cancer diagnosis: survived within 1 year, 1-5 years or survived after 5 years after the diagnosis.

We restricted survival analyses to those with grade II-IV gliomas because of small numbers of cerebrovascular deaths among patients with grade I glioma (N=6) and lack of events in some subgroups. Univariable analyses were performed and variables with p-value<0.10 were retained in the final multivariable regression model, which included age, sex, ethnicity/race, marital status, calendar year, tumour grade, tumour size, and treatment status. We assessed the potential

TABLE 1 Characteristics of the study cohort SEER 2000-2018.

Characteristics Number of patients (% of total)	[ALL] N=72916	Grade 1 N=1754 (2.4)	Grade 2 N=10673 (14.6)	Grade 3 N=16303 (22.4)	Grade 4 N=44186 (60.6)
Sex					
Female	31511 (43.2%)	823 (46.9%)	4667 (43.7%)	7454 (45.7%)	18567 (42.0%)
Male	41405 (56.8%)	931 (53.1%)	6006 (56.3%)	8849 (54.3%)	25619 (58.0%)
Age, median (IQR)[a], years	59.0 [46.0;70.0]	31.0 [22.0;44.0]	46.0 [34.0;59.0]	50.0 [37.0;64.0]	64.0 [55.0;73.0]
Age group					
≤65 years	47091 (64.6%)	1659 (94.6%)	8936 (83.7%)	12623 (77.4%)	23873 (54.0%)
>65 years	25825 (35.4%)	95 (5.42%)	1737 (16.3%)	3680 (22.6%)	20313 (46.0%)
Year of diagnosis					
2000-2004	17795 (24.4%)	454 (25.9%)	3131 (29.3%)	4072 (25.0%)	10138 (22.9%)
2005-2009	18892 (25.9%)	433 (24.7%)	3015 (28.2%)	4287 (26.3%)	11157 (25.3%)
2010-2014	20023 (27.5%)	509 (29.0%)	2603 (24.4%)	4523 (27.7%)	12388 (28.0%)
2015-2018	16206 (22.2%)	358 (20.4%)	1924 (18.0%)	3421 (21.0%)	10503 (23.8%)
Race/ethnicities					
Non-Hispanic White	55510 (76.1%)	1207 (68.8%)	7777 (72.9%)	11721 (71.9%)	34805 (78.8%)
Hispanic (All Races)	8669 (11.9%)	266 (15.2%)	1519 (14.2%)	2256 (13.8%)	4628 (10.5%)
Non-Hispanic Black	4385 (6.01%)	149 (8.49%)	642 (6.02%)	1096 (6.72%)	2498 (5.65%)
Asian/Pacific Island/American Indian/other	4352 (5.97%)	132 (7.53%)	735 (6.89%)	1230 (7.54%)	2255 (5.10%)
Marital status					
Married/Partner	43306 (59.4%)	645 (36.8%)	5957 (55.8%)	9061 (55.6%)	27643 (62.6%)
Single/Separated/Divorced	26618 (36.5%)	1021 (58.2%)	4261 (39.9%)	6452 (39.6%)	14884 (33.7%)
Unknown	2992 (4.10%)	88 (5.02%)	455 (4.26%)	790 (4.85%)	1659 (3.75%)
Tumour size:					
< 3 cm	16206 (22.2%)	684 (39.0%)	2838 (26.6%)	4680 (28.7%)	8004 (18.1%)
3 to < 6 cm	41026 (56.3%)	833 (47.5%)	5523 (51.7%)	8304 (50.9%)	26366 (59.7%)
≥ 6 cm	15684 (21.5%)	237 (13.5%)	2312 (21.7%)	3319 (20.4%)	9816 (22.2%)
Diagnostic confirmation					
Microscopically Confirmed	66301 (90.9%)	1711 (97.5%)	10129 (94.9%)	13539 (83.0%)	40922 (92.6%)
Not Microscopically Confirmed	6168 (8.46%)	40 (2.28%)	498 (4.67%)	2672 (16.4%)	2958 (6.69%)
Unknown	447 (0.61%)	3 (0.17%)	46 (0.43%)	92 (0.56%)	306 (0.69%)
Surgery performed:					
Yes	52763 (72.4%)	1547 (88.2%)	7540 (70.6%)	10472 (64.2%)	33204 (75.1%)
No	20153 (27.6%)	207 (11.8%)	3133 (29.4%)	5831 (35.8%)	10982 (24.9%)
Radiation					
Yes	45396 (62.3%)	271 (15.5%)	4938 (46.3%)	8962 (55.0%)	31225 (70.7%)
None/Unknown/Refused	27520 (37.7%)	1483 (84.5%)	5735 (53.7%)	7341 (45.0%)	12961 (29.3%)
Chemotherapy					
Yes	36394 (49.9%)	99 (5.64%)	3608 (33.8%)	6627 (40.6%)	26060 (59.0%)
No/Unknown	36522 (50.1%)	1655 (94.4%)	7065 (66.2%)	9676 (59.4%)	18126 (41.0%)
Survival months	12.0 [4.00;35.0]	86.0 [34.0;149]	44.0 [12.0;105]	30.0 [8.00;87.0]	7.00 [3.00;16.0]
Survival Months, median (IQR)[a]					
< 1 year	35858 (49.2%)	181 (10.3%)	2607 (24.4%)	5024 (30.8%)	28046 (63.5%)
1 to < 2 year	13544 (18.6%)	145 (8.27%)	1309 (12.3%)	2315 (14.2%)	9775 (22.1%)
2 to < 5 years	10777 (14.8%)	338 (19.3%)	2191 (20.5%)	3318 (20.4%)	4930 (11.2%)
≥5 years	12737 (17.5%)	1090 (62.1%)	4566 (42.8%)	5646 (34.6%)	1435 (3.25%)
Vital status					
Alive	53975 (74.7%)	5293 (49.6%)	7470 (45.8%)	4419 (10.0%)	18661 (25.6%)
Dead	18277 (25.3%)	5380 (50.4%)	8833 (54.2%)	39767 (90.0%)	54255 (74.4%)
Death from cerebrovascular disease(n)	377	6	68	124	179

Glioma was classified into four grades based on WHO criteria higher grade indicates increasing tumour aggressiveness. Grade I incudes pilocytic astrocytoma, Grade II includes low grade diffuse astrocytoma, Grade III includes anaplastic astrocytoma and Grade IV includes the most aggressive and malignant glioblastoma multiforme. Grade I classified as a non-malignant tumour by WHO, this histology has been historically classified as malignant for mandatory US cancer registry reporting.
[a]Number presented in median/Interquartile range (IQR).

for effect modification by age group (18-65 years, >65 years), sex, and race/ethnicity by including interaction terms between the exposures (tumour grades, tumour size and treatment) and these variables. Where we found a significant interaction, we conducted subgroup analyses to demonstrate the different HRs for relevant subgroups according to age, sex and/or ethnicity.

In sensitivity analyses to assess the robustness of our results, we repeated the above analyses with the study period limited to after 2005 to assess whether the introduction of adjuvant chemotherapy treatment from 2005 influenced the results (22, 23). To reduce the chance of reverse causality, we also performed landmark analyses, with follow-up commencing 1 month after cancer diagnosis, thereby excluding patients with an event of death from cancer or cerebrovascular disease within one month of diagnosis (23). Associations and interactions were considered statistically significant when the two-sided p value was < 0.05. We prepared and analysed data using R version 4.0.

Data availability

Anonymized data not published within this article will be made available by request from any qualified investigator. No additional informed consent was required as there was no individual patient involvement.

Results

Cohort characteristics

We identified 91,655 patients diagnosed with a malignant brain tumour in SEER between 2000 and 2018. There were 72, 916 cases of glioma with a total follow-up time of 266,491 person-years (median survival=12 months [IQR 4, 35]; 56.8% males) (Table 1). The derivation of the final cohort is illustrated in Supplemental Figure 1. Most patients were aged ≤ 65 years at diagnosis, especially for lower grade tumours (Grade 1: 94.6%; Grade II 83.7%; Grade III 77.4%; Grade IV: 54.0%). The majority of patients had grade IV glioma, including the most aggressive glioblastoma (60.6%). A total of 377 patients died from cerebrovascular disease during the study period (Table 2). Over half of the cerebrovascular deaths occurred in those diagnosed ≤65 years and 80% occurred among those with higher grades: Grade III (n=124, 32.9%) and Grade IV gliomas (n=179, 47.5%).

Factors associated with cerebrovascular mortality in patients with glioma

We observed increased cerebrovascular mortality in glioma patients with higher grade (Grade IV: HR=2.47, 95% CI=1.69-3.61 compared to Grade II, p<0.001), and those with larger brain tumours (size 3 to <6 cm: HR=1.40, p<0.05; 6 to <9 cm: HR=1.47, p<0.05 compared to size < 3cm) after adjusted by age, sex, race/ethnicity, marital status and calendar years(Figure 1). Having cancer treatment was associated with decreased risk: surgery (yes VS no: HR= 0.60; p<0.001), radiation (yes VS no: HR= 0.69, p<0.001), chemotherapy (yes VS no: HR=0.42, p<0.001).

We found a significant interaction (p<0.001) between tumour grade and age group with no evidence of interaction for sex and ethnic group. In subgroup analyses of the effects of tumour grade on cerebrovascular mortality by age group, the relative risk of cerebrovascular mortality was significantly higher in younger than older patients with grade IV (aHR grade IV versus grade II in patients aged 18-65 years: 2.02, 95% CI 1.24-3.26, and in patients aged > 65 years: 1.09, p5% CI 0.61-1.96) (Figure 2). We found no evidence of significant interaction between tumour size, cancer treatment and sex, ethnic group, or age.

Effects of cancer treatment on cerebrovascular mortality by different follow-up periods

Overall, having cancer treatment was associated with decreased risk of cerebrovascular mortality: (surgery: HR= 0.65, 95% CI 0.46-0.79, p<0.001; chemotherapy: HR=0.42, 95% CI 0.31-0.59, p<0.001; radiation: HR= 0.69, 95% CI 0.52-0.93, p<0.05) (Figure 1). The effects of each type of treatment on cerebrovascular mortality in different survival periods are shown in Figure 3. The associations of surgery and chemotherapy with cerebrovascular mortality were qualitatively similar for analyses restricted to the first 5 years after diagnosis and for patients surviving more than 5 years from their cancer diagnosis. By contrast, while radiotherapy was associated with a reduced risk of cerebrovascular mortality in the first year (HR=0.22, 95% CI 0.14-0.35, p<.0001), in glioma patients who survived more than 5 years from their cancer diagnosis, patients having radiotherapy had an almost 3-fold risk of cerebrovascular mortality (HR 2.73, 95% CI 1.49-4.99, p<0.01) (Figure 3). We repeated the analysis in high grade (Grade 3 & 4) and low-grade group (Grade 2). Radiotherapy was associated with increased cerebrovascular mortality 5 years after diagnosis in both low grade (HR: 3.89, 95% CI 1.50-10.10, p<0.01) and high grade glioma patients (HR 2.47, 95% CI 1.09-5.58, p<0.5) (Table 3).

Sensitivity analysis

Similar results to those noted above were observed when we restricted analyses to those patients who survived one month from tumour diagnosis (Supplemental Tables 1, 2). Broadly comparable results were also found among those diagnosed after 2005 (Supplemental Tables 3, 4).

TABLE 2 Cerebrovascular death in patients with gliomas SEER 2000-2018.

Characteristics	Cerebrovascular death N=377
Sex	
Female	169 (44.8%)
Male	208 (55.2%)
Age, median (IQR) a, years	64.0 [53.0;76.0]
Age group	
≤65 years	199 (52.8%)
>65 years	178 (47.2%)
Year of diagnosis	
2000-2004	112 (29.7%)
2005-2009	119 (31.6%)
2010-2014	95 (25.2%)
2015-2018	51 (13.5%)
Race/ethnicities	
Non-Hispanic White	266 (70.6%)
Hispanic (All Races)	51 (13.5%)
Non-Hispanic Black	41 (10.9%)
Other ethnic groups	19 (5.04%)
Marital status	
Married/Partner	199 (52.8%)
Single/Separated/Divorced	154 (40.8%)
Unknown	24 (6.37%)
Glioma grade	
Grade 1	6 (1.59%)
Grade 2	68 (18.0%)
Grade 3	124 (32.9%)
Grade 4	179 (47.5%)
Tumour size	
< 3 cm	79 (21.0%)
3 to < 6 cm	229 (60.7%)
≥ 6 cm	69 (18.3%)
Survival months (IQR)	8.00 [0.00;40.0]
Survival time	
< 1 year	204 (54.1%)
1 to < 2 years	50 (13.3%)
2 to < 5 years	53 (14.1%)
≥5 years	70 (18.6%)
Surgery	
Surgery	210 (55.7%)
No surgery	167 (44.3%)
Radiation	
None/Unknown/Refused	232 (61.5%)
Radiation given	145 (38.5%)
Chemotherapy	
Yes	92 (24.4%)
No/Unknown	285 (75.6%)

Discussion

Our analysis of over 70,000 cases of primary gliomas using population-based data from SEER found that patients with higher grade, particularly the most aggressive gliomas, Grade IV, and larger gliomas were at increased risk of cerebrovascular mortality. Receiving cancer treatments was associated with lower risk for cerebrovascular mortality in patients surviving less than 5 years. However, radiation therapy significantly increased the risk of cerebrovascular mortality in longer-term survivors.

Tumour-associated factors for cerebrovascular mortality in glioma patients

The association of high-grade glioma with cerebrovascular mortality suggests an important biological role for tumour aggressiveness in the risk of stroke. This is consistent with previous studies showing that patients with more advanced stage cancer, including lung, pancreatic, colorectal and gastric cancer, have increased risk of stroke (24). These findings suggest the biological plausibility of the relationship between stroke risk and aggressiveness of cancer types, implicating a systemic response to malignancy in stroke risk, for example from cancer-mediated hypercoagulability (24, 25). Glioma cells have inherent prothrombotic properties that secrete procoagulant proteins such as tissue factors, the principal initiator of coagulation that activates the clotting cascade. Tumour-induced hypercoagulability causes thrombus formation within the cerebral vasculature resulting in ischaemic hypoxia that leads to cerebral infarction (7, 26, 27). Similar mechanisms lead to the higher risk of venous thromboembolism (VTE) also seen in brain tumours, with the greatest risk in glioblastoma (27). The association of larger tumour size with higher cerebrovascular mortality risk may relate to reduced vascular perfusion from mass effect of tumour growth or to direct tumour invasion into surrounding brain tissue and vasculature (28, 29).

The findings of a particularly strong association between high grade glioma and cerebrovascular mortality in younger patients may further support the independent role of tumour aggressiveness-related hypercoagulation, because younger patients are relatively healthy and less likely than older individuals to have conventional stroke risk factors (30). The weaker association between tumour grade and cerebrovascular mortality in older patients may be attributable to unmeasured comorbidities or competing causes of mortality with increasing age. Advancing age is a risk factor for cardiovascular risk accompanied by the development of

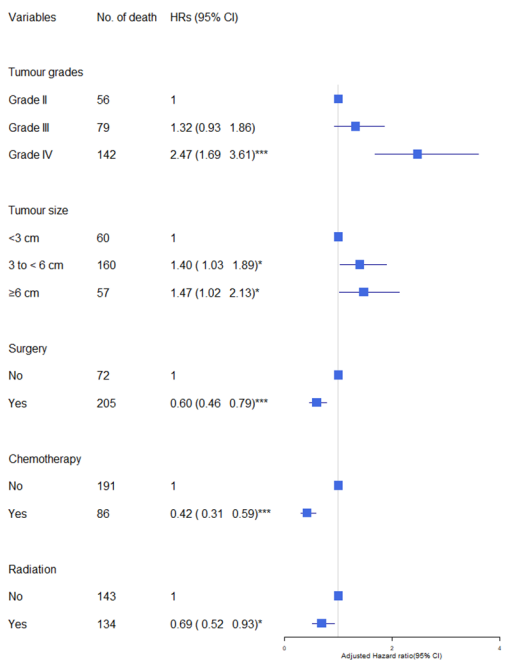


FIGURE 1
Association of tumour characteristics and cancer treatment with cerebrovascular mortality in glioma patients. The hazard ratios (HRs) were calculated using cox regression model and adjusted for variable shown, age, sex, race/ethnicity, marital status and calendar years. CI, Confidence intervals. Significance code: *** p<0.001, * p<0.05.

comorbidities such as hypertension and high cholesterol, as well as related to cerebral small vessel disease leading to stroke and cognitive decline (30).

Treatment-related cerebrovascular mortality in glioma patients

Our findings showed that tumour treatment, particularly chemotherapy and radiation therapy, were associated with lower risk of cerebrovascular mortality in glioma patients surviving less than 5 years, while having radiation increased cerebrovascular mortality risk in those surviving more than 5 years. While cancer treatment reduces cancer activity, it has been recognised that treatment increases risk of fatal and non-fatal cardiovascular outcomes including stroke in brain tumour survivors (4, 31). Our findings of radiation-associated long-term increased risk of cerebrovascular mortality in adult gliomas survivors are consistent with previous investigations in long-term survivors of childhood cancers (14). Radiotherapy is used to reduce or prevent tumour growth. However, it may damage normal tissues, leading to irreversible chemical and biological changes, and resulting in cell death. Radiotherapy can accelerate atherosclerotic changes in the arterial wall, predisposing patients to vascular dysfunction and ischemic events (3, 14, 30). Radiation-induced vasculopathy can develop months to years after radiation therapy (32). There is evidence that cranial radiotherapy is associated with risk of late neurovascular events and stroke in younger brain tumour survivors (14). Radiotherapy at younger age and higher radiation does are risk factors for developing radiation vasculopathy (3, 6, 8). In older adults, increased risk of cerebrovascular mortality could be due to the combination effects from radiation and age-related atherosclerosis risk factors such as hypertension, hypercholesterolemia that are more prevalent in older adults (8, 32). For example, hypertension can directly damage arteries that predispose patient more vulnerable for stoke during and after brain treatment (33). there are increasing concerns of safe radiation regimes and efficacy in elderly patients for their tolerability and side effects (34). However, there is lack of enough evidence for optimal strategies and clinical guidelines in adult patients with GBM which often occurs in those aged over 65 years. These elderly patients with co-comorbidities are often excluded from clinical trials. Future prospective studies are needed with the aim of understanding the short-and long-term cerebrovascular complications of radiation therapy to guide for the optimal intervention (34, 35).

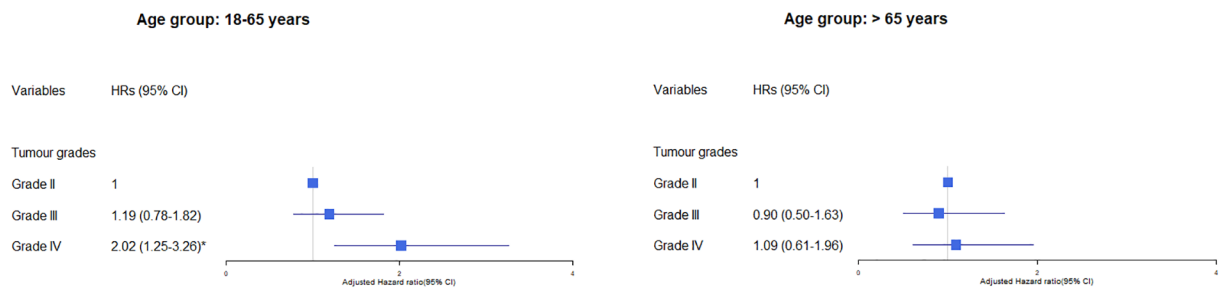


FIGURE 2
Association of tumour grade with cerebrovascular mortality in glioma patients by age group. The hazard ratios (HRs) were calculated using cox regression model and adjusted for variable shown, age, sex, race/ethnicity, marital status and calendar years. The reference group was those who did not receive the treatment: surgery, chemotherapy or radiation. CI, Confidence intervals. Significance code: * p<0.01.

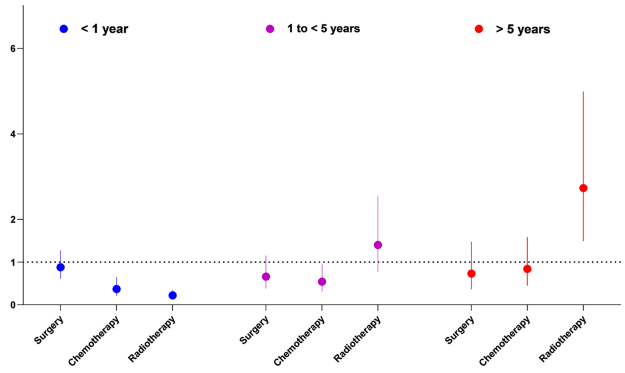
Radiation treatment remains the cornerstone of therapy for patients with brain tumour such as glioma. An awareness of the long-term risk of cerebrovascular mortality is not intended to detract from this standard care therapy, but rather to encourage incorporation of screening, mitigation and prevention methods where supported by an evidence-base (35). This may include mitigating cardiovascular risk factors. For patients with lower grade tumours and longer survival, consideration may be given to investigation of what schedules of radiotherapy reduce cerebrovascular risk whilst optimising tumour control (35).

Strengths and limitations

Using the large population-based data, our study showed the important role of tumour aggressiveness and radiation therapy in cerebrovascular mortality in patients with gliomas. Our study is the largest and most comprehensive analysis to date of the associations of tumour characteristics and cancer treatments factors with cerebrovascular mortality in glioma patients, and used population-based data, enhancing the generalizability of our findings. Our findings provide important evidence for planning future clinical trials to understand the role of prophylaxis against arterial thrombosis and to guide clinical management. Our findings of long-term fatal cerebrovascular outcome from radiotherapy should enable better identification of groups of high-risk patients requiring surveillance and prevention of cerebrovascular complications, for example, assessing and treating cardiovascular risk factors such as hypertension. Importantly, long-term glioma survivors who have a more favourable oncologic prognosis may benefit the most from follow-up clinical screening and monitoring to improve their survival outcomes, particularly in those who have had radiotherapy.

The absolute number of glioma patients who died from cerebrovascular deaths are low in this population. However, this number may be under reported and not reflect the true burden of this disease, because in patients with a brain tumour a cerebrovascular event may not be considered as a cause of clinical deterioration. Prompt diagnosis of cerebrovascular diseases, including stroke is needed to achieve maximal functional recovery, and quality of life (36). This is especially important for patients with GBM where life expectancy is short. Stroke diagnosis is clinically challenging in patients with a brain tumour because of the overlapping symptoms. It can be difficult to distinguish tumour tissue from ischemic stroke on MR image in the setting of a pre-existing brain tumour (37). One study showed the initial clinical diagnosis was correct in only 45% of ischemia stroke episodes in patients with primary brain tumour (8), reflecting the difficulty of diagnosing stroke and possibility of undetected cases. Further, in addition to the traditional risk factors, stroke in cancer patients may involve complex underlying biology that remains poorly understood (1). Advances in molecular and gene profiling of brain tumour may have a role to understand the complex phenomenon, and how to mitigate stroke risk. Our study, by far, is the largest study to examine this under-research but clinically important issue, may pave the way for further research.

Our study has limitations. First, it was retrospective in nature, and lacked granular details of stroke diagnosis, including stroke subtypes. Future prospective studies are needed with more granular detail of stroke diagnosis such as stroke subtypes, timing of the event, biomarkers by including neuroimaging and laboratory data to improve the diagnosis of stroke and determine the cause of stroke. Second, we did not have baseline cardiovascular risk factors (i.e., hypertension, diabetes) and/or cardiovascular disease (i.e, coronary heart disease, atherosclerosis). However, our analysis in the younger age group who were relatively healthy has shown the strong association between tumour aggressiveness and cerebrovascular mortality. In addition, a population-based cohort study using UK Clinical Practice Research Datalink (CPRD) showed adjustment for shared CVD risk factors had little effect on CVD risk including stroke in adult survivors of multiple site-specific cancer including central nervous system (CNS) tumours



< 1 year			1 to < 5 years			> 5 years		
Surgery	Chemotherapy	Radiation	Surgery	Chemotherapy	Radiation	Surgery	Chemotherapy	Radiation
Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
0.88 (0.61, 1.27)	0.37(0.21, 0.65)***	0.22(0.14, 0.35)***	0.66(0.38, 1.15)	0.54(0.31, 0.94)*	1.40(0.77, 2.54)	0.73(0.36, 1.47)	0.84(0.45, 1.58)	2.73(1.49, 4.99)**

FIGURE 3
Association of cancer treatment with cerebrovascular mortality in glioma patients by different follow-up periods. The hazard ratios (HRs) were calculated using cox regression model and adjusted for sex, race/ethnicity, marital status and calendar years, tumour size, cancer treatments. The reference groups were those who did not receive the treatment: surgery, chemotherapy, or radiation. CI, Confidence intervals. Significance code: *** p<0.001, ** p<0.01, * p<0.05.

TABLE 3 Association of cancer treatment with cerebrovascular mortality in glioma patients by different follow-up periods stratified by low grade and high grade.

Low grade (Grade 2)	Overall HR (95% CI)	< 1 year HR (95% CI)	1-5 years HR (95% CI)	>5 years HR (95% CI)
Surgery				
No	1	1	1	1
Yes	0.77 (0.43 1.38)	0.86 (0.25 2.89)	0.82 (0.34 1.97)	1.15 (0.41 3.26)
Chemotherapy				
No	1		1	1
Yes	0.58 (0.30 1.15)	Insufficient number	1.00 (0.37 2.66)	0.61 (0.21 1.76)
Radiation				
No	1	1	1	1
Yes	1.48 (0.84 2.60)	0.33 (0.07 1.56)	0.78 (0.31 1.98)	3.89 (1.50 10.10)**
High grade tumour (Grade 3 &4)				
Surgery				
No	1	1	1	1
Yes	0.67 (0.51 0.89) **	0.90 (0.61 1.33)	0.63 (0.31 1.27)	0.77 (0.29 2.00)
Chemotherapy				
No	1	1	1	1
Yes	0.45 (0.32 0.62) ***	0.41 (0.23 0.73) **	0.42 (0.22 0.82) *	1.07 (0.47 2.40)
Radiation				
No	1	1	1	1
Yes	0.70 (0.52 0.93) *	0.21 (0.13 0.35) ***	1.80 (0.80 4.05)	2.47 (1.09 5.58) *

Association of cancer treatment with cerebrovascular mortality in glioma patients by different follow-up periods stratified by low and high grades. The hazard ratios (HRs) were calculated using cox regression model and adjusted for sex, race/ethnicity, marital status and calendar years, tumour size, cancer treatments. The reference groups were those who did not receive the treatment: surgery, chemotherapy, or radiation. CI, Confidence intervals. Significance code: *** p<0.001, ** p<0.01, * p<0.05.

compared with the general population (38). Third, our study is also limited by the lack of detailed data on cancer treatments, such as types and doses of cancer therapy and subsequent treatment. A more comprehensive approach by linking health data from various sources such as primary care data, anti-cancer therapies, image data will provide a better measurement to examine the factors that driver cerebrovascular mortality in brain cancer patients. Another limitation is the risk of misclassification of cause of death by use of death certificate information, although previous studies have reported acceptable validity (>80%) of cause of death using SEER data (39).

Conclusions

More aggressive tumour characteristics are associated with increased cerebrovascular mortality. While receiving cancer treatments was associated with lower risk for cerebrovascular mortality, having radiation increased long-term fatal outcome for cerebrovascular disease. The complex interplay of putative risk and benefit from the tumour and its treatment underscore the need for further research. As early detection and more effective anticancer therapies extend the survival of cancer patients, avoiding treatment-related long-lasting fatal cerebrovascular outcome becomes increasingly vital. Knowledge of the risks can help clinicians be more vigilant for signs and symptoms of potential neurological complications and guide the management of long-term glioma survivors.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data/. Approval to access the SEER data was granted by the US National Cancer Institute (NCI). Data not published within this article will be made available by request from any qualified investigator.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

KJ conceived and designed the study, analysed data, developed figures, interpreted data, and developed the draft of the manuscript. PB designed the study, interpreted data, contributed to the writing, reviewing and editing of the manuscript. MP contributed to data interpretation and reviewing the manuscript. CS conceived and designed the study, interpreted and verified data, contributed to the writing, reviewing and editing of the manuscript. JF conceived and designed the study, interpreted and verified data, contributed to the writing, reviewing and editing of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the manuscript to submit for publication. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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Palliative care for patients with glioma: A recent scientometric analysis of the Web of Science in 2022

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Background: Patients with glioma present with complex palliative care needs throughout their disease trajectory. A scientometric analysis is effective and widely used to summarize the most influential studies within a certain field. We present the first scientometric analysis of palliative care for patients with glioma.

Methods: Based on a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) principle, we conducted a generalized search for articles on palliative care for glioma in the Web of Science database and evaluated the top 100 most frequently cited articles among 2,542 articles.

Results: The number of citations for the top 100 cited articles on palliative care for glioma ranged from 10 to 223. We have a narrative conclusion, as follows: most of these articles were published in oncology-specific journals (n = 53) and palliative-specific journals (n = 22). The United States, Australia, and the Netherlands were the top three countries contributing most of the articles (n = 59). Most of the research methods were quantitative analyses, qualitative analyses, and systematic reviews and meta-analyses (n = 70). In quantitative studies, 66 scales were used, and the top three scales used included the following: the Distress Thermometer, Functional Assessment of Cancer Therapy-Brain Index (FACT-Br), and Karnofsky Performance Scale (KPS). The articles were classified into six major categories based on research subjects, including patients (n = 44), caregivers (n = 16), patients and caregivers (n = 20), literature (n = 19), and healthcare providers (n = 1). Articles were classified into seven major categories based on research themes: quality of life (n = 11); end-of-life symptoms and care (n = 16); palliative and supportive care needs (n = 35); advance care planning and decision making (n = 4); psychological, social, and spiritual needs (n = 12); hospice utilization and referral (n = 3); and others (n = 19). The studies of the primary topic are correlated with the number of citations.

Conclusions: The results of the analysis indicated that patients diagnosed with glioma present a high variety of palliative care needs, including physical, psychological, social, and spiritual needs. The caregiver's burden and needs

are important as well. The proportion of quantitative analyses, qualitative analyses, and systematic reviews and meta-analyses is relatively high, but the number of randomized controlled trials (RCTs) was low. End-of-life care and supportive care needs appeared frequently. Thus, palliative care is an urgent need to be addressed in glioma management. The appropriate scales should be selected for patients with glioma and meet their palliative needs.

KEYWORDS

citation classics, citations, palliative care, hospice care, glioma, scientometric analysis

Introduction

Gliomas are the most frequent primary tumors of the central nervous system, and the 2021 WHO classification of tumors of the central nervous system combined histological features and molecular markers to improve the classification, diagnostic criteria, and grading of gliomas (Grading of adult diffuse gliomas according to 2021 WHO Classification of Tumors of the Central Nervous System) (1–4). While the effective treatment of glioma is limited, and the clinical treatment of glioma includes surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and novel therapies (5–10). Although comprehensive treatments are used, glioma patients have poor prognoses, especially for glioblastoma (GBM). The recurrence rate is high, the reported 5-year survival rate of patients with GBM remains less than 10%, and the median survival is still less than 2 years. Patients who underwent gross total resection had a median overall survival (OS) of 14.53 months, while patients who underwent subtotal resection had a median survival (OS) of 10.44 months (11). General and disease-specific symptoms are common in the disease trajectory, especially in the end-of-life phase. All of these symptoms result in difficult and complex situations for the patient. Family caregivers face a high level of distress as well. In this complex situation, palliative and supportive care become more and more important, and the demand increases.

Modern hospice and palliative care began at St. Christopher's Hospice in London, England, and continues to expand today (12–16). The definition of palliative care provided by the WHO is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness through the prevention and relief of suffering based on the early identification and impeccable assessment and treatment of pain and other problems, including physical, psychosocial, and spiritual needs (17). An update indicated that palliative care is a crucial part of integrated, people-centered health services. Relieving serious health-related suffering, regardless of whether it is physical, psychological, social, or spiritual suffering, is a global ethical responsibility (18). International Association for Hospice and Palliative Care (IAHPC), as one of the partners of WHO, has its origins in the International Hospice Institute, founded by Josefina Magno, MD, in 1980 (19). IAHPC is a global non-profit membership organization whose vision is a world free from health-related suffering with universal access to quality palliative care. The definition of palliative care provided by IAHPC is the active holistic care of individuals across all ages with serious health-related suffering due to severe illness, particularly the suffering of those near the end of life. Palliative care aims to improve the quality of life of not only patients but also their families and their caregivers (20). Due to the limitations associated with the nature of the disease, high recurrence rate, and short overall survival of patients with high-grade glioma (WHO 3–4), patients experience a complex condition during the disease trajectory. Patients experience the following common progressive focal neurological deficits with a wide range of symptoms at the end of life: cognitive deficits, paralysis, seizures, fatigue, dysphagia, headaches, drowsiness, loss of consciousness, incontinence, and psychosocial burden (21–23). Patients with high-grade glioma have higher demands for palliative care.

Scientometrics is a discipline that quantitatively analyzes information from the literature mainly using mathematical and statistical methods. The number of citations of an article may reflect the degree of concern or value of the topic in question to a certain extent, as well as the importance, influence, and quality of the article. Scientometric analysis methods have been applied to investigate different cancers treated using neurosurgery (24–26), but not to palliative care for glioma. In this study, we mainly used a scientometric method to statistically analyze the most frequently cited literature on palliative care for glioma and to summarize current research and the prospects of palliative care

Abbreviations: WHO, World Health Organization; HGG, high-grade glioma; OS, overall survival; IF, impact factor; RCTs, randomized clinical trials; IAHPC, International Association for Hospice and Palliative Care.

for patients with glioma. This article mainly analyzed the top-cited studies on palliative care for glioma, and current research hotspots and possible research directions were derived based on the results. By referring to this article, readers can quickly comprehend the major research topics on palliative care for glioma and where to find them, which will guide the direction of future studies and publications.

Materials and methods

Search strategy and selection criteria

A search of the Web of Science database was conducted on 7 April 2022, using topics and all field strategies with the following terms: ("palliative care" or "palliative medicine" or "Hospice and palliative care nursing" or "Terminal care" or "Hospice care" or "Advance care planning" or "Early palliative" or "Decision-making in the end of life" or "Quality of life in the end of life" or "limitation of life support" or "symptom burden" or "caregiver*" or "physical need* " or "psychological need*" or "psychosocial need*" or "spiritual need*" or "social need*") and ("High-grade glioma*" or "Glioblastoma*" or "HGG" or "intracranial glioma*" or "glioma*" or "malignant glioma*" or "malignant cerebral glioma*" or "primary malignant brain tumo*" or "primary malignant brain neoplasm*" or "malignant primary brain tumo*" or "malignant primary brain neoplasm*" or "GBM" or "glioblastoma multiforme" or "Neuro-oncologist*" or "Neuro-oncology" or "Neurosurgery or Neuro-oncological"). No restrictions were placed on the publication date, language, document types, or Web of Science categories. The articles were subjected to two rounds of selection: published articles were first screened by reading the title for their relevance to palliative care and glioma, and the abstracts of the remaining articles were reviewed. Articles not directly pertaining to palliative care and glioma were excluded. A total of 130 publications were included in descending order. The Pareto principle (27), which holds that a small number of factors have a disproportionate impact on any outcome, was used in 130 publications, and we identified the top 100 most-cited articles published between 2003 and 2020 on palliative care for patients with glioma that may be considered significant and impactful works, as well as the most noteworthy. However, 30 lowest-cited publications with less than the number of 10 citations were not included in this study.

Preferred reporting items for systematic reviews and meta-analyses criteria

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement consists of a 27-item checklist and a four-phase flow diagram that was published in 2009 (28) and has been updated to PRISMA 2020 version. It was designed to help authors prepare transparent accounts of their reviews, and its recommendations have been widely endorsed and adopted (29). The PRISMA flow diagram depicts the flow of information through the different phases of a systematic review. It maps out the number of records identified and included and the reasons for the exclusion (30, 31). We completed the identification of the studies under the PRISMA criteria.

Data collection

The following parameters were extracted from each article: title, first author, corresponding author, country, institution, journal, impact factor (IF) of the journal, category of the journal, total citation count, annual citation count, and publication year. The country of origin was based on the affiliation of the corresponding author. Articles were classified according to the study design and topical theme. Article types consisted of quantitative analyses, qualitative analyses, systematic reviews and meta-analyses, mixed-methods research, cohort studies, cross-sectional studies, case reviews, guidelines, and randomized clinical trials (RCTs). Articles were classified based on their primary theme to assess trends in the literature. These themes were chosen to represent major areas of palliative care in glioma research and encompass important aspects relevant to clinical practice. The themes included quality of life, end-of-life symptoms and care, palliative and supportive care needs, advance care planning and decision-making, psychosocial and spiritual needs, and hospice utilization and referral. A pie chart was drawn to describe the national contribution, and a line chart was drawn to describe the relationship between the number of published papers and research topics, subjects, and methods.

Statistics

Correlation analyses of continuous variables were conducted using SPSS version 26 (IBM Corp., Armonk, NY, USA) and GraphPad Prism 9 (GraphPad, La Jolla, CA, USA). Continuous data were expressed as mean ± standard deviation or median for normally or non-normally distributed data, respectively. The normality of the data was analyzed by the one-sample Kolmogorov–Smirnov test. The differences between groups with the t-test were tested when data were normally distributed and the variance was homogeneous. The Mann–Whitney U test was used when data were skewed. Spearman's correlation analysis was used for the non-normality of the data, and a two-sided p-value <0.05 was considered statistically significant.

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Results

Among the final list of studies obtained, the top 100 cited articles following the PRISMA principle were included in the final analysis (Figure 1). Our search query yielded 2,542 articles, with a total of 3,809 citations. The top 100 cited articles are listed in Supplementary Table 1. Among the top-cited articles, the most-cited article was referenced 223 times, and the least-cited article was referenced 10 times. The mean and standard deviation of all articles' total citation counts was 38.09 ± 32.77 (median, 27), and the mean and standard deviation of IFs were 6.59 ± 25.38 (median, 3.6). The details of the top-cited articles were analyzed.

An assessment of the sources of the articles showed that most of the top-cited articles were published in oncology-specific journals (n = 53) or palliative-specific journals (n = 22). Among the remaining articles, 25 were published in journals from various other categories. *Neuro-Oncology* and the *Journal of Neuro-Oncology* published the most top-cited articles (35 articles), and *Supportive Care in Cancer* published 17 articles (Table 1). The IFs of the journals and the number of citations showed non-normality distributions (Spearman's correlation coefficient = 0.142; $p > 0.05$). The IFs of the journals are not

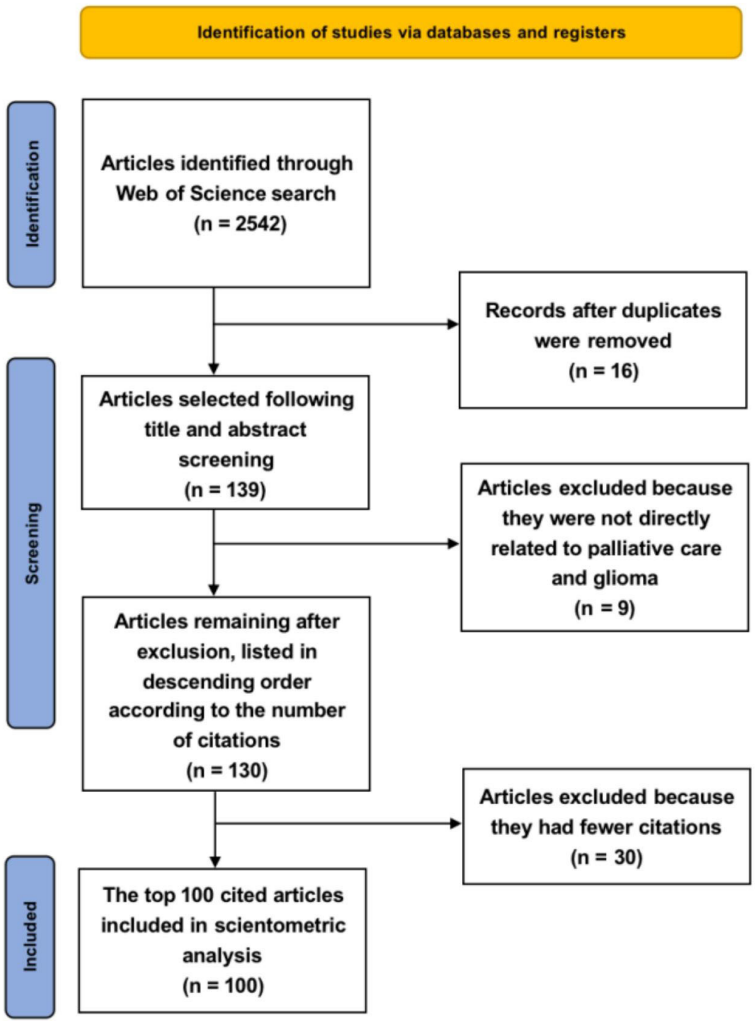

FIGURE 1
Flowchart of the literature screening process in the PRISMA style format (28–31). PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

correlated with the number of citations. When the journals were divided into two groups, the open-access journals and the standard published journals, there was no statistical difference in the number of citations ($p = 0.35$; $p > 0.05$) and the IFs of journals ($p = 0.215$; $p > 0.05$).

Overall, 14 countries contributed to the top 100 cited articles (Figure 2), with institutions from the United States contributing the greatest number (25 articles), followed by Australia (21 articles), the Netherlands (13 articles), Italy (8 articles), Germany (7 articles), the United Kingdom (7 articles), Denmark (5 articles), Belgium (3 articles), Canada (3 articles), France (3 articles), Austria (2 articles), China (1 article), Switzerland (1 article), and Turkey (1 article). European institutions produced 49 of the most frequently cited articles, North American institutions produced 28, Oceanian institutions produced 21, and Asian institutions produced 2. The Vrije University of Amsterdam and the Curtin University of Australia contributed most frequently to the top 100 cited articles, with 10 and 5 published articles, respectively. Currently, there is only one guideline on palliative care for patients with glioma, which was published in 2017 by the European Association for Neuro-Oncology (EANO) (32).

TABLE 1 Journal rankings based on publications of the top 100 cited articles on palliative care for patients with glioma.

Journal	Journal category	Publication numbers	Impact factor
Journal of Neuro-Oncology	Oncology; clinical neurology	24	3.639
Supportive Care in Cancer	Oncology; healthcare sciences and services; rehabilitation	17	2.967
Neuro-Oncology	Oncology; clinical neurology	11	7.137
Patient Education and Counseling	Public, environmental, and occupational health; social sciences, interdisciplinary	4	2.555
Frontiers in Oncology	Oncology	4	6.244
European Journal of Oncology Nursing	Oncology; nursing	3	2.116
Psycho-Oncology	Oncology; psychology; psychology, multidisciplinary; social sciences, biomedical	3	3.011
European Journal of Cancer Care	Oncology; healthcare sciences and services; nursing; rehabilitation	3	2.183
Palliative Medicine	Healthcare sciences and services; public, environmental and occupational health; medicine, general and internal	2	3.973
Oncology Nursing Forum	Oncology; nursing	2	1.352
Journal of Neuroscience Nursing	Clinical neurology; nursing	2	0.906
Cancer	Oncology	2	6.86
European Journal of Cancer	Oncology	1	6.512
PLOS One	Multidisciplinary sciences	1	3.041
Oncologist	Oncology	1	4.33
Neurosurgical Focus	Clinical neurology; surgery	1	2.857
Neuropsychological Rehabilitation	Neurosciences; psychology	1	2.503
Medicine	Medicine, general and internal	1	1.644
Lancet Oncology	Oncology	1	31.003
Journal of Palliative Medicine	Healthcare sciences and services	1	1.652
Journal of Clinical Oncology	Oncology	1	12.287
Journal of Clinical Nursing	Nursing	1	2.767
Journal of Cancer Survivorship	Oncology; social sciences, biomedical	1	3.671
Health and Quality of Life Outcomes	Healthcare sciences and services; health policy and services	1	2.965
Disability and Rehabilitation	Rehabilitation	1	2.16
Current Opinion in Oncology	Oncology	1	2.955
Current Oncology	Oncology	1	2.936
Clinical Neurology and Neurosurgery	Clinical neurology; surgery	1	1.78
Cancers	Oncology	1	6.012
Cancer Nursing	Oncology; nursing	1	2.03
Canadian Medical Association Journal	Medicine, general and internal	1	2.485
Ca-A Cancer Journal for Clinicians	Oncology	1	255.732
Brain Sciences	Neurosciences	1	3.114
BMJ Supportive & Palliative Care	Healthcare sciences and services	1	3.568
American Journal of Hospice & Palliative Medicine	Healthcare sciences and services	1	1.808

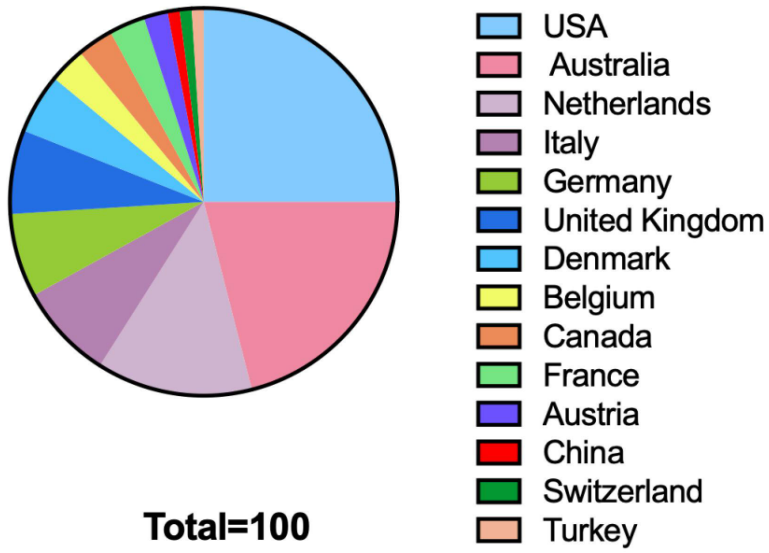

FIGURE 2
Countries contributing to the top 100 cited articles on palliative care issues of patients with glioma.

The top 100 cited research articles were subsequently divided into seven major categories based on the primary topic (Figure 3): quality of life, end-of-life symptoms and care, palliative and supportive care needs, advance care planning (ACP) and decision-making, psychosocial and spiritual needs, hospice utilization and referral, and others. The studies of the primary topic are correlated with the number of citations (Spearman's correlation coefficient = −0.206; $p < 0.05$). End-of-life symptoms and care, patient/caregiver dyads quality of life, and palliative or supportive care needs were the top three most studied topics in the past. Specifically, the top 100 cited articles were divided into the following six major research subject groups: patients, caregivers, patients and caregivers, healthcare providers, the literature, and one palliative care for glioma guideline (Figure 4). The studies of the subject are not correlated with the number of citations (Spearman's correlation coefficient = 0.128; $p > 0.05$). Furthermore, the top 100 cited articles were divided into the following nine research methods: quantitative study, qualitative study, review or systematic review and meta-analysis, cohort study, RCT, mixed-methods research, cross-sectional study, case review, and one guideline (Figure 5).

Discussion

In this study, we conducted the first scientometric analysis of palliative care issues in patients with glioma. Scientometrics may reflect the degree of attention and research hotspots in a particular field and the quality and impact of the literature.

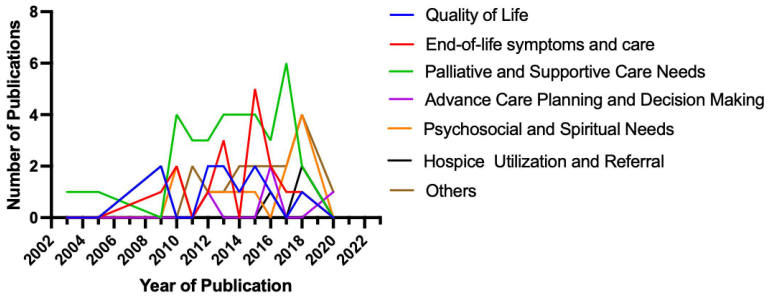

FIGURE 3
The top 100 cited article categories based on the primary topic.

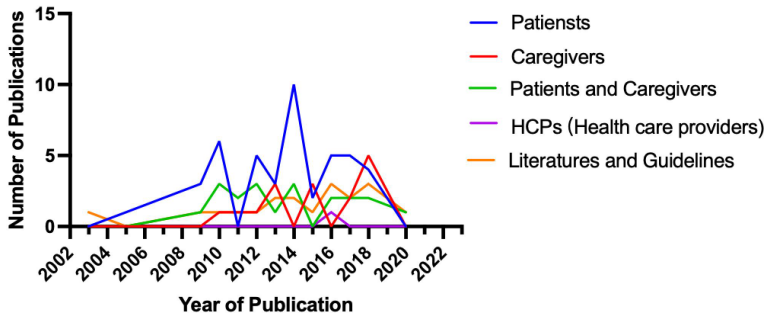

FIGURE 4
The top 100 cited article categories based on the research subjects.

We analyzed the 100 most frequently cited articles and then summarized the basic information. We analyzed the relationship between annual publications and research topics, objects, and methods. We also analyzed research hotspots and alterations in the direction of the field and, to some extent, predicted future research trends in palliative care for gliomas.

We chose the Web of Science database because it not only consists of only institutes for scientific information journals but also has the facility to view and sort articles based on the number of times an article is cited (24). Among the top 100 cited articles, we list the 10 most frequently cited articles in Table 2. The core number of times that an article was cited by Web of Science ranged from 71 to 223, and the mean number of citations was 115.4. Between the open-access journals and the standard published journals, there was no statistical difference in the number of citations and the IFs of journals. The IFs of the journals are not correlated with the number of citations. In contrast to glioma treatment, diagnosis, prognosis, and mechanism, the number of citations was fewer, and palliative-specific journals were relatively rare.

Europe, North America, and Oceania contributed the most to the top 100 cited articles. Brant JM et al. (33) summarized that some similarities exist in palliative cancer care around the world, but vast differences exist in five primary areas: 1) the epidemiology of cancer and related symptoms experienced, 2) cancer-specific integration into care, 3) palliative care education, 4) economic development of the country, and 5) cultural and religious differences that call for a tailored approach to care. While palliative care services exist in over half of the world's countries, low-to-middle-income countries (LMICs) are resource-poor and have the fewest resources and least amount of integration of palliative care, especially in remote areas; however, these programs are primarily located in high-income countries (34–36).

The number of citations is a reliable method for quantifying an article's quality and the impact of its contribution to the scientific community (25). We also analyzed the trend of articles published on primary topics related to palliative care for glioma. Among the top 100 cited articles, Figure 3 shows the relationship between the publication year of the article and the number of citations on the research themes: patient/caregiver dyads quality

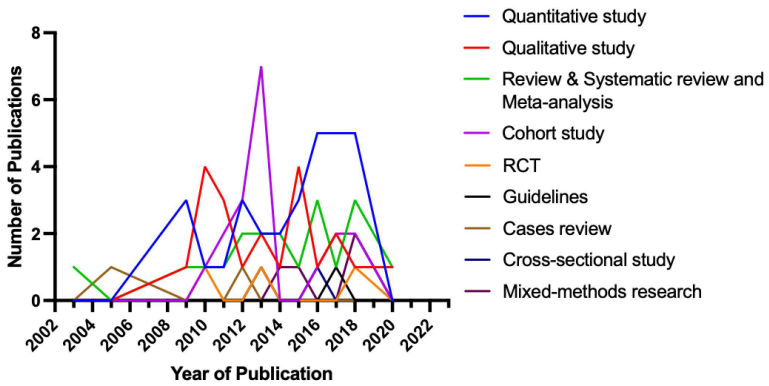

FIGURE 5
The top 100 cited article categories based on the research methods.

TABLE 2 Summary of the top 10 cited articles on palliative for patients with glioma.

Rank	Article title	Citation numbers	Annual citation numbers	Theme
1	Management of glioblastoma: state of the art and future directions	223	111.50	A review: supportive and palliative care are important considerations in the multimodal approach to management
2	Use of video to facilitate end-of-life discussions with patients with cancer: a randomized controlled trial	161	13.42	Goals-of-care video to improve end-of-life decision-making
3	Quality of life in adults with brain tumors: current knowledge and future directions	121	9.31	A review: quality of life and specific symptoms
4	Symptoms and problems in the end-of-life phase of high-grade glioma patients	110	9.17	Symptoms and problems in the end-of-life phase
5	Systematic review of supportive care needs in patients with primary malignant brain tumors	111	11.10	Supportive care needs
6	European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma	109	21.80	EANO guidelines
7	Prevalence and determinants of depression in caregivers of cancer patients: a systematic review and meta-analysis	91	22.75	Depression and quality of life in caregivers
8	End of life issues in brain tumor patients	85	6.54	Symptoms in the last weeks of disease and EoL decision-making
9	Social, psychological and existential well-being in patients with glioma and their caregivers: a qualitative study	72	7.20	Physical, social, psychological, and existential distress
10	The information and support needs of patients diagnosed with high grade glioma	71	5.92	Information and support needs and patients' experiences

of life, end-of-life symptoms and care, palliative and supportive care need, advanced care planning and decision-making, psychosocial and spiritual need, hospice utilization and referral, and others such as caregivers' economic hardship, patterns of care, social support and resource, sleep characteristics of family caregivers, and anti-epileptic drugs. The studies of the primary topic are correlated with the number of citations, which showed that end-of-life symptoms and care, patient/caregiver dyads quality of life, and palliative or supportive care needs were the top three most studied in the past, whereas the research on end-of-life symptoms and care, and hospice utilization and referral has an increasing trend. In our analysis, the number of studies focusing on patients was higher, while the number of studies focusing on family caregivers or healthcare teams has increased each year. This finding suggests that palliative care is not restricted to patients and encompasses the whole process and all members of the patient's family and healthcare team. This conclusion indicates that research on palliative care for caregivers and medical teams is a hot topic and a feasible direction for research in the near future.

We further analyzed the publication trend of research subjects. The relationship between the publication year of the article and the number of articles related to research subjects is shown in Figure 4. The main research subjects were the patient, caregiver, patient and caregiver, healthcare provider, and literature. The studies of the subject are not correlated with the number of citations. The relationship between the publication year of the article and the number of articles related to research methods is shown in Figure 5. Most of the studies performed quantitative analyses, qualitative analyses, systematic analyses, meta-analyses, and retrospective cohort studies. RCTs are less common in palliative care for the glioma field. Numerous clinical studies have documented the benefits of palliative care, and future studies should include additional RCTs to increase the level of evidence.

In quantitative studies, 66 scales were used. The top 10 scales were used 54 times, as shown in Figure 6, including the Distress Thermometer (DT), Functional Assessment of Cancer Therapy-Brain Index (FACT-Br), Karnofsky Performance Scale (KPS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTCQLQ-C30), Hospital Anxiety and Depression Scale (HADS), Short form-36 health survey questionnaire (SF-36), Supportive Care Needs Scale (SCNS-34), Barthel Index, Neurological functioning (BN-20), and Caregiver Reaction Assessment (CRA). The scales were used in various ways. The same scales were used at different stages of the disease trajectory to observe the trends in the problems being studied. On the one hand, the scales focus on patients' psychosocial, quality of life, supportive care needs, symptoms and signs during the disease trajectory especially at the end of life (21–23), personality, cognition, and activities of daily living. On the other hand, the scales focus on caregivers' quality of life, psychological features, multidimensional burden, and support needs. Of the 100 most-cited articles, 12 included both patients and caregivers in the studies. A total of six studies combined scales on patients' and caregivers' burden, in which DT, Patient-Generated Index (PGI), and coping strategies (BriefCope) were used twice. MD Anderson Symptom InvenTory-Brain Tumor (MDASI-BT) module and HADS were used one time.

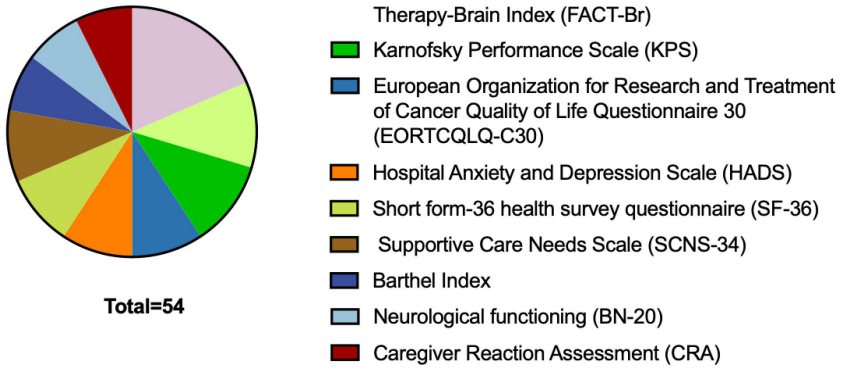

FIGURE 6
The top 10 scales used in quantitative research.

This scientometric analysis of the palliative care for glioma patients 1) helps us grasp the different aspects of palliative care needs of glioma patients and where research should be directed. 2) This is the first scientometric study on palliative care for glioma patients, which makes people realize the importance of palliative care for glioma patients and provides a treatment strategy that can be considered for terminally ill patients. 3) As the spectrum of disease changes and the population ages, palliative care is gradually being recognized and used in different life-limiting conditions; the need for palliative care is increasing, has become an important part of clinical practice, and gradually gained widespread worldwide (37, 38). Palliative care is likely to become a hot topic of research in the future, and the number of journals on this topic will increase.

Our study still has some limitations. First, we used only the Web of Science database for the literature search, which may have resulted in a certain degree of omissions, and annual citation is used to reflect attention which has some errors. Second, the length of the time since publication will affect the citations; some recently published articles were not included due to the low total number of citations. Third, most of the studies used self-report questionnaires and semistructured interviews to observe the problems of the patient and their caregivers, and a retrospective study nature, which may have selection bias and publication bias. In addition, the included population is relatively small, and the population heterogeneity is large, which may affect the results of the study.

Conclusions

This study provides the first scientometric analysis of palliative care issues of patients with gliomas, enumerates the top 100 most-cited and influential articles, summarizes historical developments, and predicts future research hotspots. We found that the core problem in this field is the palliative care issues of patients with glioma, including research topics and trends, subjects, and research methods. However, the number of RCTs investigating the palliative care of glioma was low, and the evidence is low. Literature reviews and meta-analyses on palliative care for glioma are relatively rare. Future hotspots will mainly focus on RCTs of palliative care for patients with glioma, and a considerable need for high-quality literature reviews and meta-analyses is noted.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding authors.

Author contributions

Study design and manuscript writing: ZX, WC and HZ. Medical record search and follow-up: HW, BZ, DL, TY, TL and HX. Manuscript formatting and revision: YNW, YKW and XG. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.995639/full#supplementary-material

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A necroptosis-related lncRNA signature was identified to predict the prognosis and immune microenvironment of IDH-wild-type GBM

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Introduction: Necroptosis-related genes are essential for the advancement of IDH-wild-type GBM. However, the putative effects of necroptosis-related lncRNAs (nrlncRNAs) in IDH-wild-type GBM remain unknown.

Methods: By using the TCGA and GTEx databases, a nrlncRNA prognostic signature was created using LASSO Cox regression. The median risk score was used to categorize the patients into low and high-risk groups. To confirm the validity, univariate, multivariate Cox regression and ROC curves were used. Furthermore, by enrichment analysis, immune correlation analysis, and drug sensitivity analysis, the targeted lncRNAs were selected for further verification. As the highest upregulated expression in tumor than peritumor specimens, RP11-131L12.4 was selected for phenotype and functional experiments in primary GBM cells.

Results: Six lncRNAs were proved to be closely related to necroptosis in IDH-1-wild-type GBM, which were used to create a new signature. For 1-, 2-, and 3-year OS, the AUCs were 0.709, 0.645 and 0.694, respectively. Patients in the low-risk group had a better prognosis, stronger immune function activity, and more immune cell infiltration. In contrast, enrichment analysis revealed that the malignant phenotype was more prevalent in the high-risk group. In vitro experiments indicated that RP11-131L12.4 increased the tumor proliferation, migration and invasion, but decreased the necroptosis. Moreover, this nrlncRNA was also proved to be negatively associated with patient prognosis.

Conclusion: The signature of nrlncRNAs may aid in the formulation of tailored and precise treatment for individuals with IDH-wild-type GBM. RP11-131L12.4 may play indispensable role in necroptosis suppression.

KEYWORDS

necroptosis, glioblastoma, tumor microenvironment, signature, prognosis

Introduction

GBM is the most lethal CNS tumor in adults, and it has strong heterogeneity (1). According to the 2021 WHO Classification of Tumors of CNS, GBM, integrates three genomic factors as diagnostic criteria for IDH-wild-type GBM. As a result, adults with IDH-wild-type diffuse and astrocytic gliomas should be diagnosed with IDH-wild-type GBM if there is microvascular proliferation or necrosis, TERT promoter mutation, EGFR gene amplification, or +7/10 chromosome copy number alterations (2, 3). However, patients with the same molecular type still have a large difference in prognosis, and the effects of radiotherapy, chemotherapy and immunotherapy also differ (4, 5). This shows that some modest elements continue to influence prognosis and treatment response.

Necroptosis is a type of programmed necrotic cell death that can recognize pathogens and promote tissue repair (6). Some studies have found that NRGs have a role in a variety of tumor-related activities, however they appear to be a double-edged sword (7, 8).MLKL,RIPK1 and RIPK3 are the key mediators among them (9). RIPK1 and RIPK3 activation can alter associated signaling pathways to modulate the TME and perform a beneficial effect in anticancer progression (10–12). MLKL activation, on the other hand, is linked to highly aggressive tumor behavior and an immunosuppressive microenvironment (13, 14). Moreover, tumor cells can increase metastasis and extravasation by inducing necroptosis of the epithelial microvasculature (15). Therefore, the occurrence of necrotic apoptosis in tumors and its effect on tumor cells are very complex and worth further study.

LncRNAs are a type of noncoding RNA that has a length of more than 200nt and is implicated in the growth and metastasis of GBM. They play a crucial role in transcriptional suppression, transcriptional activation, chromosomal remodeling, and nuclear transport (16–18). LncRNAs are also vital in mediating necroptosis. For instance, it has been reported that the lncRNA H19-derived microRNA-675 could decrease the expression of FADD and enhance the necroptosis of HCC (19). Furthermore, the lncRNA HABON showed a protective effect on HCC cells under hypoxia by inhibiting mPTP opening (20). However, there have been few investigations on nrlncRNAs in GBM. The predictive usefulness of nrlncRNAs in GBM and its association with the TME remain unknown.

Therefore, in order to investigate the prognostic significance and prospective therapeutic options of nrlncRNAs in IDH-wild-type GBM and to elucidate the role of nrlncRNAs in the TME, the following research was conducted: we developed a predictive risk model based on nrlncRNA to predict the prognosis of IDH-wild-type GBM patients and serve as a guide for clinical diagnosis and treatment.

Materials and methods

Ethics statement

The Institutional Review Board at Nanfang Hospital of Southern Medical University provided written authorization and ethical approval for the use of human brain tumor specimens and the database (Guangzhou, China).

Data download and processing

To determine deNRGs and delncRNAs at the transcript level, HTSeq-FPKM RNA sequencing profiles linked with primary GBM and normal brain tissues were collected from the TCGA database and the GTEx project. Initially, there were a total of 144 tumors and 1152 controls. Additionally, available clinical information of patients diagnosed with GBM, including age, sex and survival, was retrieved. ID conversion between transcripts (UCSC) and gene symbols was performed with the annotation file "gencode.v38.annotation.gtf". If multiple transcripts represented the same gene, their median was used; if one transcript represented multiple genes, this transcript was deleted.

Patient selection

The following inclusion criteria for patient enrollment were specified in order to examine nrlncRNAs and construct a

prognosis prediction model in patients with IDH-wild-type GBM (1): patients were diagnosed with primary GBM with wild-type IDH; and (2) living status (yes/no) and OS were available. Consequently, 128 patients were selected for the following analyses (Figure S1), and their clinical characteristics are described in Table S1. To develop a prediction model for survival outcome, the GBM patients were randomly divided into training and testing datasets at a ratio of 2:1.

Selection of NRGs and lncRNAs

Herein, genes involved in the KEGG pathway "Necroptosis" (hsa04217) from the NRG set and a total of 159 NRGs were retrieved through the R package "KEGGREST".

Identification of differentially expressed NRGs and lncRNAs

RNA sequencing data in FPKM values represent the intensity of transcripts on a log-2 scale. To identify deNRGs and delncRNAs between GBM and normal controls, a moderated t-statistic was carried out with the R package "limma". Both the adjusted P value (Pa, Benjamini & Hochberg) and FC were obtained, and only those with Pa< 0.05 and |log2FC| > 1.0 were selected as a deNRG or delncRNA.

Identification of OS-associated NRGs and lncRNAs

Patients with GBM were subsequently separated into two groups with expression higher or lower than the median for each deNRG and delncRNA, followed by a univariate Cox PH model. The deNRGs and delncRNAs with P<0.1 were regarded as OS-associated NRGs and lncRNAs.

Identification of necroptosis-related lncRNAs

Pearson's correlation analyses were performed to identify lncRNAs significantly correlated with OS-associated NRGs with both Pa<0.05 (Benjamini & Hochberg) and correlation coefficient |r| >0.3. Then, lncRNAs that were (1) significantly correlated with OS-associated NRGs and (2) included in the OS-associated lncRNAs were regarded as necroptosis-related lncRNAs and selected for developing the nrlncRNA signature as well as the prediction model.

Necroptosis-related lncRNA signature construction and risk score calculation

In the training dataset, a nrlncRNA signature was created and subsequently verified in the testing dataset. That is, a multivariate Cox PH model with LASSO for variable selection and 10-fold cross-validation was run on necroptosis-related lncRNAs as continuous variables using the R package "glmnet". The lncRNAs that had a nonzero coefficient in the regression finally formed the necroptosis-related lncRNA signature. Then, as shown in Equation, each patient was given a RS, which was a linear mixture of the independent prognostic indicators (expression of lncRNAs) weighted by their Cox regression coefficients. Differences in RSs among subgroups of patients with different ages and sexes were examined by Wilcoxon tests and Kruskal-Wallis tests. Additionally, subgroups of patients at low and high risk were defined based on the median RS. The Kaplan-Meier method with the log-rank test (R package "survminer") was used to generate survival curves. The necroptosis-related lncRNA signature was used to generate a heatmap (R package "pheatmap"). We calculated the RS with the following formula:

$$Score = \sum_{i=0}^{n} \beta i * Xi$$

Prediction model construction

To develop a prediction model for survival outcome, the GBM patients were randomly assigned to training and testing datasets in a 2:1 ratio. A multivariate Cox PH model with the RS and clinical characteristics was developed in the training dataset, and this prediction model was externally validated in the testing dataset. A nomogram was built based on the model to graphically forecast the 1-, 2-, and 3-year OS probabilities, and calibration curves were created to demonstrate the nomogram's goodness of fit.

Possible functions related to the necroptosis-related lncRNA signature

To determine the potential roles of the necroptosis-related lncRNA signature, patients were separated into low- and high-risk groups based on the median RS, and differential expression studies were performed. Then, utilizing the well-known GO and KEGG databases, functional enrichment analysis was done with the R tool "clusterProfiler". Differentially expressed genes were annotated using BP, MF, and CC keywords, as well as KEGG

pathways. With Pa<0.05 (Benjamini & Hochberg), GO keywords and KEGG pathways were deemed substantially enriched. Furthermore, GSVA was carried out to identify signature gene sets that reflect distinct well-defined biological states or processes (Pa<0.05 determined using the Benjamini and Hochberg technique).

Evaluation of immune cell infiltration

The immune infiltration statuses in tumors were evaluated using the findings of functional enrichment analysis and GSVA. To compute the immune cell compositions for each sample,the analytical tools CIBERSORT, XCELL, ssGSEA, EPIC, MCP-counter, and QUANTISEQ were used. Additionally, another analytical tool, "ESTIMATE", was utilized to evaluate immune cell infiltration (immune score), the presence of stroma (stromal score), and tumor purity (ESTIMATE score). The expression of 20 immunological checkpoint genes that might be targeted, as shown in Table S2 [PMID: 26420858], were retrieved. The Wilcoxon test was used to examine differences in these metrics, which included immune cell signature compositions, immunological score, stromal score, ESTIMATE score, and immune checkpoint gene expression, across subgroups of patients with high and low RSs.

Evaluation of drug sensitivity

Information from the Genomics of GDSC database, which describes 1000 human cancer cell lines and hundreds of chemicals, was utilized to assess the treatment sensitivity of GBM. The IC50 for each GBM patient was calculated using RNA sequencing data. The IC50 value was then examined using the Wilcoxon test across subgroups of individuals with high and low RSs, and its association with RS was assessed using Pearson's correlation analysis.

RNA isolation and real-time qRT–PCR

The levels of mRNA expression were determined using the qRT-PCR, as previously reported (21). The levels of mRNA expression were standardized to those of GAPDH. The Supplemental Materials and Methods, which are available online, provide a full list of primers.

Cell culture and transfection

We obtained IDH-wild-type GBM primary cells for cultivation and transient knockdown of RP11-131L12.4. The Supplemental Materials and Methods, which are available online, provide a complete list of antibodies.

Western blotting and antibodies

Western blotting was carried out as previously reported (21). The loading control was GAPDH. The Supplemental Materials and Methods, which are available online, provide a complete list of antibodies.

Cell viability assay

The vitality of cells was determined using the CCK-8 and colony-forming assays. The Supplemental Materials and Methods, which are available online, provide a complete list of reagents.

Cell migration and invasion assays

Wound healing and Transwell assays were used to measure cell migration and invasion. The Supplemental Materials and Methods, which are available online, provide a complete list of reagents.

Immunohistochemical staining

Tissue section staining was performed as previously described (22), and the details of the staining and the scoring system for determining the percentage of positive cells and staining intensity are available in the Supplemental Materials and Methods.

Statistical analysis

The analyses were carried out using the R programming environment (version 4.1.1) and GraphPad Prism 8.2.1. (GraphPad Software, San Diego, USA). See Supplemental Materials and Methods available online for details.

Results

Necroptosis-related lncRNAs in patients with IDH-wild-type GBM

As shown in Figure 1 and Figure S1, the data of 434 patients with IDH-wild-type GBM were initially retrieved from TCGA; then, a total of 128 patients with RNA sequencing data and complete survival information remained for the following

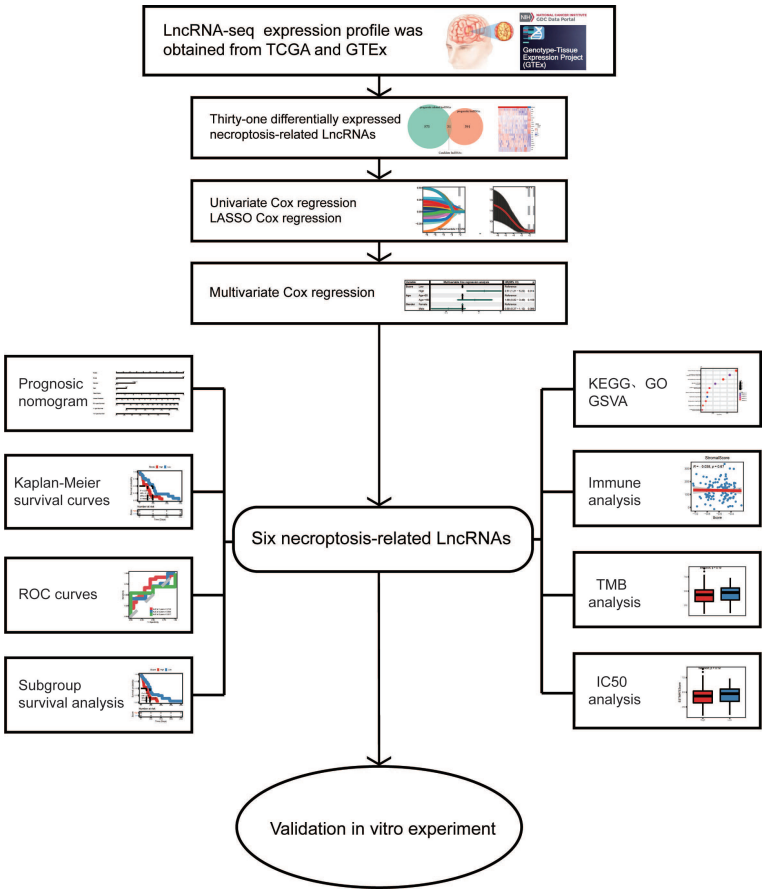

FIGURE 1
Design flow diagram for the research.

analyses (Table S1). In addition, 1152 normal brain tissues were obtained as controls from GTEx. Aberrant transcriptional profiles were examined between cases and controls; consequently, 20 out of 159 NRGs were significantly differentially expressed (|log2FC| > 1.0 and Pa< 0.05, Figure 2A and Table S3) and regarded as deNRGs. Through univariate Cox PH models, four of them were significantly associated with OS, namely, IFNA13, SLC25A5, IFNA21 and IFNA8 (Figure 2B, P<0.1). Three of them had a positive association with OS (HR, 95% CI of IFNA13: 1.48, 0.94–2.32; of IFNA21: 1.51, 0.98–2.32; of IFNA8: 1.46, 0.83–2.59), while SLC25A5 was negatively associated with OS (HR: 0.68, 95% CI: 0.46–1.00). Furthermore, the expression of 3504 lncRNAs differed substantially between patients and controls and were classified as delncRNAs. Through univariate Cox PH models, 422 lncRNAs remained with P<0.1 (Figures 2C, D and Figure S2).

Furthermore, Pearson's correlation analyses were conducted, identifying 604 lncRNAs correlated with OS-related NRGs (Pa<0.05 and |r| >0.3). Of them, 31 lncRNAs were also included in the set of OS-related lncRNAs (Figure S3) and identified as necroptosis-related lncRNAs, which were used for the following analyses.

Necroptosis-related lncRNA signature in IDH-wild-type GBM patients

A nrlncRNA signature was built with a forementioned 31 nrlncRNAs through multivariate Cox PH models; after using LASSO for variable selection, when the first-rank value of log(λ) matched to the least chance of divergence, six lncRNAs with nonzero coefficients remained (Figures 2E, F). Based on this final model, a nrlncRNA signature for OS prediction in GBM patients was established, and each patient was assigned an RS using a linear combination of lncRNA expression weighted by their individual Cox regression coefficients, as shown below: Risk score = 0.0615×PCBP3-OT1 + 0.0367×RP11-131L12.4 + 0.0017 × RP11-419I17.1 + 0.0063 ×AC002116.7 + 5.2425×RP11-29P20.1 + 0.0276×RP11-325L12.7 (Table S4). There was no

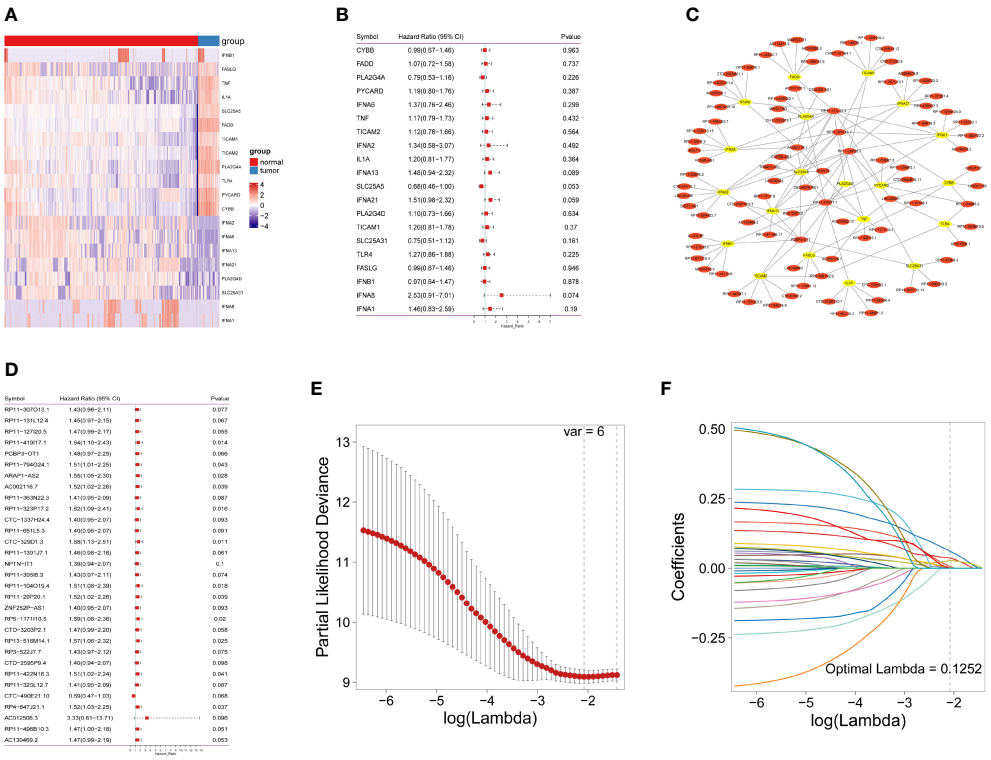

FIGURE 2
Identification of necroptosis-related lncRNAs in IDH-wild-type GBM patients. **(A)** Necroptosis-related gene expression in heatmap. **(B)** The predictive value of 20 necroptosis-related genes is depicted as a forest plot. **(C)** A network of differentially expressed genes and necroptosis-related lncRNAs. **(D)** A forest plot depicting the predictive significance of 31 necroptosis-related lncRNAs. **(E)** The vertical black line in the figure indicates the best logλ value. **(F)** Necroptosis-related lncRNA LASSO coefficient profile; each line represents an individual lncRNA.

significant variation in RS across patients of various ages or sexes (Figure S4). Furthermore, the median RS was used to divide the patients into two categories, and Kaplan-Meier curves were generated, showing a positive relationship between the RS and poor OS, which was consistently observed in the training, testing and the whole datasets (Figures 3A–F). When examining PFS, in either of these three datasets, no meaningful correlation was discovered (Figure S5). Besides that, ROC analysis was used to validate model performance in predicting IDH-wild-type GBM survival rates at 1, 2, and 3 years in entire set (0.709,0.645 and 0.694), training set (0.707,0.680 and 0.787), and validation set (0.716,0.638 and 0.617) (Figures 3G–I).

Construction of a prediction model for survival outcomes in patients with IDH-wild-type GBM

A multivariate Cox PH model was used to build a prediction model including RS, age, and gender, which revealed that RS was an independent predictor in the training, testing, and overall datasets. Patients with a high RS had a worse chance of survival than those with a low RS (Figures 4A–H). Based on the findings of this regression, a nomogram was created (Figure 4J). The nomogram is made up of nine rows, each with its own representation; the first row (points) is the point assignment for each variable. Each variable is allocated a point based on its value for an individual patient by drawing a vertical line between the exact variable value and the points line. Following that, a total point score (row 5) may be derived by adding all of the points awarded to the three variables. Drawing a vertical line between the total points and the final three rows yields the 0.5-, 1.0-, and 1.5-year survival probability. Calibration plots revealed a high degree of agreement between the predicted 0.5-, 1.0-, and 1.5-year OS and the actual OS (Figure 4I).

Biological functions related to necroptosis-related lncRNAs

In terms of the differentially expressed genes dictated by nrlncRNAs between the low- and high-risk groups, GSVA found possible hallmark gene sets with Pa<0.05, and the top ten are shown in Figure 5C and Table S5. Most of these pathways are related to cell survival. Additionally, functional enrichment

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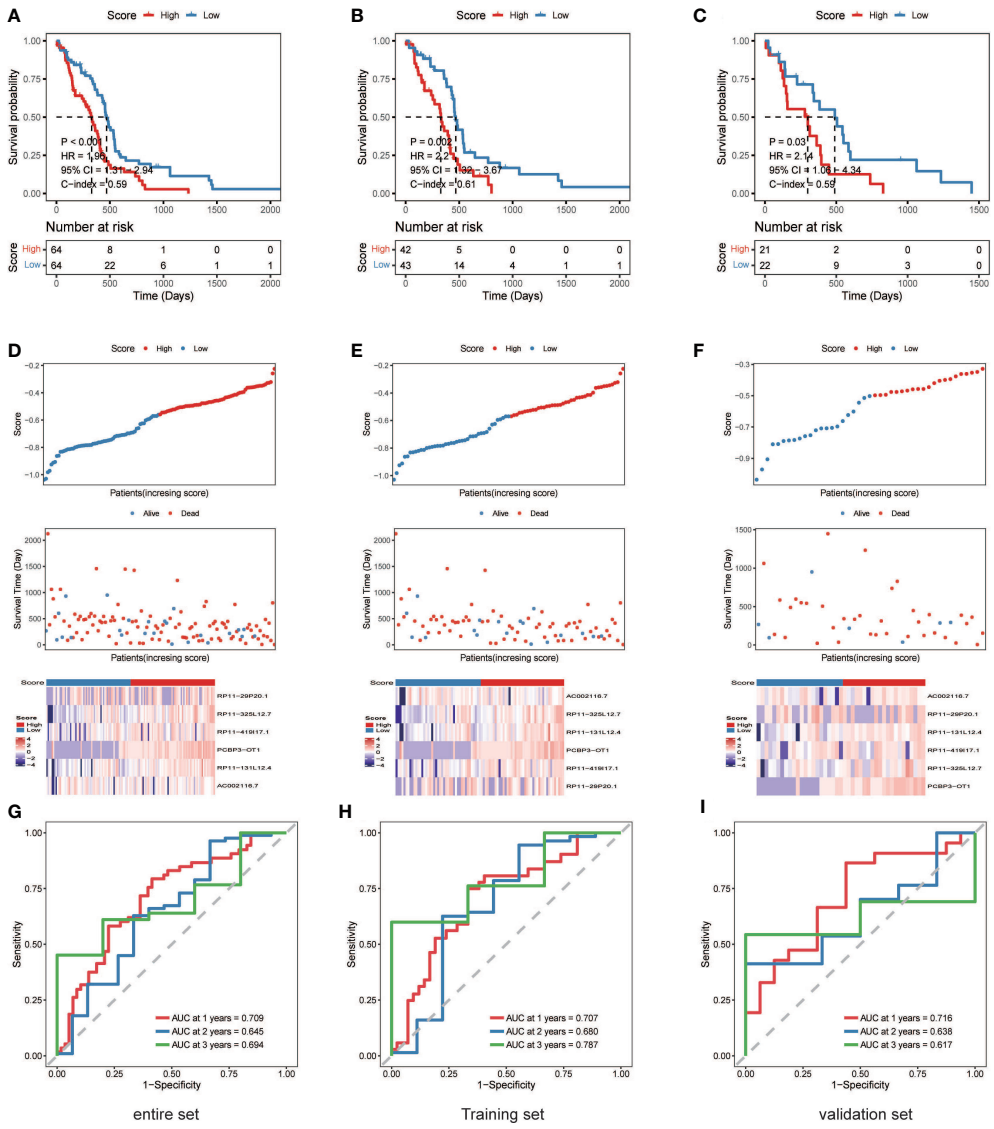

FIGURE 3
The six necroptosis-associated lncRNAs have prognostic significance. **(A)** (entire), **(B)** (training), **(C)** (validation), K-M survival curves of OS; **(D)** (entire), **(E)** (training), **(F)** (validation), Exhibition of the necroptosis-associated lncRNA model, survival time and survival status and heatmaps of the expression of 6 necroptosis-associated lncRNAs; **(G)** (entire), **(H)** (training), **(I)** (validation), ROC analysis was used to validate model performance in predicting IDH-wild-type GBM survival rates at 1, 2, and 3 years.

analysis using GO keywords and KEGG pathways confirmed the link with immunity. Five of the top ten BP terms (Pa<0.05) were immunity-relevant, namely, "humoral immune response", "production of molecular mediator of immune response", "immunoglobulin production", "regulation of B-cell activation" and "positive regulation of B-cell activation". Similarly, in KEGG, out of the top ten pathways, the pathways "cytokine –cytokine receptor interaction", "chemokine signaling pathway" and "Toll–like receptor signaling pathway" were involved in immunity (Figures 5A, B and Figure S6). Therefore, an immunity analysis was performed in the following analyses.

Immune infiltration in IDH-wild-type GBM and its association with RS

In terms of particular immune cell type infiltration, patients with a low RS had a higher abundance of most immune cells, such as MDSCs, type 2 T helper cells and activated CD8 T cells. Moreover, the low-RS group was associated with more immune cells, including eosinophils, activated CD4 T cells and CD4 T cells (Figures 5D, E). There was no variation in immunological score between subgroups of individuals with high and low RSs (Figure S7B), and no correlation between the immune score and RS was

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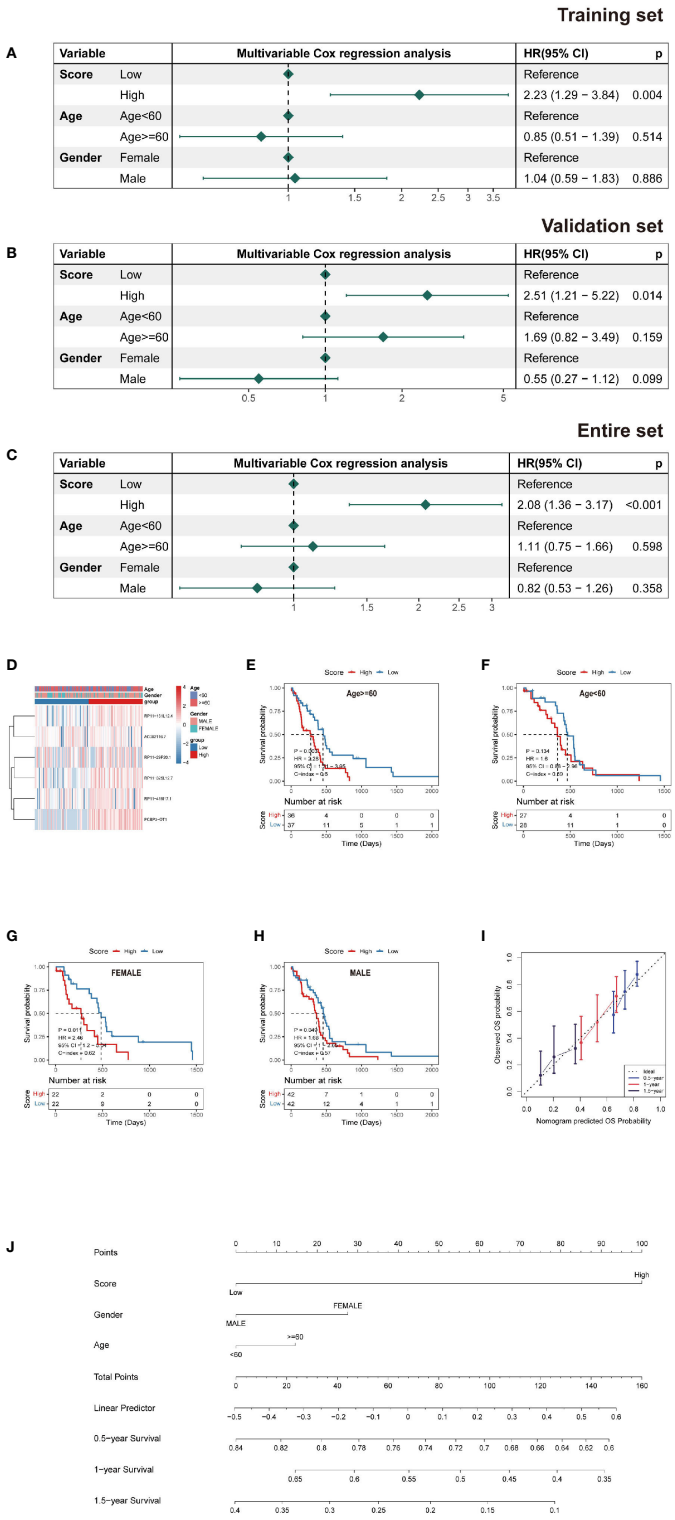

FIGURE 4
Nomogram and risk model evaluation. **(A–C)** Multivariate Cox analyses of clinical factors and risk scores with OS in the **(A)** training set, **(B)** validation set and **(C)** entire set. **(D)** Heatmap show each patient's clinical characteristics and risk score in the whole TCGA dataset. **(E–H)** Survival analysis by subgroup. **(I)** Calibration curves for 0.5-, 1-, and 1.5-year OS. **(J)** Nomogram including tumor stage, risk score and age, to estimate 0.5-, 1-, and 1.5-year OS probabilities.

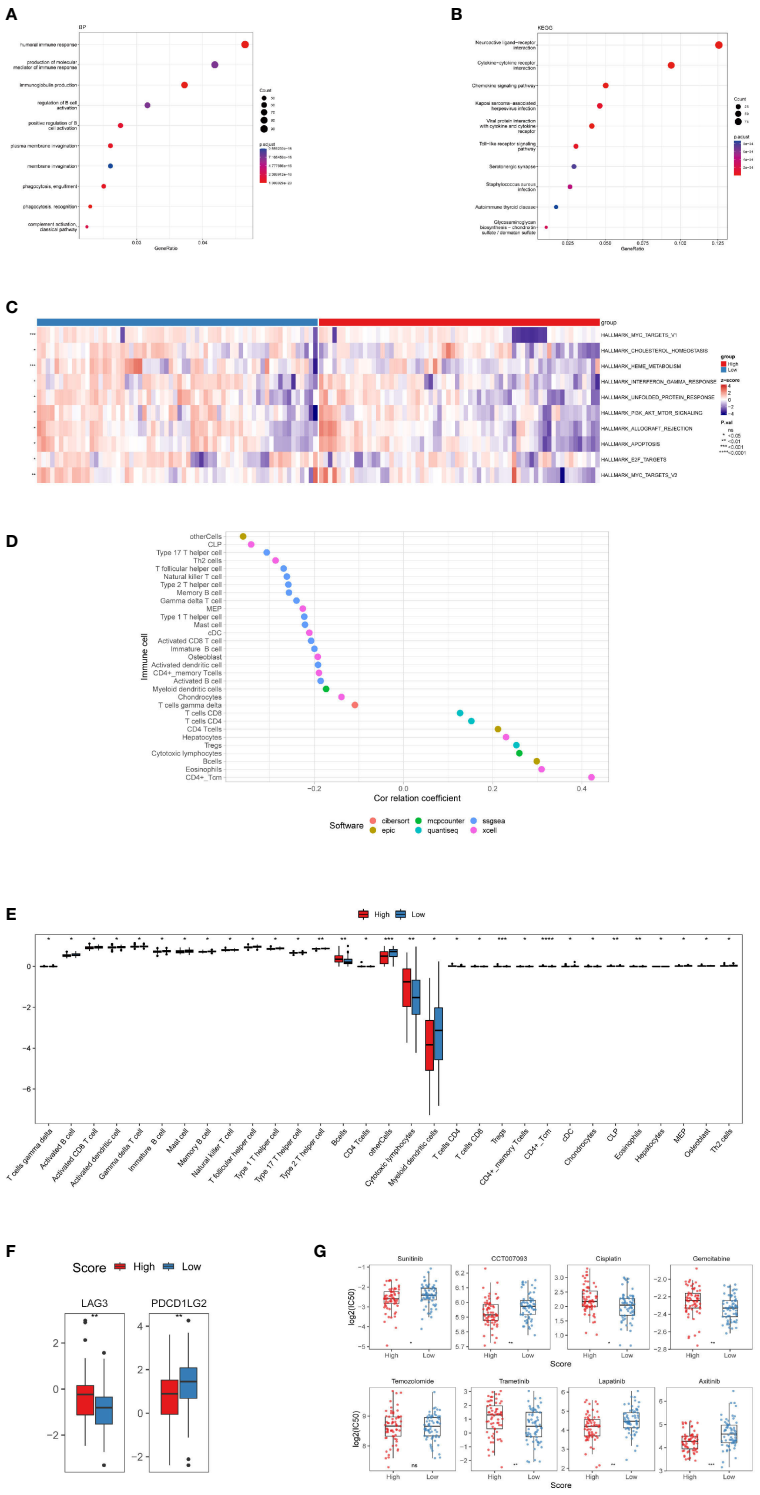

FIGURE 5
Investigation of tumor immune factors and chemotherapy. **(A)** The findings of a BP enrichment analysis of differentially expressed genes in high-risk and low-risk groups. **(B)** KEGG enrichment analysis using a bubble graph. **(C)** Gene set variation analysis (GSVA) between the high- and low-risk subgroups. **(D)** Correlation of immune cells. **(E)** A box plot depicting the differing proportions of tumor-infiltrating cells between the high-risk and low-risk groups. **(F)** LAG3 and PDCDILG2 expression levels in the high-risk and low-risk groups. **(G)** As high-risk scores were associated to the half-maximal inhibitory concentration (IC50) of chemotherapeutics, the prognostic signature was employed as an indication for chemosensitivity. (*, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001; ns, p>0.05).

observed (Figure S7A). In terms of immune checkpoint activation, two of them (PDCD1LG2 and LAG3) performed better in the low-risk and high-risk groups, respectively (Figure 5F).

Clinical treatment investigation in patients with IDH-wild-type GBM

There were significant variations in IC50 values between the high- and low-risk groups for seven medications. Four of them had lower IC50 values in the high-risk group, namely, sunitinib, CCT007093, lapatinib and axitinib, while cisplatin, gemcitabine and trametinib showed higher IC50 values in the high-risk group. However, there were no variations in temozolomide levels between the two groups (Figure 5G).

Knockdown of lncRNA-RP11-131L12.4 attenuates IDH-wild-type GBM cell proliferation and promotes necroptosis

To confirm our signature, we used PCR to verify the content of lncRNAs in clinical IDH-wild-type GBM tumor tissues and corresponding peritumor tissues. The expressions of lncRNA-RP11-131L12.4 and lncRNA-RP11-325L12.7 were found to be higher in tumor specimens. The statistical difference of lncRNA-RP11-131L12.4 expressions between tumor and peritumor tissues was greater (Figure 6). Therefore, we chose lncRNA-RP11-131L12.4 to confirm our signature. First, according to the Kaplan–Meier analysis results, increased lncRNA-RP11-131L12.4 levels predicted poor OS in GBM (Figure 7A and Table S6). In primary GBM cells, si-lncRNA-RP11-131L12.4 transfection significantly reduced lncRNA-RP11-131L12.4 expression (Figure 7B and Figure S8). The CCK-8 and colony formation tests revealed that si-lncRNA-RP11-131L12.4-transfected primary GBM cells had considerably lower colony formation than the negative control (Figures 7C, D). The wound-healing and transwell assays showed that silencing lncRNA-RP11-131L12.4 significantly suppressed the migration and invasion of primary IDH-wild-type GBM cells (Figures 7E, F). Western blot analysis illustrated that downregulation of lncRNA-RP11-131L12.4 increased P-RIPK3 and P-MLKL, indicating the potential role of lncRNA-RP11-131L12.4 in GBM cell necroptosis (Figure 7G). To further confirm the function, western blot analysis showed lower expression of P-RIPK3 and P-MLKL and higher expression of PCNA in GBM tissues with higher lncRNA-RP11-131L12.4 expressions (Figure 8A). Immunohistochemical staining showed that

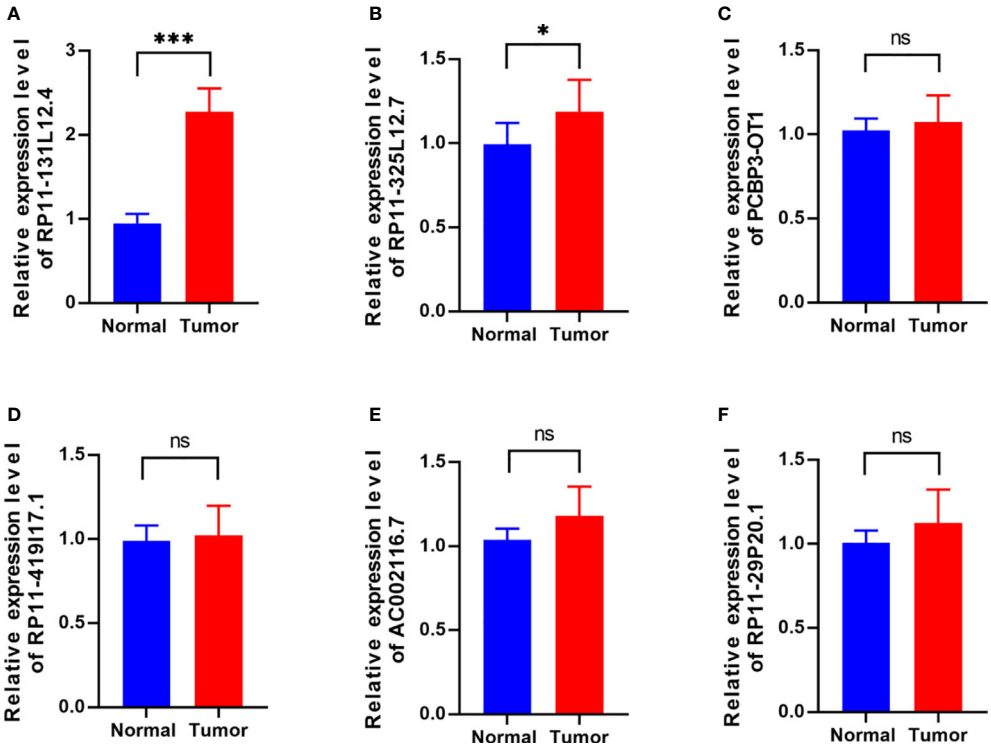

FIGURE 6
Differential expressions of six-necroptosis-associated lncRNA signature between IDH-wild-type GBM tissues and corresponding peritumor samples. **(A)** RP11-131L12.4, **(B)** RP11-325L12.7, **(C)** PCBP3-OT1, **(D)** RP11-419117.1, **(E)** AC002116.7, **(F)** RP11-29P20.1. (*, p<0.05; ***, p<0.001; ns, p>0.05).

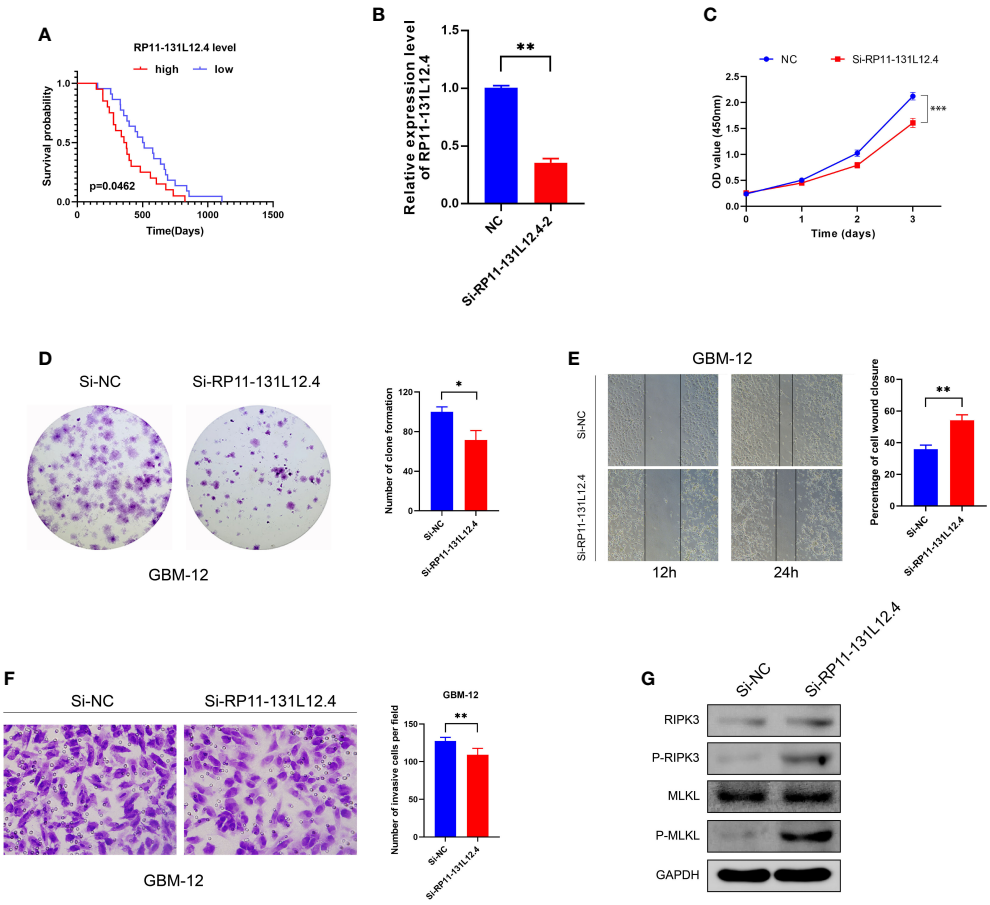

FIGURE 7
Effects of RP11-13 IL 12.4 inhibition on IDH-wild-type GBM cell proliferation, migration, invasion, and necroptosis. **(A)** Kaplan-Meier survival study for IDH-wild-type GBM patients with varying amounts of RP11-131L12.4 expressions. **(B)** RP11-131L12.4 was downregulated in IDH-wild-type GBM primary cells using siRNAs. **(C-F)** CCK-8, colony formation, wound-healing, and Transwell assays were used to assess the proliferation, migration, and invasion of IDH-wild-type GBM cells treated with siRNA targeting RP11-131L12.4. **(G)** RIPK3, P-RIPK3, MLKL, and P-MLKL were examined by Western blotting. (*, p<0.05; **, p<0.01; ***, p<0.001).

lncRNA-RP11-131L12.4-overexpressing GBM tissues showed higher Ki-67 expression and lower P-MLKL expression, suggesting higher proliferation but less necroptosis (Figure 8B).

Discussion

Many studies have found associations between PCD-related genes and lncRNAs and GBM prognosis, which can assist predict clinical prognosis (23). Necroptosis is a kind of ACD that is involved in tumor development and suppression and may be a novel therapeutic target for GBM patients (24). According to previous studies, IDH-wild-type GBM cells are more likely to undergo necroptosis, and the degree of necroptosis is often associated with the prognosis of GBM (7). However, there is a lack of necroptosis-associated characteristics associated with tumor prognosis. Herein, the aim of this study was to identify a unique nrlncRNA signature that might be used to predict the prognosis and immune microenvironment of IDH-wild-type GBM.

We initially identified 17 NRGs using gene expression differential analysis and Cox regression to build a predictive model. Among them, IFNA13, SLC25A5, IFNA21 and IFNA8 were significantly correlated with prognosis. In fact, IFNA gene deletion has been detected in a range of cancers, and this loss is positively connected with tumor malignancy (25, 26). At the same time, the impact of tumor immunotherapy and radiotherapy is linked to the expression of IFNA genes (27, 28). SLC25A5 inhibited the MAPK signaling pathway in colon cancer, reducing cell proliferation and increasing the expression of programmed cell death-related markers (29). In our study, INFA gene expression were reduced in IDH-wild-type GBM, but SLC25A5 gene expression was enhanced. Based on differential genes, our findings revealed that 31 nrlncRNAs impacted the

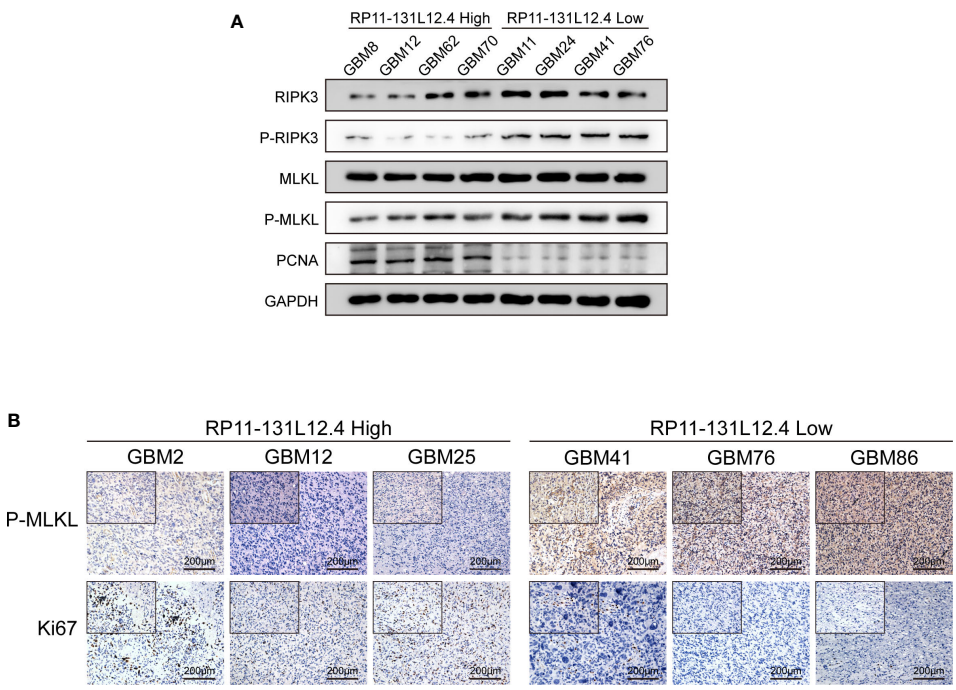

FIGURE 8
LncRNA-RP11-131L12.4 increases tumor proliferation and decreases necroptosis upon IDH-wild-type GBM tissues. **(A)** RIPK3, P-RIPK3, MLKL, P-MLKL and PCNA were examined by Western blotting in different groups. **(B)** IHC detection was used to evaluate the expression of Ki67 and P-MLKL in different groups.

survival of IDH-wild-type GBM patients, and 6 of them (RP11-131L12.4, RP11-419117.1, PCBP3-OT1, AC002116.7, RP11-29P20.1, and RP11-325L12.7) were chosen to create the prognostic signature. The six-nrlncRNA signature was found to be an independent predictive predictor in patients with IDH-wild-type GBM. The nrlncRNA signature was then used to build a prediction model.

According to our study, based on prognostic features, the 1-year, 2-year, and 3-year AUC values of the RS were 0.709, 0.645 and 0.694, respectively, which suggested that the evaluation of patient prognosis based on the RS has strong efficacy. Based on Cox regression analysis, the RS was regarded an independent risk predictor and was adversely linked with the OS of IDH-wild-type GBM patients. Moreover, we developed a nomogram to predict OS using three independent parameters (risk score, age, and gender), and the same pattern was observed in calibration plots of OS at 0.5, 1.0, and 1.5 years. These findings suggest that the risk model has a good level of stability and validity for predicting the prognosis of IDH-wild-type GBM patients.

Furthermore, employing these differentially expressed necroptosis-associated lncRNAs, GO and KEGG analyses indicated that they were predominantly engaged in the MYC signaling route, PI3K-AkT-mTOR signaling circuit, E2F target signaling pathway, immune-related biological processes, and so on. The MYC gene is one of the most studied nucleoprotein oncogenes, and previous research has discovered that MYCs regulate a wide range of genes involved in cell cycle control, metabolism, and apoptosis regulation (30). Moreover, the PI3K/Akt/mTOR signaling pathway has long been recognized to increase glioma invasiveness, angiogenesis, and migration (31–33). Phosphorylation of Akt plays an important role and is regulated by molecules such as PTEN and RTK (34, 35). IDH1 influences GBM migration by regulating the PI3K/AKT/mTOR signaling pathway (33). E2F transcription factors are members of a family that play critical roles in controlling cell cycle equilibrium *via* a transcriptional axis (36). Among them, E2F1 overexpression in patient tissues is likewise associated with a poor prognosis (37, 38).

Based on the findings of functional enrichment analysis, we conducted immune analysis to determine the link between necroptosis and the immune microenvironment in IDH-wild-type GBM. According to the immune factor analysis, the low-risk group had higher immune cell infiltration, including CD8+ T cells, MDSCs, type 2 T helper cells, and other tumor-killing immune cells, whereas the high-risk group had an immunosuppressive TME. CD8+ T cells can destroy GBM cells, and greater CD8+ T cell infiltration enhances survival (39). Through the PD-1/PD-L1 immunosuppression axis, CD8+ T cells can break immunosuppression tolerance and improve immunotherapy (40). Th2 cells do not directly cause cytotoxicity, but they do facilitate it. Their effectors function

by producing cytokines, such as IL-13,IL-4 and IL-5, that activate other immune cells (41–43). There were changes in the expression of immunological checkpoints between the two groups in addition to the degree of immune infiltration. Because the low-risk group had increased PDCD1LG2 activity, these individuals may react favorably to immunotherapy. Studies have shown that TIL deficiency and immune checkpoint expression deficiency are causes of tumor insensitivity to ICIs (44). The inflammatory response caused by necroptosis can change the TME and heighten the tumor response to ICIs (45).

Moreover, we studied the sensitivity of chemotherapeutic agents in different subgroups with the IC50 value. Cisplatin, gemcitabine, trametinib, and axitinib sensitivity was stronger in high-risk patients. Low-risk individuals were more sensitive to sunitinib, lapatinib, and CCT007093. However, temozolomide showed no significant difference. The drug sensitivity analysis results showed that the risk model and tumor subtypes may be used to guide treatment for IDH-wild-type GBM patients.

In addition, experiments were conducted to evaluate the functional phenotypic significance of lncRNA-RP11-131L12.4. The expression levels of six nrlncRNAs were compared between clinical IDH-wild-type GBM tumor and corresponding peritumor tissues, and we discovered that lncRNA-RP11-131L12.4 was substantially expressed in tumors and had a negative correlation with patient prognosis. *In vitro* analysis showed that inhibition of lncRNA-RP11-131L12.4 blocked proliferation, migration and invasion, and activated necroptosis in IDH-wild-type GBM primary cells by triggering P-RIPK3 and P-MKML. Moreover, immunohistochemical staining and western blotting also found that IDH-wild-type GBM tissues with high lncRNA-RP11-131L12.4 expression had stronger proliferation ability and less necroptosis. These results indicate that lncRNA-RP11-131L12.4 might be a potential necroptosis-related lncRNA in IDH-wild-type GBM.

In fact, the use of bioinformatics to find biomarkers to predict the prognosis of patients by different characteristics of tumors is very common in many types of tumors (46–48). However, due to the many influencing factors involved, it is often difficult to summarize the results with deterministic significance. Through our research methods and basic strategies, it is hoped that biomarkers based on other phenotypes can be mined. Meanwhile, the diagnosis and treatment of GBM patients in rural hospitals have encountered unique challenges due to the challenge of detection technology (49, 50). According to our results, if future studies identify the mechanism between biomarker and disease, the development of kits with easier results will be of great benefit to the treatment of GBM in rural hospitals.

Conclusion

Our findings constructed a prognostic prediction model for necroptosis-associated lncRNAs in IDH-wild-type GBM. Moreover, the necroptosis-associated RS corresponds with the status of the TME and the expression of TILs and immunological checkpoint markers, according to our findings. Targeting necroptosis-associated lncRNAs may be another promising approach for the immunotherapy of IDH-wild-type GBM. Therefore, the mechanisms and relationships among necroptosis, lncRNAs, immunity, and IDH-wild-type GBM are worthy of further study and verification.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

CS and LZ contributed to this research equally Conceptualization and study were assisted by YL, CS and SX. CS, LS, JG and SX contributed to the methodology, data analysis, visualization, and original draft writing. CS, LZ, SX, TW and CL all helped with writing and editing. LC and YL helped with financing procurement and project management. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Glossary

ACD	(active cell death)
AUC	(areas under the ROC curve)
BP	(biological process)
CC	(cellular component)
CCK8	(Cell Counting Kit-8)
CNS	(central nervous system)
delncRNA	(differentially expressed lncRNA)
deNRG	(differentially expressed NRG)
FC	(fold change)
GBM	(glioblastoma)
GO	(Gene Ontology)
GSVA	(gene set variation analysis)
GTEx	(Genotype-Tissue Expression)
HCC	(hepatocellular carcinoma)
ICIs	(immune checkpoint inhibitors)
IC50	(half-maximal inhibitory concentration)
KEGG	(Kyoto Encyclopedia of Genes and Genomes)
LASSO	(least absolute shrinkage and selection operator)
lncRNA	(long noncoding RNA)
MF	(molecular function)
MLKL	(mixed lineage kinase domain-like)
NRGs	(necroptosis-related genes)
nrlncRNA	(necroptosis-related lncRNA)
OS	(overall survival)
PCD	(programmed cell death)
PFS	(progression-free survival)
PH	(proportional hazard)
PTEN	(phosphatase and tensin homolog deleted on chromosome ten)
P-MLKL	(phosphorylated mixed lineage kinase domain-like)
P-RIPK3	(phosphorylated receptor interacting protein kinase 3)
qRT-PCR	(quantitative reverse transcription polymerase chain reaction)
RIPK1	(receptor interacting protein kinase 1)
RIPK3	(receptor interacting protein kinase 3)
ROC	(receiver operating characteristic)
RS	(risk score)
TCGA	(The Cancer Genome Atlas)
TME	(tumor microenvironment).

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Clinical prognostic factors for central neurocytoma and subgroup analysis of different treatment measures: A SEER database-based retrospective analysis from 2003 to 2019

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Purpose: The study aimed to identify clinical prognostic factors affecting overall survival (OS) in patients with central neurocytoma (CN) and to determine independent prognostic factors in the subgroups of different treatment modalities using a retrospective analysis based on the SEER database from 2003 to 2019.

Materials and methods: Data regarding patients with CN, including basic clinical characteristics, treatment measures, and prognosis follow-up, were extracted from the SEER database. The prognostic variables for all patients were assessed using log-rank test as well as univariate and multivariate analyses based on the Cox proportional hazards model. The same statistical methods were used for analysis in different subgroups of gross total resection (GTR), subtotal resection (STR), no surgery, radiotherapy (RT), and no RT.

Results: In total, 413 patients were enrolled in this study. Tumor size, primary site surgery, and RT were independent prognostic factors in all patients with CN. In subgroup analyses, RT was not an independent prognostic factor in patients with GTR. However, sex and race were independent prognostic factors in patients with STR. Additionally, tumor size was an independent prognostic factor in patients who did not undergo surgery. Furthermore, sex and primary site were independent prognostic factors in patients who received RT. Size and primary site surgery were independent prognostic factors in patients without RT.

Conclusion: In our study, patients with small tumors or GTR or those who did not receive RT showed a better prognosis. GTR was the preferred treatment for CN. RT was not recommended for patients after GTR. Men and African

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American showed certain advantages after STR surgery. Tumors with a size of >4 cm were recommended for active treatment. In the RT subgroup, patients with tumors outside the ventricle or women had a poorer prognosis than those with tumors within the ventricle or men, respectively. These findings will help clinicians and patients understand the treatment and prognosis of CN visually and intuitively.

KEYWORDS

central neurocytoma, SEER, prognosis, subgroup analysis, clinical application

1 Introduction

Central neurocytoma (CN) is a rare neoplasm of the central nervous system classified as a grade II tumor by the World Health Organization (WHO) (1). It typically affects people in their 30s, which is the most common age group for the onset of cancer. CN is usually found in the ventricle system (2), and few cases have been reported in previous case reports or literature reviews. However, prognostic factors for CN remain controversial. Currently, there are limited large-scale retrospective clinical prognostic studies on CN as well as subgroup analyses of various treatment modalities.

This study aimed to identify clinical prognostic factors influencing overall survival (OS) in patients with CN and to determine independent prognostic factors in different subgroups of gross total resection (GTR), subtotal resection (STR), no surgery, radiotherapy (RT), and no RT.

2 Materials and methods

2.1 Data collection

Data regarding patients with CN, including basic clinical characteristics, social factors, tumor characteristics, treatment measures, and prognosis follow-up, were extracted from the SEER Research Plus Data (17 Registries, Nov 2021) from 2000 to 2019 using SEER*Stat software (version 8.4.0).

The inclusion criteria were as follows: (1) patients with ICD-O-3 histologic codes of 9506/0 (CN, benign), 9506/1 (CN), or 9506/3 (CN, malignant); (2) those with clear vital status and OS; and (3) those with no significant data gaps.

The exclusion criteria were as follows: (1) patients with no specific OS or OS of <1 month; (2) those with tumor locations involving other primary sites, such as the spinal cord (C72.0); or (3) those with significant data gaps or unknown mode of treatment.

The following patient data were retrieved: age, sex, race, year of diagnosis, reporting source, primary site (location), tumor size, pathology, laterality, primary site surgery (therapy), RT, chemotherapy, vital status, and OS. GTR was defined as gross total resection of the tumor under the naked eyes or the absence of residual tumor in early postoperative imaging examination, and STR was defined as subtotal total resection of the tumor or less than 10% residual tumor under the naked eyes. RT was defined as the application of radiation to destroy or treat the primary or metastases of local tumors. In this paper, RT included simple RT, preoperative RT, intraoperative RT or postoperative RT without specific dose. The methods for obtaining data from the SEER database are described in Figure 1.

2.2 Endpoints

As the primary endpoint, OS was defined as the time from diagnosis to death or the last investigation.

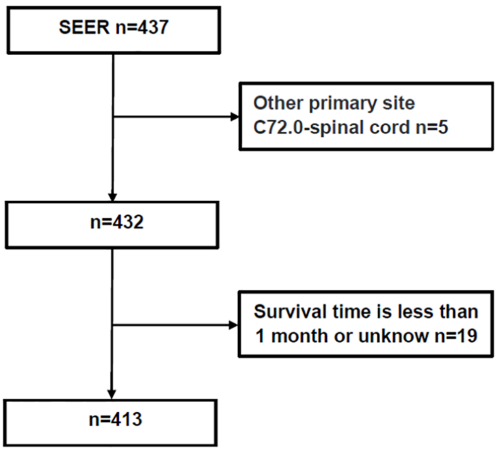

FIGURE 1
The method of obtaining data from the SEER database.

2.3 Statistical analysis

In all patients with CN, the prognostic factors were graphically assessed using log-rank test and Kaplan–Meier curves. The independent prognostic variables were identified using univariate and multivariate analyses based on the Cox proportional hazards model. Log-rank test as well as univariate and multivariate analyses were used to identify prognostic factors in different subgroups of GTR, STR, no surgery, RT, and no RT.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS 26.0) and R software (R 4.1.2). Factors with *P*-values of <0.10 in the univariate analysis were included in the multivariate analysis. A two-tailed *P*-value of <0.05 was considered to indicate statistical significance.

3 Results

3.1 Total data analysis

In total, 413 patients were included in this study (Figure 1), 203 male (49.2%) and 210 (50.8%) female. Median OS for all patients was 76 (interquartile range [IQR]: 38–128) months, 45 died (10.9%), and 368 (89.1%) survived (Table 1). As shown in Figure 2, the survival curves of tumor size (P = 0.0056; Figure 2A), primary site surgery (P = 0.024; Figure 2B), and RT (P = 0.0085; Figure 2C) were compared using log-rank test. As shown in Table 1, univariate analysis revealed that primary site (hazard ratio [HR]: 1.928, 95% confidence interval [CI]: 1.062–3.502, P = 0.031), tumor size (HR: 2.829, 95% CI: 0.971–8.245, P = 0.057), primary site surgery (HR: 0.384, 95% CI: 0.164–0.900, P = 0.028), RT (HR: 2.316, 95% CI: 1.215–4.416, P = 0.011), and chemotherapy (HR: 4.499, 95% CI: 1.388–14.583, P = 0.012) were statistically significant among the patients.

As shown in Table 1, multivariate analysis revealed that tumor size (HR: 3.552, 95% CI: 1.134–11.128, P = 0.030), primary site surgery (HR: 0.298, 95% CI: 0.122–0.728, P = 0.008), and RT (HR: 2.117, 95% CI: 1.050–4.269, P = 0.036) were independent prognostic factors in all patients with CN.

In our study, tumor size, primary site surgery, and RT were significant prognostic factors for CN. Patients with small tumors or GTR or those who did not receive RT showed a better prognosis.

3.2 Subgroup analysis

Overall, 172 patients with GTR were enrolled in subgroup analysis, 82 male (47.7%) and 90 female (52.3%). The median OS for patients with GTR was 81 (IQR: 40–128) months, 13 died (7.6%), and 159 (92.4%) survived (Table 2). As shown in Figure 3, the survival curves of RT (P = 0.15; Figure 3A) were compared using log-rank test. As shown in Table 2, univariate analysis revealed that neither RT (HR: 2.512, 95% CI: 0.689–9.165, P = 0.163) nor chemotherapy (HR: 0.046, 95% CI: 0–648364.957, P = 0.714) was statistically significant among the patients. A subgroup analysis revealed that RT did not significantly improve the prognosis of patients with GTR.

In total, 76 patients with STR were enrolled in subgroup analysis, 36 male (47.4%) and 40 female (52.6%). The median OS for patients with STR was 61.5 (IQR: 33.25–80) months, 8 died (10.5%), and 68 (89.5%) survived (Table 3). As shown in Figure 3, the survival curves of sex (P = 0.048; Figure 3B) and race (P = 0.051; Figure 3C) were compared using log-rank test. As presented in Table 3, univariate analysis revealed that sex (HR: 6.383, 95% CI: 0.780–52.215, P = 0.084), race (HR: 4.212, 95% CI: 0.991–17.904, P = 0.051), primary site (HR: 3.599, 95% CI: 0.801–16.167, P = 0.095), and chemotherapy (HR: 8.841, 95% CI: 0.981–79.670, P = 0.052) were statistically significant among the patients. As shown in Table 3, multivariate analysis revealed that sex (HR: 20.344, 95% CI: 1.589–260.418, P = 0.021) and race (HR: 13.637, 95% CI: 2.140–86.914, P = 0.006) were independent prognostic factors in patients with STR. In the STR subgroup, men and African American showed a better prognosis than women and other races, respectively.

Furthermore, 57 patients who did not undergo surgery were enrolled in subgroup analysis, 27 male (47.4%) and 30 female (52.6%). The median OS for patients who did not undergo surgery was 46 (IQR: 16.5–108) months, 9 died (15.8%), and 48 (84.2%) survived (Table 4). As shown in Figure 3, the survival curves of tumor sizes (P = 0.024; Figure 3D) were compared using log-rank test. As presented in Table 4, univariate and multivariate analyses revealed that tumor size (HR: 10.604, 95% CI: 1.216–92.460, P = 0.033) was an independent prognostic factor in patients without surgery. Tumors with a size of >4 cm showed a worse prognosis in patients who did not undergo surgery.

Overall, 65 patients who received RT were enrolled in subgroup analysis, 35 male (53.8%) and 30 female (46.2%). The median OS for patients who received RT was 67 (IQR: 30–115) months, 13 died (20.0%), and 52 (80.0%) survived (Table 5). As shown in Figure 4, the survival curves of sex (P = 0.033; Figure 4A) and primary site surgery (P = 0.0098; Figure 4B) were compared using log-rank test. As depicted in Table 5, univariate analysis revealed that sex (HR: 3.711, 95% CI: 1.018–13.535, P = 0.047), primary site (HR: 3.911, 95% CI: 1.278–11.970, P = 0.017), and pathology (HR: 0.141, 95% CI: 0.017–1.148, P = 0.067) were statistically significant among these patients. As shown in Table 5, multivariate analysis revealed that sex (HR: 5.330, 95% CI: 1.165–24.385, P = 0.031) and primary site (HR: 3.472, 95% CI: 1.098–10.983, P = 0.034) were independent prognostic factors in patients who received RT. In the RT subgroup, patients with tumors outside the ventricle or women had a poorer prognosis than those with tumors within the ventricle or men, respectively.

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TABLE 1 Details of patients with central neurocytoma.

Characteristics		Univariate analysis			Multivariate analysis		
Total	Value N=413	HR	95%CI	*P*-value	HR	95%CI	*P*-value
Age							
0-19	61(14.8%)	Reference					
20-39	226(54.7%)	12795.377	NA	0.866			
40~59	91(22.0%)	32922.761	NA	0.853			
60~	35(8.5%)	138303.359	NA	0.833			
Sex							
Male	203(49.2%)	Reference					
Female	210(50.8%)	1.311	0.725-2.372	0.370			
Race							
White	311(75.3%)	Reference					
African American	44(10.7%)	0.565	0.175-1.832	0.342			
Others/Unknown	58(14.0%)	0.657	0.234-1.840	0.424			
Year of diagnosis							
03-11	218(52.8%)	Reference					
12-19	195(47.2%)	0.641	0.316-1.300	0.218			
Reporting Source							
Hospital inpatient/outpatient or clinic	407(98.5%)	Reference					
Other	6(1.5%)	0.049	0-60514.353	0.673			
Primary Site							
Ventricle, NOS	308(74.6%)	Reference			Reference		
Other	105(25.4%)	1.928	1.062-3.502	0.031	1.401	0.715-2.748	0.326
Tumor Size(cm)							
≤2	50(12.1%)	Reference			Reference		
2~4	122(29.5%)	0.717	0.202-2.544	0.607	1.011	0.274-3.728	0.987
4~	142(34.4%)	1.444	0.475-4.390	0.517	1.881	0.577-6.130	0.294
Unknown/blank	99(24.0%)	2.829	0.971-8.245	0.057	3.552	1.134-11.128	0.030
Pathology							
Benign	5(1.2%)	Reference					
Central neurocytoma	408(98.8%)	0.448	0.062-3.261	0.428			
Laterality							
Left-origin of primary	99(24.0%)	Reference					
Right-origin of primary	93(22.5%)	0.488	0.185-1.284	0.146			
Not a paired site	216(52.3%)	0.741	0.379-1.447	0.380			
Paired or Bilateral	5(1.2%)	0	NA	0.970			
Primary Site Surgery							

(Continued)

TABLE 1 Continued

Characteristics		Univariate analysis			Multivariate analysis		
Total	Value N=413	HR	95%CI	*P*-value	HR	95%CI	*P*-value
No surgery	57(13.8%)	Reference			Reference		
excisional biopsy	63(15.3%)	0.615	0.237-1.598	0.318	0.434	0.158-1.118	0.104
Surgery NOS	45(10.9%)	0.618	0.229-1.669	0.342	0.414	0.147-1.161	0.094
STR	76(18.4%)	0.651	0.250-1.693	0.379	0.471	0.169-1.310	0.149
GTR	172(41.6%)	0.384	0.164-0.900	0.028	0.298	0.122-0.728	0.008
Radiation							
None/Unknown	348(84.3%)	Reference			Reference		
Yes	65(15.7%)	2.316	1.215-4.416	0.011	2.117	1.050-4.269	0.036
Chemotherapy							
None/Unknown	407(98.5%)	Reference			Reference		
Yes	6(1.5%)	4.499	1.388-14.583	0.012	2.223	0.612-8.706	0.225
Vital Status							
Alive	368(89.1%)						
Dead	45(10.9%)						
OS (M)	76 (38–128)						

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; STR, subtotal resection; OS, overall survival; NA, not available.

In total, 348 patients who did not receive RT were enrolled in subgroup analysis, 168 male (48.3%) and 180 female (51.7%). The median OS for patients who did not receive RT was 79 (IQR: 38.25–132) months, 32 died (9.2%), and 316 (90.8%) survived (Table 6). As shown in Figure 4, the survival curves of tumor size ($P = 0.0048$; Figure 4C) and primary site surgery ($P = 0.014$; Figure 4D) were compared using log-rank test. As presented in Table 6, univariate analysis revealed that tumor size (HR: 2.922, 95% CI: 0.856–9.975, $P = 0.087$), laterality (HR: 0.999, 95% CI: 0.089–1.171, $P = 0.085$), and primary site surgery (HR: 0.329, 95% CI: 0.130–0.836, $P = 0.019$) were statistically significant among these patients. As shown in Table 6, multivariate analysis revealed that tumor size (HR: 3.918, 95% CI: 1.116–14.261, $P = 0.034$) and primary site surgery (HR: 0.275, 95% CI: 0.104–0.727, $P = 0.009$) were independent prognostic factors in patients without RT. In the no RT subgroup, patients with GTR showed a better prognosis.

4 Discussion

In 1982, Hassoun et al. identified two cases of tumors originating in the third ventricle and named them as CN (3). CN is a rare intracranial tumor that accounts for 0.1%–0.5% of all intracranial tumors and is classified as a grade II tumor by the World Health Organization in 2021 (1, 4, 5). CN commonly occurs in the lateral ventricle but is also found in the posterior fossa or other locations (6). Its pathogenesis is associated with various chromosomal aberrations (7). Mohammad et al. revealed that with no characteristic clinical symptoms of CN, a correct diagnosis can be made by radiographic imaging, histopathology assessment, and immunohistochemistry (8). Chang et al. analyzed 781 patients with cancer and revealed a 5-year OS rate of 87.2% (9). Gabriele et al. revealed that CN were consistent with a low-grade neuronal neoplasm of the central nervous system, especially extraventricular neurocytoma (EVN) (10).

To the best of our knowledge, only few studies on CN have been reported to date. Considering the rarity of this disease, we conducted a retrospective analysis of a relatively large sample size of patients with CN using the SEER database, which covered 30% of the US population. This study aimed to identify clinical prognostic factors affecting the OS in patients with CN and to determine independent prognostic factors in the subgroups of different treatment modalities.

4.1 Age, sex, and race

Approximately 25% of CN develops in adults in their 30s (5). The most common age of onset of CN and EVN is 20–34 years (11). In our study, patients ranged in age ranged from 0 to 85 years. Further, in the overall data, >50% of patients diagnosed with CN were aged 20–39 years.

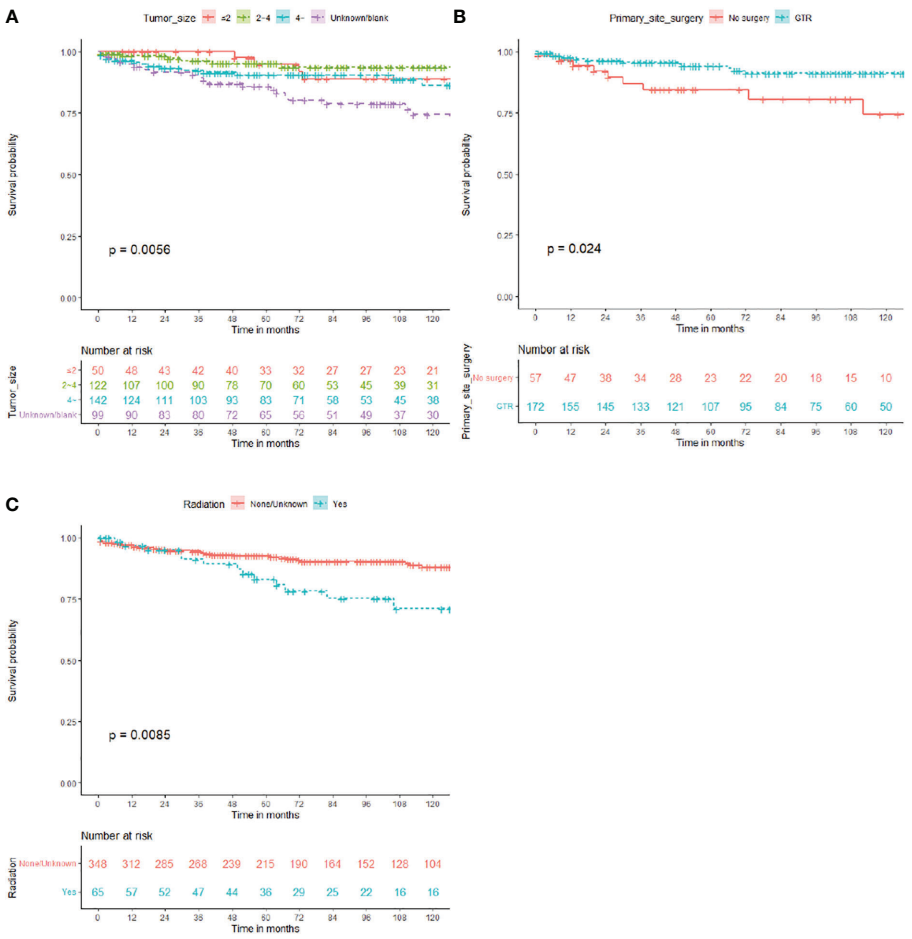

FIGURE 2
Overall survival (OS) in all patients with central neurocytoma. **(A)** OS among the different tumor size groups. **(B)** OS among the different primary site surgery (therapy) groups. **(C)** OS among the different radiation groups. OS, overall survival.

Mattar et al. revealed that age was not a significant prognostic factor in 22 patients diagnosed with atypical CN between January 2009 and March 2018. After reviewing the literature, the previous study concluded that neither age nor sex had a significant effect on the median OS (12–15).

In our univariate and multivariate analyses of 413 patients, age was not a significant prognostic factor. Further, all subgroup analyses revealed that age was not a significant factor affecting prognosis, which is consistent with the results of previous reports. In the subgroup analysis of patients with STR and those who received RT, men showed better outcomes than women. The subgroup analysis of patients with STR revealed that African American had a better prognosis than other races.

4.2 Tumor size

In a retrospective analysis of 868 neurocytomas, Dutta et al. revealed that the median tumor size was 4–5 cm and that tumor size was not a determining factor. Even patients with a tumor size of >4 cm had a 5-year OS rate of 89%. Furthermore, patients with GTR had a 5-year OS rate of 96% (16).

Our study revealed that HR increased with tumor size. In the no surgery and no RT subgroups, patients with a tumor size of >4 cm had a higher HR than those with a tumor size of <2 cm, indicating that tumors with a size of >4 cm had a lower survival rate than smaller tumors. This is also consistent with the general tumor growth pattern. Larger tumors are more likely to invade surrounding brain tissues, nerves, and the vascular system. Further, larger tumors are more difficult to treat surgically and are more likely to have residual tumor tissues and recurrence after surgery.

4.3 Primary site (tumor location)

EVNs can occur in any brain tissue except the ventricle. They are broad-spectrum, more aggressive, and have a worse

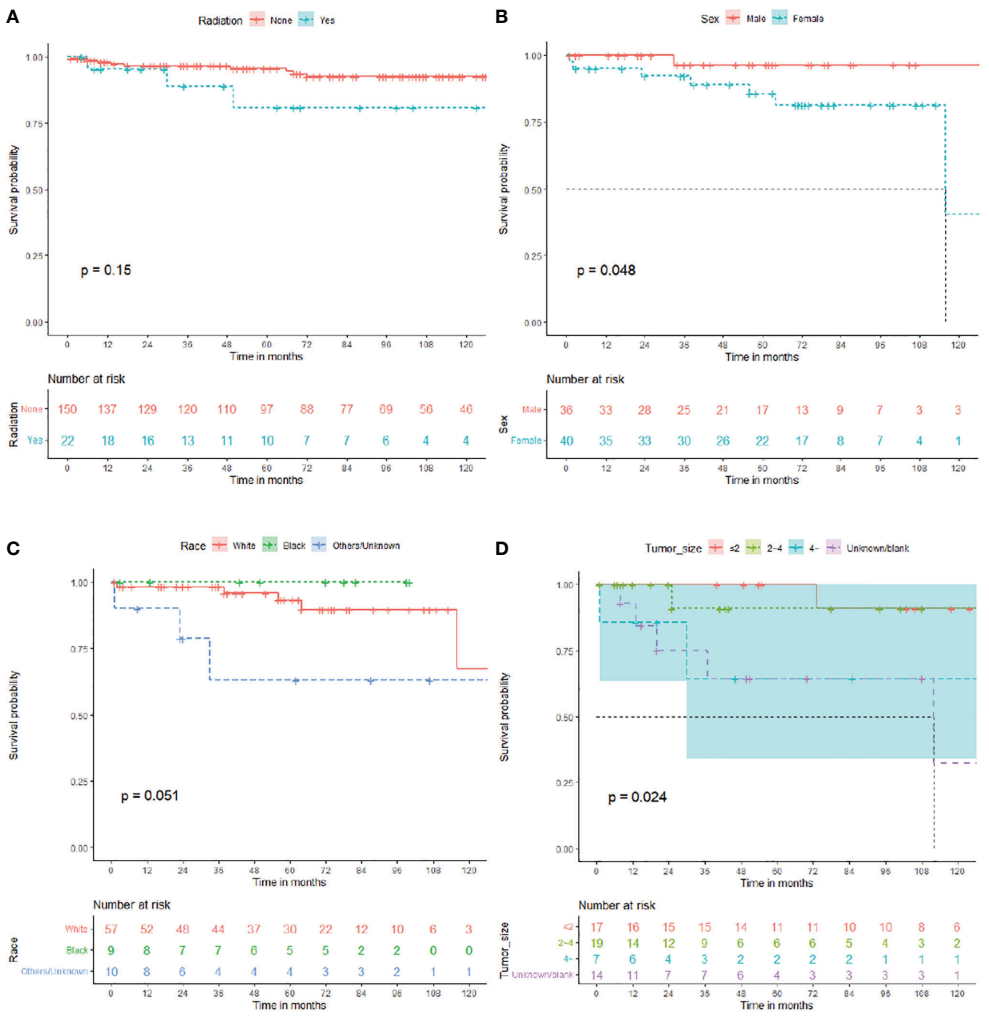

FIGURE 3
Overall survival (OS) for central neurocytoma in the gross total resection (GTR), subtotal resection (STR), and no surgery subgroups. **(A)** OS among the different radiotherapy groups in the GTR subgroup. **(B)** OS among the different sex groups in the STR subgroup. **(C)** OS among the different race groups in the STR subgroup. **(D)** OS among the different tumor size groups in the no surgery subgroup. OS, overall survival.

prognosis (5, 17, 18). Joonho et al. revealed that EVN may be a heterogenous disease entity and needed to be followed up for a long time (19). Shuran et al. revealed that an accurate diagnosis was difficult to be made preoperatively in 11 patients with EVNs. When the imaging findings are atypical, more aggressive treatment should be considered in patients (20). Treatment options and prognosis vary widely between CN and other ventricular tumors (21). According to our RT subgroup analysis, CN located outside the ventricle had a worse prognosis.

4.4 Primary site surgery (therapy)

Currently, surgery is considered the gold standard for treating CN. Han et al. conducted a single-center study involving 67 patients and found that complete tumor resection was the preferred treatment (22). In particular, patients with GTR have a favorable prognosis and a significantly lower risk of CN recurrence. In a study involving 310 patients with CN, the 5-year OS rate of patients with GTR was as high as 99% (5, 23, 24). Mattar et al. conducted a retrospective analysis of 22 cases and concluded that GTR was an independent prognostic factor for OS in patients with CN (12). Liang et al. revealed that surgery can benefit children and ensure relatively long-term progression-free survival in 14 patients with pediatric CN (25). Qiongxuan et al. revealed that use of GTR whenever possible and close imaging follow-up in 101 patients with CN (26).

Alqroom et al. used the transcortical and interhemispheric transcallosal approaches in 18 and 14 patients with CN, respectively, and found no difference in the scope of resection or protection of nerve function between the two surgical approaches (2, 27). Further, according to Sing et al.,

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TABLE 2 The median overall survival (OS) of the gross total resection (GTR) was 81 (interquartile range (IQR): 40–128) months.

Characteristics		Univariate analysis			Multivariate analysis		
GTR	Value N=172	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age							
0-19	27(15.7%)	Reference					
20-39	108(62.8%)	17780.530	NA	0.925			
40~59	32(18.6%)	41813.135	NA	0.918			
60~	5(2.9%)	171830.274	NA	0.908			
Sex							
Male	82(47.7%)	Reference					
Female	90(52.3%)	1.052	0.353-3.135	0.927			
Race							
White	134(77.9%)	Reference					
African American	17(9.9%)	0.034	0-119.940	0.416			
Others/Unknown	21(12.2%)	0.033	0-74.877	0.387			
Year of diagnosis							
03-11	89(51.7%)	Reference					
12-19	83(48.3%)	0.812	0.238-2.775	0.740			
Reporting Source							
Hospital inpatient/outpatient or clinic	172(100.0%)						
Primary Site							
Ventricle, NOS	131(76.2%)	Reference					
Other	41(23.8%)	1.358	0.417-4.422	0.611			
Tumor Size(cm)							
≤2	15(8.7%)	Reference					
2~4	52(30.2%)	0.476	0.079-2.847	0.416			
4~	62(36.0%)	0.426	0.071-2.554	0.350			
Unknown/blank	43(25.0%)	0.839	0.163-4.327	0.834			
Pathology							
Benign	1(0.6%)	Reference					
Central neurocytoma	171(99.4%)	20.297	NA	0.868			
Laterality							
Left-origin of primary	37(21.5%)	Reference			Reference		
Right-origin of primary	44(25.6%)	0.144	0.017-1.235	0.077	0.144	0.017-1.235	0.077
Not a paired site	90(52.3%)	0.464	0.146-1.569	0.192	0.464	0.146-1.569	0.192
Paired or Bilateral	1(0.6%)	0	NA	0.989	0	NA	0.989
Radiation							
None/Unknown	150(87.2%)	Reference					

(Continued)

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TABLE 2 Continued

Characteristics		Univariate analysis			Multivariate analysis		
GTR	Value N=172	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Yes	22(12.8%)	2.512	0.689-9.165	0.163			
Chemotherapy							
None/Unknown	170(98.8%)	Reference					
Yes	2(1.2%)	0.046	0-648364.957	0.714			
Vital Status							
Alive	159(92.4%)						
Dead	13(7.6%)						
OS (M)	81(40-128)						

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; OS, overall survival; NA, not available.
The Cox proportional hazards model was used for univariate and multivariate analyses in the GTR subgroup.

TABLE 3 The median overall survival (OS) of the subtotal resection (STR) was 61.5 (interquartile range (IQR): 33.25–80) months.

Characteristics		Univariate analysis			Multivariate analysis		
STR	Value N=76	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age							
0-19	13(17.1%)	Reference					
20-39	43(56.6%)	29617.474	NA	0.945			
40~59	17(22.4%)	13186.753	NA	0.949			
60~	3(3.9%)	308576.891	NA	0.932			
Sex							
Male	36 (47.4%)	Reference			Reference		
Female	40(52.6%)	6.383	0.780-52.215	0.084	20.344	1.589-260.418	0.021
Race							
White	57(75.0%)	Reference			Reference		
African American	9(11.8%)	0	NA	0.984	0	NA	0.983
Others/Unknown	10(13.2%)	4.212	0.991-17.904	0.051	13.637	2.140-86.914	0.006
Year of diagnosis							
03-11	19(25.0%)	Reference					
12-19	57(75.0%)	0.348	0.076-1.583	0.172			
Reporting Source							
Hospital inpatient/outpatient or clinic	75(98.7%)	Reference					
Other	1(1.3%)	0.049	NA	0.890			
Primary Site							
Ventricle, NOS	61(80.3%)	Reference			Reference		
Other	15(19.7%)	3.599	0.801-16.167	0.095	5.171	0.712-37.552	0.104

(Continued)

TABLE 3 Continued

Characteristics		Univariate analysis			Multivariate analysis		
STR	Value N=76	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Tumor Size(cm)							
≤2	5(6.6%)	Reference					
2~4	21(27.6%)	0	NA	0.962			
4~	40(52.6%)	0.615	0.068-5.520	0.664			
Unknown/blank	10(13.2%)	0.963	0.087-10.632	0.975			
Pathology							
Benign	0(0.0%)	Reference					
Central neurocytoma	76(100.0%)	NA	NA	NA			
Laterality							
Left-origin of primary	22(28.9%)	Reference					
Right-origin of primary	17(22.4%)	1.622	0.225-11.699	0.631			
Not a paired site	36(47.4%)	1.006	0.182-5.575	0.994			
Paired or Bilateral	1(1.3%)	0	NA	0.991			
Radiation							
None/Unknown	56(73.7%)	Reference					
Yes	20(26.3%)	1.571	0.373-6.612	0.538			
Chemotherapy							
None/Unknown	74(97.4%)	Reference			Reference		
Yes	2(2.6%)	8.841	0.981-79.670	0.052	2.251	0.174-29.157	0.535
Vital Status							
Alive	68(89.5%)						
Dead	8(10.5%)						
OS (M)	61.5(33.25-80)						

HR, hazard ratio; CI, confidence interval; STR, subtotal resection; OS, overall survival; NA, not available.
The Cox proportional hazards model was used for univariate and multivariate analyses in the STR subgroup.

intraoperative neuroelectrophysiological monitoring is important for safe lesion resection (28).

According to a systematic review by Mahavadi et al., in cases of a high risk of GTR, maximal safe resection combined with adjunct RT can be used as a suboptimal treatment alternative for cancer (29).

However, in a retrospective analysis of 868 neurocytomas, Dutta et al. revealed that the extent of resection was not an independent prognostic factor for improved survival using multivariate analysis.

In our multivariate regression analysis, GTR (HR: 0.298, 95% CI: 0.122–0.728, P = 0.008; Table 2) was an independent prognostic factor for OS. We found that no surgery, biopsy, surgery, NOS, and STR subgroups were associated with a worse prognosis than the GTR subgroup. In the no RT subgroup, patients with GTR showed a better prognosis. The therapeutic effect of GTR on CN has been fully confirmed in previous studies. GTR should be performed while preserving as many important physiological structures as possible.

4.5 Radiotherapy

Adjunct RT, such as stereotactic radiosurgery (SRS) and fractionated RT, plays an important role in the treatment of CN (5, 30–32).

According to the findings of Han et al., RT is not recommended following complete tumor resection. After the

TABLE 4 The median overall survival (OS) of the no surgery subgroup was 46 (interquartile range (IQR): 16.5–108) months.

Characteristics		Univariate analysis			Multivariate analysis		
No surgery	Value N=57	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age							
0-19	4(7.0%)	Reference					
20-39	21(36.8%)	2167.939	NA	0.947			
40~59	17(29.8%)	7083.787	NA	0.938			
60~	15(26.3%)	31849.596	NA	0.928			
Sex							
Male	27 (47.4%)	Reference					
Female	30(52.6%)	0.761	0.204-2.839	0.685			
Race							
White	38(66.7%)	Reference					
African American	7(12.3%)	0.726	0.090-5.836	0.764			
Others/Unknown	12(21.1%)	0	NA	0.971			
Year of diagnosis							
03-11	26(45.6%)	Reference					
12-19	31(54.4%)	0.207	0.025-1.723	0.145			
Reporting Source							
Hospital inpatient/outpatient or clinic	55(96.5%)	Reference					
Other	2(3.5%)	0.048	NA	0.853			
Primary Site							
Ventricle, NOS	47(82.5%)	Reference					
Other	10(17.5%)	0.161	0.671-10.964	2.713			
Tumor Size(cm)							
≤2	17(29.8%)	Reference			Reference		
2~4	19(33.3%)	1.597	0.099-25.895	0.742	1.597	0.099-25.895	0.742
4~	7(12.3%)	8.076	0.722-90.344	0.090	8.076	0.722-90.344	0.090
Unknown/blank	14(24.6%)	10.604	1.216-92.460	0.033	10.604	1.216-92.460	0.033
Pathology							
Central neurocytoma	57(100.0%)	NA	NA	NA			
Laterality							
Left-origin of primary	12(21.1%)	Reference					
Right-origin of primary	16(28.1%)	0.688	0.043-11.018	0.791			
Not a paired site	28(49.1%)	2.132	0.259-17.511	0.481			
Paired or Bilateral	1(1.8%)	0	NA	0.992			
Radiation							
None/Unknown	50(87.7%)	Reference					

(Continued)

TABLE 4 Continued

Characteristics		Univariate analysis			Multivariate analysis		
No surgery	Value N=57	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Yes	7(12.3%)	0749	0.094-6.004	0.786			
Chemotherapy							
None/Unknown	57(100.0%)						
Vital Status							
Alive	48(84.2%)						
Dead	9(15.8%)						
OS (M)	46(16.50-108)						

HR, hazard ratio; CI, confidence interval; OS, overall survival; NA, not available.
The Cox proportional hazards model was used for univariate and multivariate analyses in the no surgery subgroup.

TABLE 5 The median overall survival (OS) of the radiotherapy subgroup was 67 (interquartile range (IQR): 30–115) months.

Characteristics		Univariate analysis			Multivariate analysis		
Radiotherapy	Value N=65	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age							
0-19	7(10.8%)	Reference					
20-39	31(47.7%)	9815.430	NA	0.945			
40~59	23(35.4%)	27401.271	NA	0.939			
60~	4(6.2%)	126546.079	NA	0.930			
Sex							
Male	35(53.8%)	Reference			Reference		
Female	30(46.2%)	3.711	1.018-13.535	0.047	5.330	1.165-24.385	0.031
Race							
White	51(78.5%)	Reference					
African American	6(9.2%)	0.035	0-1469.791	0.537			
Others/Unknown	8(12.3%)	0.035	0-35.563	0.342			
Year of diagnosis							
03-11	31(47.7%)	Reference					
12-19	34(52.3%)	0.545	0.144-2.057	0.370			
Reporting Source							
Hospital inpatient/outpatient or clinic	64(98.5%)	Reference					
Other	1(1.5%)	0.049	NA	0.880			
Primary Site							
Ventricle, NOS	46(70.8%)	Reference			Reference		
Other	19(29.2%)	3.911	1.278-11.970	0.017	3.472	1.098-10.983	0.034
Tumor Size(cm)							
≤2	9(13.8%)	Reference					

(Continued)

TABLE 5 Continued

Characteristics		Univariate analysis			Multivariate analysis		
Radiotherapy	Value N=65	HR	95% CI	*P*-value	HR	95% CI	*P*-value
2~4	13(20.0%)	1.403	0.127-15.526	0.783			
4~	32(49.2%)	1.746	0.210-14.530	0.606			
Unknown/blank	11(16.9%)	2.774	0.310-24.851	0.362			
Pathology							
Benign	1(1.5%)	Reference			Reference		
Central neurocytoma	64(98.5%)	0.141	0.017-1.148	0.067	0.092	0.008-1.132	0.062
Laterality							
Left-origin of primary	16(24.6%)	Reference					
Right-origin of primary	16(24.6%)	0.999	0.201-4.961	0.999			
Not a paired site	33(50.8%)	0.829	0.212-3.238	0.788			
Primary Site Surgery							
No surgery	7(10.8%)	Reference					
excisional biopsy	6(9.2%)	3.745	0.389-36.061	0.253			
Surgery NOS	10(15.4%)	1.379	0.142-13.372	0.782			
STR	20(30.8%)	1.063	0.110-10.265	0.958			
GTR	22(33.8%)	1.139	0.118-10.971	0.910			
Chemotherapy							
None/Unknown	62(95.4%)	Reference					
Yes	3(4.6%)	3.242	0.717-14.654	0.126			
Vital Status							
Alive	52(80.0%)						
Dead	13(20.0%)						
OS (M)	67(30-115)						

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; STR, subtotal resection; OS, overall survival; NA, not available.
The Cox proportional hazards model was used for univariate and multivariate analyses in the radiation subgroup.

complete excision of the atypical CNs, adjuvant RT was not recommended, and close radiographic follow-up was required (22). In patients with incomplete tumor resections, adjuvant RT should be advocated (27); moreover, postoperative RT can improve OS in these patients.

Nakamura et al. argued that SRS is an effective method for treating recurrent or residual CNs after STR. Meanwhile, Gamma knife surgery plays an essential role in the postoperative treatment of patients with CN (30). There are no specific SRS dosage guidelines for CN treatment. Lee et al. and Matsunaga et al. recommended that a minimum of 13 Gy is required for effective tumor control (5, 33). Bui et al. and Minniti et al. suggested that an RT dose between 13 and 18 Gy is relatively safe (31, 34). They examined 150 cases and found that RT had >90% local tumor control and that radiotoxicity was uncommon (31). In addition, RT is associated with delayed complications and radiation-induced toxicity, including leukoencephalopathy, radiation-induced malignancy, and radiation necrosis (14, 30, 32).

Dutta et al. conducted a retrospective analysis of 868 cases of CN and revealed that RT was not a vital prognostic factor using multivariate analyses (16, 35). Furthermore, Dutta et al. and Hussain et al. reported that adjuvant RT did not significantly improve the OS rate of patients with CN and that the effect of salvage RT was unknown (16, 36). Dan et al. revealed that postoperative RT also did not improve local control and survival in 43 patients with CN (37). By studying 68 patients with CN, Lei She et al. revealed that postoperative RT could improve

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TABLE 6 The median overall survival (OS) of the no radiotherapy subgroup was 79 (interquartile range (IQR): 38.25–132) months.

Characteristics		Univariate analysis			Multivariate analysis		
NO radiotherapy	Value N=348	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age							
0-19	54(15.5%)	Reference					
20-39	195(56.0%)	13812.672	NA	0.882			
40~59	68(19.5%)	30233.086	NA	0.872			
60~	31(8.9%)	135487.128	NA	0.854			
Sex							
Male	168(48.3%)	Reference					
Female	180(51.7%)	0.931	0.465-1.863	0.840			
Race							
White	260(74.7%)	Reference					
African American	38(10.9%)	0.793	0.239-2.630	0.705			
Others/Unknown	50(14.4%)	0.990	0.344-2.848	0.985			
Year of diagnosis							
03-11	187(53.7%)	Reference					
12-19	161(46.3%)	0.650	0.283-1.496	0.311			
Reporting Source							
Hospital inpatient/outpatient or clinic	343(98.6%)	Reference					
Other	5(1.4%)	0.049	0-478154.076	0.713			
Primary Site							
Ventricle, NOS	262(75.3%)	Reference					
Other	86(24.7%)	1.357	0.642-2.866	0.424			
Tumor Size(cm)							
≤2	41(11.8%)	Reference			Reference		
2~4	109(31.3%)	0.596	0.133-2.666	0.498	0.740	0.135-3.301	0.702
4~	110(31.6%)	1.186	0.314-4.476	0.802	1.605	0.338-6.019	0.514
Unknown/blank	88(25.3%)	2.922	0.856-9.975	0.087	3.918	1.116-14.261	0.034
Pathology							
Benign	4(1.1%)	Reference					
Central neurocytoma	344(98.9%)	20.421	NA	0.705			
Laterality							
Left-origin of primary	83(23.9%)	Reference			Reference		
Right-origin of primary	77(22.1%)	0.999	0.089-1.171	0.085	0.300	0.081-1.110	0.071
Not a paired site	183(52.6%)	0.829	0.331-1.543	0.392	0.726	0.328-1.605	0.428
Paired or Bilateral	5(1.4%)	0	0	0.981	0	0	0.982
Primary Site Surgery							

(Continued)

TABLE 6 Continued

Characteristics		Univariate analysis			Multivariate analysis		
NO radiotherapy	Value N=348	HR	95% CI	*P*-value	HR	95% CI	*P*-value
No surgery	50(14.4%)	Reference			Reference		
excisional biopsy	57(16.4%)	0.417	0.136-1.279	0.126	0.307	0.096-0.983	0.047
Surgery NOS	35(10.1%)	0.466	0.139-1.560	0.216	0.376	0.110-1.286	0.119
STR	56(16.1%)	0.560	0.182-1.719	0.311	0.568	0.169-1.905	0.360
GTR	150(43.1%)	0.329	0.130-0.836	0.019	0.275	0.104-0.727	0.009
Chemotherapy							
None/Unknown	345(99.1%)	Reference					
Yes	3(0.9%)	3.870	0.527-28.410	0.183			
Vital Status							
Alive	316(90.8%)						
Dead	32(9.2%)						
OS (M)	79(38.25-132)						

HR, hazard ratio; CI, confidence interval; GTR, gross total resection; STR, subtotal resection; OS, overall survival; NA, not available.
The Cox proportional hazards model was used for univariate and multivariate analyses in the no radiotherapy subgroup.

Progression-free survival (PFS) in STR, but not in OS (38). Göktug et al. reported that use of RT as a primary or adjuvant treatment following surgical resection remained controversial in a study of 25 CNs (39).

In our study, the role of RT in treating patients was crucial. However, a multivariate analysis of all patient data revealed that RT may reduce the OS rate of patients. In a subgroup analysis, the RT did not significantly improve the prognosis of patients with GTR. RT was not recommended after complete tumor resection. In the RT subgroup, patients with tumors outside the ventricle or women have a poorer prognosis than those with tumors within the ventricle or men, respectively. This suggests that RT is recommended for men or those with tumors located within the ventricle.

This result may be attributed to the limitations of the SEER database and the insufficient sample size. Our findings suggested that the patient's condition should be thoroughly assessed prior to RT. Physicians should consider RT toxicity and the harm caused by subsequent cognitive decline to patients (16). GTR or RT may impair important brain structures and functions, leading to a decline in quality of life. Extent of tumor resection and adjuvant treatments should always be balanced between prognosis improvement and maintenance/worsening of quality of life.

4.6 Chemotherapy

Currently, chemotherapy for treating patients with CN is controversial, with no corresponding treatment guidelines (40). According to Dutta et al., chemotherapy might be considered when patients are unable to complete surgery or RT. However, the most effective chemotherapy drugs are yet to be identified (16).

Johnson et al. conducted a retrospective analysis of 39 cases of CN treated with chemotherapy and concluded that there is significant heterogeneity in chemotherapy for CN. Furthermore, they emphasized that the benefits of temozolomide for treating CN are unclear and need further investigation (40). There are no prospective, multicenter, large-scale studies on chemotherapy for CN. In the multivariate regression analysis and the five treatments subgroup analysis, chemotherapy was not an independent prognostic factor for OS. Finally, only six patients completed chemotherapy, indicating that the efficacy of chemotherapy requires further investigation.

5 Limitations

Due to multiple changes in the diagnostic criteria for CN between 2000 and 2019, there was heterogeneity among patients included in the SEER database. In other words, there was a particular patient selection bias based on the SEER database. In our study, after data cleaning, there were no patients with malignant CN. The limitation of the article mentioned that our study lacked immunohistochemical data. In addition, the sample size is relatively small in this study. Longer follow-up and further multicenter studies with more sample sizes are needed.

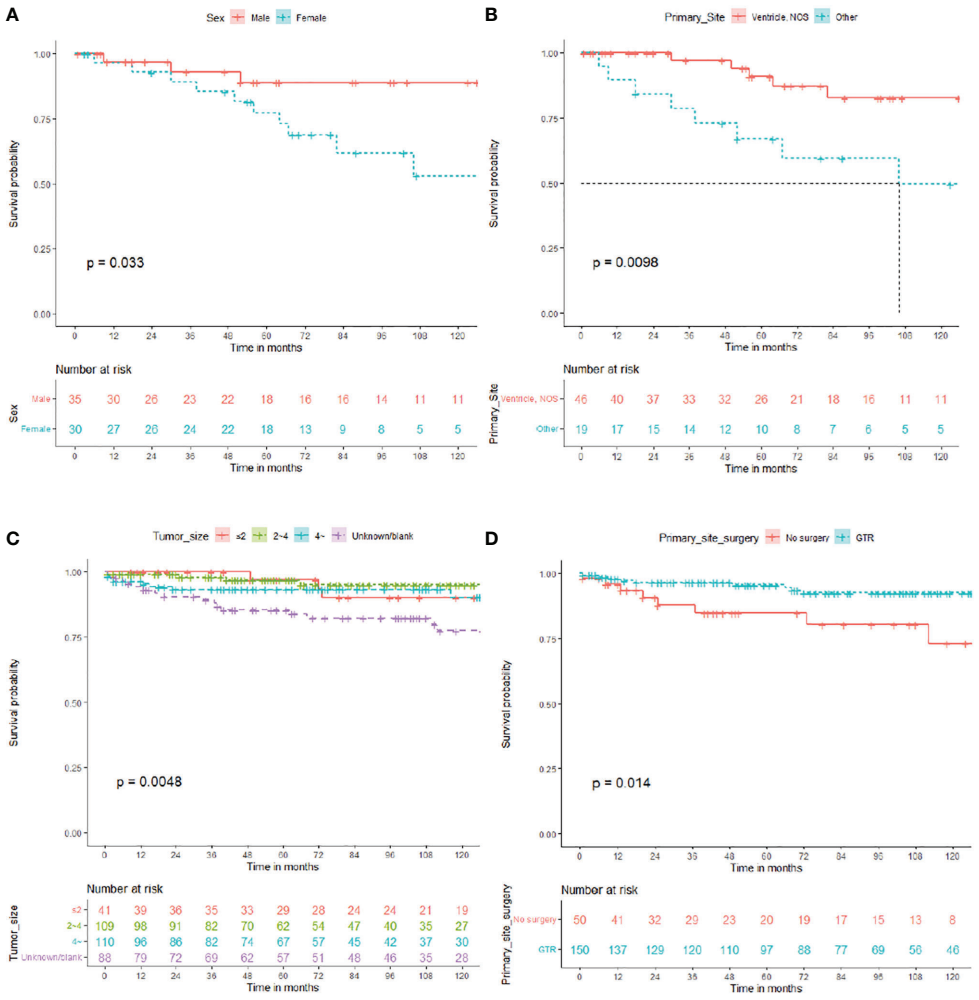

FIGURE 4
Overall survival (OS) for central neurocytoma in the radiotherapy and no radiotherapy. **(A)** OS among the different sex groups in the radiotherapy subgroup. **(B)** OS among the different primary site groups in the radiotherapy subgroup. **(C)** OS among the different tumor size groups in the no radiotherapy subgroup. **(D)** OS. among the different primary site surgery groups in the no radiotherapy subgroup. OS, overall survival.

6 Conclusion

In our study, patients with small tumors or GTR or those who did not receive RT showed a better prognosis. GTR was the preferred treatment for CN. RT was not recommended for patients after GTR. Men and African American showed certain advantages after STR surgery. Tumors with a size of >4 cm were recommended for active treatment. In the RT subgroup, patients with tumors outside the ventricle or women had a poorer prognosis than those with tumors within the ventricle or men, respectively. These findings will help clinicians and patients understand the treatment and prognosis of CN visually and intuitively.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to

participate in this study in accordance with the national legislation and the institutional requirements. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

RZ and ZZ: conceived the design of the study. XJ and JY: perfected the researched idea and obtained detailed data resources. CZ, XP and YW: used and implemented statistical methods to data. QL, HC and ZZ: finished the preliminary writing of the paper. †: these authors contributed equally to this work. *: corresponding author. All authors: offered valuable advice and confirmed the final revision of the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Effectiveness and safety of tumor-treating fields therapy for glioblastoma: A single-center study in a Chinese cohort

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Objective: Tumor-treating fields (TTFields) are a new therapeutic modality for patients with glioblastoma (GBM). However, studies on survival outcomes of TTFields are rarely reported in China. This study aimed to examine the clinical efficacy and safety of TTFields therapy for GBM in China.

Methods: A total of 93 patients with newly diagnosed GBM (ndGBM) and recurrent GBM (rGBM) were included in our study retrospectively. They were divided into two groups based on whether they used TTFields. Progression-free survival (PFS), overall survival (OS), and toxicities were assessed.

Results: Among the patients with ndGBM, there were 13 cases with TTFields and 39 cases with no TTFields. The median PFS was 15.3 [95% confidence interval (CI): 6.5–24.1] months and 10.6 (95% CI: 5.4–15.8) months in the two groups, respectively, with $P = 0.041$. The median OS was 24.8 (95% CI: 6.8–42.8) months and 18.6 (95% CI: 11.4–25.8) months, respectively, with $P = 0.368$. Patients with subtotal resection (STR) who used TTFields had a better PFS than those who did not ($P = 0.003$). Among the patients with rGBM, there were 13 cases with TTFields and 28 cases with no TTFields. The median PFS in the two groups was 8.4 (95% CI: 1.7–15.2) months and 8.0 (95% CI: 5.8–10.2) months in the two groups, respectively, with $P = 0.265$. The median OS was 10.6 (95% CI: 4.8–16.4) months and 13.3 (95% CI: 11.0–15.6) months, respectively, with $P = 0.655$. A total of 21 patients (21/26, 80.8%) with TTFields developed dermatological adverse events (dAEs). All the dAEs could be resolved or controlled.

Conclusion: TTFields therapy is a safe and effective treatment for ndGBM, especially in patients with STR. However, it may not improve survival in patients with rGBM.

KEYWORDS

newly diagnosed glioblastoma, recurrent glioblastoma, tumor-treating fields, survival benefit, adverse events

1. Introduction

Glioblastoma (GBM) is the most common primary malignant intracranial tumor, with characteristics of remarkably high heterogeneity, strong invasiveness, and poor outcomes (1, 2). Currently, the standard therapy for newly diagnosed GBM (ndGBM) involves maximal safe resection followed by concurrent radiotherapy and temozolomide (TMZ) administration (3). However, such therapy only shows a median progression-free survival (PFS) of 6.9 months [95% confidence interval (CI): 5.8–8.2] and median overall survival (OS) of 14.6 (95% CI: 13.2–16.8) months (4). To improve the survival outcomes for GBM, clinical trials for targeted therapy, immunotherapy, and a combination of TMZ with other chemotherapeutics have been extensively evaluated, and most of them are phase I/II clinical trials (5–7). Only a few phase III clinical trials have been reported for the ndGBM population (8–10). Despite the standardized treatment, ∼85% of GBM cases relapse within 2 years (11, 12). The outcome in patients with recurrent GBM (rGBM) is even worse, with a median OS of ∼6 months (13). Currently, there is no category 1 recommendation for the treatment of rGBM, and the majority of patients receiving comprehensive treatment experience a decline in their quality of life, including neurocognitive and physical functions (14, 15).

Tumor-treating fields (TTFields) therapy provides low-intensity, intermediate frequency, and alternating electric fields. The mechanism of action underlies interference with the mitosis of cancer cells through the action of microtubulins, eventually suppressing cancer cell growth (16, 17). In a previous phase III clinical trial (EF-11) on rGBM, TTFields therapy did not show any remarkable improvement in median OS (6.6 vs. 6.0 months; $P = 0.27$) or PFS (2.2 vs. 2.1 months; $P = 0.16$) as compared to chemotherapy, whereas it was superior in improving the quality of life of patients owing to fewer severe adverse events (AEs) (6 vs. 16%; $P = 0.022$) (18). Given these positive results, the TTFields therapy was officially adopted in the National Comprehensive Cancer Network (NCCN) guidelines in 2013 for the treatment of rGBM. The Patient Registry Dataset (PRiDe) study reported that the TTFields therapy contributed to the 1-year survival of 44% in patients with rGBM (19). In the subsequent phase III clinical trial (EF-14) on patients with ndGBM, the combination of TTFields therapy with TMZ was found to be superior to TMZ alone, with both higher median PFS (6.7 vs. 4.0 months; $P < 0.001$) and OS (20.6 vs. 16.0 months; $P < 0.001$). The combination strategy did not increase the incidence of AEs (44 vs. 48%; $P = 0.58$) (20, 21). In 2019, the NCCN guidelines recommended the Stupp regimen plus TTFields therapy as the category 1 treatment for ndGBM and the TTFields therapy as the category 2B treatment for rGBM (22), in accordance with the *Chinese Standard Diagnosis and Treatment for Glioma, 2018*.

Clinical studies about TTFields, including EF-11, EF-14, and PRiDe, have been mostly performed in European and American populations, except for the 39 Korean patients included in EF-14. However, studies on survival outcomes of TTFields are rarely reported in China. This study aimed to examine the clinical efficacy and safety of TTFields therapy for GBM in a retrospective cohort in China.

2. Methods

2.1. Patients selection

Between January 2013 and May 2021, data from 93 patients were evaluated retrospectively at the Xiangya Hospital of Central South University. Patients with ndGBM and rGBM eligible for this study were 18 years or older, with a Karnofsky performance score (KPS) of 50 or higher, and histologically, the pathology was confirmed as supratentorial glioblastoma. All participants had undergone the safest debulking surgery possible, followed by concurrent chemoradiotherapy. Patients with implanted electronic medical devices, as well as those with other malignant tumors or serious diseases, were excluded from our study. They were divided into groups with TTFields group and without TTFields group based on whether they used TTFields.

2.2. Treatment strategy

Patients with ndGBM received surgery (maximum tumor resection with safety), intensity-modulated radiotherapy (IMRT) (2.0 Gy/day, 5 days a week for 60 Gy), temozolomide (TMZ) concurrent chemotherapy (75 mg/m^2/day), and TMZ adjuvant chemotherapy (AC) (150 mg/m^2/day in the first cycle, 200 mg/m^2/day from the second cycle). Patients in the TTFields group got extra electric field treatment during AC.

Patients with rGBM were treated with TMZ chemotherapy or targeted treatment (nimotuzumab, bevacizumab, or anlotinib). Electric field treatment was used on patients in the TTFields group in addition to chemotherapy and targeted therapy.

All patients treated with electric field underwent examinations for full-length of the 68 genes most related to glioma. The specific process of TTFields was as follows. The NovaTTFields-200A device (Novocure, Israel) was used. Low-intensity (2 V/cm), intermediate frequency (200 kHz), and alternating electric fields were placed at the tumor regions. Two pairs of electric field patches were attached to the scalp surface of patients. Specific procedures of the TTFields therapy were in four steps. (1) Before initiating the therapy, the general conditions and indications of patients were assessed. Written informed consent was obtained from all patients. (2) Patients were asked to provide the latest head magnetic resonance

imaging (MRI) scan data (within the last 1 month), and learning the use of the NovaTTFields-200A device was aided by the specialists from the Novocure company. Head size and MRI scan data were combined to determine the best patch position, and patients were guided to place the patches. (3) After patch placement, regular follow-up was performed to observe toxicity, general conditions, and provide treatment for symptomatic individuals. The MRI scan was required every 2 months or on suspicion of tumor progression. The RANO criteria were used to assess the therapeutic efficacy. Patients were encouraged to have the patches placed for more than 18 h each day. (4) Compliance report was generated every month with the support of the NovaTTFields-200A device and subsequently sent to doctors. The contents included the average daily use of the device and the overall compliance data of patients during the treatment period.

2.3. Evaluation of the therapeutic efficacy and toxicity

MRI scans were examined every 2 months or on suspicion of tumor progression. The disease progression was accessed every 2 months after radiotherapy according to the Response Assessment in Neuro-Oncology (RANO) criteria. Progression in the radiation field within 3 months (12 weeks) after the completion of chemoradiotherapy was needed to observe carefully to differentiate from pseudoprogression. Regular follow-up visits were performed until disease progression or death. According to Common Terminology Criteria for Adverse Events, v5.0 (CTCAE v5.0) and TTFields dermatological adverse events (dAEs) criteria, the toxicity in each patient was evaluated. Scalp examination was performed every 2 weeks after the removal of the sensor arrays. Upon skin toxicity, interventions were provided, including scalp cleansing, topical application of corticosteroids for contact dermatitis during array exchange, and anti-infection treatment with topical application of antibiotics.

2.4. Treatment compliance and quality of life

Treatment compliance was evaluated monthly through the data on the use of the NovaTTFields-200A device and calculated as a percentage of the daily TTFields usage. The quality of life questionnaire-core 30 (QLQ-C30) (23) and QLQ-brain cancer module (QLQ-BN20) questionnaire (24), provided by the European Organisation for Research and Treatment of Cancer (EORTC), were used to evaluate the health-related quality of life (HRQoL) every 1–3 months. The change in score < 10 was defined as stable HRQoL, or else, a decline or improvement was considered.

2.5. Statistical analysis

The patient baseline and AEs were obtained by direct counting, and the measured data that did not conform to normal distribution were expressed as the median. The χ^2 test or Fisher exact test was used for comparison. Data processing was performed using GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA) and SPSS 23.0 (IBM Corporation, Armonk, New York, USA) software. The starting point of PFS and OS in patients with ndGBM was the time of the first operation, and the starting point of PFS and OS in patients with rGBM was the time of recurrence. The median PFS and OS were analyzed using the Kaplan–Meier survival curves. Multivariate analysis affecting PFS and OS was conducted using the Cox proportional hazards model. Treatment compliance of each patient was expressed in percentage (mean). Comparison of independent datasets between two groups was through the *t*-test, while that among more than two groups was through the one-way ANOVA–Bonferroni multi-comparison test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Patient clinical data

In our analysis, a total of 93 patients with GBM were enrolled between January 2013 and May 2021, including 52 ndGBM (55.9%) and 41 rGBM cases (44.1%). Of the 52 ndGBM cases, 13 patients were in the with TTFields group, including seven men and six women with an average age of 54 years (range 33–63 years). Gross total resection (GTR) was performed in six patients, subtotal resection (STR) in seven patients. All patients were IDH wild type; three patients showed the methylation of the MGMT promoter, whereas 10 were unmethylated. Among the 39 patients in the without TTFields group, 24 were men and 15 were women, with an average age of 48 years (range 22–75 years). GTR was performed in 23 patients and STR in 16 patients. All patients were IDH wild type; 13 patients showed MGMT promoter methylation, whereas 26 were unmethylated. No significant differences were noted in gender, age, degree of surgical resection, or MGMT promoter status between the two groups ($P > 0.05$).

Of the 41 rGBM cases, 13 patients were in the with TTFields group, including eight men and five women with an average age of 51 years (range 27–68 years). All patients were IDH wild type; four patients showed the methylation of the MGMT promoter, whereas nine were unmethylated. Among the 28 patients without the TTFields group, 15 were men and 13 were

women with an average age of 45 years (range 26–68 years). A total of 14 patients showed MGMT promoter methylation, whereas 14 were unmethylated. No significant differences were noted in gender, age, degree of surgical resection, number of recurrences, or MGMT promoter status between the two groups ($P > 0.05$). Table 1 lists the clinical characteristics of ndGBM and rGBM cases.

3.2. Survival outcome

The follow-up period was 34.7 months (95% CI: 26.5–42.9) in the ndGBM cohort. Among the patients with ndGBM, there were 13 cases with TTFields and 39 with no TTFields. The median PFS was 15.3 months (95% CI: 6.5–24.1) and 10.6 months (95% CI: 5.4–15.8) in the two groups, respectively, with $P = 0.041$. The 1-year PFS rate was 67.3 and 44.8% in the two groups, respectively. The median OS was 24.8 months (95% CI: 6.8–42.8) and 18.6 months (95% CI: 1.4–25.8), respectively, with $P = 0.368$. The 1-year OS rate was 65.8 and 66.7% in the two groups, respectively (Figures 1A, B).

The follow-up period was 21.8 months (95% CI: 20.6–23.1) in the rGBM cohort. Among the patients with rGBM, there were 13 cases with TTFields and 28 with no TTFields. The median PFS was 8.4 months (95% CI: 1.7–15.2) and 8.0 months (95% CI: 5.8–10.2) in the two groups, respectively, with $P = 0.265$. The 1-year PFS rate was 7.7 and 26.2% in the two groups, respectively. The median OS was 10.6 months (95% CI: 4.8–16.4) and 13.3 months (95% CI: 11.0–15.6), respectively, with $P = 0.655$. The 1-year OS rate was 38.5 and 62.2% in the two groups, respectively (Figures 1C, D). Dynamic changes in the MRI scans of representative ndGBM and rGBM cases are shown in Figures 2, 3.

Among the patients with ndGBM, the patients with female ($P = 0.026$), KPS > 70 ($P < 0.001$), GTR ($P < 0.001$), and TTFields ($P = 0.041$) had better PFS. The patients with KPS > 70 and MGMT methylation had better OS. A multivariate analysis showed that KPS > 70 ($P < 0.001$; HR 0.181, 95% CI: 0.072–0.456) and GTR ($P = 0.001$; HR 0.23, 95% CI: 0.1–0.527) were favorable independent prognostic factors for PFS in patients with ndGBM. KPS > 70 ($P = 0.003$; HR 0.247, 95% CI: 0.099–0.616) and MGMT methylation ($P = 0.004$; HR 3.443, 95% CI: 1.484–7.987) were favorable independent prognostic factors for OS (Table 2).

Among the patients with rGBM, a single-factor analysis showed that females ($P = 0.02$), KPS > 70 ($P = 0.012$), re-operation (STR + GTR) ($P = 0.002$), and first recurrence ($P = 0.027$) had better PFS. The patients with KPS > 70 ($P = 0.001$), re-operation ($P = 0.003$), and first recurrence ($P = 0.003$) had better OS. The multivariate analysis also confirmed that females ($P = 0.012$; HR 2.785, 95% CI: 1.25–6.203), re-operation ($P < 0.001$; HR 4.23, 95% CI: 2.026–8.834), and first recurrence ($P = 0.032$; HR 0.434, 95% CI: 0.203–0.931) were favorable independent prognostic factors for PFS. KPS > 70 ($P = 0.022$; HR 3.778, 95% CI: 1.211–11.787), re-operation ($P = 0.019$; HR 3.125, 95% CI: 1.207–8.235), and first recurrence ($P < 0.001$; HR 0.148, 95% CI: 0.057–0.387) were favorable independent prognostic factors for OS (Table 3).

Through the subgroup analysis of patients with ndGBM, we found that in patients without TTFields, the PFS of patients with GTR was significantly better than that of patients with STR (median survival:19.6 vs. 5.3 months; $P < 0.001$). Among the patients using TTFields, there was no significant difference in PFS between GTR and STR ($P = 0.518$). However, we also found that patients with STR who used TTFields had better PFS than those who did not ($P = 0.003$). Among the patients who did not use TTFields, the OS of patients with GTR was significantly better than that of patients with STR (median survival: 24.8 vs. 13.7 months; $P = 0.008$). Among the patients using TTFields, there was no significant difference in OS between total and subtotal resection ($P = 0.403$).

3.3. Toxicity, treatment compliance, and quality of life

Among all patients treated with an electric field, 21 cases had dAE (21/26, 80.8%), including 17 cases of grade 1, three cases of grade 2, and one case of grade 3. Common dAEs were dermatitis, ulcers, and bursitis. All the dAEs could be resolved or controlled by the topical application of glucocorticoids or antibiotics. The average treatment compliance rate was 91.9% in ndGBM cases vs. 91.7% in rGBM cases ($P = 0.90$, Figure 4A), while 92.3% in men vs. 91.3% in women ($P = 0.21$, Figure 4B). Based on the different age groups, the treatment compliance rate was 93.8% in 20–39-year individuals vs. 91.6% in 40–59-year individuals vs. 90.7% in the>59 years old group ($P = 0.62$, Figure 4C). In addition, according to the preoperative KPS scores, the treatment compliance rate in patients with KPS scores of 50–60, 70–80, and 90 was 88.4, 92.3, and 94.1%, respectively, with no statistically significant differences ($P = 0.11$, Figure 4D). A total of 22 cases showed a stable HRQoL, two showed improvement, manifested in cognitive and social functioning, and two showed a decline, mainly in emotional and role functioning.

3.4. Biomarkers of patients with TTFields

Gene detection in patients with GBM treated with an electric field is shown in Table 4. We explored the relationship between some genes and survival and found no statistically significant correlation. However, of the 13 ndGBM cases, four cases with BRAF-V600E mutations did not show recurrence during follow-up. In addition, three cases with amplification in the EGFR gene showed worse PFS. Of the six patients with rGBM showing the first recurrence, two with the activation of proangiogenic

TABLE 1 Clinical characteristics of GBM patients.

Characteristics	Newly diagnosed GBM ($n = 52$)			Recurrent GBM ($n = 41$)		
	With TTFields ($n = 13$)	Without TTFields ($n = 39$)	*P*	With TTFields ($n = 13$)	Without TTFields ($n = 28$)	*P*
Median age (year)						
≤50	3 (23.1%)	19 (48.7%)	0.105	4 (30.8%)	18 (64.3%)	0.091
>50	10 (76.9%)	20 (51.3%)		9 (69.2%)	10 (35.7%)	
Sex						
Male	7 (53.8%)	24 (61.5%)	0.624	8 (61.5%)	15 (53.6%)	0.632
Female	6 (46.2%)	15 (38.5)		5 (38.5%)	13 (46.4%)	
KPS						
≤70	4 (30.8%)	9 (23.1%)		8 (61.5%)	16 (57.1%)	
>70	9 (69.2%)	30 (76.9%)	0.579	5 (38.5%)	12 (42.9%)	0.79
Tumor location						
FL/TL/PL/OL	8 (61.5%)	35 (89.7%)	0.159	9 (69.2%)	23 (82.1%)	0.374
Corpus callosum	4 (30.8%)	2 (5.1%)		3 (23.1%)	2 (7.1%)	
Others	1 (7.7%)	2 (5.1%)		1 (7.7%)	3 (10.7%)	
Extent of surgery						
GTR	6 (46.2%)	23 (59.0%)	0.42			
STR	7 (53.8%)	16 (41.0%)				
MGMT methylation status						
Methylated	3 (23.1%)	13 (33.3%)	0.729	4 (30.8%)	14 (50.0%)	0.248
Unmethylated	10 (76.9%)	26 (66.7%)		9 (69.2%)	14 (50.0%)	
Combination therapy						
TMZ	10 (76.9%)	31 (79.5%)	1	3 (23.1%)	2 (7.1%)	0.348
TMZ + targeted therapy	3 (23.1%)	8 (20.5%)		10 (76.9%)	26 (92.9%)	
Number of recurrence						
1st recurrence				6 (46.2%)	20 (71.4%)	0.118
≥2nd recurrence				7 (53.8%)	8 (28.6%)	
Re-operation						
GTR				3 (23.1%)	8 (28.6%)	0.362
STR				2 (15.4%)	9 (32.1%)	
No				8 (61.5%)	11 (39.3%)	

GBM, glioblastoma; TTFields, tumor-treating fields; KPS, Karnofsky performance status; FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanine-DNA methyltransferase; TMZ, temozolomide.

pathways, including amplifications in KIT, FGFR, PDGFR, or KDR genes, showed the longest PFS.

4. Discussion

The findings of this study showed that the median compliance rates among the ndGBM and rGBM cases for TTFields therapy were 94 and 91%, respectively. TTFields therapy was performed for an average of 18 h daily (100%) in all patients. This could be attributed to careful education before treatment, family support, close monitoring during treatment, and timely management of toxicity. The *post-hoc* analysis of the EF-14 study suggests the necessity for the continuous use of the TTFields device as the treatment efficacy was found to be positively associated with patient compliance. It was proven

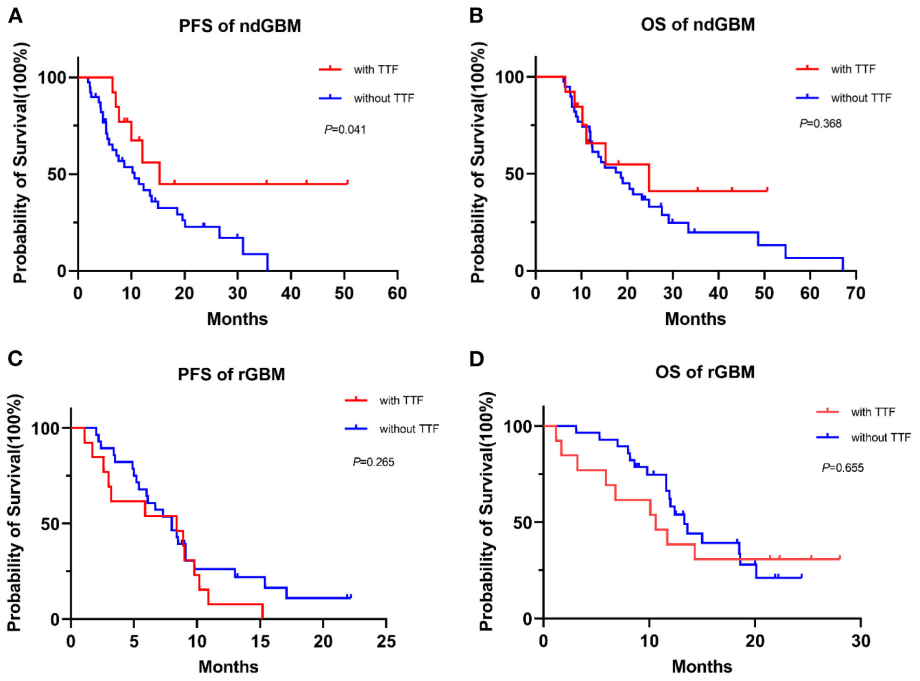

FIGURE 1
The survival analysis of the newly diagnosed glioblastoma (ndGBM) and recurrent GBM (rGBM) in two groups. **(A)** Progression-free survival (PFS) of ndGBM; **(B)** overall survival (OS) of ndGBM; **(C)** PFS of rGBM; **(D)** OS of rGBM.

that the duration of TTFields up to 18 h daily, with a treatment compliance of >75%, could lead to significant therapeutic outcomes. A duration >22 h daily is reportedly associated with a 29.3% survival rate in 5 years (25). Based on our findings, we found that high treatment compliance was independent of age, gender, preoperative KPS score, and the stage of disease of the patients. This implied that elderly patients or those with a poor quality of life could also undergo TTFields. In our cohort, two patients accepted the TTFields therapy for over 19 months and continue to use it with good compliance. The long-term use of TTFields appeared to show no substantial effects on patient compliance. In the EF-11 study, the median compliance rate of patients was 86%, and in the EF-14 study, <10% of patients showed a compliance rate of 90% (18, 20). In our study, the compliance rate was markedly higher, which may have contributed to the more favorable survival outcomes.

In the ndGBM group in our study, the median PFS of patients with TTFields was better than that of patients without TTFields (15.3 vs. 10.6 months; $P = 0.041$). This result was similar to the EF-14 study. However, the 1-year PFS rate of the TTFields group was 67.3%, markedly better than the results reported in the EF-14 study (1-year PFS <40%). In detail, 90% compliance in the EF-14 study was <10%, while according to our findings, it was 76.9%. This may be accounting for the superior PFS in our study. The median OS was 24.8 months (95% CI: 6.8–42.8) and 18.6 months (95% CI: 11.4–25.8), respectively, with $P = 0.368$. The median OS of the two groups in our study was comparable, which might be attributed to our patients' continued active therapy following recurrence.

It has been reported that in ndGBM, the survival of patients with GTR is significantly better than that of patients with STR (26, 27). Our study also found that GTR ($P = 0.001$; HR 0.23, 95% CI: 0.1–0.527) was a favorable independent prognostic factor for PFS. Among patients without TTFields, patients with GTR had significantly better PFS and OS than patients with STR ($P < 0.001$; $P = 0.008$). This is consistent with data in the literature (28). However, there was no significant difference between PFS in patients with GTR and STR in patients with TTFields ($P = 0.518$). Therefore, a subgroup analysis was performed and found that in the STR group, patients with TTFields had better PFS than those without TTFields ($P = 0.003$). This may be because TTFields improved the survival of patients with STR, thereby narrowing the survival gap between patients with GTR and STR in the TTFields group. By univariate analysis, we found that KPS > 70 was also an independent prognostic factor for PFS and OS. MGMT methylation is a favorable independent prognostic factor for OS. The results were similar to the findings in other studies (29, 30).

There is no consensus on whether mutations in BRAF-V600E are associated with a better prognosis, but several studies support that EGFR amplification is a significant

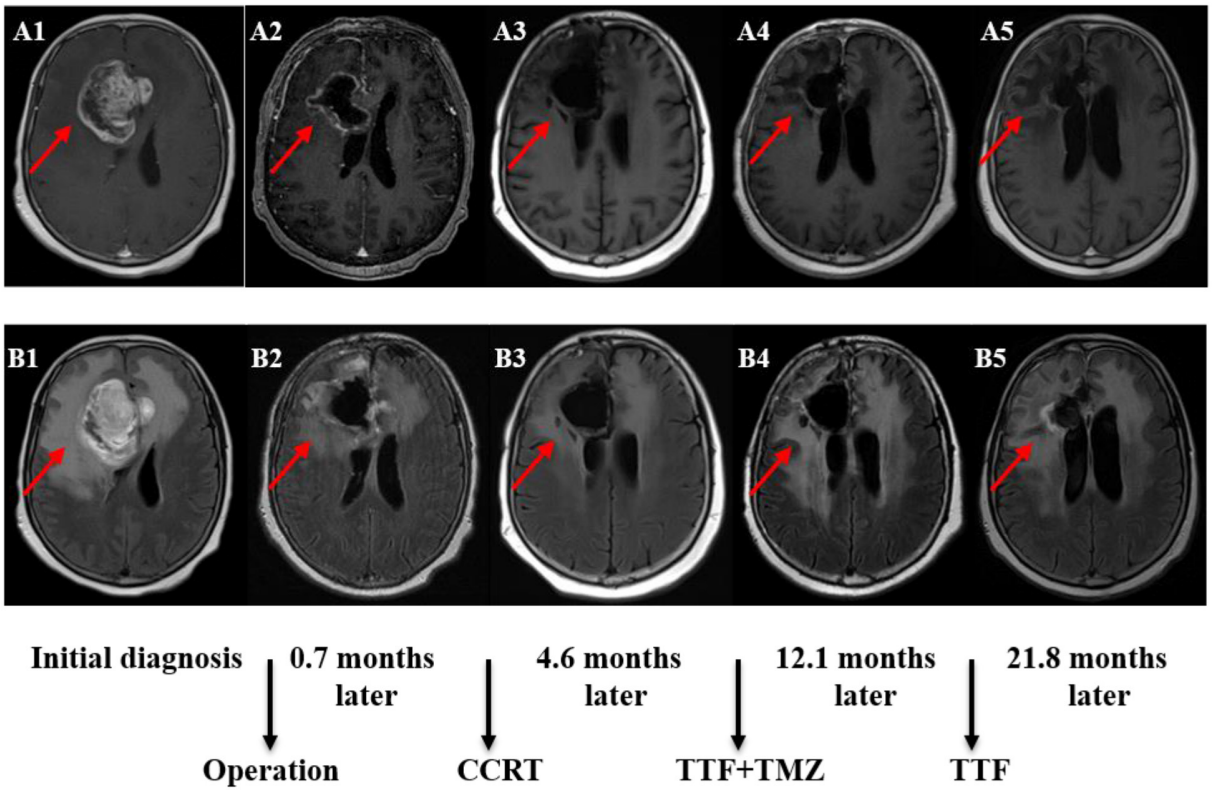

FIGURE 2
MRI (Magnetic Resonance Imaging) changes of newly diagnosed glioblastoma (GBM). **(A1–A5)** Contrast-enhanced MRI; **(B1–B5)** MRI-Flair. MRI images followed-up every 2 months before and after treatment. Only some of the images were exhibited. The arrow indicates the tumor and tumor bed. This patient has followed-up for 35.4 months with a stable disease.

risk factor for poor survival outcomes (31–34). In our study, four with BRAF-V600E mutations showed better PFS. Contrastingly, three cases of ndGBM with EGFR amplification exhibited worse survival outcomes. Due to the small sample size, we cannot determine whether BRAF-V600E and EGFR are biomarkers of favorable outcomes from TTFields, and subsequent studies with large samples are needed to further determine.

In the rGBM group in our study, the median PFS and OS data showed no significant difference between the two groups with and without TTFields, which was consistent with the findings of the EF-11 study. The 6-month PFS and 1-year OS rates of the TTFields group were 53.8 and 38.5%, respectively. While in the EF-11 study, the 6-month PFS in rGBM cases who underwent TTFields therapy was 21.4%. As compared to the EF-11 study, patients with rGBM in our study showed higher survival rates. Several possible reasons may account for it. First, in the EF-11 study, all patients underwent TTFields therapy alone. In our study, all rGBM cases received TTFields combination therapy, including re-operation, targeted therapy, or TMZ-based chemotherapy. Many studies confirm that combining TTFields and other anti-tumor therapies (such as radiotherapy, chemotherapy, and immunotherapy) yield better therapeutic outcomes (35–38). In addition, in our cohort, 46.2% of patients showed a first recurrence, significantly higher than the 9% in the EF-11. The median compliance of patients with rGBM in our study (91%) was also higher than that in the EF-11 study (86%).

Univariate and multivariate analyses of rGBM showed that gender, KPS, re-operation, and a number of recurrences were significant prognostic factors for PFS, while KPS, re-operation, and a number of recurrences were significant prognostic factors for OS. This was similar to the results of other previous studies (39, 40). Several treatment regimens for rGBM were used in our study, so the results demonstrate that using TTFields was not a prognostic factor for survival. In follow-up studies, a more rigorous research protocol should be developed to remove the influence of confounding factors and to draw more reliable conclusions.

In the six rGBM cases with the first recurrence, five cases underwent re-operation. As evidenced by sequencing the tumor samples acquired after re-operation, we found two cases with the activation of proangiogenic pathways, including amplifications in KIT, FGFR, PDGFR, or KDR, and they exhibited the longest

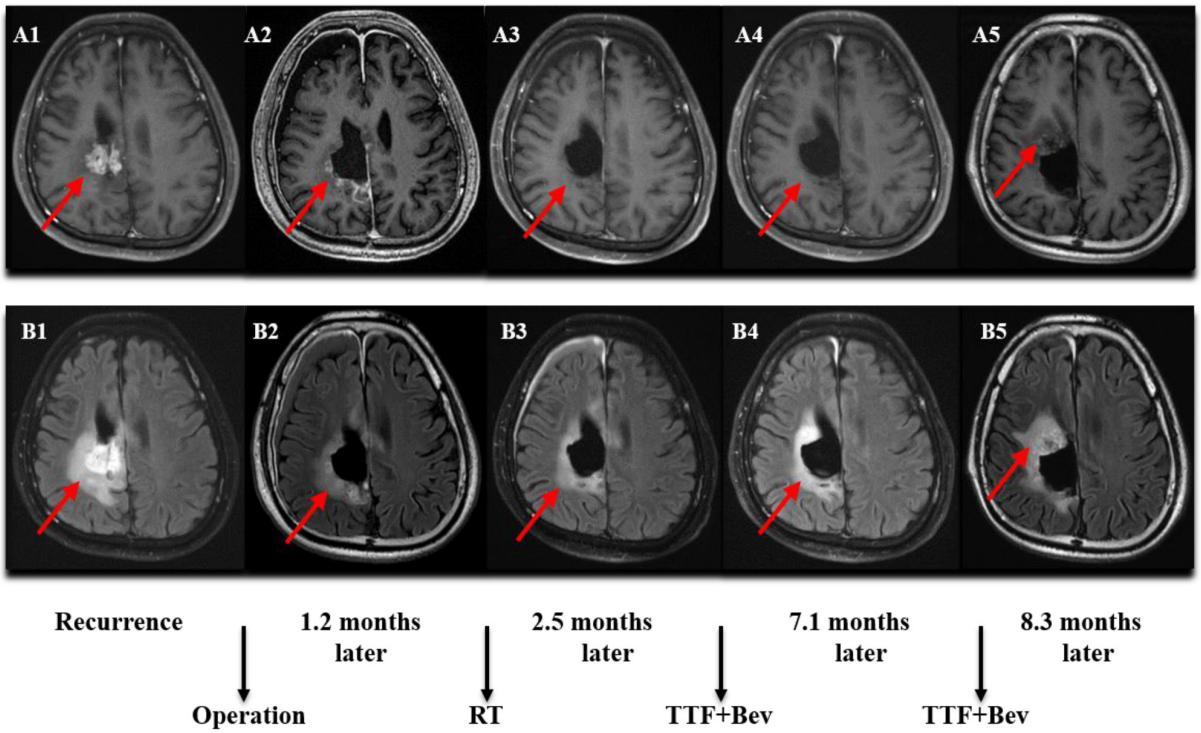

FIGURE 3
MRI (Magnetic Resonance Imaging) changes of recurrent GBM (rGBM). **(A1–A5)** Contrast-enhanced MRI; **(B1–B5)** MRI-Flair. MRI images followed-up every 2 months before and after treatment. Only some of the images were exhibited. The arrow indicates the tumor and tumor bed. This patient was followed-up for 8.3 months and he developed a disease progression.

TABLE 2 Univariate and multivariate analysis for PFS and OS of ndGBM.

Variable	PFS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value (log-rank)	Hazard ratio (95% CI)	*P*-value	*P*-value (log-rank)	Hazard ratio (95% CI)	*P*-value
Age (years): ≤50 vs. >50	0.476			0.172		
Sex: female vs. male	**0.026**	1.427 (0.978–2.082)	0.065	0.071	1.164 (0.796–1.704)	0.434
KPS: >70 vs. ≤70	**<0.001**	0.181 (0.072–0.456)	**<0.001**	**0.014**	0.247 (0.099–0.616)	**0.003**
Extent of surgery: GTR vs. STR	**<0.001**	0.23 (0.1–0.527)	**0.001**	0.088	0.498 (0.246–1.007)	0.052
MGMT: meth vs. unmeth	0.122			**0.02**	3.443 (1.484–7.987)	**0.004**
TTFields: with vs. without	**0.041**	0.609 (0.203–1.825)	0.375	0.371	1.21 (0.445–3.286)	0.709

PFS, progression-free survival; OS, overall survival; KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection; MGMT, O6-methylguanine-DNA methyltransferase; 95% CI, 95% confidence interval; TTFields, tumor-treating fields. The bold values mean the difference is statistically significant.

PFS. None of these gene amplifications are known to be associated with favorable survival outcomes (41). This suggested that the rGBM cases with active angiogenic signaling might benefit more from the TTFields therapy. A previous study reports that PTEN mutations predict benefits from TTFields therapy in patients with rGBM (42). However, in our study, no PTEN mutations were identified in the rGBM group. This may be attributed to the tumor samples used for sequencing in their study, which were acquired from initial surgery; genetic alterations occur over time, and with treatment intervention, the genetic characteristics in rGBM may differ from those after primary resection (43, 44).

TABLE 3 Univariate and multivariate analysis for PFS and OS of rGBM.

Variable	PFS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value (log-Rank)	Hazard ratio (95% CI)	*P*-value	*P*-value (log-rank)	Hazard ratio (95% CI)	*P*-value
Age (years): ≤50 vs. >50	0.893			0.814		
Sex: female vs. male	**0.02**	2.785 (1.25–6.203)	**0.012**	0.204		
KPS: >70 vs. ≤70	**0.012**	1.723 (0.727–4.082)	0.217	**0.001**	3.778 (1.211–11.787)	**0.022**
Re-operation: no vs. STR + GTR	**0.002**	4.23 (2.026–8.834)	**<0.001**	**0.003**	3.152 (1.207–8.235)	**0.019**
MGMT: meth vs. unmeth	0.262			0.173		
TTFields: with vs. without	0.265			0.655		
Number of recurrence: 1st vs. ≥2nd	**0.027**	0.434 (0.203–0.931)	**0.032**	**0.003**	0.148 (0.057–0.387)	**<0.001**

PFS, progression-free survival; OS, overall survival; KPS, Karnofsky performance status; MGMT, O6-methylguanine-DNA methyltransferase; 95% CI, 95% confidence interval; TTFields, tumor-treating fields. The bold values mean the difference is statistically significant.

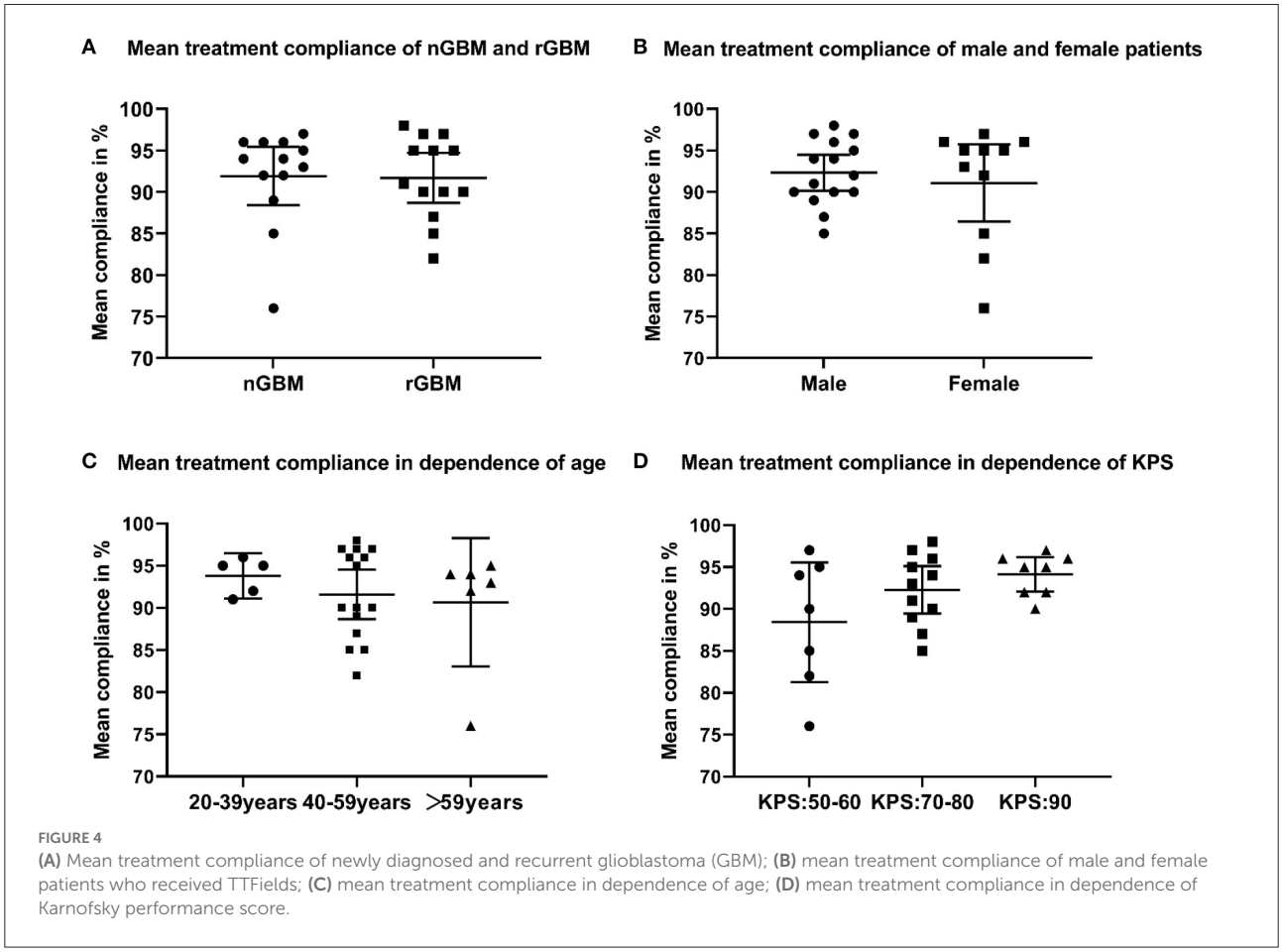

FIGURE 4
(A) Mean treatment compliance of newly diagnosed and recurrent glioblastoma (GBM); **(B)** mean treatment compliance of male and female patients who received TTFields; **(C)** mean treatment compliance in dependence of age; **(D)** mean treatment compliance in dependence of Karnofsky performance score.

TABLE 4 The gene detection of TTFields group.

Gene detection	Newly diagnosed GBM ($n = 13$) No. of patients (%)	Recurrent GBM ($n = 13$) No. of patients (%)
BRAF-V600E mutation	4 (30.8)	
PI3K mutation	3 (23.1)	3 (23.1)
EGFR amplification	3 (23.1)	2 (15.4)
KIT, FGFR, PDGFR, or KDR amplification	2 (15.4)	3 (23.1)
TERT mutation	6 (46.2)	8 (61.5)
P53 mutation	2 (15.4)	4 (30.8)
PTEN mutation	2 (15.4)	
CDKN2A/2B co-deletion	1 (7.7)	
FGFR3-TACC3 refusion		1 (7.7)
MET amplification		1 (7.7)
DDR1 mutation		1 (7.7)
CK4 amplification	1 (7.7)	

GBM, glioblastoma; TTFields, tumor-treating fields.

Moreover, we also used the QLQ-C30 and QLQ-BN20 questionnaires to assess the safety of the TTFields therapy. Of the 26 cases, 22 showed a stable HRQoL and two exhibited improvements, which mainly manifested in cognitive and social functioning. This was consistent with the findings of a previous report (45). The common AE was dAEs in 21 cases (21/26, 80.8%), a little higher than for the Korean patients reported in the EF-14 study.

The current study has some limitations. This was a single-center study, and potential biases may exist in patient selection. The sample size was relatively small. A large sample size and prospective control trials are needed in future.

5. Conclusion

In conclusion, TTFields showed good efficacy in ndGBM, especially in patients with STR. However, TTFields failed to improve the survival of rGBM. In addition, this treatment is safe and tolerable. A larger sample size and randomized controlled clinical trials are needed to further verify the effectiveness of TTFields treatment.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Xiangya Hospital of Central South University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CL: conceptualization and supervision. LSh, LSu, XG, and CL: data curation. LSh: formal analysis and methodology. XG and CL: funding acquisition. LSu and CL: investigation. LSh and LSu: visualization. LSh and XG: writing the original draft. LSh, XG, and CL: writing, reviewing, and editing. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prognostic and predictive factors of secondary gliosarcoma: A single-institution series of 18 cases combined with 89 cases from literature

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Introduction: Secondary gliosarcomas (SGS) are rare malignancies that are diagnosed subsequent to pre-existing glioma. Clinical features and optimal treatment strategies for SGS have not been conclusively established. This study aimed to assess the clinicopathological features and outcomes of SGS.

Methods: We assessed the clinicopathological features and outcomes of SGS via retrospective analysis of data for SGS patients at Tangdu Hospital. Data from SGS patients in prior publications were also analyzed in accordance with PRISMA guidelines.

Results: Eighteen SGS patients who had been treated at Tangdu Hospital between 2013 and 2020 were enrolled in this study. Additional 89 eligible SGS patients were identified from 39 studies. The median age for the patients was 53 years old, and the most common location was the temporal lobe. The most common initial diagnosis was glioblastoma (GBM) (72.0%). Radiology revealed enhanced masses in 94.8% (73/77) of patients. Ten patients (10/107, 9.35%) had extracranial metastases at or after SGS diagnosis. Patients with initial diagnosis of non-GBM and who were younger than 60 years of age were significantly associated with a long duration of disease progression to SGS. After SGS diagnosis, patients with initial non-GBM diagnosis, gross total resection and chemoradiotherapy exhibited prolonged survival outcomes. Patients who had been initially diagnosed with GBM and received both chemoradiotherapy and active therapy after disease progression to SGS, had a significantly longer overall survival than patients who did not.

Conclusion: Initial diagnosis of GBM was a poor prognostic factor for SGS. Patients who underwent gross total resection and chemoradiation had better overall survival outcomes than those who did not. However, during treatment, clinicians should be cognizant of possible extracranial metastases.

KEYWORDS

secondary gliosarcoma, prognosis, glioblastoma, extracranial metastasis, chemoradiation

Introduction

Gliosarcomas (GS) are rare malignant central nervous system (CNS) tumors that are characterized by a mixture of gliomatous and sarcomatous elements (1). In the 2016 & 2021 World Health Organization (WHO) classification of tumors of the CNS, GS was classified as a subtype of isocitrate dehydrogenase (IDH)-wildtype GBM (2) and a variant of GBM (3, 4) respectively. Therefore, a similar therapeutic regimen for GS and GBM was recommended by the National Comprehensive Cancer Network (NCCN) (5) and the European Association of Neuro-Oncology (EANO) (6) guidelines. In clinical practice, GS and GBM are also perceived as the same type of lesion and the prognosis of GS patients has been postulated to be comparable to that of GBM patients (7–9). Other studies found that GS has worse prognostic outcomes than GBM (1, 10, 11), with a distinct genomic landscape, indicating that GS are distinctly different tumors from GBM (12).

Among the GBM patients, about 2% are GS cases (1, 13), which are divided into the predominant primary gliosarcomas (PGS) that are *de novo* in origin and secondary gliosarcomas (SGS) that arise from pre-existing gliomas (14–17) and constitute 21% of GS (18, 19). Extremely low incidences of SGS have resulted in a few case reports and studies, creating a paucity of information on its clinical features and optimal treatment strategies. To elucidate on the disease and inform the design of effective treatment strategies for its management, it is important to investigate the prognosis and associated risk factors of SGS.

In this study, data for SGS patients at Tangdu Hospital were retrospectively analyzed, and data for SGS patients in prior published studies were also analyzed. Based on these analyses, we comprehensively elucidate on SGS, specifically its clinical and radiological presentations, pathological diagnosis, and treatment outcomes.

Methods

Patient enrollment and data collection

A retrospective analysis was conducted on data from patients treated at Tangdu hospital between 2013 and 2020. The inclusion criteria were: (1) Patients with a history of glioma, (2) Pathological confirmation of GS from subsequent resection. The exclusion criteria were patients with a previously diagnosed intracranial malignant glioma that had GS components. Data from 18 SGS patients were finally analyzed. The ethics committee of Tangdu Hospital approved this study, which had been pre-registered on PROSPERO (Registration number: CRD42022303335).

To obtain patient data from prior studies on GS patients, the following criteria were used: (1) present clinical data of patients, (2) no time restrictions on studies, (3) studies published in English were reviewed by two independent investigators, (4) studies were identified by searching for the terms "Secondary gliosarcoma," "Recurrence gliosarcoma," "postirradiation gliosarcoma," and "post radiotherapy gliosarcoma" alone or in combination in PubMed, EMBASE, Cochrane and Ovid/Medline databases. The reference lists of identified articles were also screened to identify potentially relevant articles.

The titles and abstracts of the identified studies were independently screened by two investigators. Studies that did not meet the inclusion criteria were excluded. Then, full articles were screened and those that did not meet the entire inclusion criteria eliminated, leaving 39 studies, from which data on 89 eligible SGS patients were included in the final analysis. These data were reported as per the PRISMA guidelines (Figure 1). A total of 107 patients were included in the final analysis. Data that were extracted from patients' records included: age at diagnosis, sex, tumor location, radiological features of SGS, initial pathological diagnosis, adjuvant therapy for

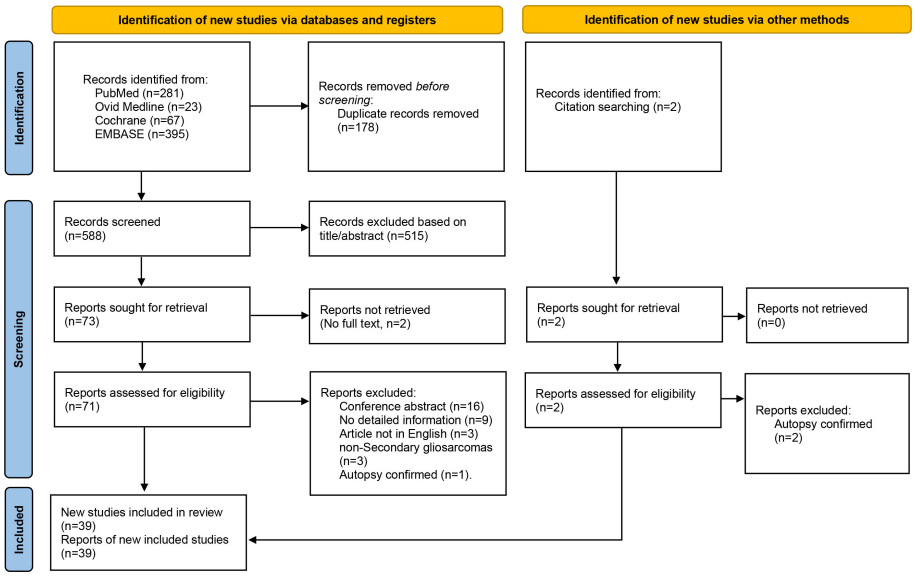

FIGURE 1
PRISMA flow diagram showing the inclusion and exclusion process for the analysis.

glioma, time from initial diagnosis to SGS, extent of resection for SGS, adjuvant therapy for SGS, survival from SGS, and overall survival after initial diagnosis.

Quality assessment

To determine the risk of bias in prior studies, two investigators independently assessed the following characteristics: treatment allocation concealment; completeness of outcome data and selective outcome reporting. Disagreements between investigators regarding the risk of bias was resolved by discussion, and when necessary, mediated by a third investigator.

Statistical analysis

Univariate survival analysis was conducted using the Kaplan Meier method with the logrank test. Factors with $p<0.10$ on univariate analysis were included in multivariable analyses. Multivariate survival analysis was conducted using the Cox proportional-hazards regression model. Notably, $p \leq 0.05$ was set as the threshold for statistical significance. The SPSS® software (Version 20.0) was used for statistical analyses.

Results

Demographic characteristics

Clinical records for 18 SGS patients who had diagnosed between 2013 and 2020 at Tangdu Hospital were analyzed. Their clinical information is presented in Table 1. Data from these patients were pooled with those from 89 patients in prior SGS studies, totaling to 107 patients. The demographic data for these patients are summarized in Table 2. In summary. There were 66 men and 41 women, 93.5% (100/107) of whose records had age data. Median age at SGS diagnosis was 53 years (range 9–82 years). About 72.0% (77/107) of the patients had their radiological data presented, among them, 94.8% (73/77) had enhancing masses. Moreover, 98.1% (105/107) of patients had SGS in known locations; in the temporal lobe (n=51), frontal lobe (n=37), parietal (n=25), and occipital lobe (n=8). Low frequency tumor locations were the insular lobe (n=3), basal ganglia (n=2), and scalp (n=2, 1.9%). In one patient, tumors were located in the cerebellum, brainstem, corpus callosum, dura, subdural, pterygomaxillary region, skull, spinal cord and paranasal sinus. Ten patients had extracranial metastases at or after SGS diagnosis (Supplementary Table).

Most of the patients (82, 76.6%) had prior GBM diagnoses, 77 of which were initial GBM diagnoses. At initial diagnosis, 97 patients were subjected to surgical resection, 4 only received biopsies while 6 patients had unreported treatments. Before SGS diagnosis, 91 and 86 patients had received radiotherapy and chemotherapy, respectively. For chemotherapy, temozolomide (TMZ) was administered to 66 patients. At SGS diagnosis, 85 patients underwent surgical resection, 4 received biopsies only, while 18 had unreported treatments. After SGS diagnosis, 6 patients received radiotherapy only, 40 received chemotherapy only, 18 received chemoradiotherapy, while 16 had unreported treatments (Supplementary Table).

Time to progression to SGS

For 105 patients (98.1%), the median disease progression duration from initial disease diagnosis to SGS was 14.0 months (range 0.5–156 months). Gender and chemotherapy before SGS diagnosis were not significantly associated with duration of disease progression to SGS, as per univariate analysis. Compared with patients younger than 60 years, patients who were aged over 60 years had longer durations of disease progression to SGS (15.0 vs. 11.0 months, p=0.003) (Figure 2A). A significantly long duration of disease progression to SGS was seen in patients with initial pathological diagnosis non-GBM, relative to GBM (40.3 vs. 12.0 months, p<0.001) (Figure 2B). Furthermore, multivariate analysis revealed that patients with initial diagnosis of non-GBM had significantly longer duration of disease progression to SGS (HR 3.651, 95%CI: 2.269-5.876, p<0.001).

Survival outcomes post SGS diagnosis

For 92 patients (86.0%), survival duration post SGS diagnosis was known and had a median of 6.0 months (95% CI, 4.72-7.28). Univariate analysis revealed that post SGS diagnosis, gender, age <60 years and chemotherapy before SGS diagnosis were not significantly associated with survival duration. A significantly longer survival duration post SGS diagnosis was observed in patients with initial diagnoses of non-GBM, compared to GBM (8.0 vs. 5.0 months, p=0.004) (Figure 3A). Compared to patients who had not been subjected to radiotherapy before SGS diagnosis, we observed a significantly worse survival duration for patients with radiotherapy before SGS diagnosis (7.5 vs. 5.0 months, p=0.022) (Figure 3B). To analyze the effects of resection of SGS, only data for patients from Tangdu Hospital were used, as that from prior studies often lacked the resection extent. After SGS diagnosis all patients underwent surgical resection and gross total resection (GTR) was achieved in 16 (88.9%) of the patients. Compared to subtotal resection (STR), GTR had a significantly longer median overall survival (OS) time (5.3 vs 1.5 months, p=0.003).

For patients who received radiotherapy after SGS diagnosis, their survival duration was longer than that of patients that were not subjected to radiotherapy after SGS (10.0 vs. 4.6 months, p=0.001) (Figure 3C). A longer survival duration was also observed in patients who received chemotherapy after SGS diagnosis, compared to those who did not receive chemotherapy after SGS (7.6 vs. 3.0 months, p<0.001) (Figure 3D). Compared to patients who received chemotherapy or radiotherapy alone, those who received chemoradiotherapy had longer survival durations (14.0 vs. 6.7 months, p=0.006). Notably, among patients with extracranial metastases, the median survival duration from diagnosis of metastasis to death was 3 months (range 1–8 months). Multivariate analysis revealed that either chemotherapy (HR 3.282, 95%CI: 1.987-5.420, p<0.001) or radiotherapy (HR 2.737, 95%CI: 1.562-4.796, p<0.001) after SGS diagnosis were independent prognostic factors for survival outcomes.

TABLE 1 Clinical data and outcomes of SGS patients in our hospital.

Case n	Age sex	Initial diagnosis	Location of primary glioma	EOR of primary glioma	Adjuvant therapy for primary glioma	Time to SGS (months)	Location of SGS	EOR of SGS	Adjuvant therapy for SGS	OS from SGS (months)	OS from initial diagnosis (months)
1	54-year, F	GBM	temporal	GTR	SRS+TMZ	10.5	temporal	GTR	TMZ	8.5	18.5
2	48-year, M	GBM	temporal	GTR	SRS+TMZ	6.8	temporal	GTR	none	5.3	11.8
3	42-year, F	AO, GBM	frontal	GTR	TMZ	21.3	frontal	GTR	TMZ	7.5	28.8
4	49-year, M	GBM	temporal	GTR	RT+TMZ	14.6	temporal	GTR	none	3.1	17.7
5	41-year, F	GBM	frontal	GTR	RT+TMZ	11	frontal	GTR	Re-op+Bev	16.7	27.7
6	46-year, M	GBM	temporal	GTR	RT+TMZ	13.8	temporal	GTR	TMZ	4.7	18.5
7	49-year, M	GBM	temporal	GTR	SRS	13.6	temporal	GTR	none	3.3	16.9
8	38-year, M	AO	temporal, insular	GTR	none	11.3	temporal, insular	GTR	none	2.1	13.4
9	59-year, F	GBM	frontal, temporal	PR	none	3.9	frontal, temporal	PR	none	1.5	5.4
10	50-year, F	AA	frontal	GTR	RT	19.7	frontal	GTR	TMZ	7.3	27
11	21-year, M	AE	fourth ventricler	GTR	SRS+TMZ	29.1	thoracic, lumbar	GTR	none	2	31
12	67-year, M	GBM	temporal, parietal	GTR	RT+TMZ	19.8	temporal, parietal	GTR	TMZ	25.5	5.7
13	45-year, M	GBM	frontal	GTR	RT+TMZ	12.5	frontal	GTR	none	1.5	14
14	63-year, M	GBM	temporal	GTR	RT+TMZ	14.6	temporal	GTR	none	4.4	19
15	45-year, F	GBM	temporal	GTR	RT+TMZ	40.2	temporal	GTR	TMZ	11.5	51.7*
16	40-year, F	AA	frontal	GTR	RT+TMZ	16	frontal	GTR	TMZ	6.1	22.1
17	27-year, F	LGO	temporal, insular	GTR	None	62.3	temporal	PR	RT+TMZ	16.3	82.6
18	58-year, M	GBM	temporal	GTR	RT+TMZ	62.4	temporo-occipital	GTR	none	2.8	65.2

M, male; F, female; GBM, glioblastoma; AO, anaplastic oligodendroglioma; AA, anaplastic astrocytoma; AE, anaplastic ependymoma; LGO, low grade oligodendroglioma; EOR, extent of resection; GTR, gross total resection; PR, partial resection; SRS, stereotactic radiosurgery; TMZ, temozolomide; RT, radiotherapy; Re-op, reoperation; Bev, bevacizumab; OS, overall survival
*The patient remained alive at the end of follow-up.

Survival outcomes of patients with initial GBM diagnosis

For 72 patients (93.5%), the median OS time for patients with initial GBM diagnosis was known and had a median of 18.5 months (range 5.4–65.2 months). For treatment, 67 patients (88.3%) received radiotherapy and chemotherapy. The median survival time post SGS diagnosis was known for 73 patients and had a median of 5.0 months (range 0.73–46.4 months). After SGS diagnosis, 46 patients received adjuvant radiotherapy and/or chemotherapy while seven patients were re-operated on due to SGS recurrence. Compared with patients who did not receive any treatment after SGS diagnosis, patients who treated with adjuvant radiotherapy, chemotherapy and/or re-operated had longer survival outcomes after SGS diagnosis (6.7 vs 2.8 months, $p<0.001$). Patients who had received radiotherapy and chemotherapy for GBM and active therapy for SGS had a median survival time of 18.6 months.

Discussion

Gliosarcoma is a rare tumor that is classified as either primary or secondary gliosarcoma. In a recent meta-analysis, incidences of IDH1/2 mutation, EGFR mutation, and MGMT methylation between PGS and SGS were found to be comparable, however, survival analysis revealed that compared with PGS, SGS is associated with significantly worse PFS and OS outcomes (20). A retrospective study from the MD Anderson Cancer Center showed that the median OS outcome from pathological diagnosis of primary and secondary GS were 17.3 months and 10.2 months, respectively ($p < 0.01$) (21). A retrospective analysis found that PGS patients had significantly high PFS ($p < 0.03$) and OS ($p < 0.031$), compared to SGS patients (9). To gain a better understanding of SGS and design effective treatment strategies for its management, apart from our cases, we performed a systematic review and analysis of literature.

To the best of our knowledge, with a total of 107 patients, this is the largest SGS study. Analysis of patient data revealed disease

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TABLE 2 Demographic data for all patients.

Characteristics	n=107
Age, years; median(range)	53 (9-82)
Sex, n (%)	
Male	66 (61.7%)
Female	41 (38.3%)
Tumor location, n (%)	
Temporal	51 (47.7%)
Frontal	37 (34.6%)
Parietal	25 (23.4%)
Occipital	8 (7.5%)
Insular	3 (2.8%)
Basal ganglia	2 (1.9%)
Scalp	2 (1.9%)
Other	10 (9.4%)
Unreported	2 (1.9%)
Extracranial metastases, n (%)	
Yes	10 (9.4%)
No	85 (79.4%)
Unreported	12 (11.2%)
Initial diagnosis, n (%)	
GBM	77 (72.0%)
non-GBM	30 (28.0%)
Adjuvant treatment before SGS diagnosis, n (%)	
Radiotherapy	91 (85.1%)
Chemotherapy	86 (80.4%)
Palliative treatment	9 (8.4%)
Unreported	2 (1.9%)
Surgery of SGS diagnosis, n (%)	
Resection	85 (79.4%)
Biopsy	4 (3.7%)
Unreported	18 (16.8%)
Adjuvant treatment after SGS diagnosis, n (%)	
Radiotherapy	24 (22.4%)
Chemotherapy	57 (54.2%)
Palliative treatment	27 (25.2%)
Unreported	16 (15.2%)

SGS, secondary gliosarcoma.

characteristics and optimal treatment strategies. Lesions were most often located in the temporal lobe (48.6%), and GBM was the most common initial diagnosis (72.0%). After SGS diagnosis, aggressive radiotherapy and chemotherapy were most effective therapeutic options.

Clinically, SGS have been defined in different ways, one of which is tumors diagnosed at recurrence after initial GBM diagnosis (14). Another is tumors detected after a high-grade glioma was either resected or irradiated (16, 22, 23). Other studies defined SGS as those arising from non-irradiated WHO grade II glioma (15, 24). Gliosarcoma originating from grade II oligodendroglioma that had been pretreated with radiotherapy has also been reported in other studies (17, 25). Based on the above studies, we propose the definition of SGS as tumors that originate from a pre-existing glioma, usually after radiation treatment.

Extracranial metastasis of CNS tumors is rare due to the blood-brain barrier and the absence of lymphatic vessels in the CNS (26, 27). The reported incidences of extracranial metastases for GBM vary between 0.4–0.5% (26), which is comparatively low than the 11% frequency for GS, which is commonly known to metastasize to the lungs, liver, and lymph nodes (28). In 2010, Han et al. (14) reported 30 cases of confirmed SGS, of which one patient had scalp/subgaleal metastasis. In 2013, 44 SGS cases were reported, of which five patients had extra-cranial metastases (29). In this study, ten patients developed extracranial metastases at or after SGS diagnosis with the lungs being the most common metastatic site (three patients). This implies that SGS is likely to undergo extracranial metastasis, therefore, identification of potential extracranial diseases, during initial diagnosis and continued surveillance is necessary.

The association between extracranial metastases of glioma and prognosis has been previously investigated. In a meta-analysis of 88 cases of extracranial glioblastoma (five were GS) (26), the median time from diagnosis of primary glioblastoma to detection of extracranial metastasis was 8.5 months, while from metastasis to death was 1.5 months, with lung metastasis patients having the worst survival outcomes. Sun et al. (30) reported cases of two patients who developed extracranial metastases after surgery for primary glioma, and died within 2 months of metastasis diagnoses. In this study, the median survival time from diagnosis of metastasis to death was 3 months (range 1–8 months). Therefore, when patients present with dyspnea or physical pain without deterioration of their neurologic status, clinicians should be cognizant of the possibility of metastatic disease.

In this study, among non-GBM patients at initial diagnosis, median durations from initial diagnosis to SGS and median OS post SGS diagnosis were 36 months and 8 months, respectively. These survival durations were comparable to those of patients with secondary glioblastoma (sGBM), which have been reported to be 158.9 weeks (31), and 7.8 months (32), respectively. In contrast, patients with initial GBM diagnosis had significantly shorter survival outcomes as the median duration from initial diagnosis to SGS and median OS post SGS diagnosis was 12.0 and 5.0 months, respectively. This was comparable to that of recurrent glioblastoma (rGBM) patients, who had a median survival time of approximately 6 months (33, 34). This disparity indicates that different initial diagnoses have potentially different clinical and molecular characteristics, such as sensitivity to treatment and IDH mutation rates.

In this study, the extent of resection was a significant prognostic factor for GS and this corroborated extent of resection as a crucial prognostic factor for primary GBM (35, 36), rGBM (37, 38) and sGBM (31, 39). Smith et al. (23) analyzed 22 PGS patients and showed

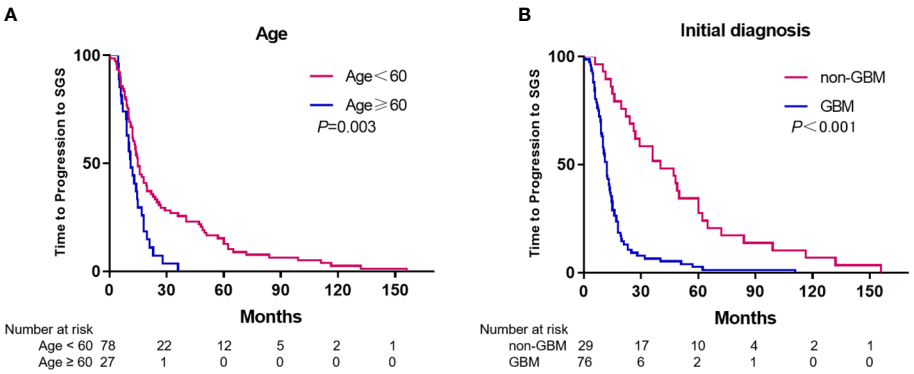

FIGURE 2
Kaplan-Meier estimates of time to progression to SGS stratified by age **(A)** and initial diagnosis **(B)**.

that the extent of resection was a significant prognostic factor in univariate but not in multivariate analysis. Moreover, for 34 GS patients (24 PGS and 10 SGS), those who had GTR at the time of first diagnosis lived longer than those with STR (40), however, this study did not analyze the SGS separately. In tandem with previous studies, we found that the median OS was significantly longer in GTR patients than STR patients, demonstrating that GTR can significantly prolong the OS outcomes of SGS patients.

In this study, for patients whose initial diagnoses were non-GBM and treated with radiotherapy, the median survival time after SGS diagnosis was longer, compared to those treated with only chemotherapy or palliative care (20.9 vs 7.3 vs 2.0 months p<0.001). However, all SGS cases were recurrent gliomas, and thus, some patients were ineligible for re-irradiation. Prior studies have noted the importance of active treatment on survival time of sGBM patients. In a single-center retrospective study of 39 sGBM patients, patients who had been subjected to adjuvant treatment exhibited longer OS, compared to patients without adjuvant treatment (18.3 vs 8.8 months, p=0.003) (39). Moreover, Gessler F et al. (31) conducted a retrospective study of 45 sGBM patients and found that radiotherapy

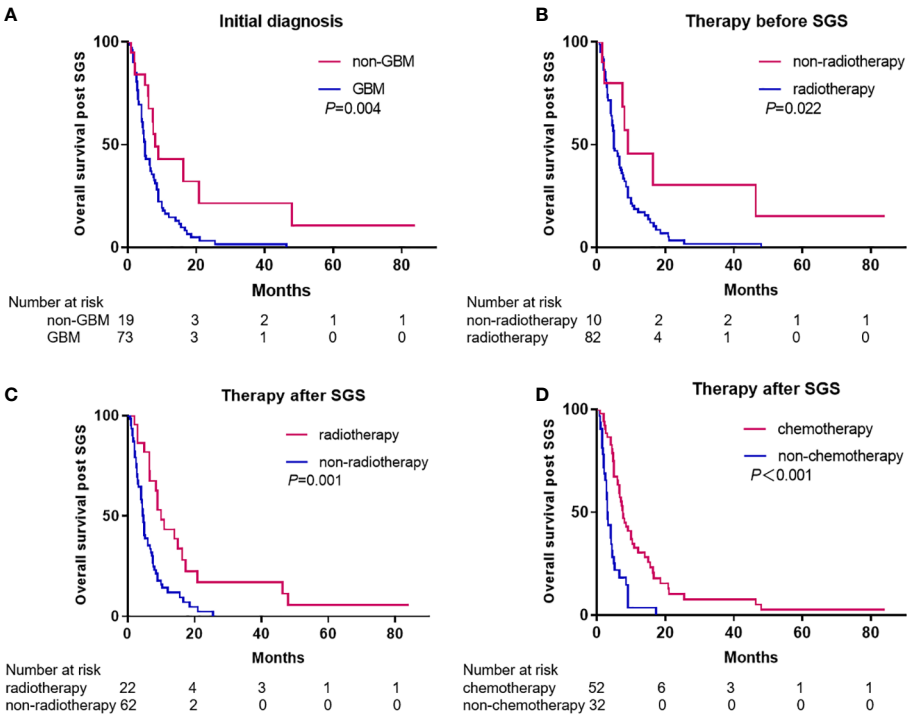

FIGURE 3
Kaplan-Meier estimates of overall survival post SGS diagnosis stratified by initial diagnosis **(A)**, therapy before SGS **(B)**, and therapy after SGS **(C, D)**.

and chemotherapy are associated with prolonged OS. Further, patients treated with chemoradiotherapy had significantly longer survival outcomes, compared with those treated with a standalone treatment (87.3 vs 54.3 weeks, $p<0.001$). These results are in tandem with our findings.

A retrospective study from the MD Anderson Cancer Center showed that the median OS time for PGS was 17.5 months (40), which was similar to that of GBM. Conversely, a multi-center study conducted by Castelli J et al. (41) found that the median OS time for PGS was only 13 months and TMZ chemotherapy was not associated with improved OS, compared to patients who received radiation therapy only. Another study involving 30 SGS patients, who relapsed after progression to GBM, found that the median OS after original GBM diagnosis was 12.6 months (14). Therefore, GS patients tend to have poor prognostic outcomes. However, a study involving 10 SGS patients (9 patients with initial GBM diagnoses and one with anaplastic oligodendroglioma) showed the median OS post original diagnosis as 18.6 months (23). This corroborates our results where the median OS was 18.6 months in patients who had received chemoradiotherapy and active therapy for treatment GBM and SGS respectively. Compared with previous studies, we enrolled a large number of SGS patients, which increased the degree of accuracy and robustness. We show that recurrence of GBM as SGS does not affect the OS time.

The O6-methylguanine DNA methyltransferase (MGMT) promoter methylation is the most important prognostic factor in GBM, especially in relation to temozolomide efficacy (42). The MGMT promoter methylation is also a significant prognostic factor for temozolomide rechallenge in rGBM (43).The MGMT status is significantly associated with OS in temozolomide-treated PGS patients, yet the frequency of MGMT promoter methylation is significantly low in PGS (26.1%) than GBM (54.6%) (8). Furthermore, the median OS time for GS patients with MGMT promoter methylation is 16.4 months versus 9.4 months for those with unmethylated MGMT promoter (44). Singh et al. detected MGMT promoter methylation in five of 16 GS patients who had been treated with temozolomide, however, the MGMT status did not significantly affect OS. Singh et al. (45) detected MGMT promoter methylation in five of 16 GS patients who had been treated with temozolomide, however, the MGMT status did not significantly affect OS. There are no relevant studies on the association between MGMT promoter methylation and OS of SGS patients. Despite this study having 16 patients with known MGMT status, no further statistical analyses were performed as only four and seven of the sixteen patients had MGMT methylation and treatment with temozolomide post SGS diagnosis, respectively. Further studies should investigate whether TMZ rechallenge is a treatment option for SGS, especially for those with MGMT promoter methylation.

Limitation

Although our findings are generally encouraging, this study has some limitations. First, this was a retrospective study, which has its inherent limitations. Second, given that most cases were based on previously published articles, it was inevitable that some clinical data were not available in all studies, such as pre- and postoperative KPS scores, extent of resection and number of chemotherapy cycles. Third, for data from studies that spanned long durations, treatment regimens often differed between patients and treatment-related adverse effects were not always recorded. Fourth, several important molecular markers, such as IDH and telomerase reverse transcriptase (TERT) promoter mutations as well as epidermal growth factor receptor (EGFR) amplification were not available. Studies should aim at elucidating the clinicopathologic features, treatment strategies, and outcomes of SGS patients.

Conclusion

Despite the rarity of SGS, 107 SGS patients were included in the final analysis, making this the largest study of SGS patients to date. Patients with an initial non-GBM diagnosis had favorable prognostic outcomes. After SGS diagnosis, there was a high risk of extracranial metastasis, and the lung was the most common metastatic site. Extracranial metastases were associated with poor prognoses. Patients with GTR and chemoradiation after SGS diagnosis exhibited better overall survival outcomes, therefore, we recommend that the most suitable SGS treatment strategy is maximal safe resection combined with adjuvant chemoradiotherapy. However, during treatment, clinicians should be cognizant of possible extracranial metastases.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author contributions

JL performed the data analyses and drafted the manuscript. CL performed the clinical analyses (imaging data) with YW and contributed to writing of the manuscript. PJ, SG and YZ contributed to data analyses. NW and MX performed the clinical follow up. LW performed the clinical analyses and designed the study with JW. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that this study was performed in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1026747/full#supplementary-material

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Association of smoking with the survival of patients with brain metastasis of lung cancer

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Background: Smoking is associated with increased mortality in patients with cancer. However, there are limited data on the impact of smoking on the survival of patients with brain metastases. Therefore, this study aimed to evaluate whether smoking was associated with survival and whether smoking cessation was beneficial to these patients.

Methods: This study used lung cancer with a brain metastasis cohort of the West China Hospital of Sichuan University from 2013 to 2021. Patients were stratified according to smoking history; the distribution, clinical characteristics, and survival data of each group were estimated. Kaplan-Meier analysis and risk analysis were performed for the survival endpoint.

Results: Of the 2,647 patients included in the analysis, the median age was 57.8 years, and 55.4% were men. Among them, 67.1% had no smoking history, 18.9% still smoked, and 14% reported quitting smoking. Compared with never smokers, current smokers [HR, 1.51 (95% CI, 1.35-1.69), $p < 0.01$] and former smokers [HR, 1.32 (95% CI, 1.16-1.49), $p < 0.01$] had an increased risk of death. However, quitting smoking was not associated with improved survival [HR, 0.90 (95% CI, 0.77-1.04), $p = 0.16$]. The overall survival increased with the increase of smoking cessation years.

Conclusions: In lung cancer patients with brain metastases, smoking was associated with an increased risk of death, but quitting smoking was not associated with improved survival.

KEYWORDS

smoking, lung cancer, brain metastasis, smoking cessation, the overall survival

Introduction

Lung cancer is the leading cause of cancer-related death (1). Approximately 81.3% of patients with lung cancer are related to smoking (2). Although the overall smoking prevalence has decreased significantly in the past years, cigarette smoking remains the leading cause of lung cancer cases and deaths (3). Smoking in patients with cancer increases overall mortality, cancer-specific mortality, treatment-related toxicity, and second primary cancer (4, 5). The 2020 Surgeon General's Report on quitting smoking added many new pieces of evidence and conclusions to reveal the benefits of quitting smoking even after the diagnosis of cancer (6). The American Association for Cancer Research, EMSO, the WHO, and other organizations advocate smoking cessation as a standard cancer treatment (7–10). More than half of lung cancers develop into brain metastasis during the course of the disease (11). However, guidelines rarely specifically recommend smoking cessation for brain

metastasis. Brain metastasis is a sign of poor prognosis in patients with lung cancer, and the expected survival time is short (12). Patients with advanced cancer are willing to quit smoking differently from those diagnosed early. Pain, second-hand smoke exposure, guilt about smoking, fear of stigmatization, and fatalism of disease may represent obstacles to smoking cessation in patients with cancer, particularly in those with advanced disease (13–16).

There is less evidence about the impact of smoking on the survival of patients with brain metastases and the benefits of quitting smoking on patients with brain metastases. Only a small study of 366 brain metastases in patients with lung cancer found that smoking had no effect on overall survival (17). Therefore, we conducted this study to evaluate whether smoking affects the overall survival rate of lung cancer patients with brain metastasis and the benefits of quitting smoking on survival.

Methods

Study population

This study is a single-center retrospective cohort study on the survival rate of lung cancer patients with brain metastasis in China. From December 2013 to August 2021, lung cancer patients with

TABLE 1 Clinical and smoking characteristics of lung cancer patients with brain metastases.

Characteristic	All patients	Smoke			*P*-value
		Never	Former	Current	
Participants, *n* (%)	2,647 (100.0)	1,775 (67.1)	371 (14.0)	501 (18.9)	
Mean age (SD), y	57.8 (11.0)	57.4 (11.5)	59.6 (10.3)	57.9 (9.8)	0.002
Gender, *n* (%)					<0.001
Male	1,468 (55.4)	620 (35.0)	362 (97.5)	486 (97.0)	
Female	1,179 (44.6)	1,155 (65.0)	9 (2.5)	15 (3.0)	
Histology, *n* (%)					<0.001
Adenocarcinoma	2,416 (91.3)	1,672 (94.1)	316 (85.1)	428 (85.4)	
Non-adenocarcinoma	231 (8.7)	103 (5.9)	55 (14.9)	73 (14.6)	
KPS, *n* (%)					0.593
≤70	636 (24.0)	424 (23.8)	84 (22.6)	128 (25.5)	
>70	2,011 (76.0)	1,351 (76.2)	287 (77.4)	373 (74.5)	
Past medical history, *n* (%)					
Hypertension	439 (16.5)	287 (16.1)	72 (19.4)	80 (15.9)	0.287
Diabetes	233 (8.8)	126 (7.0)	53 (14.2)	54 (10.7)	<0.001
Alcohol drinking, *n* (%)					<0.001
Yes	545 (20.6)	69 (3.8)	188 (50.9)	288 (57.4)	
No	2,102 (79.4)	1,706 (96.2)	183 (49.1)	213 (42.6)	
BMI, *n* (%)					0.005
<18.5	221 (8.4)	157 (8.8)	20 (5.4)	44 (8.8)	
18.5–23.9	1,801 (68.0)	1,228 (72.6)	239 (64.4)	334 (66.7)	
≥24	625 (23.6)	390 (18.6)	112 (30.2)	123 (24.5)	
Number of brain metastases, *n* (%)					0.677
<3	1,680 (63.4)	1,128 (63.5)	241 (64.9)	311 (62.0)	
≥3	967 (36.6)	647 (36.5)	130 (35.1)	190 (38.0)	
Extracranial metastasis, *n* (%)					0.006
Yes	515 (19.4)	321 (18.1)	94 (25.3)	100 (19.9)	
No	2,132 (80.6)	1,454 (81.9)	277 (74.7)	401 (80.1)	
Treatment, *n* (%)					
Chemotherapy alone	445 (16.8)	282 (15.8)	57 (15.3)	106 (21.1)	0.015
Radiotherapy alone	80 (3.0)	49 (2.7)	16 (4.3)	15 (2.9)	0.283
Target therapy alone	147 (5.5)	116 (6.5)	9 (2.4)	22 (4.3)	0.003

BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status.

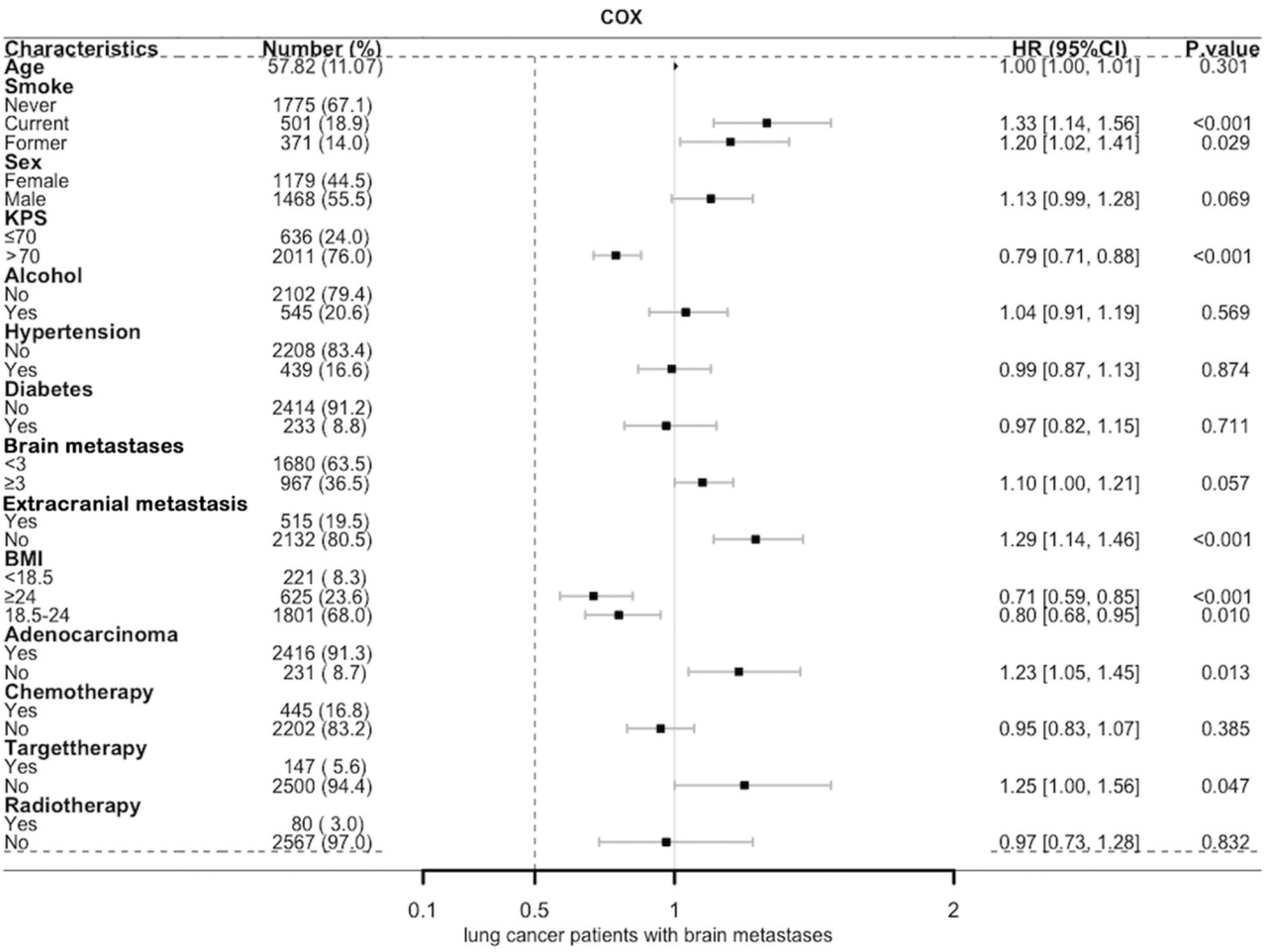

FIGURE 1
Multivariate Cox forest map of lung cancer patients with brain metastases. BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status; Brain metastases, number of brain metastases.

brain metastasis coded C34 and secondary invasive C79.3 were screened from the West China Hospital of Sichuan University database according to the 10th edition of the International Classification of Diseases for Oncology (18).

Data collection and follow-up

Electronic medical records and social population registration records collected information about demographic characteristics, family, medical history, and survival time. We actively collected data on smoking behavior through the electronic medical record, including the years of smoking, the average amount of smoking per day, whether they had quit smoking, and the time they had quit smoking. We multiplied the number of cigarette packs smoked per day by the patient's number of years and calculated the cumulative smoking per pack-year (based on 20 cigarettes per pack). A patient was classified as a current smoker if he/she had evidence of active smoking or had <1 year of smoking cessation. Moreover, we classified patients who quit smoking at least 1 year before diagnosis as former smokers.

Patients' general conditions when diagnosing diseases were also obtained, including anthropometric data, functional status, chronic health conditions, and Karnofsky performance status (KPS) score. The number of brain metastases and other metastases was also recorded. We also collected their history of drinking in their life. Drinking is defined as drinking alcoholic drinks at least one time a week in a year. We sorted all relevant treatment history, imaging, and histopathological information into the patient's data, and determined electronic medical records and follow-up records after the patient's diagnosis, life state, tumor progression, and the treatment process during the disease. This study was approved by the ethics committees of the West China Hospital and the written consent for patients included 161 in the study was exempted by the ethics committees since the study only used retrospective observation data (No. 2022127).

Statistical analyses

Descriptive statistics were conducted to summarize baseline characteristics, with numbers and percentages for categorical

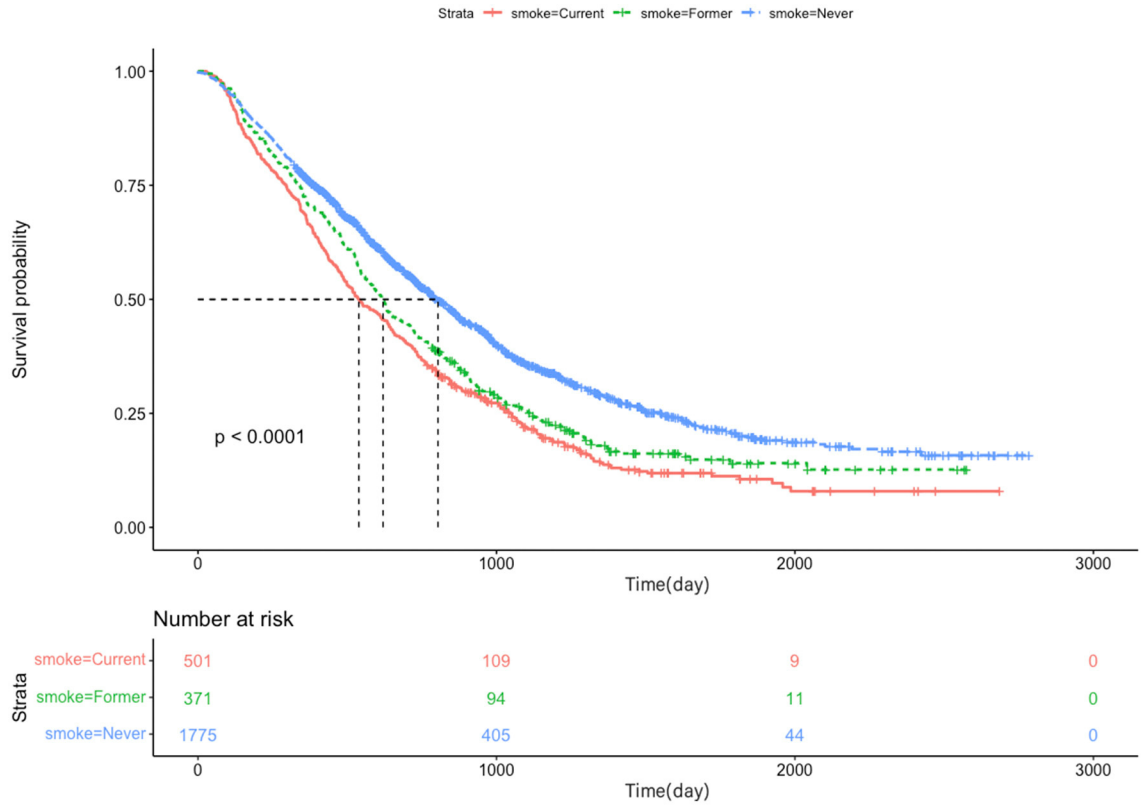

FIGURE 2
Kaplan–Meier plots of overall survival for lung cancer patients with brain metastases based on smoking status.

variables and means for continuous variables. We imputed the missing values with the average value. Hazard ratios (HR) and 95% confidence interval (95% CI) for survival associated with smoke were estimated using Cox proportional hazards model. Stratified analyses and multivariate Cox proportional hazards analyses controlled for potential confounding. The multivariable model was adjusted according to the age, gender, KPS score at diagnosis, histological type (including adenocarcinoma and non-adenocarcinoma), past medical history (including diabetes mellitus and hypertension), the number of intracranial metastases, the presence of extracranial metastasis, the radiotherapy alone, target therapy alone, chemotherapy alone, the cumulative amount of smoking at diagnosis, whether to quit smoking, the time of quitting smoking, and the drinking status at diagnosis. The model covariates were selected based on the available literature to include the suspected prognostic factors for lung cancer with brain metastasis survival and the variables that might influence the assessed exposure (19–22). Kaplan–Meier survival curves were used to compare the survival of current, former, and never smokers, and the log-rank test was used to test this difference.

In this model, the start time is defined as the patient's first admission date and diagnosis as brain metastasis of lung cancer. To assess the effect of smoking and quitting smoking on overall survival, the date of death from any cause was set as the end time. If the patient is still alive within the follow-up time, we set the follow-up time (15 August 2021) as the end date for the patient. Overall survival (OS) was defined as the interval from diagnosis of brain metastases to death. A subgroup analysis was also performed among current and former smokers, including the smoking intensity and duration since smoking cessation. *P*-values that were reported as two-sided and <0.05 were considered statistical differences. All statistical analyses were bilateral and performed using R statistical software (version 4.0.3, Vienna, Austria).

Results

The study collected 2,647 lung cancer patients with brain metastasis, the median age was 57.8, and 55.4% were men. Among them, 67.1% had no smoking history, 18.9% still smoked, and 14% reported quitting smoking. The median overall survival for the cohort was 2 years (95%CI: 1.9–2.1). The median overall survival rates of never smokers, former smokers, and current smokers were 2.2 years (95%CI: 2.1–2.3), 1.7 years (95%CI: 1.5–1.9), and 1.5 years (95%CI: 1.3–1.7), respectively. The baseline characteristics of patients are shown in Table 1.

In a univariate analysis of the entire population, current smokers [HR, 1.51 (CI, 1.35–1.69), $p < 0.01$] and former smokers [HR, 1.32 (CI, 1.16–1.49), $p < 0.01$] had an increased risk of death compared with never smokers. After adjustment for potential confounders and risk factors, smokers (current and former smokers) still had an increased risk of death (Figure 1). However, compared with the current smoker, we did not see the

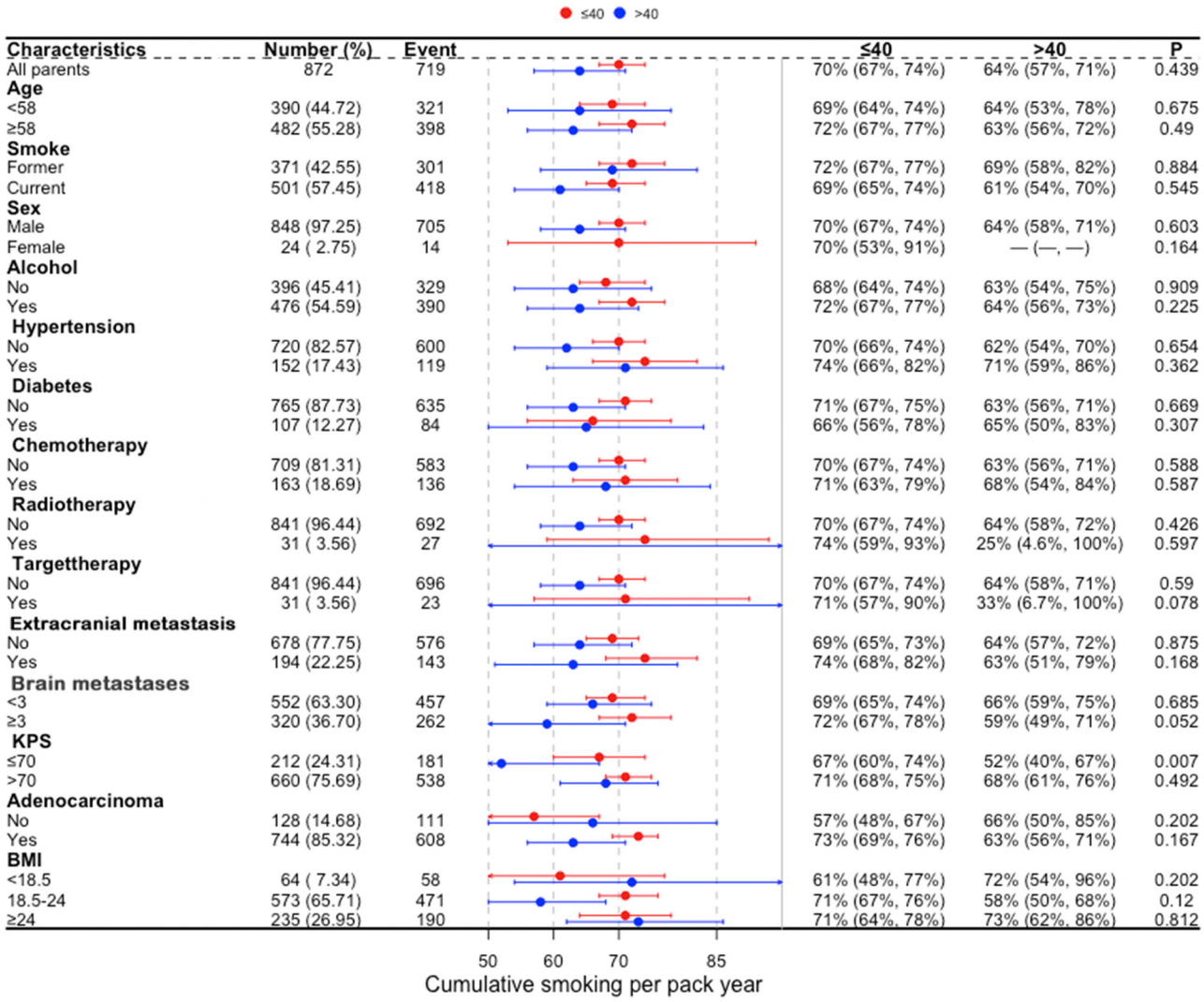

FIGURE 3
Subgroup analysis of cumulative smoking in current smokers and former smokers for lung cancer patients with brain metastases. BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status; Brain metastases, number of brain metastases.

benefits of quitting smoking for the overall survival of patients [HR, 0.90 (CI, 0.77–1.04), $p = 0.16$] (Supplementary Figure 1). Figure 2 shows the Kaplan–Meier plots of overall survival for patients based on smoking status. The cumulative pack years of smoking and smoking cessation duration of 371 former smokers and 501 current smokers were analyzed by subgroup analysis. According to the Cox proportional hazard analysis, annual cumulative smoking was used as a categorical variable, and smokers were divided into cumulative package years of ≤40 pack-year and cumulative package years of >40 pack-year; we found that cumulative smoking was not associated with overall survival in current smokers and former smokers (Figure 3). To assess the "time response" effect of quitting smoking, a total of five groups were generated according to the time of quitting smoking: current smokers, quitting smoking for 1–5 years, quitting smoking for 5–10 years, quitting smoking for ≥10 years, and never smokers. Figure 4 shows that the overall survival rate increased with smoking cessation years, but this was not statistically significant.

Discussion

This retrospective study analyzed the survival of 2,647 lung cancer patients with brain metastasis. The results showed that smoking affected the overall survival rate of lung cancer patients with brain metastasis. However, smoking cessation was not associated with higher survival than current smoking.

Contrary to our study, previous studies did not find an association between smoking and lung cancer brain metastasis. Kim et al. analyzed 313 non-small-cell lung cancer (NSCLC) patients with brain metastasis, and univariate analysis showed that smoking affected the overall survival; however, there was no difference in the overall survival in the multivariate analysis (23). In another study of patients with non-small-cell lung cancer, only non-smokers in stage I had a significant survival advantage over smokers, and smokers who quit smoking in stage II or III disease had no significant reduction in the risk of death (24). But our

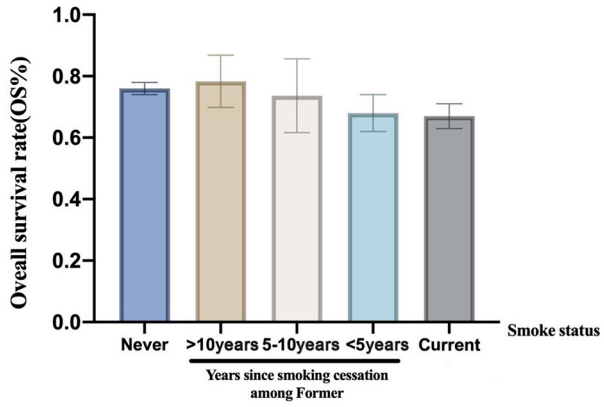

FIGURE 4
The overall survival rate stratified according to smoke status and years since tobacco cessation.

study found that smoking increased the risk of death in lung cancer patients with brain metastases. This difference in part may be explained by our large size simple to make the results more precise.

Previous studies have shown that smoking increases the risk of brain metastasis (17, 25). Nicotine promotes brain metastasis by polarizing microglia and inhibiting innate immune function (25, 26). In addition, smoking affects the effect of chemotherapy in advanced patients (27), and a significant difference in tumor biology is the higher EGFR mutation rate of never smokers, which may explain the better prognosis of never smokers after treatment for the EGFR gene (28). It is shown that smoking and tobacco products alter biological pathways of cancer leading to increased proliferation, invasion, migration, angiogenesis, decreased response to cytotoxic therapy, and activation of pro-survival cellular pathways (29, 30). These may be the reasons for the difference in prognosis between never smokers and patients with a history of smoking. Some study also suggests that there is a dose-dependent relationship between smoking and the survival of patients with lung cancer (31, 32). In contrast to these results, our study showed that compared with light to moderate smokers, the overall survival of the heavy smoker (>40 pack-years) was not significantly decreased.

Smoking is a main prognostic factor of lung cancer. Evidence has shown that smokers who quit smoking for more than 1 year had higher survival than current smokers. Zhou et al. suggested that overall survival increased with the increase in smoking cessation time among patients with early-stage NSCLC (33). Nia et al. concluded that patients with early-stage NSCLC who quit smoking have significantly less mortality than current smokers (34). In a study of 4,200 smokers in the National Comprehensive Cancer Network NSCLC cohort, only young patients with stage IV disease who quit smoking >12 months before the diagnosis gained survival benefits (35). However, we did not find the benefits of quitting smoking for lung cancer patients with brain metastasis. Our study suggested that long-term continuous quitting smoking may have the trend of increasing survival. Paradoxically, when patients with lung cancer have brain metastasis, the median survival time is short, thus, they may not get the benefits of long-term quitting smoking. However, cumulative smoking cessation time before the diagnosis of brain metastasis may be essential to improve survival.

This study has several limitations. First, the patient's smoking history and smoking cessation are from electronic medical records, which will deviate from the patient's self-report. A study revealed that up to 50% of cancer patients' self-reporting about smoking may be inaccurate (36). Second, our information collection on tobacco intake is based on cigarettes, ignoring alternative products such as tobacco and nicotine. Third, although the large sample size is a strength of our study, this is a study of a single agency and the patients included in the cohort are all Asian. Therefore, the generalizability of the results to other populations is questionable.

Conclusion

Different from previous studies, this study is not limited to patients with non-metastatic lung cancer. Although the survival time of patients with metastatic lung cancer is short, our results still show the harm of smoking to patients with brain metastasis of lung cancer. The survival rate of patients with smoking is lower than that of patients without smoking. We failed to find the relationship between quitting smoking and survival.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

XP and FF conceived the study. JY performed the main analysis and wrote the original draft. ZL retrieved the data. YZ participates in the revision of the manuscript. The study reported in the manuscript has been performed by JY, YZ, ZL, YH, YP, RZ, XP, and FF unless clearly specified in the text. All authors read, approved the manuscript, and conducted data screening and collation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1036387/full#supplementary-material

SUPPLEMENTARY FIGURE 1
Multivariate Cox forest map of lung cancer patients with brain metastases. BMI, body mass index (recorded when brain metastases was diagnosed); KPS, Karnofsky performance status; Brain metastases, number of brain metastases.

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