

Contribution of combined intraoperative electrophysiological investigation with 3-T intraoperative MRI for awake cerebral glioma surgery: comprehensive review of the clinical implications and radiological outcomes

*Diana Ghinda, MD,^{1,2} Nan Zhang, MSc,¹ Junfeng Lu, MD, PhD,¹ Cheng-Jun Yao, MD,¹ Shiwen Yuan, MD,¹ and Jin-Song Wu, MD, PhD¹

¹Glioma Surgery Division, Department of Neurosurgery, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China; and ²Department of Neurosurgery, The Ottawa Hospital, University of Ottawa, Ontario, Canada

OBJECTIVE This study aimed to assess the clinical efficiency of combined awake craniotomy with 3-T intraoperative MRI (iMRI)-guided resection of gliomas adjacent to eloquent cortex performed at a single center. It also sought to explore the contribution of iMRI to surgeons' learning process of maximal safe resection of gliomas.

METHODS All patients who underwent an awake craniotomy and iMRI for resection of eloquent area glioma during the 53 months between January 2011 and June 2015 were included. The cases were analyzed for short- and long-term neurological outcome, progression-free survival (PFS), overall survival (OS), and extent of resection (EOR). The learning curve was assessed after dividing the cohort into Group A (first 27 months) and Group B (last 26 months). Statistical analyses included univariate logistic regression analysis on clinical and radiological variables. Kaplan-Meier and Cox regression models were used for further analysis of OS and PFS. A p value < 0.05 was considered statistically significant.

RESULTS One hundred six patients were included in the study. Over an average follow-up period of 24.8 months, short- and long-term worsening of the neurological function was noted in 48 (46.2%) and 9 (8.7%) cases, respectively. The median and mean EOR were 100% and 92%, respectively, and complete radiographic resection was achieved in 64 (60.4%) patients. The rate of gross-total resection (GTR) in the patients with low-grade glioma ($89.06\% \pm 19.6\%$) was significantly lower than that in patients with high-grade glioma ($96.4\% \pm 9.1\%$) ($p = 0.026$). Thirty (28.3%) patients underwent further resection after initial iMRI scanning, with a 10.1% increase of the mean EOR. Multivariate Cox proportional hazards modeling demonstrated that the final EOR was a significant predictor of PFS (HR 0.225, 95% CI 0.070–0.723, $p = 0.012$). For patients with high-grade glioma, the GTR ($p = 0.033$), the presence of short-term motor deficit ($p = 0.027$), and the WHO grade ($p = 0.005$) were independent prognostic factors of OS. Performing further resection after the iMRI ($p = 0.083$) and achieving GTR ($p = 0.05$) demonstrated a PFS benefit trend for the patients affected by a low-grade glioma. Over time, the rate of performing further resection after an iMRI decreased by 26.1% ($p = 0.005$). A nonsignificant decrease in the rate of short-term ($p = 0.101$) and long-term ($p = 0.132$) neurological deficits was equally noted.

CONCLUSIONS Combined awake craniotomy and iMRI is a safe and efficient technique allowing maximal safe resection of eloquent area gliomas with possible subsequent OS and PFS benefits. Although there is a learning curve for applying this technique, it can also improve the surgeon's ability in eloquent glioma surgery.

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KEY WORDS glioma; awake craniotomy; intraoperative MRI; extent of resection; survival; clinical outcome; quality of life; eloquent areas; intraoperative neurophysiological monitoring

ABBREVIATIONS BOLD = blood oxygen level-dependent; DTI = diffusion tensor imaging; EOR = extent of resection; GTR = gross-total resection; HGG = high-grade glioma; iMRI = intraoperative MRI; LGG = low-grade glioma; MEP = motor evoked potential; OS = overall survival; PFS = progression-free survival; QOL = quality of life.

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* Dr. Ghinda and Mr. Zhang contributed equally to this work.

THE natural history of brain gliomas has been extensively studied. Multiple studies have demonstrated the benefits of radical surgery in terms of overall outcome and recurrence-free survival.^{2,4,13–15,22,28–30,32,34} Although there is currently a lack of Class I evidence, these studies suggest a survival benefit derived from maximal resection for both low-grade gliomas (LGGs) and high-grade gliomas (HGGs). Current technological improvements, such as 5-aminolevulinic acid fluorescence and intraoperative MRI (iMRI), circumvent the brain shift that occurs during the surgical procedure. They also enhance the rate of complete tumor resection by providing surgeons with updated information, allowing them to precisely localize tumor remnants intraoperatively and guide their resection accordingly.^{10,17,21,25,31,36} Specifically, the application of iMRI for patients with glioma continues to expand because it can enable maximal resection while maintaining the integrity of uninvolved brain tissue.^{12,17,36} Nonetheless, as depicted in a recent Cochrane Review, first-level evidence for the clinical applications of such expensive technologies is still lacking and there is no clear answer with regard to the overall benefit in terms of survival and quality of life (QOL).¹ A prospective, randomized, triple-blinded study is currently being performed at our center in an attempt to answer these critical questions.³⁶

Although the extent of resection (EOR) represents a crucial factor in terms of clinical outcome, the ultimate goal of the surgery is a maximally safe resection. As such, radical surgery of infiltrative glioma might compromise the patient's QOL if the procedure causes new neurological sequelae. Currently, the functional and electrophysiological mapping remains the gold standard for identifying and preserving eloquent structures.^{6,7}

The potential role and benefit of combining iMRI and awake craniotomy have been discussed in few studies to date, with no clear results in terms of the clinical benefit obtained by the use of iMRI-guided resection during awake craniotomies.^{16,19,24,33} Our group has previously demonstrated the safety of combining awake functional mapping with high-field (3-T) iMRI for the resection of gliomas located in proximity to language areas.¹⁹ Herein, we present the outcome of a consecutive series of 106 patients with eloquent gliomas who underwent an awake craniotomy in an iMRI-integrated neurosurgical suite.

Besides describing the clinical and radiological outcomes of the patients, we equally attempted to identify the prognosticators of progression-free survival (PFS) and overall survival (OS). To our knowledge, no other study has analyzed those factors. We equally analyzed the associated learning process and delineated the value of using this technique between the 2 different groups: HGG and LGG. To our knowledge, this represents the largest case series reported to date and provides further insights into the potential benefits and pitfalls of this combined approach.

Methods

Patient Selection

All cases of cerebral supratentorial glioma resections performed in the iMRI suite between January 2011 and

June 2015 were identified from our prospectively maintained database. From those, patients who underwent an awake craniotomy with iMRI guidance were included in our study. In all of the awake cases, the tumor location was in proximity to eloquent brain regions such as receptive and expressive speech areas in the dominant hemisphere and motor or sensory cortex. The study was approved by Huashan Hospital's institutional review board.

Preoperative Evaluation

Clinical variables included age, sex, symptoms, and signs at initial presentation and Karnofsky Performance Scale score. Prior to each procedure, the attending surgeon performed a complete neurological assessment and the language function was assessed in detail, as described in a previous study performed at our center.¹⁹ The language function was assessed using the Aphasia Quotient score (spontaneous speech, comprehension, repetition, and naming).

Radiological data included the size and location of the tumor and the hemisphere involved (dichotomized into dominant and nondominant). The tumor location was classified into frontal, temporal, parietal, and insular lobes. Tumor infiltration and/or proximity of presumed eloquent cortex was also recorded and was classified in motor and language areas (such as supplementary motor area, precentral gyrus/central gyrus/internal capsule, and dominant hemisphere perisylvian language areas [superior temporal, inferior frontal, and inferior parietal areas]). All preoperative brain images were obtained in the diagnostic room of an iMRI-integrated neurosurgical suite using a 3-T scanner (MAGNETOM Verio 3.0 T, Siemens AG) 1 day prior to the procedure. The imaging protocol included a FLAIR sequence or contrast-enhanced 3D magnetization-prepared rapid-gradient echo sequence as well as diffusion tensor imaging (DTI). A blood oxygen level-dependent (BOLD) functional MRI was also performed preoperatively for all patients. A postprocessing workstation (Syngo MultiModality Workplace, Siemens AG) was used to reconstruct and merge the motor and language pathways and activation areas. The 3D reconstructed series were used intraoperatively.

Postoperative Neurological Evaluation

The clinical outcome was recorded prospectively by a certified senior neurosurgeon (J.S.W.). Serial clinical evaluations were performed at 1 month, 3 months, and 6 months after the initial surgery and thereafter on a yearly basis. Standard adjuvant treatment consisting of radiotherapy and/or chemotherapy was prescribed in all patients with HGG and in patients with LGG with no total resection or with risk factors according to published clinical guidelines.³

To analyze the neurological morbidity and functional outcome, we defined a short-term worsening language and motor neurological function as any new-onset or worsening function occurring within 1 month after the surgical intervention. Given the retrospective nature of the study, we attempted to distinguish the deficits directly related to the surgical intervention versus those that were related to

tumor recurrence or treatment side effects. As such, we classified the patients as having a permanent deficit if their best neurological function recorded during the period between the third postoperative month and the end of the follow-up was worse than preoperatively. The percentage of worsening language and motor function was calculated from the total number of patients tested for that specific function.

Volumetric Analysis

Board-certified neuroradiologists blinded to the patient outcome performed the pre-, intra-, and postoperative volumetric assessment for all patients, using 3D magnetization-prepared rapid-gradient echo images with gadolinium for contrast-enhancing gliomas and T2-weighted FLAIR images for nonenhancing gliomas. For all cases, the final iMRI scan was either obtained immediately in the iMRI suite while the patient was still under anesthesia or within 72 hours after the procedure if further resections were performed with no iMRI confirmation (Fig. 1). All pre-, intra-, and postoperative tumor segmentations were performed manually on a Macintosh platform using the OsiriX image processing software (Pixmeo).²⁷ The volumes of original lesions or subsequent remnants were measured (Figs. 2 and 3). The EOR was calculated as follows: (preoperative tumor volume – postoperative tumor volume)/preoperative tumor volume.³¹

End Points

The primary end point was the EOR, and the secondary end points were PFS, OS, and surgery-related morbidity. Gross-total resection (GTR) was defined as the complete disappearance of all enhancing lesions (T1-weighted) and the complete disappearance of all T2-weighted FLAIR abnormalities for nonenhancing lesions. The interval be-

tween the date of surgery and the date of death or the date of last follow-up was used as the follow-up period for the OS analysis. Similarly, the follow-up duration for the PFS analysis was defined as the interval between the date of surgery and the date on which the first evidence of radiological progression was detected (defined as an increase in FLAIR/T2 abnormality or new contrast enhancement) or the date of the last known MR image without evidence of disease progression. A subgroup analysis was also performed according to the LGG (WHO Grade II) and HGG (WHO Grades III and IV) subgroups.¹⁸

The findings of positive intraoperative functional cortical mapping were also recorded and classified as motor, verbal, or both. Because the results of subcortical mapping were not consistently recorded, they were not analyzed in this study. The learning curve was assessed after dividing the cohort into Group A (first 27 months) and Group B (last 26 months).

Surgical Intervention and iMRI

All procedures using iMRI were performed according to the technique described in a previously published study performed at our institution.¹⁹ This entails a novel minimally draping technique combined with a monitored anesthesia care approach. The detailed anesthesia technique was described in a previous publication and involves initially achieving a moderate sedation with boluses of intravenous propofol followed by continuous administration of a low dose of remifentanyl (0.01 µg/kg/min) or dexmedetomidine (0.1 µg/kg/hr) during mapping.¹⁹ Throughout the operation, supplemental inspired oxygen was delivered by nasal cannula or facemask, and no laryngeal mask airway or endotracheal tubing was applied during the iMRI acquisition phase. The iMRI-integrated neurosurgical suite included an operating room and a diagnostic room that

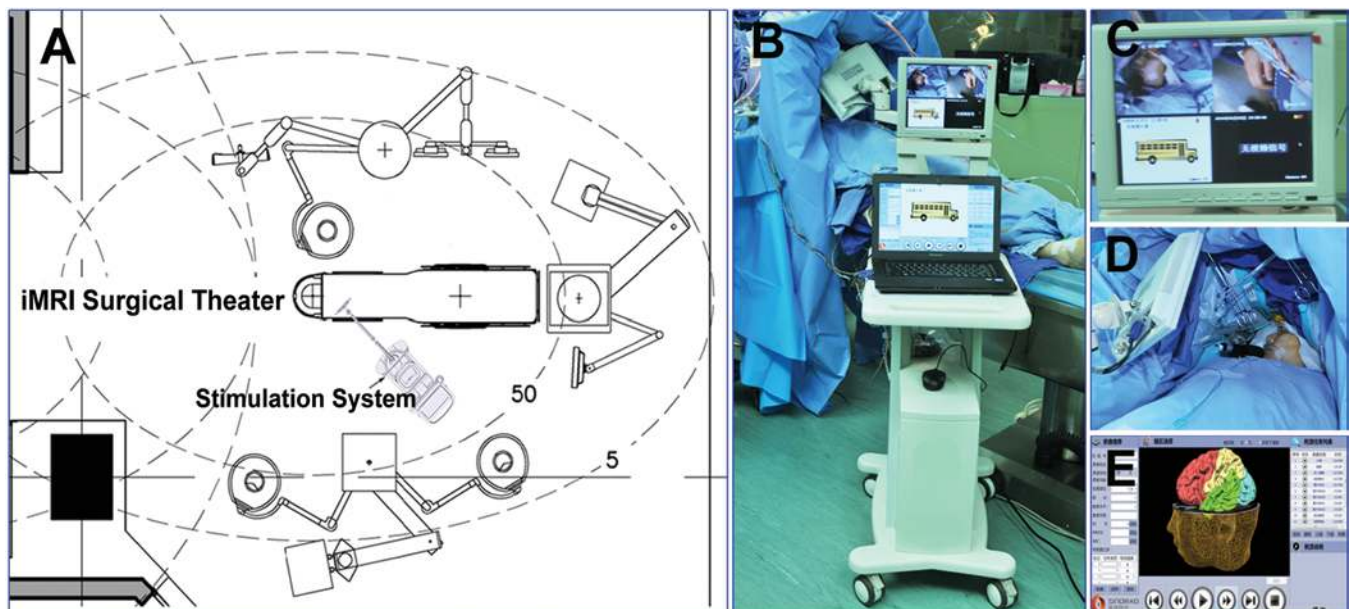


FIG. 1. The location of the brain function stimulation system in the iMRI suite is shown (A and B). The surgeon's interface screen shows the patient's response (C) to stimulus signals sent by the working station to the patient's interface (D). The stimulation tasks are automatically chosen according to the location of the tumor (E).

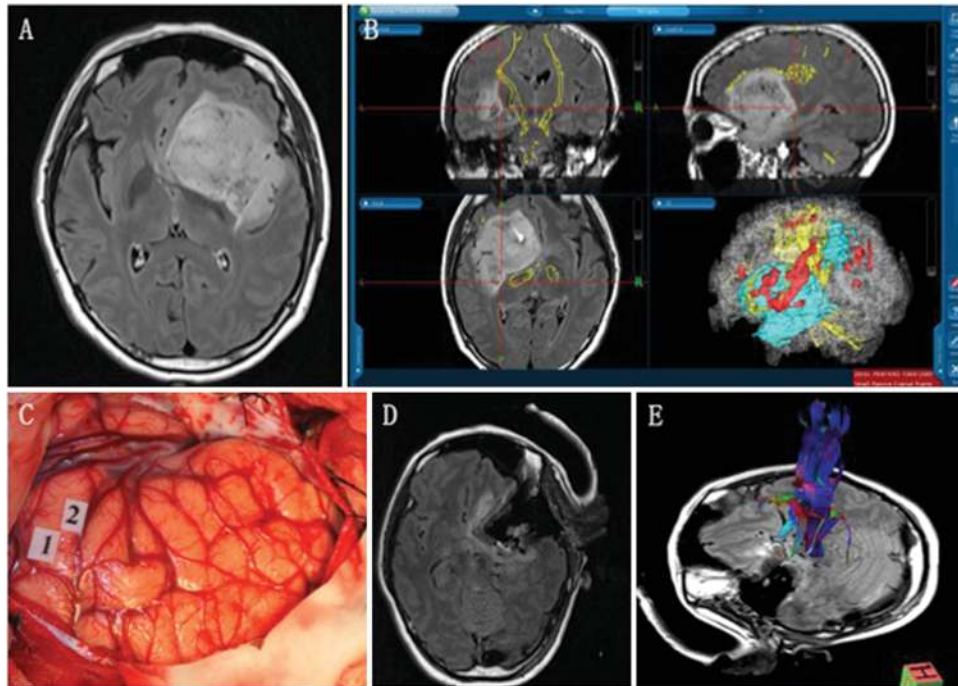


FIG. 2. Illustrative Case 1. A 43-year-old woman with a 113.96-cm³ left frontotemporal astrocytoma (WHO Grade II). Preoperative structural and functional MR images (BOLD and DTI, respectively) show the relationship among the tumor, the language area (depicted in red), and the pyramidal tract (depicted in yellow) (A and B). Intraoperative functional language mapping confirmed the preoperative functional MRI results (C). Resection of the tumor to the functional margin, as manifested by a decrease of the MEP potential, was performed. The intraoperative structural and DTI images (D and E) confirmed that maximal resection was obtained, with a residual tumor volume of 8.86 cm³. The patient experienced transient right limb weakness in the immediate postoperative period but was completely recovered 1 month after the operation.

had a movable 3-T magnet with a 70-cm working aperture. If a residual tumor that was amenable to further resection was identified according to the mapping and electrophysiological result, the navigational images were updated for further resection guidance. Lu et al. have given a detailed description of the technique used.¹⁹ During the operation, the communication channel between surgeons and patients used a brain function stimulation system that was designed in 2012 by our center and Sinorad Corporation.

Brain Function Stimulation System

During the process of accumulating experiences with awake surgery in the iMRI suite, we developed the brain function stimulation system (Chinese patent no. ZL 1220303939.1). The system can easily give stimuli signals (including images, text, sounds, and music) to the patient and simultaneously send the response messages of the patients (presented via language, limb motor, and finger touch) to the surgeons.

As illustrated in Fig. 1, this system is composed of 3 parts including the patient interface, the operator interface, and the relative application software. The patient interface consists of the following parts: a light-emitting diode screen to project the stimuli, a camera to monitor the face and body of the patient, and a microphone to receive feedback from the patient. The operator interface includes the computer workstation that produces stimuli signals and the monitor display that allows the surgeon to observe the patient's responses. The software is specific-

ly designed to define the stimulating mode preoperatively, thus facilitating the intraoperative maneuvers consisting of projecting and receiving the stimulation signal and response, for both the surgeon and the patient, respectively. This system facilitates the process of functional mapping, guarantees the safety of the patients, and provides an effective communication channel between the medical staff and the patients in the intraoperative environment.

Intraoperative Mapping

Intraoperative functional mapping was performed using cortico-subcortical electrical stimulation. A 5-mm wide bipolar electrode with a pulse frequency of 60 Hz and an amplitude of 2–10 mA was used. Subcortical stimulation was performed using a biphasic square-wave pulse delivered at 60 Hz with a current amplitude ranging from 2 to 20 mA. The somatosensory evoked potential was recorded with a 6-contact subdural strip electrode. If after-discharge activity indicated that the stimulation current was too high, the current amplitude was decreased by 0.5–1 mA. The central sulcus was identified by an N20 to P20 phase reversal. Intraoperative continuous transcortical motor evoked potential (MEP), followed by confirmatory subcortical stimulation, was performed when the resection was in proximity to the motor areas. All of the positive sites were marked on the surface of the cortex with sterile tags, and the resection margin was taken within 0.5–1 cm of eloquent cortical areas. After defining both the functional mapping and anatomical landmarks,

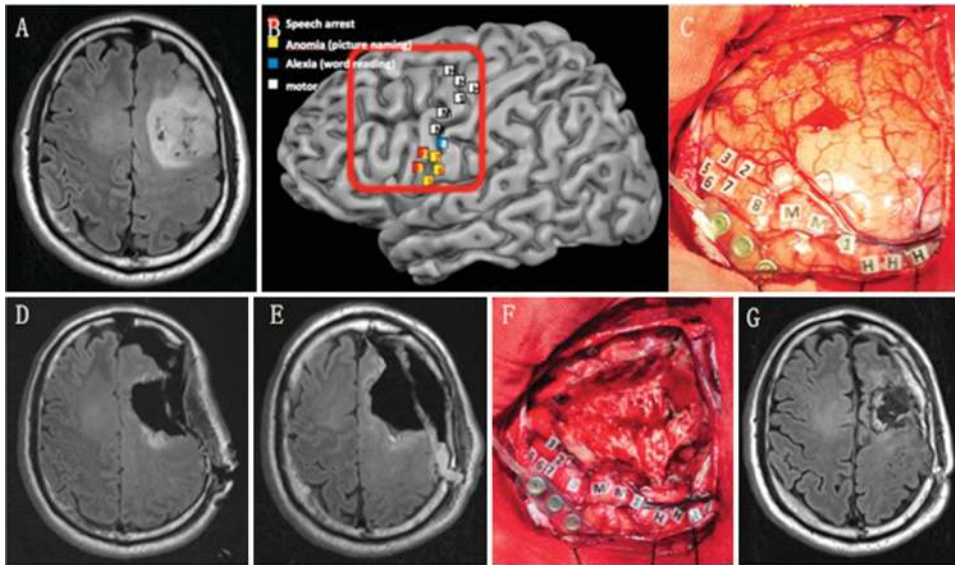


FIG. 3. Illustrative Case 2. A 48-year-old man with a left frontal lobe astrocytoma (WHO Grade II). Preoperative structural imaging showed the tumor was in proximity to the language and motor areas (A). Intraoperative mapping results confirmed that the language and motor areas (B and C) were at the posterior margin of the tumor. The first iMRI evaluation showed a residual at the posterior part of the tumor cavity (D). Because the electrophysiological result allowed further resection, that area was resected (E) while preserving the areas with positive functional mapping (F). The patient had mild language and motor deficits in the immediate postoperative period but was completely recovered 1 month after the operation (G).

tumor resection was conducted with guidance from structural (T2-weighted FLAIR or T1-weighted contrast images) and functional (BOLD or DTI tractography images) navigation. The DTI tractography-based navigation, combined with continuous transcortical MEP monitoring and subcortical stimulation, was performed to localize the adjacent pyramidal tracts and to monitor the subcortical motor pathway. The resection was not continued when the tumor was found to be close to an eloquent area (the safe distance was considered to be approximately 8 mm), as evidenced by the occurrence of 1 or more of the following conditions: 1) obvious deterioration of language function (i.e., speech arrest without oropharyngeal movement) or deterioration of motor movement; 2) more than a 50% decline of compound muscle action potential in either extremity, elicited by subdural strip electrode during continuous transcortical MEP monitoring; and 3) the radiological margin of the tumor was reached in accordance with the intraoperative updated real-time MRI guidance. An iMRI was performed when the attending surgeon deemed that the resection was complete or when the functional mapping was positive on the surgical margin (Figs. 2 and 3).

Statistical Analysis

Descriptive results are summarized as the mean, SD, median, and ranges for continuous variables, and as proportions for categorical variables. The EOR and clinical outcome were compared via the Pearson chi-square test or Fisher exact test. When assessing the impact of EOR, GTR was defined as 100% resection. For Kaplan-Meier curves plotting the EOR and OS or PFS, we divided EOR into $\geq 90\%$ and $< 90\%$ categories for LGG, because this is a common cutoff point for volumetric assessment of the impact of EOR.³⁰ Kaplan-Meier methods were used for

time-to-event measures, log-rank tests were used to make comparisons, and Cox regression models were used to analyze the potential prognostic factors for the main outcome measures. All analyses were conducted using SPSS software version 19.0.0 (IBM, Inc.). A p value < 0.05 was considered statistically significant.

Results

Between January 2011 and June 2015, resections were performed in 672 patients with supratentorial gliomas in the 3-T iMRI integrated surgical suite. Of those, 139 (20.7%) patients underwent an awake craniotomy, among whom 106 (15.8%) had an iMRI scan (Fig. 4). Patients' ages ranged from 18 to 76 years (mean 41.7 years). Seventy-four (69.8%) patients were men and 94 (88.7%) tumors involved the dominant side. A seizure was the presenting symptom in 56 (52.8%) patients. The demographic and radiological characteristics of patients are depicted in Table 1.

Extent of Resection, OS, and PFS

The number of iMRI evaluations ranged from 1 to 2 scans. The median and mean EOR were 100% and 91.97%, respectively. A GTR (complete radiographic resection) was achieved in 64 (60.4%) of patients.

The rate of GTR in patients with an LGG ($89.06\% \pm 19.6\%$ [mean \pm SD]) was significantly lower than that in patients with HGG ($96.4\% \pm 9.1\%$) ($p = 0.026$). For the HGG group, the GTR ($p = 0.033$), the presence of short-term motor deficit ($p = 0.027$), and the WHO grade ($p = 0.005$) were independent prognostic factors of OS (Fig. 5). Further analysis of PFS, performed for patients with LGG, demonstrated a survival benefit trend for patients who underwent a GTR ($p = 0.05$) and those who under-

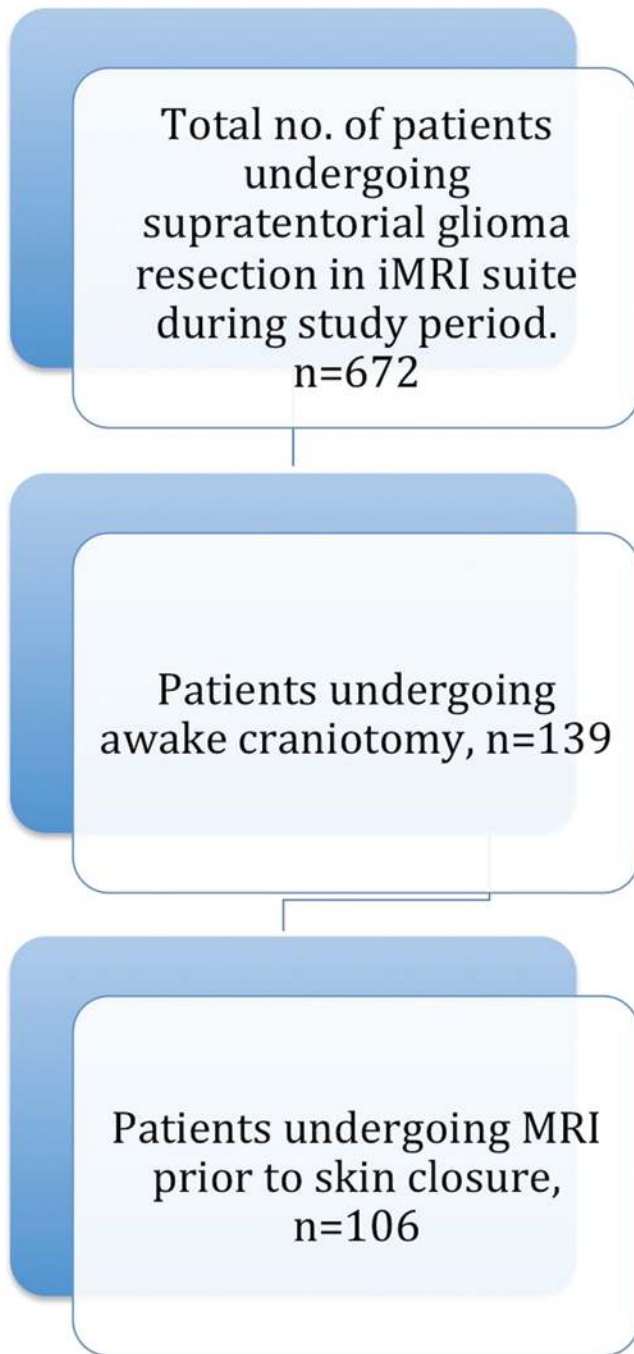


FIG. 4. Description of the cohort.

went further resection after the iMRI ($p = 0.083$) (Fig. 6). The rate of GTR achieved was not significantly associated with the rate of short- or long-term deficits ($p = 0.538$ and $p = 0.847$, respectively).

For 62 patients, the iMRI demonstrated residual tumor. Further tumor resection was continued on the basis of the iMRI dynamic control in 30 cases (28.3%), with a median increase of the EOR of 10.1% (mean 11.4%, range 1%–25.8%). A GTR was achieved in 20 (67%) of 30 patients, and only 4 patients had less than 90% residual after the second resection was performed. A log-rank test was run to determine if there were differences in the survival

TABLE 1. Demographic, clinical, and neuroradiological characteristics of 106 patients undergoing combined awake craniotomy and iMRI for glioma resection

Characteristic	Value
Age at time of op, yrs	
Mean \pm SD	41.7 \pm 12.5
Range	18–76
Sex, n (%)	
M	74 (69.8)
F	32 (30.2)
Location of lobe, n (%)	
Frontal	48 (45.3)
Parietal	9 (8.5)
Temporal	18 (17.0)
Insular	31 (29.2)
Seizure as presenting symptom, n (%)	56 (52.8)
Preop tumor vol, cm ³	
Mean \pm SD	58.0 \pm 37.9
Range	3.5–181.3
Follow-up, mos	
Mean \pm SD	24.8 \pm 15.1
Range	3–57
Adjuvant therapy, n (%)	
None	12 (11.3)
Radiotherapy	22 (20.8)
Chemotherapy	22 (20.8)
Radiochemotherapy	48 (45.3)
NA	2 (1.9)
Dominant hemisphere involvement, n (%)	94 (88.7)
WHO grade, n (%)	
II	64 (60.4)
III	17 (16.0)
IV	25 (23.6)

NA = not available.

distribution of the 62 patients based on whether further resection was performed. The difference in survival distributions for the 2 groups was not statistically significant (chi-square = 0.440, $p < 0.507$). No surgery-related death occurred and there were no complications related to the iMRI nor any adverse events caused by the high-field MRI.

Eloquent Site Involvement and Identification

The preoperative MRI showed that the following functional areas were involved or were found to be close to the tumor: both the motor and speech areas in 80 patients, language cortex in 12 patients, and motor cortex in 14 patients. The positive functional mapping site was detected in 91 patients (85.8%) intraoperatively and determined the functional boundaries of the resection.

Intraoperative Seizures

Three patients (2.8%) had partial intraoperative seizures and 1 patient (0.9%) had a generalized seizure; all seizures developed after direct cortical stimulation of the

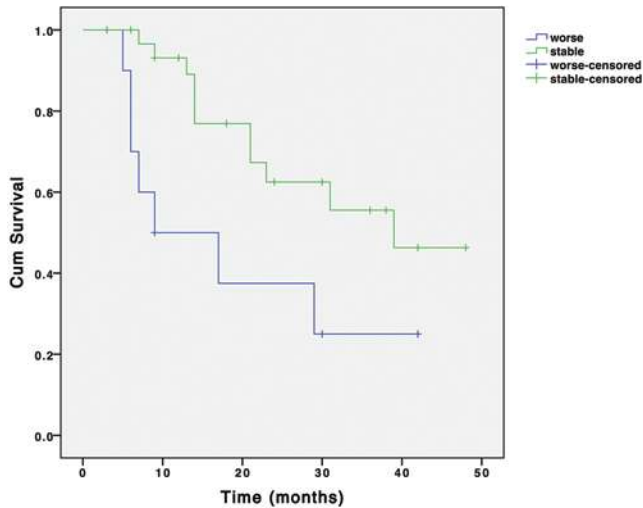


FIG. 5. Kaplan-Meier curve of OS for the 42 patients with HGG, stratified by presence of short-term motor deficits (log-rank test, $p = 0.016$). Cum = cumulative.

primary motor cortex. The focal seizures were controlled with ice irrigation, and an intravenous antiepileptic agent was administered to the patient who had a generalized seizure. The occurrence of seizures in these patients did not affect additional tumor resection, because the patients did not experience prolonged postictal paresis and were able to cooperate for the rest of the surgery.

Functional Outcomes

Over an average follow-up of 24.8 months, 2 patients were excluded when assessing neurological condition because of lack of functional follow-up data. At 1-month follow-up, 34 (37.4%) patients were found to have a worsening language function and 7 (7.7%) had a permanent language deficit (follow-up data were not available for 1 patient). In terms of the motor function, among the 94 patients in whom the motor area was involved, 19 (20.7%) patients had a worse motor function at the 1-month follow-

up and 4 (4.3%) still had lower motor function at subsequent follow-up (data not available for 3 patients). As for the overall neurological deficit (involving language and/or motor deficit), after excluding 2 patients in whom no clinical follow-up data were available, the short-term neurological deficit rate was 46.2%, and the long-term neurological deficit rate was 8.7%.

Reason for Subtotal Resection

In our cohort, 30 (28.3%) patients underwent further resection after the iMRI showed residual tumor, and 4 (13.3%) of those 30 patients had an EOR < 90%. In those cases, further resection was precluded by functional mapping results when the tumor was infiltrating eloquent cortical or subcortical structures.

Learning Curve

The learning curve for using the combined technique was assessed for the neurological and radiological outcomes according to the period when the surgery was performed in the entire cohort. This was stratified as the first 27 months (Group A) and the last 26 months (Group B). In the first group, 34 (59.6%) of the 57 patients had an LGG, whereas in the second group, 30 (61.2%) of the 49 patients had an LGG (Fig. 7).

Although it did not reach statistical significance, the cumulative experience gained by using iMRI seemed to impact the surgeon’s ability to estimate the EOR, because the rate of GTR increased by 1.6% with time ($p = 0.869$). Also, the rate of performing further resection after an iMRI decreased significantly in the second group by 26.1% ($p = 0.005$). The improved ability to perform a maximal safe resection also manifested a decreased rate of postoperative short-term ($p = 0.101$) and long-term ($p = 0.132$) neurological deficits.

Discussion

Mounting evidence supports an aggressive EOR, because it might increase OS of patients. In the review per-

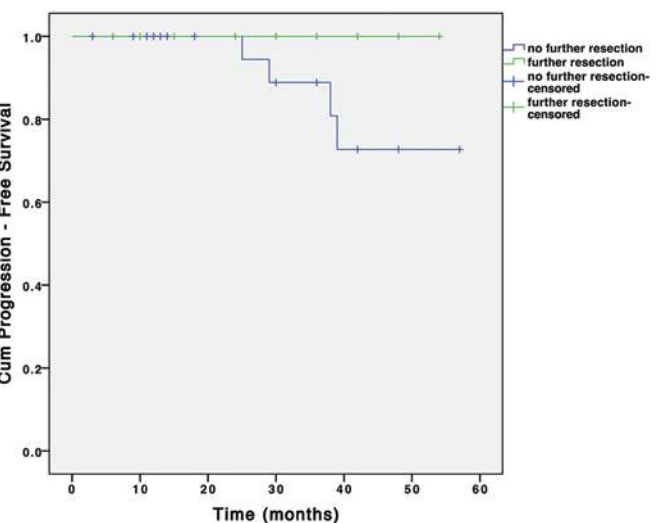
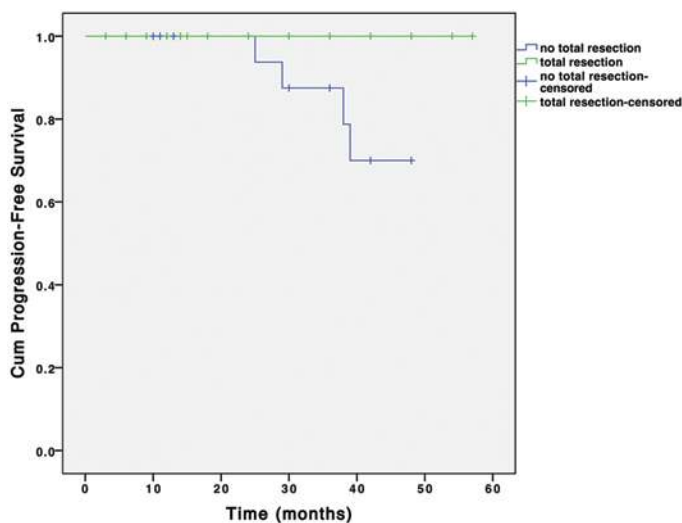


FIG. 6. Kaplan-Meier curves showing PFS for the 64 patients with LGG, stratified by GTR (log-rank test, $p = 0.050$) (left) and by whether further resection was performed ($p = 0.083$) (right).

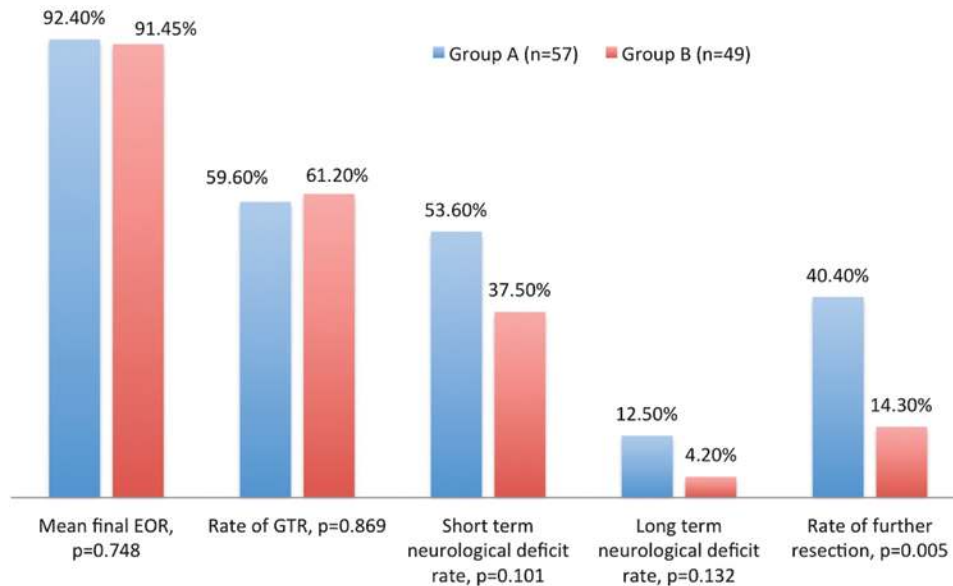


FIG. 7. Neurological and radiological outcomes according to time period when procedure was performed.

formed by Sanai and Berger,²⁹ GTR (defined as complete radiographic resection) improved the mean survival time for patients with all WHO grades. Some surgeons also advocate for early resection of LGG, because it is associated with increased survival and has the potential to decrease the chance of malignant progression.²³ Nonetheless, for both low- and high-grade tumors, the invasion of eloquent areas and the difficulty in distinguishing glioma infiltration from the normal brain significantly impact the extent of GTR performed. The combination of iMRI and awake craniotomy is demanding but well tolerated by patients. Careful preoperative preparation for both the iMRI process and the cortical stimulation is essential to ensure patient compliance. Assuring adequate cooperation between intraoperative personnel and the patient also has significant impacts on the flow and success of the surgery. None of our patients had adverse events during the scanning period and all images yielded a good diagnostic quality.

In this study, we present our clinical experience with 106 patients with gliomas who underwent combined awake functional mapping and iMRI guidance. Clinical and radiographic data were collected and analyzed to identify preoperative predictors of OS, PFS, and EOR. To our knowledge, this is the first study that assessed the impact of combined awake craniotomies with iMRI-guided resection for patients suffering from gliomas located in the vicinity of the eloquent cortex.

One hypothesis is that with accurate identification of functional tissue, supramaximal resection could be performed despite the occurrence of a possible transient neurological deficit, because tissue plasticity and reorganization could allow subsequent recovery. This aggressive approach could provide a survival benefit; however, individualized factors should be taken into account. For instance, given the dismissal prognosis of patients with HGG, the impact of immediate/short-term neurological deficits on QOL should be balanced with the survival benefit of such an aggressive approach.

In our study, the utility of iMRI to identify residual

glioma was 58.5%, which is in accordance with previous reports. However, additional further resection was feasible in only 30 of 62 patients (48.4%), given the fact that tumor proximity to eloquent areas precluded further resection. Although functional imaging, such as DTI and functional MRI, is used preoperatively to plan the tumor resection, the brain shift that occurs as the resection proceeds makes their use less reliable. Intraoperative real-time DTI tractography was performed in most patients; however, due to the retrospective nature of the study, we were unable to compare the results obtained by this technique with the subcortical stimulation.³⁷ The other alternative would be to perform intraoperative BOLD functional MRI,²⁰ but the benefit of prolonging the amount of time required for an awake case to perform functional imaging instead of direct brain mapping is not clear. Further prospective studies should investigate how closely these modalities replicate the accepted gold standard of electrophysiological monitoring.

Table 2 compares the studies investigating the benefit of iMRI to guide further resection in awake craniotomies for supratentorial glioma. As depicted, just 2 other studies performed a volumetric analysis of the resection rate. The rate of GTR achieved in our study is similar to the rates reported previously.^{16,19,21,33,35} Although OS and PFS were different between the LGG and HGG groups, the relatively short observational period (a mean of 24.8 months) prevents us from making any definitive conclusion for the LGG group based on these results. Nonetheless, to our knowledge this is the first study to analyze the clinical outcomes, and the follow-up period is considerably longer than in the previous reports.

Impact on Neurological Outcome

Cortical and subcortical stimulation represents an established technique used to identify functional cortical areas or connective fiber tracts. This technique is essential for gliomas located near the eloquent cortex because if cortical stimulation results in reversible deficits, this area cannot be

TABLE 2. Review of the literature on the radiological and clinical results obtained with combined high-field iMRI guidance and awake craniotomy

Authors & Year	No. of Procedures	Strength of iMRI	Volumetric Analysis	Follow-Up (mos)	Further Resection After iMRI	Outcome Measure	EOR Increase After Further Resection	GTR
Nabavi et al., 2009	38	1.5 T	No	0	NR	NR	NR	NR
Weingarten et al., 2009	10	1.5 T	No	0	7 of 10 cases	30% (3 of 10) transient short-term deficits	NR	70%
Goebel et al., 2010	25	1.5 T	No	NR	20 of 22	32% had a decline in neurological deficits that persisted at 5 days postop	NR	NR
Parney et al., 2010	1	1.5 T	No	NR	Not performed	No deficit	NR	NR
Leuthardt et al., 2011	12	1.5 T	No	1	6 of 12	50% (5 of 10) worse in the immediate postop period; 10% (1 of 10) persisted at 1-mo follow-up	NR	5 (41.7%)
Tuominen et al., 2013	20	0.23 T	No	NR	NR	Transient deficit (10%); permanent (5%)	ND	50%
Lu et al., 2013	30	3 T	Yes	6	11 of 30 (36.7%)	40% suffered from transient language deficits; 1 (3.3%) permanent	7.5%	18 (60%)
Maldaun et al., 2014	42	1.5 T	Yes	1	17 of 42 (40.5%)	11 (26.2%) in the postop period; 1 (2.3%) persisted at 1-mo follow-up	11%	17 (40.5%)

ND = not determined; NR = not recorded.

surgically removed, even if tumor infiltration is present. In a previous study, a presumed eloquent LGG location was found to be associated with both a lowered PFS and shorter OS.⁵ The eloquent brain involvement was found to be a strong predictor of subtotal resection, and incomplete debulking of the tumor burden directly affected the PFS and long-term OS. Also, Haglund et al. reported that the risk of transient language deficit is 36% and that of permanent deficit is 0% when resection is limited to a distance of > 1 cm from the nearest language site, whereas with a margin < 0.7 cm, the risks were 100% and 43%, respectively.¹¹ In our study, the rate of neurological deficits was higher than in previous reports, and this is probably accounted for by the more aggressive EOR performed. Although the presence of neurological deficits was not found to affect the PFS, a longer observational period with prospective clinical follow-up, including QOL measures, should be undertaken to assess the impact on long-term survival. We nonetheless observed a significant association between worsening neurological function in patients with HGG and OS. This should raise awareness in terms of the impact of performing an aggressive resection that causes a subsequent deficit in patients who have a poor prognosis.

Given the ability of iMRI to improve EOR, patients treated with iMRI guidance would be expected to have a survival advantage compared with patients for whom intraoperative assessment of residual tumor is performed using conventional measures. In our study, obtaining GTR (p = 0.033) was an independent prognostic factor of OS in the patients with HGG who had an iMRI. Similarly, a possible survival benefit trend for the patients who underwent a GTR (p = 0.05) was noticed in the patients with LGG. No definitive conclusions can be drawn in terms of the impact of iMRI-guided resection on survival time, given the retrospective nature of this study and the lack of a control group. However, our results are in accordance with the previous literature that suggests a survival benefit with the use of iMRI.

Thus, combining methods that enable the neurosurgeon to appreciate the full extent of the glioma infiltration and to visually distinguish these areas from eloquent brain regions represents state-of-the-art surgery, because it enables a safe radical resection according to individual cortico-subcortical functional boundaries.^{7-9,16,24,33} To unequivocally demonstrate the value of iMRI, a prospective, randomized, controlled clinical trial is underway at our center.

Learning Curve

As outlined in Fig. 7, some general trends were noticed when assessing the outcomes, according to the time period when the surgery was performed. Although no statistical significance was reached, the data depict the dilemma faced by surgeons when resecting tumors located in eloquent areas. Surgeons often perform a less aggressive approach to decrease the rate of postoperative neurological deficits, but this might result in a suboptimal tumor resection. Although the final EOR and GTR were relatively similar between the 2 groups, there was a significant decrease in the rate of further resection after the iMRI demonstrated residual tumor in the second group. This suggests that

the ability to judge maximal safe resection of gliomas in eloquent areas improves with time, allowing the surgeon to reach the functional margins more accurately. Although the contribution of iMRI to improving that skill can play an important role, increased experience of the surgeon— independent of the surgical technique used—might also affect this result.

Strengths and Limitations

Independent clinical reviewers with standardized follow-up formats followed all cases, and only 6 patients were lost to follow-up. Although the outcomes are limited to 2 observers and we could not present reliability data, the staff performing the data collection were senior members with extensive experience (> 20 years) and were not primarily involved in care of the patients.

Furthermore, the retrospective nature of the study prevented us from performing a detailed assessment of the exact neurological function or assessing other factors that might have interfered with the results. This might have an impact on the ability to accurately measure OS and PFS. Also, given that we are reporting a single-center experience, extrapolation of our results should be performed carefully.

Another limitation is that we did not assess the impact of obtaining the MRI on the length of the surgery. Nonetheless, at our institution, we often perform additional sequences for research purposes, so the image scanning time might not reflect the actual time required for clinical data acquisition. Furthermore, because this is a retrospective study, the time spent positioning, draping the open skull, and transferring the patient into and out of the magnetic bore could not be assessed. However, compared with other studies, the use of the monitored anesthesia care technique should decrease the total time required for these preparations because no additional airway management was performed for our patients.

In summary, this retrospective study outlines the dichotomy presented by the synergistic use of combined intraoperative imaging and neurophysiological monitoring for gliomas located in proximity to eloquent areas. Dealing with these challenging tumors requires extensive knowledge of the natural history and anatomical peculiarities of the tumor. The use of iMRI allows the surgeon to achieve a more aggressive resection based on the intraoperative evaluation of the EOR. Nonetheless, as outlined above, to achieve a maximally safe tumor resection, protection of the functional areas is paramount and the localization of functional structures is a prerequisite for safe resection. Although intraoperative real-time DTI tractography can be realized based on iMR images acquired, in our center the use of intraoperative brain mapping is considered the gold standard for identification of eloquent cortex and subcortical functional pathways. Positive responses to white matter stimulation prompt the surgeon to change the surgical strategy because damage of the functional structures could cause irrevocable neurological deficits.

Conclusions

Combined awake craniotomy and iMRI is a safe and efficient technique, allowing maximal safe resection of

lesions situated near eloquent cortex. This large case series adds to the existing literature that suggests a possible survival benefit derived from maximal resection for both LGG and HGG. Furthermore, a worsening short-term neurological function seems to affect the OS in HGG. The use of iMRI allows the surgeon to achieve a greater EOR, while the neurophysiological testing and functional mapping delineate the cortico-subcortical functional boundaries. Further well-designed prospective studies are required to validate these results. Meanwhile, the decision between supramaximal resection and functional preservation should continue to be individualized and take into account the QOL of the patient.

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Disclosures

Dr. Wu is a patent holder for Sinorad Medical Electronics Co., Ltd.

Author Contributions

Conception and design: Wu, Ghinda. Acquisition of data: Zhang, Lu, Yao, Yuan. Analysis and interpretation of data: Wu, Ghinda, Zhang, Lu. Drafting the article: Ghinda. Critically revising the article: Wu, Ghinda, Lu. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Wu. Statistical analysis: Wu, Ghinda, Zhang. Administrative/technical/material support: Zhang. Study supervision: Wu.

Correspondence

Jin-Song Wu, Glioma Surgery Division, Department of Neurological Surgery, Huashan Hospital, Shanghai Medical College, Fudan University, No. 12 Middle Wulumuqi Rd., Shanghai 200040, China. email: wjsongc@126.com.