Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period

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OBJECT Awake craniotomy is currently a useful surgical approach to help identify and preserve functional areas during cortical and subcortical tumor resections. Methodologies have evolved over time to maximize patient safety and minimize morbidity using this technique. The goal of this study is to analyze a single surgeon's experience and the evolving methodology of awake language and sensorimotor mapping for glioma surgery.

METHODS The authors retrospectively studied patients undergoing awake brain tumor surgery between 1986 and 2014. Operations for the initial 248 patients (1986–1997) were completed at the University of Washington, and the subsequent surgeries in 611 patients (1997–2014) were completed at the University of California, San Francisco. Perioperative risk factors and complications were assessed using the latter 611 cases.

RESULTS The median patient age was 42 years (range 13–84 years). Sixty percent of patients had Karnofsky Performance Status (KPS) scores of 90–100, and 40% had KPS scores less than 80. Fifty-five percent of patients underwent surgery for high-grade gliomas, 42% for low-grade gliomas, 1% for metastatic lesions, and 2% for other lesions (cortical dysplasia, encephalitis, necrosis, abscess, and hemangioma). The majority of patients were in American Society of Anesthesiologists (ASA) Class 1 or 2 (mild systemic disease); however, patients with severe systemic disease were not excluded from awake brain tumor surgery and represented 15% of study participants. Laryngeal mask airway was used in 8 patients (1%) and was most commonly used for large vascular tumors with more than 2 cm of mass effect. The most common sedation regimen was propofol plus remifentanyl (54%); however, 42% of patients required an adjustment to the initial sedation regimen before skin incision due to patient intolerance. Mannitol was used in 54% of cases. Twelve percent of patients were active smokers at the time of surgery, which did not impact completion of the intraoperative mapping procedure. Stimulation-induced seizures occurred in 3% of patients and were rapidly terminated with ice-cold Ringer's solution. Preoperative seizure history and tumor location were associated with an increased incidence of stimulation-induced seizures. Mapping was aborted in 3 cases (0.5%) due to intraoperative seizures (2 cases) and patient emotional intolerance (1 case). The overall perioperative complication rate was 10%.

CONCLUSIONS Based on the current best practice described here and developed from multiple regimens used over a 27-year period, it is concluded that awake brain tumor surgery can be safely performed with extremely low complication and failure rates regardless of ASA classification; body mass index; smoking status; psychiatric or emotional history; seizure frequency and duration; and tumor site, size, and pathology.

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KEY WORDS awake craniotomy; glioma; glioblastoma; cortical stimulation mapping; cigarette smoking; diagnostic and operative techniques

THE prevailing evidence suggests that a greater extent of resection positively affects overall survival, progression-free survival, and malignant transformation (low-grade gliomas) in adult patients with hemispheric gliomas.^{3,14,21,26,30,48,50,51,55,56,58,61,64,65,72,77,79,82,89,95–97,100,102,103,109–}

^{111,113} Mapping of language and sensorimotor function is the gold standard to achieve maximal safe resection, particularly for tumors in presumed functional areas. Throughout the history of neurosurgery, awake craniotomies have been used for various indications with the overarching

ABBREVIATIONS ASA = American Society of Anesthesiologists; BMI = body mass index; ECoG = electrocorticography; KPS = Karnofsky Performance Status; LMA = laryngeal mask airway; MSI = magnetic source imaging; UCSF = University of California, San Francisco.

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goal of enhancing safety. Since the original description of awake craniotomy by Horsley more than 120 years ago, popularization by Penfield, and subsequent introduction into the modern era by Ojemann and others, different techniques and methodologies have been described in the literature for the testing and identification of functional sites.^{34,47,69,74,87} A meta-analysis examining the usefulness of intraoperative stimulation mapping revealed a 58% reduced morbidity and improved extent of resection with the use of stimulation mapping (compared with no stimulation mapping).²⁹ Yet, despite its utility, awake craniotomy for mapping is used in less than 22% of glioma surgeries.²⁰ This is possibly due to the complexity of the procedure, variable patient selection criteria, prevalence of stimulation-induced seizures, and failure rates as high as 6.4%.^{66,67} Over the past 20 years, studies involving more than 3000 patients have suggested failure rates of 2.3%–6.4%, with reasons including poor patient selection, inadequate anesthetic regimen, and intraoperative stimulation-induced seizures (Table 1).^{1,2,5,15,16,23,27,28,38,39,41,44,49,54,59,60,66,67,69,71,73,75,76,83–85,87,90,92,94,99,104,107,108} Previously published studies have demonstrated the value of cortical and subcortical mapping for glioma resections, along with the importance of extent of resection for both high- and low-grade gliomas.^{11,17–19,29,35,36,43,52,53,80,81,86–89,98,100,101,106} Due to the reported variability of success rates for completing an awake craniotomy, along with the many published techniques and methods of performing the procedure, we decided to review the extensive experience of a single surgeon with the goal of identifying the optimal techniques and regimen to maximize perioperative safety and minimize the risk of failure for patients undergoing awake craniotomies during the removal of a glioma.

Methods

We retrospectively studied 859 patients undergoing

awake brain tumor surgery (asleep-awake-asleep sedation technique) performed by 1 surgeon (M.S.B.) for tumors in functional regions of the brain for the period 1986–2014. The series began in 1986 and was carried out at the University of Washington School of Medicine until early 1997. During that time, 248 patients underwent an awake language and sensorimotor mapping craniotomy. Because these patient records were not available in full detail, we could not comment on perioperative complications or patient risk factors. We were, however, able to identify the number of patients who successfully completed awake language and sensorimotor mapping craniotomy after review of intraoperative brain maps and pre- and postoperative imaging. The remaining 611 patients were treated between 1997 and April 2014 at the University of California, San Francisco (UCSF) and constitute the data set for this study.

Patient Selection

Patients were included in the study if they had a supratentorial lesion located within or adjacent to regions presumed to have language or sensorimotor function on preoperative MRI. Initial concerns about awake craniotomy necessitated the adoption of relative contraindications to guide proper patient selection. As the technique evolved, solutions were adopted to prevent these concerns from allowing a safe awake craniotomy, even in high-risk patients (Table 2). For example, patients with significant mass effect (more than 2 cm of midline shift), despite preoperative diuretics and corticosteroids, were offered a staged procedure, although this approach was seldom needed. Stage 1 involved internal debulking for removal of mass effect in an asleep patient using functional and anatomical imaging (magnetic source imaging [MSI]) followed by reoperation several weeks later with awake mapping for the identification and preservation of functional sites. Obese patients (body mass index [BMI] > 30) and those with obstructive

TABLE 1. Prior published series of awake craniotomies

Authors & Year	No. of Patients	Intraop Seizures	Failure	Complications
Nossek et al., 2013 ⁶⁷	477	12.6%	2.3%	NS
Trinh et al., 2013	214	NS	NS	New neurological deficit (38%); 3-mo neurological deficit (3%)
Nossek et al., 2013 ⁶⁶	424	NS	6.4%	4.7%
Grossman et al., 2013	90	2.2%	NS	New motor deficit (14%); new language deficit (8.7%); hemorrhage (3.3%)
Peruzzi et al., 2011	22	NS	NS	18%
Sacko et al., 2011	214	5.7%	NS	33.6%
Conte et al., 2010	238	16%	NS	Emergency intubation (5%); apnea (4%); agitation (6%)
Pereira et al., 2009	79	21.5%	2.5%	Stroke (6.3%); infection (2.5%); DVT/PE (5.1%)
Serletis & Bernstein, 2007	511	4.9%	NS	New neurological deficit (15.3%)
Gupta et al., 2007	26	NS	NS	New neurological deficit (23%)
Skucas & Artru, 2006	332	3%	NS	5%
Sarang & Dinsmore, 2003	99	5%	NS	NS
Archer et al., 1988	354	16%	NS	NS
Gignac et al., 1993	30	16.7%	NS	NS
Herrick et al., 1997 ⁴⁵	37	18.9%	NS	NS

DVT = deep venous thrombosis; NS = not stated in study; PE = pulmonary embolism.

TABLE 2. Relative contraindications and solutions for awake craniotomy patients

Prior Concerns	Current Solutions
Significant mass effect (>2-cm midline shift) despite preoperative diuretics & steroid	Staged internal debulking (asleep) using functional imaging (MEG/MSI) followed by reoperation w/ awake mapping or LMA
Obese patient (BMI >30)/obstructive apnea	LMA before & after mapping (limits subcortical mapping during resection if LMA is used)
Psychiatric history/emotional instability	Treated mood disorders no longer a contraindication
Age (yrs)	
>10	Awake
<10	2-stage procedure w/ implanted grid
Intraop seizures	Iced Ringers solution, propofol IV 6 inches from vein
Smoker	Cough suppressants w/ or w/o light sedation
Intraop nausea	Preop medication w/ antiemetic drugs (ondansetron hydrochloride, scopolamine) & high-dose dexamethasone (10 mg)
Reop (dural scar)	Focused craniotomy w/ negative mapping is acceptable
Severely impaired preoperative function*	Attempt to improve function w/ up to 5 days of preoperative high-dose steroids w/ or w/o diuretics
Tumor location presumed to be w/in functional cortical or subcortical pathways on preop imaging	The decision to offer surgery is not made based on preop anatomical or functional imaging (attempt is always made to map, identify, & preserve functional sites).

BMI = body mass index; IV = intravenous; MEG = magnetoencephalography; MSI = magnetic source imaging.

* Motor function < 2/5 or baseline naming/reading errors.

sleep apnea may be treated with a laryngeal mask airway (LMA) to control hypercapnia. Patients with a psychiatric history and emotional instability were treated preoperatively with antidepressant mood-stabilizing medications. Children younger than 10 years of age were treated with a 2-stage procedure using subdural grids, while children older than 10 years underwent an awake craniotomy. Patients with frequent preoperative seizures who experienced seizures during the intraoperative mapping had iced Ringer's solution applied to the cortex during stimulation. Intravenous propofol was maintained in a large-bore intravenous line within 6 inches from the vein for rapid administration. Smokers and patients with a chronic cough were treated preoperatively with chronic cough suppressants and light sedation. Intraoperative nausea was treated with preoperative antiemetic medications (ondansetron hydrochloride, and scopolamine). Patients with severely impaired preoperative function (greater than 25% naming errors and a Medical Research Council scale score less than 2 of 5) were treated with 3–5 days of high-dose corticosteroids (intravenous dexamethasone, 4–8 mg every 6 hours) and/or diuretics (mannitol 20%, 30 g every 6 hours for 48–72 hours) followed by reassessment of preoperative function. If language function did not improve, a staged procedure as described above was offered. Tumor location presumed to be within functional cortical or subcortical sites on preoperative anatomical imaging was never a contraindication to attempting intraoperative mapping to identify function as opposed to assuming that the patient could not be mapped. The decision to offer surgery was not made based on preoperative functional imaging due to the less-than-ideal specificity and sensitivity of localized function.^{12,40,46,62,63,93,105,112} The patient was always taken to the operating room, and the tumor and surrounding brain were mapped to determine how much of a resection could

be performed.^{5,6,29,59,70,84,85,87} Absolute contraindications to surgery included uncontrolled coughing, severe dysphasia, greater than 25% naming errors despite a trial of preoperative dexamethasone and mannitol, and hemiplegia with less than antigravity motor function.

Preoperative Evaluation

Preoperative imaging included MRI with and without gadolinium enhancement, diffusion tensor imaging for white matter pathways including the corticospinal tract, superior longitudinal fasciculus, arcuate fasciculus, uncinate fasciculus, inferior orbitofrontal fasciculus, optic pathways, and connectivity maps using MSI with magnetoencephalography.^{8,68,105} Preoperative clinical evaluation included baseline language assessment performed by our surgical neurophysiology team (D.W.P.). All patients were counseled prior to surgery, during which time the procedure was described in detail. Baseline language and sensorimotor testing was performed 24–48 hours prior to surgery and included naming (64-object panel), reading, spelling, calculations, visuospatial, and comprehension testing depending on tumor location (Fig. 1).³⁷ The full 64-object naming battery was modified preoperatively, removing objects, words, and tasks that the patient had difficulty performing. Intraoperative testing used only pictures and words that an individual patient was able to reliably answer correctly based on preoperative evaluation. Preoperative neuropsychological evaluation was performed for selected individuals especially if requested by the patient (performed in 2% of cases).

Current Technique

Patient Positioning and Anesthesia Regimen

Specialized neuroanesthesia is critical for a success-

FIG. 1. Site-specific testing for the identification of functional sites.

ful awake craniotomy and requires clear communication between the surgeon and anesthesiologist to ensure ideal intraoperative mapping conditions (Fig. 2). Patient monitors are applied (including blood pressure cuff and arterial line placement), followed by premedication with 1–2 mg of midazolam and 50 µg of fentanyl prior to positioning. The operating room is preheated, and warm blankets and Bair Huggers (3M Corp.) are used to keep the patient warm to avoid shivering and allow for an optimal patient temperature between 36.0° and 37.0°C for mapping. Demerol is not used to treat shivering during any awake craniotomies because of its prolonged sedating effects. All patients are given supplemental oxygen via nasal cannula. A nasal trumpet is placed if the patient shows evidence of airway obstruction or snoring with sedation. A low-dose propofol infusion is started during the Foley catheter insertion and Mayfield headholder pin placement. After the Foley catheter is inserted, an initial dose of mannitol may be given to lessen cerebral edema (particularly for patients with > 2 cm mass effect, high-grade tumors, or high BMI). Monitored sedation using propofol or dexmedetomidine plus remifentanyl is used; however, if the patient becomes disinhibited, this initial drug regimen may be adjusted. On occasion, the patient remains fully awake during surgery to improve participation and maximize safety. The patient is positioned semilateral with his or her head positioned optimally for the surgical procedure while allowing access for the potential LMA placement, if needed. These

early steps require a great deal of flexibility on the part of the surgeon, as the initial sedation regimen can change depending on patient tolerance. Using neuronavigation, a focused craniotomy is planned and the scalp incision is outlined. A complete scalp block or regional field block just behind the incision (a 1:1 mixture of 1% lidocaine with 1:100,000 epinephrine, 0.5% bupivacaine, plus 4.5 ml of 8.4% sodium bicarbonate) is injected. A dedicated intravenous line is filled with a 1-mg/kg bolus of propofol 6 inches from the vein if needed for suppression of intraoperative seizures. Sedation is achieved with propofol (up to 100 µg/kg/min) and remifentanyl (0.07–2.0 µg/kg/hr). Patients who show apnea or intolerance to propofol (particularly young males) may be given dexmedetomidine (up to 1 µg/kg/min) as an alternative to propofol.^{4,7,9,10,13,22–25,71,78,90} In patients who tend to be anxious, a very-low-dose remifentanyl infusion may be used during and after cortical mapping.

Craniotomy Opening

The overall goal is to perform a focused exposure encompassing the lesion plus a 2- to 4-cm margin, depending on the need to map adjacent functional tissue. For reoperations and patients with an extensive dural scar, the craniotomy is focused to open the dura only overlying the lesion so as to avoid cortical injury to the surrounding brain. The temporalis muscle is separated and retracted inferiorly for most anterior frontal and insular lesions, or

FIG. 2. UCSF awake craniotomy flowchart.

anteriorly for posterior frontal and temporal lesions. Upon removal of the bone flap, all medications are discontinued unless the patient is very anxious, and the patient is asked to take multiple deep breaths for controlled hyperventilation before opening the dura. The dura is opened in whichever manner best suits optimal exposure of the lesion. Care is always taken to not coagulate the dura, using a heavy clamp to cut down on dural bleeding at the edges followed by tack-up sutures. Upon opening the dura, the brain is assessed for swelling, at which time the patient may be instructed to perform additional controlled hyperventilation. Alternatively, the patient may be given additional mannitol, the head of the bed raised, and the arachnoid space opened for release of CSF as additional maneuvers to decrease brain swelling. Mannitol is avoided in patients with deep lesions in the ventricle, in any situation in which the ventricle will be opened, or in lesions close to a cistern or deep fissure, since copious amounts of CSF will be lost early in the procedure, promoting too much brain relaxation. A dural block is performed using a

30-gauge needle with 1% lidocaine to infiltrate the region around the middle meningeal artery.

Cortical and Subcortical Stimulation Mapping

Before stimulation mapping begins, we ensure that iced Ringer's solution is readily available on the surgical field for rapid termination of intraoperative stimulation-induced seizures, as previously described.⁹¹ Stimulation is delivered using a bipolar electrode, beginning with 2 mA increased to a maximum of 6 mA until somatosensory or motor function is established, or after-discharge potentials are detected on intraoperative electrocorticography (ECoG) when mapping language.^{84,85,87} A constant current generator delivers 1.25-msec biphasic square waves in 4-second trains at 60 Hz. Stimulation is delivered across 1-mm bipolar electrodes separated by 5 mm.

Stimulation begins with identification of primary sensory and motor areas if the posterior frontal and anterior parietal lobes are exposed. When cortical sensory and motor areas are not exposed, a 4-contact strip electrode can

be advanced under the edges of the dura opening to elicit a motor or sensory response. As the technique has evolved, there is growing reliance on negative language and sensorimotor mapping with focused craniotomies, which do not contain positive stimulation sites.⁸⁷ Intraoperative ECoG is performed using a 16-array cortical electrode and holder assembly designed to record electroencephalography readings from the exposed cortex (Grass Model CE1, Natus Medical Inc.). An epileptologist deciphers ECoG readings for detection of after-discharges or epileptiform activity following cortical stimulation. During language testing, a current is used that is 1 mA lower than the current that evoked after-discharge potentials to an upper limit of 6 mA. The typical current used is 3–4 mA.

When in the perisylvian region of the frontal and temporal operculum, the patient is asked to either count from 1 to 30 or speak the letters of the alphabet to identify sites of speech arrest. Approximately 10–20 numerically marked stimulation sites separated by 1 cm are placed on the surgical field. Language testing seeks to identify sites responsible for speech arrest, anomia, and alexia on stimulation. Speech arrest is defined as discontinuation in number counting without a simultaneous motor response (e.g., mouth or pharynx motor response).⁸⁷ Dysarthria is distinguished from speech arrest by an absence of involuntary muscle contractions affecting speech.⁸⁷ Stimulation is applied for 3–4 seconds at sequential sites with tasks separated by 4–10 seconds. During testing, a neurophysiologist (D.W.P.) displays each slide to the patient and records the positive or negative result and the type of language disturbance of each stimulation point as the site number stimulated is called out by the neurosurgeon. According to the established protocol initially established by Ojemann et al., all language stimulation testing is repeated at least 3 times, and a positive site is defined as the inability to count, name objects, or read words during stimulation in more than 66% of attempts.^{28,69,84,87} A 1-cm margin of tissue is usually preserved in all cases around positive language sites to protect language function.^{55,84} However, the 1-cm margin rule can be violated to enhance extent of resection while the patient is being tested to avoid postoperative language deficits. The patient is tested both for the identification of cortical as well as subcortical sites using the same stimulation parameters.⁵³ In our previously published experience focusing specifically on cortical language mapping, 58% of patients had at least 1 positive site.⁸⁷ Similarly, our previously published motor mapping experience found that 45% of patients had positive cortical or subcortical mapping with a 2.1% morbidity associated with negative subcortical mapping and 7.4% morbidity associated with positive subcortical mapping.⁵³ The morbidity associated with positive subcortical language function has yet to be examined in the literature.

Evolution of Technique

The awake mapping technique has evolved over 27 years. The reasons for this change can be summarized into 4 basic categories: 1) improved neuroanesthesia, 2) improved intraoperative seizure management, 3) improved surgical technique and broadened intraoperative testing, and 4) a better understanding of functional language pathways and brain remodeling. Initially, anesthesia involved

no sedation with local scalp and regional blocks using lidocaine and bupivacaine hydrochloride (Fig. 3).⁶⁹ Neuroleptic anesthesia using droperidol was the initial sedation regimen until monitored anesthesia care using propofol was introduced in the early 1990s. Propofol was immediately recognized for its sedating characteristics in addition to its ability to suppress seizure activity. An early publication by Herrick et al. compared these 2 agents in a prospective fashion, noting significantly fewer seizures in patients undergoing awake craniotomy using propofol.⁴⁴ In the early 2000s, dexmedetomidine was identified as another potential alternative for patient sedation with the addition of the short-acting opioid remifentanyl.⁴ Regardless of the anesthetic regimen, over-sedation during the sleep portion of surgery can lead to carbon dioxide retention, which can be particularly problematic in overweight patients, those with significant tumor mass effect (greater than 2 cm of midline shift), or in cases of expected high-volume blood loss. When the LMA became commercially available in the early 1990s, it offered a potential solution to this problem and became a useful tool for the sleep portion of surgery, allowing airway management and potential hyperventilation. Additionally, a nasal trumpet may be placed for those patients who snore excessively or retain carbon dioxide.

An understanding of the value of negative mapping altered surgical technique by allowing smaller, tailored craniotomies based on the extent and location of each individual tumor (Fig. 4).⁸⁷ The initial testing paradigm included naming and reading; now using preoperative MRI, each patient receives tailored, site-specific testing.

Intraoperative seizure control has always been a major concern during awake brain tumor surgery. Early on it was identified as a major contributor to aborted procedures and associated with increased perioperative morbidity. The introduction of intraoperative ECoG allowed not only the identification of after-discharge potentials, but also marked the threshold current for intraoperative testing, thereby initiating testing at lower currents (1 mA below after-discharge potentials). Intraoperative stimulation-induced seizures were initially controlled with intravenous lorazepam. Treatment with these short-acting benzodiazepines often necessitated cessation of intraoperative testing. Therefore, the discovery that iced Ringer's solution applied locally to the cortical surface offered a mechanism of seizure control without the sedating effects of short-acting benzodiazepine drugs was a major contribution leading to improved success rates.⁹¹

A heightened understanding of the importance of brain remodeling (plasticity) and an appreciation of functional white matter pathways in glioma patients led to further changes in technique. Before functional imaging modalities were readily available in the operating room, early studies stated the significance of stimulation within 2 cm of sites for stimulation-induced anomia.⁶⁹ In an attempt to perform even more complete resections, further analysis identified 1 cm as the critical distance necessary to maintain normal language function.⁴² We now know that glioma resections can take place within 1 cm of functional sites with excellent short- and long-term outcomes. This is likely due to a growing acceptance of the activation of latent functional pathways in addition to functional path-

FIG. 3. Evolution of the anesthetic regimen over time. Figure is available in color online only.

way remodeling in glioma patients.³² Based on recently published work recognizing cortical plasticity in glioma patients, partial resections are now reasonable when tumor occupies functional regions. At the time of recurrence, the tumor and surrounding cortical surface are remapped to attempt further resection if plasticity has allowed function to move away from the tumor.^{31–33} Although the incidence and mechanism of this are poorly understood, they are both thought to be contributing factors to the short- and long-term recovery of language function.

Once functional sites are identified, a distance of 2 cm to the resection margin was originally advocated,⁶⁹ and then a shift was made to 1 cm;⁴² however, resections are now advanced to within 1 cm of functional sites or until intraoperative language deficits begin to occur. Based on recently published work recognizing cortical plasticity in glioma patients, partial resections are now allowed when tumor occupies functional regions. At the time of recurrence, the tumor and surrounding cortical surface are remapped to attempt further resection if plasticity has allowed function to move away from the tumor.^{31–33}

Statistical Analysis

Descriptive statistics are given as median (range) unless otherwise specified for continuous variables and frequency of distribution for categorical variables. The Pearson chi-square test was used for categorical analyses, and t-tests were performed for mean comparisons of continuous variables. The Fisher exact test was used if more than 80% of values were less than 5. All statistics were analyzed using JMP statistical software, version 10.0.2 (SAS Institute). A biostatistician contributed in the statistical analysis for this study (A.M.M.). The UCSF institutional review board approved the study.

Results

A total of 611 consecutive patients were treated between

June 1997 and April 2014 at UCSF with records complete for identification of perioperative complications, mapping details, and successful completion of the surgical procedure (Table 3). The median patient age was 42 years (range 13–84 years). Sixty percent of patients had KPS scores of 90–100, and 40% had KPS scores lower than 80. Lesion location was most commonly temporal (36%), followed by frontal (27%), insular (21%), and parietal (15%). Ninety-four percent of patients had left-sided lesions. Language mapping was performed in 98% of patients and motor mapping in 56%. Three hundred thirty-five (55%) patients had high-grade tumors (WHO Grades III and IV), 259 (42%) had low-grade tumors (WHO Grades I and II), 3 (1%) had metastatic lesions, and 14 (2%) had other lesions (cortical dysplasia, encephalitis, necrosis, abscess, or hemangioma). The median BMI was 25 (range 16.6–56). Patients with low BMI (< 24.9) represented 42% of patients and those with high BMI (> 25) represented 58% of patients. The majority of patients (84%) had mild systemic disease (American Society of Anesthesiologists [ASA] Class 1 or 2); however, 15% of patients had severe systemic disease. Preoperative airway analysis revealed complete visualization of the soft palate and uvula in 87% of patients (Mallampati Class 1 or 2); however, those with incomplete visualization (Mallampati Classes 3 and 4) represented 13% of patients. Twelve percent of patients had a preoperative history of depression, 12% of patients were active smokers, and 5% had a chronic cough at the time of awake craniotomy. Mannitol was used in 54% of patients.

Sedation Technique

The asleep-awake-asleep monitored anesthesia care technique employed the following drug regimens for sedation: dexmedetomidine plus remifentanyl (4%), propofol plus remifentanyl (54%), or an adjusted technique (42%) in which the initial anesthetic regimen was modified by the addition or subtraction of sedating drugs due to patient

FIG. 4. Evolution of the surgical and mapping technique over time. LR = lactate Ringer's. "> 2 cm from functional sites" image from Ojemann et al: *J Neurosurg* 71:316–326, 1989. Published with permission. "Subcortical motor mapping" image from Keles et al: *J Neurosurg* 100:369–375, 2004. Published with permission. "1 cm rule" image from Haglund MM et al: *Cortical localization of temporal lobe language sites in patients with gliomas. Neurosurgery* 34:567–576, 1994. Published with permission. "Cold irrigation to break seizure activity" image from Sartorius et al: *J Neurosurg* 88:349–351, 1998. Published with permission. "Value of negative mapping" image from *New England Journal of Medicine*, Sanai et al: Functional outcome after language mapping for glioma resection, vol 358, pp 18–27. Copyright © 2008 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Figure is available in color online only.

intolerance before the skin incision (propofol plus remifentanyl switch to dexmedetomidine; propofol plus remifentanyl with addition of dexmedetomidine; or dexmedetomidine plus remifentanyl). Further analysis of the sedation technique revealed no correlation between sedation technique and tumor grade, tumor site, stimulation-induced seizures, LMA use, patient BMI, or aborted procedure (Table 4). This suggests no benefit of one drug regimen over another and the need for the surgical team to be flexible to successfully complete the awake craniotomy and mapping.

Use of the LMA

To successfully complete mapping and maximize safety in select high-risk patients, the LMA was used in 1% of patients ($n = 8$). In all cases, mapping was completed and the clinical indication for its use in each case included tumors with significant mass effect (greater than 2 cm of midline shift) and the need for hyperventilation due to tumor vascularity and venous engorgement secondary to hypercapnia. Patient BMI ranged from 24.1 to 47.5 (median 26.7). Tumor locations included temporal (6 patients), insular (1 patient), and frontal (1 patient) lobes. Tumor histopathologies included glioblastoma (5 patients), anaplastic astrocytoma (1 patient), and oligodendroglioma (2 patients). Subsequent analysis revealed no correlation between tumor site, tumor

pathology, Mallampati score, ASA classification, aborted procedure, or patient BMI with use of an LMA (Table 5). There was a modestly increased length of stay for those patients in whom an LMA was used (3 days when LMA not used vs 5 days when LMA was used; $p = 0.001$).

Stimulation-Induced Seizures

Preoperative seizure history was noted in 70% of awake craniotomy patients and 68% were on antiepileptic medications prior to surgery (Table 3). The majority of these patients were on a single drug regimen (59%); however, 10% used 2 or more antiepileptic drugs preoperatively. Cortical and subcortical mapping stimulation intensity was determined by intraoperative ECoG and was carried out at between 2 and 6 mA in all patients. Stimulation-induced seizures occurred in 3% of patients regardless of the stimulation current and were rapidly terminated with ice-cold Ringer's lactate solution except in 2 patients (see below).⁹¹ The incidence of stimulation-induced seizures ranges between 2.2% and 21.5% in the literature.^{1,23,38,39,44,45,66,75,83,90,94,99} The use of preoperative antiepileptic medications, tumor grade, and BMI had no effect on the occurrence of intraoperative stimulation-induced seizures (Table 6). A preoperative history of seizures (95% vs 69%; $p = 0.01$) and tumor location (frontal lesions; $p = 0.0003$) were associated with stimulation-induced seizures.

TABLE 3. Demographics of patients undergoing awake craniotomy (n = 611)*

Variable	Value
Age, yrs	
Median	43
Range	13–84
Tumor site	
Frontal	168 (27)
Insular	128 (21)
Parietal	92 (15)
Temporal	223 (36)
Mallampati score	
1	147 (24)
2	387 (63)
3	71 (12)
4	6 (1)
ASA classification	
1 (healthy patient)	50 (8)
2 (mild disease)	466 (76)
3 (severe disease)	94 (15)
4 (life-threatening disease)	1 (0.1)
Mannitol	327 (54)
Tumor side	
Left	572 (94)
Right	39 (6)
Motor mapping	342 (56)
Language mapping	598 (98)
Tumor pathology	
High grade	335 (55)
Low grade	259 (42)
Metastasis	3 (1)
Other†	14 (2)
Preop seizure history	427 (70)
Preop anticonvulsant medications	418 (68)
No. of anticonvulsant medications	
0	193 (32)
1	358 (59)
2	55 (9)
3	5 (0.8)
Stimulation-induced seizures	20 (3)
LMA	8 (1)
Depression history	75 (12)
Smokers	75 (12)
Chronic cough	30 (5)
BMI	
Median	25
Range	16.6–56
Low (<24.9)	255 (42)
High (>25)	356 (58)

(continued)

TABLE 3. Demographics of patients undergoing awake craniotomy (n = 611)* (continued)

Variable	Value
KPS score	
<80	243 (40)
90–100	368 (60)
Aborted procedure	3 (0.5)
Length of stay, days	
Median	3
Range	2–20

* Values are presented as the number of patients (%) unless noted otherwise.

† Other includes cortical dysplasia, encephalitis, necrosis, abscess, heman-gioma.

All 3 aborted cases had intraoperative stimulation-induced seizures. In the last few years, a technique is used to stimulate under a stream of cold irrigation fluid when either a seizure occurs or if the functional area is infiltrated with tumor. This does not prevent testing of the desired function, yet it often prevents a seizure from occurring.

Awake Craniotomy Failure Rate

An awake craniotomy failure (aborted mapping) was defined as the inability to complete cortical stimulation mapping and the tumor resection. Mapping was aborted in 3 cases (0.5%) due to repetitive intraoperative seizures (2 cases) and emotional intolerance of the patient after a single stimulation-induced seizure (1 case). In the 2 operations aborted due to intraoperative seizures, 1 patient's stimulation-induced seizures were poorly controlled with iced Ringer's solution; therefore, the craniotomy was closed without resection. This patient was loaded on additional antiepileptic medications and returned to the operating room 3 days later for successful mapping and tumor resection. The other patient was able to complete half of the standard mapping protocol (1.5 rounds of testing); however, due to repeated stimulation-induced seizures that were poorly controlled with iced Ringer's solution, further intraoperative mapping was aborted and the resection was performed using the available mapping data combined with preoperative diffusion tensor imaging and neuro-navigation. Another patient's surgery was aborted due to emotional intolerance and unwillingness to proceed with further surgery after a single stimulation-induced seizure (which was controlled with iced Ringer's solution). Thus, in all 3 patients, intraoperative stimulation-induced seizures were encountered. This is in comparison with the awake craniotomy failure rate reported in the literature which ranges between 2.3% and 6.4%, whereas our failure rate was only 0.5%.^{66,75}

Smoking status has long been considered to be associated with worse perioperative outcomes in neurosurgery patients.⁵⁷ Twelve percent of patients were active smokers at the time of surgery. Smokers were more commonly found to have a depression history (20 smokers [27%] and 55 nonsmokers [10%]; $p = 0.001$), as were those with chronic cough (6 smokers [8%] and 14 nonsmokers [3%]; $p = 0.01$). However, there was no difference in any adverse

TABLE 4. Sedation technique analysis (n = 611)

Variable	No. of Patients (%)			p Value
	Adjusted Technique (n = 258)	Dexmedetomidine + Remifentanyl (n = 26)	Propofol + Remifentanyl (n = 327)	
Stimulation-induced seizures	9 (3)	1 (4)	10 (3)	0.95
Tumor site				0.65
Frontal	74 (29)	7 (27)	87 (27)	
Insular	57 (22)	7 (27)	64 (20)	
Parietal	33 (13)	2 (8)	57 (17)	
Temporal	94 (36)	10 (38)	119 (36)	
Tumor pathology				0.82
High grade	139 (54)	14 (54)	182 (56)	
Low grade	114 (44)	12 (46)	133 (41)	
Metastasis	1 (0.4)	3 (12)	2 (1)	
Other	4 (2)	0 (0)	10 (3)	
Aborted procedure	0 (0)	0 (0)	3 (1)	0.27
LMA	2 (1)	1 (4)	5 (2)	0.37
BMI				0.08
Low (<24.9)	96 (37)	9 (35)	150 (46)	
High (>25)	162 (63)	17 (65)	177 (54)	

TABLE 5. Laryngeal mask airway use in awake craniotomy

Variable	No. of Patients (%)		p Value
	No LMA (n = 603)	LMA Used (n = 8)	
Tumor site			0.14
Frontal	167 (28)	1 (13)	
Insular	127 (21)	1 (13)	
Parietal	92 (15)	0 (0)	
Temporal	217 (36)	6 (75)	
Tumor pathology			0.7
High grade	329 (55)	6 (75)	
Low grade	257 (43)	2 (25)	
Metastasis	3 (0.5)	0 (0)	
Other	14 (2)	0 (0)	
Mallampati score			0.42
1	144 (24)	3 (38)	
2	384 (64)	3 (38)	
3	69 (11)	2 (25)	
4	6 (1)	0 (0)	
ASA classification			0.76
1 (healthy patient)	50 (8)	0 (0)	
2 (mild disease)	460 (76)	6 (75)	
3 (severe disease)	92 (15)	2 (25)	
4 (life-threatening disease)	1 (0.2)	0 (0)	
Aborted procedure	3 (0.5)	0 (0)	0.84
BMI			0.15
Low (<24.9)	254 (42)	1 (13)	
High (>25)	349 (58)	7 (88)	
Average length of stay, days	3	5	0.001

perioperative outcome including stimulation-induced seizures (2 smokers [3%] and 18 nonsmokers [3%]; $p = 0.75$), aborted mapping (0 smokers [0%] and 3 nonsmokers [1%]; $p = 0.99$), or LMA use (3 smokers [4%] and 5 nonsmokers [1%]; $p = 0.06$) between smokers and nonsmokers undergoing awake craniotomy. Smokers had a modestly increased but clinically insignificant length of stay (4 days for smokers and 3 days for nonsmokers; $p = 0.001$).

Perioperative Complications

The perioperative complications included hemorrhage (0.5%), stroke (0.7%), infection (1%), deep vein thrombosis or pulmonary embolism (0.5%), early neurological deficit (status at time of discharge; 9%), and late neurological deficit (3-month postoperative status; 3%) (Table 7). The overall complication rate was 10%, and the 30-day readmission rate was 1%. Postoperative complications in awake glioma surgery had no association with tumor location, pathology, LMA use, Mallampati score, ASA classification, sedation technique, or smoking status (Table 8). Smoking status and BMI have long been considered to be associated with worse perioperative outcomes in neurosurgery patients; however, our data suggest that smoking status is not a negative risk factor for patients undergoing awake brain tumor surgery. Postoperative complications were more prevalent in those with aborted mapping (3% in patients with postoperative complications vs 0.2% in those without complications; $p = 0.03$) and stimulation-induced seizures (10% with complications vs 3% in those without complications; $p = 0.003$) (Table 8).

Discussion

Using the largest single-surgeon experience ever reported to date, we describe the current indications, con-

TABLE 6. Stimulation-induced seizures during awake craniotomy

Variable	No. of Patients (%)		p Value
	Stimulation-Induced Seizures (n = 20)*	No Stimulation-Induced Seizures (n = 591)	
Preop history of seizures	19 (95)	408 (69)	0.01
Preop anticonvulsant use	17 (85)	401 (68)	0.14
Tumor site			0.0003
Frontal	14 (70)	154 (26)	
Insular	1 (5)	127 (21)	
Parietal	2 (10)	90 (15)	
Temporal	3 (15)	220 (37)	
Tumor pathology			0.89
High grade	11 (55)	324 (55)	
Low grade	9 (45)	250 (42)	
Metastasis	0 (0)	3 (0.5)	
Other	0 (0)	14 (2)	
BMI			0.12
Low (<24.9)	5 (25)	250 (42)	
High (>25)	15 (75)	341 (58)	

* Stimulation intensity 3–6 mA.

traindications, and evolving techniques for successful completion of awake language and sensorimotor mapping craniotomies to maximize perioperative safety and improve extent of resection for glioma patients. Our findings suggest that awake brain tumor surgery can be safely performed with few complications and a low failure rate, regardless of ASA classification, tumor site, tumor pathology, Mallampati score, BMI, smoking status, psychiatric history, seizure history, or tumor mass effect. We apply a team approach using trained operating room personnel employing specialized neuroanesthesia, which allows for better communication and prompt response to perioperative events if and when they occur. The anesthetic technique has evolved, offering improved patient comfort and limiting the influence CO₂ retention and tumor mass effect through the use of a nasal trumpet, LMA, and acceptance of the importance of flexibility with regard to the initial sedation regimen on the part of both the neurosurgeon and the anesthesiologist. While some institutions rely heavily on the LMA for an awake craniotomy, we used it sparingly in 1% of cases with a very low failure rate.^{49,108} The identification and management of stimulation-induced seizures is critical for the successful completion of an awake craniotomy. Using intraoperative ECoG to minimize the stimulation current based on identifying after-discharge potentials, we found a low rate of stimulation-induced seizures (3%), which were almost always controlled with iced Ringer's solution applied directly to the cortex.

Despite published series with failure rates of 2.3%–6.4% and complication rates of 14%–32%, these data illustrate a technique that offers a high degree of success and a low degree of morbidity.^{10,66,76,94,107} The failure rate using this technique is very low, occurring in 0.5% of awake craniotomies. The most common cause of failure was stimulation-induced seizures, which illustrates the importance of both preoperative and intraoperative seizure management for improved patient safety along with using lower stimula-

tion current and iced Ringer's solution during stimulation when indicated as described above.

The limitations of this study are those inherent to a retrospective analysis. To overcome these limitations, we reviewed a large series of patients and included only those patients who had complete records available. Overall, the methodology as described in this study has evolved over time to be a safe, practical, reproducible, versatile, and reliable surgical procedure with few contraindications and a low failure rate. As such, it should be used as the neurosurgical standard of care for the removal of gliomas within or close to presumed functional areas.

Conclusions

Awake craniotomy for glioma patients can be safely performed with extremely low complication and failure rates regardless of ASA classification, Mallampati score, patient BMI, performance status, smoking status, psychi-

TABLE 7. Complications in awake craniotomy*

Variable	Value
Overall periop complication rate†	63 (10)
Infection	6 (1)
Postop hemorrhage	3 (0.5)
Postop DVT or PE	3 (0.5)
Postop stroke	4 (0.7)
Early neurological deficit (at discharge)	58 (9)
Late/residual neurological deficit (at 3 mos postop)	16 (3)
30-day readmission	9 (1)

* Some patients experienced more than 1 complication. Values are expressed as the number of patients (%) unless noted otherwise.

† All complications captured in the study, including postoperative hemorrhage, infection, stroke, deep vein thrombosis/pulmonary embolism, new neurological deficit.

TABLE 8. Complication analysis for awake craniotomy patients (n = 611)

Variable	No. of Patients (%)		p Value
	Complications (n = 63)	No Complications (n = 548)	
Tumor pathology			0.57
High grade	36 (57)	299 (55)	
Low grade	27 (43)	232 (42)	
Metastasis	0 (0)	3 (0.5)	
Other	0 (0)	14 (3)	
Sedation technique			0.61
Adjusted technique	30 (48)	228 (42)	
Dexmedetomidine + remifentanyl	3 (5)	23 (4)	
Propofol + remifentanyl	30 (48)	297 (54)	
Mallampati score			0.62
1	17 (27)	130 (24)	
2	41 (65)	346 (63)	
3	5 (8)	66 (12)	
4	0 (0)	6 (1)	
ASA classification			0.21
1 (healthy patient)	1 (2)	49 (9)	
2 (mild disease)	53 (84)	413 (75)	
3 (severe disease)	9 (14)	85 (16)	
4 (life-threatening disease)	0 (0)	1 (0.2)	
Tumor site			0.77
Frontal	17 (27)	151 (28)	
Insular	16 (25)	112 (20)	
Parietal	10 (16)	82 (15)	
Temporal	20 (32)	203 (37)	
Smoker	11 (17)	64 (12)	0.2
LMA	2 (3)	6 (1)	0.2
Stimulation-induced seizure	6 (10)	14 (3)	0.003
Aborted mapping	2 (3)	1 (0.2)	0.03

atric and seizure history, tumor site, and tumor pathology. Surgeon flexibility with regard to the initial sedation regimen and adequate management of stimulation-induced intraoperative seizures are critical for successful completion of an awake craniotomy during glioma surgery.

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