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Supratotal Resection of Diffuse Frontal Lower Grade Gliomas with Awake Brain Mapping, Preserving Motor, Language, and Neurocognitive Functions

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■ OBJECTIVE: **Extended margin tumor resection beyond the abnormal area detected by magnetic resonance imaging, defined as supratotal resection, could improve the outcomes of patients with lower grade gliomas (LGGs). The aim of the present study was to assess the surgical outcomes of awake brain mapping to achieve supratotal resection with determination of the normal brain tissue boundaries beyond the tumor of frontal LGGs, in both dominant and nondominant hemispheres.**

■ METHODS: **We analyzed the data from 9 patients with diffuse frontal LGGs who had undergone supratotal resection with awake surgery from January 2016 to November 2017.**

■ RESULTS: **The frontal aslant tract was identified as the functional boundary in 4 of 5 left frontal tumor cases (80%). Working memory impairments during dorsolateral prefrontal cortex stimulation with digit span and/or visual N-back tasks were detected in all 4 patients (100%) with right-frontal tumor. The neurocognitive outcomes were significantly improved after surgery, as shown by the mean Wechsler adult intelligence scale III scores for verbal intelligence quotient ($P = 0.04$) and verbal comprehension ($P = 0.03$) and the mean Wechsler memory scale-revised scores for generalized memory ($P = 0.04$) and delayed recall ($P = 0.04$).**

■ CONCLUSIONS: **The results of the present study have provided evidence that awake mapping can enable the preservation of higher neurocognitive function, including working memory and spatial cognition in patients with nondominant right frontal tumors. Despite the small number of cases, our findings suggest the surgical benefit of awake surgery for supratotal resection of diffuse frontal LGGs.**

INTRODUCTION

Lower-grade gliomas (LGGs), including the World Health Organization (WHO) classification of grade II and III gliomas, are slow-growing tumors that arise from the supporting glial cells of the central nervous system.[1,2] In particular, isocitrate dehydrogenase (IDH) gene mutations are potential prognostic markers for LGGs and have been included in the updated WHO classification.[3] As previously described,[1,2] diffuse LGGs, including grade II and III gliomas, can be genetically classified into 3 distinct subtypes according to the IDH mutation status and codeletion of chromosome 1p and 19q (1p/19q). Patients with LGGs are often young adults and have a median overall survival (OS) of ≥10 years. Nevertheless, LGGs have been associated with potential features that can lead to inevitable malignant transformation and progression to highly malignant gliomas.[4,5]

Key words
- Awake brain mapping
- Frontal lower grade gliomas
- Neurocognitive function
- Working memory

Abbreviations and Acronyms
DLPFC: dorsolateral prefrontal cortex
EOR: extent of resection
FAB: frontal assessment battery
FAT: frontal aslant tract
IDH: isocitrate dehydrogenase
IFG: inferior frontal gyrus
IFOF: inferior fronto-occipital fasciculus
iMRI: intraoperative magnetic resonance imaging
LGGs: lower grade gliomas
MRI: magnetic resonance imaging
OS: overall survival
SLTA: standard language test of aphasia
WAIS-III: Wechsler adult intelligence scale
WHO: World Health Organization
WMS-R: Wechsler memory scale—revised

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Citation: World Neurosurg. (2018) 119:30-39.
https://doi.org/10.1016/j.wneu.2018.07.193

Journal homepage: www.WORLDNEUROSURGERY.org

Available online: www.sciencedirect.com

Owing to the lack of well-designed randomized controlled clinical trials with adequate follow-up data to account for the longer survival of patients with LGGs, the optimal management of LGGs remains controversial in clinical neuro-oncology regarding surgical and oncological management and the timing of radiotherapy and chemotherapy.[6-9] In addition, because of due to ethical considerations, no randomized controlled trial comparing radical surgical resection and no surgery has been performed for patients with LGGs.

However, recent large observational studies and literature reviews using the objective evaluation of the extent of resection (EOR) for gliomas revealed that maximal tumor resection and early surgical intervention are significantly associated with better outcomes for patients with LGGs.[10-16] In a retrospective study of 216 patients with hemispheric LGGs, those patients with >90% EOR had 5-year OS rates of 97%. In contrast, patients with a <90% EOR had 5-year OS rates of 76%.[10] Furthermore, population-based parallel cohorts of LGGs in Norway showed that the survival of the "early surgical resection" group was significantly greater than that of the "biopsy and watchful waiting" group with LGGs.[14,15] It was reported that extended tumor resection beyond the margins of the abnormal magnetic resonance imaging (MRI)—verified area, also known as supratotal resection, improves the outcomes of LGG patients.[17] Although it is not curative, the performance of supratotal resection prevents or delays malignant transformation, a new concept in the surgical management of LGGs.[17-19] Therefore, a greater EOR, including total or supratotal surgical LGG resection, can significantly increase survival.

In the present study, we performed awake brain mapping with cortical and subcortical stimulation for diffuse frontal LGGs to achieve supratotal resection with determination of the functional brain tissue boundaries beyond the tumor margin. With frontal tumors of left-dominant hemispheres, we could preserve language function mainly using counting and picture-naming tasks. In contrast, when the tumor had affected the right frontal dominant hemisphere, we performed electrical brain stimulation to preserve the sensorimotor and neurocognitive functions, including working memory and spatial awareness. We investigated the surgical outcomes of awake brain mapping to accomplish supratotal resection of frontal LGGs in both dominant and nondominant hemispheres.

METHODS

Patient Selection

We retrospectively collected data from 9 patients with diffuse frontal LGGs of the dominant and nondominant hemisphere who had undergone supratotal resection. All 9 patients had undergone awake brain surgery at the Nagoya University Hospital from January 2016 to November 2017. The ethics committee of Nagoya University Hospital approved the present study (approval number, 2017-0459), and all the patients provided written informed consent.

Preoperative Neuropsychological Evaluation

All patients underwent neuropsychological testing, and the preoperative neurological findings were assessed at admission, before the awake brain surgery. The dominant hand was assessed using the Edinburgh inventory standardized questionnaire.[20] Hemispheric language dominance was determined according to the comprehensive interpretation of the results of both functional MRI and navigated repetitive transcranial magnetic stimulation.[21] Functional MRI studies were performed using a Siemens Magnetom Verio (Siemens, Erlangen, Germany) 3.0-Tesla scanner with a 32-channel head coil. The navigated repetitive transcranial magnetic stimulation language mappings with the use of picture-naming tasks were performed with the Magstim Rapid (Magstim Co., Whitland, United Kingdom). The patients' neuropsychological status and language function were evaluated by speech and occupational therapists. The neuropsychological tests used included the standard language test of aphasia (SLTA), the third edition of the Wechsler adult intelligence scale (WAIS-III), the Wechsler memory scale—revised (WMS-R), and the frontal assessment battery (FAB). The FAB is a cognitive and behavioral test to assess frontal lobe function.[22] The FAB consists of 6 subtests that detect the following frontal functions: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy.[22]

Table 1. Preferred Testing Paradigms for Bilateral Frontal Areas

Frontal Lobes	Tasks Performed Intraoperatively
Language nondominant hemisphere (right)	Motor function: movement of upper and lower limb
	Working memory
	Verbal working memory: digit span test
	Spatial working memory: N-back test; double task
	Spatial awareness: line bisection task
Language dominant hemisphere (left)	Motor function: movement of the upper and lower limb
	Language function: picture naming task; counting task
	Working memory: double task, digit span test

Surgery

Preoperative anatomical images with 3-dimensional T1-weighted images, conventional MRI (T1- and T2-weighted images), and diffusion-weighted imaging data were acquired on a 3.0-Tesla scanner (Trio Siemens; Siemens Medical Solutions, Erlangen, Germany) and sent to the navigation system (Vector Vision Compact; BrainLAB, Munich, Germany).[23] In all 9 cases, intraoperative awake brain mapping with direct brain stimulation was performed using an asleep-awake-asleep protocol, as previously reported.[24-27] In brief, a wide craniotomy was performed, and in accordance with the neuronavigation system, we initially placed letter tags along the tumor borders before the occurrence of brain shifts. The awake surgery was performed with cortical and subcortical mapping using direct electrical stimulation. Standard number tags were used to identify several brain functions, including motor and