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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Management, functional outcomes and survival in a French multicentric series of 118 adult patients with cerebellar glioblastoma

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Abstract

Purpose To analyze the outcomes and predictors in a large series of cerebellar glioblastomas in order to guide patient management.

Methods The French brain tumor database and the Club de Neuro-Oncologie of the Société Française de Neurochirurgie retrospectively identified adult patients with cerebellar glioblastoma diagnosed between 2003 and 2017. Diagnosis was confirmed by a centralized neuropathological review.

Results Data from 118 cerebellar glioblastoma patients were analyzed (mean age 55.9 years, 55.1% males). The clinical presentation associated raised intracranial pressure (50.8%), static cerebellar syndrome (68.6%), kinetic cerebellar syndrome (49.2%) and/or cranial nerve disorders (17.8%). Glioblastomas were hemispheric (55.9%), vermian (14.4%) or both (29.7%). Hydrocephalus was present in 49 patients (41.5%). Histologically, tumors corresponded either to IDH-wild-type or to K27-mutant glioblastomas.

Surgery consisted of total (12.7%), subtotal (35.6%), partial resection (33.9%) or biopsy (17.8%). The postoperative Karnofsky performance status was improved, stable and worsened in 22.4%, 43.9% and 33.7% of patients, respectively. Progression-free and overall survivals reached 5.1 months and 9.1 months, respectively.

Compared to other surgical strategies, total or subtotal resection improved the Karnofsky performance status (33.3% vs 12.5%, $p<0.001$), prolonged progression-free and overall survivals (6.5 vs 4.3 months, $p=0.015$ and 16.7 vs 6.2 months, $p<0.001$, respectively) and had a comparable complication rate (40.4% vs 31.1%, $p=0.29$). After total or subtotal resection, the functional outcomes were correlated with age ($p=0.004$) and cerebellar hemispheric tumor location ($p<0.001$) but not brainstem infiltration ($p=0.16$).

Conclusion In selected patients, maximal resection of cerebellar glioblastoma is associated with improved onco-functional outcomes, compared with less invasive procedures.

Keywords Cerebellar glioblastoma · Neuro-oncology · Neurosurgery · Onco-functional outcome · Survival analysis

Abbreviations

cGB	Cerebellar glioblastoma
CNO-SFNC	Club of Neuro-Oncologie of the Société Française de Neurochirurgie
FBTDB	French brain tumor database
GB	Glioblastoma
KPS	Karnofsky Performance Status
OS	Overall Survival
PFS	Progression-free survival
stGB	Supratentorial glioblastoma

Luc Bauchet, Jacques Guyotat have contributed equally to the manuscript.

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Introduction

Cerebellar glioblastomas (cGBs) are particularly rare, representing only 0.3–1.2% of de novo glioblastomas (GBs) (Stark et al. 2010; Babu et al. 2013; Jeswani et al. 2013; Adams et al. 2013; Takahashi et al. 2014). Large series are lacking, and cGB characteristics have been relatively less described. Previous series included patients diagnosed over a 30-year time-lapse, who were consequently not homogeneously managed (Tsung et al. 2011; Babu et al. 2013; Jeswani et al. 2013; Adams et al. 2013). Recent series extensively described the molecular parameters of cGBs but analyzed neither the surgical results nor the onco-functional outcomes (Nomura et al. 2017; Nakata et al. 2017; Tauziède-Espariat et al. 2018; Hong et al. 2018; Reinhardt et al. 2019). Concerning supratentorial GBs (stGBs), several studies suggest that age, KPS (Karnovsky performance status) and extent of resection represent the main prognosis factors (Carson et al. 2007; Audureau et al. 2018). Subsequently, it is accepted that maximal safe stGB resection improves both functional and oncological prognoses (Lacroix et al. 2001; Sanai et al. 2011; Chaichana et al. 2014; Li et al. 2016; Fabbro-Peray et al. 2019; Molinaro et al. 2020). However, cGBs and stGBs have different clinical characteristics (Picart et al. 2018a) and there are finally no available guidelines specifically dedicated to the management of cGBs (Babu et al. 2013; Yang et al. 2013).

The aim of the present study was, therefore, to analyze clinical, imaging, surgical data, functional outcomes and survival in a large French retrospective series of adult cGB in order to identify parameters of interest to guide patient management.

Methods

Identification of cerebellar glioblastoma patients

The French brain tumor database (FBTDB) identifies and records patients with newly diagnosed and histologically confirmed primary central nervous system in France (hospital-based). Its methodology has been previously published (Rigau et al. 2011; Zouaoui et al. 2012; Darlix et al. 2017; Ng et al. 2019).

For this study, the FBTDB and the Club of Neuro-Oncology of the Société Française de Neurochirurgie (CNO-SFNC) were screened to identify cases with sufficient information, collected from 2003 to 2017 (Fig. 1).

Prior to inclusion, it was verified by one investigator (TP or one local neurosurgeon specialized in neuro-oncology) that all patients met the following inclusion criteria: (1) age ≥ 18 years at diagnosis, (2) cerebellar location with a brainstem invasion ≤ 5 mm and (3) surgical management between November 1st, 2003 and August 1st, 2017. The exclusion criteria were (1) the presence of a supratentorial or medullar tumor larger than the cerebellar tumor and (2) recurrent tumor.

Data collection

In each neurosurgical center, data collection was performed by one neurosurgeon specialized in neuro-oncology (TP or one local neurosurgeon). Demographics, clinical data, imaging features, surgical details, postoperative course, type of adjuvant treatment and follow-up data were locally extracted from medical records using a chart designed for the study. The diagnosis of leptomeningeal seeding was considered to be "documented" if CSF analysis demonstrated the presence of glial cells. When CSF analysis was not available, the diagnosis of leptomeningeal seeding was considered to be "suspected" if there were both clinical arguments for leptomeningeal seeding and a leptomeningeal contrast enhancement.

In patients who underwent a surgical resection, the extent of resection was calculated by volumetric assessment on preoperative and early postoperative MRI scan (performed in the 48 h following surgery) using the formula for volume of an ellipsoid ($V = abc/2$) which is validated for routine use (Sreenivasan et al. 2016). Total resection was defined by a complete resection of contrast-enhanced tissue. In patients with incomplete resection, subtotal and partial resection corresponded to a resection rate $\geq 90\%$ or $< 90\%$ of contrast-enhanced tissue, respectively. In the absence of available postoperative MRI scan, it was considered that macroscopically complete and incomplete resection, defined by the surgeon's intraoperative impression combined with early postoperative CT-scan, corresponded to subtotal and partial resection, respectively. Tumor progression was defined according to the RANO criteria (Wen et al. 2010). Postoperative mortality referred to deaths occurring within 3 months following surgery. Follow-up data were centralized and completed (general practitioner or oncologist call) by one investigator (TP).

Centralized neuropathological review and molecular analysis

All selected cases were submitted to a centralized pathological review which was performed by a senior neuropathologist (DM). It was verified that the histopathological characteristics of grade IV glioblastoma were met according to the 2016 WHO classification of tumors of the central nervous system (Louis et al. 2016) (Fig. 1).

The molecular analysis locally performed at diagnosis was not comprehensive (screenings for IDH1-2 mutations, histone H3, mutation EGFR amplification, and MGMT methylation were performed in 35.6%, 19.5%, 35.6% and

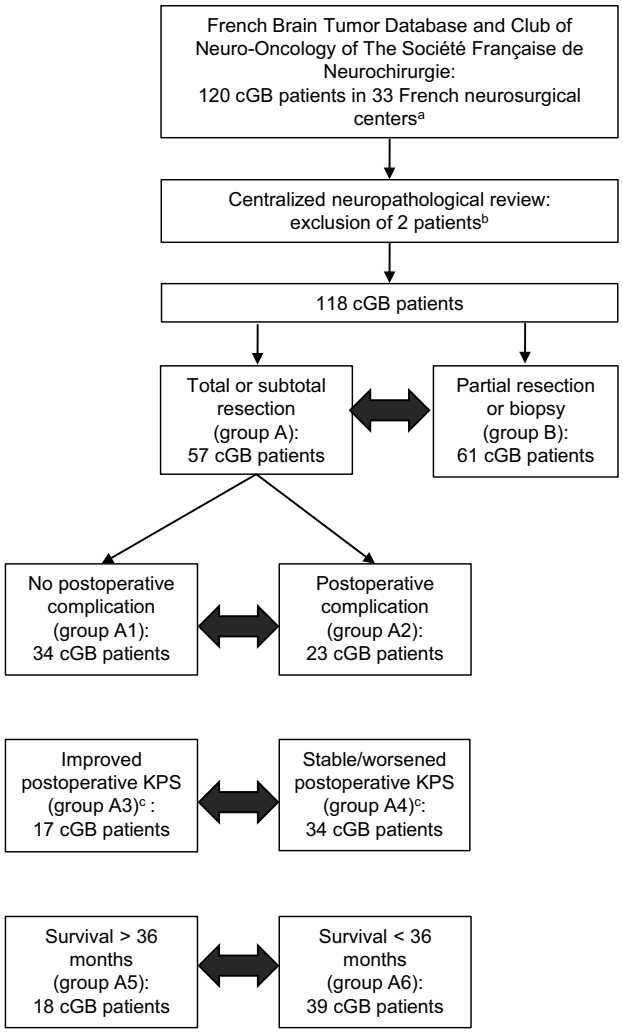

Fig. 1 Study design. Double-sided arrows symbolize the statistical comparisons that were performed. *cGB* cerebellar glioblastoma, *GB* glioblastoma, *KPS* Karnofsky Performance Status. **a** Amiens, Angers, Bayonne, Besançon, Bordeaux, Brest, Caen, Clermont-Ferrand, Colmar, Dijon, Grenoble, Lille, Lyon, Marseille, Nancy, Nantes, Nice, Nîmes, Orléans, Paris-Beaujon, Paris-Foch, Paris-Fondation-Ophtalmologique Rothschild, Paris-Kremlin-Bicêtre, Paris-Lariboisière, Paris-Pitié-Salpêtrière, Paris-Sainte-Anne, Perpignan, Rennes, Rouen, Saint-Etienne, Toulon, Toulouse and Tours. **b** These tumors corresponded to one anaplastic ganglioglioma and one anaplastic pleomorphic xantho-astrocytoma. **c** In groups A3 and A4, only patients with available KPS were considered

26.3%, respectively). IDH1-R132H and histone H3-K27M screenings were completed using immunostaining whenever possible (in 67.1% and 65.3% of cGB without comprehensive molecular analysis, respectively).

Standard protocol approvals and registrations

This study was approved by the French legislation (CCTIRS n°10.548; CNIL n°911,013) and the CNO-SFNC.

Statistical analysis

Categorical comparisons were performed using the Chi-squared test or Fisher's exact test when the Chi-squared test was not applicable. Quantitative variables were compared using the Student *t* test as data were normally distributed.

Overall Survival (OS) and Progression-free Survival (PFS) were measured from the date of the surgery to the date of death from any cause and to the date of progression or of death, respectively. For surviving patients, these intervals were censored at the date of last follow-up. The actuarial data were represented with Kaplan–Meier plots and compared using the log-rank test.

The statistical tests were bilateral and the level of significance was calculated according to post-hoc Bonferroni adjustment (0.05/number of tests performed). Statistical analyses were conducted using R free software version 3.5.1 (R Core Team).

Results

The FBTDB and the CNO-SFNC identified 120 cases with sufficient information, collected from 2003 to 2017 in 33 French Departments of Neurosurgery. Two cases were excluded after the centralized neuropathological review and 118 patients were included (Fig. 1).

Characteristics of adult patients with cerebellar glioblastoma

There were 55.1% of males and the median age at diagnosis was 55.9 ± 16.6 years (Table 1). Clinically, half of the patients presented with raised intracranial pressure ($n = 60$, 50.8%). More than two-thirds of patients had a static cerebellar syndrome ($n = 81$, 68.6%) while about half of the patients had a kinetic cerebellar syndrome ($n = 58$, 49.2%). Cranial nerve disorders were less frequent ($n = 21$, 17.8%). cGBs were hemispheric ($n = 66$, 55.9%), vermian ($n = 17$, 14.4%) or both ($n = 35$, 29.7%). Initial hydrocephalus was diagnosed in 49 patients (41.5%).

According to the 2016 WHO classification of Tumors of the Central Nervous System (Louis et al. 2016), cGBs corresponded either to IDH wild-type GBs or to K27-mutant GBs (Table 1).

Tumor resection and tumor biopsy were performed in 97 (82.2%) and 21 patients (17.8%), respectively. An early postoperative MRI scan was performed in 39 patients after tumor resection (40.2%) and classified as total ($n = 15$), subtotal ($n = 12$) or partial resection ($n = 12$). In the 58 remaining patients, as defined in the "Methods" part, tumor resection, which was macroscopically complete ($n = 30$) or incomplete ($n = 28$) according to the surgeon's peroperative impression

combined with early postoperative CT-scan, was defined as subtotal ($n=30$) and partial ($n=28$), respectively. Thus, total, subtotal and partial resections were achieved in 15 (12.7%), 42 (35.6%), and 40 patients (33.9%), respectively.

Postoperative complications were frequent (35.6%). Their different types are detailed below Table 1. Functionally, the postoperative KPS was improved, stable and worsened in 22.4%, 43.9% and 33.7% of patients, respectively.

Postoperatively, 88/115 patients (76.5%) received an adjuvant treatment that consisted of Stupp radio-chemotherapy ($n=62/88$, 70.4%), chemotherapy alone ($n=11/88$, 12.5%), radiotherapy alone ($n=10/88$, 11.4%) or radiotherapy followed by chemotherapy ($n=5/88$, 5.7%). The remaining patients ($n=27$, 23.5%) were referred to palliative cares or died before the initiation of any oncological treatment.

The 3-month postoperative mortality reached 25.2%, notably because of a high rate of aspiration pneumonia ($n=14$) linked to brainstem or mixed nerves disorders. PFS and OS reached 5.1 months and 9.1 months, respectively. One-year and two-year survival rates reached 42.6% and 20.9%, respectively.

Analysis of the characteristics of cerebellar glioblastoma patients based on the surgical strategy

In order to analyze the onco-functional results associated with the different surgical strategies, the 57 patients (48.3%) with total and subtotal resection were pooled in a group referred to as "optimal tumor resection" (group A) and were compared to the 61 cGB patients (51.7%) who underwent partial resection or tumor biopsy (group B) (Table 2).

The mean age at diagnosis was comparable in group A than in group B (52.9 vs 58.7 years, $p=0.05$). The clinical presentation was not homogeneous as raised intra-cranial pressure was more frequent in group A (66.7% vs 36.1%, $p<0.001$) while cranial nerve disorders were more frequent in group B (7.0% vs 27.9%, $p=0.003$). Satellite supratentorial tumor location (15.8% vs 36.1%, $p=0.02$) and brainstem infiltration (10.5% vs 24.6%, $p=0.04$) were less frequent in group A than in group B but the difference was not significant. Conversely, other radiological parameters did not differ significantly.

Although total rates of postoperative complications did not differ significantly in groups A and B (40.4% vs 31.1%, $p=0.29$), an improvement of the 1-month postoperative KPS was more frequently observed in group A than in group B (33.3% vs 12.5%, $p<0.001$).

Postoperative management and progression modes did not differ significantly. PFS (6.5 months vs 4.3 months, $p=0.015$, Fig. 2a) and OS (16.7 months vs 6.2 months, $p<0.001$, Fig. 2b) were longer in group A than in group B.

Table 1 Initial characteristics and surgical results in patients managed for cerebellar glioblastoma ($n=118$)

	$n=118$	
	N (%)	Mean (SD)
Initial characteristics		
Gender		
Female	53 (44.9%)	
Male	65 (55.1%)	
Mean age (years)	118	55.9 (16.6)
Clinical presentation		
Raised intra-cranial pressure	60 (50.8%)	
Static cerebellar syndrome	81 (68.6%)	
Kinetic cerebellar syndrome	58 (49.2%)	
Cranial nerve disorders	21 (17.8%)	
Tumor location		
Hemisphere	66 (55.9%)	
Vermis	17 (14.4%)	
Vermis and hemisphere	35 (29.7%)	
Initial tumor volume (mL)	75	17.4 (14.5)
Missing	43	
Initial hydrocephalus		
Yes	49 (41.5%)	
No	69 (58.5%)	
Satellite supratentorial tumor at diagnosis		
Yes	31 (26.3%)	
No	87 (73.7%)	
Brainstem infiltration		
Yes	21 (17.8%)	
No	97 (82.2%)	
Leptomeningeal seeding at diagnosis		
Yes, documented	2 (1.7%)	
Suspected	12 (10.2%)	
No	104 (88.1%)	
IDH status		
Wild-type	93 (100%)	
Mutated	0 (0%)	
Missing	25	
Histone H3 status		
Wild-type	72 (84.7%)	
K27M mutation	13 (15.3%)	
Missing	33	
EGFR status		
Amplified	12 (27.3%)	
Not amplified	32 (72.7%)	
Missing	74	
MGMT status		
Methylated	10 (32.3%)	
Unmethylated	21 (67.7%)	
Missing	87	

Table 1 (continued)

	$n=118$	
	N (%)	Mean (SD)
Surgical characteristics and outcomes		
Surgical procedure		
Total resection	15 (12.7%)	
Subtotal resection	42[a] (35.6%)	
Partial resection	40[b] (33.9%)	
Tumor biopsy	21 (17.8%)	
Postoperative complications[c]		
Yes	42 (35.6%)	
No	76 (64.4%)	
1-month postoperative KPS (compared to preoperative KPS)		
Improved	24 (22.4%)	
Stable	47 (43.9%)	
Worsened	36 (33.7%)	
Missing	11	
Postoperative management		
Stupp radio-chemotherapy	62 (53.9%)	
Other treatments[d]	26 (22.6%)	
None	27 (23.5%)	
Missing	3	
Progression	($n=78$)	
Supratentorial	31 (39.7%)	
Leptomeningeal	26 (33.3%)	
Multifocal	22 28.2%)	
< 3-month postoperative survival		
Yes	86 (74.8%)	
No[e]	29 (25.2%)	
Missing	3	
Progression-free survival (months)	118	5.1 95% CI 3.7–7.0
Overall survival (months)	118	9.1 95% CI 6.4–12.7

KPS Karnofsky performance status

[a]In 12 patients, subtotal resection was confirmed by early postoperative MRI scan, showing a resection rate ≥ 90%. In the 30 remaining patients, tumor resection was macroscopically complete, based on the surgeon's impression combined with postoperative CT-scan

[b]In 12 patients, partial resection was confirmed by early postoperative MRI scan, showing a resection rate < 90%. In the 28 remaining patients, tumor resection was macroscopically incomplete, based on the surgeon's impression combined with postoperative CT-scan

[c]Postoperative complications consisted in hydrocephalus ($n=13$), neurological impairment ($n=12$), infection ($=11$), intra-cranial haemorrhage ($n=5$) and gas embolism ($n=4$). Several complications sometimes co-existed in the same patients

[d]Other treatments consisted in chemotherapy ($n=11$), radiotherapy (n = 10), radiotherapy followed by chemotherapy ($n=5$)

[e]Deaths occurring within the 3 postoperative months were attributable to aspiration pneumonia ($n=14$), tumor progression in patients who did not undergo tumor resection ($n=6$), sepsis/meningitis ($n=4$), cerebellar hematoma ($n=2$), status epilepticus ($n=1$), cardiogenic shock ($n=1$) and massive gas embolism ($n=1$)

Predictors of onco-functional outcomes after optimal cerebellar glioblastoma resection

In order to better identify the patients who had the best onco-functional outcomes after optimal tumor resection, additional analyses were conducted in group A (Table 3).

In group A, patients free of postoperative complications (n = 34, group A1) and patients who presented postoperative complications ($n=23$, group A2) were compared. Age ($p=0.46$), tumor location ($p=0.34$), supratentorial location ($p=0.99$), and brainstem infiltration ($p=0.21$) did not differ. Conversely, a preoperative leptomeningeal seeding was more frequently present in group A2 than in group A1 (17.4% vs 0%, $p=0.02$) but the difference was not significant. An impairment of the 1-month postoperative KPS was less frequently observed in group A1 than in group A2 (16.1% vs 50%, $p=0.009$). An adjuvant oncological treatment was more frequently performed in group A1 than in group A2 (88.2% vs 65.2%, $p=0.05$) and the OS was longer in group A1 than in group A2 (20.2 months vs 7.4 months, p = 0.01, Fig. 2c), but the difference was not significant.

In group A, patients with an improved 1-month postoperative KPS ($n=17$, group A3) and patients with a stable or worsened 1-month postoperative KPS (n = 34, group A4) were compared. Group A3 patients were significantly younger than group A4 patients (43.2 years vs 56.7 years, $p=0.004$). Glioblastomas were more frequently located in a cerebellum hemisphere in group A3 (58.8%) while they were more frequently vermian in group A4 (73.6%, $p<0.001$). Other radiological parameters and post-operative management ($p=0.29$) did not differ significantly. The OS was longer in group A3 (37.4 months vs 12.3 months, $p=0.03$, Fig. 2d) but the difference was not significant.

In group A, patients who survived more than 36 months postoperatively ($n=18$, group A5) and patients who survived less than 36 months postoperatively ($n=39$, group A6) were compared. Age ($p=0.08$), radiological parameters, postoperative KPS ($p=0.08$) and postoperative complication rates ($p=0.46$) did not differ significantly. An adjuvant oncological treatment was more frequently performed in group A5 than in group A6 (100% vs 69.2%, $p=0.01$) but the difference was not significant. At progression, a leptomeningeal seeding was more frequently observed in group A6 than in group A5 (44.8% vs 0%, $p=0.003$).

Discussion

This French collaborative study reports the characteristics of one of the largest series of adult cGB patients with an homogeneous management as the inclusion period was 2.5 times shorter compared to previous series (Babu et al. 2013; Jeswani et al. 2013; Adams et al. 2013). Complementarily to

Table 2 Clinical, radiological, molecular features and onco-functional results in cerebellar glioblastoma patients who underwent optimal (total or subtotal) resection (group A, $n=57$) and cerebellar glioblastoma patients who underwent partial resection or tumor biopsy (group B, $n=61$)

	Optimal tumor resection (group A) ($n=57$)		Partial resection/Tumor biopsy (group B) ($n=61$)		p
	N (%)	Mean (SD)	*N* (%)	Mean (SD)	
Preoperative parameters					
Mean age (years)	57	52.9 (16.3)	61	58.7 (16.5)	0.05
Clinical presentation					
Raised intra-cranial pressure	38 (66.7%)		22 (36.1%)		< 0.001*
Static cerebellar syndrome	36 (63.2%)		45 (73.8%)		0.29
Kinetic cerebellar syndrome	28 (49.1%)		30 (49.2%)		0.99
Cranial nerve disorders	4 (7.0%)		17 (27.9%)		0.003*
Tumor location					0.08
Hemisphere	27 (47.4%)		39 (63.9%)		
Vermis	12 (21.0%)		5 (8.2%)		
Vermis and hémisphère	18 (31.6%)		17 (27.9%)		
Satellite supratentorial tumor at diagnosis					0.02
Yes	9 (15.8%)		22 (36.1%)		
No	48 (84.2%)		39 (63.9%)		
Brainstem infiltration					0.04
Yes	6 (10.5%)		15 (24.6%)		
No	51 (89.5%)		46 (75.4%)		
Leptomeningeal seeding at diagnosis					0.19
Yes, documented	0 (0%)		2 (3.3%)		
Suspected	4 (7%)		8 (13.1%)		
No	53 (93%)		51 83.6%)		
Postoperative course					
Postoperative complication[a]					0.29
Yes	23 (40.4%)		19 (31.1%)		
No	34 (59.6%)		42 (68.9%)		
1-month postoperative KPS (compared to preoperative KPS) 1-month postoperative KPS (compared to preoperative KPS)					< 0.001*
Improved	17 (33.3%)		7 (12.5%)		
Stable	19 (37.3%)		28 (50%)		
Worsened	15 (29.4%)		21 (37.5%)		
Missing	6		5		
Postoperative management					

Table 2 (continued)

	Optimal tumor resection (group A) ($n=57$)		Partial resection/Tumor biopsy (group B) ($n=61$)		p
	N (%)	Mean (SD)	N (%)	Mean (SD)	
Stupp radio-chemotherapy or other treatment	45 (78.9%)		43 (74.1%)		0.54
None	12 (21.1%)		15 (25.9%)		
Missing	0		3		
Progression	($n=42$)		($n=36$)		
Supratentorial	18 (42.9%)		13 (36.1%)		0.70
Leptomeningeal	13 (30.9%)		13 (36.1%)		0.62
Multifocal	16 (38.1%)		6 (16.7%)		0.06
Median progression-free survival (months)	$n=57$	6.5 95% CI 4.2–9.6	$n=61$	4.3 95% CI 3.2–5.1	0.015
Median overall survival (months)	$n=57$	16.7 95% CI 7.5–20.8	$n=61$	6.2 95% CI 4.2–9.9	< 0.001*

KPS Karnofsky performance status

*Significant after Bonferroni correction ($p<0.003$)

[a]Postoperative complications consisted in hydrocephalus ($n=7$ in group A and $n=6$ in group B), neurological impairment ($n=6$ in group A and $n=6$ in group B), infection (local, meningeal, ventricular or pulmonary; $n=5$ in group A, $n=6$ in group B), intra-cranial haemorrhage ($n=2$ in group A and $n=3$ in group B) and gas embolism ($n=3$ in group A and $n=1$ in group B). Several complications sometimes co-existed in the same patients

recent studies that are focused on molecular characterisation (Nomura et al. 2017; Nakata et al. 2017; Tauziède-Espariat et al. 2018; Hong et al. 2018; Reinhardt et al. 2019), this study rather analyzed the management and the onco-functional results in cGB patients.

Onco-functional outcomes in cerebellar glioblastoma patients

A stratified analysis based on the extent of resection (optimal resection, group A vs partial resection or tumor biopsy, group B) was conducted to identify the factors that guided the surgical strategy and to assess surgical results. Patients with total and subtotal resection were mixed in the same group as a total resection was not achievable in all patients, particularly when eloquent structures were infiltrated. Moreover, the two groups were homogeneous in size.

From a functional viewpoint, compared to partial resection or biopsy, optimal resection did not result in an increased postoperative complication rate but was more frequently associated with an improvement of the 1-month postoperatively KPS. Consistently, the rate of raised intracranial pressure, well relieved by tumor debulking (Salvati et al. 2003; Patil et al. 2012; Picart et al. 2018b), was higher in group A than in group B. Conversely, cranial nerve disorders were more frequent in group B.

From an oncological viewpoint, patient ability to undergo an adjuvant treatment, progression rate and mode were not influenced by the surgical technique. Consequently, the hypothesis according to which surgical removal promotes leptomeningeal seeding (Chamberlain et al. 1990; Singla et al. 2016) is not validated by the present results. OS was improved by optimal tumor resection, in accordance with previous series of stGB (Lacroix et al. 2001; Sanai et al. 2011; Chaichana et al. 2014; Li et al. 2016; Fabbro-Peray et al. 2019) and cGB (Djalilian and Hall 1998; Weber et al. 2006; Babu et al. 2013; Jeswani et al. 2013). Although targeted therapies could be proposed in selected patients (Cho et al. 2019; Flower and Gallo 2019), maximal safe surgical resection undoubtedly improves the onco-functional outcomes of cGB and has consequently to be systematically discussed. However, it is evidently required to identify cGB patients who are the best candidates for this type of surgery given the high rate of postoperative complications and the heterogeneous outcomes after maximal resection.

Predictors of onco-functional outcomes after optimal resection of a cerebellar glioblastoma

Three stratified analyses were performed within the optimal resection group (group A) in order to identify the factors influencing the onco-functional outcomes.

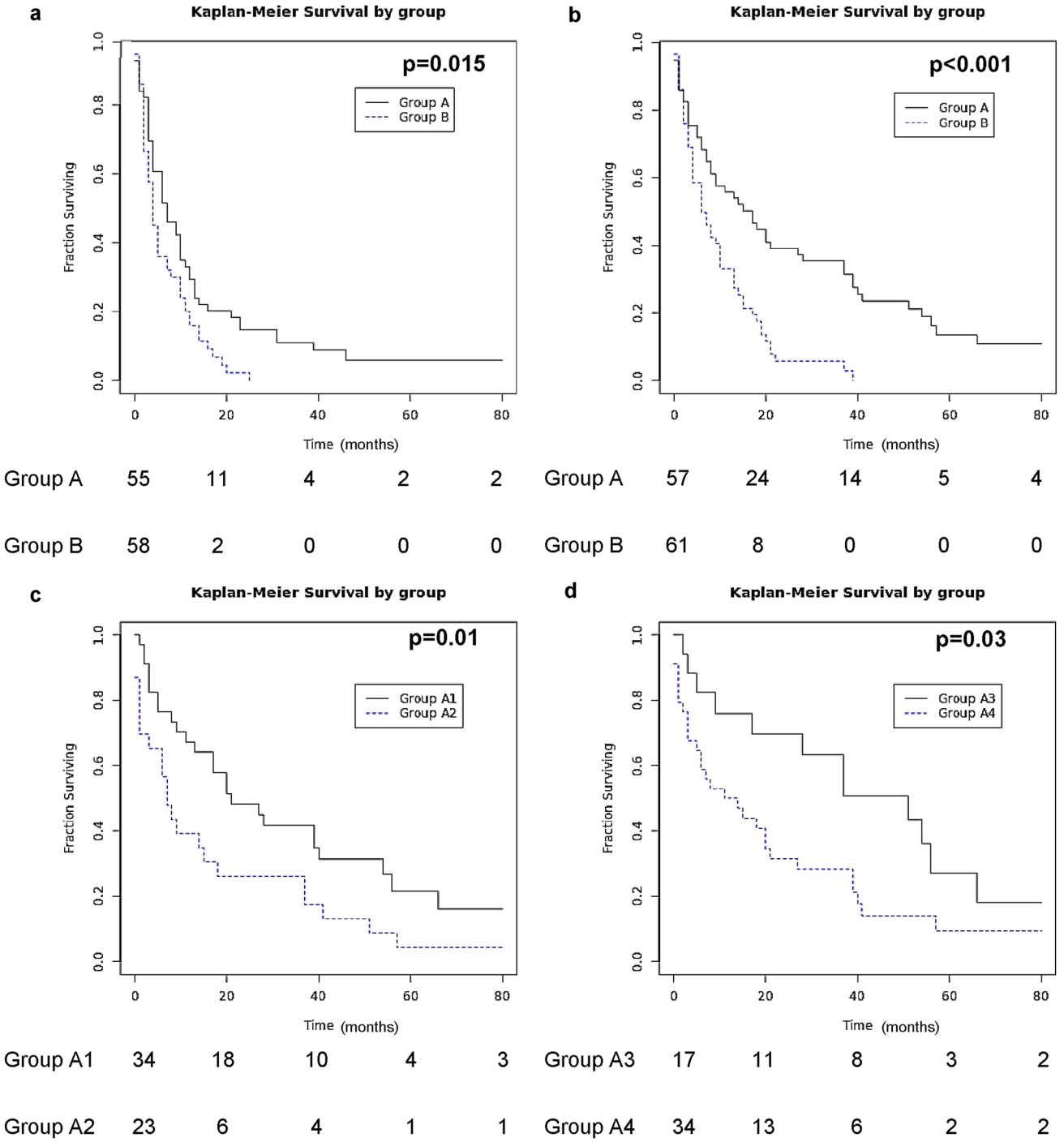

Fig. 2 Kaplan–Meier survival analysis of cerebellar glioblastomas according to the surgical strategy and within group A. **a** Progression-free survival for patients who underwent optimal resection (Group A) and patients who underwent partial resection or tumor biopsy (Group B). Progression-free survival was available for 55 patients in group A and 58 patients in group B. **b** Overall survival for patients who underwent optimal resection (Group A) and patients who underwent partial resection or tumor biopsy (Group B). **c** In group A, overall survival for patients without postoperative complication (Group A1) and patients with postoperative complication (Group A2). **d** In group A, overall survival for patients with improved 1-month postoperative KPS (Group A3) and patients with stable or worsened 1-month postoperative KPS (Group A4). *KPS* Karnofsky Performance Status

Table 3 Subgroup comparisons performed among patients who underwent optimal tumor resection (group A). (1) Comparison of patients without postoperative complication (group A1, $n=34$) with patients with postoperative complication (group A2, $n=23$). (2) Comparison of patients with improved 1-month postoperative KPS (group A3, $n=17$) with patients with stable or worsened 1-month postoperative KPS (group A4, $n=34$). (3) Comparison of patients who survived more than 36 months (group A5, $n=18$) with patients who survived less than 36 months (group A6, $n=39$)

	Patients without postoperative complication		Patients with postoperative complication[a]		$p_{A1 \text{ vs } A2}$	Patients with improved 1-month postoperative KPS		Patients with stable or worsened 1-month postoperative KPS		$p_{A3 \text{ vs } A4}$	Patients who survived more than 36 months		Patients who survived less than 36 months		$p_{A5 \text{ vs } A6}$
	Group A1		Group A2			Group A3		Group A4			Group A5		Group A6		
	N (%)	Mean (SD)	*N* (%)	Mean (SD)		*N* (%)	Mean (SD)	*N* (%)	Mean (SD)		*N* (%)	Mean (SD)	*N* (%)	Mean (SD)	
Initial characteristics															
Mean age (years)	34	52.7 (16.0)	23	53.1 (17.0)	0.46	17	43.2 (13.4)	34	56.7 (16.0)	**0.004***	18	47.4 (16.5)	39	55.4 (15.7)	0.08
Tumor location					0.34					< 0.001*					0.65
Hemisphere	17 (50%)		10 (43.5%)			10 (58.8%)		3 (8.8%)			7 (38.9%)		20 (51.3%)		
Vermis	5 (14.7%)		7 (30.4%)			0 (0%)		25 (73.6%)			4 (22.2%)		8 (20.5%)		
Vermis and hémisphere	12 (35.3%)		6 (26.1%)			7 (41.2%)		6 (17.6%)			7 (38.9%)		11 (28.2%)		
Satellite supratentorial tumor at diagnosis					0.99					0.24					0.04
Yes	5 (14.7%)		4 (17.4%)			1 (5.9%)		7 (20.6%)			0 (0%)		9 (23.1%)		
No	29 (85.3%)		19 (82.6%)					27 (79.4%)			18 (100%)		30 (76.9%)		
Brainstem infiltration					0.21					0.16					0.16
Yes	2 (5.9%)		4 (17.4%)			0 (0%)		6 (17.6%)			0 (0%)		6 (15.4%)		
No	32 (94.1%)		19 (82.6%)			17 (100%)		28 (82.4%)			18 (100%)		33 (84.6%)		
Leptomeningeal seeding at diagnosis					0.02					0.28					0.29
Suspected	0 (0%)		4 (17.4%)			0 (0%)		4 (11.8%)			0 (0%)		4 (10.3%)		
No	34 (100%)		19 (82.6%)			17 (100%)		30 (88.2%)			18 (100%)		35 (89.7%)		
Postoperative management and onco-functional results															
1-month postoperative KPS															
Improved or stable	26 (83.9%)		10 (50%)		0.009						16 (88.9%)		20 (60.6%)		0.08
Worsened	5 (16.1%)		10 (50%)								2 (11.1%)		13 (39.4%)		
Missing	3		3								0		6		
Postoperative complication										0.31					0.46
Yes						5 (29.4%)		15 (44.1%)			6 (33.3%)		17 (43.6%)		

Table 3 (continued)

	Patients without postoperative complication		Patients with postoperative complication[a]		$p_{A1 \text{ vs } A2}$	Patients with improved 1-month postoperative KPS		Patients with stable or worsened 1-month postoperative KPS		$p_{A3 \text{ vs } A4}$	Patients who survived more than 36 months		Patients who survived less than 36 months		$p_{A5 \text{ vs } A6}$
	Group A1		Group A2			Group A3		Group A4			Group A5		Group A6		
	N (%)	Mean (SD)	*N* (%)	Mean (SD)		*N* (%)	Mean (SD)	*N* (%)	Mean (SD)		*N* (%)	Mean (SD)	*N* (%)	Mean (SD)	
No						12 (70.6%)		19 (55.9%)			12 (66.7%)		22 (56.4%)		
Adjucant oncological treatment					0.05					0.29					0.01
Yes	30 (88.2%)		15 (65.2%)			15 (88.2%)		25 (73.5%)			18 (100%)		27 (69.2%)		
No	4 (11.8%)		8 (34.8%)			2 (11.8%)		9 (26.5%)			0 (0%)		12 (30.8%)		
Progression															
Supratentorial											3 (23.1%)		15 (51.7%)		0.10
Leptomeningeal											0 (0%)		13 (44.8%)		**0.003***
Multifocal											4 (30.8%)		12 (41.4%)		0.73
Median overall survival (months)	*n* = 34	20.2 95% CI 11.1–39	*n* = 23	7.4 95% CI 1.3–13.9	0.01	*n* = 17	37.4 95% CI 9.1–56.4	*n* = 34	12.3 95% CI 5.3–20.4	0.03					

KPS = Karnofsky performance status

*Significant after Bonferroni correction ($p < 0.006$ for $p_{A1 \text{ vs } A2}$ and $p_{A3 \text{ vs } A4}$; $p < 0.004$ for $p_{A5 \text{ vs } A6}$)

[a]Postoperative complications are detailed in Table 2 legend

First, from a functional viewpoint, a leptomeningeal seeding was more frequent in patients with postoperative complications than in other patients although the difference was not significant. Consistently, leptomeningeal seeding has previously been identified as a poor prognosis factor in cGB patients (Tsung et al. 2011) and may account for a deteriorated preoperative KPS. Not surprisingly, patients whose 1-month postoperative KPS was not improved had more frequently a vermian GB than other patients, which is consistent with cerebellum functional anatomy (Konczak et al. 2005; Ilg et al. 2008; Schoch et al. 2010), and were also older.

Second, from an oncological viewpoint, long-survivors after cGB optimal resection tended to have less frequently a multicentric GB and to receive more frequently an adjuvant treatment than other patients, similarly to stGB long-survivors (Lacroix et al. 2001; Salvati et al. 2003; Weber et al. 2006; Patil et al. 2012; Picart et al. 2018b; Fabbro-Peray et al. 2019). Conversely, patients with postoperative complications and patients with stable or decreased 1-month postoperative KPS tended to have shorter OS than other patients.

Although brainstem infiltration is associated with shorter OS in cGB patients (Weber et al. 2006; Yang et al. 2013), the rate of brainstem infiltration did not differ in patients with postoperative complications compared to patients without. Consequently, brainstem infiltration *per se* should not represent an obstacle to tumor resection but implies that the surgical procedure does not aim at reaching total removal at all costs, analogically with the principles guiding medulloblastoma (Wong et al. 2015; Srinivasan et al. 2016) and 4th ventricle ependymoma resection (Wu et al. 2016). The use of an intra-operative monitoring of facial and mixed nerves should be highly recommended in such patients.

Finally, a thorough preoperative patient selection for maximal resection is critical to optimize the postoperative onco-functional results. In other words, the surgical management has to be individually tailored, depending on the onco-functional balance, as should always be the case in neurooncology (Duffau 2009; Fabbro-Peray et al. 2019; Picart et al. 2019).

Cerebellar glioblastoma specificities

It has been evidenced that patients with cGBs are three times less likely to receive standard therapy than stGB patients (Dressler et al. 2019). As an indication, we, therefore, compared the characteristics of the present series of cGBs with those of a series of stGBs to determine if tumor location also influences the surgical outcomes. A monocentric series of 103 consecutive adult IDH wild-type stGB, histologically confirmed, which has already been used as a comparative group in previous studies (Picart et al. 2018a), was chosen (Online Resource).

Consistent with previous studies (Weber et al. 2006; Babu et al. 2013; Adams et al. 2013; Picart et al. 2018a), cGB patients seem to be younger than stGB patients. The surgical management was not homogeneous as a tumor resection was more frequently performed in cGB than in stGB patients (82.2% vs 48.5%, $p < 0.001$). These proportions are close to literature data as a surgical resection was performed in 82.2% of cases in a previous American series of cGB patients (Babu et al. 2013) while a tumor biopsy was performed in 41.2% of cases in a recent French series of stGB patients (Fabbro-Peray et al. 2019). This aggressive management of cGB patients is warranted not only by a younger age but also by an increased frequency of raised intracranial pressure in this group (Picart et al. 2018a). Moreover, the diagnosis of cerebellar metastasis, rather than of cGB, may have frequently been suspected preoperatively, particularly when there was a satellite supratentorial lesion (Akimoto et al. 2009; Gopalakrishnan et al. 2012; Lakičević et al. 2014; Picart et al. 2018a). Metastases resection is well validated, especially in case of raised intracranial pressure, which may finally have contributed to increase the rate of patients with cGB resection.

The rate of patients with an improved 1-month postoperative KPS was comparable in cGB and stGB patients. Nonetheless, the surgical management of cGBs is undoubtedly more challenging than this of stGBs as postoperative complication and mortality rates were higher in cGB patients, regardless of the surgical technique. Thus, all deaths occurring within the 3 postoperative-months were considered as "postoperative" because there was a high rate of delayed complications leading to death, mainly aspiration pneumonia resulting from brainstem or cranial nerve disorders.

The increased rate of postoperative complications in cGB patients compared to stGB patients is explained by surgical specificities. First, postoperative hydrocephalus was frequent and explained by cerebellar swelling. Second, conversely to metastasis, cGBs borders are badly defined and a too extensive resection in the vicinity of the brainstem resulted in swallowing disorders, sometimes responsible for aspiration pneumonia or respiratory failure. Third, other complications, particularly gas embolism, were imputable to the sitting position that is currently avoided as frequently as possible (Porter et al. 1999).

Finally, the proportion of leptomeningeal dissemination was particularly high in patients with documented tumor progression (26/78 = 33.3%). Consistently, in previous series the incidence of leptomeningeal dissemination in cGB varied between 19% and 29.4% (Tsung et al. 2011; Picart et al. 2018a) and was consequently higher than this observed in stGB (< 5%) (Mandel et al. 2014). The over-representation of leptomeningeal seeding in cGB compared to stGB could be attributable to anatomical factors, as cGB may be more frequently close to leptomeninges or ventricular cavities,

and more probably to molecular factors that remained to be determined.

Limitations

The main limitations of this study are attributable to its retrospective design which was unavoidable given the rarity of the disease. Notably, molecular data are not comprehensive. This study was rather designed to provide guidelines for preoperative management of cGB and molecular data are currently not taken into account in the surgical decision. However, the optimal management of cGB may depend on the molecular subgroup in the future. Moreover, an early postoperative MRI scan was available in only 40.2% of patients who underwent tumor resection. Evidently, the surgeon assessment of the extent of resection is not always reliable (Albert et al. 1994) and it was considered that macroscopically complete and incomplete resection corresponded to subtotal and partial resection, respectively. Moreover, in the statistical analysis, patients with total and subtotal resection were pooled in the same group. These strategies may, therefore, compensate for the low rate of early postoperative MRI scan.

Conclusions

This large series of cGBs highlights that the surgical management of these tumours is more challenging and riskier than this of stGBs. It is particularly important to carefully assess patients preoperatively because, in thoroughly selected patients, cGB maximal resection is associated with improved onco-functional outcomes, compared with less invasive surgical procedures. Optimal onco-functional results after cGB maximal resection are obtained in patients that are young, with tumors located in a cerebellar hemisphere and free of leptomeningeal seeding or satellite supratentorial tumor. Conversely, brainstem infiltration is not systematically associated with poor functional outcomes and should not prevent performing an extensive tumor resection provided that an appropriate neurophysiologic monitoring is used per-operatively.

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Author contributions TP, LB and JG designed and conceptualized the study. TP, DM, JP, CD, SZ and all members from the French Brain Tumor DataBase and the Club de Neuro-Oncologie of the Société Française de Neurochirurgie had a major role in the acquisition of data. TP and DM analyzed and interpreted the data. TP, LB and JG drafted the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version.

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Compliance with ethical standards

Conflicts of interest/Competing interests Drs. Thiébaud Picart, David Meyronet, Johan Pallud, Chloé Dumot, Philippe Metellus, Sonia Zouaoui, Moncef Berhouma, François Ducray, Luc Bauchet, Jacques Guyotat, all members of the French Brain Tumor DataBase and Club de Neuro-Oncologie of the Société Française de Neurochirurgie declare that they have no conflict of interest.

Ethics approval This study was approved by the French legislation (CCTIRS n°10.548; CNIL n°911013). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate (include appropriate statements) All living patients provided written informed consent either for study inclusion.

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