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CLINICAL STUDY

Awake craniotomy for gliomas involving motor-related areas: classification and function recovery

Shengyu Fang[1,2] · Yiming Li[1] · Yinyan Wang[1] · Zhong Zhang[1] · Tao Jiang[1,2,3]

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Abstract

Purpose Motor mapping with direct cortical stimulation (DCS) is useful for motor function preservation. Nevertheless, many patients still experience postoperative motor dysfunction after motor mapping. This study aimed to provide a classification of gliomas involved in motor-related areas to help understand which types of gliomas are prone to induce postoperative motor impairments.

Methods Sixty-four patients were retrospectively recruited. Based on tumor location, four types of gliomas were identified: (I) precentral gyrus; (II) premotor and/or supplementary motor areas but not invading pre-central gyrus; (III) adjacent to the posterior limb of the internal capsule; and (IV) other supra-tentorial area. The recovery of motor function was evaluated by muscle strength testing before surgery and 3 days, 7 days, 14 days, and 3 months after surgery.

Results Half of the patients experienced postoperative transient motor impairment within a week. Six patients suffered from permanent motor dysfunction, and four of them had type III glioma. Compared with types I and IV, patients with type III gliomas took more than three times as long to recover. Furthermore, patients with types I and II gliomas were more susceptible to preoperative epilepsy than those with types III and IV. There was no difference in postoperative seizure control between the four types.

Conclusions Our classification of gliomas involving motor-related eloquent areas was useful for predicting postoperative motor functional prognosis in patients who underwent motor mapping with DCS. Even if no positive sites were detected, a conservative strategy of tumor resection is recommended in cases that gliomas located close to the posterior limb of the internal capsule.

Keywords Awake craniotomy · Glioma · Motor function · Recovery

Introduction

Gliomas are the most common and fatal primary tumors in the central nervous system [1, 2]. Maximal surgical resection positively affects both progression-free survival and overall survival in patients with hemispheric gliomas [3–7]. For tumors involving the motor-related cortex or subcortical structures, a balance must be struck between maximal tumor resection and preservation of motor function [8].

Awake craniotomy (AC) is a widely used surgical intervention that helps to maximize the extent of resection (EOR) of gliomas located in eloquent regions [9, 10] Previous studies revealed that awake craniotomy with direct cortical stimulation (DCS) is more likely than motor evoked potential under general anesthesia to preserve motor function (Supplemental Figs. 1, 2) [11–13]. However, neurological deficits cannot be completely avoided with the AC procedure, and

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Dr. Yinyan Wang, Zhong Zhang and Tao Jiang were equal corresponding to this manuscript.

✉ Yinyan Wang
tiantanyinyan@126.com

✉ Zhong Zhang
zhangzhong0502@163.com

✉ Tao Jiang
taojiang1964@163.com

Extended author information available on the last page of the article

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the EOR differs among patients. In terms of motor function, based on current protocols of functional monitoring and tumor resection, 13–25% of patients who undergo AC have transient motor dysfunction, and 0–10.9% of patients experienced permanent motor dysfunction [14–17]. The risk factors for permanent postoperative deficits or functional impairments are unclear. Therefore, a classification system for preoperatively evaluating the possibility of neurological deficits is necessary. To date, no such classification system exists to guide neurosurgeons.

Our study aimed to construct a classification system for preoperatively evaluating the risk of motor functional deficits in patients undergoing AC based on tumor locations. Detailed functional changes after AC were compared among different subtypes. We hypothesized that this proposed classification system could improve the management of patients undergoing AC.

Materials and methods

Patients

The current study retrospectively collected data from 64 patients with primary gliomas involving motor-related eloquent regions, who underwent AC from 2017 to 2019 at the Glioma Treatment Center at Beijing Tiantan Hospital. The inclusion criteria were as follows: (1) glioma located in motor-related eloquent areas or subcortical structures; (2) underwent an AC using DCS to identify motor-related structures; (3) age ≥ 18 years; (4) no history of surgical treatment or radiotherapy; and (5) without preoperative paralysis. Ethical approval for this retrospective study was received from the Local Institutional Review Board.

Tumor classification

According to our observation and clinical experience, four sub-types were identified based on tumor location (Figs. 1, 2): (I) tumors that invaded the precentral gyrus; (II) tumors that invaded premotor area and/or supplementary motor areas but did not invade the pre-central gyrus; (III) tumors that invaded or were close to the posterior limb of the internal capsule; (IV) tumors that invaded other supra-tentorial regions. If more than one motor-related area was invaded, the tumor was sequentially classified by numerical order from types I to IV. The tumor location was determined with T2-FLAIR and T1 contrast enhanced images.

Tumors were defined as close to or invading the posterior limb of the internal capsule if the shortest distance from a glioma to the cortical-spine tract at the level of the internal capsule was less than 5 mm based on diffusion tensor imaging. The distance was calculated by the coordinates (Supplemental Material in Part 1).

Awake craniotomy procedure

The AC procedure was performed by one of the authors with more than 15 years of experience in AC. Ojemann stimulators (Radionics, Burlington, Massachusetts) were used for stimulation mapping during AC (intensity 1–4 mA, frequency 60 Hz, square wave, duration 1 s). In addition to identifying the positive sites on the precentral, postcentral, and supplementary motor area, the subcortical structures were also monitored before removing tumors. A positive reaction was defined as the lead hand or finger moving involuntarily when the motor-related structures (primary motor cortex and subcortical structures) were stimulated, or suddenly stopped moving

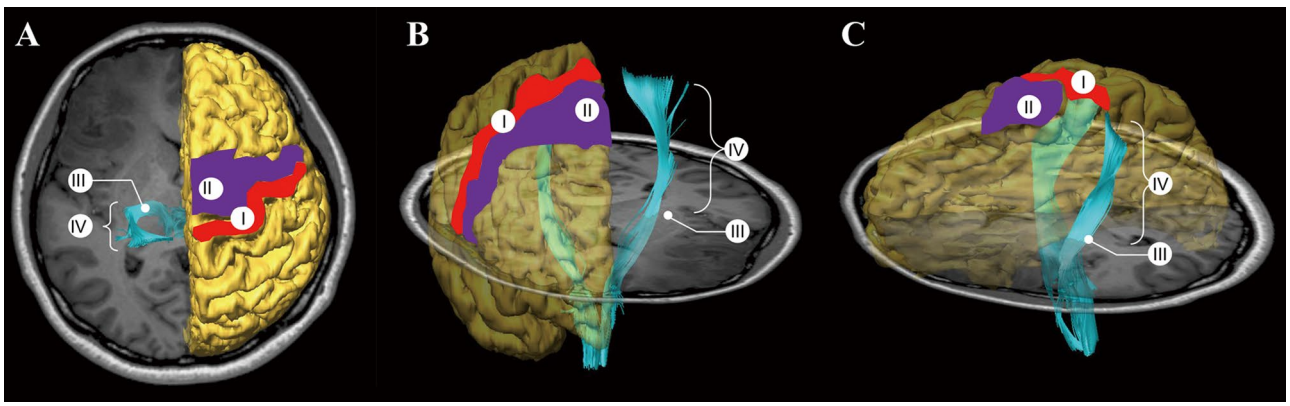

Fig. 1 Classification of motor-related eloquent areas. **a** On axial plane, **b** on coronal plane and **c** on sagittal plane. Type I, tumors that invaded the precentral gyrus, type II, tumors that invaded premotor area and/or supplementary motor areas but did not invade the pre-central gyrus, type III, tumors that invaded or close to the posterior limb of the internal capsule and type IV, tumors that invaded other supra-tentorial regions

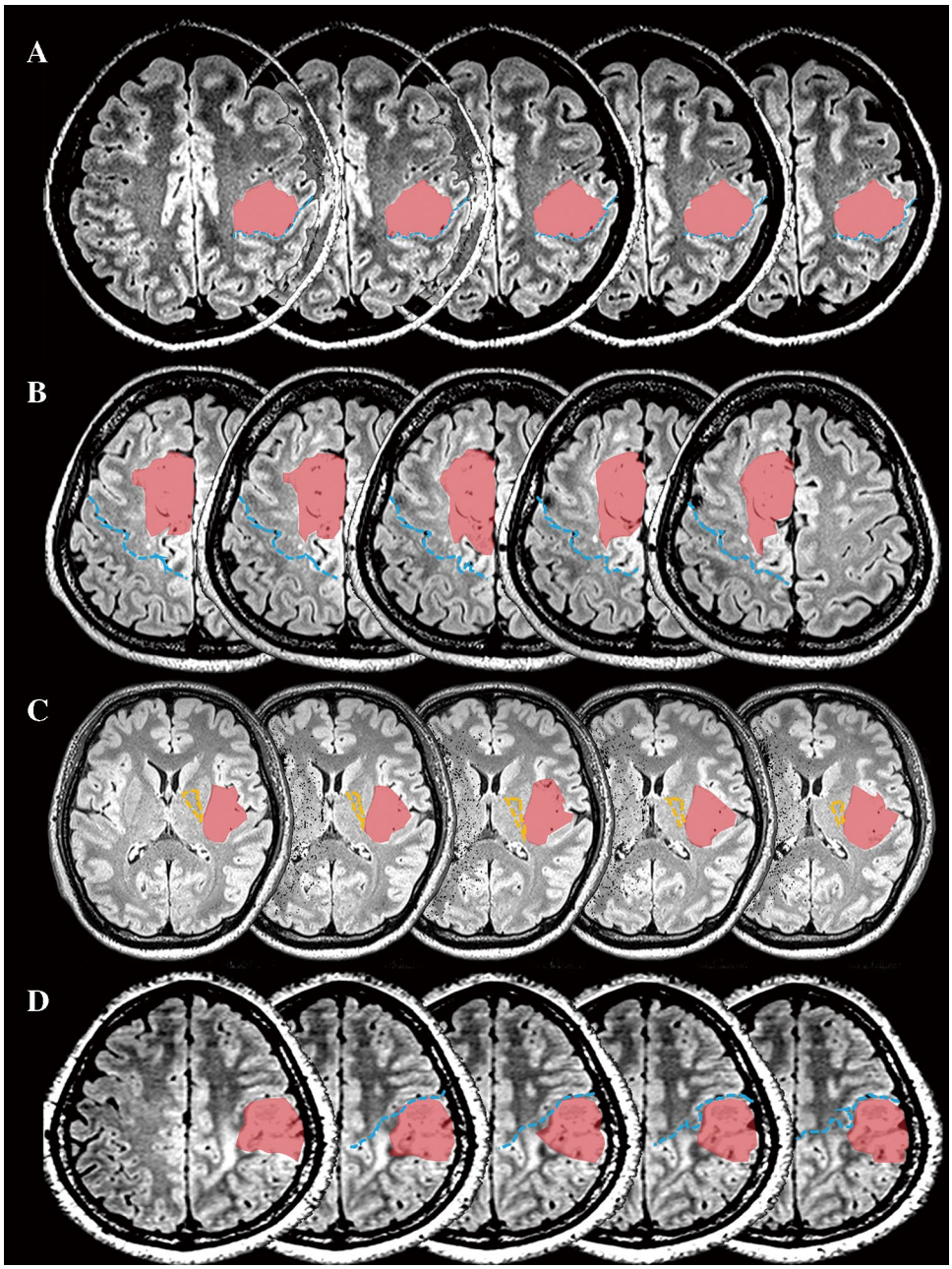

Fig. 2 The examples of four sub-groups on axial plane. **a** Type I, tumors that invaded the precentral gyrus, **b** type II, tumors that invaded premotor area and/or supplementary motor areas but did not invade the pre-central gyrus, **c** type III, tumors that invaded or close to the posterior limb of the internal capsule and **d** type IV, tumors that invaded other supra-tentorial regions. The red region = tumor. The light blue line = the central sulcus. The dotted-yellow region = the posterior limb of the internal capsule

when the supplementary area was stimulated. Each site was stimulated three times. If two or more stimulations induced a positive reaction, the site was defined as a positive site. The positive sites were subsequently labeled by circular markers with diameters of 5 mm. The tumor was resected under the guidance of circular markers and neuro-navigation system (BrainLab®, Munich, Germany). Important blood vessels were preserved using engraving resection.

Data collection

We retrospectively collected patient characteristics from inpatient records, including pathology, the EOR, tumor location, onset of symptoms, seizures, and complications. The muscle strength motor function was evaluated by a neurosurgeon (one of the authors) using the muscle strength test of the UK Medical Research Council before AC, and at 3 days, 7 days, 14 days, and 3 months after AC. Follow-up

information from the period during the recovery of motor function was obtained by telephonic interviews. Based on muscle strength recovery, the patients were divided into recovered and unrecovered groups. The standard of recovery was defined as the postoperative muscle strength of patients recovering to the preoperative status.

Evaluation of tumor volume and extent of resection

A volumetric method was used to calculate tumor volume based on preoperative magnetic resonance imaging (MRI) scans. If the tumor was defined as lower grade glioma (grades II and III), the tumor volume was calculated based on the T2-FLAIR images. In contrast, the tumor volume of the glioblastoma was calculated based on T1-contrast images. Additionally, the EOR was calculated using both preoperative and postoperative MRI scans with the following formula:

$$\mathrm{EOR} = 1 - \frac{\mathrm{Tumorvolume(postoperative)}}{\mathrm{Tumorvolume(preoperative)}}.$$

The EOR was classified into four types: (1) total resection ($\mathrm{EOR} \geq 0.9$); (2) subtotal resection ($0.8 \leq \mathrm{EOR} < 0.9$); (3) partial resection ($\mathrm{EOR} < 0.8$); and (4) cannot be resected ($\mathrm{EOR} = 0$).

Statistical analysis

All statistical analyses were performed with GraphPad Prism 7 software. The Student's *t*-test was used to conduct parametric comparisons between two groups. The Mann–Whitney *U*-test was employed to perform nonparametric comparisons between the two groups. Categorical comparisons between the two groups were conducted using the chi-square test or Fisher's exact test according to data. All the statistics used in the current study were two-tailed. A *p*-value of < 0.05 was considered statistically significant.

Results

A total of 64 right-handed patients (mean age ± SEM = 41.5 ± 1.4 years, 32 males) participated in this study (Table 1). There were 28 patients in type I. In addition, 14 gliomas were determined as type II, 10 as type III, and 12 as type IV. The tumor volume (mean volume ± SEM) was 28.71 ± 4.85 cm^3 in type I, 33.24 ± 4.52 cm^3 in type II, 44.98 ± 6.38 cm^3 in type III, and 44.91 ± 9.37 cm^3 in type IV. There were no differences in tumor volume among these four subtype groups ($p = 0.151$, one-way ANOVA). There were no differences in isocitrate dehydrogenase (IDH) mutation status among these four subtype groups ($p = 0.740$, chi-square test, Supplemental Table 1).

Regarding preoperative motor impairment, there were 7, 3, 2, and 2 patients with type I, II, III, and IV tumors, respectively. No difference in the distribution of patients with preoperative motor impairment was found among these four sub-types ($p = 0.945$, chi-square test).

Table 1 Demographic and clinical characteristics of patients

Demographic and clinical characteristics	Value
Gender	
Male	32
Female	32
Age (years)	41.5 ± 1.4
Handedness	
Right	64
Left	0
Histopathology	
Grade II	
Astrocytoma	13
Oligodendroglioma	22
Grade III	
Anaplastic astrocytoma	8
Anaplastic oligodendroglioma	4
Grade IV	
Glioblastoma	17
Subtype basing on the tumor location	
Type I	28
Type II	14
Type III	10
Type IV	12
Tumor volume (cm^3)	
Type I	28.71 ± 4.85
Type II	33.24 ± 4.52
Type III	44.98 ± 6.38
Type IV	44.91 ± 9.37
Preoperative epilepsy	
Epilepsy	46
Non-epilepsy	18
Preoperative MRC status	
Impaired	14
Healthy	50
Extent of resection	
Total resection	24
Sub-total resection	31
Partial resection	8
Cannot be resected[a]	1

MRC the muscle strength test of the UK Medical Research Council Test

[a]The patient's tumor cannot be resected because the motor-related functional cortex was located on entire tumor by DCS monitoring. Values are means ± standard deviations, unless indicated otherwise

Most gliomas were totally (24/64) or sub-totally (31/64) resected. Eight gliomas were partially resected, and only one glioma was unable to be resected due to functional positive points located on these tumors. In addition, the mean EOR of all patients was 0.85 ± 0.02. No difference of EOR was found among four sub-type groups ($p = 0.462$, ANOVA test).

Proportion of functional motor impairments according to subtypes

Although all patients underwent AC, half of these patients experienced motor impairments or motor dysfunction within 1 week after surgery. In addition, 2 weeks postoperatively, the rate of motor impairment obviously decreased except in type III patients. The proportion of motor impairment was 21.4% type I (6/28), 42.9% type II (6/14), and 16.7% type IV (2/12); and the proportion in type III patients remained high (70%, 7/10). Furthermore, motor function in most patients recovered at 3 months after AC. The proportion of motor impairments was 3.5% for type I (1/28), 7.1% for type II (1/14), 40.0% for type III (4/10), and 0% for type IV (0/12). The rate of permanent motor dysfunction (dysfunction lasting more than 3 months) was 1.5% (1/64).

Prognosis of motor function according to subtype

The prognosis of motor function at 3 days, 7 days, 14 days, and 3 months after AC was investigated in different subtypes (Supplemental Table 2). At 3 and 7 days after AC, no significant differences were observed in the prognosis of motor function between subtypes (chi-square test, $p > 0.05$). At 14 days after AC, type III patients had a poorer prognosis for recovery of motor function than that of types I and IV (I vs. III, $p = 0.016$; IV vs. III, $p = 0.027$, Fisher's exact test, Fig. 3a, b). There was no significant difference in motor functional recovery between types II and III ($p = 0.240$, Fisher's exact test). In addition, there were no significant differences between types I and II ($p = 0.147$, chi-square test) or between types II and IV ($p = 0.216$, Fisher's exact test) patients. Similarly, at 3 months after AC, type III patients had a poorer prognosis for motor functional recovery than that of types I and IV patients (I vs. III, $p = 0.012$; IV vs. III,

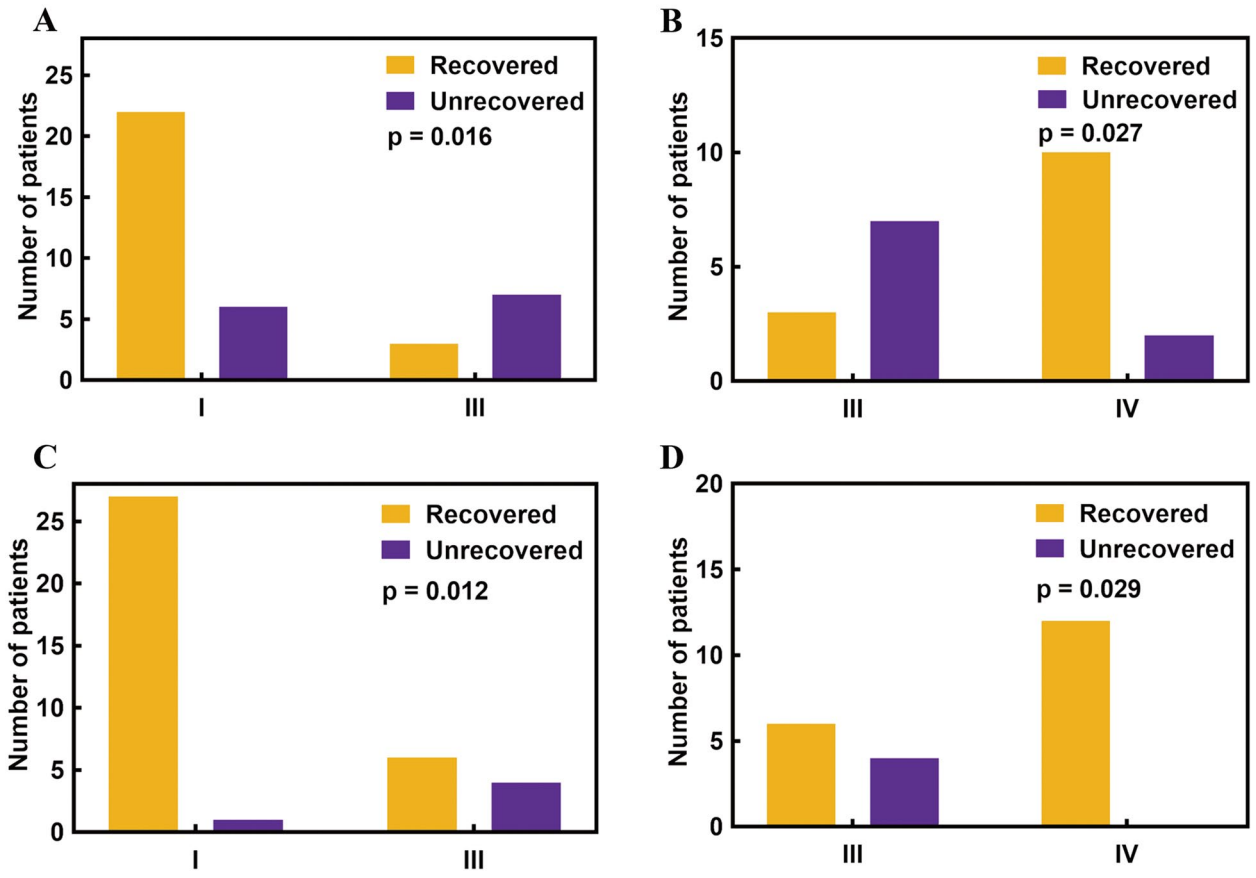

Fig. 3 Differences in prognosis of motor function among subtypes. **a** Between types I and III after awake craniotomy (AC) for 14 days, **b** between types III and IV after AC for 14 days, **c** between types I and III after AC for 3 months and **d** between types III and IV after AC for 3 months

p = 0.029; Fisher's exact test, Fig. 3c, d). There was no difference in functional motor recovery between types II and III (p = 0.122, Fisher's exact test).

Muscle strength recovery time

The muscle strength recovery time differed for the different subtypes (Fig. 4). The mean recovery time was 12.0 ± 3.6 days in type I, 25.9 ± 9.3 days in type II, 47.0 ± 12.2 days in type III, and 10.2 ± 5.6 days in type IV patients. A Mann–Whitney test revealed that compared with that of type I or IV patients, the muscle strength of type III patients required more days to recover to the preoperative status (type I vs. III, p = 0.005; type IV vs. III, p = 0.014). However, there was no significant difference between types II and III patients (p = 0.114).

Other clinical characteristics and prognosis of motor function

There were no histological differences between type I (p = 0.275, chi-square test), II (p = 0.521, chi-square test), and IV patients (p = 0.571, chi-square test, Supplemental Table 3). No difference in EOR was found regardless of the inclusion or exclusion of oligodendroglioma (0.82 ± 0.03 vs. 0.87 ± 0.02, p = 0.07, t-test). There was no difference between the distribution of tumor grades and preoperative motor function impairments (p = 0.062). Moreover, no differences were found between the distribution of tumor grades and postoperative motor function impairments at 3 days (p = 0.723), 7 days (p = 0.957), 14 days (p = 0.684), and 3 months (p = 0.144) after AC.

There were no differences between EOR (total resection and subtotal resection) and recovery of motor function in each subtype at each time of muscle strength evaluation (Supplemental Table 4). Similarly, preoperative motor functional impairments (Supplemental Table 5) and preoperative tumor-related epilepsy (Supplementary Table 6) were not significantly different for recovery of motor function in each subtype.

Preoperative epileptic status according to subtype

In our cohort, there was no difference in the ratio of preoperative epilepsy occurrence between the oligodendroglioma (and anaplastic oligodendroglioma) and astrocytoma (and anaplastic astrocytoma, and glioblastoma, p = 0.944, chi-square test). In addition, the preoperative epileptic status differed among the four subtypes. There were 24 type I patients, 12 type II patients, 5 type III patients, and 5 type IV patients with epileptic history before surgery (Supplementary Table 7). The incidence of epilepsy was 85.7%, 85.7%, 50.0%, and 41.7% in subtypes I, II, III, and IV, respectively. The incidence of epilepsy was more frequent in type I than in type III (p = 0.036, Fisher's exact test) or type IV (p = 0.008, Fisher's exact test) patients. Similarly, patients in the type II group had a higher incidence of epilepsy than those in the type IV group (p = 0.038, Fisher's exact test).

Postoperative epilepsy control according to subtype

In our cohort, with regular antiepileptic drugs, 19 patients had transient seizures, and 5 patients had multiple seizures. In total, 46 patients had a preoperative seizure history, and 89.1% of these patients (41/46) controlled their seizures well and reached Engel class I after tumor resection. Generalized seizures of five patients were controlled unsatisfactorily, and these patients were classified into Engel class II. Although the rate of seizures controlled in type I (89.2%) were lower than that in the three other types (100%, type II; 90%, type III; and 91.7%, type IV), there were no significant differences among these four subtypes (p = 0.09, chi-square test).

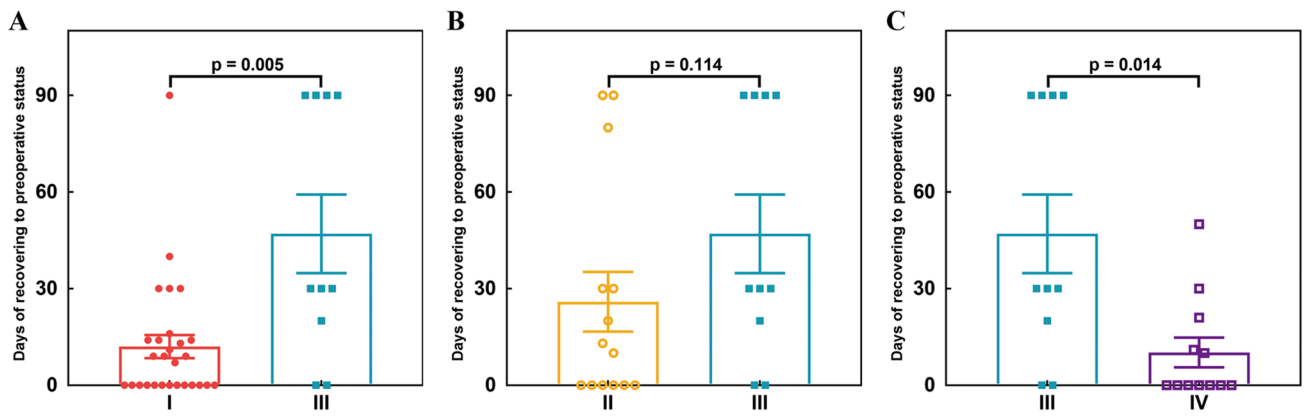

Fig. 4 Muscle strength recovery time is different between type III and the other three types. **a** Types I and III, **b** types II and III and **c** types III and IV. The Mann–Whitney test was used for comparisons

Discussion

AC and intraoperative mapping to guide tumor resection is currently a useful approach for preserving function and increasing quality of life [3]. However, many patients suffer permanent motor dysfunction [14–17], and it remains unclear which patients are more susceptible. Hence, we divided 64 patients who underwent AC and motor functional monitoring into four subtypes based on tumor location. Compared with other sites, tumors involving or close to the posterior limb of the internal capsule tended to result in more permanent motor deficits than those involving other places.

Postoperative functional motor impairments in four subtypes

Our results demonstrated that nearly half of the patients experienced transient motor deficits within 7 days after AC. These results were consistent with previous studies [14, 17]. The transient motor deficits were mainly related to edema or transient retraction injury [17].

The motor dysfunction could possibly be associated with subtypes of gliomas involving the motor area. For patients with type I tumors, motor dysfunction could be caused by direct injury of the primary motor cortex. For patients with type II tumors, motor weakness could be due to postoperative supplementary motor area syndrome, and the motor function may recover several months after surgery. However, the contralesional supplementary motor area needs several months to compensate for the functional motor network through plasticizing interhemispheric connections [18]. Our findings were consisted with this explanation that less than 50% of type II patients were unable to recover to preoperative muscle strength within 2 weeks, and only one patient had permanent impairment of muscle strength at 3 months after AC. Furthermore, for patients with type III tumors, postoperative motor dysfunction may be associated with either fiber injury or ischemia. Although we used DCS to identify the motor pathway, the relevant area is close to the tract, and subtle damage of fibers and small vessels may easily occur. Distinct to the cortex, subcortical pathways are difficult to compensate for, especially pathways responsible for a single function [19]. Hence, our findings indicated that the surgeon should be more cautious and conservative around parts of the tumor that are close to the posterior limb of the internal capsule. In these cases, diffusion tensor imaging and arterial spin labeling imaging would be useful to assess the reason for motor dysfunction.

Preoperative epileptic status in four subtype groups

In this study, preoperative seizures occurred more frequently in type I and II patients. Simultaneously, our findings showed that the frequency of preoperative seizures in type III patients was lower than that in patients with the other three types. These findings were consistent with previous observations that preoperative seizure occurs more frequently in the frontal lobe than in other lobes. This may be because discharges of frontal neurons are likely to extend to subcortical structures (thalamus and basal ganglia) and induce epileptic seizures [20]. Frontal lobe lesions seldom destroy white matter fibers, which contributes to the preservation of pathways of lesion discharge [20, 21]. If the tumor directly invades or is close to the posterior limb of the internal capsule, the corticospinal tracts will be more seriously affected. Hence, the frequency of preoperative seizures in type III patients was the lowest among these four subtypes. In addition, preoperative seizure was a susceptibility factor to induce intraoperative seizure [3, 22]. Hence, our results suggest that taking anti-epileptic drugs to control preoperative seizure is crucial to prevent intraoperative seizures, especially for type I and II patients. Moreover, no significant differences in the rate of postoperative seizure control were observed among these four groups. Postoperative seizure control was mainly related to the EOR [23], and there were no differences in EOR among these four groups.

The value of this classification

This classification indicates that AC is presently a near-perfect approach to protect motor function. However, if tumors invade or are close to the posterior limb of the internal capsule (type III), some patients can suffer from postoperative motor impairments. For type III patients, a conservative strategy of tumor resection should be applied to avoid postoperative impairment of motor function even if no positive site is found. This classification could provide new decisional components that can be preoperatively discussed with patients and their families. In addition, this classification implies that anti-epilepsy drugs should be regularly taken to avoid intraoperative seizures, especially for type I and II patients. Furthermore, this classification helps to select preoperative fMRI techniques that should be applied to accurately identify the hand-motor cortex.

Although the results of the present study are encouraging, a principal limitation that the sample size is small must be addressed. A larger sample size is required for further validation of our results. Additionally, due to the short follow-up time of some patients, analysis of survival information was not possible. In the future, a prospective study evaluating motor functional preservation in patients

undergoing AC should be implemented to verify the value of our classification.

Conclusion

Our classification of motor-related eloquent areas is a useful approach for predicting postoperative motor function and guiding tumor resection. The AC with DCS is a useful approach for preserving motor functions. When the tumor involved the posterior limb of the internal capsule, a conservative strategy of tumor resection should be applied even if no positive site is found by DCS. In addition, if gliomas grow in the motor-related cortex, an antiepileptic drug should be administered to prevent a preoperative or intraoperative seizure.

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Author contributions Study concept and design: FSY and LYM. Data acquisition and analysis: FSY and LYM. Statistics/verified analytical method: FSY, LYM, ZZ, and WYY. Writing the first draft: FSY, LYM, and WYY. Supervision: ZZ, WYY, and JT. Read and approved final version: all authors.

Data availability Anonymized data will be available on request.

Compliance with ethical standards

Conflicts of interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Ethics approval Ethical approval for this retrospective study was received from the Local Institutional Review Board

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Affiliations

Shengyu Fang[1,2] · Yiming Li[1] · Yinyan Wang[1] · Zhong Zhang[1] · Tao Jiang[1,2,3]

[1] Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, 119, The Western Road of the Southern 4th Ring Road, Beijing 100070, China

[2] Beijing Neurosurgical Institute, Capital Medical University, Beijing, China

[3] Beijing Institute for Brain Disorders Brain Tumor Center, Beijing, China