RESEARCH ARTICLE

Natural Course and Prognosis of Primary Spinal Glioblastoma

A Nationwide Study

Aymeric Amelot, MD, PhD, Louis-Marie Terrier, MD, PhD, Bertrand Mathon, MD, Christophe Joubert, MD, Thiebaud Picart, MD, PhD, Vincent Jecko, MD, Luc Bauchet, MD, PhD, Florian Bernard, MD, PhD, Xavier Castel, MD, PhD, Louis Chenin, MD, Ann-Rose Cook, MD, Evelyne Emery, MD, PhD, Dominique Figarella-Branger, MD, PhD, Guillaume Gauchotte, MD, PhD, Thomas Graillon, MD, PhD, Anne Jouvet, MD, PhD, Michel Kalamarides, MD, PhD, Steven Knafo, MD, PhD, Arnaud Lazard, MD, Vincent Lubrano, MD, PhD, Karima Mokhtari, MD, PhD, Valérie Rigau, MD, PhD, Vincent Roualdes, MD, PhD, Audrey Rousseau, MD, PhD, Romuald Seizeur, MD, PhD, Emmanuelle Uro-Coste, MD, PhD, Jimmy Voirin, MD, PhD, Philippe Metellus, MD, PhD, Johan Pallud, MD, PhD, and Ilyess Zemmoura, MD, PhD, and the Medullary Glioblastoma study group

Correspondence
Dr. Amelot
aymmed@hotmail.fr

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Abstract

Background and Objectives

Primary spinal glioblastoma (PsGBM) is extremely rare. The dramatic neurologic deterioration and unresectability of PsGBM makes it a particularly disabling malignant neoplasm. Because it is a rare and heterogeneous disease, the assessment of prognostic factors remains limited.

Methods

PsGBMs were identified from the French Brain Tumor Database and the Club de Neuro-Oncologie of the Société Française de Neurochirurgie retrospectively. Inclusion criteria were age 18 years or older at diagnosis, spinal location, histopathologic diagnosis of newly glioblastoma according to the 2016 World Health Organization classification, and surgical management between 2004 and 2016. Diagnosis was confirmed by a centralized neuropathologic review. The primary outcome was overall survival (OS). Therapeutic interventions and neurologic outcomes were also collected.

Results

Thirty-three patients with a histopathologically confirmed PsGBM (median age 50.9 years) were included (27 centers). The median OS was 13.1 months (range 2.5–23.7), and the median progression-free survival was 5.9 months (range 1.6–10.2). In multivariable analyses using Cox model, Eastern Cooperative Oncology Group (ECOG) performance status at 0–1 was the only independent predictor of longer OS (hazard ratio [HR] 0.13, 95% CI 0.02–0.801; $p = 0.02$), whereas a Karnofsky performance status (KPS) score <60 (HR 2.89, 95% CI 1.05–7.92; $p = 0.03$) and a cervical anatomical location (HR 4.14, 95% CI 1.32–12.98; $p = 0.01$) were independent predictors of shorter OS. The ambulatory status (Frankel D–E) (HR 0.38, 95% CI 0.07–1.985; $p = 0.250$) was not an independent prognostic factor, while the concomitant standard radiochemotherapy with temozolomide (Stupp protocol) (HR 0.35, 95% CI 0.118–1.05; $p = 0.06$) was at the limit of significance.

From the Department of Neurosurgery (A.A., A.-R.C., I.Z.), CHRU de Tours; Department of Neurosurgery (L.-M.T., P.M.), Clairval Private Hospital, Ramsay Generale de Sante, Marseille; Department of Neurosurgery (B.M., M.K.), CHU Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris; Department of Neurosurgery (C.J.), HIA St Anne, Toulon; Department of Neurosurgery (T.P.), Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Bron; Department of Neurosurgery A (V.J.), CHU Pellegrin, Bordeaux; Department of Neurosurgery (L.B.), Hôpital Saint Eloi–Gui de Chauliac, Montpellier; Department of Neurosurgery (F.B.), CHU d'Angers; Department of Neurosurgery (X.C.), CHU de St-Etienne, St Etienne; Department of Neurosurgery (L.C.), CHU Amiens-Picardie; Department of Neurosurgery (E.E.), CHU de Caen; Department of Neuropathology (D.F.-B.), La Timone, AP-HM, Marseille; Department of Pathology (G.G.), CHU Nancy, Nancy; Aix Marseille Univ (T.G.), INSERM, APHM, MMG, UMR1251, Marmara Institute, La Timone Hospital, Neurosurgery Departement, Marseille; Department of Pathology (A.J., E.U.-C.), Cancer University Institute of Toulouse Oncopole, CHU Toulouse; Department of Neurosurgery (S.K.), le Kremlin-Bicêtre, AP-HP, Kremlin-Bicêtre; Department of Neurosurgery (A.L.), CHU Grenoble-Alpes; Department of Neurosurgery (V.L.), CHU Rangueil, Toulouse; Department of Neuropathology (K.M.), Pitié-Salpêtrière, AP-HP, Paris; Department of Neuropathology (V. Rigau), CHU Gui de Chauliac, Montpellier; Department of Neurosurgery (V. Roualdes), CHU Laennec, Nantes; Department of Pathology (A.R.), CHU d'Angers; Department of Neurosurgery (R.S.), CHU de la Cavale Blanche, Brest; Department of Neurosurgery (J.V.), Pasteur Hospital, HCC, Colmar; and Department of Neurosurgery (J.P.), GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, France.

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Glossary

CT = chemotherapy; **ECOG** = Eastern Cooperative Oncology Group; **FBTDB** = French Brain Tumor Database; **FLAIR** = fluid-attenuated inversion recovery; **FU** = follow-up; **GBM** = glioblastoma; **HR** = hazard ratio; **IDH** = isocitrate dehydrogenase; **KPS** = Karnofsky performance status; **MGMT** = O(6)-methylguanine-DNA methyltransferase; **OS** = overall survival; **PFS** = progression-free survival; **PsGBM** = primary spinal glioblastoma; **RENOCLIP** = Réseau de Neuro-Oncologie CLInico Pathologique; **RENOP** = Réseau de Neuro-oncologie pathologique; **RT** = radiotherapy; **STR** = subtotal resection surgery; **TERT** = telomerase reverse transcriptase; **WHO** = World Health Organization.

Discussion

Preoperative ECOG performance status, KPS score, and the location are independent predictors of OS of PsGBMs in adults. Further analyses are required to capture the survival benefit of concomitant standard radiochemotherapy with temozolomide.

Primary spinal cord cancers are rare entities, accounting for 2%–4% of all CNS tumors.[1,2] Therefore, primary spinal glioblastoma (PsGBM) is extremely rare, accounting for only 1.5% of all spinal cord tumors.[3,4] Low-grade histology is predominant, with high-grade tumors accounting for only 10%–15% of pediatric tumors and a slightly higher proportion in adults.[5-7] These lesions are highly aggressive and lead to rapid and dramatic neurologic deterioration and death after only a short history of presentation.[4,6] The therapeutic management for PsGBM is poorly defined because of the scarcity of cases and usually consists of a biopsy followed by radiotherapy (RT) with chemotherapy (CT), mainly the concomitant standard radiochemotherapy with temozolomide.[8,9]

Our current knowledge of primary PsGBM is incomplete, and an understanding of epidemiology, diagnosis, and optimal treatment modalities is warranted.[1] While survival predictors have been well described for supratentorial hemispheric isocitrate dehydrogenase (IDH) wild-type glioblastomas[10] and cerebellar glioblastomas[11]; prognostic factors for overall survival (OS) and progression-free survival (PFS) cannot be ascertained for PsGBM; so far, only case reports or small retrospective studies have been conducted.[5,12] Moreover, most case series evaluating spinal cord astrocytomas usually pool low-grade and high-grade lesions together, children and adults together, limiting the generalizability of the results.[2,3,9,13,14]

The aim of this study was to assess the natural history and clinicopathologic and therapeutic factors that influence the prognosis of patients with PsGBM. We report the largest multicentric, nationwide cohort with a central histomolecular review of adult patients harboring a primary PsGBM.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

Data collected during the study were stored in a computer file in accordance with the law of the French Data Protection Act of January 6, 1978, amended in 2004. The protocol can be found in the reference methodology MR003 chapter adopted by the CNIL to which conform the different University Hospitals of this project. Ethical approval for this study was obtained from the Ethics Committee in Human Research of the Hospital of Tours (approval number: 2018 005).

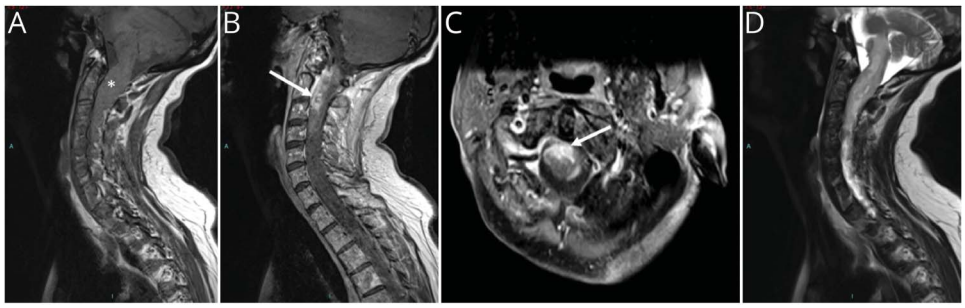
Identification of Patients With PsGBM and Data Collection

The French Brain Tumor Database (FBTDB) identifies and records patients with newly diagnosed and histologically confirmed primary CNS tumors in France (hospital based). Its methodology has been previously published.[11,15] For this study, the FBTDB and the Club of Neuro-Oncology of the Société Française de Neurochirurgie were screened to identify cases of glioblastoma (GBM) with spinal location. Before inclusion, it was verified by 1 investigator (A.A. or 1 local neurosurgeon specialized in neuro-oncology) that all patients met the following inclusion criteria: (1) age 18 years or older at diagnosis, (2) spinal location, (3) histopathologic diagnosis of newly GBM according to the World Health Organization (WHO) classification, version 2016 (prevailing classification during the study), and (4) surgical management between January 1, 2004, and December 31, 2016. The exclusion criteria were (1) the presence of a supraspinal tumor at diagnosis, (2) recurrent tumor, and (3) another glioma than primary GBM. In each neurosurgical center, data collection was performed by 1 neurosurgeon specialized in neuro-oncology (A.A. or 1 local neurosurgeon). Demographics, clinical data, imaging features, surgical details, postoperative course, type of adjuvant treatment, and follow-up (FU) data including cause of death were locally extracted from medical records using a chart designed for the study.

Detection of Sequence Variations

IDH1 and H3K27M sequence variations were first screened by immunohistochemistry labeling and completed by genomic DNA amplification with Sanger method or Next-Generation Sequencing depending on the pathology center. Telomerase reverse transcriptase (TERT) mutation was searched by DNA amplification with Sanger method or droplet digital PCR. The methylation status of O(6)-methylguanine-DNA methyltransferase

Figure 1 MRI of Cervical PsGBM



(A) Sagittal T1-weighted MRI showing a thickening of the cervical spinal cord (white star). (B) Sagittal and (C) axial T1-weighted MRI with gadolinium injection demonstrating an enhancement of the anterior cervical spinal cord (white arrow). (D) Sagittal T2-weighted MRI of the same tumor showing peripheral edema in hypersignal. PsGBM = primary spinal glioblastoma

(MGMT) promoter was determined by pyrosequencing of cytosine-phosphate-guanine sites from MGMT promoter.

Histopathologic Diagnosis

We included patients whose histomolecular diagnosis of PsGBM had been reviewed by the French neuropathologic network (RENOP, "Réseau de Neuro-oncologie pathologique") for clinical purposes during the initial diagnosis. Cases that did not benefit from this central neuropathologic review systematically underwent a post hoc central neuropathologic review by the new French neuro-oncology network RENOCLIP ("Réseau de Neuro-Oncologie Clinico Pathologique") to confirm or exclude the diagnosis.

Frankel Score

The Frankel grade classification provides an assessment of spinal cord function and is used as a tool in spinal cord injury.[16]

Progression Measures

GBM progression occurring within the initial tumor site was defined as local progression. The progression was defined as an MRI recurrence or progression according to RANO criteria.[17] Therefore, progression was defined by at least one of these criteria: (1) increase of 25% or more in the sum of the products of the perpendicular diameters of the contrast-enhancing T1 MRI lesions compared with the examination that measured the smallest tumor dimensions; (2) increase in fluid-attenuated inversion recovery (FLAIR) MRI sequence not related to comorbidity; or (3) any new measurable or nonmeasurable lesion associated with clinical deterioration.

Review of Case Reports

A search was conducted in Medline through PubMed, from 2005 to 2022, using the following keywords: primary/spinal/glioblastoma. With these keywords, 234 articles were found. Inclusion criteria of articles in our review were as follows: adult patients, PsGBM histologic proof, year of diagnosis >2005, and outcome (survival and treatments). With these inclusion criteria, we included 33 case report/series and identified 72 patients with PsGBM.[e1-e33]

Statistical Analyses

All tests were 2-sided; p values <0.05 were considered statistically significant. Univariate and multivariable Cox proportional hazard regression models were conducted using SPSS software, version 22.0 (SPSS, Chicago, IL). Establishment and verification of nomograms were implemented using the open-source software R, version 3.2.5, with Rms packages (Design, Vienna, Austria). Categorical variables (sex, treatment, histopathology, location, and medical history) were described with frequencies and percentages, whereas continuous variables (age, FU, and survival) were described with mean/median ± SD. OS was measured from the date of histopathologic diagnosis to the date of death. PFS was measured from the date of histopathologic diagnosis to the date of first radiologic evidence of progression, or to the date of death. Surviving patients were censored at last FU. In univariate analyses, categorical variables were assessed using the Pearson χ^2 or Fisher exact test. Multivariable analyses were conducted separately for each diagnosis, and the Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% CIs.[18] All potential explanatory variables included in the multivariable analyses were subjected to collinearity analysis with a correlation matrix. Variables associated with one another were not included in the model. The Kaplan-Meier method was used to estimate the OS and the PFS.[19]

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Population

Fifty patients were enrolled. We excluded 17 patients (34.0%): 14 because what was believed to be a spinal location was in fact a metastasis from a primary cerebral GBM and 3 for which a misclassification was revealed by a simple review of the neuropathologic records (astrocytoma WHO grade 3). Finally, a total of 33 patients with a diagnosis of PsGBM were retained for full analyses (Figure 1). Only 11 of the 33 patients had already benefited from an initial RENOP review. Hence, the remaining 22 patients (66.6%) were independently reviewed by the RENOCLIP, which confirmed the diagnosis in all cases. The 33 PsGBM were WHO grade 4 glioblastomas according to the WHO classification, version 2016.[20]

Table 1 Clinical, Cancer, and Treatment Characteristics of the Cohort

	N (range or %)
Sex	
Men	18 (54.5)
Women	15 (45.5)
Median age, y	50.9 (19–78)
<40	14 (42.4)
40–60	10 (30.3)
>60	9 (27.3)
KPS	
30–50	10 (30.3)
60–80	16 (48.5)
>80	7 (21.2)
ECOG status	
0	8 (24.2)
1	10 (30.3)
2	7 (21.2)
3–4	8 (24.2)
Frankel score	
D–E	22 (66.7)
A–C	11 (33.3)
History of cancer	2 (6.0)
PsGBM anatomical location	
Cervical	12 (36.3)
Thoracic	14 (42.4)
Conus	7 (21.2)
Surgery	
Partial resection	12 (36.4)
Biopsy	21 (63.6)
Radiotherapy	21 (63.6)
Alone	6 (18.2)
Stupp protocol	11 (33.3)
With other chemotherapy	4 (12.1)
Chemotherapy	
TMZ Stupp	14 (42.4)
TMZ alone	5 (15.1)
Other	2 (6.0)
Immunotherapy (nivolumab and ipilimumab)	1 (3.0)
Immunotherapy (bevacizumab)	2 (6.0)
Third line treatment (progression)	
Bevacizumab	5 (15.1)
Chemotherapy	5 (15.1)
No treatment	3 (9.1)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; PsGBM = primary spinal glioblastoma; TMZ = temozolomide; TMZ Stupp = concomitant radiochemotherapy with temozolomide according to the Stupp protocol.

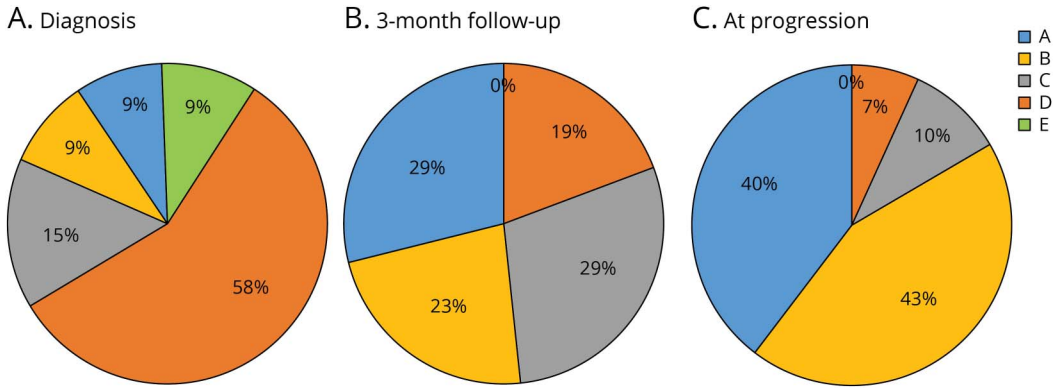
Epidemiologic and Clinical Data

Clinical data are summarized in Table 1 and demonstrated 15 (45.5%) women and 18 (54.5%) men, with a median age of 50.9 years (range 19–78 years). Two patients (6.0%) had a history of cancer of non-neurologic origin. Neurologic symptomatology at the initial discovery was graded according to Frankel score[16]: 22 (66.6%) were ambulatory (Frankel D–E) and 11 (33.3%) were not (Frankel A–C). At diagnosis, the Karnofsky performance status (KPS) score was between 30 and 50 in 10 patients (30.3%), between 60 and 80 in 16 patients (48.5%), and >80 in 7 patients (21.2%). The ECOG status was at 0 in 8 patients (24.3%), 1 in 10 patients (30.3%), 2 in 7 patients (21.1%), and 3–4 in 8 patients (24.3%). The patients had typical imaging findings of a unifocal mass, extending from 1 to 3 vertebrae with intense annular contrast enhancement surrounding a central necrosis (Figure 1). The medullar anatomical repartition was cervical in 12 cases (36.3%), thoracic in 14 cases (42.4%), and lumbar medullaris in 7 cases (21.2%).

Oncological Treatment

Therapeutic data are summarized in Table 1. Twelve patients (36.4%) underwent a subtotal resection surgery (STR), and 21 patients (63.6%) underwent surgical biopsy. The distribution of STR in cervical, thoracic, and lumbar regions was 2/12 (16.6%), 6/12 (50%), and 4/12 (33.3%), respectively (p = 0.453). Twenty-one patients (63.6%) received spinal RT: alone (6/33 patients; 18.2%), with concomitant adjuvant temozolomide CT according to Stupp et al.[21] (11/33, 33.3%), or with another CT (4/33, 12.1%). Five patients (15.1%) received CT with temozolomide alone. Two patients (6.0%) received another CT (lomustine, carmustine), 1 patient (3.0%) was treated with an immunotherapy (nivolumab and ipilimumab), and 2 patients (6.0%) with bevacizumab. Finally, 3 patients (9.1%) did not receive CT nor RT and received supportive care management. The therapeutic strategies at tumor progression were as follows: a second resection for 3 cases and a second-line treatment for 10 cases with continuation of temozolomide (3) and bevacizumab (5), RT alone (1) or concomitant with temozolomide (2), and supportive care in 19 cases.

Figure 2 Evolution of Frankel Scores (Neurologic Function) of Patients With PsGBM During the Follow-up



(A) At presentation, 67% of patients were ambulatory (Frankel D and E), before early presentation (B) at the 3-month follow-up, a degradation was noted and only 19% of patients remained ambulatory (Frankel D). At lesion progression, 83% of patients developed plegia (Frankel A and B) and only 7% were ambulatory. PsGBM = primary spinal glioblastoma.

Neurologic Damages

Neurologic condition evolution is presented in Figure 2. At diagnosis, 22 patients (67%) were ambulatory (Frankel D–E) (Figure 2A). In the postoperative period, 6/33 (18.2%) patients (4 cervical and 2 thoracic) developed a neurologic deterioration, 2/6 after biopsy and 4/6 after surgery. For these 6 patients, 3 presented an increase in sensory disorders, and 3 presented a motor deterioration due to hematoma (2 patients: 1 biopsy and 1 surgery) or an increase in medullary edema (1). For the 21 patients (63.6%) who received spinal RT, no side effect related to irradiation was observed. At 3-month FU, neurologic evolution deteriorated, and only 6 patients (19%) remained ambulatory (Figure 2B). Nine of 12 (75%) patients who underwent STR developed a neurologic deterioration at 3-month FU, vs 13/21 (61.9%) for biopsy, $p = 0.703$. By contrast, the patients who developed neurologic deterioration at 3-month FU had a significantly larger PsGBM lesion at presentation (4.2 cm^3, SD 2.9) ($p = 0.029$). At progression, only 2 patients were ambulatory, and 22 patients (67%) presented a complete disappearance of motor function (Figure 2C).

Progression Analyses

The median FU was 10.5 months (range 1.3–61.4). Thirty-one patients (93.3%) presented a progression during the FU period. The median PFS was 5.9 months (range 1.6–10.2). The 6-month, 12-month, and 24-month PFS estimates were 45.5% (SD 8.7), 32.5% (SD 8.3), and 10.8% (SD 5.8), respectively (Figure 3A). Progression occurred locally in 29 patients (87.9%). Intracranial spreading was observed in 7 patients (21.2%) with a mean delay of 18.4 months (SD 1.9). Four patients (12.1%) developed leptomeningeal progression evaluated on MRI, 2 patients (1 lumbar and 1 thoracic) developed distal C3-C4 and C5 dissemination, and 3 patients with cervical lesions presented a thoracic spreading. We did not perform autopsies in our series.

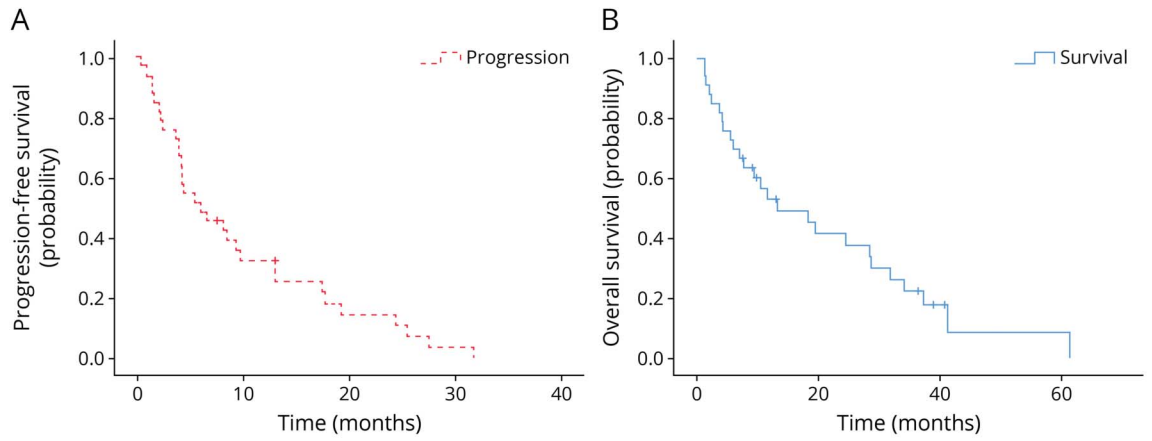
Survival Analyses

The median OS was 13.1 months (range 2.5–23.7 months). The 6-month, 12-month, 36-month, and 60-month OS estimates were 80.9%, 56.6%, 22.7%, and 0%, respectively (Figure 3B). Twenty-six patients (78.8%) died during the FU period. Five patients (3 thoracic and 2 lumbar) died of a brain dissemination, 2 patients with thoracic localizations died of respiratory failure, 2 patients (1 lumbar and 1 thoracic) died of cervical C3-C4 dissemination with tetraplegia, and 2 patients with thoracic PsGBM died of glial meningitis with no other medullary or cranial localizations. Finally, 5 more fragile patients (median age 72.3 years) died after general deterioration. Five patients are still alive (2 thoracic and 3 lumbar).

Prognostic factors associated with OS are summarized in Table 2. In univariate analysis, patients with a preserved ECOG performance status 0–1 (OS: 31.8 months, Figure 4A), patients with preserved ambulatory and neurologic functions at diagnosis (OS: 24.4 months, Figure 4B), and patients with a KPS score >80 (OS: 41.2 months, Figure 4C) had significantly longer survival ($p < 0.0001$). Patients with a cervical location had significantly shorter survival (OS: 5.9 months, Figure 4D) ($p = 0.029$). Patients who received a standard RT with concomitant temozolomide (Stupp protocol)[21] had a significantly longer survival (OS; 31.8 months, Figure 4E) ($p = 0.038$).

In multivariable analysis with the Cox proportional hazard model, only ECOG performance status at 0–1 (HR 0.134, 95% CI 0.02–0.801; $p = 0.02$) was an independent predictor of a longer OS, whereas KPS score <60 (HR 2.895, 95% CI 1.05–7.92; $p = 0.03$) and cervical anatomical location (HR 4.138, 95% CI 1.32–12.98; $p = 0.01$) were independent predictors of a shorter OS. Neither the standard chemoradiotherapy with concomitant temozolomide (HR 0.352, 95% CI 0.118–1.05; $p = 0.062$) nor the ambulatory status (Frankel D–E) (HR 0.378, 95% CI 0.07–1.985; $p = 0.250$) were identified as independent predictors of OS.

Figure 3 OS Analysis



	6 months	12 months	24 months
PFS % (SD)	45.5 (8.7)	32.5 (8.3)	10.8 (5.8)
Number with progression	18	22	31

	6 months	12 months	36 months	60 months
Survival % (SD)	80.9 (6.7)	56.6 (8.9)	22.7 (8.0)	0 (0.0)
Number at risk	22	14	5	0

Kaplan-Meier survival analysis. (A) PFS in months, defined by clinical and MRI progression: table demonstrated the progression rates at 6, 12, and 24 months of follow-up. (B) Overall survival (OS) in months for the 33 patients after PsGBM diagnosis: table demonstrated the survival rates at 6, 12, 36, and 60 months of follow-up. OS = overall survival; PFS = progression-free survival; PsGBM = primary spinal glioblastoma.

Molecular Profile

IDH sequence variation was investigated in 20/33 patients (60.6%) (Table 3). All these 20 patients had an IDH wild-type tumor. The MGMT promoter methylation status was investigated in 14/33 patients (51.5%). All these 14 cases were unmethylated. The TERT sequence variation was investigated in 8/33 patients (24.2%), and no case presented a TERT variation. Four patients presented an H3K27M variation (see eTable 1, links.lww.com/WNL/C617).

Review of Recent Cases Reports (2005–2022)

As summarized in eTable 1 (links.lww.com/WNL/C617), we performed an inventory in the modern literature of PsGBM diagnosed and treated since 2005, date of introduction of radiochemotherapy (temozolomide) according to the Stupp protocol for brain GBM.[21]

In an integrative survival analysis performed by extracting individual patient data from the 72 cases reported in the recent literature (2005–2022) associated with our 33 patients, we determined for these 105 patients (median age 37 years, SD 16.5) a median OS of 13.1 months (SD 1.6 months) and a median PFS of 8.0 months (SD 0.629). We confirmed that the extent of resection was not associated with better OS for PsGBM: biopsy (11 months, SD 1.8), gross total resection (8 months, SD 1.4), and subtotal resection (15 months, SD 2.7). The anatomical localization (cervical, thoracic, or lumbar) was not associated with a better survival. Furthermore, we noted that complementary treatments, no matter the type, improved the survival of patients compared with the absence of any complementary treatment: CT alone (10.5 months, SD 1.0), RT alone (11 months, SD 4.6), RT + temozolomide (16 months, SD 1.5), RT + temozolomide + immunotherapy/CT (13 months, SD 3.5), and palliative treatment (3.4 months, SD 1.4). Moreover, patients aged younger than 60 presented better survival.

Discussion

This study determines the median PFS and OS of adult PsGBM, which are 5.9 and 13.1 months, respectively. We highlighted 2 independent predictors of survival: the preoperative clinical status (ECOG and KPS) and the anatomical location.

Previous studies concerning PsGBM are limited to small case series, individual case reports, or literature reviewing.[2,4,9,13,14,22,23] In addition, previous studies were composed of both adult and pediatric cases, assorted different WHO grades of malignancy, without expert central histomolecular review, and did not detail clinical, imaging, or therapeutic data. In this study, the median age at diagnosis was older than what has previously been reported,[3,14,23,24] explained by the exclusion of the pediatric population and the careful selection of PsGBM excluding anaplastic or low-grade astrocytoma or oligodendroglioma. However, the median age at diagnosis seems lower for PsGBM than for supratentorial hemispheric glioblastomas.[25]

Regarding survival, the previous series of PsGBM reported an OS of approximately 10 months, in contrast to a somewhat better prognosis of 14 months for supratentorial hemispheric glioblastomas.[3,13] In this study, we identified a median OS (13.1 months), which is comparable with the one reported for supratentorial hemispheric glioblastomas.

Table 2 Univariate and Cox Proportional Hazards Models of OS for Patients With PsGBM

	Univariate		Multivariate		
	OS, mo (SD)	*p* Value	OR	95% CI	*p* Value
Sex		0.339			
Men/women	24.5/10.5				
Age, y		0.222			
<40	13.1 (6.8)				
40–60	28.7 (11.6)				
>60	5.4 (1.9)				
ECOG status		**<0.0001**			
0	28.4 (13.1)		**0.134**	**0.02–0.80**	**0.028**
1	34.1 (3.8)				
2	7.0 (1.3)				
3–4	3.4 (1.0)				
KPS		**<0.0001**			
30–50	3.6 (2.0)		**4.138**	**1.31–12.99**	**0.015**
60–80	18.2 (5.3)				
>80	41.2 (7.2)				
Brain spreading	10.5 (3.7)	0.876			
Frankel score		**<0.0001**			
D–E	24.5 (9.3)		0.378	0.07–1.95	0.250
A–C	5.4 (1.2)				
PsGBM anatomical location		**0.029**			
Cervical	5.98 (2.7)		**2.895**	**1.06–7.92**	**0.038**
Thoracic	13.13 (5.8)				
Lumbar	37.24 (6.2)				
Surgery		0.688			
Subtotal resection	24.5 (12.2)				
Biopsy	11.5 (2.2)				
Radiotherapy					
Alone	5.9 (4.3)	0.308			
Stupp protocol	31.8 (8.3)	**0.038**	0.352	0.12–1.05	0.06
With other chemotherapy	18.2 (10.0)	0.278			
Chemotherapy					
TMZ Stupp	31.8 (8.3)	**0.038**	0.352	0.12–1.05	0.06
TMZ alone	13.3 (2.01)	0.127			
Other	41.2 (17.8)	0.066			
Immunotherapy (nivolumab)	—				
Bevacizumab	12.3 (2.7)	0.379			
Third-line treatment (progression)					

Continued

Table 2 Univariate and Cox Proportional Hazards Models of OS for Patients With PsGBM *(continued)*

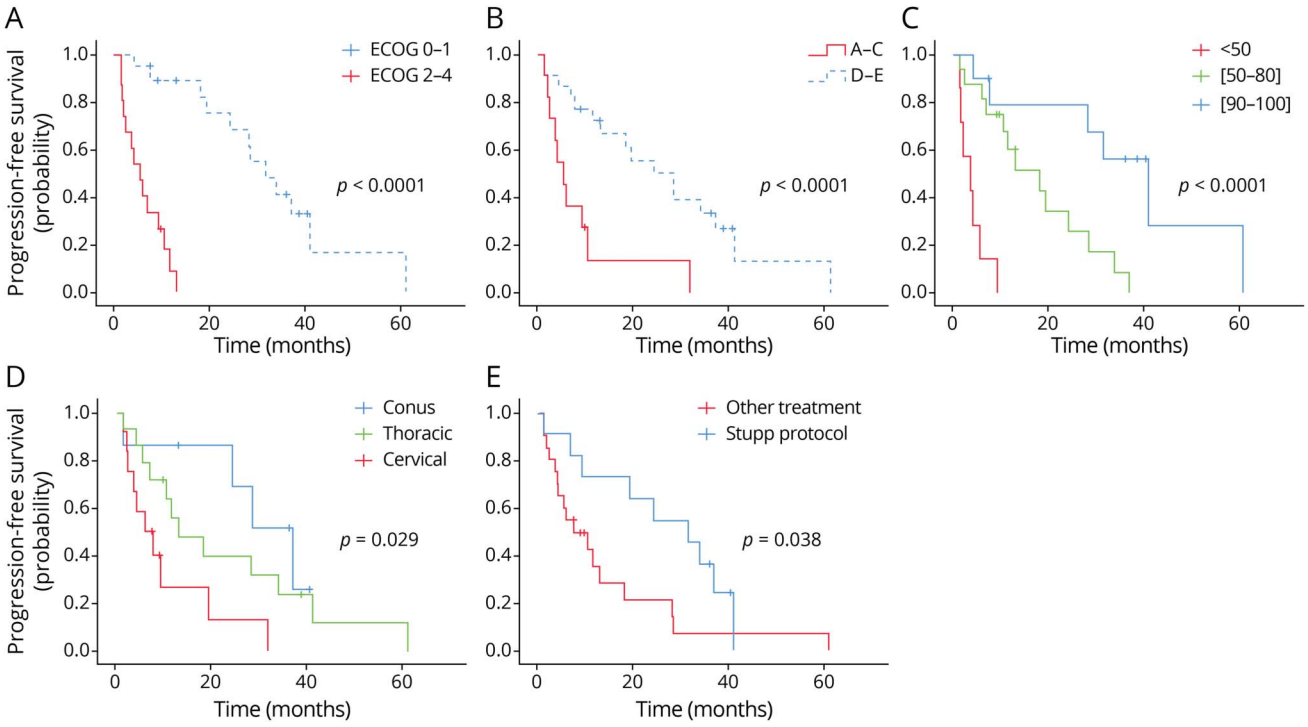
	Univariate		Multivariate		
	OS, mo (SD)	*p* Value	OR	95% CI	*p* Value
Bevacizumab	17.8 (4.6)	0.610			
Chemotherapy	11.8 (2.1)	0.251			
No treatment	2.1 (0.5)				

Abbreviations: ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; OR = odds ratio; OS = overall survival; PsGBM = primary spinal glioblastoma; TMZ = temozolomide; TMZ Stupp = concomitant radiochemotherapy with temozolomide according to the Stupp protocol. Statistically significant data are in bold.

The optimal therapeutic management of PsGBM remains debated. Some studies have litigated for aggressive resections,[4,6] but the lack of a clear surgical plane between the infiltrative tumor and the healthy tissue of the spinal cord makes gross total resection quite unachievable. Furthermore, the extent of resection has proved to correlate with better OS,[8,24] even if Adams et al.[3] identified the extent of resection as an independent prognostic factor including both adults and children and both anaplastic astrocytomas and PsGBM.

To date, there are highlights that MRI diffusion tensor imaging and perfusion-weighted imaging could be useful for differentiating between intramedullary tumors and tumor-like lesions (tumefactive demyelinating lesion, inflammatory/infectious diseases). Nevertheless, the presentation of spinal tumors (i.e., astrocytomas, ependymomas, unspecified gliomas, medulloblastomas, metastases, neurinomas, and rarely teratomas) frequently have similarities in radiologic appearances: occupying a large portion of the spinal cord, intratumor necrosis, cystic

Figure 4 OS in Univariate Analyses



(A) The median OS for good prognosis ECOG (0–1) was 31.8 months (SD 3.6) vs 5.4 months (SD 1.5) for poor ECOG (2–4) ($p < 0.0001$). (B) The median OS for ambulatory patients (Frankel D and E) was 24.4 months (SD 9.3) vs 5.4 months (SD 1.2) for nonambulatory (Frankel A–C) ($p = 0.002$). (C) The median OS for patients with a KPS <50 was 3.6 months (SD 2.0) vs 18.2 months (SD 5.3) for KPS (50–80), vs 41.2 months (SD 7.2) for KPS >80 ($p < 0.0001$). (D) The median OS for patients with a cervical PsGBM was 5.9 months (SD 2.7) vs 13.1 months (SD 5.8) for thoracic lesions, vs 37.2 months (SD 6.2) for lumbar PsGBM ($p = 0.029$). (E) The median OS for patients with concomitant radiochemotherapy with temozolomide according to the Stupp protocol was 31.8 months (SD 8.1) vs 7.6 months (SD 4.07) for other oncological treatment ($p = 0.055$). ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; OS = overall survival; PsGBM = primary spinal glioblastoma.

Table 3 IDH, MGMT Promoter Methylation, TERT Sequence Variation, and the H3K27M Sequence Variation Status Detailed for Each Patient

Patient	Age, y	MGMT	IDH	TERT	Braf	H3K27M
1	61	—	—	—	—	NA
2	20	UM	Wild	Wild	Wild	NA
3	62	UM	Wild	—	—	NA
4	64	—	Wild	—	—	NA
5	79	UM	Wild	Wild	—	NA
6	20	—	Wild	—	—	NA
7	25	UM	Wild	—	—	NA
8	25	UM	Wild		—	NA
9	55	—	Wild	—	—	NA
10	39	—	—	—	—	NA
11	45	—	—	—	—	NA
12	56	—	—	—	—	NA
13	73	—	—	—	—	NA
14	18	—	—	—	—	NA
15	18	—	Wild	—	—	NA
16	21	—	Wild	—	—	NA
17	32	UM	Wild	Wild	Wild	NA
18	43	UM	Wild	Wild	Wild	NA
19	51	UM	Wild	Wild	Wild	NA
20	59	UM	Wild	Wild	—	NA
21	69	—	Wild	—	—	NA
22	24	—	Wild	Wild	—	NA
23	52	UM	Wild	—	—	NA
24	61	UM	Wild	Wild	—	NA
25	23	—	—	—	—	NA
26	58	—	—	—	—	NA
27	62	—	—	—	—	NA
28	66	—	—	—	—	NA
29	19	—	—	—	—	NA
30	34	UM	Wild	—	Wild	Variation H3.3
31	51	UM	Wild	—	—	Variation H3.3
32	53	UM	—	—	Wild	Variation H3.3
33	19	—	—	—	—	Mutation H3.3

Abbreviations: IDH = isocitrate dehydrogenase; MGMT = O(6)-methylguanine-DNA methyltransferase; UM = unmethylated MGMT; M = methylated MGMT; NA = not available; TERT = telomerase reverse transcriptase.

degeneration, and massive edema, such that it was difficult to differentiate the various kinds of tumors based solely on morphological and signal characteristics on MRI. Recently, Michalopoulos et al.,[26] in a meta-analysis of 39 studies reporting the diagnostic performance and complications of 3,598 medullar biopsies, identified a diagnostic accuracy of 86% for a

complication rate of 1%. Despite the possible postbiopsy neurologic complications described in the literature and the findings in our series, we believe that the risk is worth taking if an intramedullary tumor is suspected because with an appropriate treatment, the prognosis is much better for the differential spinal tumor lesions.

In our series, we did not perform CSF sampling analyses that remain debated due to their poor diagnosis efficiency and accuracy.[27] Concerning pediatric studies, the previous clinical series did not find conclusive evidence on OS to support the aggressive administration of CT.[4,9,28] There exists a paucity of literature regarding the use of CT in the adult population. Our results concerning the absence of OS improvement with CT recall those from Raco et al.[22] and Chamberlain et al.[29] for high-grade astrocytomas or recurrent low-grade astrocytomas. More recently, Hernández-Durán et al.[14] performed a literature review (64 adult patients) and demonstrated no significant therapeutic impact with the adjuvant use of temozolomide and with RT. The survival benefit from the use of RT also remains highly debated.[30-32] In 2005, the introduction of adjuvant RT concomitant with temozolomide to the treatment of GBM, the so-called standard chemoradiotherapy, dramatically improved OS and became the gold standard of care for patients harboring a supratentorial hemispheric GBM.[21] To date, no series studied the impact of the standard chemoradiotherapy protocol in PsGBM.

In our series, the standard chemoradiotherapy with concomitant temozolomide was not an independent predictor of OS, possibly due to the low rate of MGMT promoter methylation observed in this population. Moreover, for the 17/33 (51.5%) patients of our series in whom we sought the MGMT promoter methylation status, no hypermethylated tumor had been identified. This point may reveal a molecular particularity of PsGBMs because in hemispheric localizations, approximately 40% of primary GBM harbor a MGMT promoter hypermethylation.[33,34] Considering other molecular data in our cohort, we found no IDH variation in PsGBM, which is consistent with data from primary brain GBM, in which IDH variation is very rare (<5%).[35] Similarly, although it was investigated in only a small sample of our cohort (12/33 (36.4%) patients), none of the 12 cases investigated presented a TERT variation. These data are very different from primary brain GBM, in which TERT variation is found in 67% of cases.[36] The cervical spinal cord is the most affected region by PsGBM.[24,37] In agreement with our data, Raco et al.[22] and Konar et al.[23] demonstrated that thoracic and lumbar tumors had a decreased risk of mortality.

These findings should be interpreted with caution, given the retrospective design, exploratory design of statistical analyses, absence of a control group, and lack of an external validation set, all limiting the generalizability of the results. The precise topography of the tumor is not always well specified in the FBTDB. It is possible that we have underestimated the number of cases in some centers. However, the rarity of this condition makes the inclusion of a large number of patients difficult, and a prospective study seems unrealistic. Further confirmatory analysis is required. Moreover, we have to highlight that we were not able to inform all the histomolecular markers, that is, MGMT, TERT, and IDH variation, particularly for the cases with biopsies in which biological material was limited. Finally, it is also important to note that we included 4 cases of H3K27M mutated gliomas in our cohort, although they should be nowadays classified as diffuse midline glioma rather than GBM. We decided not to exclude them not only because the primary diagnosis of GBM of these 4 patients was made on morphological features several years before the availability of histone variation characterization but also because we did not find any OS statistical difference for these 4 patients ($p = 0.362$) compared with the rest of the cohort, although this result may be the consequence of the small size of the sample (very large SD, data not shown).

We report the largest study on PsGBM for which a central histopathologic review was conducted. Unlike cerebral GBM, PsGBM has received little attention in the literature, and very limited data exist to support treatment guidelines. Although treatments of PsGBM generally mirror those used for intracranial GBM, optimal therapeutic strategies for PsGBM have not been established, and the rarity of the disease precludes the conduct of clinical trials to test for treatment efficacy. To date, the various literature reviews that have studied PsGBM over different periods spread out, up to 2016: 38, 1970–2014: 14, and 1938–2015: 22, did not demonstrate efficacy on OS neither of different surgical treatments (biopsy, subtotal vs total resection) nor of different types of CT. Thanks to our series and our integrative reported literature (2005–2022), we confirmed that for these infiltrative lesions, the extent of resection causes more surgical morbidity and no survival gain. Whatever the implemented complementary treatment (RT alone or with temozolomide/immunotherapy), there is a benefit on survival compared with palliative care. Unfortunately, very little histomolecular results for IDH variation and for the MGMT promoter methylation status were investigated in our series or in the case reports. Therefore, through our recent review of the literature and our series, it remains impossible to establish a molecular profile of "better survival prognosis." The trend that seems to emerge would be that there is almost no identification of mutated IDH (1/47 cases informed). On the contrary, the MGMT promoter methylation seems to be more commonly found (18/32 informed).

Despite the PsGBM are currently best treated similarly to intracranial GBM with radiation ± temozolomide depending on age/KPS, the poor survival prognosis and the dramatic neurologic decline makes the PsGBM one of the most disabling malignancies. Extensive surgical resection of contrast-enhanced and FLAIR infiltration areas is not possible and does not confer to better survival. Molecular testing is encouraged, if tissue available, to help guide other possible targeted treatment options and/or immunotherapy. Routinely performing molecular testing on these patients in the future

and forming an international registry may help better understand this entity and assist in establishing novel treatment options. The management of such patients would have to be conducted "à la carte" with complementary treatment adapted to DNA sequencing (temozolomide, immunotherapy, and third-generation epidermal growth factor receptor tyrosine kinase inhibitor).

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Appendix Authors

Name	Location	Contribution
Aymeric Amelot, MD, PhD	Department of Neurosurgery, CHRU de Tours, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Louis-Marie Terrier, MD, PhD	Department of Neurosurgery, Clairval Private Hospital, Ramsay Generale de Sante, Marseille, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Bertrand Mathon, MD	Department of Neurosurgery, CHU Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Christophe Joubert, MD	Department of Neurosurgery, HIA St Anne, Toulon, France	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Thiebaud Picart, MD, PhD	Department of Neurosurgery, Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Bron, France	Major role in the acquisition of data
Vincent Jecko, MD	Department of Neurosurgery A, CHU Pellegrin, Bordeaux, France	Major role in the acquisition of data; analysis or interpretation of data
Luc Bauchet, MD, PhD	Department of Neurosurgery, Hôpital Saint Eloi–Gui de Chauliac, Montpellier, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data
Florian Bernard, MD, PhD	Department of Neurosurgery, CHU d'Angers, France	Major role in the acquisition of data
Xavier Castel, MD, PhD	Department of Neurosurgery, CHU de St-Etienne, France	Major role in the acquisition of data
Louis Chenin, MD	Department of Neurosurgery, CHU Amiens-Picardie, France	Major role in the acquisition of data
Ann-Rose Cook, MD	Department of Neurosurgery, CHRU de Tours, France	Major role in the acquisition of data
Evelyne Emery, MD, PhD	Department of Neurosurgery, CHU de Caen, France	Major role in the acquisition of data
Dominique Figarella-Branger, MD, PhD	Department of Neuropathology, La Timone, AP-HM, Marseille, France	Major role in the acquisition of data
Guillaume Gauchotte, MD, PhD	Department of Pathology, CHU Nancy, France	Major role in the acquisition of data
Thomas Graillon, MD, PhD	Aix Marseille Univ, INSERM, APHM, MMG, UMR1251, Marmara Institute, La Timone Hospital, Neurosurgery Departement, Marseille, France	Major role in the acquisition of data
Anne Jouvet, MD, PhD	Department of Pathology, Cancer University Institute of Toulouse Oncopole, CHU Toulouse, France	Major role in the acquisition of data
Michel Kalamarides, MD, PhD	Department of Neurosurgery, CHU Pitié-Salpêtrière, AP-HP, Sorbonne Université, Paris, France	Major role in the acquisition of data
Steven Knafo, MD, PhD	Department of Neurosurgery, le Kremlin-Bicêtre, AP-HP, Kremlin-Bicêtre, France	Major role in the acquisition of data
Arnaud Lazard, MD	Department of Neurosurgery, CHU Grenoble-Alpes, France	Major role in the acquisition of data
Vincent Lubrano, MD, PhD	Department of Neurosurgery, CHU Rangueil, Toulouse, France	Major role in the acquisition of data
Karima Mokhtari, MD, PhD	Department of Neuropathology, Pitié-Salpêtrière, AP-HP, Paris, France	Major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Valérie Rigau, MD, PhD	Department of Neuropathology, CHU Gui de Chauliac, Montpellier, France	Major role in the acquisition of data; analysis or interpretation of data
Vincent Roualdes, MD, PhD	Department of Neurosurgery, CHU Laennec, Nantes, France	Major role in the acquisition of data
Audrey Rousseau, MD, PhD	Department of Pathology, CHU d'Angers, France	Major role in the acquisition of data
Romuald Seizeur, MD, PhD	Department of Neurosurgery, CHU de la Cavale Blanche, Brest, France	Major role in the acquisition of data
Emmanuelle Uro-Coste, MD, PhD	Department of Pathology, Cancer University Institute of Toulouse Oncopole, CHU Toulouse, France	Major role in the acquisition of data
Jimmy Voirin, MD, PhD	Department of Neurosurgery, Pasteur Hospital, HCC, Colmar, France	Major role in the acquisition of data
Philippe Metellus, MD, PhD	Department of Neurosurgery, Clairval Private Hospital, Ramsay Generale de Sante, Marseille, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Johan Pallud, MD, PhD	Department of Neurosurgery, GHU-Paris Psychiatrie et Neurosciences, Hôpital Sainte Anne, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Ilyess Zemmoura, MD, PhD	Department of Neurosurgery, CHRU de Tours, France	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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