The Merits of Awake Craniotomy for Glioblastoma in the Left Hemispheric Eloquent Area: One Institution Experience

Ying-Ching Li
Chang Gung Memorial Hospital https://orcid.org/0000-0001-6789-4211
Hsiao-Yean Chiu
Chang Gung Memorial Hospital
Ya-Jui Lin
Chang Gung Memorial Hospital
Ko-Ting Chen
Chang Gung Memorial Hospital
Peng-Wei Hsu
Chang Gung Memorial Hospital
Yin-Cheng Huang
Chang Gung Memorial Hospital
Pin-Yuan Chen (pinyuanc@cgmh.org.tw)
Chang Gung Memorial Hospital
Kuo-Chen Wei
Chang Gung Memorial Hospital

Research article

Keywords: Awake craniotomy, eloquent area, glioblastoma, KPS, PFS, OS

Posted Date: April 22nd, 2020

DOI: https://doi.org/10.21203/rs.2.15627/v2

Version of Record: A version of this preprint was published at Clinical Neurology and Neurosurgery on January 1st, 2021. See the published version at https://doi.org/10.1016/j.clineuro.2020.106343.

Abstract

Background Awake craniotomy (AC) with intraoperative stimulation mapping is the standard treatment for gliomas, especially those on the eloquent cortex. Many studies have reported survival benefits with the use of AC in patients with glioma, however most of these studies have focused on low-grade glioma. The aim of this study was to evaluate the experience of one treatment center over 10 years for resection of left hemispheric eloquent glioblastoma.

Methods This retrospective analysis included 48 patients with left hemispheric eloquent glioblastoma who underwent AC and 61 patients who underwent surgery under general anesthesia (GA) between 2008 and 2018. Perioperative risk factors, extent of resection (EOR), preoperative and postoperative Karnofsky Performance Score (KPS), progression-free survival (PFS) and overall survival (OS) were assessed.

Results The postoperative KPS was significantly lower in the GA patients compared to the AC patients ($p=0.002$). The EOR in the GA group was 90.2% compared to 94.9% in the AC group ($p=0.003$). The mean PFS was 18.9 months in the GA group and 23.2 months in the AC group ($p=0.001$). The mean OS was 25.5 months in all patients, 23.4 months in the GA group, and 28.1 months in the AC group ($p<0.001$). In multivariate analysis, the EOR and preoperative KPSindependently predicted better OS.

Conclusion The patients with left hemispheric eloquent glioblastoma in this study had better neurological outcomes, maximal tumor removal, and better PFS and OS after AC than surgery under GA. Awake craniotomy should be performed in these patients if the resources are available.

Background

Achieving maximal surgical resection in patients with a supratentorial glioma has been shown to have a positive effect on overall survival (OS).[1,2,3,4,5,6,7,8,9,10] The most difficult challenge in cases of gliomas located in eloquent regions of the cortex is to find a balance between maximizing tumor resection and preserving surrounding functional structures. The traditional method of debulking a tumor from within, which has been used for a long time in glioma surgery in order to avoid new neurological deficits, can still lead to such deficits due to functional tissue being contained inside the tumor.[11,12] To overcome this problem, awake craniotomy (AC) allows for surgical mapping of sensorimotor and language functions by directly stimulating the cortical and subcortical areas that are in proximity to or even inside the tumor, and it has been shown to enhance safety and maximize the extent of resection of tumors in eloquent regions of the brain.[13,14,15] AC has enabled removal of tumors from highly functional eloquent regions that were once considered to be inoperable.[16] Surgical resection reduces tumor burden, relieves symptoms caused by the tumor mass effect, and has been proven to be a prognostic factor for survival in glioma patients. Moreover, the improved survival in glioma patients treated with AC has been attributed to a maximized extent of resection (EOR).

Many studies have reported the benefits of how AC can improve the survival of patients with glioma. However, most of these studies have focused on low-grade glioma, and few studies have reported patients with high-grade glioma or glioblastoma, and some studies have included a mix of tumor pathologies. In this study, we aimed to evaluate the experience of one treatment center over 10 years for resection of left hemispheric eloquent glioblastoma using direct brain stimulation and neuromonitoring with either AC or surgery under general anesthesia (GA). We compared the EOR and postoperative functional outcomes between the two methods. This represents the largest comparative study of AC and surgery under GA for treatment focused on glioblastoma located in left hemispheric eloquent areas in the literature.

Methods

Patient Selection

A list of patients with a diagnosis of glioma from June 2008 to December 2018 was requested from Chang Gung Memorial Hospital Cancer Center, and 1054 glioma patients who had undergone tumor resection surgery at Chang Gung Memorial Hospital, Linkou Branch, from 2010 to 2018 were collected. The inclusion criteria were: (1) age ≥18 years, (2) WHO grade IV glioblastoma in the left hemispheric eloquent area, defined as a tumor within or involving the primary motor cortex, primary sensory cortex, premotor cortex, and language cortex (Broca's area or Wernicke's area) based on magnetic resonance imaging (MRI), (3) an elective procedure, (4) a single lesion, and (5) new onset tumor. Patients who underwent a diagnostic biopsy alone, without pathological proof, and those < 18 years of age were excluded from the analysis. A total of 48 patients who underwent AC were included in this study. In addition, 61 patients who underwent craniotomy under GA with neuromonitoring (motor evoked potentials, somatosensory evoked potentials, phase reversal) were also included in this study. The patients' characteristics, treatment course and follow-up status were reviewed via electronic medical records or provided by Chang Gung Memorial Hospital Cancer Center.

Preoperative Evaluation

Preoperative MRI imaging with and without gadolinium was performed within the 2 weeks prior to surgery. Preoperative clinical evaluations, which included basic neurological and physical examinations and Karnofsky Performance Score (KPS) were performed by the surgeon. For the patients who planned to receive AC, baseline language and neurophysiological examinations were performed and rehearsed by the AC team, which included a neurologist, psychiatrist and speech therapist in order to determine the patients' suitability for the procedure.

Intraoperative Technique

Neuronavigation (Metronic) was used in all cases, and helped to plan the scalp incision. For every case, the craniotomy exposed the lesion plus about a 1- to 3-cm margin that allowed for mapping of the nearby functional cortex. The monitored anesthesia care technique was used for sedation for patients undergoing AC. A complete scalp block was applied using 2% lidocaine with 1:200000 epinephrine. The patient was placed in the supine position, and a skull clamp was employed to position the head optimally for surgery. Upon removal of the bone flap, the patient was allowed to wake up. Local anesthetic was applied again with a 30-gauge needle into the dural leaflets, and the dura was opened in a manner to expose the lesion.

Stimulation mapping then followed using an Ojemann cortical stimulator (Radionics Inc., Burlington, Mass., USA). The initial setting was 5 mA and was increased to a maximum of 10 mA until motor or sensory function was found or after discharge potentials were detected. A current generator delivered biphasic square waves at a pulse duration of 0.5 ms and pulse rate of 50 Hz as previously reported.[13,14] Stimulation was applied for 2 to 3 s at the indicated sites, with a 4 to 10 s pause between stimulations. Both the cortical and subcortical regions were identified using the same stimulation technique.

For motor mapping, the area of interest was stimulated and the patient

or rehabilitation physician reported whether there was any movement of the arm, leg, or face. Positive stimulation sites were repeated up to 3 times to verify the location. Negative sensorimotor mapping was indicated when no positive stimulation response occurred at the areas of interest.

For language mapping, the area of interest was stimulated and the patient or rehabilitation physician reported whether there was any abnormal number counting or visual object naming. During this time, we also performed continuous motor function testing. During surgical resection, continuous functional monitoring was performed using the object naming task and continuous motor function testing.

For surgery under GA, somatosensory evoked potentials were applied

preoperatively and phase reversal was used to help localize the motor strip prior to the corticectomy. In stimulation mapping for surgery under GA, the Ojemann cortical stimulator (Radionics Inc., Burlington, Mass., USA) was used in a similar manner to AC. A biphasic square wave pulse was delivered at a brief intermittent current varying from 2 to 8 mA to elicit a motor response. A multichannel electromyography recording was used to identify motor responses during the procedure.

Tumor Volume Analysis

The preoperative tumor volume was determined using T1-weighted MRI with gadolinium contrast for high-grade glioma. After surgery, all patients were admitted to the neurosurgical intensive care unit (NSICU). Postoperative MRI was performed within 48 hours to determine the quality of tumor removal. The extent of tumor resection was assessed by a neuroradiologist according to the classification system reported by Sawaya et al.: (i) gross total resection (GTR) was achieved if > 95% of the tumor was removed; (ii) subtotal resection (STR) if 85–95% was removed; (iii) or partial resection (PR) if < 85% of the tumor was removed.[17]

Outcome Evaluation

The patients who underwent AC with intraoperative stimulation mapping and those who underwent conventional craniotomy under GA were identified according to surgical records. The primary outcome was the postoperative KPS, which was defined as the general daily performance status score recorded within 3 months after surgery. Secondary outcomes in this study were progression-free survival (PFS), which was defined as the duration from diagnosis to either disease progression or the latest follow-up imaging study if no disease progression had been observed, and OS, which was defined as the duration from diagnosis to either death or the latest follow-up.

Statistical Analysis

The patients were stratified into AC and GA groups. The Student's t test, X^2 test and Fisher's exact test were used to examine the associations between demographic and clinical factors. Survival curves were estimated using the Kaplan-Meier method. To test whether AC was an independent prognostic factor of OS, a multivariate Cox proportional hazard model was used. The level of significance was set at 0.05, and all tests were performed using IBM, SPSS version 21.

Results

Patient Characteristics

One-hundred and nine patients were treated for left hemispheric eloquent gyrus, glioblastoma between 2008 and 2018 at our institution, of whom 61 underwent surgery under GA and 48 underwent AC. The demographics and preoperative comorbidities are shown in Table 1. Preoperative functional activity according to KPS was similar between the GA and AC groups (Table 1).

Tumor Characteristics

There were no significant differences in the tumor location including the primary motor cortex (GA vs AC, 67.2% vs 54.2%; p=0.165), primary sensory cortex (GA vs AC, 6.6% vs 12.5%; p=0.286), premotor cortex (GA vs AC, 6.6% vs 8.3%; p=0.724), and language cortex (GA vs AC, 19.7% vs 22.9%; p=0.68) between the two groups. There was also no significant difference in first, second, or third surgeries (GA vs AC, 83.6% vs 85.4%; 13.1% vs 8.3%; and 3.3% vs 6.3%, respectively, p=0.581) (Table 2).

Extent of Resection

Twenty-eight (45.7%) patients in the GA group achieved GTR compared to 40 (83.3%) patients in the AC group. Eighteen (29.5%) patients in the GA group achieved STR compared to six (12.5%) in the AC group, and 15 (24.6%) patients in the GA group achieved PR compared to two (4.2%) in the AC group. There was a significant difference in the percentage of resection between the two groups (p<0.0001) (Table 3).

The mean preoperative tumor volume in the GA and AC groups were similar (42.5mm^3 +/- 11.8 vs 43.6mm^3 +/- 10.2, p=0.155). The mean EOR in the GA group was 90.2% compared to 94.9% in the AC group (p=0.003, Table 3).

Table 4 shows the different EOR between the GA and AC groups according to tumor location. There was a significantly different EOR between the two groups in tumors located in the language cortex ($p<0.001$), but there were no significant differences in tumors located in the primary motor cortex, primary sensory cortex, or premotor cortex.

Postoperative Functional Outcomes

We defined KPS 80-100 as a good functional outcome and KPS < 80 as a bad functional outcome, and there was a significant difference in postoperative KPS between the two groups ($p=0.002$) (Table 6).

Progression-Free Survival

There was a significant difference in PFS between the GA group and AC group ($p=0.001$) (Fig. 1). The mean PFS was 18.9 months in the GA group and 23.2 months in the AC group.

Overall Survival

There was a significant difference in OS between the GA group and AC group ($p<0.001$) (Fig. 2). The mean OS was 25.5 months in all patients, 23.4 months in the GA group, and 28.1 months in the AC group. Tables 5 and 6 show the results of univariate and multivariate analyses for the factors associated with OS, respectively. Better OS was not significantly associated with age, gender, preoperative KPS, or postoperative KPS in univariate Cox proportional hazard analysis, however AC (OR 2.366; 95% CI 1.466-3.817; $p < 0.001$, univariate logistic regression), the percentage of resection (STR vs GTR, OR 0.104; 95% CI 0.077-0.255, $p < 0.001$; PR vs STR, OR 0.265; 95% CI 0.135-0.518, $p < 0.001$ univariate logistic regression), and the EOR (OR 0.913; 95% CI 0.887-0.938; $p < 0.001$, univariate logistic regression) were associated with better OS. In multivariate analysis, the EOR and preoperative KPS were independently associated with better OS (Table 6).

Discussion

Both AC and surgery under GA are viable options to treat left hemispheric glioblastoma in eloquent regions of the brain. To the best of our knowledge, this is the largest study to compare the feasibility, postoperative functional outcomes, progression free survival and overall survival of GA and AC for single hemisphere, single pathology glioblastoma in eloquent regions of the brain.

Despite advances in functional MRI and neuronavigation techniques that allow for anatomic localization of brain function under general anesthesia, real-time feedback regarding the patient's neurological status remains a distinct advantage of the AC procedure.[18] Brain mapping during removal of intra-axial tumors enables surgeons to reduce the risk of morbidity.[19,20] AC is a practical and effective standard surgical approach for supratentorial intrinsic eloquent area lesions, and it is an excellent alternative to craniotomy under GA because it allows for brain mapping and avoids the risks associated with GA.[21] Our results showed that compared to surgery under GA, AC for glioblastoma resulted in a higher frequency of radiographic total resection of enhanced tumors, better KPS within 3 months after surgery, and also better PFS and OS.

Extent of Resection

At least STR was achieved in more than 90% of the glioblastoma patients in the AC group. However, comparisons of the EOR between different studies is difficult because this highly depends on localization, tumor burden, and functional reorganization.[22] Many studies have reported resection rates and the merits of AC. Gupta et al.[23] reported that complete resection was achieved in 47.6% of patients who underwent AC, and also that complete/gross total tumor excision was achieved in a greater number of patients who underwent GA (63%) than AC (47%). In addition, Meyer et al.[24] reported that GTR was achieved in 52% of their patients who underwent AC. However, these studies included either different pathologies or varying grades of glioma.

In the present study, only glioblastoma patients were included, and all of the lesions were in left hemispheric eloquent regions. The average EOR was 94.9%, and 83.3% of the patients achieved GTR in the AC group which was a very convincing result showing that AC can improve the tumor resection rate (Table 3). Furthermore, we also compared the EOR between the GA and AC groups according to the tumor location, and the results were interesting but not surprising. The mean EOR was significantly lower in the GA group (80.08%) for tumors located within the language cortex compared to the AC group (93.9%) ($p<0.001$). This finding is compatible with the study of Sawaya et al.,[17] in which tumor functional grade was the most important variable for determining the risk of a new neurological deficit after surgery. To preserve neurological function, tumors in eloquent brain areas can only be biopsied or partially resected, whereas lesions in non-eloquent brain regions can be more aggressively resected. Thus, when evaluating associations between survival and surgical treatment, it is important to take the tumor location into account. We hypothesize that one of the main causes of this difference may be because language function is very complex and hard to monitor using only cortical and subcortical stimulation during surgery. The most accurate and direct method to monitor language is to interact with the patient. Second, since the language region could not be accurately identified from the information provided from neurophysical monitoring in the GA group, the surgeon would perform relatively conservative tumor resection to prevent the occurrence of new neurological deficits.

Progression-free Survival and Overall Survival

There were significant differences in both PFS and OS between the AC and GA groups in this study. To the best of our knowledge, these two major outcomes are fully dependent on the EOR. The mean OS was 25.5 months in the overall cohort, and 30 months and 24.7 months in the patients with GTR and STR, respectively. These results are similar to those of Bloch et al.[25], who reported OS ranging from 18.4 months to 20.4 months depending on the EOR. In their study, only 48.6% of the patients achieved GTR initially and the remaining patients achieved STR (51.4%), which is lower than in our study (Table 3).

The optimal EOR in any patient depends on the tumor size and location, the patient's general and neurological status, and the experience of the surgeon. Lacroix et al.[26] reported that the EOR in patients with glioblastoma began to be associated with a survival advantage at 89% of the tumor volume. In addition, aggressive resection of 98% or more of the tumor volume was a significant independent predictor of patient survival. In the field of neuro-oncology, many large retrospective cohort studies have also demonstrated enhanced survival with increased EOR in patients with newly diagnosed GBM, and mathematical modeling of retrospective data suggests incremental improvements in survival with EORs ranging from 78% to 98%.[27] In this study, the mean EOR in both groups (GA vs. AC, 90.2% vs. 94.9, respectively) also reached 89%, the threshold of survival advantage.

Some previous studies have reported that age is the most important prognostic factor associated with OS in glioblastoma patients,[28,29,30] and other studies have suggested that female glioblastoma patients have a better OS.[31] However, in the present study, neither age nor gender was a significant prognostic factor for OS in multivariate analysis (p=0.074 and 0.08, respectively) (Table 6).

With regards to KPS, some studies have suggested that with the current clinical armamentarium, glioblastoma patients with a preoperative KPS <60 are unlikely to survive >5 years.[32] In this study, we demonstrated that preoperative KPS was an independent predictive factor of OS (Table 6).

Postoperative Characteristics

In this study, there was no difference in the distribution of preoperative KPS between the AC and GA groups, however there were differences after surgery (Table 7). The proportion of patients with a postoperative KPS >80 increased from 70.8% to 85.4%. This result indicates that AC may not only preserve a patient's neurological functional activities, but also that intact neurological function can further improve a patient's general performance status for daily activities.

Our results also showed that the immediate postoperative neurological function in the AC group was significantly better than that in the GA group. Furthermore, in the first few days (within 3-7 days), the KPS in the AC group was even better. It has been shown that mild to moderate postoperative neurological deficits secondary to aggressive tumor debulking in an AC can quickly recover over several days.[24,33,34] This clinical finding is compatible with the concept of "brain plasticity" proposed by Duffau.[35]

Limitations

First, selection bias and a lack of randomization are limitations of this retrospective study. Second, due to the inclusion criteria, the number of case numbers was not large. Third, the prognosis of GBM is influenced by molecular markers including IDH1 and MGMT, however we lacked information on these markers. Fourth, patients undergoing AC require both the ability to and willingness to participate in the operation, and this may be a source of selection bias. A well-designed prospective validation study with independent cohorts is needed to verify our results.

Conclusions

In summary, we demonstrated that AC can be performed in adult patients with left hemispheric eloquent GBM, with a better postoperative KPS, better PFS and OS compared with surgery under GA. We also found that preoperative KPS and EOR were the most important independent prognostic factors of survival. We recommend AC as standard care for patient with left hemispheric eloquent GBM if the resources are available.

List Of Abbreviations

AC: Awake craniotomy; GA: General anesthesia; PFS: progression-free survival; OS: overall survival; EOR: extent of resection; KPS: Karnofsky Performance Status; GTR: gross total resection; STR: subtotal resection

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee of **Chang Gung Medical Foundation Institutional Review Board**, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Authors:

Ying-Ching Li

Hsiao-Yean Chiu

Kuo-Chen Wei

Ya-Jui Lin

Ko-Ting Chen

Peng-Wei Hsu

Yin-Cheng Huang

Pin-Yuan Chen

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare to have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. There is no conflict of interest.

Funding

Not applicable.

Authors' contributions

Ying-Ching Li : Conception and design, Statistical analysis, Drafting the article

Hsiao-Yean Chiu: Statistical analysis

Kuo-Chen Wei: Study supervision

Ya-Jui Lin: Study supervision

Ko-Ting Chen: Study supervision

Peng-Wei Hsu : Study supervision

Yin-Cheng Huang: Study supervision

Pin-Yuan Chen: Critically revising the article, Study supervision
*All authors have read and approved the manuscript

Acknowledgements

The study was supported by Chang Gung Medical Foundation Grant

CMRPG2J0111 / CMRPG2G0723

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Tables

Table 1. Demographic characteristics of the 109 patients who underwent resection for left hemispheric eloquent region glioblastoma

Characteristics, n (%)	Type of Surgery		
	GA (n = 61)	AC (n = 48)	P-value
Age at surgery, years (SD)	57.17 (19.6)	53.89 (15.4)	0.344
Gender (Male)	37 (60.7)	28 (58.3)	0.806
Preoperative Karnofsky Performance Score (KPS)			0.447
100–80, n (%)	39 (63.9)	34 (70.8)	
70 or less, n (%)	22 (36.1)	14 (29.2)	
Comorbidities			
Diabetes mellitus, n (%)	4(6.6)	4(8.3)	0.724
COPD, n (%)	3(4.9)	4(8.3)	0.47
Hypertension, n (%)	3(4.9)	4(8.3)	0.47
CABG/stents, n (%)	0(0)	0(0)	n/a
Pulmonary emboli, n (%)	0(0)	0(0)	n/a
Deep venous thromboses, n (%)	0(0)	0(0)	n/a

GA: craniotomy under general anesthesia , AC: awake craniotomy, COPD: chronic obstructive pulmonary disease, CABG: coronary artery bypass graft

Table 2. Tumor characteristics of the 109 patients who underwent resection for left hemispheric eloquent region glioblastoma

Characteristics, n (%)	Type of Surgery		
	GA (n = 61)	AC (n = 48)	P-value
Tumor location, n (%)			
Primary motor cortex	41(67.2)	26(54.2)	0.165
Primary sensory cortex	4(6.6)	6(12.5)	0.286
Premotor cortex	4(6.6)	4(8.3)	0.724
Language cortex	12(19.7)	11(22.9)	0.68
Resection number, n (%)			0.581
First	51(83.6)	41(85.4)	
Second	8(13.1)	4(8.3)	
Third or more	2(3.3)	3(6.3)	

Table 3. Percent of resection in the 109 patients who underwent resection for left hemispheric eloquent region glioblastoma

	Type of Surgery		
	GA (n = 61)	AC (n = 48)	P-value
Percentage of resection			**<0.0001**
Gross total (>95%), n (%)	28 (45.9)	40 (83.3)	
Subtotal (85–95%), n (%)	18 (29.5)	6 (12.5)	
Partial (< 85%), n (%)	15 (24.6)	2 (4.2)	
Extent of tumor resection			
Preoperative tumor volume mL, mean (SD)	42.5 (11.8)	43.6 (10.2)	0.155
Extent of resection, mean % (SD)	90.2 (7.44)	94.9 (5.73)	**0.003**

Table 4. The average extent of resection (EOR) between the GA and AC groups according to tumor location

Tumor location	Type of Surgery			
	Total	GA group	AC group	P-value
Primary motor cortex, patient (n), EOR (%)	89	46, 92.7%	21, 95%	0.114
Primary sensory cortex, patient (n), EOR (%)	10	4, 96.5%	6, 98.5%	0.063
Premotor cortex, patient (n), EOR (%)	8	4, 96.5%	4, 93.75%	0.285
Language cortex, patient (n), EOR (%)	23	12, 80.08%	11, 93.9%	**<0.001**

Table 5. Predictors of overall survival in univariate analysis

Clinical Data	Median Survival (months)	OR (95% CI)	P-value
Age, years	25.53†	1.004 (0.991-1.017)	0.514
Awake craniotomy, **yes**	28.17	2.366 (1.466-3.817)	**<0.001**
Gender, **male** vs. female	23.5	1.265 (0.809-1.98)	0.303
Preoperative KPS, **80–100** vs. ≤70	27.26	1.496 (0.945-2.367)	0.086
Postoperative KPS, **80–100** vs. ≤70	25.64	1.34 (0.849-2.114)	0.209
Percentage of resection, subtotal vs. **gross total**	30	0.104 (0.077-0.255)	**<0.001**
Percentage of resection, partial vs. **subtotal**	24.7	0.265 (0.135-0.518)	**<0.001**
Extent of resection, %	25.53†	0.913 (0.887-0.938)	**<0.001**

† Whole cohort.

KPS, Karnofsky Performance Score

Table 6. Multivariate analysis of overall survival

Independent Factors	Odds Ratio	95% CI	P-value*
Age, years	1.012	0.999-1.026	0.074
Awake craniotomy, yes	0.601	0.34-1.06	0.08
Gender, male vs. female	1.32	0.822-2.12	0.251
Preoperative KPS, 80–100 vs. ≤70	0.422	0.22-0.809	**0.009**
Postoperative KPS, 80–100 vs. ≤70	1.494	0.772-2.889	0.233
Percentage of resection, subtotal vs. gross total	0.687	0.12-3.93	0.674
Percentage of resection, partial vs. subtotal	0.56	0.178-1.808	0.338
Extent of resection, %	0.914	0.841-0.993	**0.034**

*All covariates with p value <0.2 in the univariate analysis. According to the multivariate Cox proportional hazard model.

KPS, Karnofsky Performance Score

Table 7. Postoperative Karnofsky Performance Score of the 109 patients who underwent brain stimulation for resection of left hemispheric eloquent region glioblastoma

Characteristics, n (%)	Type of Surgery GA (n = 61)	AC (n = 48)	P-value
Preoperative Karnofsky Performance Score (classification)			0.447
100–80, n (%)	39 (63.9)	34 (70.8)	
70 or less, n (%)	22 (36.1)	14 (29.2)	
Postoperative Karnofsky Performance Score (classification)			**0.002**
100–80, n (%)	35 (57.4)	41 (85.4)	
70 or less, n (%)	26 (42.6)	7 (14.6)	

Figures

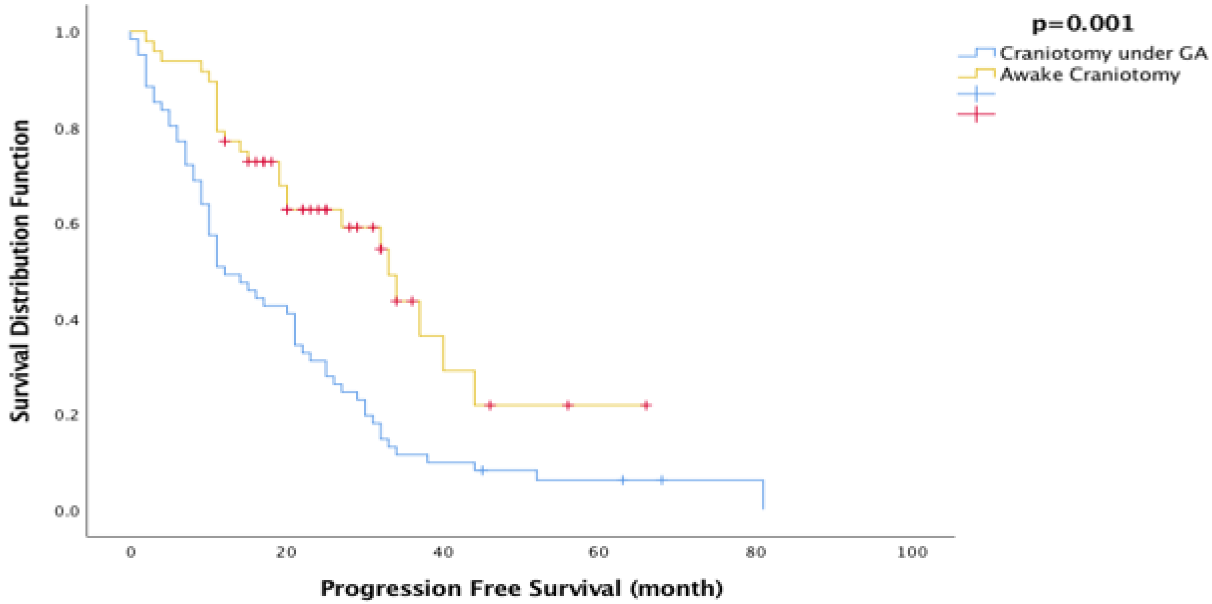

Figure 1

Progression free survival (PFS) in patients with left hemispheric eloquent region glioblastoma (p=0.001)

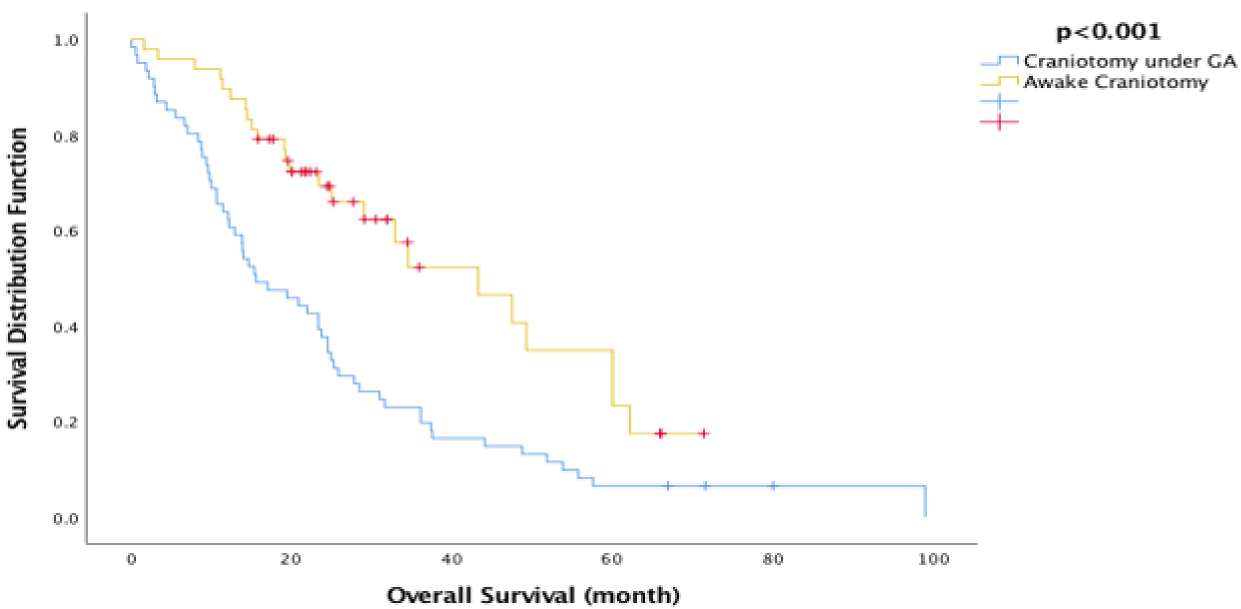

Figure 2

Overall survival (OS) in patients with left hemispheric eloquent region glioblastoma (p<0.001)