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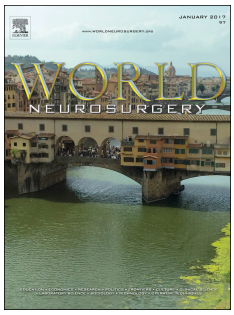

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Title Page

Pineal Region Glioblastomas: Clinical Characteristics, Treatment and Survival Outcome

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ABSTRACT

OBJECTIVE: Given the rarity in the pineal GBM patients, clinical characteristics, treatment, and prognostic factors are not well characterized. This study aimed to investigate these characteristics and identify the prognostic factors of overall survival (OS).

METHODS: A retrospective analysis of newly diagnosed pineal GBM patients, including our three cases and an additional forty-four cases from published articles, was conducted. Survival analysis was performed by Kaplan-Meier analysis and Cox regression analysis was used to determine the prognostic factors.

RESULTS: A total of 47 patients (28 males and 19 females) were enrolled, with a median of 46 years (range, 5-74 years). Forty-four patients (90.9%) had preoperative obstructive hydrocephalus. Among 38 patients, 21 (55.3%) had distal leptomeningeal dissemination. Forty-five (95.7%) patients had resection/biopsy, in which 6 had GTR, 22 had STR, 7 had PR, and 10 had biopsy. Adjuvant therapy included radiotherapy in 36 patients and chemotherapy in 27 patients. The median OS was 10.0 months. The 6-month, 1-year and 2-year survival rates were 68.0%, 42.6% and 17.0%, respectively. COX regression analysis revealed that patients receiving biopsy ($p = 0.042$) or chemotherapy ($p = 0.029$) had the better OS and these were regarded as independent prognostic factors. Further survival analysis showed that chemoradiotherapy had better survival benefit than other regimens.

CONCLUSIONS: In this study, we summarized the characteristics of pineal GBM patients and revealed the correlation between clinical characteristics and prognosis. This study may make the readers have a deep understanding of these rare GBMs and provide some references for future management.

Key words Pineal region; Glioblastoma; H3 K27M; Survival analysis; Prognostic factors

INTRODUCTION

Pineal region tumors account for about 0.4%-1% of all intracranial tumors in adults and contain a wide variety of histological types, generally comprising of germ cell, pineal parenchymal, and extra-pineal tumors arising from the surrounding parenchyma.[1–4] Glioma arising from the surrounding glial stroma is a rare subtype of pineal region tumors and malignant gliomas or glioblastoma (GBMs) located in this region are extremely rare.[4–7] To our knowledge, pineal region gliomas are either included in larger series along with other tumors or reported as case reports/series.[6–11] So far, very few cases with pineal region glioblastoma (also called pineal GBM) have been reported in the English-language literature. Little is known about the clinical characteristics, treatment, and prognosis of this rare entity. In this study, we report three cases with pineal GBM and thoroughly review the English-language literature, to summarize the clinical characteristics and treatment strategy in the pineal GBM patients, and determine the prognostic factors of overall survival (OS).

METHODS

Patients Source

We searched the Glioma database in our institution and identified three patients with newly diagnosed pineal GBM between 2016 and 2019. We also thoroughly retrieved the English-language literature about pineal GBM from PubMed and Web of Science and ultimately identified 44 cases with pineal GBM from 28 articles published between 1954 and 2020.[6,7,16–25,8,26–33,9–15] The key terms used for the standard retrieval strategy were “pineal region glioblastoma” OR “pineal glioblastoma” OR “pineal region glioma” OR “pineal glioma”. Meanwhile, references of included articles were tracked. The inclusion criteria were as follows: (a) the cases published in English-language articles were newly diagnosed pineal GBM, including these cases originating from the pineal region and simultaneously involving the thalamus or midbrain; (b) non-English-language articles were also included only if an English abstract was available; (c) the main clinical data (age, sex, and duration of symptoms, tumor extending, diameter, preoperative hydrocephalus), treatment (surgery, radiotherapy, and chemotherapy) and time to events (OS, status) for survival analysis were available. Articles without important clinical and survival data, including age, sex, survival time, and status, were excluded. Informed consent of three cases in our institution was obtained from patients or their families.

Date Extraction and Definition

Clinical and radiological features, surgical and adjuvant therapy, and survival data of pineal GBM

patients were extracted and collected from three cases in our institution and forty-four cases published previously. Surgical resection or biopsy was performed for all patients and the obtained tissue samples were used for pathological examination. The surgical extent of resection (EOR) included gross total resection (GTR), subtotal resection (STR), and partial resection (PR). Postoperative adjuvant therapies including radiotherapy and chemotherapy were extracted according to the records. For survival analysis, all patients were divided into two groups by age (<18 and ≥18 years). The duration of symptoms was classified into two groups (≤1/>1 month) by the median value. The OS was recorded from the included cases.

Immunohistochemistry

Immunohistochemistry of tissue samples from our three cases was performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections. Molecular subtyping including IDH1, ATRX, 1p/19q, MGMT promoter (MGMTp) methylation status, P53, EGFRvIII, Ki-67, and H3 K27M were examined by immunohistochemistry or genetic testing according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System [34]. All H3K27M detections were confirmed finally by genetic testing. Positive staining in less than 50% of cells was considered negative. The details of the molecular features of other cases were also extracted.

Statistical Analysis

All statistical analysis was performed using Stata (version 15.0, StataCorp LLC) and GraphPad Prism (version 8, San Diego, USA). Continuous variables were presented as means ± standard deviations and median. The median value of a continuous variable was considered as the cut-off. The relationship between categorical variables was evaluated using Fisher's exact test or Chi-squared test. Estimates of the OS were calculated with the Kaplan–Meier analysis, and the differences between the subgroups were evaluated using the log-rank test. Cox regression analysis was utilized to calculate the hazard ratio (HR) and 95% confidence interval (95% CI) and to determine the possible independent prognostic factors concerning OS. $P < 0.05$ was considered statistically significant.

RESULTS

Patient Demographics and Clinical Characteristics

A total of 47 patients (28 males and 19 females) with pineal GBM were included in this study. The flow diagram of cases selection and inclusion according to the PRISMA guidelines was shown in **Figure 1**. The mean age of all patients was 41.5 ± 18.9 years, and the median age was 46 years (range,

5-74 years). The duration of symptoms ranged from one day to 108 months, with a median duration of 1 month. In cases available for the data of tumor diameter, the median diameter of tumors was 2.75cm. Of 42 patients available for the tumor extent data, the tumors in 25 patients (59.5%) extended into the third ventricular (8 patients) or involved thalamus/midbrain (17 patients) structures. Forty-four patients (90.9%) had preoperative obstructive hydrocephalus and the majority of these had mild hydrocephalus. Among 38 patients available on distal recurrence data, 21 patients (55.3%) had distal dissemination, including 15 patients with intracranial dissemination and 6 patients with spinal dissemination. The details and summary of demographics and clinical characteristics of all patients were shown in **Tables 1 and 2**. In addition, the summary of clinical presentation types of pineal GBM patients was shown in **Table 3**.

Surgical Resection and Adjuvant Therapy

Of all included patients, the date of surgical resection or biopsy was available in 45 patients (95.7%). Among these 45 patients, 6 had GTR, 22 had STR, 7 had PR, and 10 had biopsy. Due to more than half of the patients with preoperative obstructive hydrocephalus, the majority of these patients underwent cerebral spinal fluid (CSF) draining to relieve intracranial pressure and improve clinical symptoms in the whole course of this disease. Draining types of CSF included ventriculoperitoneal shunt (VPS), endoscopic third ventriculostomy (ETV), and external ventricular drainage (EVD). Among 40 patients available on draining timing of CSF, 12 (30.0%) patients had pre-operation draining, 14 (35.0%) had intra-operation draining, and 6 (15.0%) had post-operation draining, and 8 patients (20.0%) had not undergone CSF draining in the whole course of the disease. Among patients available for adjuvant therapy data, 36 (90.0%) patients had received radiotherapy, and 27 (73.0%) patients had received chemotherapy. Furthermore, among these 44 patients, 27 (61.4%) had received chemoradiotherapy, and 9 (20.5%) had received radiotherapy only, 2 had received chemotherapy only, and 6 had no adjuvant therapy (**Table 2**).

H3 K27M Mutant Characteristics

In this study, H3 K27M detection was available in 11 cases. Among these, H3 K27M in 5 (45.5%) cases were mutant, whereas the remaining were wild type (WT). IDH1 detection data was available in 10 patients and IDH1 mutant was found in only one patient (10%). Of 9 patients available for ATRX data, 6 patients (66.7%) had ATRX loss. None had 1p/19q co-deletion in 3 patients with 1p/19q detection. MGMT promoter (MGMTp) methylation status was available in 7 patients and only 1

patient (14.3%) showed methylation. P53 expression status was available in our three patients and all were positive. EGFRvIII detection was available in 7 patients and only one (14.3%) was positive (**Table 4**).

Kaplan–Meier and Cox Regression Analysis

The OS of all patients ranged from one week to forty-one months, with a median OS of 10.0 months and a mean OS of 12.1 months. The 6-month, 1-year and 2-year survival rates were 68.0%, 42.6% and 17.0%, respectively. Kaplan-Meier analysis was performed to determine the impact of variables on OS (**Figure 2**). The analysis results revealed that a biopsy has better outcomes compared to surgical resection, whereas no significant difference of OS was found between GTR, STR, and PR in pineal GBM patients. Meanwhile, patients receiving radiotherapy or chemotherapy had better outcomes compared with counterparts. Furthermore, the chemoradiotherapy regimen had the best outcome compared with radiotherapy/ chemotherapy only or no adjuvant therapy by Kaplan-Meier analysis. Univariate and multivariate Cox regression analysis revealed that surgery type (HR 0.214, 95%CI 0.048-0.946, p = 0.042) and chemotherapy (HR 0.308, 95%CI 0.108-0.885, p = 0.029) were the independent prognostic factors of OS (**Table 5**). Furthermore, survival analysis of adjuvant therapy showed that chemoradiotherapy had better survival benefit than only radiotherapy/chemotherapy or other ($p < 0.05$).

Illustrative Case (case 1)

A 21-year-old male with a complaint of headache for one week was admitted to our institution (Oct. 2018). Physical examination on admission was unremarkable. Preoperative brain MRI examination (**Figure 3A-F**) revealed a lesion located in the pineal region with extending the posterior third ventricular and left thalamus region and without hydrocephalus. Based on our surgical experience of deep brain tumors in our center, surgical resection with STR of the tumor was successfully carried out due to infiltrating the left thalamus **(Figure 3G-L)**. Histological detection of tissue sample revealed necrosis and microvascular proliferation with the consideration of glioblastoma. Immunohistochemistry revealed GFAP (+), Olig-2 (+), ATRX (-), P53 (+), PD-1 (-), PDL1 (-), VEGF (-), VEGFR2 (-), EGFRvIII (-) and Ki-67 (MIB-1) 5-8%. Genetic testing showed IDH1/2 (-), MGMTp methylation (-), TERT (-) and H3 K27M (+). Thus, the definitive diagnosis of this patient was considered as diffuse midline glioma (DMG), H3K27M mutant (Grade IV). The postoperative course was uneventful. He was discharged and transferred to the rehabilitation hospital. However, he

complained of a headache again eighteen days after surgery, and brain CT showed increased hydrocephalus **(Figure 3M)**. Thus, ventriculoperitoneal shunt (VPS) was performed (Nov. 2018) and his symptoms and the hydrocephalus were alleviative postoperatively **(Figure 3N)**. The patient was improved gradually. Subsequently, concurrent chemoradiotherapy (Dec. 2018) and adjuvant chemotherapy (Jan. 2019) with temozolomide (TMZ) were administrated. Three months after surgery, follow-up brain MRI revealed the enhancement of pineal region, left thalamus, and dura mater in the left frontal lobe, considering the pseudo-progression of glioma or the possibility of local recurrence and distal dissemination **(Figure 3O, P)**. Although the patient continued chemotherapy with TMZ, the enhancement nidus of pineal remained enlarged until 7 months after surgery **(Figure 3Q, R)**. Fourteen months after surgery, however, brain MRI revealed the regression of the tumor **(Figure 3S, T)**. He had finished 12 cycles of TMZ (Apr. 2020) and he had good performance status and no progression of the disease.

DISCUSSION

Pineal GBMs are extremely uncommon intracranial tumors.[1–4,10] A previous review showed that pineal GBMs accounted for approximately 20% of pineal gliomas.[4] Usually, pineal GBMs were reported in case reports/series. To the best of our knowledge, there is a lack of integrative study focusing on the clinical characteristics, treatment, and prognosis of exclusive pineal GBMs. This study included 47 patients with pineal GBM and the findings demonstrated that these patients had poor survival outcomes (median OS of 10 months), which was similar to diffuse intrinsic pontine glioma (DIPG) or diffuse midline glioma (DMG), H3 K27M mutant.[35–37] Meanwhile, this study, for the first time, revealed the correlation between clinical characteristics, treatment, and survival outcome in these rare patients with pineal GBM.

Unlike other common midline gliomas, such as thalamus or brainstem gliomas, usually occurred in children,[34,36,37] this study and previous reviews showed pineal GBMs commonly occurred in adults, accounting for 87.2% of all included patients. A peak period of age with the onset of the disease was found in this study, which was an age range of 40-64 years. Interestingly, there was sex preference within the two populations of children and elder patients, in which all children were female and the majority of elder patients were male. However, due to basing on the published case series and possible selective bias, this finding should be further confirmed.

Duration of symptoms, referring to the interval between the onset of symptoms and diagnosis, may

reflect the development process and growth speed of tumors. The duration of symptoms of pineal gliomas is usually shorter than them of hemispheric gliomas.[29] Previous studies showed that duration of symptoms was associated with survival outcome and shorter duration implied poorer outcome.[38–40] In this study, the patients with a shorter duration of symptoms had a worse outcome, although the duration of symptoms was not significantly associated with OS. This finding was similar to previous reports on midline gliomas.[38,39] Patients with pineal GBM generally present with symptoms related to increased intracranial pressure (ICP) due to obstructive hydrocephalus.[4,37]

The majority of pineal GBMs have similar radiological features. These malignant tumors are often presented solid lesions with/without involving adjacent structures and commonly with contrast-enhancement.[6,10,11] About half of pineal tumors are with the involvement of adjacent structures, including the third ventricle and thalamus/midbrain, which easily lead to obstructive hydrocephalus. Previous studies showed over half of the common midline gliomas had obstructive hydrocephalus,[38,39] and the majority of pineal GBM patients occurred preoperatively.[4,11,23] Most diffuse gliomas including common midline gliomas, such as thalamus or brainstem gliomas, are infrequent with distal recurrence/metastasis, whereas our study and reviews revealed that common distal leptomeningeal dissemination occurred in pineal GBMs, including intracranial and spinal dissemination.[6,8,9,11,16] Usually, these patients with distal leptomeningeal dissemination previously had local recurrence, which can indicate disease progression and poor outcome, although distal dissemination was not significantly associated with OS.

Several previous studies have shown that maximal resection of gliomas, including cerebral hemisphere gliomas and adult thalamic gliomas, was associated with longer survival.[40–42] A recent study on surgery of pineal region tumors revealed that complete microsurgical resection was associated with better tumor-free survival and long-term survival, except for diffuse gliomas.[43] A previous study[7] showed that maximal resection didn't benefit the OS of diffuse gliomas, especially high-grade gliomas. Due to no relative consensus or guideline, previous studies showed that surgical resection (77.8%) was mainly performed for the diagnosis and treatment of pineal gliomas. However, this study demonstrated that surgical resection had a worse survival outcome compared to biopsy in pineal GBM patients. This result should be explained cautiously because it may be influenced by some factors. Firstly, due to anatomical complexity and profound surgical risks, surgical resection is usually difficult, and easily result in the direct injury of the critical adjacent structures and high probability of disseminating

subarachnoid/ventricular spaces.[44–47] Sometimes, surgical resection may be performed for patients with larger tumors and improved intracranial hypertension and these patients had poor survival in itself. Besides, this result may also be affected by significant selection/publication bias based on the published articles. From the view of our result, biopsy may have a better outcome than surgical resection, however, this conclusion should be further verified by multicentric studies with larger sample size.

Postoperative adjuvant radiotherapy and chemotherapy are helpful for prolonging the survival of gliomas.[48,49] This study revealed chemotherapy can prolong the OS of these patients with pineal GBM and was considered as an independent prognostic factor. Although radiotherapy was not an independent prognostic factor, survival analysis of adjuvant therapy demonstrated that patients receiving chemoradiotherapy had longer OS than other regimens, including radiotherapy/chemotherapy only or no adjuvant therapy. These findings were consistent with previous studies on cerebral GBM.[48,49] However, this study revealed patients receiving only radiotherapy or chemotherapy compared without any adjuvant therapy still had a similar outcome, which may be associated with poor compliance and incomplete course of treatment.

DMGs occur primarily in midline locations, such as brainstem, thalamus, and spinal cord,[34–37] whereas uncommon in the pineal region.[10,11,13] After the revised 2016 World Health Organization (WHO) central nervous system (CNS) tumor classification, H3 K27M mutant status is detected commonly in CNS tumors in midline locations, such as brainstem and thalamus.[50] However, little is known about H3 K27M mutant in pineal gliomas due to the rarity of these tumors. In this study, H3 K27M mutant status was available in 11 pineal GBM patients and H3 K27M mutant was found in 5 (45.5%) patients. Similar to common midline gliomas, H3 K27M-mutant GBMs in this study are usually associated with a high frequency of P53 alteration.[51] Several studies showed H3 K27M-mutant patients had a poor outcome compared to WT.[36,37,40] However, a recent study of a larger series of H3 K27M-mutant DMG in different anatomical locations demonstrated that H3K27M mutation was not significantly associated with a poorer prognosis in supratentorial gliomas compared with WT gliomas.[37] In this study, survival analysis of H3 K27M mutant status on OS was not performed due to the small sample size. The prognostic value of H3 K27M mutation in pineal GBM patients should be further studied with larger sample size.

Limitations

Our study had some limitations that should be noted. This study was a retrospective analysis and includes a limited sample size of pineal GBM patients from case reports/series, which could lead to selection/publication bias and low statistical power. Besides, due to the incomplete data of included cases, such as Karnofsky Performance Status (KPS), subgroup analyses for treatment options were not performed. Moreover, included cases had and wide time span and had different options of adjuvant therapy, such as chemotherapy, however, subgroup analysis of adjuvant treatment by periods was unable to be compared, due to limited samples and being not available for detailed information of therapy. Based on these limitations, the conclusions in this study should be cautiously explained and should be further verified by the multicentric studies with larger sample size.

CONCLUSIONS

In this study, we summarized the characteristics of pineal GBM patients based on individual data and revealed the correlation between clinical characteristics and prognosis. This study may make the readers have a deep understanding of these rare tumors and provide some references for future management. However, these conclusions should be cautiously explained and further studied.

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Table1 Details of the included 47 cases with pineal GBM.

Study	Age	Sex	Pre-op hydro	Extending	Diameter (cm)	Dissemination	Surgery	CSF Drainage	Radio	Chemo	Survival (months)
Our case 1	21	M	Yes	Thalamus	2.5	Intracranial	STR	VPS	Yes	Yes	16, alive
Our case 2	30	M	Yes	Thalamus, Midbrain	6	Intracranial	STR	VPS	Yes	Yes	12
Our case 3	55	M	No	No	2.5	Intracranial	STR	No	No	No	10
Sajan, 2020	39	F	Yes	Midbrain	2.5	No	Biopsy	EVD, VPS	Yes	Yes	12, alive
Li, 2020	54	F	Yes	Thalamus	4.5	No	STR	-	No	Yes	4
	54	F	Yes	Thalamus, Midbrain	4.7	No	STR	-	No	Yes	6
	50	F	Yes	Thalamus	3.5	Intracranial	PR	-	No	No	5
	54	F	Yes	Third ventricular	3	No	GTR	-	No	No	7, alive
D'Amico, 2018	52	M	Yes	Thalamus	2.3	No	STR	ETV	No	No	2
	38	M	Yes	No	2	No	STR	ETV	Yes	Yes	20
	51	M	Yes	Thalamus	2	Intracranial	STR	ETV	Yes	Yes	24
	46	F	No	Third ventricular	2.6	No	STR	No	Yes	Yes	15
	74	M	Yes	No	2.3	No	STR	VPS	Yes	Yes	8
	36	M	Yes	Thalamus	2.6	No	STR	ETV	Yes	No	10
	38	M	Yes	Third ventricular	3	No	STR	ETV	Yes	Yes	23
Granados, 2018	5	F	Yes	Midbrain	-	Spinal	Biopsy	EVD	Yes	Yes	3, alive
Nadvi, 2018	19	F	Yes	No	-	No	Biopsy	VPS	Yes	Yes	12, alive
Gilbert, 2018	12	F	No	No	2.7	Intracranial	STR	No	Yes	Yes	8, alive
Orrego, 2017	48	F	Yes	No	4.5	No	STR	VPS	Yes	No	12
	50	M	Yes	Thalamus, Midbrain	2.8	No	PR	VPS	Yes	No	6
	56	M	Yes	Midbrain	2.8	Intracranial	PR	VPS	Yes	Yes	29
	25	M	Yes	Midbrain	-	No	GTR	VPS	Yes	Yes	32
Stowe, 2017	65	M	No	No	2.5	-	Biopsy	-	Yes	Yes	41, alive
Sugita, 2016	52	F	Yes	No	-	Intracranial	PR	ETV	Yes	Yes	24
	18	M	Yes	No	-	Spinal	PR	EVD	Yes	Yes	13
Liu, 2015	30	M	No	Thalamus	5	Intracranial	GTR	-	Yes	Yes	14, alive
Matsuda, 2015	31	M	Yes	No	-	Spinal	STR	VPS	Yes	Yes	5
Mansour, 2014	69	M	Yes	No	2	-	Biopsy	ETV	Yes	Yes	16
Suzuki, 2014	65	M	Yes	Third ventricular	-	-	STR	ETV	Yes	Yes	3, alive
Peterson, 2014	20	M	Yes	No	-	Spinal	Biopsy	ETV, EVD, VPS	-	-	10

Ozgural, 2013	60	M	Yes	No	-	-	Biopsy	VPS	Yes	Yes	24, alive
Birbilis, 2010	54	F	Yes	No	-	Spinal	Biopsy	VPS	Yes	Yes	40
Moon, 2008	68	M	Yes	Thalamus, Midbrain	4	Intracranial	STR	VPS	No	No	2
Amini, 2006	40	M	Yes	Midbrain	-	Intracranial	STR	ETV, VPS	Yes	Yes	5
	43	M	Yes	Third ventricular	-	Intracranial	GTR	ETV	Yes	Yes	7
	52	F	Yes	No	-	Intracranial	Biopsy	ETV	Yes	No	2
Toyooka, 2005	40	M	Yes	No	-	Intracranial	PR	VPS	Yes	Yes	11
Gasparetto, 2003	29	F	Yes	Thalamus	-	-	PR	VPS	No	No	2
Cho, 1998	10~15	F	-	No	-	-	STR	-	Yes	No	6
Pople, 1993	6	F	Yes	Third ventricular	3	Intracranial	GTR	VPS	Yes	Yes	4
Vaquero, 1990	63	F	-	-	-	-	STR	VPS	Yes	No	6
Edwards, 1988	12	F	-	-	-	-	STR	-	Yes	Yes	18
Frank, 1985	52	F	Yes	-	-	No	Biopsy	-	Yes	-	4
Norbut, 1981	36	M	Yes	Third ventricular	-	Spinal	No	VPS	Yes	-	4
Kalyanaraman, 1979	68	F	Yes	No	-	-	GTR	-	Yes	-	4
Bradfield, 1972	5	F	Yes	-	-	No	No	VPS	-	-	27
	52	F	Yes	-	-	No	STR	-	-	-	0.2

M, male; F, female; Pre-op hydro, preoperative hydrocephalus; GTR, gross total resection; STR, subtotal resection; PR, partial resection; VPS, ventriculoperitoneal shunt; ETV, endoscopic third ventriculostomy; EVD, external ventricular drainage; Radio, Radiotherapy; Chemo, chemotherapy; CSF, cerebral spinal fluid; -, not available or not performed.

Table 2 Summary of demographics and clinical features of all pineal GBM patients

Characteristics	No.*
Age	47
< 18 years	6/47 (12.8%)
≥18 years	41/47 (87.2%)
Sex (Male)	47
Male	28/47 (59.6%)
Female	19/47 (40.4%)
Duration of symptoms	35
≤1 month	19/35 (54.3%)
>1 month	16/35 (45.7%)
Extending	42
Third ventricular	8/42 (19.0%)
Thalamus/Midbrain	17/42 (40.5%)
No	17/42 (40.5%)
Diameter	24
< 2.75cm	12/24 (50.0%)
≥2.75cm	12/24 (50.0%)
Preoperative hydrocephalus	47
No	7/47 (14.9%)
Mild	32/47 (68.1%)
Severe	8/47 (17.0%)
Distal recurrence	38
Intracranial	15/38 (39.5%)
Spinal	6/38 (15.8%)
No	17/38 (44.7%)
Surgery	45
GTR	6 /45 (13.3%)
STR	22/45 (48.9%)
PR	7 /45 (15.6%)
Biopsy	10/45 (22.2%)
Draining timing of CSF	40

Pre-operation	12/40 (30.0%)
Intra-operation	14/40 (35.0%)
Post-operation	6/40 (15.0%)
No	8/40 (20.0%)
Radiotherapy	44
Yes	36/44 (81.8%)
No	8/44 (28.2%)
Chemotherapy	41
Yes	29/41 (70.7%)
No	12/41 (29.3%)
Adjuvant therapy	44
Chemoradiotherapy	27/44 (61.4%)
Radiotherapy only	9/44 (20.5%)
Chemotherapy only	2/44 (4.5%)
No	6/44 (13.6%)

* referred as the available data from all included cases.

Table 3 Summary of clinical presentation types of pineal GBM patients

Symptoms	Percentage
Headache	90.0%
Nausea/vomiting	43.3%
Visual impairment	26.7%
Parinaud's syndrome	23.3%
Gate disturbance	23.3%
Behavioral disorder (memory/aypnia/concentration/irritability/hyperhidrosis)	23.3%
Conscious disturbance	13.3%
Vertigo/balance	13.3%
Limb numbness/weakness	10.0%
Urinary incontinence	6.7%
Seizure	3.3%

Table 4 Summary of molecular profiles of 11 pineal GBMs with H3 K27M detection

Study	Age	Sex	H3K27M	Ki-67 (%)	IDH1	ATRX loss	1p/19q co-deletion	MGMTp methylation	P53	EGFRvIII
Our case 1	21	M	Mut	5-8	WT	Lost	-	Unmethylated	Positive	Negative
Our case 2	30	M	Mut	10-20	WT	Maintained	-	-	Positive	-
Our case 3	55	M	WT	20	WT	Maintained	-	Unmethylated	Positive	-
Sajan, 2020	39	F	Mut	-	Mut	-	-	methylated	-	Positive
D'Amico, 2018	52	M	WT	5.20	WT	Lost	-	-	-	Negative
	51	M	WT	40	WT	Maintained	Negative	Unmethylated	-	Negative
	46	F	WT	12	WT	Lost	NA	Unmethylated	-	Negative
	74	M	WT	13.2	WT	Lost	Negative	Unmethylated	-	Negative
	36	M	WT	40.5	WT	Lost	Negative	Unmethylated	-	Test failed
	38	M	Mut	9.3	WT	Lost	-	-	-	-
Gilbert, 2018	12	F	Mut	-	-	-	-	-	-	-

M, male; F, female; Mut, mutant; WT, wild type; -, not available or not performed.

IDH, isocitrate dehydrogenase; ATRX, α-thalassemia/mental retardation X-linked protein, MGMTp, O6-methylguanine-DNA methyltransferase promoter; EGFRvIII, epidermal growth factor receptor variant III.

Table 5 Univariate and multivariable analysis for overall survival of pineal GBMs

Variable	No.	Univariate analysis		Multivariable analysis		
		χ^2	p value	HR	95%CI	p value
Age						
<18/≥18 years	6/41	0.007	0.933	-	-	-
Sex						
Male/Female	28/19	0.383	0.536	-	-	-
Duration of symptoms						
≤1/ >1 month	19/16	0.008	0.927	-	-	-
Extending						
Yes/No	24/18	1.083	0.298	-	-	-
Diameter						
<2.75/≥2.75 cm	12/12	1.572	0.210	-	-	-
Pre-op hydrocephalus						
Yes/No	40/4	2.377	0.123	-	-	-
Distal recurrence						
Yes/No	21/17	0.031	0.860	-	-	-
Surgery type						
Resection/Biopsy	35/10	5.388	**0.020**	0.214	0.048-0.946	**0.042**
Drainage timing						
Pre/Intra/Post	12/14/6	0.283	0.595	-	-	-
Radiotherapy						
Yes/No	36/8	11.941	**0.001**	0.389	0.126-1.199	0.100
Chemotherapy						
Yes/No	29/12	17.410	**<0.001**	0.308	0.108-0.885	**0.029**

The bold P value underlines the statistically significant outcome measure (HR).

Figure legends

Figure 1. The flow diagram of cases selection and inclusion according to the PRISMA guidelines.

Figure 2. Kaplan-Meier survival curve of prognostic factors on OS in pineal GBM patients. **(A) S**urvival curve of OS in all patients. **(B)** Kaplan–Meier survival curve stratified by EOR (P = 0.419). **(C)** Kaplan–Meier survival curve stratified by resection or biopsy (P = 0.020). **(D)** Kaplan–Meier survival curve stratified by radiotherapy (P = 0.001). **(E)** Kaplan–Meier survival curve stratified by chemotherapy (P < 0.001). **(F)** Kaplan–Meier survival curve stratified by adjuvant therapy (P < 0.001).

Figure 3. Illustrative case. Case1. A 21-year-old male diagnosed with pineal GBM (diffuse midline glioma, H3K27M mutant, Grade IV). **(A-F)** Preoperative brain MRI revealing a lesion located in the pineal region extending the posterior third ventricular and left thalamus/brainstem regions, with obstructive hydrocephalus. **(G-L)** Postoperative 48h MRI showing the STR of the tumor and the remission of hydrocephalus. **(M, N)** Eighteen days after surgery, brain CT revealing the recurrence of hydrocephalus. Subsequently, ventriculoperitoneal shunt (VPS) was performed and the hydrocephalus was alleviative postoperatively. **(O, P)** Three months after surgery of tumor, axial brain MRI revealing the enhancement of pineal region and left thalamus, without hydrocephalus. **(Q, R)** Seven months after surgery, axial MRI showed the enhancement nidus of pineal remained enlarged compared with the last follow-up. **(S, T)** Axial MRI revealing decreasing lesion of pineal and left thalamus 14 months after surgery.

Figures

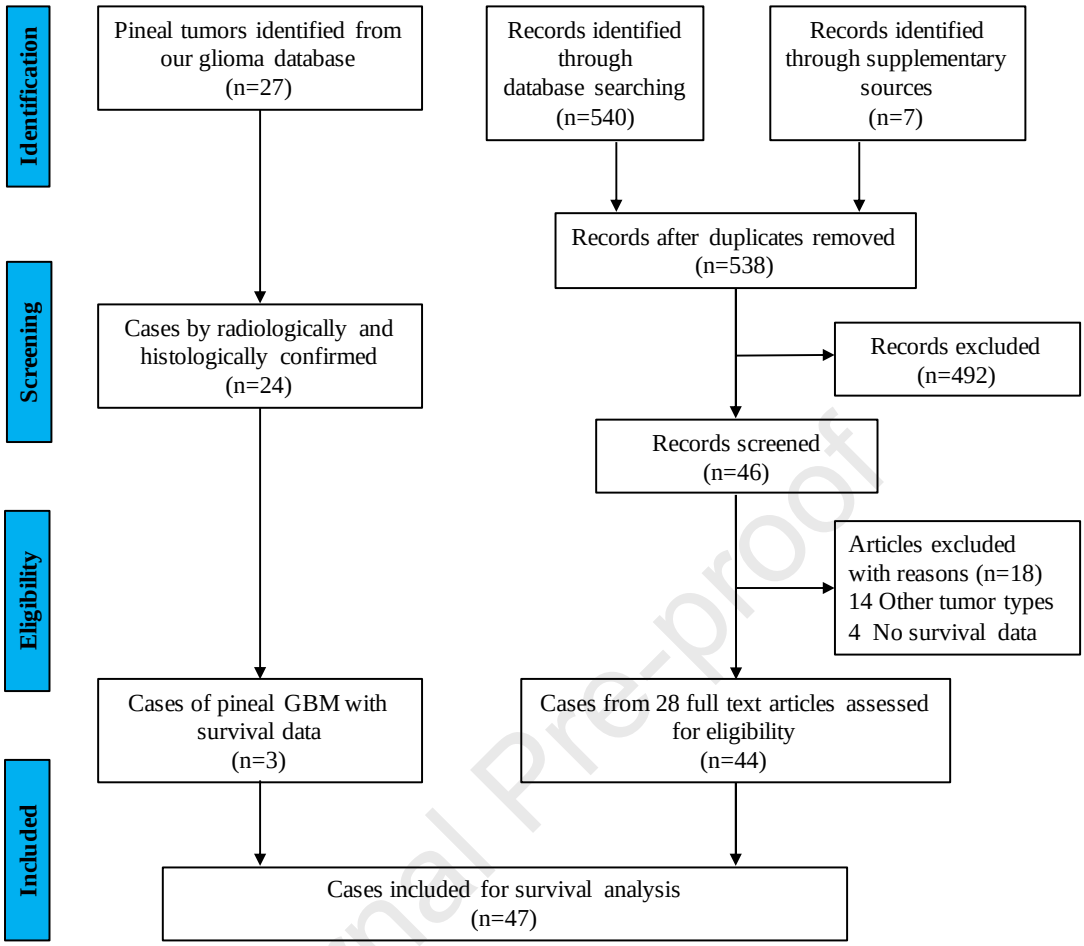

Figure 1. The flow diagram of cases selection and inclusion according to the PRISMA guidelines.

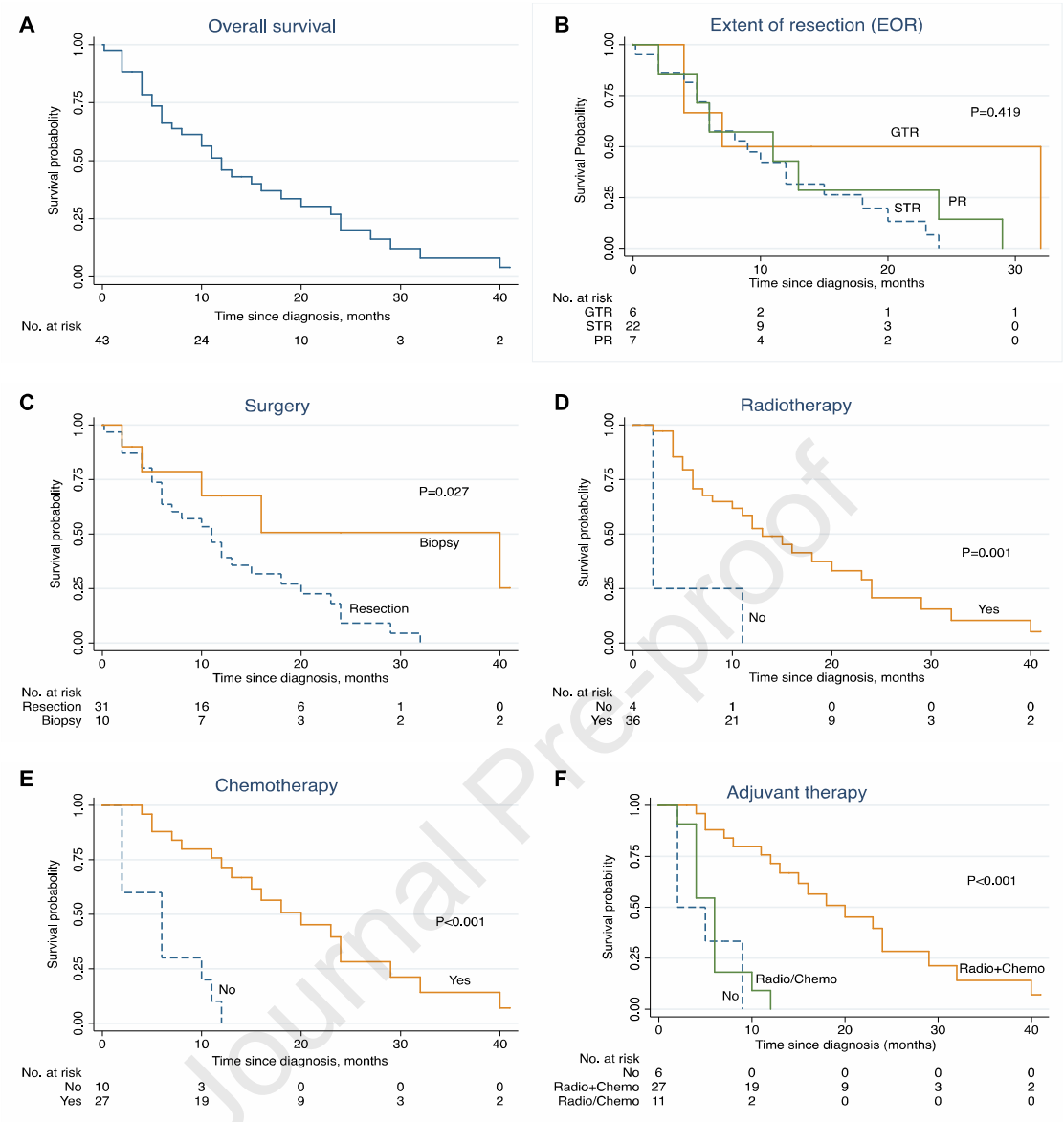

Figure 2. Kaplan-Meier survival curve of prognostic factors on OS in pineal GBM patients.

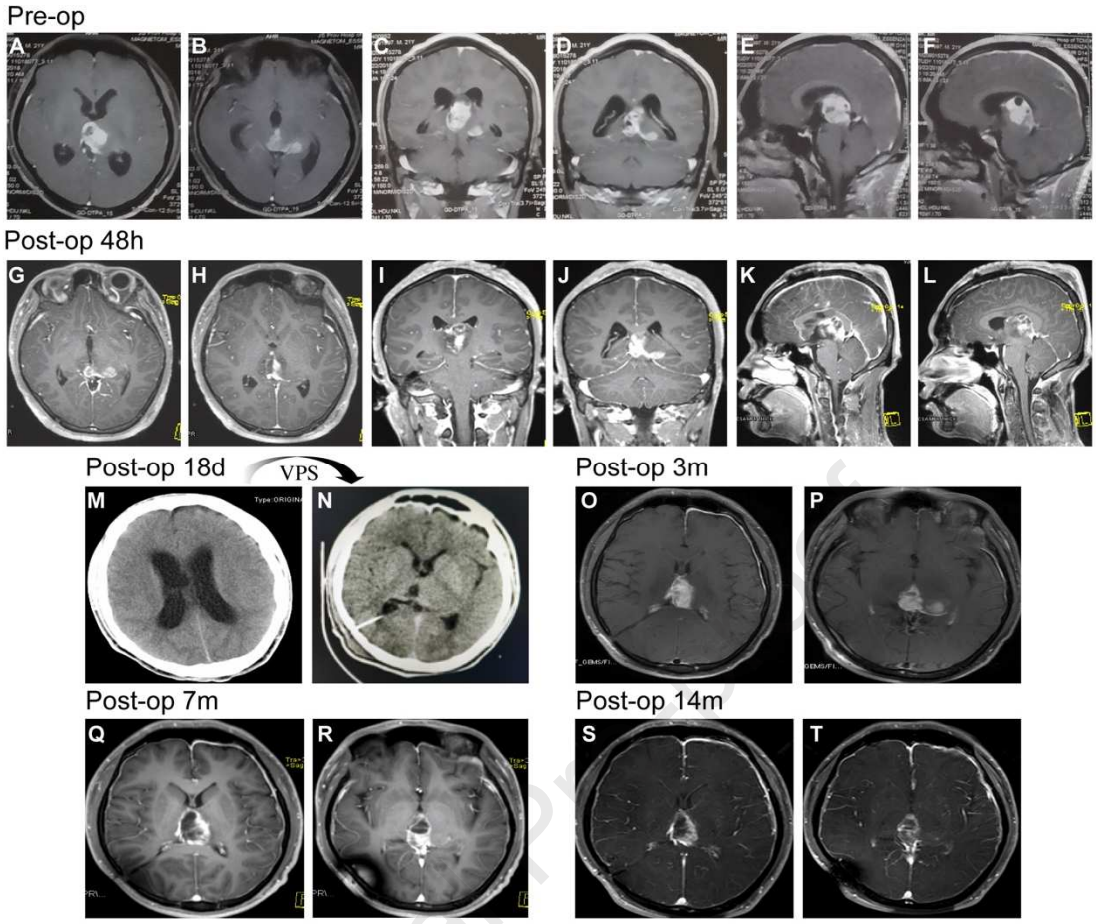

Figure 3. Illustrative case.

Abbreviations and Acronyms

CSF: Cerebral spinal fluid

DMG: Diffuse midline glioma

ETV: Endoscopic third ventriculostomy

EVD: External ventricular drainage

GBM: Glioblastoma

GTR: Gross total resection

MRI: Magnetic resonance imaging

OS: Overall survival

PR: Partial resection

STR: Subtotal resection

VPS: Ventriculoperitoneal shunt

Disclosure

Statement

We certify that this manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium.

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Conflict of Interests

The authors declare no conflict of interests.

Informed consent

Informed consent was obtained for all included patients in our institution.

Ethical approval

This retrospective study was approved by the Institutional Review Board (IRB) of our hospital.

Credit Author Statement

Xiaodong Niu: Conceptualization, Methodology, Software, Writing- Original draft preparation.

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