Awake Craniotomy vs Craniotomy Under General Anesthesia for Eloquent Glioma: Postoperative General Functional Preservation

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Ying-Ching Li  
Chang Gung Memorial Hospital

*ORCiD: 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  
Email: pinyuanc@cgmh.org.tw

Kuo-Chen Wei  
Chang Gung Memorial Hospital

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- Awake craniotomy
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Abstract
Background Awake craniotomy (AC) with intraoperative stimulation mapping is the standard treatment for glioma, especially when present on the eloquent cortex. The purpose of this study was to investigate whether functional preservation after AC compromises patient survival as compared with craniotomy under general anesthesia (GA).

Methods The medical records of 339 patients who underwent tumor resection surgery for gliomas from January 2010 to December 2014 were retrospectively reviewed. Among these patients, 62 underwent AC with intraoperative stimulation mapping. The primary outcome was the Eastern cooperative oncology group (ECOG) performance score at 3 months postoperatively. Secondary outcomes were the progression-free survival (PFS) and overall survival (OS). A generalized linear model and the Cox proportional hazard model were used to evaluate potential factors influencing general functional status and progression-free survival.

Results The newly-diagnosed disease AC and repeat-surgery groups were comparable in terms of sex, age, pathologic grade, extent of resection (EOR) and preoperative Karnofsky Performance Status (KPS). Among the patients with newly-diagnosed disease, the postoperative ECOG score of the AC group was significantly better than that of the GA group. Pathologic grade and the EOR determined the PFS and OS in both the AC and GA groups.

Conclusion AC with intraoperative stimulation mapping is safe and allows maximal removal of lesions around the eloquent cortex. Greater preservation of neurologic function may have resulted in a better postoperative general functional status in the AC group.

Background
Achieving maximal surgical resection in patients with a supratentorial glioma has been shown to have a positive effect on progression-free survival (PFS) and overall survival (OS) [1–10]. 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 avoiding surrounding functional tissues. The traditional method of debulking a tumor from within, which has been used for a long period of time in glioma patients in order to avoid new neurological deficits, is made more difficult in these cases, as evidence has shown
that neurologic deficits may occur due to functional tissue being contained inside the tumor [11, 12]. To overcome this dilemma, awake craniotomy (AC) for surgical mapping of sensorimotor and language functions presents an approach that could be used to attempt to enhance safety and maximize the extent of resection of tumors in eloquent regions of the brain [13, 14]. By directly stimulating the cortical and subcortical areas that are in proximity to the tumor, AC allows for identification of functionally-relevant areas of the brain [15]. This technique has enabled removal of tumors from highly-functional eloquent regions that were once considered inoperable [16]. Surgical resection reduces the tumor burden, relieves symptoms caused by the tumor mass effect, and has been proven to be a prognostic factor for survival in glioma patients. With improvement in intraoperative techniques and increased surgical experience, intraoperative stimulation mapping, which is performed while the patient remains awake for a short time during brain tumor surgery, is now recognized as a reliable method for use when brain tumors involve eloquent areas (i.e., structures related to sensory, linguistic or motor function). Apparent advantages of intraoperative stimulation mapping in terms of survival in glioma patients were observed from evidence of a maximized extent of resection. Our study aimed to evaluate the experience of one treatment center over 5 years of resection of eloquent gliomas using direct brain stimulation and neuromonitoring, with either AC or surgery under general anesthetic (GA). We compared the extent of resection (EOR) and postoperative functional outcomes between the two methods. This represents the largest comparative study of AC and surgery under GA for the treatment of gliomas located in eloquent motor areas in the literature.

Materials And Methods
Patient selection
A list of patients with the diagnosis code ICD-O-3 C71 from 2008 to 2015 was requested from Chang Gung Memorial Hospital Cancer Center. Patients aged over 18 years with a histopathologically-proven malignant brain tumor who underwent treatment at Chang Gung Memorial Hospital, Linkuo Branch, were eligible for this study. Considering that AC with intraoperative stimulation mapping has been used since 2010 in this treatment center, and the expected survival of WHO grade IV glioblastoma
patients is 1.5 years, only patients who underwent surgery from 2010 to 2014 were enrolled for analysis. Patients who underwent a diagnostic biopsy alone, without pathological proof; those under 18 years of age; and those who were followed-up for less than one month were excluded from the analysis. Patient 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 evaluation, which included a neurological exam, was performed by the surgeon. For the AC patients, baseline language sensorimotor testing was performed and the Karnofsky Performance Status (KPS) was obtained by the AC team in order to determine their suitability for the procedure.

Intraoperative technique
Anesthesia regimen: 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.

Tumor volume analysis
The preoperative tumor volume was determined using T1-weighted MRI with gadolinium contrast for high-grade glioma, or T2-weighted MRI images for low-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 reported by Sawaya et al. [17]: gross total resection (GTR) was achieved if more than 95% of the tumor was removed; subtotal resection (STR) if 85–95% was removed; or partial (PR) if < 85% of the tumor was removed.

Outcome evaluation
Whether a patient underwent AC with intraoperative stimulation mapping or conventional craniotomy under GA was determined according to surgical records. The primary outcome was the postoperative
ECOG score, which was defined as the general daily performance status score recorded within 7 days after surgery. Secondary outcomes in this study were 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. All patients were followed-up to Dec 31, 2016.

Statistical analysis

The samples were stratified into newly-diagnosed and repeat-surgery groups. In the survival analysis, patients were further divided into groups according to WHO tumor grade (II/III/IV). The Student 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 by the Kaplan-Meier method. To evaluate the prognostic value of AC with intraoperative stimulation mapping as compared with conventional craniotomy, the log-rank test was adopted. To test whether AC intervention was an independent prognostic factor of PFS and OS, the multivariate Cox proportional hazard model was applied, adjusting for other risk factors. The level of significance was 0.05, and all tests were performed using SAS software (SAS Institute Inc., Cary, NC).

Study period

This study was conducted from 1 April, 2016 to 31 March, 2017.

Results

Baseline characteristics

Three-hundred and sixty-one tumor resection surgeries performed on 339 glioma patients at Chang Gung Memorial Hospital, Linkou Branch, from 2010 to 2014 were eligible for inclusion in this study. Among the 339 patients, 62 underwent AC with intraoperative stimulation mapping during either an initial surgical intervention or repeat surgery. In the case of a patient undergoing two or more ACs, the first surgical intervention was sampled. Information on initial and repeat surgeries for twenty-two patients in the reference group was obtained. The median follow-up duration in the newly-diagnosed surgery group was 19.2 months (range, 1.2–70.2 months) (Table 1). The mean age of the AC patients in the newly-diagnosed group was 48.6 years, which was slightly younger than the mean of 53.9
years in the GA group ($p = 0.0510$). The age distribution of the patients in the recurrent group was similar to that in the newly-diagnosed group (Table 1). The preoperative KPS demonstrated that the patient populations in the newly-diagnosed group and recurrent group were similar (Table 1).

### Tumor characteristics

A significant difference in WHO grade in the recurrent and the residual glioma patients was observed between the AC group and the reference group ($p = 0.0123$), while no difference between groups was observed when examining the newly-diagnosed glioma patients ($P = 0.239$). Of our overall patient population, more than half had grade IV gliomas, and 53% and 75% had a newly-diagnosed glioma and recurrent glioma, respectively. In the AC group, tumors were present in the left hemisphere in 79.5% and 78.3% of patients in the newly-diagnosed glioma group and the recurrent glioma group, respectively, greater than the corresponding percentages in the GA group. In the GA group, tumors in the right hemisphere were observed in 46.6% and 46% of patients in the newly-diagnosed glioma group and the recurrent glioma group, respectively, greater than the corresponding percentages in the AC group (Table 1).

### Postoperative ECOG score

In the newly-diagnosed disease group, a significantly better postoperative ECOG score was observed in the AC group than in the GA group in this study (ECOG 0–1 vs 2–4; $p = 0.0098$) (Table 1). In addition, in the multivariate analysis, AC was demonstrated to be an independent prognostic factor of a better postoperative ECOG score in the newly-diagnosed disease group (Supplementary Table S1).

### Extent of resection

In the newly-diagnosed group, GTR was achieved in 97 (41.1%) of the GA cases and 19 (48.7%) of the AC cases; STR was observed in 57 (24.2%) of the GA cases and 7 (18%) of the AC cases, and PR was attained in 82 (34.8%) of the GA cases and 13 (33.3%) of the AC cases. In the newly-diagnosed group, there was no difference in the EOR between the AC group and the GA group.

In the recurrent group, GTR was achieved in 25 (39.7%) of the GA cases and 10 (43.5%) of the AC cases; STR was observed in 8 (12.7%) of the GA cases and 4 (17.4%) of the AC cases, and PR was attained in 30 (47.6%) of the GA cases and 9 (39.1%) of the AC cases. In the recurrent group, there
was no difference in the EOR between the AC group and the GA group.

**Progression-free survival**

No significant difference in PFS was observed between the AC with intraoperative stimulation mapping group and the conventional craniotomy group in all strata of disease status (newly-diagnosed/repeat-surgery) or WHO grade (II/III/IV) (Supplementary Table S2; Fig. 1). Multivariate Cox proportional hazard model analysis revealed that AC was not a prognostic factor of PFS in the glioma patients. The adjusted hazard ratios for newly-diagnosed grade II, grade III and grade IV gliomas were 1.67, 0.99 and 1.54, respectively, and the 95% confidence intervals all included 1. The adjusted hazard ratios for repeat-surgery grade II, grade III and grade IV gliomas were 0.28, 1.80 and 0.97, respectively, and the 95% confidence intervals all included 1 (Table 2).

**Overall survival**

In the newly-diagnosed group, no significant difference in OS was observed between the AC group and the reference group in any WHO grade subgroup (Supplementary Table S3; Fig. 2). The adjusted hazard ratios estimated using the Cox proportional hazard model were 0.76, 0.41 and 0.63 for newly-diagnosed grade II, grade III and grade IV gliomas, respectively, and all 95% confidence intervals included 1 (Table 3).

**Subgroup analysis**

One-hundred and sixty-four patients who underwent craniotomies in the left frontal, temporal, or parietal regions were enrolled in the subgroup analysis. In the newly-diagnosed group, patients who underwent AC were of a younger mean age and had a better postoperative ECOG performance status. No significant differences in tumor laterality, tumor number, extent of resection or preoperative KPS were observed between the AC group and the reference group. Survival analyses yielded similar results to those observed for the whole sample. AC with intraoperative stimulation mapping was not associated with PFS, regardless of disease status or WHO grade. After controlling other risk factors (including WHO grade), the adjusted hazard ratios were 1.01 (95% CI 0.57–1.77) in the newly-diagnosed group and 0.60 (95% CI 0.18–2.01) in the repeat-surgery group. In addition, no significant association was observed between AC and OS in the newly-diagnosed group, with an adjusted hazard
Discussion
Despite advances in functional MRI and neuronavigation techniques that allow 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 identify a safe corridor to a tumor and facilitates maximum resection with a decreased risk of morbidity [19, 20]. AC is a practical and effective standard surgical approach for supratentorial intrinsic eloquent area lesions and provides an excellent alternative to craniotomy performed with patients under GA, because it allows the opportunity for brain mapping and avoids the risks associated with GA [21].

Progression-free survival and overall survival
In our study, no significant differences between the AC and GA groups were observed in either the newly-diagnosed group or the recurrent group. Compared with Sacko et al. [19], with the exception of high-grade gliomas, significant differences were observed between the AC and GA groups in the overall patient population and the low-grade glioma patients; however, it may be the case that a longer follow-up duration is required for low-grade glioma patients owing to their longer average survival duration.

These two major outcomes, to the best of our knowledge, are fully-dependent on the EOR, although many studies have demonstrated benefits of AC, including a lesser risk of neurologic deficit, fewer intraoperative complications, a shorter duration of hospitalization, and a shorter duration of surgery [19, 22, 23]. This study may be the first to classify surgical technique and the EOR as two different independent factors related to major outcomes (Table 2), and we found that AC was not a prognostic factor of PFS or OS in glioma patients.

Extent of resection
In our study, there were no significant differences between the AC group and the GA group, as was also reported by Gupta et al. [22]. In that series, complete resection was achieved in 47.6% of patients in the AC group, and it was also observed in that study that complete/gross total tumor
excision was achieved in a greater number of patients in the GA group (63%) than in the AC group (47%). However, in our study, the GTR rate in the AC group was 48.7% and 43.3% in the newly-diagnosed patients and repeat-surgery patients, respectively, this result being similar to that reported by Meyer et al., who observed GTR in 52% of cases [24]. Sacko et al. [19] and Eseonu et al. [23] stated that according to statistical analysis, AC can improve the EOR, but it might be the case that different criteria or smaller numbers of patients influenced the results in these two studies. Patients with vascular lesions and metastases were included in the study by Sacko et al. [19], and there were only 27 patients in the AC group and 31 patients in the GA group in the study by Eseonu et al. [23]. In the present study, only glioma patients were included, and no vascular lesions or metastases were present in the patient population. Sixty-two AC patients were included in this study, and the total patient population numbered 339; all surgeries were carried out in a single treatment center.

Postoperative characteristics
In our study, significant differences in the postoperative ECOG performance status (classification) were observed between the AC patients and the GA patients in the newly-diagnosed group. Patients in whom mapping successfully identified functional tissue had a higher postoperative ECOG performance status (86.8%) than patients with negative brain mapping (64%), with \( p = 0.0096 \) (Table 1). This may be explained by the fact that although the GTR rate was not significantly elevated in the AC group in our selected study population (48.7% vs. 43.3%), this was likely due to better identification of functional cortex boundaries during surgery while the patient remained awake. Thus, it may be that the greater tumor tissue resection in the GA group came at the price of greater functional tissue loss and increased neurological morbidity.

Conclusions
We have demonstrated that AC can be performed in cases of perirolandic, eloquent and motor-region glioma, with a better postoperative ECOG score as compared with surgery under GA. However, PFS and OS, which were strongly-dependent on the EOR, did not differ significantly between groups. In this study, we also found that the AC procedure was not an independent prognostic factor of patient survival, in contrast to the EOR. In summary, the benefits of AC for functional preservation are clear,
but when it comes to survival rate, the most important prognostic factor is the EOR.

Abbreviations
AC: Awake craniotomy; GA: General anesthesia; ECOG: Eastern cooperative oncology group; 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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Author:
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.

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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

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Tables

Table 1 Baseline characteristics of the patients in the awake craniotomy and reference groups.

| Characteristics, n (%) | Reference* (n = 236) | Awake craniotomy (n = 39) |
|------------------------|----------------------|--------------------------|
| Disease status         |                      |                          |
| Newly-diagnosed        | 236 (100.0)          | 39 (100.0)               |
| Residual               | 0 (0.0)              | 0 (0.0)                  |
| Recurrent              | 0 (0.0)              | 0 (0.0)                  |
| Age at surgery, years, mean (SD) | 53.9 (15.6) | 48.6 (14.7) | 0.0510 |
| Gender                 |                      |                          |
| Female                 | 99 (41.9)            | 18 (46.1)                |
| Male                   | 137 (58.1)           | 21 (53.9)                |
| WHO grade              |                      |                          |
| II                     | 57 (24.2)            | 12 (30.8)                |
| III                    | 48 (20.3)            | 11 (28.2)                |
| IV                     | 131 (55.5)           | 16 (41.0)                |
| Laterality (classification) |                |                          |
| Bilateral/midline involvement | 51 (21.6) | 7 (18.0) | <0.0001 |
| Left                   | 75 (31.8)            | 31 (79.5)                |
| Right                  | 110 (46.6)           | 1 (2.6)                  |
| Extent of resection    |                      |                          |
| Gross-near total       | 97 (41.1)            | 19 (48.7)                |
| Subtotal               | 57 (24.2)            | 7 (18.0)                 |
| Partial                | 82 (34.8)            | 13 (33.3)                |
| Preoperative Karnofsky performance status (classification) | 180 (76.3) | 28 (71.8) | 0.5463 |
| 100–80                 |                        |                          |
| 70 or less             | 56 (23.7)            | 11 (28.2)                |
| Postoperative ECOG performance status (classification) | 150 (63.6) | 33 (84.6) | 0.0098 |
| 0–1                    |                        |                          |
| 2–4                    | 86 (36.4)            | 6 (15.4)                 |

Table 2 Multivariate analysis: awake craniotomy → PFS, according to the multivariate Cox proportional hazard model, stratified by disease status and WHO grade.
| Covariate | Grade II glioma (n = 67) | Grade III glioma (n = 58) |
|-----------|--------------------------|--------------------------|
|           | P value | Hazard ratio (95% CI) | P value | Hazard ratio (95% CI) |
| **Newly-diagnosed disease** | | | | |
| Awake craniotomy, yes | 0.4131 | 1.669 (0.490–5.687) | 0.9931 |
| Age, per 10 increase | 0.4446 | 1.192 (0.760–1.869) | 0.1133 |
| Gender, male vs. female | 0.0002 | 9.198 (2.886–29.317) | 0.4452 |
| Preoperative KPS, ≤70 vs. 80–100 | 0.0468 | 0.251 (0.064–0.981) | 0.7176 |
| Postoperative ECOG PS, 2–4 vs. 0–1 | 0.0004 | 12.517 (3.083–50.811) | 0.7952 |
| Laterality, right vs. left | 0.0512 | 2.778 (0.995–7.756) | 0.5890 |
| Laterality, bilateral/midline involvement vs. left | 0.3529 | 1.625 (0.583–4.528) | 0.6569 |
| Extent of resection, near total/subtotal vs. gross total | 0.1549 | 2.478 (0.710–8.654) | 0.1269 |
| Extent of resection, partial vs. gross total | 0.1106 | 2.904 (0.784–10.757) | 0.0222 |
| **Residual/recurrent disease** | | | | |
| Awake craniotomy, yes | 0.6080 | 0.430 (0.017–10.792) | 0.0384 |
| Age, per 10 increase | 0.5457 | 1.962 (0.220–17.465) | 0.4399 |
| Gender, male vs. female | 0.7384 | 1.892 (0.045–79.643) | 0.9455 |
| Preoperative KPS, ≤70 vs. 80–100 | 0.5991 | 6.942 (0.005–9523.172) | 0.0524 |
| Postoperative ECOG PS, 2–4 vs. 0–1 | 0.7690 | 0.611 (0.023–16.351) | 0.0129 |
| Laterality, right vs. left | 0.5843 | 2.346 (0.111–49.743) | 0.0106 |
| Laterality, bilateral/midline involvement vs. left | N/A | N/A | 0.3659 |
| Extent of resection, near total/subtotal vs. gross total | 0.7787 | 2.635 (0.003–2271.344) | 0.1268 |
| Extent of resection, partial vs. gross total | 0.1763 | 9.244 (0.368–232.203) | 0.0804 |

Note: Missing PFS information in newly-diagnosed disease: grade II = 2, grade III = 1, grade IV = 7; Missing PFS information in residual/recurrent disease: grade III = 2, grade IV = 6.

Table 3 Multivariate analysis: awake craniotomy → overall survival, according to the multivariate Cox proportional hazard model, stratified by disease status and WHO grade.
Figures
Progression-free survival (PFS) in newly-diagnosed patients: (A) Grade II, (B) Grade III, (C) Grade IV; and PFS in repeat-surgery patients: (D) Grade II, (E) Grade III, (F) Grade IV.
Figure 2

Overall survival (OS) in newly-diagnosed patients. (A) Grade II, (B) Grade III, (C) Grade IV.