Awake Craniotomy: Cortical and Subcortical Mapping for Glioma Resection

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Over 70,000 patients are diagnosed each year with a glioma, and the majority of these tumors are within areas of the brain with presumed functional significance. It has been well established that extent of tumor resection impacts both overall and progression-free survival. Direct stimulation of the cerebral cortex was first employed by Foerster in 1931 and later popularized by Penfield and Ojemann. Intraoperative mapping is the gold standard approach for the identification and preservation of functional areas of the brain. This chapter outlines the evidence supporting the extent of resection for low- and high-grade gliomas, including procedural steps and technical nuances to maximize success and minimize perioperative morbidity.

12.1 Introduction

An estimated 700,000 people in the United States are currently living with a glioma [1]. The role of surgery in the treatment of both low- and high-grade gliomas is to establish the correct histologic and molecular diagnosis, relieve mass effect, and provide maximal safe resection to improve both overall and progression-free survival. More than 50% of gliomas are within areas with presumed functional significance; therefore surgical decisions must balance reduction of tumor volume with preservation of function. Extent of tumor resection impacts outcome. Therefore an awake craniotomy permits maximal extent of resection while minimizing postoperative morbidity [2]. For this reason direct cortical and subcortical stimulation mapping via an awake craniotomy is the gold standard approach for the identification and preservation of functional areas. This chapter will discuss the rationale, indications, and technique for cortical and subcortical mapping during awake craniotomies using the asleep-awake-asleep protocol for patients with low- and high-grade gliomas.

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K. Fountas, E. Z. Kapsalaki (eds.), *Epilepsy Surgery and Intrinsic Brain Tumor Surgery*,
https://doi.org/10.1007/978-3-319-95918-4_12

12.2 Cytoreduction Improves Overall and Progression-Free Survival in Low- and High-Grade Glioma Patients

A growing body of literature has established that overall and progression-free survival is strongly influenced by cytoreduction surgery. Additional predictors of longer survival include patient age, oligodendrocyte histopathology, patient performance status, O^6-methylguanine-DNA-methyltransferase promoter methylation status, and the presence of the isocitrate dehydrogenase 1 (IDH1) mutation [1, 3–8]. Intraoperative direct cortical and subcortical stimulation mapping using an awake craniotomy facilitates a greater extent of resection with lower rates of perioperative complications. The goal of intraoperative mapping during awake craniotomy is to balance tumor removal with preservation of function. Intraoperative mapping permits both greater extent of resection and less functional morbidity [2]. A recently published meta-analysis including 8091 glioma patients demonstrated that intraoperative mapping reduced the number of severe neurologic deficits (3.4% late severe neurologic deficits after intraoperative mapping versus 8.2% late severe neurologic deficits without the use of functional mapping) and improved the extent of tumor resection (75% extent of glioma resection with intraoperative mapping versus 58% without intraoperative mapping) [2].

The mean survival for patients with WHO grade II gliomas is 2.2–9.5 years and varies based on isocitrate dehydrogenase, 1p19q codeletion, and ATRX gene mutation status. The median time to malignant progression for WHO grade II gliomas to either WHO III or IV tumors is 5 years [9–12]. The median survival for patients with WHO III gliomas is 3.4 years, again with a strong dependency of extent of resection and molecular markers [9–12]. Many studies have investigated the role of the extent of tumor resection for patients with low- and high-grade gliomas. A survival benefit of 61–90 months with maximal resection can be seen for WHO II and III gliomas [4–7, 11, 13–29]. Similarly, gross total resection of WHO IV gliomas improves overall survival from 11.3 to 18.5 months [1, 3, 10, 30–59]. Perhaps the strongest evidence in support of cytoreduction surgery for gliomas was provided by Jakola et al. [60] in a large population study of Norwegian glioma patients. Neurosurgeons from two adjacent regions offered differing clinical practice patterns. Hospital A favored an initial tumor biopsy followed by watchful waiting, while Hospital B offered early tumor resection at the time of diagnosis. Overall survival was longer for individuals treated at Hospital B. The median survival was 5.9 years for patients receiving tumor biopsy, while the group receiving early resection did not reach median survival by the end of the study period (median follow-up of 7 years) [60]. Five-year survival was 60% for the biopsy group and 74% for those receiving early surgery [60]. This evidence has offered insight about how to manage asymptomatic incidentally found gliomas. These tumors are typically smaller at diagnosis and offer a greater likelihood of achieving a gross total resection, making early resection the favored approach [61, 62].

12.3 Indications and Contraindications to Awake Glioma Surgery

An awake craniotomy is considered for any patient with a supratentorial glioma located within or adjacent to an area presumed to have functional significance. Because safety is of paramount importance during an awake craniotomy, patient selection is critically important. Several factors center on the size and location of the tumor. Amount of mass effect, patient smoking status, patient body-mass index, seizure frequency, and medical comorbidities are associated with increased perioperative risk during awake glioma surgery (Table 12.1) [63, 64]. Absolute contraindications to an awake craniotomy include (1) severe psychiatric illness limiting one's ability to cooperate, (2) severe aphasia with greater than 50% naming errors, (3) large tumors with mass effect resulting in more than 2 cm of midline shift, (4) severe chronic cough, and (5) hemiplegia with less than antigravity motor function resulting in severe limitations in passive or active movement of the extremity to be mapped. As the technique has evolved, a number of strategies have allowed higher risk patients to undergo awake craniotomy despite comorbidities and relative contraindications. Intraoperative nausea can be treated with antiemetic medications (such as ondansetron hydrochloride or scopolamine) prior to induction and throughout the procedure. Severe aphasia may be caused by either tumor infiltration of cortical and subcortical language pathways or pathway irritation from perilglioma edema. Therefore patients with greater than 25% naming errors may be treated with high-dose corticosteroids (dexamethasone, 4–8 mg intravenously every 6 h) and/or osmotic diuretics (mannitol 20%, 30 gm every 6 h for 48–72 h) followed by reassessment prior to surgery. Obesity may be problematic because most sedating and analgesic medications tend to relax the airway, resulting in hypercapnia and cerebral edema. Obese patients (body mass index >35) can be treated with a laryngeal mask airway (LMA) or nasal trumpet to prevent hypercapnia. Patients with generalized anxiety or a severe untreated psychiatric history should be treated with antidepressant and mood-stabilizing medications prior to surgery. Older age is not an absolute contraindication to this procedure. In a study comparing patients over age 65 years to younger individuals, intraoperative mapping proved to be feasible without any increase in perioperative morbidity [65]. Intraoperative seizures are the most common reason for intraoperative failure. Seizures are treated with topical iced Ringer solution applied to the cerebral cortex. Moreover, IV propofol, diazepam, or lorazepam may be used for sustained stimulation-induced intraoperative seizures.

Table 12.1 Contraindications and solutions to awake xraniotomy

Relative contraindications	Solutions
Intraoperative seizures	Iced ringer solution, intravenous lorazepam, or propofol
Mass effect (>2 cm midline shift)	Staged procedure with internal debulking of presumed nonfunctional areas asleep (± functional imaging) followed by reoperation with awake mapping for presumed functional areas
Chronic cough	Light sedation and cough suppressants
Obese patient (BMI >35)	Laryngeal mask airway before and after mapping, intubation after mapping
Severely impaired preoperative function	3–5 days of preoperative high-dose steroids ± mannitol
Emotional instability/ psychiatric history	Presurgical treatment with antidepressants and antipsychotic medications
Chronic or intraoperative nausea	Preoperative medication with antiemetic drugs and dexamethasone

12.4 Imaging and Neuro-Navigation Adjuvants

Initial imaging for a patient with suspected glioma who is being considered for an awake craniotomy begins with a brain magnetic resonance image (MRI) or computed tomography (CT) scan with and without contrast enhancement, including T1, T2, fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted MRI (DWI) sequences. MRI spectroscopy or MRI perfusion may offer additional insight into the metabolism and vascularity of the mass to assist in prediction of tumor biology. MRI spectroscopy for gliomas demonstrates raised choline peaks with depressed N-acetyl aspartate peak (increased choline, decreased NAA) [66]. MRI perfusion studies rely on the passage of paramagnetic agents through tumor vasculature to estimate blood volume [67]. A critical aspect of glioma surgery is the identification of functional and nonfunctional areas within and around the tumor. Structural and functional imaging such as functional MRI (fMRI) and diffusion tensor imaging (DTI) MRI tractography illustrates this relationship and is useful for preoperative planning (Fig. 12.1). Changes in regional blood flow and deoxyhemoglobin associated with neuronal activity are known as blood oxygenation level–dependent (BOLD) signal and serve as the hallmark of fMRI. During the MRI, each patient is asked to perform a language or motor task during which a dependent BOLD signal identifies regions of the brain in which there is neuron activation [68, 69]. Another approach involves identifying subcortical tracts of interest using DTI tractography. DTI tractography differentiates the corticospinal tract and dorsal or ventral language in the region of the tumor, which aids preoperative understanding of pathway displacement by the mass [70–72]. Neither fMRI nor DTI tractography are 100% sensitive for the identification of cortical and subcortical functional areas. These studies are challenged by imprecision caused by distortion from mass effect, individual patient anatomic variability, and functional reorganization caused by cortical and subcortical plasticity [73–75]. Furthermore, imaging highly vascular high-grade gliomas can be challenging because of uncoupling of the BOLD signal, making interpretation of fMRI results difficult. Resting state coherence measured with magnetoencephalography (MEG) is a noninvasive measure of functional connectivity of the brain. Malignant brain tumors with decreased resting state connectivity have a lower risk of causing postoperative neurologic deficits, while those with increased resting state connectivity are associated with a higher risk of postoperative neurologic deficits [76].

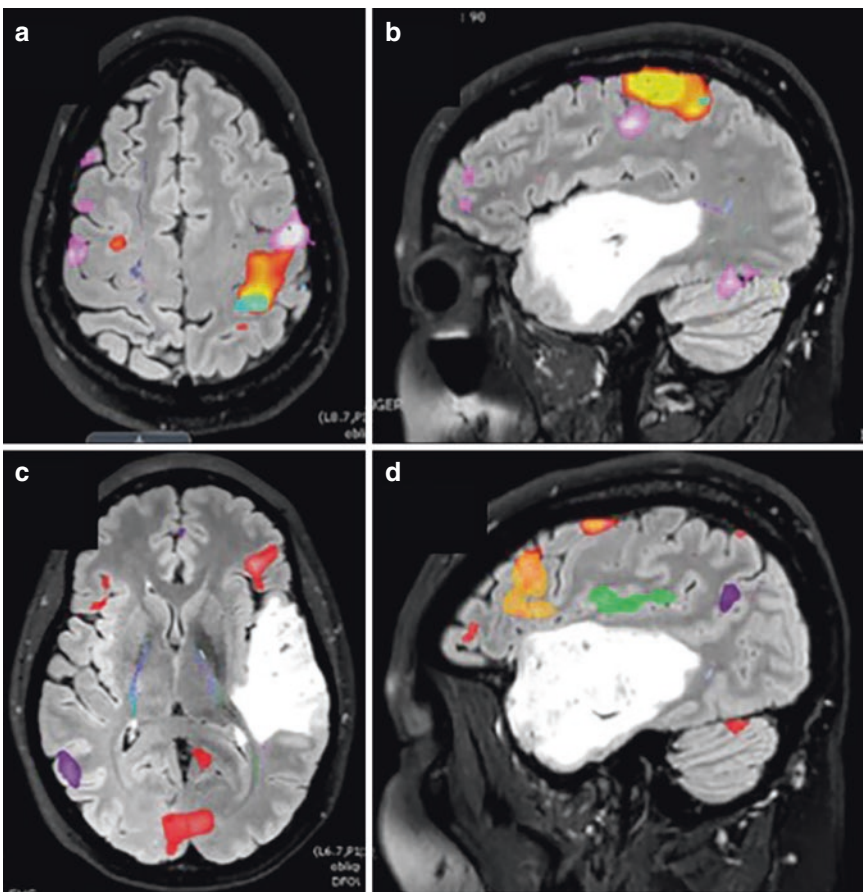

Fig. 12.1 Axial (**a**) and sagittal (**b**) fluid-attenuated inversion recovery (FLAIR) functional magnetic resonance imaging (fMRI) for motor tasks reveals frontal activation above the left temporal nonenhancing glioma (*yellow* and *red*). Axial (**c**) and sagittal (**d**) FLAIR fMRI for language tasks reveals receptive language superior and posterior to the tumor (*green*)

12.5 Planning the Procedure and Preoperative Preparation

Prior to surgery each patient should have a detailed history, physical examination, and review of medications. Preoperatively, each patient should be evaluated by his or her neurosurgeon, anesthesiologist, speech pathologist, neuropsychologist, or intraoperative monitoring specialist. A detailed motor examination, neuropsychological examination, and Boston Naming Test (BNT) are performed at baseline. Patients are counseled about what to expect during the procedure in addition to perioperative risks. Management of seizures is particularly important before intraoperative mapping of craniotomies because stimulation-induced seizures are the most common reason for an aborted mapping procedure. Corticosteroids such as dexamethasone should be administered to control periglioma edema, with doses ranging between 2 and 24 mg daily. Antiepileptic medications such as levetiracetam or Dilantin should be considered preoperatively for patients who will undergo an awake mapping craniotomy [64, 77].

12.6 Awake Craniotomy Procedural Steps and Technical Considerations

12.6.1 Patient Positioning

Clear communication is thought to be the most important aspect of performing a safe awake craniotomy [78]. This early stage requires a great deal of flexibility, as the initial sedation plan can change depending on patient tolerance. In the preoperative area invasive and noninvasive monitors are placed. This includes intravenous and arterial lines, cardiac rhythm monitors, and Foley catheter placement. Many patients benefit from receiving short-acting antianxiolytic medications such as midazolam, or dexmedetomidine [64]. All patients are given supplemental oxygen via nasal cannula or face mask. Positioning the patient must balance patient and surgeon comfort with safety. If possible, even when using an asleep-awake-asleep technique, the patient is briefly awakened to allow active participation in relieving any painful or pressure points. The lateral decubitus or semilateral positions are used with the aid of pillows and a foam mattress placed behind the ipsilateral back and shoulder. Giving the patient a small amount of neck extension ensures easy access to the airway, should placement of an LMA be needed. A nasal trumpet may be placed for the patient who is exhibiting partial airway obstruction.

12.6.2 Initial Sedation

The most common anesthetic technique used during an awake craniotomy for glioma resection is the asleep-awake-asleep approach. Sedation for an awake craniotomy is unique in that it requires the anesthesiologist to alter states of both painlessness and sedation during the procedure. Early in the procedure sedation is often heavier while drilling the calvarium; however, during dural opening sedation can be lighter, although there is a continued need for analgesia. A topical scalp block using a combination of 1% lidocaine with 1:100,000 epinephrine and 0.5% bupivacaine is applied. To avoid burning during delivery, sodium bicarbonate can be added to the local analgesic mixture. When using the asleep-awake-asleep technique, sedation is achieved with intravenous propofol (up to 100 μg/kg/min) or dexmedetomidine (up to 1 μg/kg/min) and remifentanil (0.07–2.0 μg/kg/hr) [79–81]. It is often beneficial to begin sedation prior to placement of the Foley catheter and of the Mayfield headholder pin. Following skin incision and removal of the bone flap, all sedating medications are held or reduced before dural opening. Either 500 mg or 1 gm of intravenous oral acetaminophen is an excellent addition, particularly for patients having continued pain despite intravenous medications.

12.6.3 Craniotomy and Exposure

The goal of exposure is to expose the tumor and surrounding cortical areas with presumed functional significance. This is typically done via a focused exposure encompassing the lesion plus a 2-cm margin. Early intraoperative mapping techniques involved large craniotomies with the goal of finding cortical language and motor sites as positive controls. Over the past decade, however, there has been greater reliance on negative mapping through smaller focused craniotomies, which offer the same degree of perioperative safety. Additionally, a focused craniotomy avoids unneeded exposure of cortical surfaces, thereby preventing injury. Following removal of the bone flap, sedation is held prior to dural opening.

12.6.4 Intraoperative Cortical Mapping

Prior to beginning cortical mapping, it is important to confirm with the neuro-anesthesiologist that a dedicated intravenous line with a 1-mg/kg bolus of propofol is available in the event it is needed for suppression of an intraoperative seizure. However, the first-line agent for treatment of intraoperative stimulation-induced seizures is topical ice-cold Ringer lactate solution. Intraoperative electrocorticography is performed using either a 16-array cortical electrode or a 1 × 6 strip electrode to detect seizure activity and afterdischarge potentials. A bipolar electrode is used for stimulation via 2-mm tips with 5 mm of separation [82]. Typical stimulation parameters include a current of 1.5–2 mA using a constant current generator that delivers 1.25-ms biphasic square waves in 2–4-s trains at 50 or 60 Hz. Cortical stimulation excites local neurons via diffusion of current using both orthodromic and antidromic propagation. Numerical markers are placed 1 cm apart on the surgical field. Intraoperative motor tests may be performed either actively (the patient is asked to tap a finger, wiggle toes, or move the tongue from side to side) or passively (no movement) during stimulation.

12.6.5 Intraoperative Subcortical Mapping

Following mapping to identify cortical language and motor sites, a safe corridor of entry into the tumor is identified, and tumor resection begins. The subpial dissection permits the surgeon to remain within the negatively mapped gyrus and identify the moment a sulcal depth is reached, under which subcortical u-fibers reside. The subcortical map is used to prevent transecting the corticospinal tract or dorsal or ventral language pathways. Intraoperative tasks used for subcortical mapping are similar to cortical tasks. However, stimulation thresholds for subcortical mapping vary but commonly begin with an increase of 1–6 mA above the stimulation threshold used for cortical mapping.

12.6.6 Closure

After the maximal extent of glioma resection has been achieved, sedation is resumed. Sedation for closure may include either resumed monitored anesthesia care (MAC) anesthesia, placement of an LMA, or an endotracheal tube. The patient is then awakened and taken to the postanesthesia care unit for recovery followed by overnight observation in the intensive care unit.

12.7 Complication Avoidance and Perioperative Outcome

The goal of intraoperative mapping for low- and high-grade gliomas is to balance reduction of tumor volume with preservation of language, motor, and neurocognitive functions. Intraoperative mapping offers a greater extent of tumor resection and improved functional outcomes [2]. Postoperative language outcomes following direct cortical and subcortical stimulation mapping of dominant hemisphere low- and high-grade gliomas have been studied in numerous large series [24, 83, 84]. Immediately following surgery (within 2 weeks), language deteriorates in 14–50% of patients [24, 84, 85]. However, after 3 months 78–100% of patients have return of language to baseline preoperative function. Aphasia recovery correlates with structural integrity of the arcuate fasciculus and superior longitudinal fasciculus [24, 84]. After 6 months of aphasia recovery following an awake language mapping craniotomy, only 0–2.4% of patients have worsened language function [24, 84]. Long-term motor outcomes have likewise been examined in a retrospective analysis of 294 patients with peri-rolandic region gliomas following intraoperative motor mapping [86]. Immediately following intraoperative mapping of motor cortex gliomas, 20% of patients experienced a new postoperative motor deficit; however, 58% recovered to their preoperative baseline within 1 month. Three months following motor mapping of rolandic cortex gliomas, contralateral weakness was observed in 4.8% of patients, with the greatest incidence noted in cases in which subcortical motor activity was found during mapping [86].

Conclusion

Both preservation of functional areas and maximal safe resection are critically important in the management of gliomas and impact both overall and progression-free survival. The awake craniotomy is the gold standard procedure for tumors within presumed functional areas. The pursuit of maximal extent of resection must be balanced with careful patient selection to limit perioperative morbidity.

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