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LABORATORY INVESTIGATION

What effects does awake craniotomy have on functional and survival outcomes for glioblastoma patients?

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Abstract

Purpose Neurosurgeons adopt several different surgical approaches to deal with glioblastomas (GB) located in or near eloquent areas. Some attempt maximal safe resection by awake craniotomy (AC), but doubts persist concerning the real benefits of this type of surgery in this situation. We performed a retrospective study to evaluate the extent of resection (EOR), functional and survival outcomes after AC of patients with GB in critical locations.

Methods Forty-six patients with primary GB treated with the Stupp regimen between 2004 and 2019, for whom brain mapping was feasible, were included. We assessed EOR, postoperative language and/or motor deficits three months after AC, progression-free survival (PFS) and overall survival (OS).

Results Complete resection was achieved in 61% of the 46 GB patients. The median PFS was 6.8 months (CI 6.1; 9.7) and the median OS was 17.6 months (CI 14.8; 34.1). Three months after AC, more than half the patients asymptomatic before surgery remained asymptomatic, and one third of patients with symptoms before surgery experienced improvements in language, but not motor functions. The risk of postoperative deficits was higher in patients with preoperative deficits or incomplete resection. Furthermore, the presence of postoperative deficits was an independent predictive factor for shorter PFS.

Conclusion AC is an option for the resection of GB in critical locations. The observed survival outcomes are typical for GB patients in the Stupp era. However, the success of AC in terms of the recovery or preservation of language and/or motor functions cannot be guaranteed, given the aggressiveness of the tumor.

Keywords Awake craniotomy · Glioblastoma · Functional outcomes · Survival

Abbreviations

AC	Awake craniotomy
EOR	Extent of resection
GA	General anesthesia
GB	Glioblastoma
GTR	Gross total resection
HGG	High-grade glioma
HRQoL	Health-related quality of life
IDH	Isocitrate dehydrogenase
KPS	Karnofsky performance status
LGG	Low-grade glioma
LH	Left hemisphere
OS	Overall survival
RH	Right hemisphere
PFS	Progression-free survival
PR	Partial resection
STR	Subtotal resection

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Introduction

Faced with a glioblastoma (GB) located in or near eloquent areas, neurosurgeons adopt several different surgical approaches [1, 2]. Some limit their intervention to a biopsy, whereas others perform resections limited to the tumor under general anesthesia (GA), or carry out awake craniotomy (AC) with brain mapping, in an attempt to achieve maximal safe resection. AC is now considered the gold standard for slow-growing lesions, such as low-grade gliomas (LGG), inducing functional reshaping due to plasticity [3], but doubts remain about the real benefits of AC for high-grade gliomas (HGG), and for GB in particular. Indeed, GB occur in very different conditions to LGG: the patients are generally older, tumor progression is faster, treatment is more aggressive and survival is shorter.

Several recent retrospective studies and meta-analyses have addressed this question [4–7]. For example, in a retrospective study performed between 2005 and 2015, Gerritsen et al. [4] observed that GB resection by AC was associated with a significantly greater extent of resection (EOR) than resection under GA, with no improvement in overall survival (OS). GB resection by AC was also associated with fewer minor complications three months after surgery. Nakajima et al. [6] found that long-term Karnofsky performance status (KPS) scores were significantly higher in the AC group than in the GA group, but that these scores were dependent on age and preoperative KPS score.

We conducted a retrospective study on GB patients who had undergone tumor resection by AC at our institution to complete these studies. We analyzed the efficacy of AC, in terms of the preservation of language and/or motor functions commonly mapped intraoperatively, during the three-month follow-up period. The EOR and survival outcomes were also investigated. Only patients with primary GB treated by chemoradiotherapy according to the Stupp protocol for whom brain mapping was feasible during tumor resection were included in this analysis, to prevent bias.

Methods

AC technique and study population

AC was performed on 81 adult patients with GB between 2004 and 2019. For retrospective studies of this kind, French legislation requires only prior authorization from the French National Data Protection Authority (CNIL) (registration no. ar19-0053v0). AC was performed as previously described [8–10] (Supplementary data). We analyzed the EOR, functional and survival outcomes after AC in a selected cohort of patients satisfying the following criteria: (1) newly diagnosed unilateral supratentorial GB, (2) language and/or motor brain mapping performed, (3) tumor resection, (4) no intraoperative chemotherapy treatment, (5) three months of follow-up data available and, (6) first-line adjuvant treatment according to the Stupp protocol. Forty-six GB patients met these criteria.

Functional outcomes

Deficits of motor and language functions were retrospectively noted and classified from the clinical neuropsychology, neurosurgical and neuro-oncology records of the patients. They were recorded before surgery, in the immediate postoperative period (48–72 h) and, at the one-month and three-month follow-up visits. Language deficits were stratified into four grades (extrapolated from the adult NIHSS scale [11]: 0, no aphasia/normal; 1, mild to moderate aphasia (comprehension clinically adequate but spontaneous speech non-fluent, with marked word-finding difficulties, semantic, or phonemic paraphasia); 2, severe aphasia (understanding difficult because the patient has reduced language and/or difficulties with comprehension); and 3, mute, global aphasia. Motor deficits were classified according to the modified McCormick scale, as follows [12]: 0, no deficit; 1, mild deficit (patients able to use their limbs almost normally, e.g., walking is possible, but the patient has an impairment of fine movements of the upper limbs); 2, moderate deficit (movement possible with external aid); and 3, severe deficit (limited function, dependent). Deficits were considered new if they appeared in patients without preoperative deficits.

EOR and survival analysis

EOR was recorded by the surgeon performing the operation and/or was determined from the findings of a postoperative MRI performed within 48 h of surgery by a neuroradiologist. EOR was classified as gross total (GTR; 100%), subtotal (STR; $\geq 90\%$), or partial (PR; $< 90\%$). OS was defined as the time from initial surgery until death. Progression-free survival (PFS) was defined as time to radiological progression according to the RANO criteria [13].

Statistical analyses

Values of $P < 0.05$ were considered significant. A multivariate logistic regression analysis was performed with R v3.6.2, to identify significant independent predictors of postoperative deficits three months after AC. We also used a multivariate Cox proportional hazards regression model to analyze PFS and OS in GB patients.

Results

Characteristics of GB patients undergoing tumor resection by AC

The baseline characteristics of the 46 selected GB patients are shown in Table 1. Mean age at diagnosis was 57.4 ± 12.5 years. All patients had a KPS score ≥ 70 before surgery. Forty-one patients (89%) had left hemisphere (LH) GB, and five patients (11%) had right hemisphere (RH) GB. Language mapping was performed for 45 patients (98%) and motor mapping for 10 patients (22%). Cortical and/or subcortical mapping identified eloquent areas in 33 patients (72%). Focal and transitory intraoperative seizures occurred in seven patients (15%), disappearing rapidly after cortical irrigation with iced saline. Two patients (4%) presented early postoperative complications, including hematoma and ear bleeding. Complete resection was achieved in 28 patients (61%). The duration of surgery was 2.43 ± 0.04 h and the length of hospital stay was 6.04 ± 3.26 days.

Functional outcomes after AC

Before surgery, 25 patients (54%) had no language or motor deficits, and 21 (46%) had preexisting grade 1 language and/or motor disorders (Table 1). Three months after surgery, functional status was unchanged in 24 patients (52%), had deteriorated in 15 patients (33%), and had improved in seven patients (15%) (Table 1). The details of functional outcomes for patients with and without symptoms before surgery are presented below.

Fourteen of the 25 patients (56%) asymptomatic before surgery remained asymptomatic three months after AC (Fig. 1). Functional status had deteriorated by this time point in 11 patients (44%), with the acquisition of language deficits in 10 patients and of motor deficits in one patient (Fig. 1). These newly acquired deficits were all of grade 1, with an onset detected intraoperatively for two patients, in the immediate postoperative period for six patients, at one month after surgery for one patient, and at three months after surgery for two patients.

Ten of the 21 patients with preoperative deficits (48%) retained their preoperative language and/or motor status of grade 1, four patients (19%) presented a worsening of their preoperative deficits, and seven patients (33%) displayed an improvement of their preoperative deficits, passing from grade 1 to grade 0 (Fig. 1). Improvements were observed for language, but not motor functions. Improvement was detected in the immediate postoperative period for four patients, one month after surgery for one patient,

Table 1 Characteristics, functional and survival outcomes of the 46 GB patients with primary GB treated with the Stupp regimen for whom language and/or motor function mapping was feasible during tumor resection

Patients	Number	%
Patient characteristics		
Age (mean age: 57.4 ± 12.5 years)		
< 70 years	39	85
≥ 70 years	7	15
Sex		
Male	32	70
Female	14	30
Awake surgery characteristics		
Functional brain mapping		
Language	45	98
Motor	10	22
Identification of eloquent areas	33	72
Extent of surgery		
GTR	28	61
STR	15	33
PR	3	7
Tumor characteristics		
Location		
Hemisphere		
Left	41	89
Right	5	11
Unilobar	35	74
Frontal	16	33
Temporal	11	24
Parietal	7	15
Occipital	1	2
Multilobar	11	24
2016 CNS classification		
GB IDH-wildtype	32	70
GB IDH-mutant	4	9
GB NOS	10	22
Preoperative deficits		
Without deficits	25	54
With deficits	21	46
Language	18	39
Motor	2	4
Language and motor	1	2
Three-month functional status		
Unchanged status	24	52
Worse status	15	33
Improved status	7	15
Survival outcomes		
Median PFS: 6.8 months (95% CI [6.1; 9.7])		
Median OS: 17.6 months (95% CI [14.8; 34.1])		

GTR gross total resection (100%), *STR* subtotal resection (≥ 90%), *PR* partial resection (< 90%), *IDH* isocitrate dehydrogenase, *NOS* not otherwise specified, *PFS* progression-free survival, *OS* overall survival

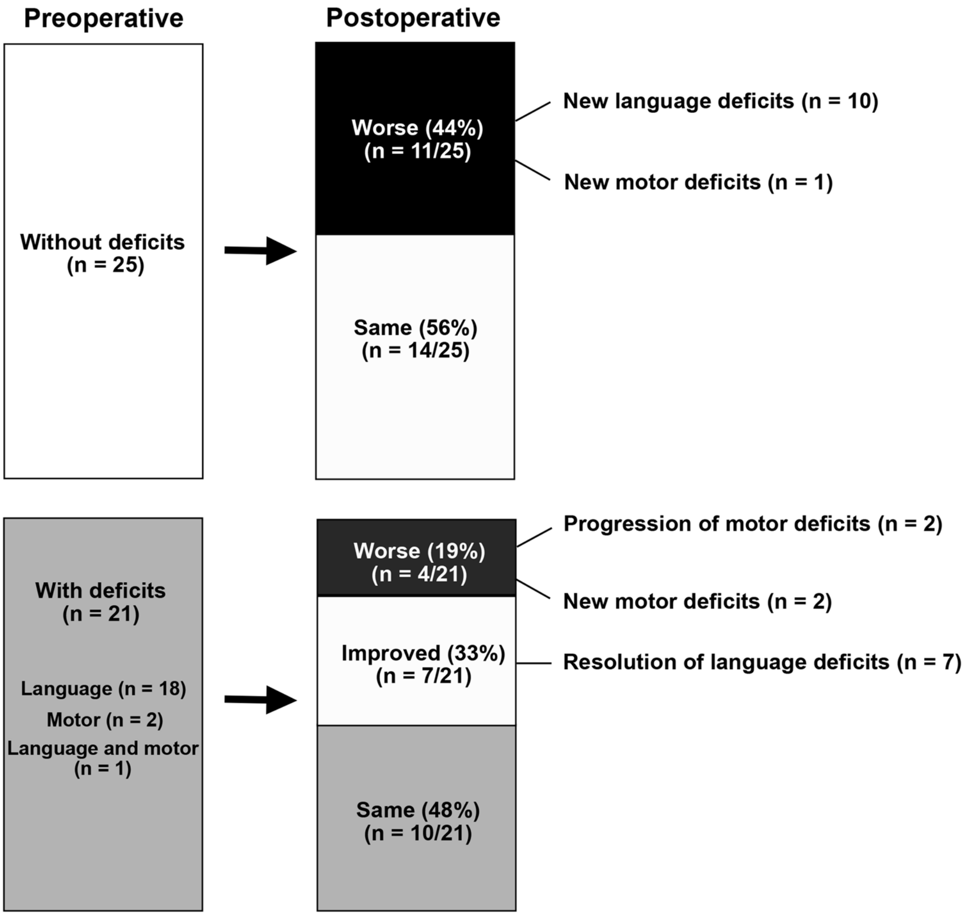


Fig. 1 Functional outcomes in AC patients at three months of follow-up. Before surgery, 25 patients (54%) had no language or motor deficits, and 21 (46%) had preexisting language and/or motor disorders. Three months after AC, more than half the patients without symptoms before surgery still had no deficits, and one third of patients with symptoms before surgery experienced an improvement in language, but not motor functions

and three months after surgery for two patients. In the four patients with a deterioration of functional status, motor functions worsened, passing from grade 1 to grade 2 in two cases, with the other two cases presenting an onset of new grade 1 motor deficits in addition to language deficits. In one patient, the aggravation occurred in the immediate postoperative period, following complications, including brain parenchyma hematoma requiring evacuation. In the other three patients, the deterioration in functional status was detected three months after surgery and was related to tumor progression.

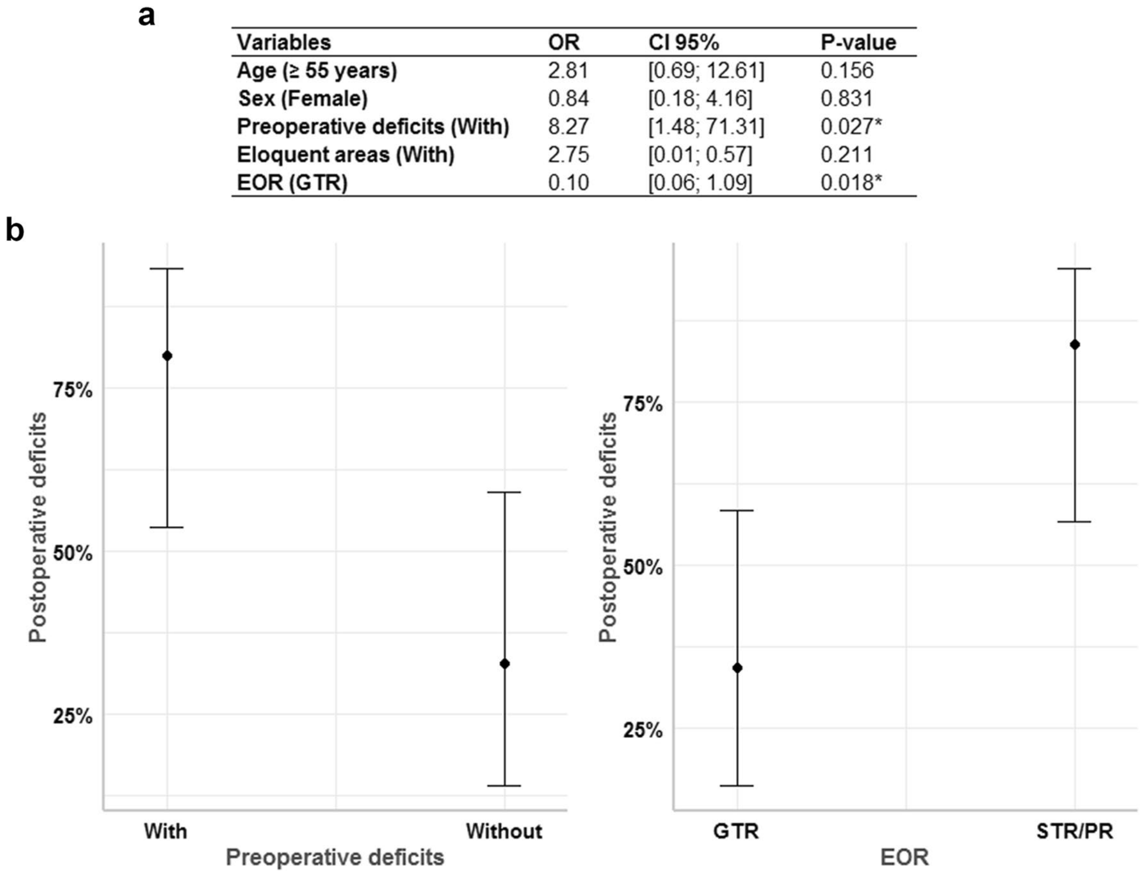
Factors predicting functional and survival outcomes

A multivariate logistic regression analysis was performed to identify factors predictive of deficits three months after AC (Fig. 2). Two independent risk factors were identified: the presence of preoperative deficits and incomplete resection (Fig. 2). Age, sex, and the identification of eloquent areas had no significant impact on the incidence of postoperative language and/or motor deficits (Fig. 2).

The 46 GB patients (considered together, whether or not they had deficits three months after AC) had a median PFS of 6.8 months (95% CI [6.1; 9.7]) and a median OS of 17.6 months (95% CI [14.8; 34.1]) (Table 1). Multivariate analysis of PFS with Cox's regression model showed that the presence of postoperative deficits (language and/or motor) three months after AC was significantly associated with a shorter PFS (Fig. 3a). Age, sex, the presence of preoperative deficits (language and/or motor), and EOR had no significant impact on PFS. Median PFS was 6.0 months (95% CI [4.4; 7.3]) for patients with postoperative deficits, and 9.8 months (95% CI [8.1; 22.2]) for patients without deficits ($P = 0.007$) (Fig. 3b). Multivariate analysis of OS showed that age, sex, the presence of pre- or postoperative deficits (language and/or motor), and EOR had no significant impact on OS (Fig. 3a). Median OS was 17.3 months (95% CI [10.7; 34.1]) for patients with postoperative deficits, and, 17.6 months (95% CI [16.6; $+\infty$]) for patient without deficits ($P = 0.135$) (Fig. 3c).

Discussion

There is currently no consensus as to whether GB in or near eloquent areas should be resected, or whether surgical intervention should be limited to biopsy [1, 14]. Resection is recommended over biopsy for patients in good clinical



a

Variables	OR	CI 95%	P-value
Age (≥ 55 years)	2.81	[0.69; 12.61]	0.156
Sex (Female)	0.84	[0.18; 4.16]	0.831
Preoperative deficits (With)	8.27	[1.48; 71.31]	0.027*
Eloquent areas (With)	2.75	[0.01; 0.57]	0.211
EOR (GTR)	0.10	[0.06; 1.09]	0.018*

Fig. 2 Factors predictive of postoperative language and/or motor deficits three months after AC. **a** Multivariate logistic regression analysis to identify factors predictive of postoperative deficits three months after AC. **b** The presence of preoperative deficits and incomplete resection (STR/PR) were identified as factors significantly associated with postoperative deficits. *CI* confidence interval, *EOR* extent of resection, *GTR* gross total resection, *STR* subtotal resection, *PR* partial resection, *OR* odds ratio

condition, but care should be taken to ensure that surgery does not have a negative impact on the neurological status of the patient [14–18]. Coluccia et al. [15] showed that patients with LH GB undergoing surgery under GA, with 5-ALA fluorescence-guided resection, had a significantly shorter PFS (7.4 months vs. 10.1 months) and a faster decline in functional abilities than patients with RH GB undergoing similar procedures. They explained this result by the preference of neurosurgeons for more conservative surgical resections, given the greater extent of language-processing cortex areas and white matter tracts in the LH than in the RH. Consistently, complete resection was achieved less often in LH GB patients than in RH GB patients (38% vs. 65%). These data have raised questions as to the extent to which the use of AC and brain mapping would affect the EOR, functional and survival outcomes of patients with GB in critical locations.

At our institution, AC is considered to be indicated for all GB located in or near critical eloquent areas, as a means of achieving an oncologically acceptable resection. Between 2004 and 2019, 81 GB patients underwent surgery by AC. This retrospective series of patients was not homogeneous (recurrent GB, secondary GB, failed mapping, open biopsies, different adjuvant therapies after surgery). We therefore decided to include only patients with primary GB treated with the Stupp regimen as a first-line treatment, for whom the mapping of language and/or motor functions was feasible during tumor resection, in the analysis of EOR, functional and survival outcomes.

Consistent with previous reports [4–6, 19–21], our findings for this selected cohort of 46 GB patients indicated that AC caused no major intraoperative or early postoperative complications. Intraoperative seizures were observed in 15% of patients, but this is not uncommon for surgery of this type [8, 22]. Complete resection was achieved in 61% of patients, including 59% of the LH GB patients, a rate higher than that reported by Coluccia et al. [15] for LH GB patients undergoing resection under GA (38%). Several studies have already reported that maximal lesion removal is achieved more frequently by AC than by surgery under GA [4, 20, 21, 23, 24]. The identification of critical and non-critical areas by awake mapping increases safety, allowing the neurosurgeon to optimize resections

a

	PFS			OS		
Variables	**OR**	**CI 95%**	**P-value**	**OR**	**CI 95%**	**P-value**
Age (≥ 55 years)	1.17	[0.57; 2.41]	0.661	2.10	[0.94; 4.70]	0.071
Sex (Female)	1.70	[0.83; 3.49]	0.146	0.97	[0.43; 2.19]	0.935
Preoperative deficits (With)	0.97	[0.45; 2.07]	0.930	0.79	[0.35; 1.79]	0.578
EOR (GTR)	1.02	[0.47; 2.20]	0.957	1.81	[0.75; 4.36]	0.186
Postoperative deficits (With)	2.35	[1.16; 4.77]	0.018*	1.86	[0.86; 4.05]	0.117

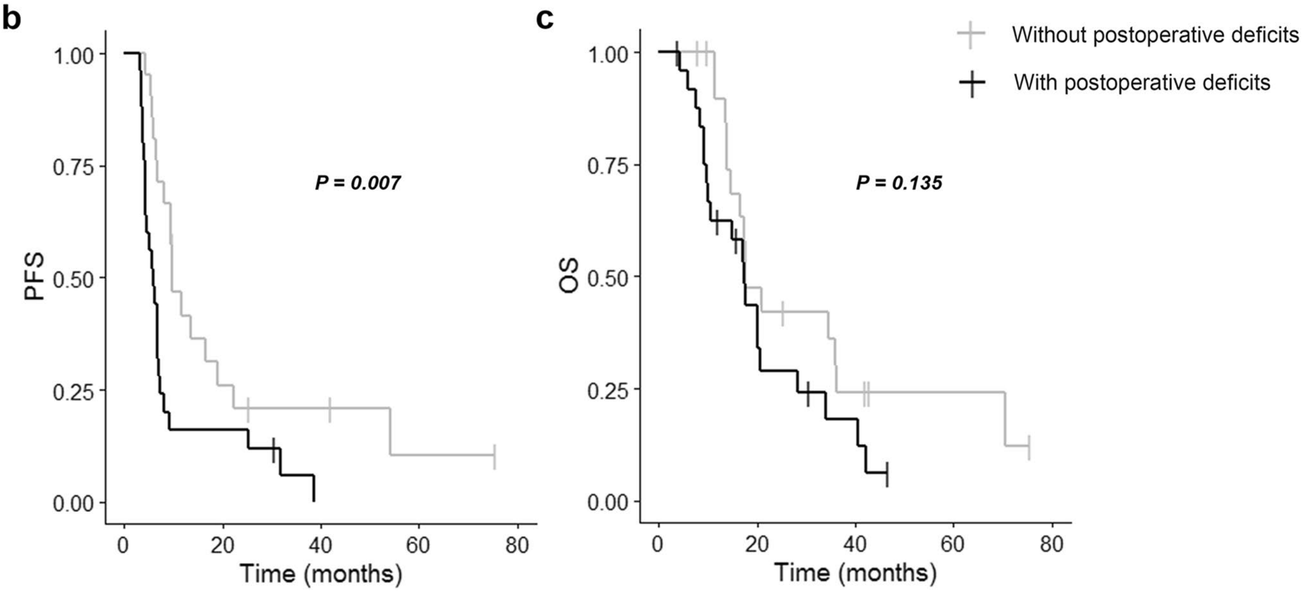


Fig. 3 Factors predictive of PFS and OS in GB patients undergoing tumor resection by AC. **a** Multivariate analyses of the factors predictive of PFS and OS, based on the Cox regression model. **b** Kaplan–Meier curve of PFS for GB patients with and without postoperative deficits three months after AC. **c** Kaplan–Meier curve of OS for GB patients with and without postoperative deficits three months after AC. *CI* confidence interval, *EOR* extent of resection, *GTR* gross total resection, *OR* odds ratio

that would necessarily have been more conservative under GA to prevent the generation of permanent postoperative deficits. We observed that three months after AC, more than half the patients without symptoms before surgery still had no deficits, and that one third of patients with symptoms before surgery experienced an improvement in language, but not motor functions. However, 25 patients (54%) displayed mild to moderate language and/or motor deficits three months after AC, with the development of new deficits or the persistence and/or progression of preoperative deficits. According to previous studies on AC [25–27], the risk of postoperative deficits is higher in patients with preoperative deficits or incomplete resection. The induction of new postoperative deficits is not uncommon after AC [21, 24, 25, 27–30]. These deficits may be due to false-negative results during brain mapping [31]. The main causes of these false negatives include subthreshold stimulation, stimulation during the refractory period following an afterdischarge and stimulation before the anesthetic agents have worn off. Stimulation-task synchronization and the selection of an inappropriate testing task can also lead to false-negative results [31]. However, most studies report deficits at three months of follow-up in only 4% to 33% of cases, despite this risk of inducing new postoperative deficits [25, 26, 30, 32, 33]. The higher rate of postoperative deficits observed here may, at least partly, reflect the inclusion in our series of GB cases only, whereas other studies also included LGG or WHO grade 3 HGG. The rate of progression is known to differ considerably between these tumors. Pre- and postoperative plasticity may account for the almost complete recovery of deficits three months after AC in patients with LGG [34]. Brain reorganization may occur in patients with HGG, including GB [35, 36]. However, the faster growth rate of GB is likely to limit the development of compensatory processes, resulting in a lack of language recovery and/or motor deficit correction after surgery. Consistently, GB patients with postoperative deficits had a median PFS of six months, versus 10 months for patients without postoperative deficits. Furthermore, it should be recognized that in the past, GB patients were not given sufficient support in terms of speech therapy to overcome language disorders, with more attention being paid to physiotherapy for motor disorders. Such rehabilitation is now routinely proposed for GB patients with early postoperative language deficits.

Several studies have indicated that postoperative neurological deficits after surgery are predictive of poor survival in GB patients [16, 17]. However, we found no significant difference in OS between patients with postoperative language and/or motor deficits three months after AC and those without deficits. A median OS of about 17 months was observed in GB patients undergoing surgery by AC, a value typical for GB patients in the Stupp era [4, 15, 37, 38]. Nevertheless, 42% of patients without postoperative deficits were still alive two years after surgery, whereas a two-year survival of 29% was observed for patients with postoperative deficits.

Limitations

The major limitations of this study are its retrospective design and the absence of a control group with GB in similar locations undergoing surgical resection under GA, to analyze the real benefits of AC. However, the aim of our study was to assess the effects of AC on the functional and survival outcomes of GB patients, and this aim can be achieved by comparing our data with published findings. Another limitation is the lack of a rigorously validated quantitative, semi-automated volumetric analysis tool for measuring preoperative tumor volume and residual volume. Furthermore, factors predicting functional and survival outcomes should be interpreted with caution, given the small sample size. Several other parameters were not studied here but should be investigated in other studies. For example, a comparison of the efficacy of AC in patients with isocitrate dehydrogenase (IDH)-mutant GB and patients with IDH-wildtype GB would be useful. An assessment of health-related quality of life (HRQoL) would also be of great interest. One study [39] reported that an early deterioration in HRQoL after surgery is an independent factor strongly associated with impaired survival in patients with GB. In this study, it was not possible to determine whether a good quality of life was maintained after AC, because quality of life is not systematically assessed at our center, other than in clinical trials. Some studies have suggested that AC may induce distress, or even symptoms of posttraumatic stress disorder [40], but others have concluded that AC is not a psychologically traumatic experience [21, 41, 42]. In a recent prospective study, Nickel et al. [43] observed that AC had no negative effect on the HRQoL of HGG patients in general, and did not result in specific emotional dysfunctions. However, given the small number of patients analyzed ($n = 18$), more detailed evaluations of patient and family satisfaction are required, in addition to HRQoL assessments in GB patients undergoing AC, for solid conclusions to be drawn. The prospective, multicenter, randomized controlled trial that Gerritsen et al. [44] will perform on such patients in the next four years will provide the necessary conclusions.

Conclusion

Consistent with the findings of previous retrospective studies, we show here that AC is an option for the resection of GB located in critical eloquent areas classically considered inoperable. Survival outcomes after AC are typical of those observed for GB patients in the Stupp era. However, the benefits of AC in terms of the recovery or preservation of language and/or motor functions cannot be guaranteed, given the aggressiveness of the tumor. A prospective study comparing different surgical approaches for GB in critical locations is required to determine whether AC could be considered a standard of care, or whether it should be used on a case-by-case basis.

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Compliance with ethical standards

Conflict of interest The author declare that they have no conflict of interest.

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