Classification of Surgery-Related Language Impairments in Patients with Glioma Based on Tumor Locations

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Research Article

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Abstract

Introduction

Many patients with glioma experience surgery-related language impairment. This study developed a classification system to predict postoperative language prognosis.

Methods

Sixty-eight patients were retrospectively reviewed. Based on their location, tumors were subtyped as follows: I) inferior frontal lobe or precentral gyrus; II) posterior central gyrus or supramarginal gyrus (above the lateral fissure level); III) posterior region of the superior or middle temporal gyri or supramarginal gyrus (below the lateral fissure level); and IV) insular lobe. The distance from the tumor to the superior longitudinal fasciculus/arcuate fasciculus was calculated. The recovery of language function was assessed using the Western Aphasia Battery before surgery, and a comprehensive language test was conducted on the day of surgery; 3, 7, and 14 days later, and 3 months later.

Results

Thirty-three patients experienced transient language impairment within 1 week of surgery. Fourteen patients had permanent language impairment. Type II tumors, shorter distance from the tumor to the posterior superior longitudinal fasciculus/arcuate fasciculus, and isocitrate dehydrogenase mutations were risk factors for surgery-related language impairment. Regarding the presence or absence of permanent surgery-related language impairments, the cut-off distance between the tumor and posterior superior longitudinal fasciculus/arcuate fasciculus was 2.75 mm.

Conclusions

According to our classification, patients with type II tumors had the worst language prognosis and longest recovery time. Our classification, which is based on tumor location, can reliably predict postoperative language status and may be used to guide tumor resection.

Introduction

Gliomas are the most common and lethal type of primary intracranial malignancy [1, 2]. Gross total and supra-total resection of gliomas enhances survival outcomes [3–7]. However, if a glioma infiltrates the language-related cortices or subcortical fibers, there should be a balance between preserving language function and achieving tumor total resection [8].

Awake craniotomy (AC) with functional mapping permits maximal resection and preservation of neurological function [9–11]. Due to the low accuracy of task functional magnetic resonance imaging (MRI) in identifying language-eloquent areas [12], many studies have recommended using AC with direct cortical stimulation (DCS) for language mapping [13, 14]. However, surgery-related language impairment

cannot be avoided during AC [15]. Under current protocols of language mapping and tumor resection, 11.7–54.5% and 1.7–18.2% of patients who underwent AC experienced transient language deficits [16–22] and developed permanent language dysfunction, respectively [16, 17, 20–23]. Furthermore, the risk factors for permanent postoperative language deficit or dysfunction remain unclear.

Recently, we established a classification system for the preoperative assessment of the risk of postoperative motor deficit based on tumor location [24]. We found that tumor location and distance between the glioma and important fibers were associated with functional prognosis. The superior longitudinal fasciculus/arcuate fasciculus [SLF/AF] went throughout the brain and was crucial for maintaining language function [25–27]. Accordingly, a language-recovery classification system based on tumor location and the distance between the glioma and these language-related fibers could help neurosurgeons assess the possibility of surgery-related language impairment before AC. Therefore, we developed a classification system based on tumor location and the distance between the tumor and language-related fasciculi to predict the risk of language deficits in patients undergoing AC.

Methods

Patients

Retrospective data were collected from 68 patients with gliomas in language-related areas who were treated via AC from January 2017 to October 2020 at Beijing Tiantan Hospital. The inclusion criteria were as follows: (a) glioma located in language-related cortices or subcortical fibers, (b) use of DCS to identify language-related structures, (c) patients aged > 18 years, (d) primary glioma, and (e) ability to complete a picture-naming task. This retrospective study was approved by the Institutional Review Board of Beijing Tiantan Hospital. All participants provided informed written consent before data acquisition.

Classification

Based on tumor location, four tumor subtypes were identified (Figs. 1): (I) tumors invading the inferior frontal lobe (classical Broca's area) or precentral gyrus, (II) tumors invading the posterior central gyrus or supramarginal gyrus (above the lateral fissure level), (III) tumors invading the posterior region of the superior or middle temporal gyri (classical Wernicke's area) or the supramarginal gyrus (below the lateral fissure level), and (IV) tumors mainly invading the insular lobe. When more than one language-related area was invaded, the tumor was classified as type IV, if the insular lobe was also invaded. Otherwise, the tumor was classified according to the area with the greatest tumor invasion. Tumor location was determined using T2-fluid-attenuated inversion recovery (FLAIR) and T1 contrast-enhanced images.

Distance calculation

Using a neuronavigation system (BrainLab®, Feldkirchen, Germany), the shortest distance from the region of tumor resection to the margin of the SLF/AF was measured. The SLF/AF was divided into

anterior, posterior, and inferior SLF/AF based on the coronal plane of the central sulcus and axial plane of the lateral fissure (Fig. 1C).

To identify the region of tumor resection, T2-FLAIR images were acquired within 72 h after surgery. Moreover, to track the SLF/AF distribution, diffusion tensor images were acquired preoperatively. The parameters and regions of interest of the diffusion tensor images are shown in supplementary materials.

Procedure of awake craniotomy

All ACs were performed by one of the authors with over 15 years of experience with AC. The procedure of AC was similar to our previous study.[24] The detailed information was shown in the supplementary materials.

Tumor volume and extent of tumor resection

We used a volumetric measurement to calculate tumor volume. If a tumor was not diagnosed as a glioblastoma, we calculated its volume and the extent of tumor resection (EOR) based on T2-FLAIR images. Otherwise, we calculated tumor volumes and the EOR of glioblastomas based on T1-contrast images. The formula for EOR calculation was as follows [24]:

$$\text{EOR} = 1 - \frac{\text{Tumor volume (postoperative)}}{\text{Tumor volume (preoperative)}}$$

EOR was defined as follows: (1) total resection, $\text{EOR} = 1$; (2) subtotal resection, $0.8 \leq \text{EOR} < 1$; and (3) partial resection, $\text{EOR} < 0.8$.

Data collection

From inpatient records, we collected patient characteristics data. Patients completed a Western Aphasia Battery test before AC. Comprehensive assessments were also conducted by a neurosurgeon (one of the authors) to evaluate language recovery before AC, on the day of tumor resection, on postoperative days 3 and 14, and 3 months after surgery. Details of the comprehensive assessment are provided as supplementary materials. (Table 1).

Table 1
Comprehensive language assessment of language deficit

Grade	Performance	Categories criteria
0	Severe language dysfunction such as dysphonia or comprehension disorder	Unpronounceable and unable to understand and express at all
1	Pronounceable but with mixed aphasia	Only can pronounce but unable to speak a whole word and cannot express their meanings at all
2	Expressive or receptive aphasia	Unable to finish picture naming task, and unable to speak a whole sentence or to accurately express their meanings
3	Anomic aphasia or incomplete expressive or receptive aphasia	Difficult to name pictures correctly but can tell the usage of things in pictures. Or when naming some pictures, speech arrest or unable to correctly speak as the sentence structure that the task asked
4	Without aphasia but with speech slow or incomplete anomia	Correctly naming 30 pictures but spoke slowly when named some pictures
5	Without any language deficit	Correctly and fluently naming 30 pictures

Follow-up information about language functional recovery was obtained by telephone interviews (once a month). Based on their preoperative and 3-month postoperative language status, the patients were divided into a surgery-related impairment group and a non-surgery-related impairment group. Patients were allotted to the surgery-related impairment group if their 3-month postoperative degree of language impairment was worse than the preoperative degree of impairment.

Statistical analyses

All statistical analyses were performed using SPSS 19 software (Microsoft®, IBM). Based on the type of data, Student's *t*-test, Mann–Whitney *U*-test, chi-squared test, or Fisher's exact test and one-way analysis of variance (ANOVA) were used for analysis. If results showed significant differences between the four subtypes, Bonferroni correction was applied as a post-hoc test. Moreover, we used clinical information and distance information to perform binary logistic regression analysis (method: backward elimination). Additionally, Pearson's correlation was used to identify the association between recovery time and distance from the tumor to the SLF/AF. Furthermore, the receipt of curve analysis was applied to obtain the cut-off value of the distance, which could induce surgery-related language impairment.

Results

Clinical information

All of 68 patients (age, mean $\pm$ standard mean deviation [SEM] = 43.5 ± 1.3 y, 30 males, right-handed) were reviewed in this study (Table 2, Figures S1 and S2). No differences were found in tumor volume, the proportion of biomarkers, and EOR. (Tables S1 and S2). There were 21 patients with preoperative language impairment. Although they had some language deficits, all enrolled patients enabled to finish the task of picture naming during AC. The EOR of all patients was 0.95 ± 0.01 (mean $\pm$ SEM). The proportion of EOR was not different among the four subtypes ($p = 0.391$, ANOVA test).

Table 2
Demographic and clinical characteristics of patients

Demographic and clinical characteristics	Value
Gender	30
Male	38
Female	
Age (y)*	43.5 ± 1.3
Handedness	68
Right	0
Left	
Histopathology	27
Grade II	23
Astrocytoma	2
Oligodendroglioma	3
Grade III	13
Anaplastic astrocytoma	
Anaplastic oligodendroglioma	
Grade IV	
Glioblastoma	
Subtype basing on the Tumor Location	17
Type I	15
Type II	18
Type III	18
Type IV	
Tumor Volume (cm³)*	20.54 ± 3.04
Type I	29.81 ± 4.05
Type II	32.87 ± 7.38
Type III	38.01 ± 6.00
Type IV	

* Values are means ± standard mean deviations.

Demographic and clinical characteristics	Value
Preoperative Epilepsy	40
Epilepsy	28
Non-epilepsy	
Preoperative language impairments	21
Impaired	47
Healthy	
Extent of resection	40
Total resection	26
Sub-total resection	2
Partial resection	
* Values are means $\pm$ standard mean deviations.	

Distribution of postoperative language status in different time points

On the day of tumor resection, the language function of 25 patients (36.8%) weakened and 13 patients (19.1%) strengthened. While, 33 patients (48.5%) experienced language dysfunction at the postoperative day 3. Moreover, postoperative day 14, the ratio of language impairment obviously decreased except the patients in types II and IV. The proportion of language impairment in type II and type IV remained high and were respectively 60.0% (9/15) and 44.4% (8/18). In addition, the language function in most patients recovered better than preoperative status at 3 months in postoperation. If the language function of patients was equal to or better than preoperative status on the day of tumor resection, their function will be bound to recover within 3 months.

Prognosis of language function

On the day of tumor resection and postoperative day 14, the patients in type II and type IV had a worse prognosis for language functions than that of type I and type III ($p = 0.012$ and $p = 0.018$, Fisher's exact test), but these differences were not significant by Bonferroni correcting. Moreover, at 3 months after surgery, type II and type IV patients had a significantly worse prognosis for language functional recovery than that of type I and type III patients ($p = 0.008$, post-hoc test with Bonferroni correction).

Risk factors of surgical-related language impairments

The results of logistic regression indicated that IDH wildtype ($p = 0.044$, hazard ratio = 0.033, 95% confidence interval [CI] = 0.001 to 0.909), higher distance from tumor to SLF/AF ($p = 0.005$, hazard ratio =

0.573, 95% CI = 0.388 to 0.846), and non-type II tumor ($p = 0.012$, hazard ratio = 0.020, 95% CI = 0.001 to 0.428) were individual favorable factors of patients without surgical-related language impairments.

Recovery time of language function

Recovery time of language function differed for the different subtypes (Fig. 2). The mean time of language recovery was 12, 45, 12, and 26 days from type I to IV, respectively. Compared with that of type I or III, the language function of the patients in type II and type IV required more time to recover equal to or better than preoperative status ($p = 0.004$, one-way ANOVA test). After post-hoc test with bonferroni correction, the recovery time in type II was significant longer than type I ($p = 0.028$, 95% CI = 2.44 to 64.25) and type III ($p = 0.025$, 95% CI = 2.74 to 63.02). However, there was no difference between type II and IV in recover time ($p = 0.680$, 95% CI = -12.52 to 48.49).

The correlation between recover time and the shortest distance from SLF/AF to tumor

Twenty-one gliomas were closest to posterior SLF/AF. The number of patients was 0, 14, 3, and 4 from type I to IV, respectively. The mean distance from tumor to posterior SLF/AF was 3.20 mm. There were 9 patients that their language functions were weaker than preoperative status after AC in 3 months. A significant correlation between recovery time and distance from tumor to posterior SLF/AF was found ($r^2 = 0.7393$, $p < 0.0001$, Fig. 3A).

Cut-off value of distance from posterior SLF/AF and glioma for resulting in postoperative unrecovered language function

The cut-off value of the shortest distance from posterior SLF/AF to glioma for resulting in postoperative unrecovered language function was 2.75 mm (sensitivity % = 81.82, 95% CI = 48.22–97.72%; specificity % = 90.91, 95% CI = 58.72–99.77%, $p = 0.0014$). The accuracy under curve was 0.901 (Fig. 3B).

Other clinical characteristics and prognosis of language function

No difference was found between EOR (total or subtotal resection) and ratio of recovery among four subtypes at each time point of language evaluation ($p > 0.05$, Table S3). Moreover, no difference was found of the proportion of preoperative language deficits (Table S4) and preoperative glioma-related epilepsy (GRE, Table S5) for ratio of recovery in four subtypes at each time of language functional evaluation.

Intraoperative stimulate-induced epilepsy

There were 19 patients experienced ISE (27.9%, 19/68). All ISEs enable to be controlled by iced Ringer's solution. A significant different distribution of ISE occurring in the four subtypes was found that the ISE

more easily occurred in type IV than other three subtypes ($p = 0.006$, Chi-square test with bonferroni correction).

Discussion

Language mapping during AC to guide tumor resection is a widespread approach for preserving language function while achieving maximal tumor resection and improving the postoperative quality of life [15]. Even with the most efficient approach, many patients experience permanent partial or total language dysfunction following AC [16, 17, 20–23], and it remains unclear which patients are more susceptible to surgery-related language impairments. We found that of the four subtypes, type II tumors and tumors that were close to the posterior SLF/AF were most likely to result in permanent language impairment postoperatively.

Key time point for predicting the postoperative language status

In this study, we defined permanent postoperative language impairment as impairment that remained at the 3-month follow-up, based on previous related studies [28–30]. Transient language impairment is a common complication after AC [15]. In this study, the percentage of patients who had a transient language deficit is consistent with those of previous studies [16, 18, 20]. Moreover, the number of patients with transient language deficits gradually increased within the first 3 days after AC and subsequently decreased after the third day following AC. The transient language deficits may be associated with edema or a transient retraction injury [31]. The time of peritumoral edema onset was significantly short to induce functional impairment on the day of tumor resection [32–34] in cases of worse postoperative language function compared with the preoperative status. The presence of new-onset infarctions was another reason for postoperative language impairment. In this study, no patient exhibited new-onset infarction, based on postoperative MRI performed within 72 h after surgery. To avoid new brain infarctions, we applied pledgets soaked in papaverine to the drainage vessels in some patients, as recommended by Berger et al. [35]. Hence, language function was damaged during AC in these patients. All patients who did not experience language impairment on the day of tumor resection recovered their language function. However, over 50% of patients who experienced language impairment on the day of tumor resection did not recover after 3 postoperative months. Thus, the key time point to predict long-term language prognosis is the day of tumor resection. If language deficit is detected on the day of tumor resection, systemic rehabilitation training [36, 37] for language function should be implemented to accelerate patient recovery.

Risk factors associated with permanent surgery-related language impairments

In this study, type II tumors, shorter distance between the glioma and the SLF/AF, and IDH mutation were negative factors in patients with surgery-related language impairment.

Type II tumors were associated with the worst language prognosis and longest recovery time, which could be due to two reasons. First, compared with the anterior and inferior SLF/AF, the posterior SLF/AF has the lowest capacity to reorganize and compensate for damaged functions [38]. This vulnerability of the anterior and inferior SLF/AF could be compensated by the actions of the uncinate fasciculus, inferior longitudinal fasciculus, and inferior frontal-occipital fasciculus [39, 40]. Because type II tumors are close to or directly invaded the posterior SLF/AF, language impairment easily results when the posterior SLF/AF is accidentally transected during tumor resection. Second, the sensitivity of the bipolar electrical stimulator for subcortical structure identification is not as high as that for cortical identification [41]. This phenomenon was also identified in a previous study on motor-related subcortical structure mapping [24]. Regarding the regions of tumor resection in language-eloquent areas, the recommended safety region for tumor resection is > 5 mm from positive sites [42, 43]. However, the diameter of the bipolar stimulator is 5 mm, and the effective stimulating depth is 2.5 mm (Figure S3). Hence, even if we identify positive sites on the SLF/AF with a bipolar stimulator, the EOR exceeds the safety margin. This could explain why shorter distance from the tumor to the SLF/AF was a risk factor.

Moreover, we did not expect that IDH mutation would be unfavorably associated with surgery-related language impairment. In previous studies, IDH mutation was considered a favorable factor for total resection [44, 45]. However, the mutation was not beneficial for subcortical fiber protection, such as in the removal of type II tumors under the current and standardized subcortical stimulation protocol (the reasons are described above). Regarding gliomas with IDH mutations, although many studies indicate the associated benefits of longer survival outcomes after gross total resection [45–47], the focus should be on the preservation of language function in cases where the tumor has invaded the posterior SLF/AF.

Furthermore, patients with type IV tumors required longer time for language recovery than those with types I and III. This finding indicates that transcortical resection for insular gliomas may have more serious postoperative complications than cortical glioma resection. However, no difference in the ratio of permanent language deficit was found between types I, III, and IV, supporting the notion that transcortical insular glioma resection via AC and language mapping is a safe and reliable approach [48, 49].

Intraoperative epileptic status in the four tumor subtype groups

We found that patients with types I and IV tumors were susceptible to ISE during functional mapping. Our findings are consistent with those of a previous study that demonstrated that the occurrence of ISE was related to tumor location in the frontal lobe [30]. For type IV tumors, all insular gliomas were removed by transcortical resection, and most of the removed cortices were taken from the frontal lobe. This could explain why patients with type IV tumors were significantly more susceptible to ISE. Therefore, for types I and IV, we recommend caution when increasing stimulation intensity during functional mapping and the administration of anti-epilepsy drugs [30] before AC to avoid ISE.

Value of our language recovery classification

Our classification method revealed that AC is the optimal approach to preserve language function. However, if tumors have invaded the posterior central gyrus or supramarginal gyrus (above the lateral fissure level) and are close to the posterior SLF/AF (within 2.75 mm), there is an increased risk of postoperative permanent language impairment. Conservative tumor resection under a neuronavigation guiding system should be performed in patients with type II tumors to avoid postoperative language impairment. Moreover, our classification provides a new preoperative decision component that could help patients and their families better understand the risk of language deficit and possible surgical outcomes. Additionally, our classification suggests that anti-epilepsy drugs should be regularly administered to patients with brain tumors to avoid ISE.

Conclusions

Our classification based on tumor location can sufficiently predict postoperative language recovery and is useful for guiding tumor resection. Our study has three significant findings: (1) of the four subtypes, type II tumors had the worst language prognosis and were associated with the longest recovery time; (2) if the distance from the tumor to the posterior SLF/AF is < 2.75 mm, the patient is likely to experience language impairment post-surgically; and (3) the language status of patients on the day of tumor resection played a key role in predicting the long-term language-related prognosis of patients after AC.

Declarations

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Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material

Anonymized data will be made available on request.

Authors' contributions

Study concept and design: Shengyu Fang, Yuchao Liang, and Lianwang, Li

Data acquisition and analysis: Shengyu Fang, Yuchao Liang, and Lianwang Li

Statistical analyses/verified the analytical method: Shengyu Fang, Yuchao Liang, and Yinyan Wang

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Read and approved final version: All authors.

Ethics approval

This study was approved by the IRB of Beijing Tiantan Hospital

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Figures

Figure 1

Classification of language-related areas based on tumor locations (types I–IV). (A) Types I–III; (B) type IV; (C) distribution of superior longitudinal fasciculus/arcuate fasciculus (SLF/AF), the dark orange part = anterior SLF/AF, the light orange part = posterior SLF/AF, and the green part = inferior SLF/AF; and (D) distribution of four subtypes and superior longitudinal fasciculus/arcuate fasciculus

Figure 2

Language recovery time was different among the four subtypes. The label “*” indicates that the compared results were significant with one-way analysis of variance test and simultaneously significant with post-hoc tests after Bonferroni correction

Figure 3

(A) The correlation results of the distance from the tumor to posterior superior longitude fasciculus/arcuate fasciculus. (B) The cut-off value result of distance from the tumor to posterior superior longitude fasciculus/arcuate fasciculus

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