

Original Investigation

DTI-Based Neuronavigation Guided Eloquent Area Glioma Resection with Awake Craniotomy: Supra-Functional Resection of Eloquent Area Gliomas

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This study has been presented at the 32nd Annual Scientific Congress of Turkish Neurosurgical Society between 20 and 24 April 2018 at Antalya, Turkey and 18th European Congress of Neurosurgery between 21 and 25 October 2018 at Brussels, Belgium.

Corresponding author: Ali AKAY ✉ dr.aliakay@gmail.com**ABSTRACT**

AIM: To present an overview of our awake craniotomy practices performed with complementary use of diffusion tensor imaging (DTI)-based neuronavigation (DTI-bN) and cortical-subcortical electrical stimulation for glioma resection located in eloquent areas, and the clinical outcomes of these practices regarding neurological morbidity and residual tumour volume.

MATERIAL and METHODS: This study was conducted between October 2016 and December 2017 involving 18 cases. The DTI-bN method, in addition to cortical-subcortical stimulation, was done with awake craniotomy. Changes in the neurological status of the patients and results of the method regarding residual tumour volume were recorded. This retrospective study use data obtained from patients' records and radiological examinations.

RESULTS: Of the 18 patients, a gross total resection was performed on nine patients (50%), a near total resection was performed on seven patients (38.8%) and a subtotal resection was performed on two patients (11.1%). Intraoperative neurological deterioration was observed in 14 of 18 patients during their surgical procedures, and neurological examinations in the sixth post-operative month revealed permanent deficits in two patients.

CONCLUSION: This study is one of the rare series to have presented the results of the use DTI-bN method as well as cortical-subcortical stimulation during awake craniotomy, according to literature review. In 88% of cases, tumour resection rates are over 90%.

KEYWORDS: Awake craniotomy, Cortical-subcortical stimulation, DTI-based neuronavigation, Eloquent area glioma, Supra-functional

INTRODUCTION

Maximal surgical resection of gliomas is known to be the most effective method of prolonging the survival time of patients (15,23,24). Several different terminologies have been used to define maximal resection, such as supra-marginal, supra-complete and supra-zonal resection, in all of which the radiological boundary is defined

as the removal of contrasting tissue in high-grade tumours and the removal of hyperintense lesions on T2-weighted sections in low-grade gliomas (7,11,14,21,30).

Supra-total resection was reported to have positive effect on the survival time by inhibiting anaplastic transformations in case of invasions that cannot be radiologically detected at the 20-mm area of the tumour periphery (33). Supra-complete

resection in a single surgical session has become an ideal practice for gliomas with the introduction of intraoperative magnetic resonance imaging (iMRI), although it is not always possible to call it as 'a safe complete resection' for the excision of glial tumours in eloquent areas (8,34). The use of iMRI for these tumours cannot assist surgeons in preserving functional structures while performing complete radiologic resections (6). Thus, currently, the awake craniotomy method is the optimum safe resection method in cases that involved eloquent areas. During awake craniotomy, other methods such as cortical-subcortical stimulation (CSC) and intraoperative neurophysiological monitoring are used to distinguish and map eloquent areas and allow safe resections, although complete resection cannot be achieved in eloquent area-localised gliomas (5,19). Intraoperative neuronavigation, which has gained popularity as a key technology during surgical procedures, has been commonly used in glial tumour surgeries; however, it has potential for errors, e.g. brain shift (9,12,20).

Thus, this study aimed to present an overview of our awake craniotomy practices performed with complementary use of diffusion tensor imaging (DTI)-based neuronavigation (DTI-bN) and CSC for glioma resection located in eloquent areas and to reveal the clinical outcomes of these practices in terms of neurological morbidity and residual tumour volume. Given the difference in other terms –supra-marginal, supra-complete and supra-total resection–used thus far in literature to define the extent of tumour resection, this study used the term 'supra-functional resection' to define the maximal extent of glioma resection that evades permanent, irreversible functional deficits at the expense of temporary functional impairments in patients with eloquent area glioma during awake craniotomy.

■ MATERIAL and METHODS

This study involved initially 20 patients operated on in our clinic between October 2016 and December 2017, with a diagnosis of glial tumour located in, or close to, the eloquent area. During the awake craniotomy, Mayfield skull pin fixation was used together with CSC to prevent DTI-bN-tract damage. Given the deviations in the navigation system due to poor input data quality during surgical operations, two patients were excluded from this study. The post-operative neurological status of all patients was recorded at post-operative day 1, week 1, month 3 and month 6 and retrospectively studied to present the results of tumour resections and the residual tumour volume of the eloquent area-located lesions.

Radiology

Pre-operative radiological examination

Contrast- and non-contrast-enhanced MRIs and functional and DTI examinations were made with 1 mm sections on the day before the operation. Pre-operative MR images (T2-weighted and contrast-enhanced T1 imaging) and DTI-MR images were fused on the S7 Medtronic Stealth Station and used as guides during the excision (Figure 1A).

Post-operative radiological examination

All patients underwent a post-operative control cranial MRI within 72 hours (Figure 1D).

Results of the pre-operative and post-operative cranial MRI were examined, and residual tumour volumes were calculated by neuroradiologists. In these calculations, T2-weighted fluid attenuation inversion recovery images were used for low-grade glioma and contrast-enhanced T1-weighted images were used for high-grade glioma to determine the tumour boundaries. The OsiriX MD software was used for the volumetric calculation.

Surgical Procedure

Following the placement of skull pin fixation and insertion of the urine catheter and the scalp block with mild sedation, the entire surgical procedure was performed while the patients were fully awake. A local anaesthetic agent was applied to the incision line after the optimum incision boundaries were drawn on the skin based on the navigation.

The awake craniotomy method which has been performed in our clinic with the guidance of mapping by CSC with skull pin fixation has been reported in detail in a previous article (1). Eloquent areas were mapped via cortical stimulation, and a safe cortical incision was made with a rigid DTI-bN (Figure 1G). The bipolar cautery used during the excision of the glial tumours was introduced into the navigation system and used as a navigation probe (Figure 1H). During awake craniotomy, 50–80 Hz, 0.5 msec biphasic waves were used for direct stimulation (Ojeman Cortical Stimulator, OCS2 Integra Neurosciences, Plainsboro, NJ). The electrical current was increased from 1 mA to 3–5 mA with 0.5 mA steps. White matter fibres (corticospinal tracts, arcuate fasciculus, uncinate fasciculus, superior longitudinal fasciculus, middle longitudinal fasciculus, inferior longitudinal fasciculus, frontal aslant tracts) adjacent to the lesion were identified in the intraoperative DTI-bN programme (Figure 1B, C, E, F). Tumour excision was initiated at the safe tumour boundaries without neighbouring tracts, and any neurological changes observed during surgical excisions were shared with the surgical team. When neurological deteriorations associated with the excision of lesions adjacent to tracts were detected, resections were stopped and interventions were directed accordingly (Figure 1I).

Deteriorations of speech and motor-sensory function during neurophysiological follow-up and tumour boundaries demonstrated by DTI-bN with a rigid pin fixation were parameters that determined the boundaries of the surgical excision.

■ RESULTS

This study involved 18 patients with functional lesions, including 15 male and three female patients with a median age of 46 (age range, 26–75) years. In all patients, the left hemisphere was dominant. Table I presents demographic characteristics, symptoms that led to the diagnosis, and radiologic and functional tumor locations.

Intraoperative Neurological Deficits

Neurological examination of patients revealed pre-operative neurological deficits in four of 18 patients involved in the study and no such deficits in the remaining 14 patients. Neurological

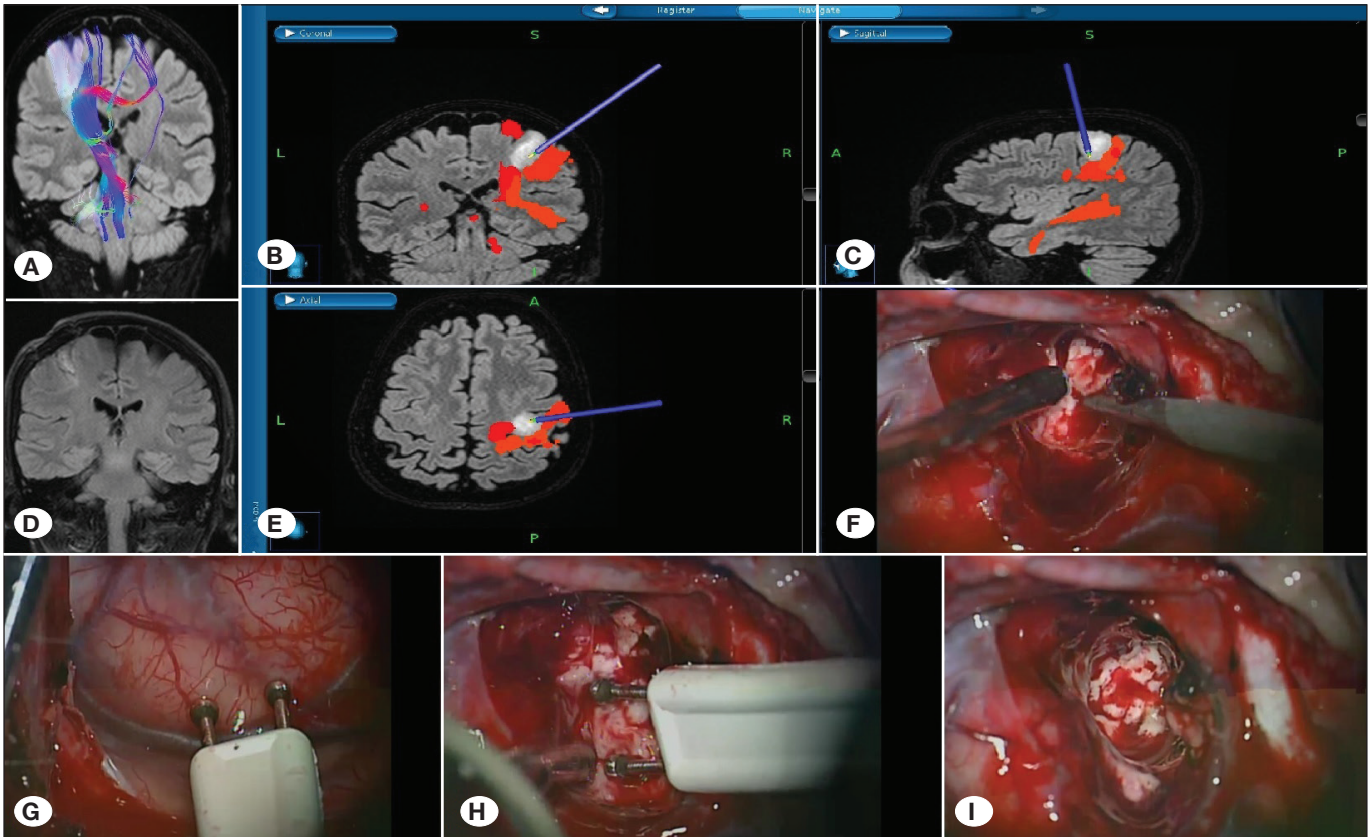


Figure 1: Precentral gyrus oligodendroglioma resection. **A)** Pre-operative diffusion tensor images showing relations between corticospinal tracts and glioma. Intraoperative neuronavigation images (**B:** coronal; **C:** sagittal) showing the position of the navigation probe with the resection border and corticospinal tracts. **D)** Post-operative fluid attenuation inversion recovery T1-weighted magnetic resonance imaging showing gross total resection. **E)** Axial intraoperative neuronavigation images showing the position of the navigation probe, resection border and corticospinal tracts. **F)** Simultaneous intraoperative microscope image of intraoperative navigation image shown in Figure 1E. **G)** Intraoperative microscope photography showing cortical stimulation by bipolar stimulation. **H)** Intraoperative microscope photography showing subcortical stimulation by bipolar stimulation. **I)** Intraoperative microscope photography showing cavity after tumour removal.

deterioration was recorded during surgeries of three of the four patients with a pre-operative deficit: worsening hemiplegia and aphasia (1), monoplegia (1) and severe hemiparesis (1), while no change was intraoperatively observed in the level of the neurological deficit in the remaining one patient.

Neurological deficits developed at various levels during surgery in 11 of these 14 patients, who had no pre-operative neurological deficits, i.e. hemiparesis (6), hemiparesis with aphasia (4) and monoparesis (1), while the remaining three patients maintained their neurological status.

Intraoperative Complications

None of the patients developed any complications such as vascular injury, post-operative bleeding or infection due to the surgical procedure. Although 1000 mg of levetiracetam was infused intravenously for each patient during skin incision, intraoperative focal seizures were observed in three patients during CSC, i.e. focal seizure in the upper extremities in two patients and facial seizure in one patient. Patients with focal seizure in upper extremities developed Todd's paresis. The resection was terminated in one of the two patients having

paresis, as the seizure occurred almost at the end of the tumour resection during the CSC in that patient. In the second patient with focal seizure in upper extremities, Todd's paresis developed after motor cortex mapping was completed, but with the assumption that the limits of tumour resection defined by DTI-bN were valid, the surgery continued and resection was completed. According to the post-operative residual tumour volume results, a near total tumour resection was performed in patient 1, whereas a gross total resection (GTR) was achieved in patient 2.

Surgical Resection Rates

Of the 18 patients in this study, GTR was performed in nine patients (50.0%), near total resection in seven patients (38.9%) and subtotal resection in two patients (11.1%) (Table II). The histopathological distribution of the gliomas were oligodendroglioma in six patients, glioblastoma (GBM) in five patients, anaplastic oligodendroglioma in three patients, astrocytomas in three patients and pilocytic astrocytomas in one patient. Table II presents numbers and rates of surgical resection according to glioma grades.

Post-Operative Neurological Follow-Up

Intraoperative neurological deterioration was seen in 14 of 18 patients who underwent glioma resection. In nine of the 11 patients who had no pre-operative neurological deficits

Table I: Data of Patients Who Underwent Suprafunktional Resection (Demographic, Symptom, Functional, Radiological Site)

Demographic Characteristics	
Age, median (range) (years)	46 (26-75)
Male / Female (n)	15/3
Symptoms leading to diagnosis	n (%)
Headache	4 (22.2)
Epileptic seizure	9 (50)
Sensory / motor deficit	4 (22.2)
Cognitive symptom	1 (5.6)
Tumor Location; Functional	n (%)
Right precentral cortex	4 (22.2)
Left precentral cortex	5 (27.8)
Right postcentral cortex	2 (11.1)
Speech area (broca)	3 (16.7)
Right capsula interna	2 (11.1)
Left capsula interna	1 (5.6)
Left postcentral cortex	1 (5.6)
Tumor Location; Radiological	n (%)
Right frontal	6 (33.3)
Left frontal	7 (38.7)
Right parietal-occipital	1 (5.6)
Left temporal-insular	1 (5.6)
Left fronto-temporal-insular	1 (5.6)
Right fronto-bazal-temporal-insular	1 (5.6)
Left temporol-occipital	1 (5.6)

but who had intraoperative neurological deterioration, the neurological deficits were observed to have recovered in post-operative month 1. The neurological deficit of one patient was seen recovered in post-operative month 3. On the contrary, no recovery was observed in the neurological deficit –hemiparesis and aphasia–of the final patient at the post-operative month 6. Compared to their pre-operative status, at the post-operative month 6, recovery was observed in two of the three patients whose pre-operative neurological deficits were worsened intraoperatively. No recovery of neurological deficit was observed in one remaining patient, who had monoparesis in the lower extremities. Table III presents the neurological deficits seen in all patients involved in the current study, along with their pathological diagnoses and recovery times.

Of the nine patients in whom GTR was achieved, five patients were observed to develop intraoperative neurological deficits. The deficits in the four of these five patients recovered within 1 month after surgery, whereas the deficit of the remaining patient became permanent. The patient with permanent deficit was diagnosed with GBM-isocitrate dehydrogenase (IDH) wildtype. Intraoperative neurological deterioration was seen in six of the seven patients who underwent near total resection: neurological deterioration was restored at post-operative month 1 in four patients, and recovery in neurological deterioration was observed at post-operative month 3 and 6 in other two patients, without leaving any permanent deficits. Patients with late recovery were diagnosed with anaplastic oligodendroglioma-IDH mutant (former patient) and GBM-IDH mutant (later patient). Intraoperative deteriorations were seen in both patients who underwent subtotal resection; patient 1 achieved neurological recovery within the first month, while patient 2 still had permanent neurological deficit (Figure 2). Of the 18 patients, surgery-related deficits were observed to have become permanent in two patients (11.1%) at the 6-month follow-up. The patient with pre-operative neurological deficits was one of the two patients who retained their permanent neurological deficits at the 6-month post-operative follow-up. The follow-up period lasted for 6 months following awake craniotomy with an assumption that the post-operative rehabilitation programmes were completed at that time.

DISCUSSION

The awake craniotomy method is preferred for safe resection of tumours that are in close proximity to or within eloquent areas, and intraoperative stimulation, which is used during awake craniotomies, is the main tool for the mapping of

Table II: Numbers and Rates of Surgical Resection According to Glioma Grades

WHO glioma grade (n)	Grosstotal Resection (50.0%)	Neartotal Resection (38.9%)	Subtotal Resection (11.1%)
I (1)	1	0	0
II (8)	3	5	0
III (4)	3	1	0
IV (5)	2	1	2

Table III: Histopathologic Diagnoses of Cases and Per-Op / Intra-Op / Post-Op Neurological Status of Patients

WHO Glioma Grade (n)	Pre-op neurological deficit	Intra-operative neurological deterioration (77.7%)	Post-op day 1 neurological condition	Post-op 1st week neurological condition	Post-op 1st month neurological condition	Post-op 3rd month neurological condition	Post-op 6th month Neurological condition / Surgery-induced permanent deficit
I → (1) Pilocytic astrocytoma → (1)	0	0	1↔	1↔	1↔	1↔	1↔/0
II → (8) Oligodendroglioma → (6) Diffuse astrocytoma → (2)	0	2↔/6↓	8↔	1↑/4↔/3↓	5↑/3↔	8↔	8↔/0
III → (4) Anaplastic oligodendrogliom-IDH mutant → (3) Anaplastic gemistocytic astrocytoma → (1)	2	4↓	2↔/2↓	2↑/2↔	3↑/1↔	4↔	4↔/0
GBM → (5) IDH wild → (4) IDH mutant → (1)	2	1↔/4↓	4↔/1↓	1↑/4↔	5↔/0	1↑/4↔	5↔/2

↑: Neurological deficit recovery, ↔: Neurological conditions table, ↓: Neurological deficit increase, **WHO:** The 2016 World Health Organization Classification of Tumors of the Central Nervous System.

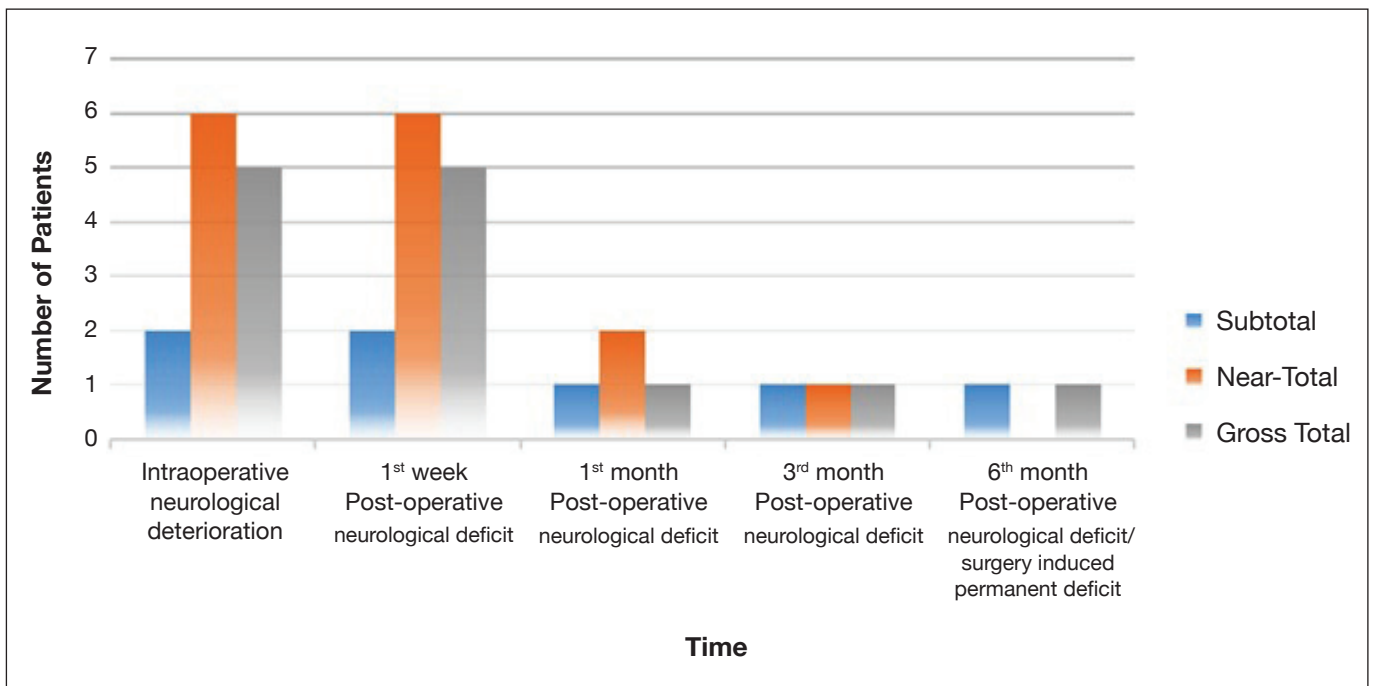


Figure 2: Distribution of the number of patients with neurological deficit according to glioma resection subgroups during follow-up.

eloquent areas. As reported in a meta-analysis, permanent neurological deficits could be prevented by using CSC while the extent of tumour resection is increased particularly in cases with gliomas involving eloquent areas (4).

With this, it is hard to consider GTR or supra-total resection for tumours that involve eloquent areas despite the benefits of functional mapping for partial tumour resection. In this study, we report the use of DTI-bN for tumour resection in eloquent areas and its value for post-operative tumour volume and the occurrence of postoperatively persistent neurological deficits in patients who underwent awake craniotomy with functional mapping. A comparison of the frameless navigation system and frame-based stereotaxy reveals that both provided similar positional accuracy, with errors –usually being clinical or technical in nature–that occur during surgeries performed with neuronavigation (18,20). Leaks of cerebrospinal fluid (CSF) during surgery and other volume-reducing activities such as decompression of cystic masses may lead to a brain shift and a shift of the tumour position, which invalidates the patient-to-image registration (29). Potential sources of technical problems can be listed as low-quality pre-operative surgery images and errors made during the identification of patient data (31). In this study, navigation-related deviations were detected in the pre-operative cranial MRIs of two patients; therefore, those patients were excluded from this study. Additionally, the deviations were attributable to poor data input. In the presence of fast-growing neoplasms, data obtained days and weeks earlier should not be used during surgery. In several studies using data from iMRI examinations for neuronavigation systems, minimising errors that may occur when using such systems was suggested (9,10,12). The images that become invalid because of brain shift due to CSF leak during surgery, or decompression of cystic lesions should be repeated with intraoperative MRI. Further studies have shown that iMRIs contribute to the survival times of patients with gliomas (3,16). In a study of Senft et al., iMRIs have been reported to be superior to neuronavigation regarding complete resection during glioma surgery (26). However, iMRIs is sometimes not practical to use, particularly when using the awake craniotomy method, as there may be problems with the patient being awake, body movements and increased operative duration (13,26).

Moreover, not all operating rooms facilitate iMRIs, which could limit the current experience in awake craniotomy practices. Considering all these, we used DTI-bN during awake craniotomies in this series to minimise errors of shifts that could occur due to intraoperative CSF loss and other volume-reducing activities during glioma resection. In this way, errors related to brain shift were detected through subcortical stimulation, thus reducing the margin of error. While functional MRI reveals cortical functional areas, DTI shows the course of white matter fibre tracts. The use of images that include DTI-derived data in the neuronavigation also helps protect fibre tracts located adjacent to the tumour. The randomised controlled study of Wu et al. showed that DTI-bN reduces the rate of neurological deficits when compared to methods that involved navigation without DTI (32). However, in patients with brain shift, the position of fibre tracts changes with the

positions of other brain structures. Currently, no system has accurately calculated this shift, and the use of subcortical electrical stimulation could be an invaluable help to surgeons performing awake craniotomy. In a study conducted by Zolal et al., the actual localisation of the corticospinal region in 36 patients was predicted through subcortical electrical stimulation of the white matter during brain tumour resection, and a rough estimate of the true localisation of the corticospinal tract can be possible with DTI (35). In general, a response can be obtained by performing stimulation at an 8-mm distance from the corticospinal path predicted by DTI (13). However, the measured tumour-to-track distance with a positive stimulation was reported to be up to 15 mm in case of complementary use of intraoperative tractography and motor evoked potential (MEP) monitoring (17,22). Additionally, conductivities of different brain structures and stimulation parameters are among those factors that affect the accuracy of subcortical mapping (2).

The study by Sollman et al., which was recently published as the first study in relevant literature, has presented the use of DTI-bN with direct electrical stimulation for the resection of highly eloquent gliomas as adjunct to awake craniotomy and analysed the clinical outcomes of this approach (28). The current study reports a series of patients with gliomas located in eloquent areas, and most gliomas were detected to be within and adjacent to the corticospinal tract. Additionally, this study presents the clinical outcomes of the adopted approach regarding the residual tumour volume and the occurrence of surgery-related neurological deficits.

The rate of stimulation-related epileptic seizure in awake craniotomy ranges from 3% to 20% (5,25,27). In the current series, the rate of intraoperative focal epilepsy was 13.3%, although the stimulation current intensity for cortical and subcortical mapping varied from 3 to 5 mA. No generalised epilepsy was observed during surgical interventions. Of two patients with seizure-induced paresis, the resection was discontinued in patient 1, but it was continued in patient 2 since the motor cortex mapping had already been completed. The paresis of patient 1, who had a subcortical stimulation-induced seizure during the resection, recovered within one week, while the paresis of patient 2, which was caused by the seizure that developed during the motor cortex stimulation (motor mapping), recovered within 72 hours postoperatively. Post-operative MRI results of patient 2, who underwent resection within the boundaries defined by the DTI-bN, revealed that GTR was achieved despite the development of Todd's paresis during surgery.

Of the 18 patients included in this series, four patients were diagnosed with GBM-IDH wildtype and one patient was diagnosed with GBM-IDH mutant. Two of the four patients with GBM-IDH wildtype developed surgery-related deficits, and these neurological deficits were observed to have become permanent at the 6-month follow-up, which constitutes 11.1% of the patients involved.

There could be several potential reasons for the occurrence of persistent neurological deficits in patients with GBM-IDH wild type, i.e. plasticity due to rapid tumour progression

did not occur, the size of the peritumoural oedema did not regress after the operation, and there were brain shifts during the excision of cystic and necrotic tumour tissues and damage to the peritumoural region and oedema occurring after brain radiotherapy. Thus, particularly, in high-grade gliomas adjacent to the precentral cortex, aggressive tumour excisions could have a negative effect on the median survival times by increasing the risk of permanent functional deficits. Intraoperative neurological deterioration was seen in six of the eight patients with grade II gliomas, and complete neurological recovery was observed in five patients within the first month and in one patient at the 6-month follow-up. All four patients with gliomas classified as grade III were observed to have intraoperative neurological deterioration, but neurological recovery was observed in three patients within the first month and in the other patient at the end of the sixth month. The neurological recovery rates of patients with grade II and III gliomas were similar. Permanent neurological deficits were not seen in these two patient groups. Of the 12 patients with gliomas (graded as II and III gliomas), GTR was possible in six patients, and a near total resection in the other six patients, and no permanent neurological deficits were identified in this group at the 6-month follow-up (Figure 3). The slow development of the glial tumours with grades II and III, the existence of plasticity and the non-existence of necrotic-cystic areas that may avoid brain shift during tumour excisions are thought to have a significant role in preventing permanent functional impairments caused by tumour excision in this series.

Based on our experience with combined use of DTI-bNof CSC in awake craniotomy, we believe this approach could have positive effects on survival times of patients and their having less surgery-related neurological deficits, particularly when applied to grade II and III functional area gliomas. Long-term follow-ups in future studies will clearly elucidate the effects of this approach on survival rates.

Study Limitations

Despite being one of the rare series reported so far on eloquent area glioma resection with complementary use of DTI-bN and CSC with awake craniotomy, this study has some limitations. First, due to the small patient population, there is no 'stand-alone CSC use with awake craniotomy' group of patients as a control group. Moreover, as stated in the discussion, forming homogeneous experimental and control groups that have the same characteristics in terms of plasticity of the functional area, glioma grade, distance between glioma and functional area could not be possible in a controlled trial with such a limited patient population. Thus, larger studies with a controlled design, which ensures that any difference found between the groups will be independent of any bias—by blinding the patients, investigators and assessors—are required to present findings that will discuss the effectiveness of the aforementioned approach for eloquent area-localised glioma resection.

CONCLUSION

In this study, the term 'supra-functional resection' has been used to define the maximal extent of glioma resection that

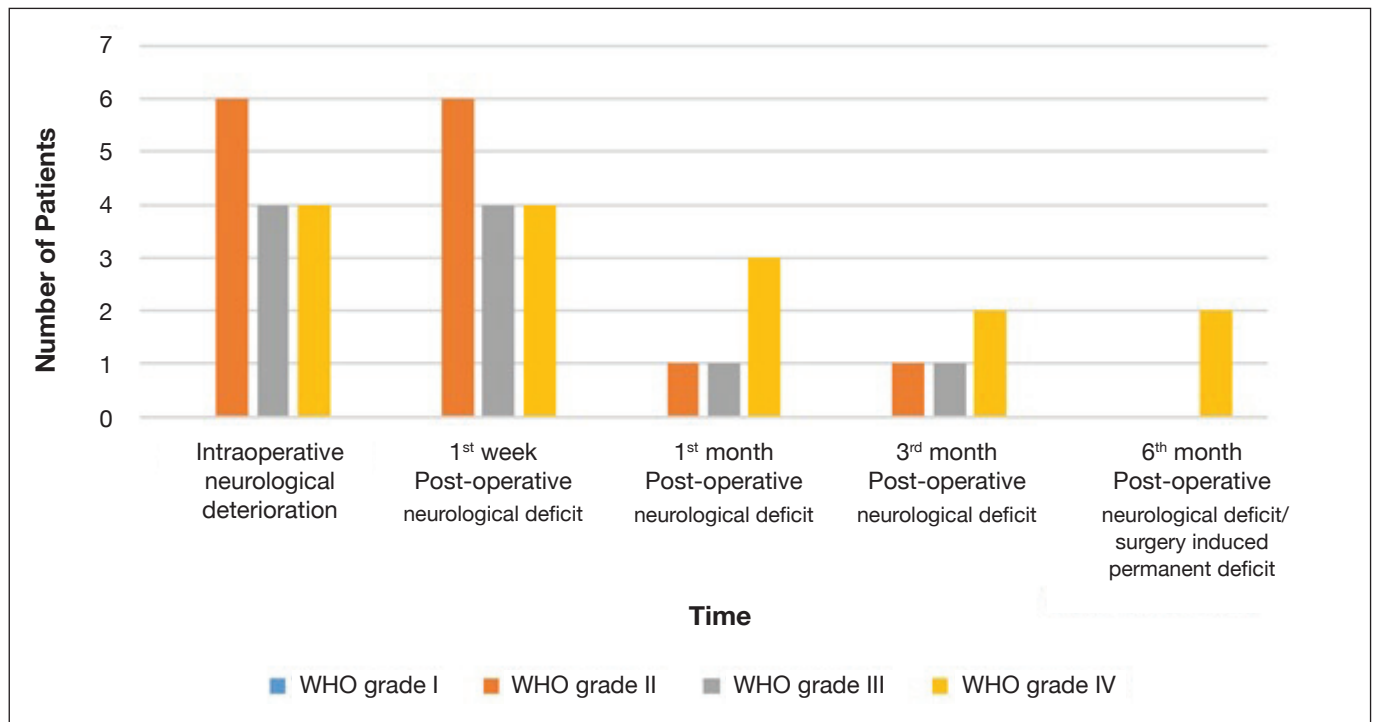


Figure 3: Distribution of the number of patients with neurological deficit according to the World Health Organization grade glioma classification during follow-up.

evades permanent, irreversible neurological deficits at the expense of temporary functional impairments in patients. The combined use of DTI-bNand cortical-subcortical electrical stimulation for these tumours could help preserve functional areas during eloquent area glioma resection, while the damage to white matter fibre tracts and to cortical structures due to brain shift could be kept at a minimum degree with the help of this approach.

Therefore, further studies are needed on multimodal neuroimaging techniques for eloquent area glioma surgery in the setting of awake craniotomy, which will integrate neuronavigational information into the operative workflow to prevent any navigational errors that may lead to permanent functional deficits and provide surgeons with the opportunity for maximised EOR and minimised the risk for surgery-related neurological morbidity.

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