Glioblastoma Multiforme In The Pineal Region: Systematic Review Of The Survival Outcomes

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Research Article

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Abstract

Purpose: Glioblastoma multiforme of the pineal region harbors high mortality in the first year of treatment. This study aims to deepen the study of pineal GBM patients for finding independent predictors of mortality, focusing on the therapeutic modalities and genetic features.

Methods: We present a systematic review of the long-term outcomes of the disease with a focus on the therapeutic modalities and genetic features.

Results: The median overall survival of the disease is 12 months. Biopsy (HR:4.2, p=0.002, and a median survival of 19 months) and radiochemotherapy (HR:4.1, p<0.001, and a median survival of 18 months) represent independent predictors of pineal glioblastoma survival. H3K27M mutant patients had a median survival of 23 months versus the ten-months median survival of the H3K27 wild type. However, no statistical difference exists due to the limited number of cases. The disease's local progression and recurrence seem higher in patients undergoing surgical removal than biopsy procedures (p=0.021).

Conclusions: Biopsy and radiochemotherapy represent independent predictors of pineal GBM survival. Surgical resection different from biopsy seems to increase the risks of local progression and recurrence. However, further studies should focus on the impact of the genetic profile on long-term outcomes.

Introduction

Pineal region glioblastoma multiforme (GBM) represents a very aggressive disease with high mortality in the first year after initial treatment. Previous reports with a few cases have suggested gross total resection (GTR) as an independent predictor of mortality, and biopsy and radiochemotherapy delivery represent independent predictors of pineal GBM patient survival [1, 2]. However, previous studies did not evaluate the pineal GBM genetic profile due to the limited report of cases [1]. Thus, the analysis of genetic mutations in GBM patients remains essential to draw adequate conclusions regarding the benefits and disadvantages of the therapeutic modalities.

This study aims to deepen the study of pineal GBM patients to define the independent predictors of mortality, focusing on the therapeutic modalities and genetic features.

Methods

Population study and design

We present a systematic review of all reported pineal GBM patients focused on the survival outcomes after different treatments. The systematic review followed PRISMA guidelines. Besides, we introduce two GBM patients operated on in Helsinki University Hospital, one of them as an illustrative case.

Data management

We conducted a systematic review of all pineal GBM patients published in the literature. The literature search was conducted using PubMed and SCOPUS databases on March 20, 2021, and actualized in June 2021 (Figure 1). Keywords in the search were: “((tectal) OR pineal) AND glioblastoma”. All available languages were included in the review. The inclusion criteria required histological confirmation. Two independent authors performed a comprehensive search of the literature and the data extraction for the study. Discrepancies were solved by consensus. The limited number of cases allowed an individual data analysis of all reported patients; however, it avoided performing the meta-analysis. Quality assessment tools were planned.

Statistical methods

We performed a descriptive analysis of the study population. Fisher exact test and T-test were appropriately used. Besides the individual data analysis, we compared the survival outcomes in terms of the presence of hydrocephalus, the regional dissemination of the disease, the size of the tumor, the extent of surgical resection, adjuvant radiotherapy, and chemotherapy. For this, a univariate and multivariate Cox regression model for survival analysis was performed. Log Rank test helped to determine the median overall survival (MOS) of the patients. IBM ® SPSS ® Statistics Version 27 was used for the statistical analysis. Only available data were analyzed, and missing data were not extrapolated. P-value was set at 0.05 for significance.

Results

Illustrative case

A 64-year-old female presented with headaches, progressive short-term memory deficits, and some degree of unbalance without other physical dysfunction. Figure 2 illustrates the pre and postoperative imaging. Brain MRI revealed a single highly contrast-enhanced 2x2x2cm lesion in the pineal region lying over the tectal plate associated with some degree of ventricular enlargement but minimal periventricular lucency. Serum hormonal tests for the pineal tumor diagnosis became negative, and the patient was prepared for direct microsurgical resection.

The patient underwent a right paramedian supracerebellar infratentorial approach in a sitting position with complete tumor removal and opening of the posterior third ventricle. During the immediate postoperative course, the patient did not develop new deficits. The histologic diagnosis was a World Health Organization (WHO) grade IV GBM. The patient received two cycles of temozolomide 150 mg/m2 and fractionated radiation therapy of 36 Gy distributed in daily doses of 3 Gy. However, she developed a Pneumocystis infection and Eaton-Lambert syndrome. Thus, radiochemotherapy was discontinued. The patient ´s last evaluation was performed 10 months after surgery. MRI studies did not show any recurrence in the pineal region. However, multiple tumor foci with significant perilesional edema in the right cerebellar parenchyma and the right incisural space resulted in obstructive hydrocephalus. The patient died ten months after surgery due to disease progression.

Systematic review

Bibliography details

Patients were retrieved from 43 studies published between 1977 and 2021 (see data in brief-repository data) [1–43]. Moreover, three patients were retrieved from references of one published study [1] after full-text evaluation and diagnosis confirmation [44–46]. Other three patients were retrieved from other sources after diagnosis confirmation [47–49]. Individual participant data was collected to organize the study characteristics table. The original language of publications included English for all of them.

Patient related variables

We report 72 pineal region GBM patients (42% female) with an average age of 39 ± 19.2 (1 – 74) years. A summary of the findings is provided in Tables 1, 2, and 3. The clinical presentation of the patients did not differ from other pineal region lesions. However, 86% of the pineal GBM patients harbored hydrocephalus.

Disease characteristics

Among the 72 pineal GBM cases, four were reported as WHO grade IV Gliosarcomas [4, 38, 46]. At initial presentation, 22 (31%) patients did not have tumor imaging reports. 11/50 patients (22%) had intracranial dissemination [1, 3, 11, 12, 22, 24, 43], and only one case reported spinal dissemination [43]. The few cases with CT scan reports did not describe calcifications. MRI studies mostly reported an unspecific lesion with a mean diameter of 29 ± 11 (6-50) mm, irregular borders, and heterogeneous enhancement without cystic components. Tumors with and without hydrocephalus had average diameters of 33.4mm and 26mm, respectively. No statistical difference was found due to the reduced number of cases with reported dimensions. Hydrocephalus management included direct removal of the tumor (10.6%), endoscopic third ventriculostomy (38.3%), and ventriculoperitoneal shunt (51.1%).

Immunogenetics

Immunogenetic reports were very limited to draw appropriate conclusions since only 30 (42%) patients detailed genetic profile information (Table 4) [1, 2, 6, 11–13, 15, 22, 24, 26, 29, 32, 35, 37, 38, 43, 46, 47]. Among 30 patients, H3K27 gene mutation was studied in 15 patients. IDH1 mutation in 15 patients, and Ki67 in 18 patients. Other common glioma genes mutations such as the PTEN mutation, ATRX lost, 1p/19q co-deletion, MGMTp methylation, EGFRvIII mutation underwent evaluation in 10 or a smaller number of patients. The few cases prevented to find of correlations between the genetic profile and disease progression. The survival analysis of the patients with the genetic profile is described in the section “predictors of overall survival”.

We did not find any association under the univariate and multivariate analysis as well. Thus, the H3K27M mutation did not correlate with any clinical or surgical variable. However, none of the seven H3K27M mutant patients followed GTR while 4/8 (50%) H3K27 wild type followed GTR (Fisher test p:0.077).

Surgical intervention and complementary therapy

Biopsy in 33% of this series, usually associated with radiochemotherapy, represented the most frequent treatment modality. Only 19% of the patients underwent gross total resection. Moreover, 89% and 76% of the patients underwent radiotherapy and chemotherapy, respectively. 75% of the patients underwent both radiochemotherapy and radiotherapy. Radiotherapy protocols included in most cases external boost radiotherapy of 60Gy distributed in daily doses of 2Gy. Chemotherapy protocols included Temozolomide in different schemes. Moreover, vincristine, cisplatin, optune, nivolumab, dichloroacetate, KPT-330, Avastin, bevacizumab, nimustine, valproic acid, thioguanine, lomustine, dibromodulcitol, ifosfamide, and etoposide were also reported.

Follow up and outcome

Table 1 summarizes the survival and radiological outcomes. The average follow-up (FU) of pineal region GBM patients was 12 ± 10 (0 – 42) months. 30% of the patients were alive at the last FU. The MOS of this series was 12 months. Information regarding the functional status of the patients at the last clinical evaluation was limited. At the last MRI evaluation of the patients, 23 (32%) patients did not report postoperative imaging. 13/49 (27%) patients did not present disease progression, and four of them were tumor-free. Among the rest of patients, 24/49 (49%) had local progression, 12/49 (25%) had intracranial metastasis, although 6/11 (55%) patients with intracranial metastasis at initial presentation did not report postoperative imaging. 7/49 (14%) patients presented spinal metastasis. All seven spinal metastases presented without pineal tumor progression but with intracranial metastasis in five cases. Similarly, 10/12 (83%) patients with regional intracranial metastasis presented without the primary pineal tumor progression. Thus, 12/14 (86%) patients with regional or spinal metastasis at the last FU did not associate primary pineal tumor progression. 4/49 (8.2%) patients had postoperative complications characterized by postoperative hemorrhage and infarctions.

Table 2 compares the differences among the primary surgical management of the patients. Metastatic disease at initial presentation did not have any association with the type of surgical treatment (Biopsy versus surgical removal) (Fisher exact test, p = 0.7). Regional and spinal metastases at the last MRI evaluation was similar among the different surgical treatment. However, patients undergoing biopsy and complementary therapy had reduced local progression of the disease compared to those following a more invasive surgical removal of the tumor (Fisher exact test, p = 0.021). Under univariate analysis, no other variables had a significant association with the progression of the disease at the last evaluation. The mortality of patients following biopsy was significantly inferior compared with patients undergoing surgical removal. The MOS of patients following biopsy was 19 months, while the MOS of patients following surgical removal was 12 months (Long Rank test, p = 0.018). Table 3 details the radiochemotherapy delivery. The mortality of patients following radiochemotherapy was significantly inferior compared with patients undergoing surgery alone. The MOS of patients following radiochemotherapy was 18 months, while the MOS of patients following surgery alone was six months (Long Rank test, p = 0.002). Moreover, the mortality of patients following biopsy

plus radiochemotherapy (MOS of 19 months) was significantly inferior to patients following surgical removal without radiochemotherapy (MOS of 10 months) (Long Rank test, p = 0.010).

Predictors of overall survival

After univariate Cox survival analysis, predictors of better overall survival included biopsy procedures, radiotherapy, chemotherapy, and the association of radiotherapy plus chemotherapy (Table 5, Figure 3). After Cox survival multivariate regression analysis, independent variables associated with better survival rates included biopsy procedures and the association of radiotherapy plus chemotherapy (Table 5, Figure 4). It is worth noting that after multivariate regression analysis, radiotherapy (OR: 2.47, 95% CI: 0.78 – 7.86, p: 0.13) and chemotherapy (OR: 2.87, 95% CI: 0.75 – 10.97, p: 0.12) separately did not show independent association with better survival of the patients.

Due to the limited number of cases, we did not find differences in the Cox survival model evaluation among the 30 patients with different genetic profiles. Thus, the MOS of patients with H3K27M mutant was 23 months, and the MOS of patients with H3K27 wild type was ten months (Long Rank test, p = 0.3). However, it is worth noting that 5/7 (71%) patients with H3K27M mutant kept alive along 12±6 (7-23) months compared with the 88% (7/8) mortality of the H3K27 wild type patients after 13±7 (2-24) months (Fisher p = 0.041). Regarding other genetic markers, the distribution of the genetic profile did not significantly affect the overall survival of the patients.

Pediatric population

Table 1 details the characteristic of the study population classified as patients younger and older than 20 years old. High male frequency in the adult population contrasted with the high female frequency in the pediatric population. However, the differences were not statistically significant (p = 0.063). Regarding treatment modalities, while adult patients followed surgical removal in most cases, pediatric patients followed biopsy (p = 0.023). Differences were insignificant regarding the sex, hydrocephalus, tumor dimensions, intracranial or spinal dissemination at initial presentation, the extent of surgical resection, radiotherapy delivery, chemotherapy delivery, postoperative complications, disease progression at the last MRI evaluation, clinical FU, nor survival rate.

Discussion

Pineal region GBM are uncommon lesions. Here, we present a systematic review of 72 pineal region GBM, the most comprehensive series reported in the literature. An evaluation of 47 pineal GBM performed by Niu et al. in 2020 represents the only available structured evaluation of this aggressive disease [1]. Our main findings are summarized as follow:

- Pineal GBM is present in adults without gender differences. Pineal GBM associates hydrocephalus in around 90% at the initial presentation of the cases.
- The MOS of pineal GBM patients is 12 months.
- Biopsy represents an independent predictor of pineal GBM survival with a MOS of 19 months versus the 12-months MOS of the surgical removal group.
- Radiochemotherapy represents an independent predictor of pineal GBM survival with a MOS of 18 months versus the 6-months MOS of the surgical group without radiochemotherapy.
- The MOS of patients with H3K27M mutant was 23 months compared with the 10-months MOS of patients with H3K27 wild type. However, no statistical difference exists between the groups due to the limited number of cases.
- The pineal GMB local progression and recurrence seem higher in patients following surgical removal other than biopsy procedures.

The findings of this systematic review include some similar conclusions to the previous publication. The average age of presentation was 39 years, unlike other common midline gliomas, such as thalamus or brainstem gliomas present in children [50–52]. However, pineal GBM does not have gender preference in this review differently from the previous report [1]. The clinical presentation of the disease was similar as previously reported. Most pineal GBM appear associated with Hydrocephalus. Imaging studies also showed different features without a standard pattern.

After univariate and multivariate analysis, biopsy and radiochemotherapy became independent predictors of pineal GBM survival. This finding correlates with previous reviews [1, 2]. The literature supports maximal GBM resection in cerebral hemisphere diffuse gliomas [53–56]. However, complete resection in pineal GBM was previously questioned [1, 2, 21, 57, 58]. This research supports biopsy and RT-CMT delivery as the most suitable approach for pineal region GBM. However, as discussed later in this section, the independent GBM survival prediction of biopsy and RT-CMT delivery may mask the genetic differences of the patients.

On the other hand, the risk of collateral damage and leptomeningeal dissemination produced by the radical pineal GBM removal -as showed in the illustrative case of this report-, may play a role in patient survival [1, 57, 58]. Postoperative regional and spinal metastasis are uncommon in most diffuse midline gliomas, such as thalamus or brainstem gliomas [50–52]. However, pineal GBM presents distal leptomeningeal intracranial and spinal dissemination. The multivariate analysis of our series did not demonstrate differences in the survival of those patients with leptomeningeal dissemination. Finally, the type of radiochemotherapy delivery would also affect the survival outcomes. Thus, further research is still required to validate the findings of this study.

According to the WHO Classification of Central Nervous System tumors published in 2016 [51], the classification of glial cell-derived tumors has changed based on the genotype-based diagnosis. Diffuse and non-diffuse gliomas characterize the two major groups of this classification. Multiple genetic markers to complement glioma diagnosis include the following: the isocitrate dehydrogenase (IDH1/IDH2) mutation, 1p/19q codeletion, histone H3 K27M mutation, RELA fusion, ATRX mutation, TP53 mutations, TERT promoter mutation, BRAF V600E mutation, and KIAA1549-BRAF fusion [59, 60]. In the 2016-WHO review, H3K27M mutation commonly belongs to the midline location tumors [51]. Previous studies reported different outcomes after comparing H3K27M mutant and wild types [50, 52, 56]. However, the limited number of pineal region GBM remains a limitation to discover the genetic background of these tumors [1].

The available comprehensive study on pineal GBM could not draw significant conclusions regarding the genetic features of the patients [1]. The few patients with genetic studies remain a limitation for obtaining appropriate inferences. Subsequently, although we could not find differences in the Cox survival analysis of genetic features regarding the H3K27 mutation, the rate of survivors at the same FU period was superior in the H3K27M mutant group compared to the H3K27 wild type patients. Moreover, none of the H3K27 mutation patients underwent GTR, compared to the 50% of H3K27 wild-type patients that underwent GTR. This finding suggests that independent prediction of survival by biopsy and RT-CMT delivery may mask the genetic differences of the GBM patients. Thus, the tumor aggressiveness reflected in the prompt recurrence and the regional and spinal dissemination may represent just the phenotypic expression of the genetic mutations. H3K27 and IDH mutations were the most common genetic aberrations in the few reports. The literature lacks information on other common glioma-gene mutations such as the PTEN mutation, ATRX lost, 1p/19q co-deletion, MGMTp methylation, EGFRvIII mutation, among others. Thus, further studies with proper genetic evaluation in pineal GBM patients remain essential to determine the real impact of the surgical approach and RT-CMT delivery in the patients´ survival.

The main limitation of this study represents the retrospective data collection from case reports or small series of patients. Moreover, we have tried to avoid losing patient data. Thus, all available data underwent analysis without extrapolating missing data. The conclusions of this study require further evaluation.

Declarations

GBM of the pineal region is a very aggressive disease with high mortality in the first year after initial treatment. Biopsy and radiochemotherapy represent independent predictors of pineal GBM survival. However, further studies should evaluate the impact of the genetic profile on long-term outcomes. Surgical resection different from biopsy seems to increase the risks of local progression and recurrence.

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Tables

Table 1. General characteristics of pineal glioblastoma multiforme patients.

	All* (N: 70)	Age ≤ 20 years (N:15)	Age > 20 years (N:55)	N	p-value
Sex (male)	41 (60%)	5 (36%)	36 (67%)	68	0.063
Hydrocephalus	52 (87%)	10 (83%)	42 (88%)	60	0.7
Tumor diameter	29 ± 11 (6 – 50) mm	30 ± 12 (20-50) mm	29 ± 11 (6-50) mm	36	0.8
Intracranial dissemination at initial presentation	11 (22%)	1 (9%)	10 (26%)	50	0.4
Spinal dissemination at initial presentation	1 (3%)	0	1 (3%)	40	1
Biopsy	21 (33%)	8 (62%)	13 (26%)	63	**0.023**
Complete microsurgical resection	12 (19%)	0	12 (24%)	63	0.057
Radiotherapy	53 (88%)	11 (85%)	42 (89%)	60	0.6
Chemotherapy	44 (77%)	9 (75%)	35 (78%)	57	1
Radiotherapy plus chemotherapy	41 (76%)	8 (73%)	33 (77%)	54	1
Last MRI evaluation					
No disease progression	13 (27%)	3 (33%)	10 (25%)	49	0.7
local progression and recurrence	24 (49%)	2 (22%)	22 (55%)	49	0.1
Intracranial dissemination	12 (25%)	4 (44%)	8 (20%)	49	0.2
Spinal dissemination	7 (14%)	2 (22%)	5 (13%)	49	0.6
Postoperative complications	4 (8%)	1 (11%)	3 (8%)	48	1
Follow-up (months)	12 ± 10 (0-42) months	12 ± 11 (0-42) months	12 ± 10 (0-42) months	54	0.8
Mortality	44 (69%)	7 (50%)	37 (74%)	64	0.1

*Age was unreported in 2 patients.

Table 2. Pineal glioblastoma multiforme patients distributed by tumor management.

	All* (N: 64)	Biopsy (N:21)	Surgical Removal (N:43)	N	p-value
Age	38±19 (1-74)	35±22 (8-69)	40±18 (1-74)	63	0.2
Sex (male)	38 (61%)	10 (48%)	28 (68%)	62	0.2
Hydrocephalus	47 (86%)	18 (90%)	29 (83%)	55	0.7
Tumor diameter	30±10 (6-50)	24±5 (20-32)	30±11 (6-50)	35	0.2
Intracranial dissemination at initial presentation	10 (21%)	4 (25%)	6 (19%)	47	0.7
Spinal dissemination at initial presentation	1 (3%)	1 (9%)	0	38	0.3
Radiotherapy	49 (88%)	19 (91%)	30 (86%)	56	0.7
Chemotherapy	41 (77%)	13 (77%)	28 (78%)	53	1
Radiotherapy plus chemotherapy	38 (76%)	13 (77%)	25 (76%)	50	1
Last MRI evaluation					
No disease progression	11 (24%)	5 (39%)	6 (18%)	46	0.3
local progression and recurrence	24 (52.2%)	3 (23%)	21 (64%)	46	**0.021**
Intracranial dissemination	11 (24%)	4 (31%)	7 (21%)	46	0.7
Spinal dissemination	7 (15%)	4 (31%)	3 (9%)	46	0.087
Postoperative complications	4 (9%)	2 (14%)	2 (7%)	45	0.6
Follow-up (months)	12±10 (0-42)	14±13 (0-42)	11±8 (0-32)	63	0.2
Mortality	40 (68%)	9 (45%)	31 (80%)	59	**0.017**
MOS (95% CI) (months)	12±2 (8-16)	19±2 (15-23)	12±1 (10-14)	59	**0.018**

Table 3. Pineal glioblastoma multiforme patients distributed by radiochemotherapy delivery. MOS, median overall survival; MRI, magnetic resonance imaging.

	All (N: 56)	Radiochemotherapy (N: 42)	Surgery alone (N: 16)	N	p-value
Age	39 ± 19 (5-74)	38 ± 19 (5-74)	41 ± 21 (8-68)	54	0.6
Sex (male)	36 (67%)	29 (71%)	7 (54%)	54	0.3
Hydrocephalus	43 (86%)	32 (84%)	11 (92%)	50	1
Tumor diameter	28 ± 10 (6-50)	27 ± 11 (6-50)	29 ± 9 (20-46)	27	0.6
Intracranial dissemination at initial presentation	10 (23%)	9 (28%)	1 (9%)	43	0.4
Spinal dissemination at initial presentation	1 (3%)	1 (4%)	0	36	1
Biopsy	17 (34%)	13 (34%)	4 (33%)	50	1
Complete microsurgical resection	11 (22%)	10 (26%)	1 (8%)	50	0.3
No disease progression at last MRI	11 (29%)	10 (33%)	1 (13%)	38	0.4
Follow-up (months)	13 ± 10 (0-42)	14 ± 10 (1-42)	9 ± 11 (0-42)	53	0.08
Mortality	36 (68%)	24 (60%)	12 (92%)	53	**0.041**
MOS (95% CI) (months)	15±4 (8-22)	18±3 (13-23)	6±1 (3-9)	53	**0.002**

Table 4. Genetic profile of pineal glioblastoma multiforme patients

Case	Year and author	Age	Sex	Initial regional metastasis	Extent of resection	Radiotherapy	Chemotherapy	PTEN mutation	H3K27M Mutation	Ki-67(%)	IDH1 Mutation	ATRX lost	1p/ co-del
1	2010 Birbilis	57	F	No	B	Yes	Yes	*nai*	*nai*	*nai*	*nai*	*nai*	*nai*
2	2011 Nemer	45	F	No	PR	No	No	*nai*	*nai*	50	*nai*	*nai*	*nai*
3	2014 Miyaji	67	M	No	*nai*	*nai*	*nai*	*nai*	*nai*	30	-	*nai*	*nai*
4	2014 Peterson	20	M	No	B	Yes	Yes	*nai*	*nai*	25	*nai*	*nai*	*nai*
5	2015 Liu	30	M	Yes	PR	Yes	Yes	+	*nai*	*nai*	*nai*	*nai*	-
6	2015 Matsuda	31	F	No	STR	Yes	Yes	*nai*	*nai*	44	*nai*	*nai*	*nai*
7	2016 Sugita	18	M	No	PR	Yes	Yes	*nai*	*nai*	*nai*	-	*nai*	*nai*
8	2016 Sugita	52	F	No	GTR	Yes	Yes	*nai*	*nai*	*nai*	-	*nai*	*nai*
9	2017 Orrego	25	M	No	GTR	Yes	Yes	*nai*	*nai*	30	*nai*	*nai*	*nai*
10	2017 Orrego	50	M	No	PR	Yes	No	*nai*	*nai*	9	*nai*	*nai*	*nai*
11	2017 Orrego	56	M	No	PR	Yes	Yes	*nai*	*nai*	40	*nai*	*nai*	*nai*
12	2017 Stowe	65	M	No	B	Yes	Yes	*nai*	*nai*	*nai*	-	*nai*	*nai*
13	2018 Damico	36	M	No	STR	Yes	No	*nai*	-	41	-	+	-
14	2018 Damico	38	M	Yes	PR	Yes	Yes	*nai*	+	9.3	-	+	*nai*
15	2018 Damico	38	M	No	GTR	Yes	Yes	*nai*	*nai*	50	*nai*	*nai*	*nai*
16	2018 Damico	46	F	No	GTR	Yes	Yes	*nai*	-	12	-	+	*nai*
17	2018 Damico	51	M	No	GTR	Yes	Yes	*nai*	-	40	-	-	-
18	2018 Damico	52	M	No	GTR	No	No	*nai*	-	5.2	-	+	*nai*
19	2018 Damico	74	M	No	GTR	Yes	Yes	*nai*	-	13	-	+	-
20	2018 Demir	8	M	Yes	B	Yes	Yes	*nai*	+	*nai*	*nai*	*nai*	*nai*
21	2018 Gilbert	12	F	No	STR	*nai*	Yes	*nai*	+	*nai*	*nai*	*nai*	*nai*
22	2018 Granados	5	F	*nai*	*nai*	Yes	Yes	*nai*	*nai*	90	*nai*	*nai*	*nai*
23	2020 Lim	22	F	Yes	B	Yes	Yes	*nai*	+	*nai*	-	-	*nai*
24	2020 Niu	21	M	Yes	STR	Yes	Yes	*nai*	+	8	-	+	*nai*
25	2020 Niu	30	M	Yes	STR	Yes	Yes	*nai*	+	20	-	-	*nai*
26	2020 Niu	55	M	Yes	STR	No	No	*nai*	-	20	-	-	*nai*
27	2020 Sajan	39	F	No	B	Yes	Yes	*nai*	+	*nai*	+	*nai*	+
28	2020 Yerneni	51	M	Yes	B	Yes	Yes	+	*nai*	*nai*	*nai*	*nai*	*nai*
29	2021 Dono	24	M	*Nai*	B	Yes	Yes	*nai*	-	*nai*	*nai*	*nai*	*nai*
30	2021 Dono	54	M	*Nai*	STR	Yes	Yes	*nai*	-	*nai*	*nai*	*nai*	*nai*

Table 5. Predictors after univariate and multivariate survival Cox model of pineal region glioblastoma multiforme. HR, hazard ratio; CI, confidence interval; CMT, chemotherapy; RT, radiotherapy; GTR, gross total resection. Values with statistical significance in bold.

Overall survival						
	Univariate model			Multivariate model		
Variable	HR	95.0% CI for HR	p-value	HR	95.0% CI for HR	p-value
Sex	0.850	0.455 , 1.589	0.611			
Hydrocephalus	0.110	0.115 , 1.247	0.110			
Biopsy	2.463	1.118 , 5.427	**0.025**	4.155	1.496 , 10.291	**0.005**
CMT	2.625	1.308 , 5.268	**0.007**			
RT	4.103	1.670 , 10.083	**0.002**			
RT + CMT	2.802	1.381 , 5.685	**0.004**	4.118	1.774 , 9.558	**<0.001**
GTR	0.877	0.412 , 1.868	0.735			
Regional metastasis	0.930	0.375 , 2.303	0.875			
Maximal tumor dimension	0.997	0.960 , 1.037	0.897			

Figures

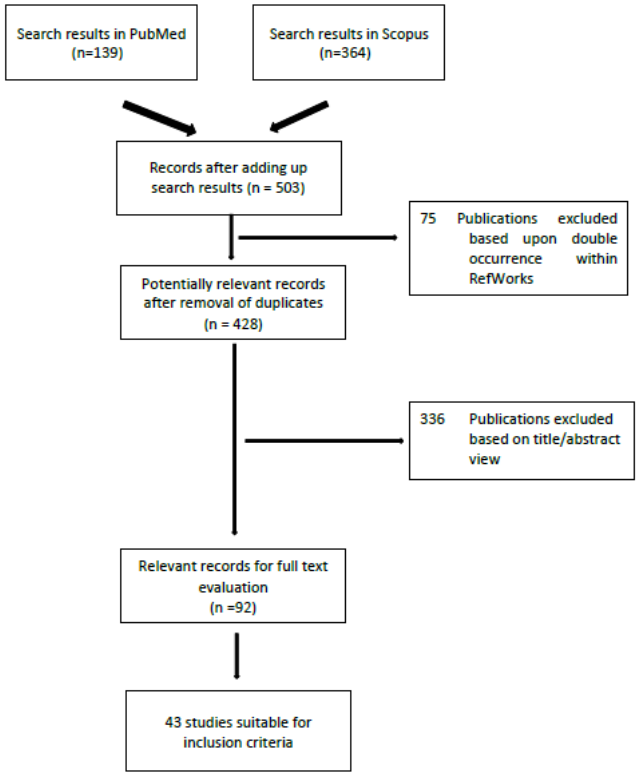

Figure 1

A literature search of pineal region glioblastoma multiforme using PubMed and SCOPUS databases.

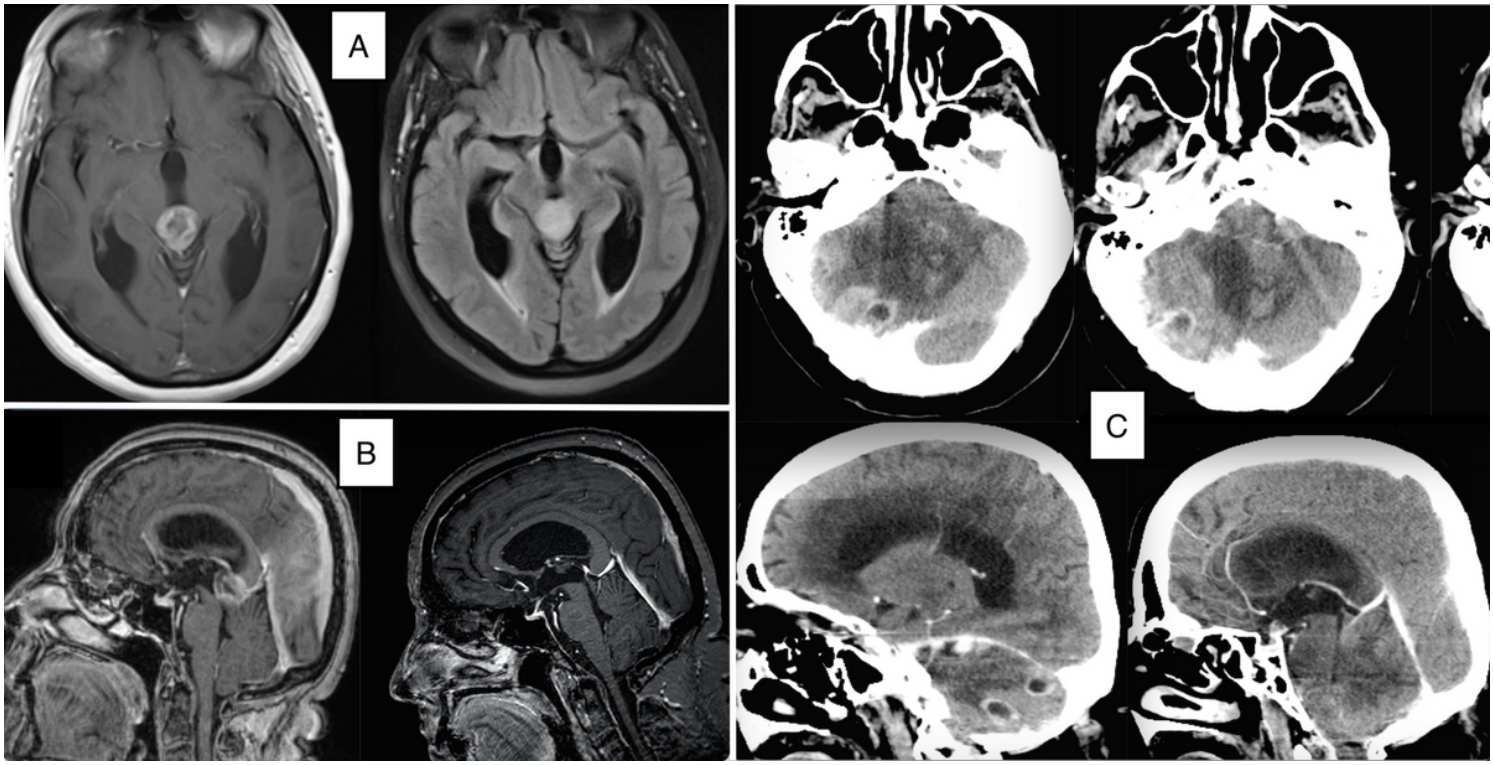

Figure 2

Preoperative and postoperative (A-C) imaging studies of a pineal region GBM. C. Postoperative CT scan with multiple tumor foci in the right cerebellar parenchyma and incisural space.

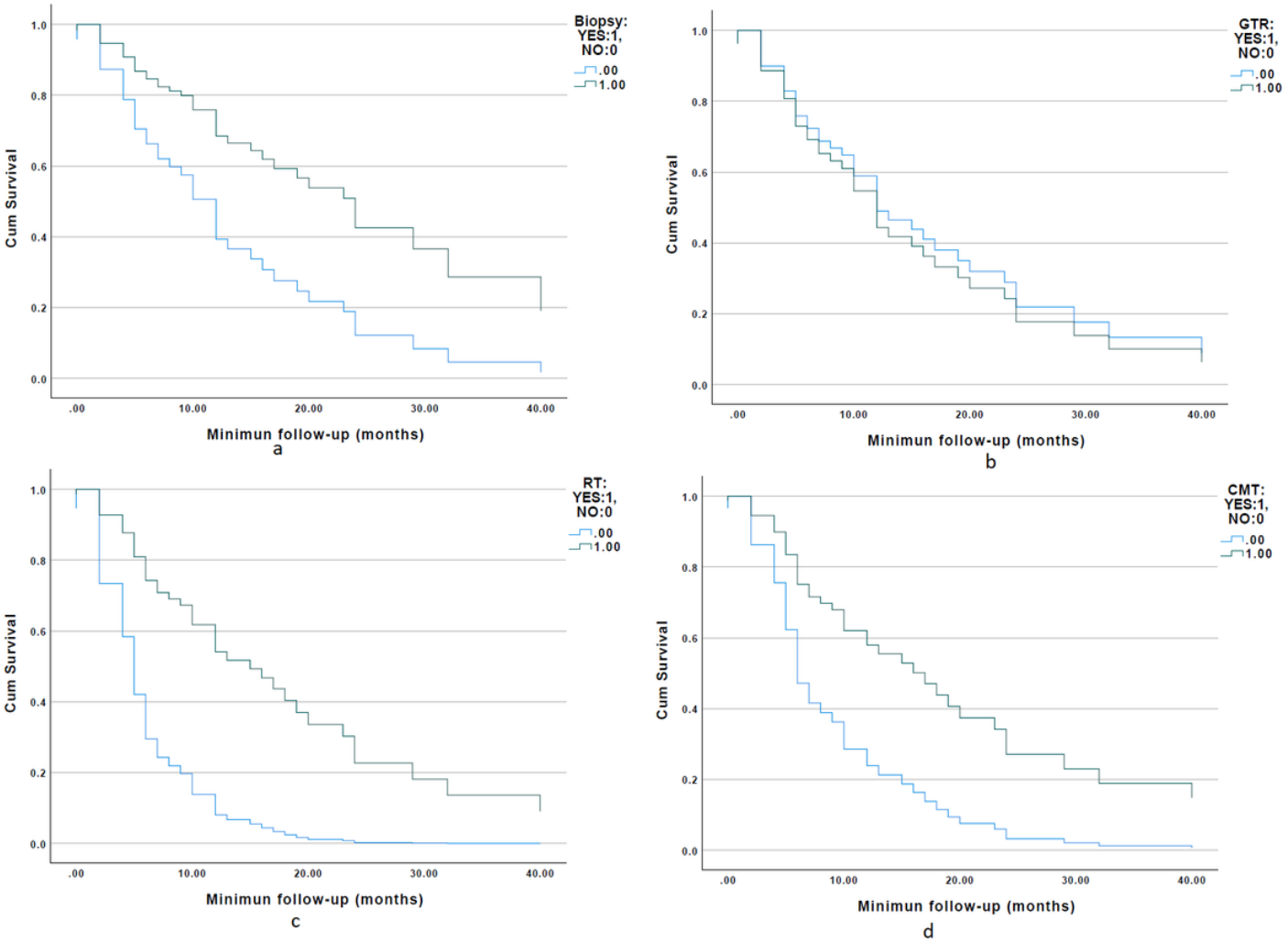

Figure 3

Pineal GBM univariate survival models: biopsy (A), gross total resection (B), radiotherapy (C), and chemotherapy (D).

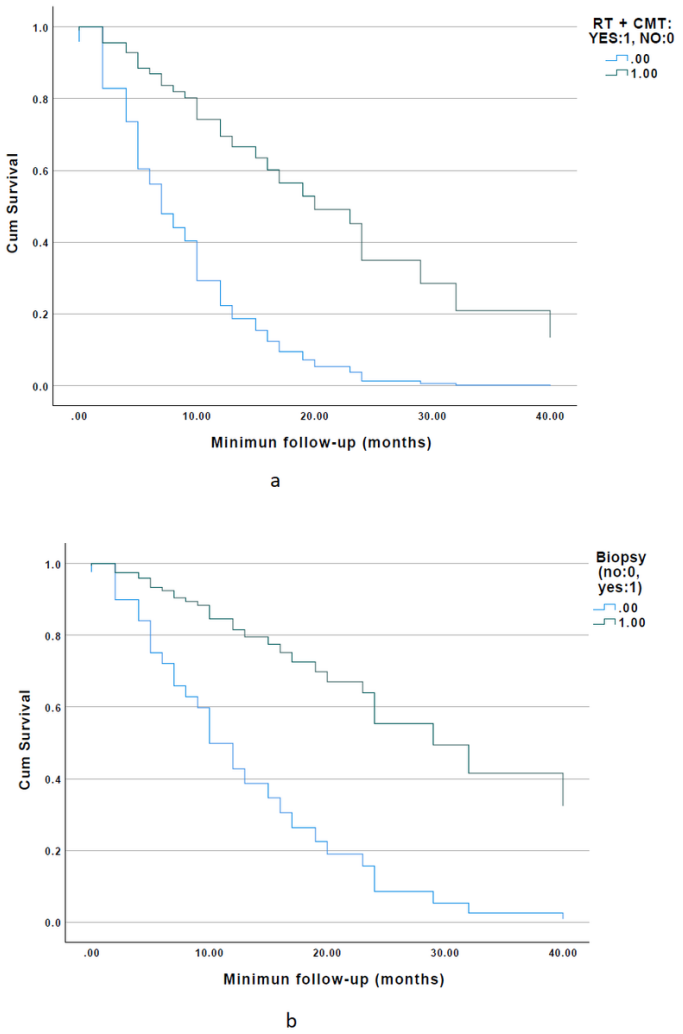

Figure 4

Pineal GBM multivariate survival models including radiochemotherapy and biopsy: radiochemotherapy (A) and biopsy (B).