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RESEARCH

Clinicopathological, immunohistochemical and therapeutic approaches on survival in patients with epithelioid glioblastoma: Institutional experience in the management of 58 patients

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Abstract

Epithelioid glioblastoma (Ep-GBM) is a rare variant of glioblastoma characterized by a high recurrence rate and poor prognosis. Currently, there is no established standard treatment for Ep-GBM. Therefore, we identified 58 Ep-GBM cases to investigate these characteristics and identify the possible prognostic factors of survival. There were 30 male and 28 female patients with a median age of 39 years. Headaches and dizziness were the most common clinical symptom. The tumor is most frequently located in the temporal lobe (36.2%). The positivity rate for BRAF-V600E is 56.9% (33/58), for MGMT is 56.9% (33/58), and for INI-1 is 75% (30/40). Tumor recurrence was observed in 39 patients. The median progression-free survival (PFS) of all patients was 12.7 months, while the median overall survival (OS) was 29.1 months. Additionally, the median survival time after recurrence was 14.3 months. Both univariate and multivariate COX regression analyses revealed that individuals who received more than six cycles of adjuvant oral temozolomide experienced a longer median PFS compared to those who received fewer cycles. Characteristics associated with poorer PFS included tumor dissemination prior to initial surgery. Additionally, both analyses identified tumor dissemination, radiotherapy and adjuvant oral temozolomide as predictors of OS. Notably, for patients with recurrent Ep-GBM, reoperation was shown to significantly increase survival time after recurrence. In conclusion, the standard Stupp regimen is also applicable to patients with Ep-GBM, extending adjuvant oral temozolomide could further improve survival for Ep-GBM patients, reoperation may also prolong survival for recurrent Ep-GBM.

Keywords Epithelioid glioblastoma · Chemoradiotherapy · Reoperation · Recurrent Ep-GBM

Introduction

Glioblastoma (GBM) stands as the most common malignant tumor of the central nervous system, with the highest occurrence rate among all brain tumors [1]. In 2016, a new GBM subtype, epithelioid glioblastoma (Ep-GBM), was added to the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS). In the 2021 WHO classification of CNS tumors [2], Ep-GBM was still recognized as a subtype of GBM. Ep-GBM distinguished it from other GBM types [3]. Histologically, Ep-GBM is manifests with abundant epithelioid and melanoma-like cells, which exhibit features such as abundant cytoplasm, eccentric nuclei, prominent nucleoli, and rhabdomyosin-like attributes [4]. Unlike conventional GBM, Ep-GBM is more prevalent in children and young adults and exhibits aggressive behaviors such as cerebrospinal

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fluid dissemination and central nervous system metastases. Ep-GBM presents a notably poor prognosis, with significantly worse outcomes than other GBM types [5]. Presently, therapeutic recommendations for Ep-GBM do not account for histological variations [6].

Recent studies suggest that Ep-GBM [7], as characterized by histopathological features, is not a singular diagnostic entity. Instead, it consists of at least three distinct tumor subtypes: PXA-like tumors, IDH-wildtype GBM-like tumors, and RTK1 pediatric GBM-like neoplasms. Each of these subtypes differs molecularly and biologically. They also vary significantly in their prevalence across different populations and exhibit distinct prognostic outcomes. Due to the relative rarity of Ep-GBM, comprehensive research on this tumor is limited. Most available literature consists of case reports or retrospective case series involving a relatively small number of cases. Therefore, the primary aim of this study was to thoroughly investigate and evaluate the clinicopathological features, treatment methods, and their impact on the prognosis of Ep-GBM. We anticipate that the findings of this study will provide valuable insights for facilitating the clinical diagnosis and treatment of Ep-GBM, as well as offer support and guidance to healthcare professionals and patients.

Materials and methods

Study participants

A retrospective review was conducted on glioma patients who received treatment at the Guangdong Sanjiu Brain Hospital and the First Affiliated Hospital of Jinan University. Progression-free survival (PFS) is defined as the period from surgery to the occurrence of postoperative tumor recurrence, metastasis, or the last follow-up date. Overall survival (OS) is typically defined as the duration from the surgical procedure to either the patient's demise or the last follow-up visit. Recurrent survival time refers to the duration from surgery following recurrence to the patient's death or last follow-up. For patients who were lost to follow-up midway through the study, those who died from causes unrelated to the study, or those who were still alive at the follow-up cutoff, we classified their survival time as censored data. Similarly, for patients who voluntarily withdrew from treatment, if they were still alive at the time of withdrawal, their data was also treated as censored. In this retrospective study, patient data were anonymized, eliminating the need for informed consent from the patients' guardians. The study was conducted in accordance with the principles of the Declaration of Helsinki and received authorization from the hospital's medical ethics committee.

Patient surveillance and follow-up

Patients with Ep-GBM underwent follow-up assessments involving brain MRI every 2 months after the initial radiotherapy for 2 or 3 years under the supervision of a multidisciplinary team. If a patient developed a new symptom or if the neurological symptoms deteriorated, then MRI was performed regardless of the scheduled follow-up period. When clinically indicated, surgery was performed to confirm the final diagnosis of a viable tumor. If surgery was not possible, then the viable tumor was determined using MRI in accordance with the RANO criteria and serial follow-up examinations with intervals of at least 3 months were performed. The clinicoradiological diagnosis was determined by a consensus reached during a multidisciplinary meeting involving two neuro-oncologists (all with 20 and 7 years of experience with neuro-oncology) and three neuroradiologists (with 18, 10 and 6 years of experience with neuro-oncologic imaging, respectively). When a contrast-enhancing lesion exhibited a steady increase in size during two or more successive follow-up MRI examinations within a 2- to 3-month interval. the patient was classified as having tumor recurrence. In contrast, when a contrast-enhancing lesion subsequently regressed or became stable without a change in treatment within 6 months of the index imaging, the patient was categorized as no recurrence.

The extent of tumor resection was determined by comparing a 24–72 h postoperative MRI to that of preoperative imaging. Gross total resection (GTR) was defined by the absence of visible residual tumors on postoperative T1-enhanced MRI findings, if only marginal enhancement of the resection cavity is observed on postoperative MRI imaging, it is classified as subtotal resection (STR), whereas the presence of residual tumor on these MRI results was designated as partial resection (PR). All cases were reviewed by a multidisciplinary neuro-oncology clinic comprised of neurosurgeons, neuro-oncologists, and radiation oncologists. Patients in good clinical condition with tumors that originate near the previous cavities and do not involve eloquent cortical areas, basal ganglia, diencephalic or brainstem structures, with a PFS of at least 6 months, are generally considered candidates for reoperation.

Pathological testing

Tumor tissue samples were fixed in 10% formalin and embedded in paraffin. Subsequently, the paraffin-embedded tumor sections, 3-μm thick, underwent staining using the standard hematoxylin and eosin staining method.

Immunohistochemical staining was performed using the SP method and monoclonal antibodies against several markers, including glial fibrillary acidic protein (GFAP), methylguanine DNA methyltransferase (MGMT), oligodendrocyte transcription factor 2 (Olig-2), X-linked alpha-thalassemia mental retardation syndrome (ATRX), Integrase interactor (INI-1), BRAF-V600E (VE1), IDH-1, H3K27m, P53, and Ki-67 proliferation index.

Statistical analysis

Parametric data were expressed as means ± standard deviations and compared via the Student t-test. Nonparametric data were expressed as median values (interquartile range) and compared via the Mann–Whitney U-test. Percentages were compared via the chi-square test or Fisher exact test based on sample size. Survival analysis was conducted using the Kaplan–Meier method, with intergroup comparisons facilitated by the log-rank test. Factors influencing patient endpoint events were analyzed using both univariate and multivariate Cox regression methods. Factors with a p-value < 0.2 in the univariate analysis were subsequently included in the multivariate analysis. The significance level was set at $p < 0.05$. All statistical analyses were performed using SPSS 27.0.

Results

Patient demographics

From January 2017 to January 2024, Guangdong Sanjiu Brain Hospital and the First Affiliated Hospital of Jinan University diagnosed approximately 1,500 cases of glioblastoma. Within this period, 68 cases were specifically identified as Ep-GBM. Due to incomplete clinical data for 10 of these patients, they were excluded from our study, resulting in a final cohort of 58 Ep-GBM cases for analysis. The median age was 39 years, ranging from of 5 to 70 years. Regarding the gender distribution, 30 patients were male and 28 female. The pre-operative KPS scores for all patients averaged 80, with scores ranging from 30 to 100. The most frequently reported initial symptoms among the patients were headache and dizziness, which occurred in 42 cases, followed by limb weakness and sensory abnormalities in 6 cases, epilepsy in 6 cases, memory loss in 3 cases, and blurred vision in both eyes in 1 case.

Except for 1 case located in the left cerebellar hemisphere, patients with Ep-GBM predominantly exhibited tumor onset inside the cerebral hemispheres. There were 25 cases in the right cerebral hemisphere, with 10 cases located in the right temporal lobe, 5 in the right frontal lobe, and 10 cases involving multiple lobes. Additionally, 31 cases were found in the left cerebral hemisphere, including 11 cases in the left temporal lobe, 5 cases in the left parietal lobe, 3 cases in the left frontal lobe, 1 case in the left occipital lobe, 1 case in the left thalamus, and 10 cases involving multiple lobes. In addition, 1 case was mentioned in the callosal pressure Sect. 22 cases experienced tumor metastasis, of which 17 had leptomeningeal dissemination and 5 had cerebrospinal fluid dissemination. Clinical data are summarized in Table 1.

Treatment

Initial treatment

In our study of patients diagnosed with Ep-GBMs, surgical resection was considered as the primary treatment approach. GTR was successfully completed in 41 patients, while 8 individuals underwent STR and 9 individuals underwent PR. Following the surgical procedures, 38 patients were treated using the Stupp regimen, which includes fractionated conformal three-dimensional radiotherapy to a total dose of 60 Gy in 30 daily fractions of 2 Gy each was delivered, using the entire T2/FLAIR hyperintense signal to define the clinical target volume (CTV). Concomitant chemotherapy consisted of oral temozolomide at a daily dose of 75 mg/m^2 given 7 days per week from the first to the last day of radiotherapy, for at most 49 days. After a 4-week break, patients received adjuvant oral temozolomide (150–200 mg/m^2) for 5 days every 28 days. Among the patients who received radiotherapy, only one child was treated with a radiation dose of 50 Gy in 25 fractions. 38 patients received adjuvant oral TMZ for up to 6 cycles, while 20 patients received it for 8 to 12 cycles. 2 participants were administered a BRAF inhibitor.

Treatment after recurrence

Throughout the follow-up period, tumor recurrence was observed in 39 patients, 30 individuals had local recurrence, and 9 patients had dissemination via cerebrospinal fluid. Among those who experienced recurrence, 19 patients received radiotherapy, including 12 patients reirradiation as part of their treatment. 14 patients underwent surgery combined with chemoradiotherapy, 4 patients chose surgery alone, 5 patients received radiation therapy alone, and 16 patients were solely treated with TMZ chemotherapy or other forms of supportive therapy. In the trial, 4 participants were administered a BRAF inhibitor, and 1 patient received combination therapy that included both BRAF and MEK inhibitors. The majority of patients were treated to a dose of 35 to 40 Gy in 10 total fractions. In special circumstances where overlap with prior radiation fields was minimal, doses were escalated to 50 to 60 Gy in conventional 2 Gy fractions.

Table 1 Demographics of patients with epithelioid glioblastoma

Parameter		Parameter	
Age (years)		Extent of resection (%)	
Median age	39	GTR	41(70.7%)
Range	5–70	STR	8(13.8%)
Pre-operative KPS		PR	9(15.5%)
Median KPS	80	Stupp regimen (%)	38(65.5%)
Range	30–100	Recurrence (%)	39(67.2%)
Sex (%)		Local Recurrence	30(51.7%)
Male	30(51.7%)	Distant Recurrence	9(15.5%)
Female	28(48.3%)	Recurrent KPS	
Presenting symptom (%)		Median KPS	70
Headaches & dizziness	42(72.4%)	Range	50–90
Limb weakness	6(10.3%)	Treatment after recurrence (%)	
Epileptic	6(10.3%)	Surgery & radiotherapy	14(35.9%)
Diplopia	1(1.7%)	Only Surgery	4(10.3%)
Other	3(5.2%)	Only radiotherapy	5(12.8%)
Tumor location (%)		Supportive therapy	16(41.0%)
Temporal lobe	21(36.2%)	Bevacizumab (%)	10(17.2%)
Frontal lobe	8(13.7%)	BRAF inhibitor (%)	6(10.3%)
Parietal lobe	5(8.6%)	State of survival (%)	
Other	4(6.8%)	Censored	23(39.7%)
Multiple lobes	20(34.5%)	Mortality	35(60.3%)
Tumor dissemination	22(37.9%)	Median PFS (months)	12.7
Leptomeningeal dissemination	17(29.3%)	Median OS (months)	29.1
CSF diffusion	5(8.6%)	Median survival time after Recurrence (months)	14.3

KPS Karnofsky Performance Scale, *CSF* Cerebrospinal Fluid, *GTR* Gross Total Resection, *STR* Subtotal Resection, *PR* Partial Resection, *PFS* Progression-free Survival, *OS* Overall Survival

Pathologic and immunohistochemistry

Microscopically, the tumor cells exhibited infiltrative growth with densely arranged regular or round cells. Some of these cells displayed an epithelioid or rhabdomyoid shape and lacked adhesion while maintaining a clear cellular membrane and eosinophilic cytoplasm. Nuclei were frequently enlarged and irregularly shaped, often accompanied by prominent nucleoli, indicating prevalent nuclear atypia, which occasionally led to the formation of multinucleated giant tumor cells. No intratumoral microvascular or glomeruloid-like vascular hyperplasia was observed. Tumor cells exhibited a pattern of arrangement around blood vessels, forming a pseudopapillary structure. Moreover, the presence of digitiform necrosis and pseudofenestrated necrosis features could be observed within the tissue. Immunohistochemistry findings revealed positive expression of various markers: BRAF-V600E (56.9%, 33/58), MGMT (56.9%, 33/58), GFAP (89.6%, 52/58), Olig-2 (93.1%, 54/58), ATRX (86.2%, 50/58), P53 (72.4%, 42/58), INI-1 (75%, 30/40). The Ki-67 proliferation index ranged from 3–80%, with a mean of 28.7%. Notably, IDH-1 and H3K27m were observed to be negative.

Analysis of survival prognostic factors

Progression-free Survival

The median PFS for the patients was 12.7 months (95% confidence interval [CI], 6.744–18.656). Among these patients, those who underwent GTR exhibited a significantly longer median PFS than those who underwent PR ($P=0.017$) (Fig. 1). However, the differences in median PFS between GTR and STR, as well as between STR and PR, were not statistically significant ($P=0.187$ and $P=0.542$, respectively). Additionally, patients who received more than 6 cycles of TMZ adjuvant chemotherapy demonstrated a significantly extended median PFS compared to patients who received fewer than 6 cycles ($P=0.007$) (Fig. 2). In the univariate survival analysis, the PFS of the patients was examined in relation to various parameters. Notably, only the tumor dissemination ($P=0.038$, hazard ratio [HR] = 1.974,

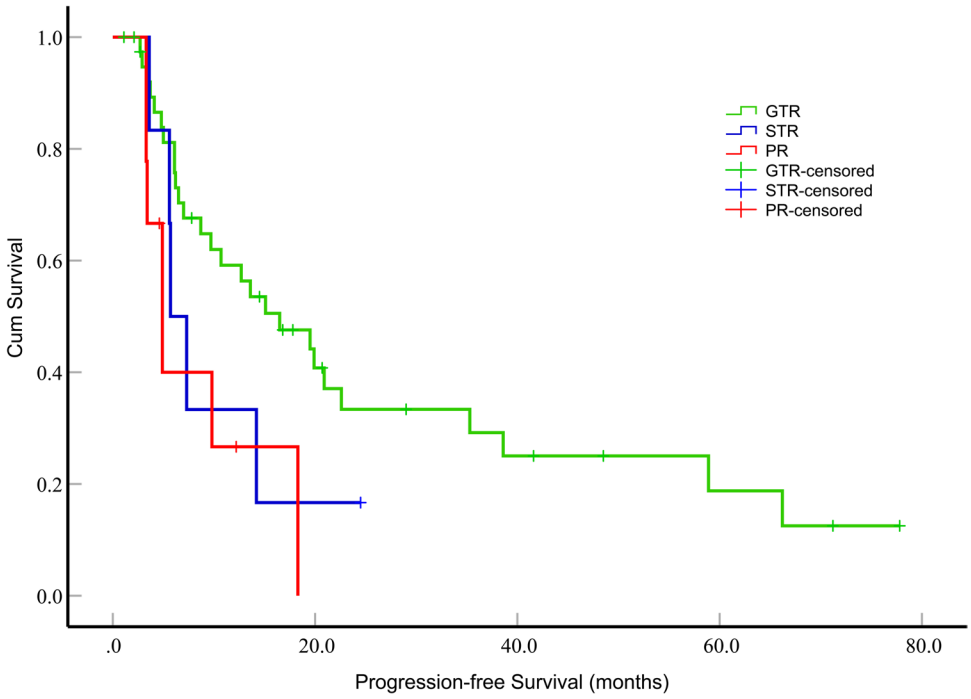

Fig. 1 Impact of the extent of resection on progression-free survival (months) in patients with epithelioid glioblastoma. The patient who underwent GTR exhibited a significantly longer median PFS compared to those who underwent PR ($P=0.017$). In contrast, patients who underwent GTR showed a longer median PFS than those who underwent STR, but this difference was not statistically significant ($P=0.187$)

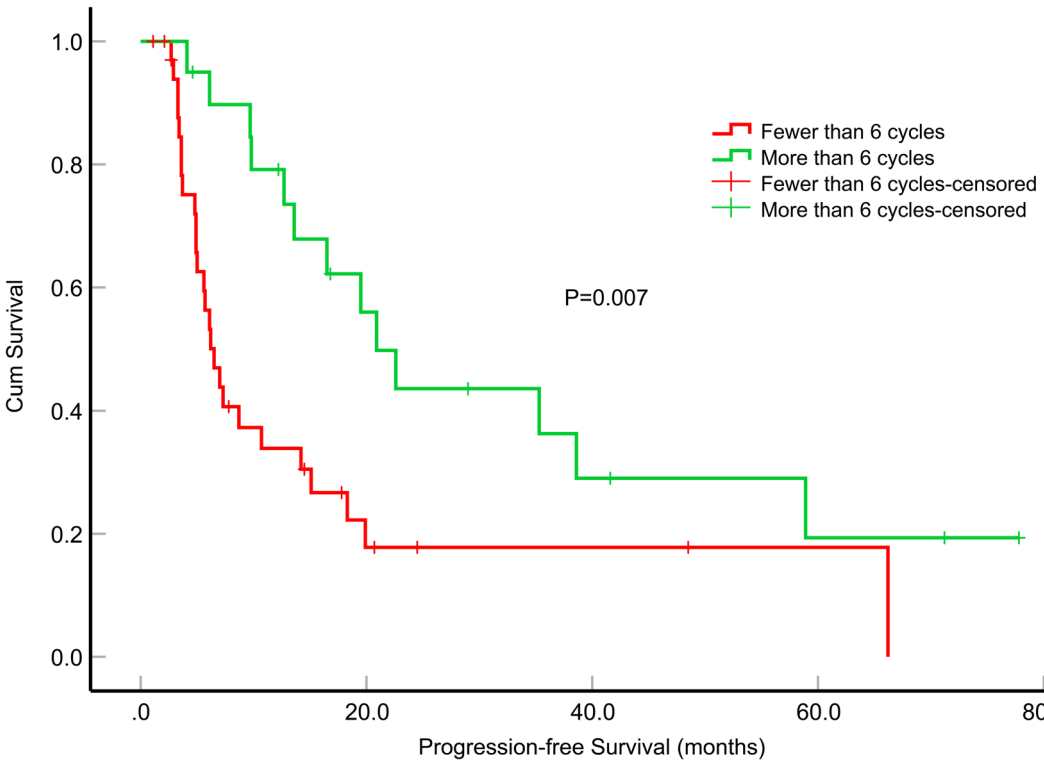

Fig. 2 Impact of the number of cycles of adjuvant oral temozolomide on progression-free survival (months) in patients with epithelioid glioblastoma

95% CI, 1.039–3.750), GTR ($P=0.019$, HR = 2.848, 95% CI, 1.186–6.837) and the number of cycles of adjuvant chemotherapy with TMZ ($P=0.009$, HR = 0.404, 95% CI, 0.204–0.799) were significantly associated with PFS. To further investigate these relationships, a multifactorial Cox proportional hazards model was constructed, which

incorporated variables such as tumor dissemination, extent of tumor resection, the number of adjuvant chemotherapy cycles with TMZ, concomitant chemoradiotherapy, and BRAF-V600E mutation status. The tumor dissemination ($P = 0.017$, HR = 2.652, 95% CI, 1.189–5.916) and the number of cycles of adjuvant chemotherapy with TMZ ($P = 0.011$, HR = 0.354, 95% CI, 0.160–0.786) were significantly associated with PFS (Table 2).

Overall survival

The median OS of the patients was 29.1 months (95% CI, 21.305–36.895). During the first year, the survival rate was 78.4%, which declined to 56.8% in the second year and further dropped to 18.9% by the fifth year. Among these patients, those who underwent GTR exhibited a significantly longer median OS than those who underwent STR ($P = 0.030$). However, the differences in median OS between GTR and PR, as well as between STR and PR, were not statistically significant ($P = 0.710$ and $P = 0.146$). Patients who received more than 6 cycles of TMZ adjuvant chemotherapy demonstrated a significantly extended median OS compared to patients who received fewer than 6 cycles ($P = 0.016$) (Fig. 3). A significant difference in the median OS was observed between patients who received radiotherapy and those who did not ($P < 0.001$) (Fig. 4). In the univariate survival analysis, GTR was associated with a longer median OS than STR ($P = 0.029$, HR = 2.861, 95% CI, 1.113–7.352), tumor dissemination ($P = 0.049$, HR = 1.984, 95% CI, 1.003–3.923), radiation therapy ($P < 0.001$, HR = 0.200, 95% CI, 0.081–0.495), the number of cycles of adjuvant chemotherapy with TMZ ($P = 0.020$, HR = 0.408, 95% CI, 0.192–0.868) showed a significant relation to OS. A multifactorial Cox proportional risk model was constructed including tumor dissemination, extent of tumor resection, administration of radiotherapy and the number of adjuvant chemotherapy cycles with TMZ. Similarly, tumor dissemination ($P = 0.004$, HR = 3.648, 95% CI, 1.507–8.975), radiotherapy ($P = 0.019$, HR = 0.223, 95% CI, 0.066–0.781), the number of cycles of adjuvant chemotherapy with TMZ ($P = 0.007$, HR = 0.254, 95% CI, 0.093–0.689) were significantly correlated with OS (Table 3).

Recurrent survival

The median survival time after relapse was 14.3 months (95% CI, 8.201–20.399). We analyzed the local recurrence cases by dividing them into subgroups based on treatment type: surgical versus non-surgical and irradiated versus non-irradiated. Patients who underwent surgical treatment experienced a significantly longer median survival time compared to those in the non-surgical group ($P < 0.001$)

Table 2 Survival analyses for prognosticators of progression-free survival in epithelioid glioblastoma patients

Parameter	Univariate			Multivariate		
	HR	95% Confidence Interval	*P*	HR	95% Confidence Interval	*P*
Age	1.007	0.985–1.029	0.524			
Sex	1.247	0.659–2.362	0.498			
Tumor stroke	0.886	0.387–2.027	0.774			
Tumor dissemination	1.974	1.039–3.750	**0.038**	2.652	1.189–5.916	**0.017**
Extent of resection						
GTR		1 (Reference)			1 (Reference)	
STR	1.873	0.708–4.957	0.206	0.653	0.202–2.110	0.477
PR	2.848	1.186–6.837	**0.019**	1.600	0.606–4.226	0.343
Pre-operative KPS	1.010	0.989–1.031	0.354			
Concomitant chemoradiotherapy	0.572	0.284–1.154	0.119	0.676	0.302–1.515	0.341
Adjuvant oral TMZ	0.404	0.204–0.799	**0.009**	0.354	0.160–0.786	**0.011**
Ki-67	0.612	0.277–1.354	0.225			
BRAF-V600E	1.691	0.870–3.287	0.121	0.772	0.364–1.637	0.500
MGMT	0.920	0.484–1.748	0.799			
GFAP	1.020	0.358–2.907	0.970			
ATRX	1.257	0.481–3.281	0.641			
Olig-2	0.618	0.188–2.035	0.429			
P53	0.897	0.460–1.750	0.750			

GTR Gross Total Resection, *STR* Subtotal Resection, *PR* Partial Resection, *KPS* Karnofsky Performance Scale, *TMZ* temozolomide, *MGMT* Methylguanine DNA Methyltransferase, *GFAP* Glial Fibrillary Acidic Protein, *ATRX* X-linked alpha-thalassemia mental retardation syndrome, *Olig-2* Oligodendrocyte Transcription Factor 2

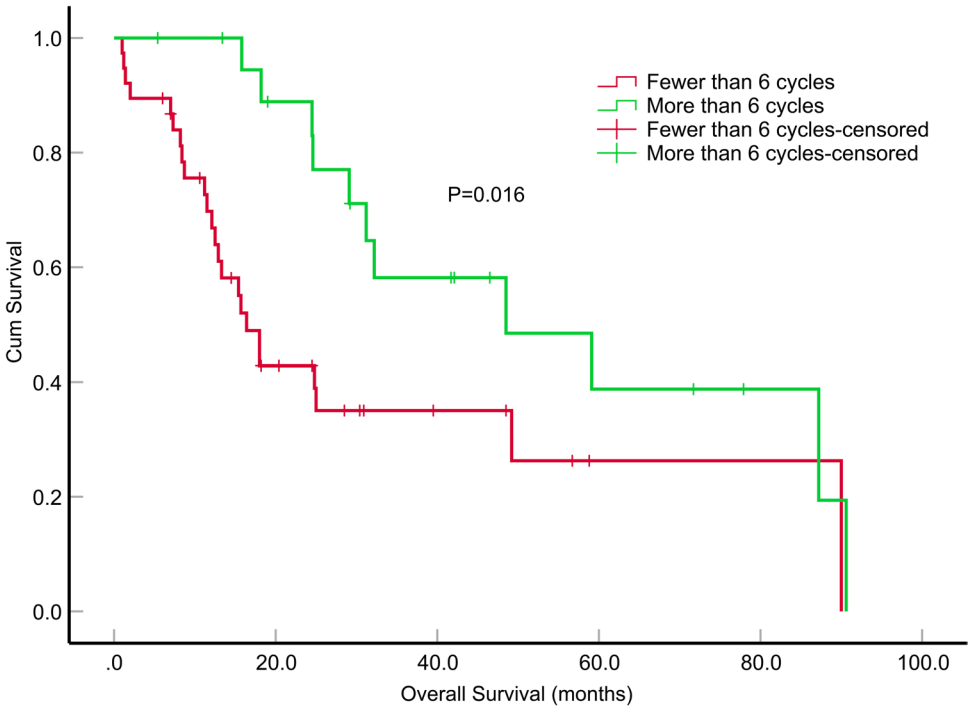

Fig. 3 Impact of the number of cycles of adjuvant oral temozolomide on overall survival (months) in patients with epithelioid glioblastoma

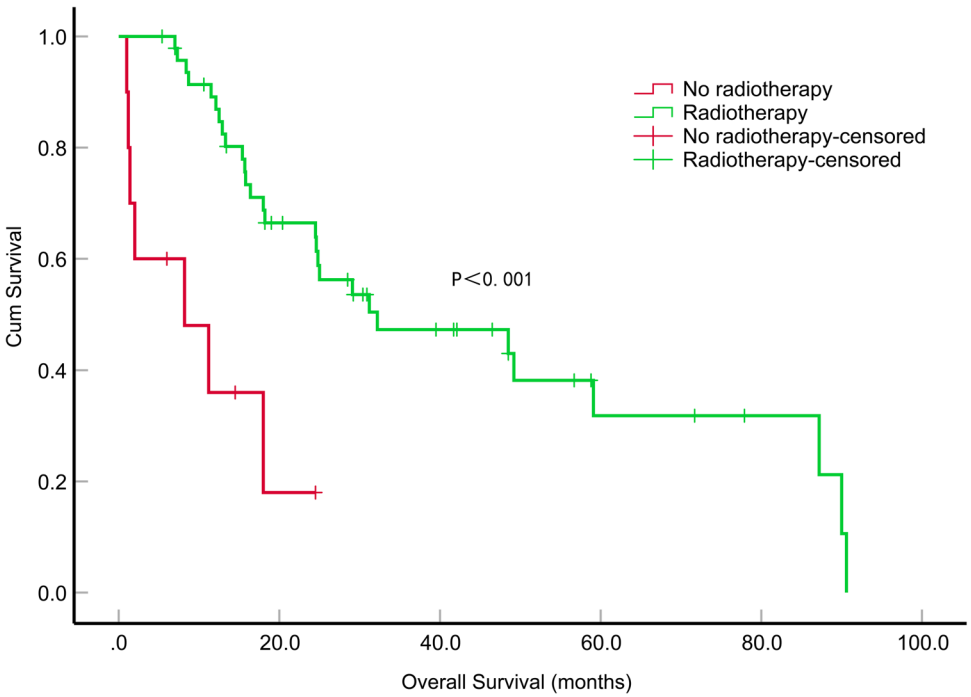

Fig. 4 Impact of radiotherapy on overall survival (months) in patients with epithelioid glioblastoma

(Fig. 5). Furthermore, patients who received a combination of reoperation and radiotherapy had an even longer median survival time than those in either of the other treatment groups ($P < 0.001$) (Fig. 6). In the univariate survival analyses, only sex ($P = 0.047$, HR = 2.451, 95% CI, 1.011–5.939) and reoperation ($P < 0.001$, HR = 0.116, 95% CI, 0.036–0.371) demonstrated a significant correlation with survival time after recurrence. A multifactorial Cox proportional risk model was constructed including sex recurrence-KPS, reoperation, re-irradiation, MGMT mutation status. Notably, reoperation ($P = 0.006$, HR = 0.179, 95% CI, 0.053–0.611) were significantly correlated with survival time after recurrence (Table 4).

Table 3 Survival analyses for prognosticators of overall survival in epithelioid glioblastoma patients

Parameter	Univariate			Multivariate		
	HR	95% Confidence Interval	*P*	HR	95% Confidence Interval	*P*
Age	1.008	0.985–1.032	0.513			
Sex	1.863	0.911–3.809	0.288			
Tumor dissemination	1.984	1.003–3.923	**0.049**	3.648	1.507–8.975	**0.004**
Extent of resection						
GTR		1 (Reference)			1(Reference)	
STR	2.861	1.113–7.352	**0.029**	0.439	0.107–1.802	0.253
PR	1.206	0.451–3.224	0.708	0.517	0.163–1.641	0.263
Tumor stroke	0.919	0.397–2.129	0.844			
Pre-operative KPS	1.015	0.991–1.039	0.221			
Radiotherapy	0.200	0.081–0.495	**< 0.001**	0.223	0.066–0.781	**0.019**
Adjuvant oral TMZ	0.408	0.192–0.868	**0.020**	0.254	0.093–0.689	**0.007**
Ki-67	0.583	0.247–1.378	0.219			
BRAF inhibitor	0.842	0.294–2.411	0.749			
BRAF-V600E	1.034	0.502–2.130	0.927			
MGMT	1.459	0.716–2.973	0.298			
ATRX	1.504	0.555–4.075	0.423			
GFAP	0.582	0.222–1.526	0.271			
Olig-2	0.403	0.119–1.368	0.245			
P53	1.027	0.488–2.160	0.944			

GTR Gross Total Resection, *STR* Subtotal Resection, *PR* Partial Resection, *KPS* Karnofsky Performance Scale, *TMZ* temozolomide, *MGMT* Methylguanine DNA Methyltransferase, *GFAP* Glial Fibrillary Acidic Protein, *ATRX* X-linked alpha-thalassemia mental retardation syndrome, *Olig-2* Oligodendrocyte Transcription Factor 2

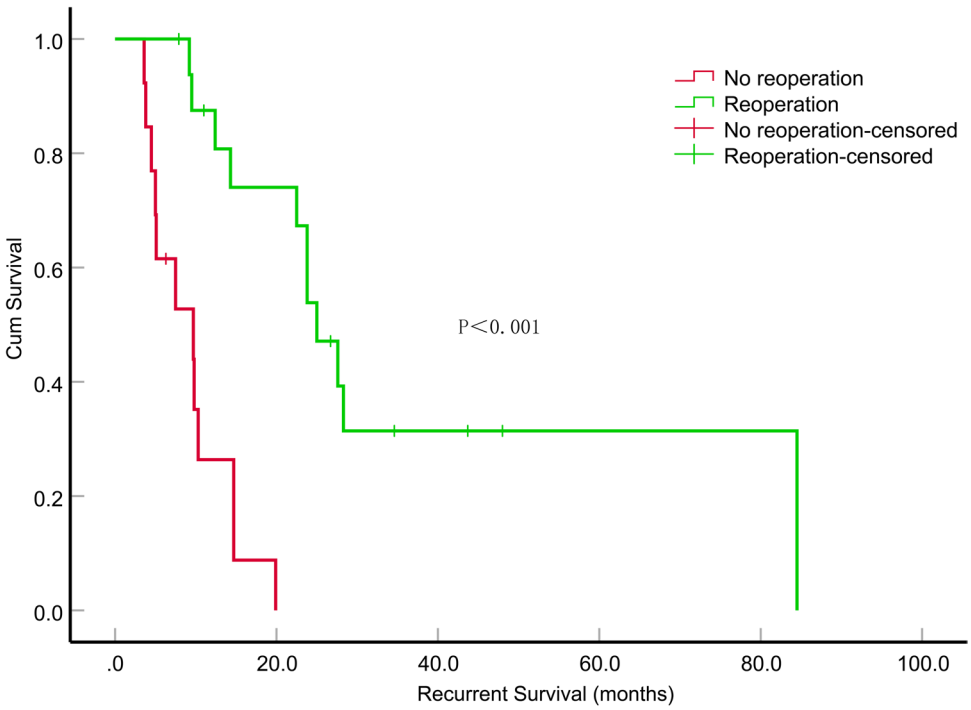

Fig. 5 Impact of reoperation on recurrent survival (months) in patients with recurrent epithelioid glioblastoma

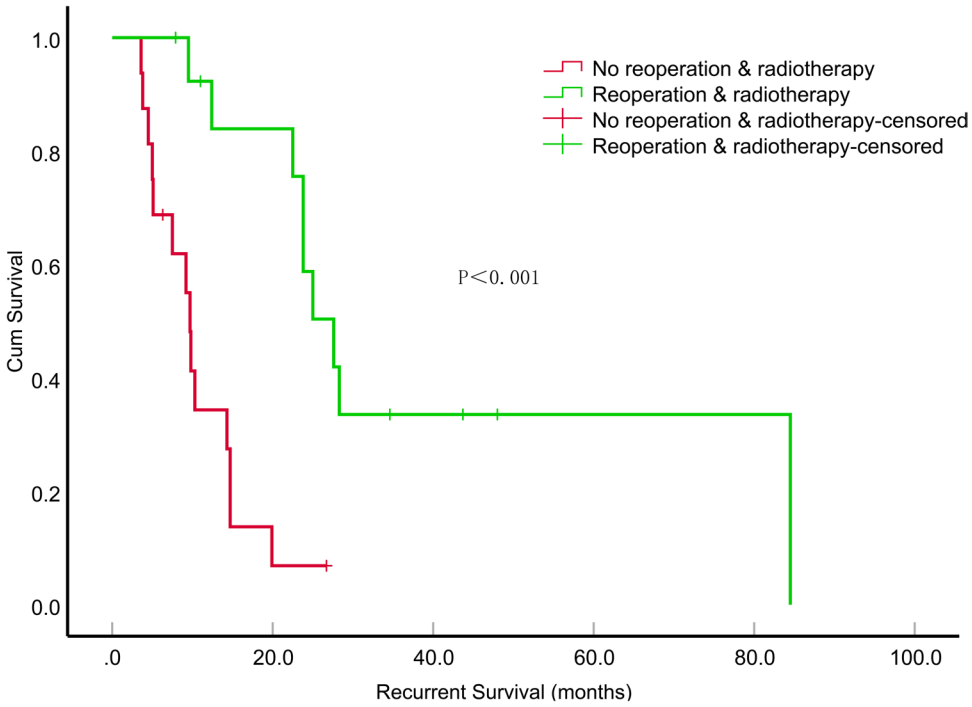

Fig. 6 The impact of combining reoperation with radiotherapy on the survival duration (in months) of patients with recurrent epithelioid glioblastoma

Table 4 Survival analyses for prognosticators of survival in recurrence epithelioid glioblastoma

Parameter	Univariate			Multivariate		
	HR	95% Confidence Interval	*P*	HR	95% Confidence Interval	*P*
Age	0.989	0.958–1.021	0.495			
Sex	2.451	1.011–5.939	**0.047**	3.010	0.993–9.127	0.052
Recurrent-KPS	0.967	0.929–1.007	0.103	1.007	0.964–1.053	0.744
Bevacizumab	1.021	0.414–2.517	0.964			
Reoperation	0.116	0.03634–0.371	**< 0.001**	0.179	0.053–0.611	**0.006**
Re-irradiation	0.542	0.220–1.337	0.183	0.494	0.177–1.380	0.179
Ki-67	0.934	0.364–2.395	0.888			
BRAF inhibitor	1.180	0.397–3.506	0.766			
BRAF-V600E	1.259	0.539–2.940	0.594			
MGMT	2.111	0.861–5.180	0.103	2.571	0.767–8.618	0.126
ATRX	1.625	0.541–4.876	0.387			
GFAP	0.285	0.035–2.324	0.241			
Olig-2	0.744	0.217–2.546	0.634			
P53	1154	0.464–2.871	0.757			

KPS Karnofsky Performance Scale, *MGMT* Methylguanine DNA Methyltransferase, *GFAP* Glial Fibrillary Acidic Protein, *ATRX* X-linked alpha-thalassemia mental retardation syndrome, *Olig-2* Oligodendrocyte Transcription Factor 2

Discussion

Ep-GBM is a newly classified histological subtype of GBM included in the 2016 WHO Classification of Tumors of the Central Nervous System [8]. Ep-GBM accounts for approximately 3% of all GBM cases [9]. The course of Ep-GBM is an aggressive one and is often complicated by early recurrence, intratumoral hemorrhage and leptomeningeal spread [10]. Ep-GBM frequently exhibit BRAF V600E, TERT promoter mutations and CDKN2A/B homozygous deletions, these alterations tend to coexist in Ep-GBM [11]. Dramatic responses to BRAF inhibitors have been reported anecdotally in BRAF-V600E mutant examples, emphasizing that this variant may have several important differences from that of conventional GBM [10].

There is a scarcity of studies focusing on the clinical and pathological characteristics, as well as treatment outcomes related to Ep-GBM, especially regarding treatment options after Ep-GBM recurrence. Therefore, this study is unique and aims to provide more specific information on the prognosis and therapeutic choices for these cancers.

The literature presents varying prognoses for Ep-GBM. Chatterjee et al. [12] conducted a study where they reported a median survival time of 25.5 months among 24 patients diagnosed with Ep-GBM. However, Wang et al. [13] reported a significantly lower median survival time of only 10.6 months for Ep-GBM. These differences in the survival outcomes could be attributed to the treatment approach employed in their study. Specifically, Wang et al. [13] found that 48.4% of patients received concomitant chemoradiotherapy, compared with that of 67.2% in our study. Additionally, the absence of a defined treatment regimen for post-tumor recurrence in their study could also contribute to the disparity in survival times. Drexler et al. [14] demonstrate a survival benefit from maximized extent of resection for newly diagnosed and recurrent glioblastomas of the RTK I and RTK II. Similarly, in a study conducted by Lu et al. [5], patients with Ep-GBM who underwent GTR had longer PFS and OS than those who underwent PR. In our study, we found that patients who underwent GTR had longer survival times than those who did not receive GTR. We found that patients who received radiotherapy experienced a significant extension in median OS compared to those who did not. This aligns with the findings of Sun et al. [15] Standard treatment for GBM was radiation with concomitant and adjuvant TMZ for 6 cycles, although the optimal number of cycles of adjuvant TMZ had long been a subject of debate. The study by Balana et al. [16] demonstrated that extending adjuvant TMZ did not improve PFS or OS in any GBM patient subset. However, we found a correlation between an increased number of cycles of adjuvant chemotherapy with TMZ and improved PFS and OS.

Our study revealed a substantial recurrence rate of 67.2% among patients diagnosed with Ep-GBM, indicating a high likelihood of recurrence in this subtype. However, there is limited literature on the treatment of this specific subtype in its recurrent state. Previous research [17] supported the potential benefits of reoperation in managing recurrent GBM. Our study findings suggest that reoperation is equally relevant and applicable in the management of recurrent Ep-GBM, offering a potential avenue for improved outcomes and extended survival. Re-irradiation has been shown to be a feasible and effective treatment option for recurrent gliomas, as supported by published evidence [18, 19]. The study suggested that combining reoperation, chemotherapy, or re-irradiation as treatment modalities leads to a substantial improvement in survival compared to using individual treatments alone [20]. In addition, no clear survival advantages have been observed by other authors [21]. Our study focused on recurrent Ep-GBM and found that the combination of re-irradiation and reoperation resulted in a significant increase in patient survival. The median survival time was 28.6 months, compared to 9.2 months with other groups.

Among BRAF mutations, V600E is most frequently observed in gliomas [22]. Reports indicate that approximately 50% of Ep-GBM cases exhibit BRAF-V600E mutations, whereas conventional glioblastomas rarely show BRAF-V600E mutations [23, 24]. In our investigation, we observed BRAF-V600E mutant protein expression in 56.9% of cases. Previous studies have shown that gliomas with BRAF-V600E mutation have better prognoses than those without this mutation [25, 26]. Vemurafenib, a BRAF-V600E inhibitor, has been approved for treating malignant melanoma, papillary thyroid carcinoma and lung cancer. Strong clinical responses have been demonstrated in these settings, effectively reducing tumor development and progression caused by the BRAF-V600E mutation [27, 28]. The clinical efficacy of vemurafenib in the treatment of Ep-GBM has been active investigation [29–32]. According to Nakagomi et al. [33], vemurafenib has shown remarkable efficacy in reducing tumor cell survival and suppressing the phosphorylation of crucial intracellular signaling proteins. In our trial, 6 patients were treated with vemurafenib, 5 patients exhibited either steady or partial remission. Research [34] has demonstrated that the combination of BRAF and MEK inhibitors effectively inhibits tumor growth by dual-targeted activation of the MAPK pathway. This finding is supported by several recent clinical studies that established combination therapy with MEK inhibitors as a recognized therapeutic strategy for treating Ep-GBM [35, 36]. In our study, 1 patient developed resistance to vemurafenib after one year of treatment. To address this issue, the patient underwent BRAF-MEK inhibitors. Consequently, the patient experienced an additional 8 months survival benefit.

Limitations

Our study has several limitations. First, the retrospective nature of this study had inherent limitations. To overcome these limitations and provide more robust evidence, prospective studies are a more suitable approach for comparing therapeutic regimens for Ep-GBM. Additionally, only a few markers were analyzed using immunohistochemistry. Finally, the small sample size of our study should be noted. This limited sample size reduced the statistical power of our findings and may potentially limit the generalizability of the results.

Conclusions

In summary, our findings suggest that the standard Stupp regimen had demonstrated positive outcomes in extending the survival of patients with Ep-GBM. Extending adjuvant temozolomide could further improve survival for Ep-GBM patients. Reoperation may also prolong survival for those with recurrent Ep-GBM. Moreover, the development of targeted therapies promises to usher in a new era for the management of Ep-GBM.

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Author contributions Conceptualization and design: MNS, DDF, MYL Acquisition of data: MNS, YG, JFZ, XYH, XJY. Analysis and interpretation of the data: SQL, YG, JFZ, XYH, XJY. Visualization: MNS, JFZ, XYH, XJY. Writing—original draft: MNS, SQL. Writing—review and editing: MNS, SQL, LBC, CZS. Final read and approval of the manuscript: all authors. Meng-nan Sun and Shao-qun Li contributed equally as the first authors of this study.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This retrospective study was approved by the Ethics Committee of Guangdong Sanjiu Brain Hospital (No.202101017), and there was informed consent exemption for all patients.

Conflict of interest The authors declare no competing interests.

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