Summary of 15 Years Experience of Awake Surgeries for Neuroepithelial Tumors in Tohoku University

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Abstract

We retrospectively analyzed 15 years experience of awake surgeries for neuroepithelial tumors in Tohoku University. Awake surgeries mostly for language mapping were performed for 42 of 681 newly diagnosed cases (6.2%) and 59 of 985 surgeries including for recurrence (6.0%). When the same histologies and locations as cases resected under awake condition are selected from the parent population treated by radical resection, awake surgeries were most frequently performed for 14 of 55 newly diagnosed cases (25.5%) and 14 of 62 surgeries (22.6%) with grade II gliomas. In the results, 8 of 59 surgeries (13.6%) could not achieve complete language monitoring until the final stage of tumor resection, considered as failed awake surgery. Gross total resection was accomplished in 20 of 42 newly diagnosed cases (47.6%) and 32 of 59 surgeries (54.2%). Mortality rate was 0%. Late severe deficits were observed in 2 of 42 newly diagnosed cases (4.8%) and 3 of 59 surgeries (5.1%). Negative language mapping cases did not suffer severe deficits in both early and late stages. In contrast, high incidence of severe deficits, 3 as early and 2 as late of 8 cases, were identified with failed awake surgery. The overall survival of patients treated by awake surgery compared favorably with those treated without stimulation mapping and with stimulation mapping under general anesthesia. Awake surgery may contribute to improve the outcome of gliomas near eloquent areas by maximizing the tumor resection and minimizing the surgical morbidity.

Key words: awake surgery, electrical stimulation, glioma, language mapping, outcome

Introduction

Awake surgeries provide an opportunity for mapping sensorimotor, language, and cognitive functions in order to maximize tumor resection and minimize surgical morbidity. Propofol, which is the essential sedative for awake surgery, became commercially available in December 1995 in Japan. Professor Tomokatsu Hori at Tottori University first reported awake surgery for meningioma using propofol in 1996.12 We first resected glioma under the awake condition with neurophysiological...
monitoring on December 5, 1996, as reported in 1997. These surgeries were the predawn of awake surgery in Japan. Thereafter, the Japan Awake Surgery Conference was established in 2002 for the purpose of continuing research into neurocognitive functions as well as establishing and promoting safe methods of awake craniotomy. Finally, guidelines for awake craniotomy for brain lesions near language areas were published in 2012. Therefore, 15 years have passed since the introduction of awake surgery for resection of gliomas in Japan.

In this paper, we would like to summarize our experiences of awake surgery in Tohoku University for 15 years, and try to answer the following questions: 1) What does awake surgery bring to glioma surgery? 2) What is the frequency of awake surgery? 3) What was the outcome?

Materials and Methods

I. Patient population

We retrospectively analyzed 42 newly diagnosed consecutive patients, 31 males and 11 females aged 22 to 70 years (mean ± standard deviation [SD] 44.4 ± 14.5 years, median 45 years) with neuroepithelial tumors located near/within the motor and/or language areas, radically resected under the awake condition with intraoperative stimulation mapping/monitoring at Tohoku University Hospital between December 1996 and December 2011 by the same neurosurgeon (first author T.K.). These areas consisted of the sensorimotor strip (precentral and postcentral gyri), dominant hemisphere perisylvian language areas (superior and middle temporal, inferior and middle frontal, and inferior parietal areas) including their connecting fibers. The results of preoperative functional imaging, such as functional magnetic resonance (MR) imaging and magnetoencephalography, were also taken into consideration. Fifty-nine awake surgeries were performed for newly diagnosed and recurrent tumors (n = 17) during this period. Four patients were treated under the awake condition for both newly diagnosed and recurrent tumors. We had limited experience of awake surgery for language mapping except during the first 15 years, because motor mapping and monitoring can be performed using simulation mapping under general anesthesia. During the same period, 681 newly diagnosed neuroepithelial tumors were surgically treated, and 985 surgeries including biopsy were performed in our hospital. Decisions regarding patient treatment were made by the same neurosurgeon (first author T.K.). The histopathological diagnosis was based on the World Health Organization (WHO) classification. Informed consent was obtained from each patient or guardian on admission, prior to computed tomography or MR imaging with contrast medium and surgical resection/radiochemotherapy. Institutional Review Board approval was waived because of the retrospective nature of the study.

II. Surgical procedure

Patients were positioned with a large roll under the shoulder and with the head lying on a soft rest without rigid pin fixation. Neuronavigation systems could be used without pin fixation using skull reference tools. The bipolar stimulator with 5-mm spacing between the electrodes was used. Under monitoring of after-discharge using electrocorticography, cortical and subcortical mapping was performed using electric stimuli of 3–16 mA (average 7.3 mA, median 8 mA), train of square waves, and biphasic pulses of 0.3-millisecond phase duration at a frequency of 50 Hz, to identify the sensorimotor and language cortices and their connection fibers, according to the method described previously. Speech arrest was defined as a discontinuation in number counting without simultaneous motor responses. For sites associated with naming, stimulation was applied for 3 seconds at sequential cortical sites during a slide presentation of line drawings. All cortical sites were stimulated three times.

Two different anesthesiology protocols for awake surgery have been applied. In the early stage, spontaneous ventilation was maintained without the laryngeal mask throughout the surgical procedures (21 newly diagnosed cases and 2 recurrent cases). During this early stage, awake surgery was also applied purely for motor mapping in the 5 gliomas in the non-dominant hemisphere, but since then the indicator for awake surgery has been confined to identify the language function. We did not map the subcortical white matter for language at this stage, but only for motor pathways under prescribed sedative. After January 2005 (late stage), we routinely applied the asleep-awake-asleep (AAA) technique, intermittent general anesthesia with controlled ventilation using the laryngeal mask (21 newly diagnosed cases and 15 recurrent cases) (Fig. 1). In general, the patients remained fully awake from the beginning of cortical mapping until the completion of tumor removal to obtain complete functional mapping for both cortical and subcortical regions. The tumor resection was carried out while the patients continued to perform the language tasks including free speech and conversation with the observer, and the surgeon modified the resection and the electrical subcortical stimulation. An awake craniotomy was
considered a failure if cortical and subcortical mapping or awake monitoring were either aborted prematurely or not performed successfully.

III. Extent of resection
In order to assess the effectiveness of awake surgery for maximizing tumor resection, the extent of surgical resection was evaluated with quantitative volumetric analysis using postoperative MR imaging performed within 72 hours of surgery. If the tumor was enhanced on the preoperative MR images, gross total resection (GTR) of the tumor was defined as resection with no residual enhanced tumor, subtotal resection (STR) as over 75% resection, and partial resection (PR) as under 75% resection. If the tumor was not enhanced on the preoperative MR images, resection was evaluated based on the residual high intensity lesion on the T2-weighted MR images. Sometimes, the high intensity lesion was difficult to define on the T2-weighted MR images as a residual tumor, so 98% or more resection was identified as GTR. STR and PR were considered as unsatisfactory resection.

IV. Postoperative neurological outcomes
The postoperative neurological outcome was recorded and confirmed by retrospective review of all hospital records and physician notes. Radiographic lesions without neurological symptoms were not defined as surgical complications. The primary outcome measure was the event rate of new postoperative neurological deficits. Deficits were categorized according to severity (severe or less severe) and timing of assessment (early and late), as proposed by De Witt Hamer et al. Mortality from any cause within 30 days after resection was included. Deficits were considered severe if involving muscle strength grades 1 to 3 on the Medical Research Council Scale, aphasia or severe dysphasia, hemianopsia, or vegetative state. All other neurological deficits were considered less severe, including grade 4 monoparesis, isolated central facial palsy or other cranial nerve deficits, dysnomia, somatosensory syndrome, or parietal syndrome. Deficits at 7 days after surgery were defined as early, and deficits at 3 months were defined as late.

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V. Statistical analysis

Statistical analysis was performed on December 31, 2012. Mean ± SD and median follow-up periods for 42 newly diagnosed cases were 2072 ± 1468 and 1652 days, respectively (range 357–5590 days). Estimate of overall survival (OS) from the time of initial surgery to death was calculated with the Kaplan-Meier method. Log rank test was used to compare the differences between groups. Qualitative variables were compared using the chi-square test, and analysis of variance (ANOVA) was used for continuous variables. Probability values ≤0.05 were considered statistically significant. JMP Pro 9.0.2 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analyses.

Illustrative Case

A 30-year-old female presented with glioblastoma that manifested as generalized tonic-clonic convolution. $T_2$-weighted MR imaging demonstrated a hyperintense lesion in the left frontal lobe, infiltrating into the anterior parts of both the insula and basal ganglia, and the corpus callosum. Administration of contrast medium caused heterogeneous enhancement (Fig. 2A). Neurological and neuropsychological examination revealed no abnormality. Functional MR imaging revealed that her language dominancy was located in the left hemisphere (Fig. 2I).

We planned to resect the tumor using the AAA protocol with intraoperative neurophysiological
monitoring to maximize tumor resection and minimize surgical morbidity. However, Dr. Kiyotaka Sato, who was our only neuro-anesthesiologist, suddenly became ill on that day. Thus, we had no other choice than to resect only the medial part of tumor located in the inferior and middle frontal gyri to avoid language dysfunction under general anesthesia (Fig. 2E, F). Postoperatively, no new neurological deficits were observed, but MR imaging disclosed PR of the tumor (Fig. 2B). The histopathological diagnosis was glioblastoma. Adjuvant therapy consisted of 60 Gy of fractionated radiation and concomitant administration of temozolomide. However, the tumor progressed without neurological deterioration (Fig. 2C).

Three months after the initial operation, we tried to resect the tumor under the awake condition as in the original plan (Fig. 2G). We identified the primary sensory sites of the tongue and orofacial area, and the motor area of the tongue using direct cortical stimulation. Positive language sites could not be detected within the cortical exposure (negative language mapping), so we removed the inferior and middle frontal gyri and anterior parts of both the insula and basal ganglia with neuronavigational assistance (Fig. 2H). The patient’s motor and language functions were maintained without interruption until the end of tumor resection. Postoperatively, neurological and neuropsychological examination revealed no abnormality, and MR imaging depicted GTR of the tumor (Fig. 2D). Functional MR imaging demonstrated that the frontal language area was preserved just behind the resection cavity (Fig. 2I). She returned to work as a home economics teacher. OS was 1124 days and she remains alive at this time.

**Results**

I. Frequency of awake surgery

Awake surgeries were performed for 42 of 681 newly diagnosed cases of glioma (6.2%) and 59 of 985 cases (6.0%) with neuroepithelial tumors. One hundred and eight newly diagnosed cases (15.9%) and 167 surgeries (17.0%) required radical resection with stimulation mapping (Table 1). When the same histologies and locations as cases resected under awake condition are selected from the parent patient population undergoing radical resection, awake surgeries were performed for 14 of 55 newly diagnosed cases (25.5%) and 14 of 62 surgeries (22.6%) with grade II gliomas, and 29 of 62 surgeries (46.8%) with grade II gliomas, and 45 of 129 newly diagnosed cases (34.9%) and 66 of 189 surgeries (34.9%) with grade III gliomas were radically resected with stimulation mapping. Among glioblastomas treated by radical resection, awake surgeries were performed only for 6 of 197 newly diagnosed cases (3.0%) and 11 of 323 total surgeries (3.4%), whereas 26 newly diagnosed cases (13.2%) and 53 surgeries (16.1%) were radically resected with stimulation mapping (Table 2).

II. Resection rates and mapping results

GTR was accomplished in 20 of 42 newly diagnosed cases (47.6%) and 32 of 59 surgeries (54.2%). During the same period, the same histopathological tumors treated by awake surgeries were resected totally in 289 of 462 radical surgeries excluding biopsies (62.6%) without stimulation mapping, and 66 of 99 radical surgeries excluding biopsies (66.7%) with stimulation mapping under general anesthesia. There was no significant difference (chi-square test, \( p = 0.298 \)). GTR could be performed in only 2 of 8 failed awake surgeries (25.0%) (Table 3). Except for these 8 failed awake surgeries, GTR was achieved in 16 of 30 surgeries with positive language mapping (53.3%) and 10 of 16 surgeries with negative language mapping (62.5%), which could maintain the fully awake condition until the end of tumor removal. Four of 5 surgeries without language mapping (only motor mapping) (80.0%) could be resected totally. There was no significant difference between these four groups (chi-square test, \( p = 0.209 \)).

III. Intraoperative events

Mean times in the fully awake condition in the early and late stages were 85 ± 42 and 231 ± 86 (mean ± SD) minutes, respectively (ANOVA, \( p < 0.0001 \)) (Fig. 1). Eight of 59 surgeries (13.6%) could not undergo complete language mapping and monitoring until the final stage of tumor resection, considered as failed awake craniotomy. Times in

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**Table 1 Surgical procedures for newly diagnosed patients and for all patients including with recurrence**

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Newly diagnosed</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy</td>
<td>126 (18.5%)</td>
<td>173 (17.6%)</td>
</tr>
<tr>
<td>Radical resection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without stimulation mapping</td>
<td>447 (65.6%)</td>
<td>645 (65.5%)</td>
</tr>
<tr>
<td>With stimulation mapping</td>
<td>108 (15.9%)</td>
<td>167 (17.0%)</td>
</tr>
<tr>
<td>under awake condition</td>
<td>42 (6.2%)</td>
<td>59 (6.0%)</td>
</tr>
<tr>
<td>under general anesthesia</td>
<td>66 (9.7%)</td>
<td>108 (11.0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>681</strong></td>
<td><strong>985</strong></td>
</tr>
</tbody>
</table>
Table 2 Surgical procedures for patients with the same histologies and locations as patients treated by radical surgery under awake condition

<table>
<thead>
<tr>
<th>WHO grade</th>
<th>Histology</th>
<th>With stimulation mapping</th>
<th>Without stimulation mapping</th>
<th>Total radical surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Under awake condition All</td>
<td>Under general anesthesia All</td>
<td>Newly diagnosed All</td>
</tr>
<tr>
<td>I</td>
<td>Pilocytic astrocytoma (supratentorial type excluding optic/hypothalamic and brain stem tumor)</td>
<td>2 3 5 7</td>
<td>1 1 0 0</td>
<td>27 30 34 40</td>
</tr>
<tr>
<td></td>
<td>Ganglioglioma</td>
<td>1 2 5 7</td>
<td>18 18</td>
<td>24 27</td>
</tr>
<tr>
<td>II</td>
<td>Diffuse astrocytoma</td>
<td>14 14 11 15</td>
<td>30 33 55 62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oligodendrogloma</td>
<td>3 3 6 7</td>
<td>8 9 17 19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oligoastrocytoma</td>
<td>8 8 3 6</td>
<td>13 15 24 29</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Anaplastic astrocytoma</td>
<td>20 30 25 35</td>
<td>84 124 129 189</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligodendrogloma</td>
<td>11 15 11 15</td>
<td>33 55 55 85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic oligoastrocytoma</td>
<td>5 7 8 10</td>
<td>27 34 40 51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic ganglioglioma</td>
<td>1 3 4 7</td>
<td>13 16 18 26</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atypical central neurocytoma (lobar type)</td>
<td>1 1 0 0</td>
<td>0 0 1 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anaplastic ependymoma (lobar type)</td>
<td>1 1 2 3</td>
<td>5 9 8 13</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Glioblastoma</td>
<td>6 12 20 42</td>
<td>171 275 197 329</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medulloblastoma supratentorial metastasis</td>
<td>6 11 20 42</td>
<td>171 270 197 323</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>42 59 61 99</td>
<td>312 462 415 620</td>
<td></td>
</tr>
</tbody>
</table>

All: all patients including with recurrence, WHO: World Health Organization.

Table 3 Correlations between the results of intraoperative mapping and resection rates

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Gross total (p Value)</th>
<th>Subtotal/partial (p Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative language mapping</td>
<td>16</td>
<td>10 (62.5%)</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Positive language mapping</td>
<td>30</td>
<td>16 (53.3%)</td>
<td>14 (46.7%)</td>
</tr>
<tr>
<td>Failed awake surgery</td>
<td>8</td>
<td>2 (25.0%)</td>
<td>6 (75.0%)</td>
</tr>
<tr>
<td>Only motor mapping</td>
<td>5</td>
<td>4 (80.0%)</td>
<td>1 (20.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>59</td>
<td>32 (54.2%)</td>
<td>27 (45.8%)</td>
</tr>
</tbody>
</table>

fully awake condition of 8 failed awake surgeries ranged from 95 to 300 (average 178 ± 75, median 175) minutes. There was no significant difference in fully awake time between failed and successful (range 50–360, average 173 ± 105, median 165 minutes) awake surgeries (ANOVA, p = 0.8978). All intraoperative seizures (3/59 surgeries, 5.1%) could be easily controlled with cold saline irrigation,20 and did not correlate with awake surgery failure. The reasons for incomplete language mapping and monitoring were as follows: further deterioration of preoperative language dysfunction influenced by prescribed propofol and remifentanil until the awake condition prevented naming objects under electrical stimulation (free conversation and checking whether patients could obey simple commands were maintained for preserving disturbed language functions) in 3 cases; developing lethargy during language subcortical mapping despite even complete withdrawal of propofol and remifentanil in 3 cases; patient’s refusal to maintain the awake condition from fear during the cortical mapping in 1 case; and emotional incontinence during the final stage of subcortical mapping in 1 case.

IV. Postoperative neurological events and mapping results

Mortality rate was 0%. Early severe deficits were
observed in 15.3% (9/59 surgeries), and early deficits of any severity were observed in 32.2% (19/59 surgeries) (Table 4). In the newly diagnosed cases, early severe deficits were observed in 16.7% (7/42 surgeries), and early deficits of any severity were observed in 35.7% (15/42 surgeries). Late severe deficits were observed in 5.1% (3/59 surgeries), and late deficits of any severity were observed in 22.0% (13/59 surgeries) (Table 4). In the newly diagnosed cases, late severe deficits were observed in 4.8% (2/42 surgeries), and late deficits of any severity were observed in 26.2% (11/42 surgeries). Both of these cases with severe late deficits were progressive and highly infiltrative anaplastic astrocytomas. Their preoperative language deficits (severe dysarthria and anomia, respectively) deteriorated postoperatively into motor aphasia, and were not improved with progressive disease. Negative language mapping cases did not suffer severe deficits in both the early (chi-square test, \( p = 0.047 \)) and late (chi-square test, \( p = 0.278 \)) stages (Table 4). In contrast, high incidence of severe deficits, 3 as early (chi-square test, \( p = 0.060 \)) and 2 as late (chi-square test, \( p = 0.006 \)) of 8 cases, occurred after failed awake surgery.

### V. Outcomes

Fifteen of 42 patients with newly diagnosed cases had died by December 31, 2012. Fourteen patients died of disease progression. One patient with left premotor anaplastic oligodendroglioma died of bladder cancer, resulting in survival period of 41 months. Eastern Cooperative Oncology Group performance status of the surviving 27 patients was grade 0 for 22, grade 1 for 4, and grade 3 for 1 because of complicated cerebral infarction during the long-term follow-up period. Thus, 96.3% of surviving patients could live independent lives.

With the same histologies and locations as cases resected under awake condition selected from the parent population with radical resection, the OS of each WHO grade is summarized in Table 5 and Fig. 3. There was no statistical significance between

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### Table 4 Correlations between the results of intraoperative mapping and neurological outcome

<table>
<thead>
<tr>
<th>Number</th>
<th>Early neurological outcome</th>
<th>Late neurological outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any deficits</td>
<td>Severe deficits</td>
</tr>
<tr>
<td><strong>Negative language mapping</strong></td>
<td>16</td>
<td>4 (25.0%, ( p = 0.470 ))</td>
</tr>
<tr>
<td><strong>Positive language mapping</strong></td>
<td>30</td>
<td>10 (33.3%, ( p = 0.850 ))</td>
</tr>
<tr>
<td><strong>Failed awake surgery</strong></td>
<td>8</td>
<td>3 (37.5%, ( p = 0.730 ))</td>
</tr>
<tr>
<td><strong>Only motor mapping</strong></td>
<td>5</td>
<td>2 (40.0%, ( p = 0.697 ))</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>59</td>
<td>19 (32.2%)</td>
</tr>
</tbody>
</table>

*Significant difference, \( p < 0.05 \).

### Table 5 Overall survival of newly diagnosed patients with the same histologies and locations as patients treated by radical surgery under awake condition

<table>
<thead>
<tr>
<th>Number</th>
<th>Median survival time (day)</th>
<th>Overall survival probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radical resection without stimulation mapping</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade I</td>
<td>27</td>
<td>NR</td>
</tr>
<tr>
<td>WHO grade II</td>
<td>30</td>
<td>NR</td>
</tr>
<tr>
<td>WHO grade III</td>
<td>84</td>
<td>NR</td>
</tr>
<tr>
<td>WHO grade IV</td>
<td>171</td>
<td>606</td>
</tr>
<tr>
<td><strong>Radical resection with stimulation mapping under awake condition</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade I</td>
<td>2</td>
<td>807</td>
</tr>
<tr>
<td>WHO grade II</td>
<td>14</td>
<td>3666</td>
</tr>
<tr>
<td>WHO grade III</td>
<td>20</td>
<td>2683</td>
</tr>
<tr>
<td>WHO grade IV</td>
<td>6</td>
<td>860</td>
</tr>
<tr>
<td><strong>Radical resection with stimulation mapping under general anesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO grade I</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>WHO grade II</td>
<td>11</td>
<td>NR</td>
</tr>
<tr>
<td>WHO grade III</td>
<td>25</td>
<td>4773</td>
</tr>
<tr>
<td>WHO grade IV</td>
<td>20</td>
<td>1160</td>
</tr>
</tbody>
</table>

NA: not available, WHO: World Health Organization.
patients treated under the awake condition, with stimulation mapping under general anesthesia, and without stimulation mapping, except for between awake surgery \((n = 2)\) and without stimulation mapping \((n = 27)\) for WHO grade I (log rank test, \(p = 0.0004\)). This difference was caused by the death of a 30-year-old male who had pilocytic astrocytoma in the left premotor area, which was totally resected under the awake condition in November 2002. The histopathological diagnosis was pilocytic astrocytoma with 3% of Ki-67 labeling index. His postoperative course was uneventful, but rapid local relapse was observed. This recurrent lesion was resected totally under general anesthesia. The tumor transformed into a glioblastoma. Although additional radiochemotherapies and reoperation were performed, the tumor disseminated throughout the leptomeningeal space. He died of disease progression, not due to local control failure but through dissemination, in January 2005 (OS 807 days).

**Discussion**

Intraoperative electrical cortico-subcortical mapping under the awake condition is crucial to allowing the most extensive removal of glioma with maximum functional preservation. Our ultimate goal during the awake condition is to obtain patient comfort to undergo the mapping in a positive manner, maximizing the functional information. The utilization of this technique is likely to vary with the surgeon. All the present series and parent populations were operated by a single neurosurgeon (first author T.K.), who was taught all the procedures for awake surgery by Dr. Berger. The present analyses may make meaningful contributions to evaluate how much impact awake surgery has for the treatment of gliomas, because all the surgeries had been performed by a single neurosurgeon, and the results including survival data were analyzed with the parent population.
I. What does awake surgery bring to glioma surgery?

The illustrative case demonstrates how important awake surgery is for glioma surgery. In this case, negative language mapping permitted this tumor to be aggressively resected without language deficits. Neurosurgeons are unable to perform GTR or maximize resection without this information for gliomas near/adjacent to eloquent areas. Awake surgery has brought “logic” into glioma surgery.

II. What is the frequency of awake surgery?

We had limited experience of awake surgery for language mapping except during the first 15 years, because motor mapping and monitoring can be performed using simulation mapping under general anesthesia. Thus, the frequency of awake surgeries might be relatively low compared to other institutes universally applying awake surgery to motor mapping and monitoring. If all simulation mapping surgeries including under general anesthesia are included, the frequency was 19.5% and 20.6%, respectively. Around 20% of radical surgery procedures for gliomas required simulation mapping techniques. Those patients most in need had WHO grade II gliomas, diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas, who required intraoperative stimulation mapping up to around 50% (Fig. 3, Table 2).

It is not so clear how often awake surgery is necessary for resection of gliomas. Bernstein in Toronto Western Hospital routinely performed 610 awake craniotomies as an adjunct for supratentorial tumor resection between 1991 and 2006, and 367 of 610 cases (60.2%) were diagnosed as gliomas. Between 1993 and 2006, a total of 310 consecutive awake craniotomy procedures for the removal of intra-axial tumors near and/or within eloquent cortices were performed at the University of Texas MD Anderson Cancer Center, and 284 of 310 procedures (91.6%) were performed for gliomas. Ram et al. performed 424 awake craniotomies including 313 gliomas (73.8%) at Tel Aviv Medical Center between 2003 and 2010. Duffau performed 140 awake craniotomies for resection of glioma in an eloquent area of the brain in Montpellier University Hospital between 2008 and 2010. Between 1997 and 2005, a total of 250 patients with gliomas underwent surgery at the University of California at San Francisco (UCSF) Medical Center, with the use of intraoperative language mapping while the patients were awake. Awake surgeries were performed for a large number of gliomas, but there is no information about the parent populations in these series.

Between 1997 and 2009, 500 consecutive adult patients with newly diagnosed supratentorial glioblastoma underwent radical surgical removal at the UCSF. Intraoperative motor mapping was conducted in 116 patients (23%), language mapping in 43 patients (9%), and subcortical mapping in 34 patients (7%). This paper did not mention how often they applied awake surgery for resection of glioblastomas, but at least 9% (language mapping) must have been resected under the awake condition. In excess of 800 patients with low-grade gliomas were treated at the UCSF between 1989 and 2005. Of these, 216 patients were radically resected, and motor and speech mapping were performed in 154 (71%) and 75 (35%) cases, respectively. The majority of surgical procedures (74%) were performed by Dr. Berger himself. By estimate, under 10% (75/800) of all low grade gliomas, including those treated by biopsy, were radically resected under the awake condition with language mapping. Chacko et al. reported that 883 patients underwent craniotomies for supratentorial tumors in Christian Medical College in India between 2002 and 2010. Of these, 84 (9.5%) were chosen for awake craniotomy, and 67 were histologically verified as gliomas. From these results, awake surgery for gliomas may be necessary for around 10% of all gliomas.

In contrast, Sacko et al. reported that 356 patients collected prospectively with supratentorial gliomas underwent open brain surgery between 2002 and 2007 in the Institut National de la Santé et de la Recherche Médicale. Awake craniotomy with intraoperative brain mapping was used in 143 of 356 patients (40%). They performed awake surgeries in 45 of 137 glioblastomas (32.8%), much higher than the results of UCSF and ours. The frequency of awake surgery must depend on the indications and the characteristics of their parent populations.

III. Intraoperative events

Duffau et al. reported that the patients remained fully awake for a mean time of 98 minutes for resection of 140 gliomas in an eloquent area using the AAA protocol. A total of 139 patients (99.2%) were considered fully cooperative during the awake phase. The reasons for this high success rate were as follows: rigorous selection of patients; quality of the information given by each team member the day before surgery; and strong motivation of the patients who are aware of their disease and its outcome. In contrast, our mean time was 231 minutes with the same AAA protocol, and 29 of 36 patients (80.6%) were considered as successful awake surgeries. Suc-
cess rate of awake surgery might depend on the definition itself. In our cases, only 1 of 24 awake surgeries (4.2%) to obtain only the cortical function (early stage) was considered as a failure. One of the reasons for our relatively low incomplete language mapping rate might be the much longer awake time. It is a matter of speculation but longer awake time might lower brain temperature resulting in lethargy and functional deterioration. I tried to reduce the time for the fully awake state (Fig. 1), but complete subcortical functional data and resection of the tumor are still difficult to obtain in a short time.

IV. Postoperative neurological events and resection rates

De Witt Hamer et al. reviewed 90 reports published between 1990 and 2010 with 8091 patients who underwent surgery for supratentorial glioma with or without intraoperative stimulation mapping. They categorized new postoperative neurological deficits on the basis of timing and severity. Early and late severe neurological deficits were observed in 36.0% and 3.4% of patients after resection with intraoperative stimulation mapping, respectively. Their conclusion was that reversible temporary loss of function of critical brain structures is more frequent with intraoperative stimulation mapping, but irreversible neurological damage is more effectively avoided, in comparison to surgery without mapping.

In the present report, we evaluated the same criteria, and early and late severe neurological deficits were observed in 15.3% and 5.1%, respectively (Table 4). The relationship between resection rate and intraoperative functional information obtained under the awake condition confirms that awake surgery contributes to maximize resection of gliomas within/adjacent eloquent areas by minimizing the rate of severe deficits.

Nossek and Ram et al. reported that a significantly lower rate of GTR (54% vs 83%) with a higher incidence of short-term speech deterioration postoperatively (23.5% vs 6.1%) as well as at 3 months postoperatively (15.4% vs 2.3%) was observed in 27 patients with failed awake craniotomy (6.4%) compared with patients with successful awake craniotomy (n = 397). They concluded that failures of awake craniotomy were associated with lower incidence of GTR and increased postoperative morbidity. Their cases included 313 gliomas (73.8%) and other 111 lesions. In contrast, negative mapping of eloquent areas provides a safe margin for surgical resection with a low incidence of neurological deficits.

Of the 200 patients in whom eloquent areas were identified, 86 (43%) experienced worsened neurological deficits in the immediate postoperative period, and 42 patients (21%) continued to have worsened deficits at the 1-month follow up. In contrast, of the 109 patients in whom eloquent areas were not localized, only 25 (23%) had deficits in the immediate postoperative period, and only 10 patients (9%) had deficits at the 1-month follow-up. Kim et al. concluded that positive cortical mapping was a statistically significant predictor of worsened neurological deficits both in the immediate postoperative period and at the 1-month follow up. Their different results from ours showed neither positive mapping nor intraoperative neurological changes had a significant impact on the overall extent of resection.

V. Outcomes

Unfortunately, little survival data of gliomas treated by awake surgery has been reported. Sacko et al. disclosed survival data about glioblastoma and low-grade gliomas (n = 48/109) in a figure without discussion. In glioblastomas, there was no significant difference in OS between patients who underwent awake surgery (n = 45) and patients who underwent surgery under general anesthesia (n = 92) (p = 0.06). In low-grade gliomas, there was a significant difference in OS between these patients (n = 48 vs n = 61, p < 0.001). Chang et al. retrospectively analyzed 281 cases with supratentorial low-grade gliomas treated in the UCSF, and categorized 4 groups, non-eloquent, no mapping, false-eloquent (all patients with tumors presumed to involve eloquent areas but which were found to be safe eloquent brain based on intraoperative mapping), and true-eloquent (all patients in whom the presumption of eloquent brain involvement was confirmed through intraoperative mapping). A major finding was that patients in the false-eloquent group had excellent survival outcomes, which suggests that mapping can drastically change the long-term progress for patients with low-grade gliomas through extensive resection. In contrast, the true-eloquent group did not have better survival even with intraoperative mapping.

At this point, it is not entirely convincing that awake surgery had improved the survival outcomes of patients with gliomas. At least in our cases, we could confirm that the OS of patients with glioma in or near eloquent areas resected using awake surgery compared favorably with those in other regions.

Conclusions

We retrospectively analyzed 15 years experience of awake surgeries with neurophysiological monitoring for neuroepithelial tumors in Tohoku Univer-
sity. Awake surgery with intraoperative stimulation mapping may contribute to improve the outcome of gliomas by maximizing the tumor resection and minimizing the surgical morbidity. The biggest benefit of this procedure is thought to be the identification and total resection of tumor in the false-eloquent group, which can be found as negative mapping results. It is still difficult to confirm the survival benefit using awake surgery for infiltrative gliomas in the true-eloquent group, but further investigations of much larger sets of meticulous retrospective data or prospective studies will reveal this assignment.

**Acknowledgment**

We express our grief at the death of Dr. Kiyotaka Sato. We would like to dedicate this manuscript to him.

**Conflicts of Interest Disclosure**

All authors have already declared conflicts of interest (COI) status to the Japan Neurosurgical Society. This manuscript has no COI that should be disclosed.

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