Impact of the extent of resection on the survival of patients with grade II and III gliomas using awake brain mapping

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Running title: Impact of the EOR on the survival of GII/III-gliomas using awake surgery

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Abstract

Purpose

The aim of this study was to assess the effect of the extent of resection (EOR) of tumors on survival in a series of patients with grade II and III gliomas (GII/III-gliomas) who underwent awake brain mapping.

Methods

We retrospectively analyzed 126 patients with GII/III-gliomas in the dominant and non-dominant hemisphere who underwent awake brain surgery at the same institution between December 2012 and May 2020.

Results

EOR cut-off values for improved progression-free survival (PFS) were determined by a receiver operator characteristic (ROC) analysis of 5-year PFS. The ROC for EOR showed a cut-off value of ≥85.3%. The median PFS rate of patients with GII/III-gliomas in the group with an EOR ≥ 100%, including supratotal resection (n = 47; median survival [MS], not reached), was significantly higher than that in the group with an EOR < 90% (n = 52; MS, 43.1 months; 95% CI: 37.7–48.5 months; p = 0.03). In patients with diffuse astrocytomas and anaplastic astrocytomas, the group with EOR ≥ 100%, including supratotal resection (n = 25; MS, not reached), demonstrated a significantly better PFS rate than did the group with an EOR < 100% (n = 45; MS, 35.8 months; 95% CI: 19.9–51.6 months; p = 0.03). Supratotal or gross total resection was correlated with better PFS in *IDH*-mutant type of diffuse astrocytomas and anaplastic astrocytomas (n = 19; MS, not reached vs. n = 35; MS, 40.6 months; 95% CI: 22.3–59.0 months; p = 0.02). By contrast, supratotal or gross total resection was not associated with longer PFS rates in patients with *IDH*-wild type of diffuse astrocytomas and anaplastic astrocytomas.

Conclusions

The present study demonstrates a significant association between tumor EOR and survival in patients with GII/III gliomas. The EOR cut-off value for 5-year PFS was ≥85.3%. It is noteworthy that supratotal or gross total resection significantly correlated with better PFS in *IDH*-mutant type of WHO grade II and III astrocytic tumors. In light of our finding that EOR did not correlate with PFS in patients with aggressive *IDH*-wild type of diffuse astrocytomas and anaplastic astrocytomas, we suggest treatments that are more intensive will be needed for the control of these tumors.

Keywords: awake brain mapping, grade II and III gliomas, progression-free survival, extent of resection, supratotal resection, *IDH*-mutant glioma, *IDH*-wild type glioma

Declarations

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- **Conflicts of interest**

The authors declare that they have no conflicts of interest.

- **Availability of data and material (data transparency)**

The data in the current study are available from the corresponding author on reasonable request.

- **Code availability (software application or custom code)**

Not applicable

- **Authors' contributions**

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- **Ethics approval**

The Ethics Committee at Nagoya University Hospital approved this retrospective data evaluation and the experimental design of the study (approval number: 2020-0079).

- **Consent to participate (include appropriate statements)**

Patient informed consents were waived due to the retrospective nature of the study.

- **Consent for publication (include appropriate statements)**

Patient informed consents were waived due to the retrospective nature of the study.

Introduction

Grade II and III gliomas (GII/III-gliomas)—World Health Organization (WHO) grade II and grade III brain tumors are diffusely infiltrative tumors of the central nervous system[1, 2]. This term has recently replaced the specification “low-grade” gliomas, which include grade II gliomas, in clinical practice. Overtime, GII/III-gliomas typically progress to WHO grade IV tumors, glioblastomas (GBMs), which are malignant tumors with a median survival of only 7.8–31 months, even with aggressive treatment such as surgery and chemoradiotherapy[3, 4]. The classification of GII/III-gliomas into molecular subtypes in the new WHO 2016 classification has important prognostic implications[5]. In the 2016 classification, isocitrate dehydrogenase (*IDH*) 1 and 2 mutations are key genetic events in GII/III-gliomas as well as in GBMs[5].

Surgical tumor resection is the initial first-line treatment to control GII/III-gliomas. Many studies have provided evidence supporting maximum safe surgical resection and early surgical intervention, which prolong survival in patients with GII/III-gliomas[6-13]. Although there are no well-designed randomized controlled clinical trials demonstrating a correlation between a higher extent of resection (EOR) and a better clinical prognosis of GII/III-gliomas, complete radiological resection of GII/III-gliomas is the currently recommended approach.

The goal of complete tumor resection should be balanced against neurological disturbances including motor, language, and neurocognitive impairments, due to the infiltrative behavior of GII/III-gliomas[14, 15]. To ensure both maximal safe resection and preservation of these neurological functions, the use of intraoperative awake brain mapping techniques has been proposed as the reference standard strategy for patients with GII/III-gliomas[16-20]. Awake surgery allows for the maximum degree of resection while determining functional boundaries, using both cortical and subcortical functional mapping[17, 21]. When functional boundaries are observed within the tumor mass, resection can be subtotal or partial. If the functional boundaries lie outside the tumor region, gross total or supratotal resection can be achieved. Extended tumor resection beyond the margins of the abnormal magnetic resonance imaging (MRI)-verified area is known as supratotal resection[22, 23]. Because there is only limited evidence for an effect of supratotal or gross total removal on the control of the tumor and histological malignant transformation[22, 24, 25], the oncological impact of the EOR on survival is still uncertain. Furthermore, it is unclear how far around the tumor mass resection can be safely extended to prolong the survival of patients with GII/III-gliomas. There is also concern regarding whether an improvement in survival due to massive tumor resection depends on the patient’s molecular genetic status, such as *IDH1/2* mutations in patients with *IDH*-mutant type or *IDH*-wild type of GII/III-gliomas.

In the present study, we performed awake brain mapping with cortical and subcortical

stimulation for GII/III-gliomas in order to achieve supratotal resection whenever possible, while determining the functional brain tissue boundaries beyond the tumor margins. We assessed the effect of tumor EOR on survival in a series of 126 consecutive patients with GII/III-gliomas who all underwent awake brain mapping. In addition, we performed a subanalysis to assess the association between clinical outcome and tumor EOR in the subtypes of GII/III-gliomas classified according to the molecular genetic status after awake surgery.

Materials & Methods

Study design

This is a retrospective analysis of 126 consecutive patients with GII/III-gliomas. All underwent awake surgery with intraoperative direct electrical stimulation at Nagoya University Hospital (Nagoya, Japan) between December 2012 and May 2020. Regarding GII/III-gliomas of the left dominant hemisphere, we performed awake functional mapping to achieve supratotal resection whenever possible, while preserving motor and language functions. Contrastingly, when the tumor affected the right non-dominant hemisphere, we performed electrical brain stimulation to preserve the sensorimotor and neurocognitive functions, including working memory and spatial awareness. Patient data on clinical information and outcomes were collected and analyzed. The Ethics Committee at Nagoya University Hospital approved this retrospective data evaluation and the experimental design of the study (approval number: 2020-0079). We obtained written informed consent prior to the surgical mapping procedure from all participants included in the study.

Pre- and postsurgical neuroradiological examination

We performed preoperative MRI, including three-dimensional T1-weighted imaging, conventional MRI (T1-, T2-, and FLAIR-weighted imaging), and diffusion-weighted imaging, using a 3.0 Tesla scanner (Trio, Siemens, Germany). To assess the EOR, MRI (T1-weighted, T2-weighted, and FLAIR-weighted) was also conducted at 1 week and 3 months postoperatively and at every 3 months thereafter.

Intraoperative awake brain mapping technique

All 126 patients underwent awake brain mapping with direct electrical stimulation using an asleep-awake-asleep protocol, as previously described[17, 23, 26-29]. In brief, we performed a craniotomy under general anesthesia. Cortical mapping with direct electrical stimulation was then performed to detect the motor and language areas. The stimulation intensity used for individual patients was

determined by increasing the amplitude in 0.5-mA increments from a baseline of 1.0 mA until a functional response was elicited. Maximum individual intensities ranged from 2 mA to 8 mA. For language mapping, the patients were asked to perform counting and picture-naming tasks, with the goal to identify the cortical language sites and subcortical fibers using direct brain stimulations[23]. The type of observed language disturbances was determined based on a detailed classification for language disorders, including speech arrest, anomia, dysarthria, anarthria, speech slowness, initiation trouble, perseveration, and paraphasia.

Working memory, which has been investigated particularly in patients with tumors in the right non-dominant hemisphere, was also assessed. Verbal working memory was tested using digit span tasks during awake mapping[30]. Patients were asked to repeat three or four strings of digits in forward and/or reverse order. In addition, spatial working memory performance was measured using a visual N-back task[31]. This test was composed of 1-back or 2-back tasks, during which plane figures were presented on a monitor. During the presentation, cortical and subcortical areas were stimulated only during the memorization (not recall) phase. With the goal of mapping spatial awareness, patients were also asked to mark the center of the presented image during a line bisection task, which is often used in patients with tumors in the parietal lobe[32]. A lateral midline deviation of approximately 5 mm from the mark was regarded as a positive response and was used to identify functional spatial regions.

After the cortical mapping was complete, tumor resection was initiated using the subpial resection technique. We removed the tumor at the level of the white matter, while frequently checking the patient's response using subcortical electrical stimulation. Subcortical mapping enabled us to determine the functional boundaries between the tumor and white matter pathways. Thus, tumor removal was accomplished according to the cortical or subcortical functional boundaries in all patients, while aiming for achieving supratotal resection whenever possible.

Degree of tumor resection and volumetric analysis

Volumetric analysis was performed using the iPlan® cranial planning software included in the BrainLAB iPlan® Cranial version 2.6 and 3.0[33] (German HealthCare Export Group, Bonn, Germany). The pre- and postoperative tumor volumes were measured in all patients to estimate the EOR using contrast T1-weighted or FLAIR-weighted MRI data obtained before and after tumor removal. If the tumor was not enhanced or partially enhanced on MRI, the EOR was evaluated based on residual high-intensity lesions on FLAIR-weighted MRI. On the other hand, if the entire tumor was enhanced on MRI, the EOR of the tumor was calculated based on the residual enhanced tumor. The EOR was calculated using the difference between preoperative and postoperative tumor volumes:

(preoperative tumor volume – postoperative tumor volume) / preoperative tumor volume[6]. Volumetric EOR was categorized as follows: supratotal resection, EOR > 100%; gross total resection, EOR = 100%; subtotal resection, EOR ≥ 90% to < 100%; and partial resection, EOR < 90%. A supratotal resection was defined as tumor resection extending beyond the MRI-verified abnormal area or the complete removal of any abnormality, with the postoperative cavity volume being larger than the preoperative tumor volume[22, 25, 34]. This was also defined as a postoperative tumor cavity/preoperative tumor volume >100%.

Tumor progression was defined as newly detected areas of contrast enhancement and/or an obvious increase in the FLAIR signal abnormality on follow-up MRI relative to the baseline postoperative MRI obtained within 72 hours of the operation.

Postoperative course

All patients underwent neurological and neuropsychological assessments 1 week and 6 months after awake brain surgery. The KPS score was evaluated 3 months after awake surgery. Furthermore, all patients were followed up at the outpatient clinic, at intervals of 3 months, and asked whether they were working or not 1 year after the surgery.

Adjuvant therapy protocol

Further treatment of grade II gliomas that underwent total or supratotal resection was based on observation. When more than 10% of the tumor was left, chemotherapy such as temozolomide (TMZ) was applied as adjuvant treatment.

For grade III gliomas, initial adjuvant treatment included focal external-beam radiation therapy by conventional radiation planning to approximately 60 Gy (±5% total dose), with daily concurrent TMZ at 75 mg/m^2 throughout the course of the radiation therapy. This was followed by adjuvant temozolomide according to the Stupp protocol[35].

Direct DNA sequencing for *IDH1* and *IDH2* mutations

Direct sequencing of *IDH1* and *IDH2* was conducted as previously described[36]. A 129-bp fragment spanning the sequence encoding the catalytic domain of *IDH1*, including codon 132, and a 150-bp fragment spanning the sequence encoding the catalytic domain of *IDH2*, including codon 172, were amplified for *IDH* sequencing.

Statistical analyses

All statistical analyses were conducted using SPSS version 27.0 (IBM Corporation, Armonk, NY,

USA) for Windows (Microsoft Corporation, Redmond, WA, USA). Survival was estimated using the Kaplan–Meier method, and the log-rank test was used to assess survival differences among groups. Progression-free survival (PFS) was calculated from the day of the first surgery till the occurrence of true tumor progression, death, or the end of the follow-up. Overall survival (OS) was calculated from the day of the first surgery until death or the end of the follow-up.

To identify EOR cut-off values and to ascertain which surgical factor was more prognostic for 5-year PFS, a receiver operator characteristic (ROC) analysis was conducted. In addition, the Youden's index (sensitivity + specificity - 1) for each data point was calculated to identify the 5-year PFS cut-off value for EOR [37]. The data point that yielded the maximum Youden index corresponded to the point on the ROC curve with the highest vertical distance from the 45° diagonal line [38]. Graphs were generated using the R package pROC [39], which is included in the statistical software R version 3.5.2 (URL: https://www.r-project.org/).

Factors influencing PFS in our cohort of patients with GII/III-gliomas during awake brain surgery were investigated using univariate and multivariate Cox proportional hazards models adjusted for major clinical prognostic factors, including age at diagnosis (>40 years vs. ≤40 years), histologic type (astrocytic vs. oligodendroglial), WHO grade (grade III gliomas vs. grade II gliomas), tumor location (frontal regions vs. other regions), *IDH1* or *IDH2* status (mutation or wild type), final EOR (≥100% vs. <100%), chemotherapy (+ vs. -), and chemoradiotherapy (+ vs. -). The covariates and the independent variables that showed significant differences in the univariate analysis were used for the analysis. The remaining factors in the multivariate Cox proportional hazards model ($p < 0.05$) were considered to be independent predictors of PFS.

Results

Patients

Between December 2012 and May 2020, a total of 126 consecutive patients (74 males, 52 females) who underwent awake surgery for GII/III-gliomas of the dominant and non-dominant hemisphere were enrolled in this study. The median follow-up time was 33.0 months (range, 0.3–89.9 months). The patients' clinical characteristics are summarized in Table 1. The mean age at the time of awake surgery was 42.8 years (range, 17–76 years). The median preoperative and postoperative Karnofsky performance status (KPS) were 100 (range, 60–100) and 100 (range, 50–100), respectively. The tumors were located in the left hemisphere in 88 cases (69.8%) and in the right hemisphere in 38 cases (30.2%). The majority of the tumors were located in the frontal lobe (n = 73, 57.9%), followed by the insular lobe (n = 27, 21.4%), the temporal lobe (n = 13, 10.3%), the parietal lobe (n = 12,

9.5%), and the occipital lobe (n = 1, 0.8%). Histologically, the present study consisted of all patients with GII/III-gliomas, including 91 WHO grade II gliomas (52 diffuse astrocytomas, 39 oligodendrogliomas) and 35 WHO grade III gliomas (18 anaplastic astrocytomas, 17 anaplastic oligodendrogliomas). *IDH1* or *IDH2* mutations were observed in 105 patients (83.3%), while *IDH1* or *IDH2* wild types were identified in 21 patients (16.7%). Ring-like or nodular enhancement by gadolinium MRI was observed in 10 (28.6%) of 35 patients with WHO grade III gliomas. Preoperative mean tumor volume was 49.5 cm^3 (range, 1.2–196.4 cm^3). The median EOR was 93.1% in all patients. The median EOR in patients with dominant left tumors and in patients with non-dominant right tumors were 91.1% and 100%, respectively. A final EOR > 100% (supratotal resection) was achieved in 15 patients (11.9%), an EOR = 100% (gross total resection) in 32 patients (25.4%), an EOR ≥ 90% and < 100% (subtotal resection) in 27 (21.4%) patients, and an EOR < 90% in 52 (41.3%) patients.

Postoperative neurological outcomes

Table 2 shows the summary of transient or permanent postoperative neurological deficits, including motor and speech disturbances, according to main tumor location. During the postoperative course, 47 (37.3%) patients exhibited new transient speech disturbances, 27 (21.4%) developed transient motor disorders, five (4.0%) exhibited permanent speech deficits, and nine (7.1%) had permanent motor deficits. Among the 73 patients with frontal tumors, 24 (32.9%) exhibited transient speech disturbances and 17 (23.3%) developed transient motor disturbances. Of these 73 patients, two (2.7%) demonstrated persistent speech deficits and three (4.1%) had permanent motor deficits. By contrast, three of the 27 patients with insular tumors (11.1%) exhibited permanent speech disorders and four (14.8%) had permanent motor deficits. In the 88 patients with left-side GII/III-gliomas, language mapping using picture-naming tasks showed a 97.6% sensitivity when compared with postoperative permanent speech disturbances. Regarding work resumption, 79 (90.8%) of 87 patients with professional activities prior to awake surgery returned to work within 1 year.

Predictors for progression-free survival of GII/III-gliomas

A ROC analysis was performed to determine the EOR cut-off values (Fig. 1A). The EOR cut-off value for 5-year PFS was determined by the highest vertical distance from the 45° line and corresponded to subjects with ≥85.3%. The AUC value for EOR was 0.738 (95% confidence interval [CI]: 0.586–0.873). At the ≥85.3% EOR cut-off, Kaplan-Meier survival curve analyses demonstrated a significantly improved median PFS (n = 81; median survival, not reached) compared to less extensive tumor resections (n = 45; median survival, 42.1 months; 95% CI: 31.8–52.3 months; *p* =

0.009; Fig 1B).

Survival and supratotal or gross total resection in GII/III-gliomas

We further analyzed whether supratotal (EOR > 100%) or gross (EOR = 100%) total resection affected the survival of our 126 consecutive patients. The Kaplan–Meier estimates for PFS according to EOR classes for all patients are shown in Figure 2. The median PFS rate of the patients in the group with an EOR ≥ 100%, including supratotal resection (n = 47; median survival, not reached), was significantly higher than that in the group with an EOR < 90% (n = 52; median survival, 43.1 months; 95% CI: 37.7–48.5 months; $p = 0.03$; Fig 2). There were no significant differences in the median PFS rate between the patients in the group with EOR >100% (n = 15; median survival, not reached) and those in the group with EOR = 100% (n = 32; median survival, not reached; $p = 0.1$). Furthermore, there were no significant differences in the median OS rates based on the EOR (EOR ≥ 100%, n = 47: median survival, not reached; EOR >90% to <100%, n = 27: median survival, not reached; EOR < 90%, n = 52: median survival, not reached). In patients with diffuse astrocytomas and anaplastic astrocytomas, the group with an EOR ≥ 100%, including supratotal resection (n = 25; median survival, not reached), demonstrated a significantly better PFS rate than the group with an EOR < 100% (n = 45; median survival, 35.8 months; 95% CI: 19.9–51.6 months; $p = 0.03$; Fig 3). The median OS rates of patients with diffuse astrocytomas and anaplastic astrocytomas showed no difference between groups classified according to EOR. By contrast, neither the median PFS nor the median OS significantly differed across EOR classes in patients with oligodendrogliomas and anaplastic oligodendrogliomas.

Benefits of supratotal or gross total resection for patients with *IDH*-mutant type of diffuse astrocytomas and anaplastic astrocytomas

We next investigated the prognostic correlations between supratotal or gross total resection and *IDH1*/*IDH2* mutations in diffuse astrocytomas and anaplastic astrocytomas. It is noteworthy that supratotal or gross total resection was correlated with better PFS in *IDH*-mutant type of diffuse astrocytomas and anaplastic astrocytomas (n = 19; median survival, not reached vs. n = 35; median survival, 40.6 months; 95% CI: 22.3–59.0 months; $p = 0.02$). By contrast, supratotal or gross total resection was not associated with longer PFS in patients in *IDH*-wild type of diffuse astrocytomas and anaplastic astrocytomas.

Factors influencing progression-free survival in patients with GII/III-gliomas during awake brain surgery

Our univariate analysis shows that PFS in patients with GII/III-gliomas was significantly associated with *IDH1* or *IDH2* status (mutation vs. wild type, hazard ratio [HR] = 0.39, 95% CI: 0.20–0.77, p = 0.006), final EOR (≥100% vs. <100%, HR = 0.43, 95% CI: 0.19–0.98, p = 0.04), and chemotherapy (+ vs. -, HR = 1.97, 95% CI: 1.03–3.79, p = 0.04; Table 3).

We further established multivariate Cox proportional hazards models for the factors influencing PFS in patients with GII/III-gliomas using the following prognostic factors: *IDH1* or *IDH2* status, final EOR, and chemotherapy. These multivariate models were subsequently adjusted to estimate the HR associated with PFS in our patients. Notably, the multivariate models also showed that PFS rates were significantly related to *IDH1* or *IDH2* status (mutation vs. wild type, HR = 0.30, 95% CI: 0.15–0.60, p = 0.001) and final EOR (≥100% vs. <100%, HR = 0.37, 95% CI: 0.16–0.87, p = 0.02; Table 3).

Discussion

Large observational studies based on the objective evaluation of the EOR for gliomas have shown that maximal resection is significantly associated with favorable clinical outcomes for WHO grade II gliomas[6-11, 40]. One retrospective study of 216 patients with WHO grade II gliomas demonstrated that patients with an EOR > 90% had a 5-year OS rate of 97%, whereas patients with an EOR < 90% had a 5-year OS rate of 76%[6]. Jakola et al. reported on a retrospective population-based parallel cohort of WHO grade II gliomas in Norway, comparing two hospitals with distinct treatment strategies. One hospital strategy favored early surgical tumor resection, while the other preferred biopsy and observation for WHO grade II gliomas. Notably, this study revealed a significant increase in survival in patients in the “early surgical resection” group[9, 10], with a 5-year OS rate of 74% compared to a rate of 60% in the “biopsy and observation” group. Furthermore, another study reported a significant survival benefit for patients under “early tumor resection” management compared to those under “biopsy management” (5-year OS: 82% vs. 54%)[11], at two different departments acting independently at the same university hospital. This suggests that glioma surgeons should aim for maximal safe resection by increasing the tumor EOR in order to prolong survival in patients with WHO grade II gliomas. A large European phase III clinical trial (EORTC-26951) found that the extent of surgery was significantly related to survival in WHO grade III anaplastic oligodendroglial tumors[41]. Nomiya et al. retrospectively estimated the prognostic factors for 170 patients with WHO grade III anaplastic astrocytoma[42]. The median survival times of their patients, classified into total resection, subtotal resection, partial resection, and biopsy-only groups, were 86.4, 61.6, 22.9, and 23.4 months, respectively. The authors emphasized that the extent of surgery is the

most powerful prognostic factor in the treatment of WHO grade III anaplastic astrocytoma. Kawaguchi et al. revealed the importance of surgical resection by investigating 124 consecutive patients newly diagnosed with WHO grade III gliomas[43]. Among these patients without 1p/19q co-deletion, those with gross total removal had significantly longer median overall survival times than those without gross total removal (median survival: not reached versus 77 months). Our results indicate that, similarly, an EOR ≥ 100%, including supratotal resection, is significantly associated with better PFS rates in patients with GII/III-gliomas ($p = 0.03$, Fig. 2). These results support the notion that maximal safe resection is a crucial prognostic factor for improving the survival of patients with GII/III-gliomas.

Duffau et al. firstly reported that supratotal resection improves the outcome of patients with WHO grade II gliomas who have undergone awake mapping, after a mean follow-up of 11 years[22]. These results suggest that supratotal resection, extending beyond the abnormalities detected by FLAIR-weighted MRI, provides a survival benefit, because tumor cells might invade sites 10–20 mm away from the tumor boundaries on MRI[44]. Since a greater EOR, such as that achieved by gross total or supratotal surgical tumor resection, could significantly increase survival in patients with WHO grade II gliomas, we tried to achieve supratotal resection of the functional boundaries whenever possible, with the aid of awake functional mapping. We previously reported on the efficacy of awake brain surgery for the supratotal resection of diffuse frontal GII/III-gliomas, while motor, language, and neurocognitive functions are preserved[23].

Recently, Rossi et al. presented a retrospective review of 319 *IDH*-mutated GII/III-gliomas in which supratotal resection was significantly related to survival, independently of molecular subtypes and WHO grades[24]. The authors found that PFS rates were significantly higher in patients with *IDH*-mutated WHO grade II and III astrocytomas or oligodendrogliomas who underwent supratotal resection than in those who underwent total resection. Moreover, supratotal resection was significantly associated with a reduced rate of malignant transformation and a better OS. The present study found that supratotal or gross total resection was significantly associated with better PFS in *IDH*-mutant type of diffuse astrocytomas and anaplastic astrocytomas, but not in *IDH*-wild type. Furthermore, our results revealed no significant correlations between PFS and supratotal or gross total resection in patients with oligodendrogliomas and anaplastic oligodendrogliomas. This difference in results might stem from a small number of patients with oligodendrogliomas (56 cases of WHO grade II and III oligodendrogliomas) in our series compared to the earlier study by Rossi et al. (180 cases of WHO grade II and III oligodendrogliomas). Moreover, WHO grade III anaplastic gliomas have been recommended to be treated by maximal safe resection followed by radiotherapy and adjuvant PCV (procarbazine, lomustine, and vincristine)[41, 45]. In addition, our study did not

reveal a significant effect of supratotal or gross total resection in patients with *IDH*-wild type of diffuse astrocytomas and anaplastic astrocytomas. Recent studies suggested that these *IDH*-wild types of astrocytic tumors belong to completely different entities and therefore require different tumor management[47].

In our study, late permanent speech and motor disturbances were observed in 4.0% and 7.1% of patients, respectively. By contrast, early transient speech and motor disturbances were observed in 37.3% and 21.4% of patients, respectively (Table 2). Compared to the total postoperative neurological deficits, however, late permanent speech and motor disturbances in insular tumor cases were relatively common (11.1% and 14.8% of patients, respectively), which indicates that they present a surgical challenge regardless of the use of awake functional mapping. Although the rate of postoperative neurological deficits in patients with insular gliomas was high, these results might stem from the small number of such patients. These observed transient neurological disturbances, due to the proximity of critical normal brain structures to the tumor cavity, usually disappeared within a few weeks or months after tumor resection. Although tumor resection with awake functional mapping may be associated with a reduction in late severe permanent neurological deficits in patients with GII/III-gliomas, despite an early increase in transient functional deficits, the surgical indications of awake surgery for GII/III-gliomas are still under debate.

Our study revealed that an EOR threshold of 85.3% was beneficial for GII/III gliomas. Improved outcomes among patients with GII/III-gliomas are predicted by greater EOR (>85.3%), possibly aiming for supratotal or gross total resection. However, these infiltrative GII/III-gliomas are often observed near or within eloquent regions, which means that the removal of tumors in these essential areas increases the risk of neurological function deficits, including dysfunction of motor, language, and cognitive functions. Therefore, the recommended treatment for GII/III-gliomas associated with eloquent regions is awake surgery with direct electrocortical stimulation to preserve brain function.[6, 16, 48]. When used with awake functional mapping techniques, our study showed that increased EOR is not associated with additional morbidities, such as motor and speech disturbances. Therefore, management of GII/III-gliomas should include maximal surgical tumor resection to improve long-term clinical outcomes while minimizing postoperative neurological deficits using awake brain mapping.

Although the current study provides novel information regarding the impact of supratotal or gross total resection with awake mapping on the survival of patients with GII/III-gliomas, our results are limited compared to those of prospective clinical trials, as retrospective studies may be influenced by unrecognized biases. Most importantly, the survival improvement associated with EOR ≥ 100% may be due to biases from differential tumor aggressiveness in non-

resectable or easily resectable portions of the brain. Furthermore, the present study was based on a small number of tumor cases; therefore, a larger cohort study is needed to further establish the effect of supratotal or gross total resection during awake surgery using cortical and direct axonal electrical stimulation. Another limitation of this study is the small number of wild type *IDH* tumors, including anaplastic gliomas (WHO grade III), which are considered potential glioblastomas, and the short follow-up period. Thus, the EOR may not be associated with longer PFS rates in patients with wild type *IDH* diffuse astrocytomas and anaplastic astrocytomas. Future studies should include a larger number of wild type *IDH* type GII/III gliomas and follow patients up over a longer period. Thus, further accumulation of evidence for this surgical strategy for GII/III-gliomas will help the improvement of the treatment of this disease and hopefully develop it into a novel therapy.

Conclusions

The present study demonstrates the significant association of tumor EOR with survival in patients with GII/III-gliomas. The EOR cut-off value for 5-year PFS was ≥85.3%. It is noteworthy that supratotal or gross total resection significantly correlated with better PFS in *IDH*-mutant type of WHO grade II and III astrocytic tumors. In light of our finding that EOR did not correlate with PFS in patients with aggressive *IDH*-wild type of diffuse astrocytomas and anaplastic astrocytomas, we suggest treatments that are more intensive will be needed for the control of these tumors.

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Figure legends

Fig 1A. Receiver operator characteristic curves for 5-year progression-free survival (PFS) for the extent of resection (EOR). The area under the curve (AUC) for EOR was 0.738 (95% confidence interval (CI): 0.586–0.873). The EOR cut-off value for 5-year PFS was ≥ 85.3%.

Fig 1B. Kaplan–Meier curves showing progression-free survival (PFS) for the entire cohort according to an extent of resection (EOR) ≥ 85.3% or < 85.3% in all patients with grade II and III gliomas

(GII/III-gliomas).

Fig. 2. Kaplan–Meier curves showing progression-free survival (PFS) for the entire cohort according to the extent of resection (EOR) ≥ 100%, ≥ 90% to < 100%, or < 90% in all patients with grade II and III gliomas (GII/III-gliomas)

Fig. 3. Kaplan–Meier curves showing progression-free survival (PFS) according to the extent of resection (EOR) ≥ 100% or < 100% in patients with diffuse astrocytomas and anaplastic astrocytomas

Fig. 4A. Kaplan–Meier curves showing progression-free survival (PFS) according to the extent of resection (EOR) ≥ 100% or < 100% in *IDH*-mutant type of diffuse astrocytomas and anaplastic astrocytomas.

Fig. 4B. Kaplan-Meier curves showing progression-free survival (PFS) according to extent of resection (EOR) ≥ 100% or < 100% in *IDH*-wild type of diffuse astrocytomas and anaplastic astrocytomas.

Table legends

Table 1. Clinical characteristics

Table 2. Summary of postoperative neurological deficits and tumor locations

Table 3. Univariate and multivariate Cox proportional hazards models for factors influencing PFS in patients with grade II and III gliomas (GII/III-gliomas)

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