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Awake craniotomy for supratentorial gliomas: why, when and how?

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Practice Points

- Awake craniotomy is a robust and versatile procedure in neuro-oncology, which can decrease iatrogenic neurological injury.
- The application of awake craniotomy to brain tumor resections can improve resection volumes and allow surgical treatment of otherwise inoperable tumors.
- Outpatient awake craniotomy represents a novel modification of the procedure with implications for improving healthcare resource utilization.
- The use of awake craniotomy in the developing world can facilitate access to neurosurgical care in very low-resource settings.
- Patients report a very high satisfaction rate with the procedure and effective communication and trust in the doctor–patient relationship are paramount.
- As the utilization of the technique expands and novel, innovative applications for its use are implemented, the ethical underpinnings of established and emerging practices must be increasingly scrutinized.

SUMMARY Awake craniotomy has become an increasingly utilized procedure in the treatment of supratentorial intra-axial tumors. The popularity of this procedure is partially attributable to improvements in intraoperative technology and anesthetic techniques. The application of awake craniotomy to the field of neuro-oncology has decreased iatrogenic postoperative neurological deficits, allowed for safe maximal tumor resection and improved healthcare resource stewardship by permitting early patient discharge. In this article, we review recent evidence for the utility of awake craniotomy in the resection of gliomas and describe the senior author's experience in performing this procedure. Furthermore, we explore innovative applications of awake craniotomy to outpatient tumor resections and the conduct of neurosurgery in resource-poor settings. We conclude that awake craniotomy is an effective and versatile neurosurgical procedure with expanding applications in neuro-oncology.

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The first applications of awake craniotomy can be traced to remote antiquity, where practitioners performed trepanations of the skull to release demons and treat a variety of conditions, including seizures, contusions and fractures [1]. It is from these humble beginnings that this technique evolved to become a robust neurosurgical tool in the management of a variety of diseases affecting the CNS. The first contemporary use of awake craniotomy was for epilepsy surgery under local anesthesia [2]. The expansion of the technique to other domains, namely neuro-oncology, is partially a result of improvements in anesthetic agents and patient-monitoring equipment, as well as enhancements in intraoperative functional mapping technology.

The main advantage of awake craniotomy is to allow for intraoperative electrocorticography and cortical mapping to identify eloquent brain areas, thereby decreasing postoperative neurological morbidity. The primary cortical regions of interest, which will be subsequently discussed, are those controlling motor and language function. A secondary advantage that has been proposed is the ability to perform more aggressive tumor resections. Furthermore, recent emphasis has been placed on innovative application of awake craniotomy to tumors that lie beyond the eloquent cortex to facilitate early patient discharge, and allow the conduct of brain tumor surgery in low-resource settings.

The current article reviews the utility of awake craniotomy in the mapping of eloquent cortex, guiding maximal safe tumor resection as well as its emerging applications to health resource management by facilitating earlier patient discharge culminating in outpatient brain tumor surgery. In addition, we explore the ethical arguments for and challenges to the widespread use of awake craniotomies and comment on its expanding application in low-resource settings. Throughout the review, we present the most recent and comprehensive evidence guiding the utilization of awake craniotomy and describe the personal experience of the senior author (Bernstein) in performing this procedure in patients with intra-axial tumors.

Technique of awake craniotomy for glioma resection

■ Patient selection

As with any surgical procedure, the importance of selecting appropriate patients to undergo awake craniotomy is of utmost importance. Because the

technique involves patient cooperation, basic criteria should be applied to screen patients who may qualify for awake craniotomy. It should be noted that many of these criteria are relative. For instance, while performing awake craniotomy in children younger than 11 years old is discouraged [3], to our knowledge, the youngest patient to successfully undergo awake craniotomy is 9 years old [4]. Therefore, although patient capacity and cooperation must be rigorously evaluated, it is important to consider the patient's unique status in presurgical decision-making.

Another factor that may influence the decision to perform an awake craniotomy is the location of the tumor. Although our experience (and that of most other centers) has been limited to supratentorial gliomas, single cases have been reported of awake craniotomy for infratentorial tumors [5]. Furthermore, the location of the supratentorial tumors must be considered. If the patient must be in the prone position, it may not be prudent to consider an awake procedure. The expected difficulty of tumor resection may also be a mitigating factor. For instance, a highly vascular tumor and/or one with a large volume of expected blood loss may be best performed under a general anesthetic.

Other exclusion criteria include issues related to the administration of the anesthetic. For example, patients with significant comorbidities (such as obstructive sleep apnea), an expected difficult airway or severe obesity may not be suitable candidates for awake craniotomy. Such individuals may be placed at greater risk of adverse events and intraoperative hemodynamic instability. The involvement of a multidisciplinary team, including surgeons and anesthesiologists in the evaluation and preoperative counseling of patients undergoing awake craniotomy may facilitate the conduct of the procedure, permit more effective communication and improve outcomes [6].

Finally, as we discuss subsequently, one can safely establish a formal protocol for outpatient awake craniotomy for the resection of supratentorial tumors [7]. An outpatient procedure entails same-day discharge following a short stay in the postanesthetic care unit and CT scan. The criteria for patient selection and the protocol for outpatient awake craniotomy are more stringent and have been described elsewhere [7].

■ Preoperative preparation

Well in advance of surgery, patients are educated on the expected course of events and potential

complications, and informed consent is obtained (see ‘Ethical considerations’ section). At our institution, the expected experiences of the patients during the awake procedures are emphasized and a pamphlet is provided, which includes additional information, frequently asked questions and contact numbers. On the day of the procedure, the patients arrive at the day surgery unit at 6:00 AM. All patients undergo MRI, which is registered to the neuronavigation system (StealthStation® image-guidance system, Medtronic Surgical Navigation Technologies, CO, USA) for intraoperative frameless stereotaxy. This is used for planning the approach, incision and craniotomy.

■ Anesthesia

The evolution of techniques in anesthesia and improvements in intraoperative monitoring technology has played a leading role in the expansion of the usage of awake craniotomy. While many combinations of anesthetic agents and techniques have been reported in the literature, the common goal for all strategies is to render the patient lucid during brain mapping, while allowing him/her to tolerate the procedure with minimal discomfort. Reported techniques for anesthesia range from general anesthesia with an inserted airway device and the ‘awake–asleep–awake’ protocol to conscious sedation with monitoring.

Our preferred approach for awake craniotomy is the simplest and least invasive. Our protocol involves local anesthesia, comprised of 2% lidocaine for pin fixation and bupivacaine 0.25% with 1:200,000 epinephrine for regional field block around the incision, concurrent with adequate sedation [8]. We do not use invasive monitors, such as a urinary catheter or arterial lines. It should be noted that other groups have modified the awake craniotomy technique to avoid pin fixation and have reported no loss of image-guidance accuracy [9].

The most common agent used for awake craniotomy is propofol with or without opioids. As we have previously reported, we routinely use conscious sedation without manipulation of the patients’ airway [10]. To do so, we use remifentanyl infusion (or occasionally fentanyl boluses) in addition to propofol. Once the patient is positioned, the propofol infusion is briefly paused to ensure the patient is comfortable. The goal of the conscious sedation for the remainder of the procedure is to maintain a level of sedation

of 3 on the Modified Observer’s Assessment of Alertness/Sedation scale [11]. At this level of anesthesia, the patient should arouse when his/her name is called out loud or repeated.

At 5 min prior to the expected mapping, the propofol and remifentanyl infusions are stopped and are subsequently resumed for the tumor resection and closure. The use of this protocol has produced an overall 93% rate of patient satisfaction at our institution [10]. Furthermore, the use of remifentanyl in lieu of fentanyl boluses has been advocated by other groups [12].

■ Stimulation technique

Once the anesthetic agents have been paused, direct cortical stimulation for mapping of eloquent cortex may begin (Figure 1). Technical considerations for electrical stimulation include the choice of stimulator device, parameters (pulse type, width and frequency) as well as the applied intensity and the probe used to deliver the current [13]. We typically use bipolar stimulation using a probe with two tips separated by 6–10 mm and a 100- μ s square wave pulse with a 50-Hz repetition rate. The patient is additionally grounded for the monopolar cautery. The intensity of stimulation begins at 8 mA and goes as high as 16 mA. An advantage of bipolar stimulation is the generation of a more homogeneous field parallel to the axis of the probe [14]. Direct cortical stimulation should be performed by increasing the stimulation intensity by increments of 1 mA until a response is observed. As a matter of principle, we discourage stimulating the same cortical areas consecutively.

■ Cortical mapping

A relatively large body of literature exists for the identification of functional motor and language areas by cortical stimulation at the time of surgery [15–18]. Awake craniotomy for mapping of the visual cortex has also been reported in the literature [19]. Mapping of the motor cortex can be performed in a patient under general anesthesia using electromyographic recordings with subdermal needle electrodes [20]; however, higher cognitive tasks, including language, require an awake and cooperative patient. For sensorimotor mapping in awake craniotomy, the anesthesiologist alerts the surgeon to movements of the face, arm or leg. We typically perform strength testing to identify any induced deficits, and the patient is informed to report any altered sensations he/she may experience. To perform language mapping,

Figure 1. Awake mapping of eloquent cortex in a patient with low-grade glioma. (A) A right-handed 24-year-old engineer presented with a low-grade glioma involving his dominant hemisphere. T₂-fluid attenuated inversion recovery MRI revealed a large, ill-defined lesion abutting the posterior frontal lobe, extending into the parietal lobe and deep into the subcortical white matter. (B) An awake craniotomy was performed for motor and language mapping. Upon dural opening, prominent gyral expansion was noted over the suspected location of the tumor. (C) Using bipolar stimulation, mapping of motor and language areas was performed (numbered area), the tumor was subsequently resected uneventfully and the patient was neurologically intact postoperatively.

we set up a microphone next to the patient and engage him/her in semantic processing tasks. The arrest or diminution of function suggests that the brain areas probed control eloquent processes [21]. It has been previously suggested that an experienced neuropsychologist should be present to administer semantic paradigms intraoperatively [22]. At our institution, we base this decision on the individual surgeon's comfort and experience. The incidence of permanent postoperative neurological deficit appears to be reduced if the distance of eloquent cortex from the resection site is greater than 1 cm [16].

■ Subcortical mapping

Even if cortical structures are preserved, neurological deficit may result from injury to subcortical white matter tracts. Intraoperative subcortical mapping allows surgeons to map descending motor pathways as well as functional language tracts, thereby potentially decreasing morbidity and maximizing safe resection of gliomas [23]. The utility of subcortical mapping in preventing iatrogenic neurological morbidity is, however, controversial, as various studies have shown that the identification of functional subcortical tracts is associated with increased postoperative deficit [23–25]. This is likely because gliomas, particularly those of low-grade histology, are

highly infiltrative and functional tracts may be found within the neoplastic tissue. One group has recently reported that awake craniotomy without subcortical mapping results in poor outcomes [26]; however, as none of the patients in this series underwent subcortical mapping, it is unclear whether the technique would have resulted in superior outcomes to those reported. The use of subcortical mapping to minimize iatrogenic neurological injury is, therefore, an area of ongoing research and inquiry.

Utility for patient safety: eloquent mapping

■ Noninvasive techniques

In recent years, a variety of noninvasive techniques have emerged to preoperatively map eloquent cortex. These include functional MRI (fMRI), magnetoencephalography, and PET [27–29]. These techniques have permitted more informed presurgical decision-making, risk stratification and more accurate informed consent discussions outlining the expected deficits involved with resective procedures [30]. Furthermore, functional subcortical mapping via diffusion tensor imaging and tractography has become increasingly utilized to visualize subcortical white matter tracts surrounding tumors in eloquent cortex [31].

These techniques have also been incorporated in frameless stereotactic technology for

intraoperative navigation of functional cortex (so-called ‘functional neuronavigation’) [32,33]. However, to date, these strategies cannot replace awake craniotomy as a gold standard for intraoperative mapping of eloquent cortex, as they suffer from limitations related to the technology itself, the underlying pathology and challenges in their application to surgery. With regards to technological limitations, validation of many of these studies continues to be challenging. For example, fMRI-derived language maps vary significantly based on the choice of language paradigm, as well as susceptibility artifacts, statistical analysis method chosen and patient head motion [34–39].

Secondly, applying noninvasive mapping in the vicinity of infiltrative neoplasms, such as gliomas, poses unique challenges. For instance, blood oxygen level-dependent signal in fMRI may differ in cortex adjacent to tumors compared with healthy tissue [40]. This may be due to neoplastic infiltration of healthy tissue or peritumoral edema. The discrepancy between tissue integrities may potentially result in inaccurate findings. Similar concerns have been raised for other noninvasive mapping methods, such as diffusion tensor imaging [41].

Finally, the application of noninvasive preoperative strategies to operative mapping using functional neuronavigation suffers from limitations related to the brain shift, volume changes and cerebrospinal fluid leakage following craniotomy and tumor debulking [42]. While some authors advocate the use of intraoperative MRI to compensate for these effects, the availability of real-time functional mapping is a unique and significant advantage of awake craniotomy. Combined techniques of awake craniotomy with intraoperative MRI have also been applied successfully to capitalize on the advantages of awake craniotomy for functional mapping and intraoperative MRI for structural assessments of residual tumor [43,44]. From early experiences with this combined approach, the addition of intraoperative MRI has been reported to change surgical decision-making by identifying inconspicuous areas of tumor amenable to resection after image acquisition [44].

■ Direct cortical stimulation in awake craniotomy

Awake craniotomy remains a gold standard for patient safety in minimizing iatrogenic neurological morbidity during resections of supratentorial

gliomas. These techniques provide the surgeon with a safe corridor to approach the tumor. In addition to resective procedures, stereotactic biopsies of the brainstem and other eloquent cortices have been successfully performed using awake techniques [45]. With low-grade gliomas, particularly, functional tissue may be found within the infiltrative tumor mass [46,47], which is supported by our finding that 2.5% of patients sustained permanent worsening of preoperative deficits despite negative brain mapping [18]. We also observed 16.5% morbidity, which included 13% new postoperative deficits (of which 4.5% were permanent). Several series have reported neurological morbidity rates of 0–21% after eloquent area surgery under awake conditions [48–50]. The most recent series (including 20 or more subjects) describing neurological morbidity following awake craniotomy are summarized in [Table 1](#).

Relatively fewer studies have directly compared awake craniotomy to surgery performed under general anesthesia. We have summarized these articles in [Table 2](#). All but one of the studies have shown that awake craniotomy reduces iatrogenic neurological injury during tumor resection. Interestingly, one study that evaluated outcomes and complications prior to and following the implementation of awake cortical mapping at the same institution, found significantly better outcomes following its implementation [17]. Gupta and colleagues are the only group, to our knowledge, to identify a trend towards a greater incidence of neurological deficits in surgery performed in the awake state, with 53 patients included in the analysis. However, limitations of this study include the definition of eloquent cortex, as well as the admittedly steep learning curve [51]. Another series also reported an unusually high incidence of postoperative deficits following awake craniotomy in a series of 25 patients (20% iatrogenic deficits) [50]. The largest study performed, which was conducted by the senior author and included 610 patients, identified an acceptable level of neurological injury at 4.7% with 0.5% mortality [52].

The utility of awake craniotomy in patients with tumors is further buttressed by evidence of unpredictable eloquent network organization. For example, studies examining multilingual patients have found that language areas were distinct for each language and not identifiable based on anatomical landmarks, suggesting that intraoperative mapping is particularly important

Table 1. Summary of recent studies with greater than 20 subjects documenting neurological deficits following awake craniotomy/intraoperative mapping for brain tumor resections.

Study (year)	Study design (number of subjects)	Eloquent area	Pathology	Permanent deficit (%)	Improvement in preoperative deficit	Comments	Ref.
Keles <i>et al.</i> (2004)	Retrospective (n = 294)	Motor	Low- and high-grade gliomas	(All deficits): 4.8	Not reported	Identification of subcortical pathways associated with deficit	[23]
Otani <i>et al.</i> (2005)	Retrospective (n = 21)	Motor and language	Low- and high-grade gliomas	0	52%	GTR in 86% of patients	[88]
Picht <i>et al.</i> (2006)	Retrospective (n = 25)	Language	Low-grade gliomas and metastases	0	Not reported	Protocol involves evaluation of individual operative risk before proceeding with awake craniotomy	[89]
Bello <i>et al.</i> (2007)	Retrospective (n = 88)	Language	Low- and high-grade gliomas	2.3% (moderate-to-severe impairment)	25%	Identification of subcortical pathways associated with deficit	[24]
Carrabba <i>et al.</i> (2007)	Retrospective (n = 146)	Motor and language	Low- and high-grade gliomas	5.4	Not reported	Identification of subcortical pathways associated with deficit	[25]
Serletis & Bernstein (2007)	Prospective (n = 610)	Motor and language	Mainly gliomas, other tumors included	4.7	Not reported	0.5% mortality and 0.3% of patients required readmission	[52]
Sanai <i>et al.</i> (2008)	Retrospective (n = 250)	Language	Low- and high-grade gliomas	1.6	Not reported		[90]
Ilmberger <i>et al.</i> (2008)	Prospective (n = 153)	Language	Mainly gliomas, other lesions included	3.9	47.4%	Risk factors for deficit include: preoperative deficit, intraoperative complication, positive language sites within tumor, and nonfrontal location	[91]
Duffau <i>et al.</i> (2008)	Retrospective (n = 115)	Language	Low-grade gliomas	1.7	Not reported	Subcortical language areas identified: arcuate fasciculus, inferior fronto-occipital fasciculus, subcallosal fasciculus, frontoparietal phonological loop and ventral premotor fibres	[92]
Pereira <i>et al.</i> (2009)	Retrospective (n = 79)	Motor and language	Low- and high-grade gliomas	Motor: 8.9; Language: 3.8–10.1	Motor: 75%; Language: 57.9–61.3%	Surgical mortality of 1.3%; 50.6% of patients achieved >95% resection	[93]
Manchella <i>et al.</i> (2011)	Retrospective (n = 26)	Motor and language	Mainly gliomas, mixed pathology	4	Not reported	Patient satisfaction with procedure was high	[82]

GTR: Gross total resection.

for this increasingly prevalent subgroup of patients [53,54]. These findings are particularly relevant as language reorganization in the context of an intrinsic brain tumor (especially a slow growing low-grade glioma) is well documented [16,55,56]. For instance, because of tumor-associated neuronal plasticity, some authors have

performed tumor resections in Broca's area without postoperative language deficits [55,57,58].

Of note, an alternative to performing direct cortical stimulation involves the implantation of a subdural electrode grid under general anesthesia, followed by extraoperative mapping and a second resective operation [59]. This technique

is often applied to epilepsy surgery, as prolonged invasive monitoring is often required in this context to capture ictal events and identify the seizure-onset zone. For resections of tumors, however, awake craniotomy can alleviate the necessity of two general anesthetics as well as a prolonged hospital stay with its associated complications. While grid insertion for eloquent mapping has been performed successfully in glioma patients [59], at our institution, awake craniotomy remains the preferred technique of choice.

Utility for oncology: maximizing safe resections

While the issue is subject to controversy, it has been suggested that more complete resection leads to improved outcomes in both low- and high-grade gliomas [60–62]. In addition to improving patient safety by reducing post-operative deficits, several reports have suggested that awake craniotomy allows more aggressive resections, thereby increasing the amount of tumor tissue removed and bestowing an oncological benefit to patients [48,63,64]. A summary of recent studies exploring the extent of tumor resection achieved with awake craniotomy compared with general anesthesia is presented in **Table 2**. In one recent prospective study, Sacko and colleagues compared 214 patients who

underwent awake craniotomy with intraoperative mapping with 361 patients who underwent brain tumor resection under general anesthesia, of whom, 72 patients harbored tumors in eloquent cortex. When comparing patients with lesions in eloquent brain areas, both neurological outcome and extent of resection were better in patients undergoing awake craniotomy [65]. Duffau and colleagues also found that the use of awake craniotomy for tumors in eloquent cortex allowed for the surgical treatment of lesions that were classically considered inoperable [17]. They report more extensive tumor resections and improvements in patients' quality of life as a result of decreased neurological morbidity [17].

Early evidence also suggests that there is a distinct advantage for awake craniotomy in repeat (re-do) operations for tumor resection. De Benedictis and colleagues have reported on nine patients with low-grade gliomas in functional sites who underwent an initial resective procedure under a general anesthetic followed by an awake procedure with intraoperative mapping [66]. They achieved a complete resection in 56% of patients, with no neurological worsening.

To our knowledge, only one conflicting report is published describing superior tumor cytorreduction in patients undergoing a procedure under general anesthetic [51]. In their randomized study, Gupta and colleagues report no statistical

Table 2. Summary of recent studies comparing awake craniotomy to general anesthesia for brain tumor resections.

Study (year)	Study design (number of subjects)	Pathology	Resection (AC vs GA)	Permanent neurological deficit (AC vs GA)	Hospital stay (AC vs GA; days)	Comments	Ref.
Reithmeier <i>et al.</i> (2003)	Retrospective (n = 70)	Mixed	Residual tumor: 27 vs 52% [†]	(Worsening): 14 vs 29%	Not reported		[94]
Duffau <i>et al.</i> (2005)	Retrospective (n = 222)	LGG	Postoperative tumor volume: 55 vs 69 ml [†]	6.5 vs 17% [†]	Not reported	Survival related to extent of resection (greater in AC cohort)	[17]
Pinsker <i>et al.</i> (2007)	Retrospective (n = 55)	Mixed	GTR: 77 vs 33%	(Any deficit): 12 vs 33%	Not reported		[22]
Gupta <i>et al.</i> (2007)	Prospective, randomized (n = 53)	Mixed	>90% reduction: 57.2 vs 73.6%	23 vs 15%	5.69 vs 4.59	Longer operative time and blood loss with AC	[51]
Shinoura <i>et al.</i> (2011)	Retrospective (n = 21)	Mixed	Not reported	(Any deficit): 19 vs 64%	Not reported		[95]
Peruzzi <i>et al.</i> (2011)	Retrospective (n = 22)	High- and low-grade gliomas	Only GTR included in analysis	(Worsened): 18 vs 27%	3.5 vs 4.6 [†]	AC associated with reduced costs	[67]
Sacko <i>et al.</i> (2011)	Prospective (n = 575)	Mixed	Total removal: 37 vs 14% [†]	4.6 vs 16% [†]	5.4 vs 12.7 [†]	Some survival benefit depending on pathology	[65]

[†]Statistical significance.

AC: Awake craniotomy; GA: General anesthetic; GTR: Gross total resection; LGG: Low-grade glioma.

difference in the proportion of patients achieving 90% resections between those who underwent awake craniotomy and those under a general anesthetic [51]. In their series, 57% achieved 90% tumor volume reduction. These data seem to indicate that awake craniotomy results vary by center, further underscoring the fact that a learning curve is involved in performing these procedures. Additionally, patient selection may have played a role in the outcomes reported by these groups and we once again highlight the importance of selecting appropriate patients for awake craniotomy.

Utility for outpatient brain tumor surgery

It has been previously shown that awake craniotomy is associated with decreased intensive care unit as well as total in-hospital length of stay compared with procedures performed under general anesthesia (Table 2) [65,67]. The implication is, therefore, that the use of awake craniotomy may reduce healthcare expenditures and conserve scarce resources. The application of awake craniotomy for secondary benefits, such as healthcare resource management, is an emerging and innovative area of research.

The senior author has performed awake craniotomy routinely and nonselectively for patients with glioma and demonstrated an acceptable complication profile with lower rates of resource utilization [18]. This has led to the establishment of an outpatient awake craniotomy protocol at our institution, whereby a patient does not stay in hospital overnight [7,68]. In a large series of 145 patients treated with outpatient craniotomy (the vast majority undergoing an awake craniotomy), the senior author has reported a 94% protocol success rate, with 6% of patients subsequently requiring conversion to inpatient status or an unscheduled hospital admission [69]. A second series describing our experience performing outpatient surgery in 1003 prospectively selected patients was recently published [70]. Of these, 228 (36%) underwent outpatient awake craniotomy. The vast majority of patients (92.8%) were discharged successfully from the day surgery unit, while 5.2% were admitted from the day surgery unit and only 2% were discharged and subsequently readmitted. The reasons for readmission included headache (one patient), nausea (one patient) and seizures (two patients). A single patient was readmitted 12 h following discharge with confusion and

drowsiness and was found to have an intracerebral hemorrhage, which was treated conservatively. At 1 month postoperatively, the patient expired from medical complications.

While outpatient awake craniotomy represents a paradigm shift in neurosurgical thinking, its introduction to clinical practice represents a surgical innovation that should be regulated accordingly [71]. Currently, few centers perform outpatient awake craniotomy, but as greater evidence accumulates for its safety and advantage, it is expected that the modification of awake craniotomy to the outpatient setting will attract greater interest. The senior author has previously demonstrated that patients reflect favorably upon outpatient awake surgery given that they trust their treating physician [72].

Utility in low-resource settings

Very little data exist on the usage of awake craniotomy in low-resource settings. Pereira and colleagues describe their experience with awake craniotomy in a self-defined developing country, but with “complete adequacy for the basic setup for neurosurgery” [6]. In this series, a good rate of neurological recovery was reported (75% and 57.9–61.3% for motor and language deficits, respectively), with acceptable morbidity and 1.3% mortality. Furthermore, the authors were able to resect over 90% of the tumor in 50.6% of patients. Reports of awake craniotomy in areas with extremely limited resources, to our knowledge, have not been published.

The senior author has extensive personal experience in teaching these techniques to neurosurgeons in the developing world, and has observed numerous advantages to awake craniotomy in this context. Firstly, administration of a general anesthetic in low-resource areas is not a trivial matter [73,74]. This is partially due to suboptimal monitoring equipment, limited choices of pharmacological agents as well as systemic shortcomings, including the lack of resources, such as consistent and reliable electricity and inadequate sterilization standards [74]. Furthermore, the reuse of endotracheal tubes poses an additional risk of equipment failure or disease transmission, particularly if the required sterilization is inadequately performed [75,76]. Awake craniotomy may be performed rather simply and inexpensively, therefore facilitating access to neurosurgical care, and avoiding the need for intensive care unit beds which are at a premium in resource-poor

countries. Finally, many medical practices in low-resource settings lack noninvasive mapping technologies, and therefore, awake craniotomy may be the only modality that can be applied to attempt to decrease iatrogenic neurological insult.

Challenges to the expansion of awake craniotomy in the developing world include inaccessibility to the technology, inadequately trained clinicians and underdeveloped regional infrastructure. In many countries, the costs of the procedure are incurred by the patients themselves. In one study of epilepsy surgery in very resource-poor countries, the inability to afford invasive monitoring equipment was a major reason for the exclusion of eligible candidates [77]. The expansion of awake craniotomy techniques to the developing world is therefore an emerging area of innovation, philanthropy and outreach.

Complications: avoidance & management

Complications that may occur during awake craniotomy may be classified as anesthetic-related, surgically induced or those related to patient-specific comorbidities. The first category encompasses hemodynamic changes that may occur intraoperatively as well as intolerance to the anesthetic. In our experience, as well as that of many others, awake craniotomy is very well tolerated by patients. While it has been reported that the incidence of hypertension, hypotension and tachycardia were significantly greater in awake craniotomy compared with a general anesthetic [78], there were no clinically relevant sequelae of these hemodynamic changes. Furthermore, it has been shown in prospective studies that patients undergoing awake craniotomy tolerate the procedure better than those undergoing a general anesthetic with respect to postoperative nausea and vomiting [79]. A single report of intraoperative asystole of a patient undergoing awake craniotomy, attributed the complication to stimulation of the trigeminocardiac reflex [80].

Surgical complications include seizures, which may result from direct cortical stimulation. The senior author has previously reported a 5.6% incidence of intraoperative seizures, with all but two being focal [18]. These events can be easily managed by cold cortical irrigation, and only two patients in the same series required conversion to a general anesthetic as a result of seizure activity. Other strategies to reduce the incidence of intraoperative seizures,

include the use of low amplitude stimulation. Furthermore, one study suggested that an anesthetic technique using fentanyl was associated with a greater frequency of intraoperative seizures [6]. At present, there is insufficient evidence to show that prophylactic perioperative anticonvulsant therapy bestows any benefit to patients who are not on these medications for preexisting disorders.

Another surgical complication that has been reported in the literature is venous air embolism (VAE) [8,81]. In our experience, the prevalence of VAE during awake craniotomies was approximately 0.64% (3 out of 470) [8]. An approach to such patients must include ruling out upper airway obstruction and the various causes decreased level of consciousness. As early diagnosis and management are essential to preventing adverse outcomes following VAE, excellent communication between the surgeon and the anesthesiologist is essential.

Patient perspective

We have previously reported through qualitative research methodology that overall patient satisfaction with awake craniotomy is high [72]. Other studies have demonstrated that approximately 90% of patients state that they are satisfied with the procedure [6,82]. Approximately one-quarter of patients have no subsequent recollection of the procedure [82,83], and the reported negative experiences include pain (8%), discomfort (12%), fear (15%) and claustrophobia (4%) [82]. A formal comparison of awake craniotomy versus general anesthetic using validated outcome measures showed superior acceptance of the procedure, and better ratings for postoperative pain for awake craniotomy [84].

In our experience, patients understand the rationale behind performing these procedures and were typically concerned more about the underlying diseases than the awake craniotomy [72]. We also identified that trust in one's surgeon was of paramount importance. This is particularly relevant as many patients had not previously heard of awake craniotomy and were still coping with the diagnosis of a brain tumor. This further underscores the importance of effective doctor–patient communication and the value of a robust physician–patient relationship.

Ethical considerations

There are numerous ethical and medico-legal considerations surrounding the expanding

usage of awake craniotomy in the treatment of intra-axial neoplasms. The senior author has previously addressed several of these issues, which include challenges in informed consent, obstacles in basing individual patient decisions on limited observational evidence, as well as difficulties in the ethical application of surgical innovations to patient care [85]. One unique challenge in the consent process for awake craniotomy occurs when the patient revokes consent to surgery while awake intraoperatively [86]. While the patient must be free to rescind consent at any stage of a procedure, it must be assured that their capacity to reach such a decision had not been affected by the anesthetic or the procedure itself. Guidelines for the management of such ethical dilemmas should be considered and discussed prior to surgery.

Another ethical conflict, which may arise, involves the utilization of awake craniotomy to reduce health resource expenditures. This can potentially create a conflict between the best interest of the patient and those of hospital administrators and financiers. It is expected that the primary allegiance of the treating physician be to the patients themselves. The selection of patients for awake craniotomy must be based on the patient's specific condition, comorbidities, expectations and values. External influence to apply awake craniotomy for the primary purpose of resource stewardship should be avoided.

Numerous additional ethical issues involving the application of awake craniotomy are beyond the scope of the current article (see Kirsch and Bernstein [85] for review). Surgeons attempting to establish this technique in low-resource settings must be cognizant of several unique considerations, including its sustainability in the local context. Additionally, outpatient awake craniotomy also entails several unique considerations, including the lack of a large body of evidence supporting its use. It is expected that as awake craniotomy expands into novel and innovative domains, the ethical underpinnings of the practice will be increasingly scrutinized.

Conclusion

Awake craniotomy is a robust neurosurgical tool for the resection of intra-axial neoplasms. Its main advantage is to allow the surgeon to identify and preserve eloquent cortex in real-time and to select a relatively safe corridor to

access tumors. Furthermore, it has been shown that the use of awake craniotomy may additionally facilitate maximal safe resection, which may improve patient outcomes. Finally, the application of this technique has been shown to reduce length of stay in hospitals, thereby improving health resource utilization. The utility of awake craniotomy to facilitate outpatient tumor resections and its use in low-resource settings remain emerging areas of research and innovation.

Future perspective

Given rapid advances in technology, we expect that noninvasive modalities for the localization of eloquent cortex will become more accurate and precise. While these techniques are currently insufficient to rival the gold standard of awake craniotomy, improvements in engineering and analysis software design are ongoing. For example, network and connectivity analysis is a rapidly emerging field in neuroscience research, with potential to improve noninvasive mapping methods. One recent study demonstrated that the increased peritumoral resting-state functional connectivity is predictive of intraoperative electrical stimulation findings [87]. This underscores the fact that intra-axial brain tumors need to be approached and evaluated presurgically using multiple modalities.

Awake craniotomy will, however, continue to be an important tool in the neurosurgeon's armamentarium. As stated, we expect that indications for awake craniotomy will expand. For instance, as evidence accumulates on the safety and efficacy of the procedure in decreasing admissions and obviating the need for general anesthesia, it may become more commonplace for surgery of tumors in noneloquent cortex. We maintain, however, that expansion of the indications for awake craniotomy must be governed by pragmatism, evidence-based outcomes and ethical principles.

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