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Original Article

Using cortical function mapping by awake craniotomy dealing with the patient with recurrent glioma in the eloquent cortex

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ABSTRACT

Background: Awake craniotomy is an effective method by which to reduce postoperative neurologic deficit in newly-diagnosed glioma patients. However, the level of functional preservation in patients undergoing resection of recurrent glioma remains unknown. Therefore, this study aimed to evaluate functional outcomes in patients with recurrent glioma undergoing awake craniotomy as compared with conservative general anesthesia craniotomy for tumor resection.

Methods: We retrospectively reviewed 225 patients who had recurrent gliomas from May 2013 to January 2016 in our institution. New-onset neurological deficits were evaluated on postoperative day 7 (early) and at 3 months (late). General performance was assessed both preoperatively and at 3 months postoperatively.

Results: The early neurological deficit rate was 3.8% in the awake craniotomy group and 21.6% in the general anesthesia group (p. 0.032), while the late neurological deficit rates were 3.8% and 11.5%, respectively (p. 0.231). Moreover, 46.1% of patients in the awake craniotomy group and 12.6% in the general anesthesia group demonstrated an improvement in the Karnofsky performance status (KPS) score ($p < 0.001$).

Conclusion: Awake craniotomy is an effective and safe method by which to perform recurrent glioma surgery. The neurological outcomes and general performance after awake craniotomy in recurrent glioma patients were better than those in patients undergoing general anesthesia craniotomy.

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At a glance of commentary

Scientific background on the subject

Awake craniotomy (AC) with intraoperative stimulation mapping is the standard treatment for gliomas, especially those on the eloquent cortex. As we all know that the recurrent tumors are especially difficult to resection owning to the poor margin between the tumor and normal brain tissue.

What this study adds to the field

However, in this article we used the cortical function mapping by awake craniotomy to help surgeon resected the tumor confidently and we also demonstrate that the better functional preservation and lower neurologic deficits by awake craniotomy.

Awake craniotomy was initially introduced to treat patients with epilepsy. Over the past few decades, it has been widely-applied in the resection of brain tumors, allowing surgeons to perform detailed brain mapping and continuous assessment of the patient's neuropsychological status. Therefore, awake craniotomy can be used to identify and avoid damage to functional areas when performing tumor resection in or near the eloquent cortex.

Improvements in treatments and surgical techniques have resulted in longer survival durations for patients with glioma; however, for recurrent gliomas, there are limited effective treatment options. Nevertheless, anecdotal experience suggests that in highly-functional patients, minimizing the tumor burden may improve the efficacy of subsequent therapy [1]. Recent studies have indicated that re-resection for recurrent gliomas can improve survival. Ramakrishna et al. reported that re-resection for recurrent gliomas appeared to provide a significant survival benefit in cases of low-grade glioma, and the extent of resection remained the strongest predictor of overall survival [2]. Similarly, Chaichana et al. reported that re-resection improved the survival of patients with recurrent glioblastomas [3]. Another study suggested that the best results in terms of survival for patients with recurrent high-grade gliomas were obtained with multimodal treatment; in these cases, cytoreductive surgery may assist adjuvant treatments in controlling the disease for a longer period of time [4].

Although re-resection of recurrent gliomas has been shown to improve survival, some researchers have suggested that more aggressive surgical resection can result in a diminished quality of life [4]. On the other hand, Kaspera et al. reported that repeat surgery on patients with recurrent low-grade gliomas, even those with tumors within the eloquent areas of the brain, does not carry a higher risk of neurological deficits as compared with the initial surgery [5]. To date, the neurologic outcomes and functional performance status of patients undergoing recurrent awake craniotomy remain unknown.

Therefore, the purpose of this study was to assess the general performance and neurological outcomes of patients with recurrent gliomas who underwent awake craniotomy for glioma resection.

Material and methods

Patients

This study was approved by the Institutional Review Board of our hospital. We retrospectively collected clinical, histological, and radiological data of 225 adult patients with recurrent gliomas who underwent tumor resection via awake craniotomy (AC) or general anesthesia (GA) between May 2013 and January 2016. Patients aged over 18 years with a tissue-proven diagnosis of supratentorial glioma (World Health Organization (WHO) grade I to IV) were included in the study. All tumors were located in the cerebral eloquent cortex. Pathological diagnoses were determined by a senior neuropathologist in all cases, and the glioma grading criteria were based on the WHO 2007 classification system. Patients with incomplete medical records or lacking pre-/post-operative magnetic resonance imaging (MRI) study were excluded.

Perioperative treatment

The general aim of surgery was to achieve maximal safe resection. However, subtotal resection was acceptable when the tumor involved the eloquent cortex region of the brain, as confirmed by intraoperative mapping and/or monitoring (awake speech language mapping, direct cortical motor stimulation, and motor-evoked or somatosensory-evoked potentials). Recurrent tumors were defined according to the RANO criteria, including any diameter enlargement and/or new contrast enhancement in the tumor remnants on follow-up MRI or newly-developed/progressed neurologic symptoms.

Postoperative management

After surgery, all patients were admitted to the neurosurgical intensive care unit (NSICU). Postoperative MRI was performed within 48 h to determine the quality of tumor removal. The extent of tumor resection was assessed by a neuroradiologist according to the classification described by Sawaya et al. [6]. Resection was considered as gross total resection (GTR) if more than 95% of the tumor had been removed, subtotal resection when 85–95% of the tumor had been removed, or partial resection when < 85% of the tumor was removed. All patients underwent a follow-up MRI and received a Karnofsky performance status (KPS) score at 3 months after surgery. Neurological deficits were defined as a speech and/or motor deficit that occurred after the surgery. In addition, all patients underwent follow-up clinical neurological examinations at 7 days and 3 months after surgery in order to assess the persistence of early and late neurological deficits, respectively. All neurological evaluations were performed by a neurosurgeon.

Statistical analysis

Comparisons between groups included the quality of tumor resection, anesthetic and surgical complications, rates of postoperative early and late neurological deficits, and changes to the KPS score. Data analysis was performed using SPSS version 25 software. Comparisons between groups were performed using contingency table analysis with Pearson's chi-squared test, Fisher's exact test, and the paired t-test to determine statistically significant differences. A P value of <0.05 was used to determine statistical significance.

Results

Patient demographics and tumor characteristics

In total, 225 patients (123 males, 54.7%) who had a recurrent glioma underwent a craniotomy for tumor resection during the study period. A total of 199 patients underwent an awake craniotomy (AC) for glioma resection, and 26 patients underwent a general anesthesia craniotomy. There were no differences between the groups with regards to baseline characteristics, hypertension, smoking habit, or body mass index (BMI), but there were differences between the American Association of Anesthesiologist (ASA) score and the presence of diabetes mellitus [Table 1]. Among the 225 patients, 154 had a high-grade glioma (HGG) and 71 had a low-grade glioma (LGG). In the general anesthesia group, 137 patients (67.3%) had a HGG and 62 (32.7%) had a LGG, while in the awake craniotomy group, 17 patients (65.4%) had a HGG and 9 (34.6%) had a LGG. The mean tumor size in all patients was 40.62 cm^3, and was approximately 41.33 cm^3 and 35.18 cm^3 for the general anesthesia group and awake craniotomy group, respectively ($p = 0.12$).

Table 1 Patient demographic and clinical data.

	All N = 225	GA n = 199	AC n = 26	p-value
Sex				
Female	102 (45.3)	94 (47.2)	8 (30.8)	0.113
Male	123 (54.7)	105 (52.8)	18 (69.2)	
Age (y)	51.23	52.15	50.56	0.169
BMI	23.14	23.26	22.89	0.441
ASA score				
1	20 (8.9)	19 (9.5)	1 (3.8)	0.011
2	86 (38.2)	82 (41.2)	4 (15.5)	
3	117 (52)	97 (48.7)	20 (76.9)	
4	2 (0.9)	1 (0.6)	1 (3.8)	
HTN				
Yes	172 (76.4)	152 (76.4)	20 (77.9)	0.951
No	53 (23.6)	47 (23.6)	6 (23.1)	
DM				
Yes	151 (67.1)	125 (62.8)	26 (100)	0.001
No	74 (32.9)	74 (37.2)	0 (0)	
Smoking				
Yes	171 (76)	148 (74.4)	23 (88.5)	0.103
No	54 (24)	51 (25.6)	3 (11.5)	

Data reported as mean, or number (percentage).

Table 2 Tumor characteristics.

	All N = 225	GA n = 199	AC n = 26	p-value
Grade				
Low-grade	71 (31.6)	62 (32.7)	9 (34.6)	0.721
High-grade	154 (68.4)	137 (67.3)	17 (65.4)	
Tumor location				
Frontal	115 (51.1)	102 (51.3)	13 (50)	0.906
Temporal	97 (43.1)	86 (43.2)	11 (42.3)	
Parietal	13 (5.8)	11 (5.5)	2 (7.7)	
Size (cm3)	40.62	41.33	35.18	0.121
EOR (%)	94.89	94.52	95.51	0.061
Degree of resection after surgery				
Gross total	129 (57.3)	112 (56.3)	17 (65.4)	0.545
Subtotal	82 (36.4)	75 (37.6)	7 (26.9)	
Partial	14 (6.3)	12 (6.1)	2 (7.7)	

Data reported as mean, or number (percentage).

The mean extent of resection (EOR) for all patients was 94.9%. In the general anesthesia group, the mean EOR was 94.5%, and in the awake craniotomy group it was 95.5% ($p = 0.06$) [Table 2]. There were no significant differences in the GTR rate, subtotal resection rate or partial resection rate between the two groups ($p = 0.545$) according to the Sawaya classification [6]. The overall GTR rate was 57.3%. In the general anesthesia group, the GTR rate was 56.3%, and in the awake craniotomy group it was 65.4% [Table 2].

Complications

There were no mortalities or major complications, including hemorrhage during surgery or leakage of cerebrospinal fluid, in either group. Five patients in the general anesthesia group developed surgical-site infections postoperatively [Table 3].

Neurological deficits

Among the whole patient cohort of 225 patients, 44 (19.6%) had early postoperative neurological deficits, and 24 (10.7%) had late neurological deficits [Table 4]. Forty-three patients with early deficits were in the general anesthesia group, and one patient was in the awake craniotomy group ($p = 0.032$). Twenty-three patients with late deficits were in the general anesthesia group, and one was in the awake craniotomy group ($p = 0.231$) [Table 4].

KPS scores

Preoperatively, there were 3, 7, 39, 79, and 97 patients with a KPS score of 60, 70, 80, 90, and 100, respectively (median: 90).

Table 3 Complications.

	All N = 225	GA n = 199	AC n = 26	p-value
Mortality	0	0	0	
Hemorrhage	0	0	0	
CSF leakage	0	0	0	
Surgical site infection	5	5	0	0.276

Table 4 Comparison of neurologic deficit and general performance scores.

	All N = 225	GA n = 199	AC n = 26	p-value
KPS score before surgery				
60	3 (1.3)	3 (1.5)	0 (0)	0.493
70	7 (3.1)	6 (3)	1 (3.8)	
80	39 (17.3)	35 (17.6)	4 (15.4)	
90	79 (35.1)	66 (33.2)	13 (50)	
100	97 (43.2)	89 (44.7)	8 (30.8)	
Median	90	90	90	
Mean	91.55	91.65	90.77	
KPS score after surgery				
50	3 (1.3)	3 (1.5)	0 (0)	
60	10 (4.4)	10 (5.0)	0 (0)	
70	40 (17.8)	40 (20.1)	0 (0)	
80	58 (25.8)	57 (28.6)	1 (3.8)	<0.001
90	65 (28.9)	53 (26.6)	12 (46.2)	
100	49 (21.8)	36 (18.2)	13 (50)	
Median	80	80	95	
Mean	84.17	82.81	94.62	
P-value	0.238	0.158	<0.001	
Early neurological deficits	44 (19.6)	43 (21.6)	1 (3.85)	0.032
Late neurological deficits	24 (10.7)	23 (11.5)	1 (3.8)	0.231

Data are reported as number (percentage), unless otherwise indicated.

The median preoperative KPS score was 90 in both groups, and the distribution of scores did not differ between groups ($p = 0.493$). Postoperatively, there were 3, 10, 40, 58, 65, and 49 patients with a KPS score of 50, 60, 70, 80, 90, and 100, respectively (median: 80). The distribution of postoperative KPS scores differed significantly between groups ($p < 0.001$). In addition, in the awake craniotomy group (AC), the post-operative KPS score was significantly increased as compared with the baseline score; however, no such trend was observed in the general anesthesia group (GA) ($p < 0.001$ and $p = 0.158$, respectively; Table 4).

At 3 months after surgery, the KPS score was unchanged from the postoperative value in 106 patients (47.1%), had deteriorated in 82 patients (36.4%), and had improved in 37 patients (16.5%) [Table 5]. In the general anesthesia group, the KPS score was unchanged in 94 patients (47.2%), had improved in 25 patients (12.6%), and had deteriorated in 80 patients (40.2%). In the awake craniotomy group, there was no change in KPS score in 12 patients (46.3%), deterioration in 2 patients (7.6%), and improvement in 12 patients (46.1%).

Table 5 Changes of KPS scores.

Postoperative to Preoperative KPS	Control[a] n = 26	AC n = 26	p = 0.009
−40	1 (3.8)	0	
−30	3 (11.5)	0	
−20	3 (11.5)	1 (3.8)	
−10	6 (23.3)	1 (3.8)	
0	11 (42.3)	12 (46.3)	
+10	1 (3.8)	11 (42.3)	
+20	1 (3.8)	1 (3.8)	

Data are reported as number (percentage).

[a] AC cases versus matching case–control, n = 52.

Discussion

Extent of resection

Despite the lack of a randomized clinical trial demonstrating its efficacy, the maximal safe tumor resection is an important factor in the surgical management of newly-diagnosed LGG and HGG. Resection of greater than 78% of the contrast-enhanced portion of a tumor as seen on MRI is associated with increased survival, and thus the majority of patients with a good functional status and tumors located in non-eloquent brain regions undergo attempted GTR [7].

Although several studies have reported a correlation between survival benefit and recurrent glioblastoma GTR [1,3,8–12], the functional outcomes of the surgery are still unknown. Most surgeons base the decision on the patient's daily performance function, though re-resection has been shown to improve overall survival in some studies. However, a second surgery is associated with increased difficulty and an increased risk of complications, and a report by De Bonis et al. [13] indicated that re-resection may result in a poorer quality of life due to an increase in the morbidity rate. However, in that prior study, intraoperative ultrasound and neuronavigation were used, and such an approach may be associated with greater neurological deficits than awake craniotomy. In our study, the EOR was similar between the general anesthesia group and the awake craniotomy group (94.5% vs. 95.5%, respectively), as was the GTR rate (56.3% vs. 65.4%, respectively), indicating that an equivalent EOR can be achieved with both surgical methods. This result was similar to that of Bloch et al. who reported a GTR rate of 48.6% for new-onset glioblastoma multiforme (GBM) and 53.2% for recurrent GBM [1].

We reviewed recent articles examining the EOR in order to draw comparisons with our results based on similar baseline characteristics, including tumor type (all glioma) and location (supratentorial). Trinh et al. reported a GTR rate of 66.4% for supratentorial gliomas in patients who underwent awake craniotomy [14]. In our study, the overall GTR rate was 57.3%, and the rate in the general anesthesia group and awake craniotomy group was 56.3% and 65.4%, respectively ($p = 0.545$). Two other studies reported GTR rates as high as 80%; however, one study included metastatic and vascular lesions, and the other included metastatic lesions [15,16], and metastatic lesions can be more easily resected due to the clear margin between the lesion and surrounding brain tissues.

Neurological deficits

A meta-analysis by De Witt Hamer et al. reported an early neurological deficit rate of 47.9% and a late neurological deficit rate of 6.4% when glioma resection was performed using stimulation mapping [17]. In our study, the early and late deficit rates were 19.6% and 10.7%, respectively, which were far lower than the rates of 38% and 13% reported by Trinh et al. [14]. This result might be related to a lower frequency of preoperative neurological deficits in our cohort. Taylor and Bernstein reported a morbidity rate of 16.5% in patients who underwent awake craniotomy (which included new postoperative neurological deficits in 13% of patients and permanent deficits in 4.5% of patients) [18]. However, the study included all patients with supratentorial lesions (i.e., intrinsic and extrinsic lesions of the supratentorial compartment) along with non-eloquent-area tumors.

In the current study, among the 199 patients who underwent treatment with general anesthesia craniotomy, 21.6% developed early neurological deficits, with only 11.5% persisting at 3 months after surgery. Of the 26 patients who underwent treatment with awake craniotomy, 3.9% experienced early neurological deficits, with 3.8% persisting at 3 months. These results indicated that general anesthesia craniotomy for glioma resection can result in a higher rate of early neurological deficits ($p = 0.032$), although there was no significant difference between the two groups with regards to late neurologic deficits ($p = 0.231$). The reason for this finding may be the fact that when we were resecting the glioma while the patient was under general anesthesia, we always resected the tumor under navigation guidance, rather than using an intraoperative neuro monitor. Surgeons are often limited by being unwilling to risk damage to more normal neurologic functions, which may lead to a lesser EOR. In our study, there was a trend of an increased EOR in the awake craniotomy group only ($p = 0.06$). Most neurologic deficits in the general anesthesia group were caused by thermal injury by bipolar rather than direct injury to neurons. Thermal injury can cause moderate injury to cells or severe injury causing cell death. Injury to cells may cause cell toxicity, leading to brain swelling. This may explain why, in the 43 patients with early neurologic deficits in the general anesthesia group, almost half recovered.

Neurological performance status

In this study, the preoperative KPS score in the patients undergoing awake craniotomy (preoperative KPS score: 90.77) was no better than that in the patients undergoing surgery under general anesthesia (preoperative KPS score: 91.65); however, the distribution of the postoperative KPS scores differed significantly between groups ($p < 0.001$). Moreover, improvement in KPS score after surgery was obvious only in the awake craniotomy group ($p = 0.158$; $p < 0.001$). Gupta et al. reported similar pre- and postoperative KPS scores (preoperative KPS score: 80.6, postoperative KPS score: 80.8) [19]. The differences in scores between these studies are likely due to the overall patient baseline condition being better in our cohort.

In a series of 65 patients who underwent awake craniotomy, Meyer et al. observed that 71% of their patients improved to a modified Rankin grade of 0 or 1 postoperatively [20]. In the present study, most of the patients returned to their preoperative KPS score after tumor decompression. However, McNamara et al. only included glioblastoma patients, and their reported frequency of Eastern Cooperative Oncology Group (ECOG) score 0–1 was 74.8% preoperatively and 70.1% postoperatively [21]. The pre-vs. postoperative KPS scores we observed in the 225 patients in this study (16.5% improved; 47.1% no change; 36.4% deteriorated) represented advancement over those recorded by Fadul et al. [22] (5% improved; 80% no change; 15% deteriorated) and Sawaya et al. [6] (32% improved; 59% no change; 9% deteriorated). However, in the awake craniotomy group, there was no change in score in 12 patients (46.3%), deterioration in 2 patients (7.6%), and improvement in 12 patients (46.1%). Overall, our results suggested that awake craniotomy for the treatment of recurrent glioma is superior to general anesthesia craniotomy.

Conclusions

Awake craniotomy is a practical and effective surgical approach for supratentorial intrinsic lesions, especially those in/near the eloquent cortex area. This approach allows real-time neurological functional mapping, which minimizes the risk of postoperative neurologic deficits. Furthermore, we also drew the conclusion that awake craniotomy for the treatment of recurrent glioma is an effective and safe method of tumor resection, with significant benefits in terms of general performance postoperatively and neurological outcomes.

Declaration of competing interest

There is no conflict of interests.

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