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TOPIC REVIEW

Awake glioma surgery: technical evolution and nuances

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Abstract

Introduction Multiple studies have demonstrated that improved extent of resection is associated with longer overall survival for patients with both high and low grade glioma. Awake craniotomy was developed as a technique for maximizing resection whilst preserving neurological function.

Methods We performed a comprehensive review of the literature describing the history, indications, techniques and outcomes of awake craniotomy for patients with glioma.

Results The technique of awake craniotomy evolved to become an essential tool for resection of glioma. Many perceived contraindications can now be managed. We describe in detail our preferred technique, the testing paradigms utilized, and critically review the literature regarding functional and oncological outcome.

Conclusions Awake craniotomy with mapping has become the gold standard for safely maximizing extent of resection for tumor in or near eloquent brain. Cortical and subcortical mapping methods have been refined and the technique is associated with an extremely low rate of complications.

Keywords Awake craniotomy · Glioma · Speech mapping · Motor mapping

Introduction

The fundamental goal in glioma surgery is to balance maximal extent of resection (EOR) with preservation of neurological function. Increased EOR is associated with improved overall survival for patients with both low and high grade glioma [1–11], whereas postoperative deficits have been associated with worse overall survival and quality of life [12–15]. Intraoperative mapping during an awake craniotomy is now a well-established technique for achieving both aims. Operating on awake patients allows for confirmation of neurological function, and electrical stimulation allows for transient and focal disruption or activation of speech and sensorimotor areas respectively, mimicking the effect of their removal.

This paper aims to summarize the history of the technique and outline current anesthetic, surgical and mapping strategies for awake craniotomy for glioma. We then summarize the literature regarding neurological and oncological outcome.

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History

By necessity, all attempts at craniotomy prior to the introduction of anesthesia were performed on awake patients. It wasn't until the late nineteenth century that awake craniotomies were performed as a management decision. Although the motor effects of electrical stimulation had been studied in animals for many years, the first reported case of electrical stimulation of a human brain was reported in 1874 in a patient with a tumor causing skull erosion [16] and caused considerable ethical controversy as the procedure was invasive and without therapeutic benefit [17]. A formalized method combining awake craniotomy with electrical stimulation was first meticulously described by Penfield and Boldrey in 1937 [18] for epilepsy surgery. Initially, current was used to identify epileptogenic foci by inducing auras, motor effects or seizures. The next major advance occurred in the 1970s, when George Ojemann introduced systemized testing to identify and avoid damaging functional brain as well as the use of biphasic current with a constant pulse [19]. In the

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following decades, Ojemann and Berger further refined this technique for use in patients with brain tumors [20–22] and, over this time period, the importance of subcortical mapping was better appreciated [23].

Early cases were performed with local analgesia only [24]. However, over time anesthetic agents and techniques improved considerably. Later series reported the use of intravenous fentanyl and droperidol for sedation combined with local analgesia [25]. Propofol was introduced in the 1990s [26] and was a marked improvement to prior anesthetic regimens because of its hypnotic, amnestic and antiemetic effects. The drugs short half-life also allows for more rapid return to consciousness for testing. The introduction of two other agents, remifentanil and dexmedetomidine, significantly improved the ability to titrate opioid effect and sedation without respiratory depression, respectively. Current anesthetic and mapping techniques will be discussed below.

Case selection

Appropriate patient selection is crucial to ensuring intraoperative success with awake mapping. We consider awake craniotomy in all patients with supratentorial lesions that are in or near possibility eloquent areas, although other groups have utilized the technique nonselectively for supratentorial tumors [27]. A full assessment of a patient's medical comorbidities, neurological deficits, seizure frequency, body habitus, and anxiety should be taken into consideration when formulating the operative plan. Preoperative mapping techniques such as tractography, functional MRI and MEG are insufficient to accurately exclude function [28–30] and should therefore not be used to justify asleep surgery. Although useful for determining laterality of language, the spatial resolution of these techniques is insufficient to determine the exact location of functional tissue [31] and may not adequately distinguish between involved and essential language sites [32]. Further, as the brain shifts during surgery, the actual position of functional cortex and tracts may differ by more than 1 cm from that predicted by navigation [30], necessitating the use of intraoperative mapping techniques. In cases where motor mapping is all that is required, we have moved towards surgery under general anesthetic using "triple motor mapping" (manuscript accepted, awaiting publication) rather than awake surgery. We use transcranial (and/or direct cortical) stimulation for monitoring during resection, monopolar stimulation for cortical mapping, and monopolar and bipolar stimulation for subcortical mapping.

In our experience, there are few absolute contraindications to awake surgery. Over the course of the senior authors practice, techniques have been developed to mitigate most potential problems (Table 1) [22]. A baseline examination with a neurophysiologist should be completed to ensure the patient's performance is reliable enough to determine intraoperative changes from baseline errors and to improve the patients understanding and expectations. Previous tumor resection limited by positive mapping should not preclude awake surgery. We and others [33, 34] have demonstrated

Table 1 Relative contraindications and solutions for awake craniotomy patients

Prior concerns	Current solutions
Significant mass effect (> 2-cm midline shift) despite preoperative diuretics and 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 (years)	
> 10	Awake
< 10	2-stage procedure w/implanted grid
Intraoperative seizures	Iced Ringers solution, propofol IV 6 inches from vein
Smoker	Cough suppressants w/ or w/o light sedation
Gastroesophageal Reflux	Increase medication dose or add second line treatment
Intraoperative nausea	Preop medication w/antiemetic drugs (ondansetron hydrochloride, scopolamine) and high-dose dexamethasone (10 mg)
Reop (dural scar) Severely impaired preoperative function[a]	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, & pre- serve

BMI body mass index, *IV* intravenous, *LMG* laryngeal mask airway, *MEG* magnetoencephalography, *MSI* = magnetic source imaging

[a]Motor function < 2/5 or baseline naming/reading errors (after Hervey-Jumper et al. (2015) [22])

functional plasticity in patients with glioma, with up to 25% of previously identified sites no longer demonstrating function at repeat surgery.

Anesthetic technique and positioning

The two major techniques for performing awake craniotomy are the "asleep-awake-asleep" approach utilizing a combination of propofol-remifentanyl and the "conscious sedation" technique. Dexmedetomidine may be utilized with either approach. Molina et al. recently showed that patients who received conscious sedation required fewer opiates, vasoactive medications, and antihypertensive drugs which resulted in shorter postoperative lengths of stay and operative times [35]. In a randomized control trial comparing dexmedetomidine to propofol-remifentanyl, the dexmedetomidine group was associated with fewer respiratory adverse events and there was no difference in the degree of sedation or the ability of patients to perform mapping tasks [36]. In general, we begin with propofol-remifentanil and add dexmedetomidine (with or without continuing propofol) if required [22].

Prior to initiation of anesthesia, premedication with an antiemetic is used to minimize nausea or vomiting during the procedure. Dexamethasone and mannitol are administered in most cases. Patients already prescribed anticonvulsants are continued on their usual dose, otherwise these are infused slowly to avoid any sedation or behavioural side effects. We place an arterial line and indwelling urinary catheter (with temperature probe) after a bolus of propofol, although these adjuncts are not used universally [27]. Local analgesia is infiltrated into the skin at the position of the anterior pin site of the Mayfield head holder (Ohio Medical) using a combination of Marcaine and xylocaine with epinephrine.

In most cases the patient is placed in a semi-lateral position with a back support (Fig. 1). This is preferred as most mapping cases as centered around the Sylvian fissure, and also this position minimizes airway obstruction and snoring. All contact points are padded. The head-clamp is then placed over the skin of its final position, local anesthetic applied around the posterior pin sites, and after a few minutes the clamp is tightened and secured. The final head position is dependent on the tumor location. We then mark the tumor and relevant anatomy using neuronavigation and outline the incision. Although other groups perform complete scalp blocks (often before pinning), we perform focal blocks of the skin, fascia and muscle of the incision and field.

A Bair Hugger (3 M Corp.) is applied and the patient's temperature is controlled so that the bladder temperature is above 36.0 °C during mapping. All patients receive a nasal canula and supplemental oxygen during the entire operation. A nasal trumpet is placed if the patient begins to snore or shows signs of airway obstruction. After skin preparation, the field is draped with a space created for the patient to see a screen during mapping, and for access by the anesthesiologist. If the patient wears reading glasses, we remove the arm of the glasses ipsilateral to the craniotomy so they may be worn during mapping.

Surgical technique

Surgery begins in a manner similar to asleep surgery. Key differences will be outlined. Ideally, the patient is sufficiently sedated during the opening so that they are not conscious. If they are lightly anesthetized, we provide continuous verbal guidance to the patient at each step to help alleviate anxiety and provide forewarning of loud aspects of the operation, such as drilling. The senior authors practice has shifted from performing larger craniotomies, to smaller exposures which may result in negative mapping (see below) [21]. This is particularly the case in repeat craniotomies where the area of mapping required is usually smaller, and the risks of increasing cortical exposure are higher.

Dural manipulation can be painful so copious irrigation is required during craniotomy and additional local anesthetic may be required during durotomy. This is administered with a 30-gauge needle, to the dural branches of the trigeminal nerve, most commonly around the middle meningeal artery during a frontotemporal approach. Irritation of the middle fossa floor during resection may cause pain or elicit the trigeminocardiac reflex causing nausea, vomiting, hypotension, bradycardia or even apnea.

We wean the patient off sedating medications toward the conclusion of the craniotomy. Prior to durotomy, the patient is asked to take five deep breaths to decrease pCO_2 and intracranial pressure. If an unacceptable degree of brain swelling occurs after durotomy, the patient is again instructed to hyperventilate, additional mannitol may be given, or exposed sulci or fissure may be opened for CSF egress.

Stimulation technique

Mapping begins with an assessment of the patients wakefulness [37]. We perform stimulation using low frequency (60 Hz, 1.0-ms biphasic square wave with 4-s) bipolar stimulation with the Ojemann probe. Intraoperative electrocorticography (ECoG) is performed using a 16-channel electrode and holder assembly (Grass Model CE1, Natus Medical Inc.) and interpreted by an epileptologist. Stimulation begins at 2 mA and then increases until positive stimulation is identified, after-discharge potentials occur, or to a maximum current of 5 mA, although others groups have utilized higher currents [38]. Current is applied for 3–4 s, with 4–10 s

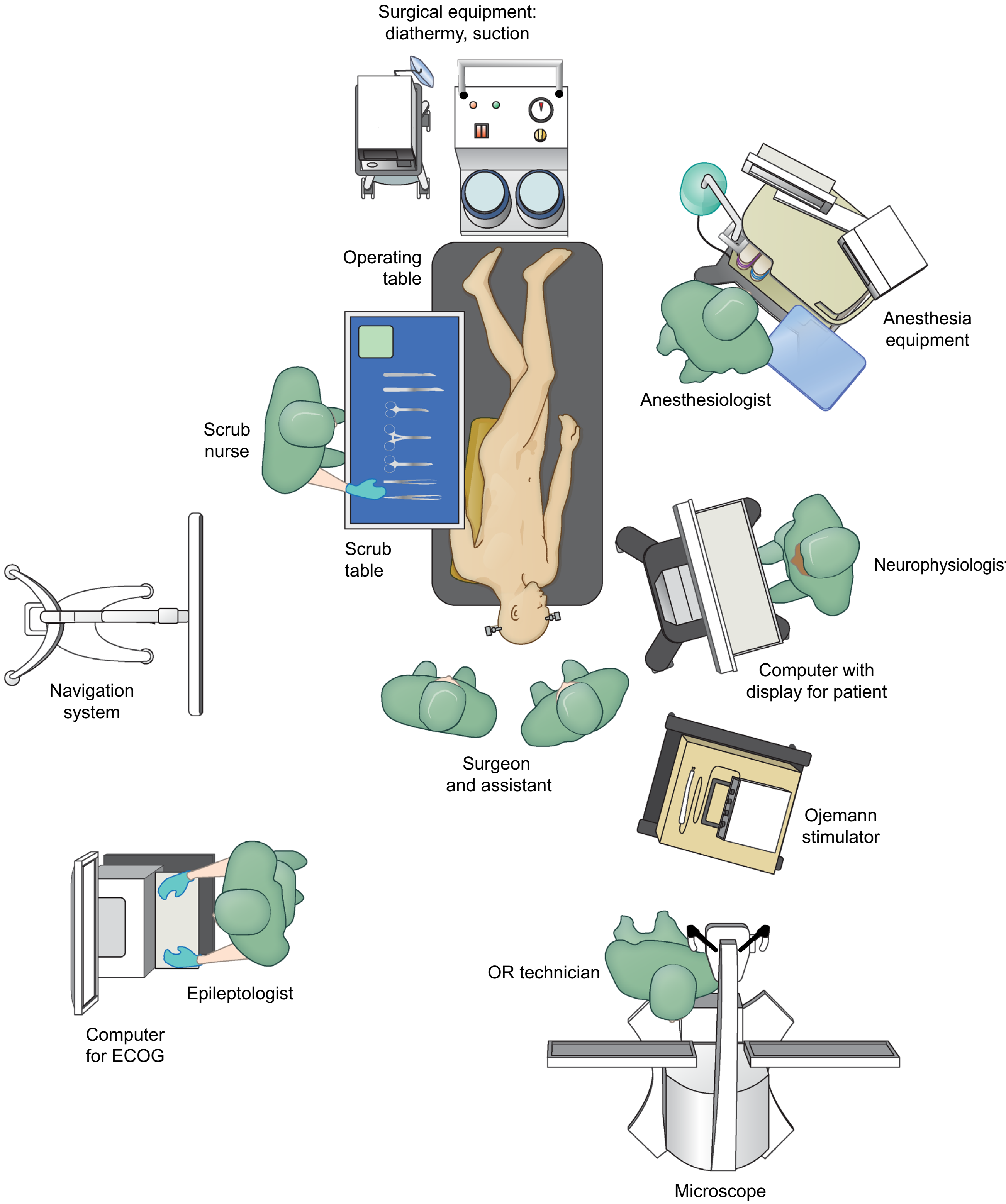

Fig. 1 Schematic of room setup for awake mapping. Positions of equipment and personal during awake mapping for a left sided tumor as performed at UCSF. *ECOG* electrocorticography, *OR* operating room. The exact setup needs to tailored to the available space and another other equipment that may be ultilised, such intraoperative ultrasound

between tasks. Typically the current required for mapping is 3–4 mA [22] and currents above this range are associated with a greater risk of seizures or after-discharge potentials.

If after-discharge potentials occur, mapping is suspended, and the field irrigated with ice cold Ringer's until the after-discharge potentials resolve. Mapping then proceeds after reducing the current by 1 mA. Intraoperative seizures are uncommon in our experience [22] and can be reliably terminated with ice cold isotonic solution [39]. However, propofol should be available (and in-line) if needed.

Although this is the most established mapping technique, recent advances using with monopolar subcortical motor mapping has led to some groups using high frequency (250–500 Hz) monopolar stimulation for awake craniotomy and language mapping with low rates of postoperative deficits, but intraoperative seizures in 7% of patients [40].

Testing paradigm and inferring function

The method and content of testing varies depending on the side and anatomical location of the tumor, and the hand dominance of the patient. In general, anything potentially at risk is mapped, as outlined in Table 2. Stimulation results in positive phenomena in primary motor and sensory areas, and disruption of function in areas subserving higher functions. Stimulation of the primary motor area results in movement that can be seen by the operative team or experienced by the patient (such as glottic tightness in the lower precentral area). Stimulation of the somatosensory area results in tingling or paresthesia and stimulation of the visual areas causes phosphenes to be experience in the corresponding portion of the visual field. For language, we observe for speech arrest (by having the patient count), naming, reading and sentence completion [21]. In the dominant and non-dominant parietal lobes we also test for acalculia and hemispatial inattention (using a line bisection task), respectively.

Testing sites are separated by 1 cm, numerically marked and tested at least three times non consecutively [22].

Table 2 Testing paradigms by anatomical location

Lobe	Modalities mapped
Frontal	Motor function
	Language—speech arrest, picture naming, reading
Temporal	Language—speech arrest, picture naming, reading
Insula	Motor function
	Language—speech arrest, picture naming, reading
Parietal	Line bisection
	Somatosensory function
	Calculation
Occipital	Visual fields

Language arrest is distinguished from dysarthria by the absence of involuntary mouth or pharyngeal contractions [41]. Positive mapping is defined as the inability to perform the task in two thirds of trials or more. This definition was established by Ojemann et al. [42] and has been used widely in the subsequent decades [21, 33, 43].

Using this technique, the false negative rate for mapping is extremely low and so the need to identify positive mapping (as a positive control) has reduced. This has led to an evolution in the senior authors practice from performing large craniotomies to map functional tissue, to smaller exposures and relying on "negative mapping" to define function free corridors to the tumor [22]. Negative mapping relies on the surgeons' anatomical knowledge and confidence in the reliability of the mapping procedure at their institution. Larger craniotomies with positive mapping may be more appropriate at the beginning of the learning curve.

Testing paradigms continue to evolve and should be incorporated into practice if their utility is demonstrated. For example, we have integrated picture-word interference and sentence generation into our subcortical mapping protocol, but not famous face recognition, as this does not predict a significant functional deficit (see discussion in the following).

Recently there has been increasing interest in passive cortical mapping. This approach uses electrocorticography to record activity with spatial and temporal resolution during language, motor or cognitive tasks. Although currently investigational and insufficiently accurate to replace stimulation mapping [44], this approach may shorten operative times, reduced the risk of intraoperative seizures, and allow for mapping in cases were stimulation mapping is not possible [45].

Resection and subcortical mapping

Following cortical mapping, it is our preference to administer mild sedation to increase the patients comfort and compliance during resection. Other groups prefer not to use sedation until after subcortical mapping is performed to prevent difficulties rousing the patient, although we have not had problems with this approach. Cortical resection proceeds through function free corridors using an ultrasonic aspirator. Diathermy is avoided within the brain to minimize the risk of vascular injury and resultant ischemia. If sedated, the patient is awakened again and subcortical mapping is performed once the resection is below the sulcal depths where white matter pathways are at risk. Testing paradigms are implemented based on anatomical location and neuronavigation tractography.

Language pathways at risk during subcortical resection are depicted in Fig. 2a. Current understanding of language

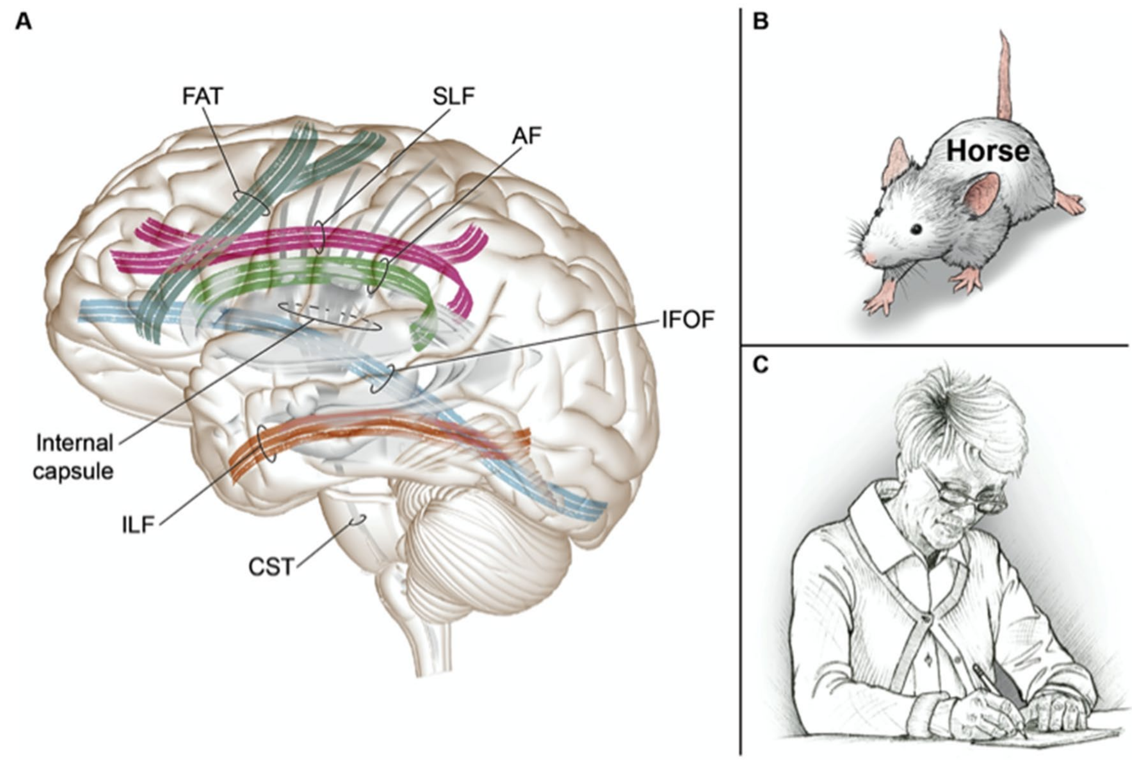

Fig. 2 Subcortical language and motor mapping. The location of subcortical pathways involved in language and motor function (**a**). Word/picture interference (**b**) and sentence completion (**c**) tasks. *AF* arcuate fasciculus, *CST* corticospinal tract, *IFOF* inferior fronto-orbital fasciculus, *ILF* inferior longitudinal fasciculus, *FAT* frontal aslant tract, *SLF* superior longitudinal fasciculus

processing is based on the dual stream model, whereby the dorsal stream (including the arcuate fasciculus and superior longitudinal fasciculus) is involved in sensorimotor integration, whereas the ventral stream (including the inferior fronto-occipital fasciculus, uncinate fasciculus and middle and inferior longitudinal fasciculi) subserve speech comprehension [46].

Ventral stream mapping commonly leads to errors during picture-word interference testing (Fig. 2b) [47], with semantic paraphasia's occurring commonly in the IFOF [46]. There is conflicting evidence regarding the function of the uncinate fasciculus, with some reporting that its removal impairs the ability to name famous faces [48], whereas other others have shown its removal does not lead to any permanent deficit [49]. We do not specifically test for this phenomenon. During dorsal stream mapping, errors are commonly seen in sentence generation (Fig. 2c), with hesitation, grammatical or semantic paraphasias occurring on the verb (rather than on the subject or object). Picture-word interference errors also occur during dorsal testing, but are seen less commonly than in the ventral stream and are manifest as speech arrest [47].

Motor function is tested subcortical in the same manner as for cortical testing. If errors or movement occur during subcortical mapping, we wait and then repeat the task. We consider mapping positive if more than two errors occur in a single area.

Tumor is resected until normal tissue or positive mapping is encountered. The patient's level of sedation is then deepened during hemostasis and closure. Rarely, a laryngeal mask airway is required during this phase [22]

Outcomes after awake mapping

Intraoperative stimulation mapping is the gold for minimizing postoperative deficits [50], and there have been numerous studies examining neurologic outcomes after intraoperative mapping during awake craniotomies (Table 3). In general, awake craniotomies can be performed safely and can allow for significant extent of resection in patients with glioma. The majority of studies report a mean extent of resection greater than 90% or a GTR rate of greater than 50%. Rates of permanent deficits range from 3 to 47.1%, however studies vary in terms of lesion location and degree of involvement of eloquent tissue. There is also a lack of consistency in the definition of a "fixed" or "permanent" neurologic deficit, with groups defining this term as a deficit persisting by anywhere from 1 to 6 months postoperatively.

Table 3 Prior reports on awake craniotomy outcome

	Number of patients	% of cases for glioma	Stimulation-induced seizure rate	Permanent deficit rate	Reported EOR
Verst (2019) [40][a]	41	98	7%	Speech: 2.4%	GTR: 48.7%
Gerritsen et al. (2019) [72]	37	100	NR	Motor 8.1%	94.9%
Zelitzki et al. (2019) [60]	44	93	NR	Language: 9.1% Motor: 2.3%	86.2%
Saito et al. (2019) [59]	30	100	NR	Motor: 33.3%	93%
Gravesteijn et al. (2018) [69]	24	100	NR	33%	WHO grade II/III: 61.4% WHO grade IV: 73.4%
Eseonu et al. (2017) [61]	27	100	7.4%	Language: 14.8% Motor: 11.1%	86.3%
Hervey-Jumper et al. (2015) [22]	859	99	3%	3%	NR
Martino et al. (2013) [70]	11	100	NR	9.1%	91.7%
Tuominen et al. (2013) [62]	20	100	5%	Language 5% Motor: 5%	GTR: 50%
Shinoura et al. (2013) [55]	102	37	NR	Motor: 7.8%	GTR: 52.9% Partial: 47.1%
Trinh et al. (2013) [56]	214	100	NR	36%	GTR: 66% STR: 8% Partial: 25%
Nossek et al. (2013) [52]	424	74	2.1%	3.1%	GTR: 83% STR: 17%
Sacko et al. (2011)	214	67	5.7%	14.6%	GTR: 37% STR: 45%
Ali et al. (2009) [68]	20	100	10%	5%	GTR: 40%
Pereira et al. (2009) [63]	79	99	21.5%	Language: 13.9% Motor: 8.9%	100%:31.6% > 95%:50.6% > 90%:72.1% > 80%:84.8% < 80%:15.1%
Sanai et al. (2008) [21]	145	100	NR	Language: 1.6%	GTR: 59.6%
Bello et al. (2007) [64]	88	100	10.2%	Language: 2.3%	GTR: 33%
Serletis and Bernstein (2007) [27]	511	60	4.9%	Language: 3.8% Motor: 6.6%	NR
Gupta et al. (2007) [65]	26	92	3.8%	Language: 25% Motor: 18.7%	100%:47.6% 90–99%:9.5% 80–89%:14.3% 70–79%:23.8% 60–69%:-4.8%

NR not reported, *GTR* gross total resection, *STR* subtotal resection

[a]Used monopolar stimulation, all others were bipolar

In the largest series of patients undergoing an awake craniotomy for tumor resection, our group previously demonstrated an overall surgical and medical complication rate of 10%, a 30-day re-admission rate of 1%, and a intraoperative failure rate of 0.5% [22]. Other groups have reported slightly higher complication rates ranging from 14 to 32% and failure rates ranging from 2.3 to 6.4% [27, 51–56].

Outcomes data demonstrate that classically "unresectable" lesions in eloquent cortex are potentially amenable to surgery when using awake intraoperative mapping [57]. For studies focused solely on lesions within the precentral gyrus (i.e. primary motor cortex) for example, mean extent of resection has been reported between 91 and 93% [58, 59]. Yet, the risk of a permanent motor deficit is not inconsequential and ranged from 33.3 to 47.1% in the subgroup of awake craniotomy patients. In Magill et al. of the permanent deficits noted, the majority were mild (Medical Research Council Grade 4+) and without impact on daily living and function. Only 4 of 16 permanent deficits in awake patients were functionally significant [58]. Long-term motor function in these prior studies was significantly correlated with stable intraoperative voluntary movement, a decreased extent of resection, and absence of ischemia on postoperative MRI [58, 59]. In terms of language outcomes after an awake craniotomy, Sanai et al. reported a transient worsening of language in 22.4% of patients 1 week after surgery, 6.4% of patients 1 month after surgery, and a persistent language deficit in 1.6% of patients by 6 months [21]. Other groups have demonstrated a persistent language deficit 2.3–25% of patients, albeit with variable threshold criteria for what was considered permanent [60–65]. This variability may be explained by differences in language testing strategies or anesthesia regimen. Therefore, technical nuances and clinical considerations as listed above need to be taken into account to help lower this risk of permanent language deficits. A further consideration is the importance of rehabilitation in ameliorating the effect of new deficits [66]. Rehabilitation should begin within the inpatient setting and, where required, continue at a dedicated facility or outpatient setting as appropriate. Rehabilitation should include motor, cognitive and speech components and the intensity and duration will vary based on patient and disease factors. Prolonged intensive rehabilitation may help a young patient with a low grade tumor return to work, but a tailored approach is more appropriate for elderly patients with high grade tumors. Evidence concerning the best approach to rehabilitation and its effectiveness of rehabilitation is limited [67].

A number of studies have also compared outcomes between awake craniotomies and craniotomies performed under general anesthesia. These studies have demonstrated mixed results with some reporting significant survival improvements or lower rates of neurologic deficits and others demonstrating no difference [58, 61, 62, 65, 68–71]. Gerritsen et al. for example examined outcomes in a retrospective matched case–control study comparing patients undergoing an awake craniotomy versus a craniotomy under general anesthesia. EOR was higher and the rate of late minor complications (as opposed to early minor/major or late major complications) was lower in the awake craniotomy subgroup. However, despite the improved EOR, overall survival did not differ between the study cohort and controls [72]. A recent meta-analysis of comparative studies demonstrated that patients undergoing awake craniotomies had a lower incidence of postoperative nausea and vomiting and a shorter length of stay when compared to patients undergoing general anesthesia. However, neither extent of resection nor the risk of permanent language or motor deficits differed between the two approaches [73]. Given the limited number of reports available (n = 9 reports), this meta-analysis was potentially underpowered to detect differences in OS, PFS, EOR, and permanent neurologic deficit. Furthermore, the majority of included studies were retrospective in nature and prone to selection bias for the surgical approach and anesthetic technique used. None of the studies were randomized, thus the choice of surgical approach (awake vs. using general anesthesia) was based on their predicted surgical risk of neurologic deficit as well as the surgeons familiarity with the technique. Thus, more prospective studies are needed to identify potential benefits of awake intraoperative mapping. Furthermore, more consistent outcome reporting is needed to allow for accurate comparisons between studies. Finally, it is worth considering that awake craniotomy is associated with lower resource utilization than surgery under general anesthesia and may be more cost effective [74].

Conclusions

The technique of awake craniotomy for glioma has been refined over a period of decades.

Many potential contraindications can now be overcome, and the cortical exposure required has been minimized. The tasked used to determine function have been refined and vary based on cortical and subcortical location. Cortical and subcortical mapping remains the gold standard for resection of gliomas near functional areas and the technique is associated with an extremely low rate of complications.

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