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Intraoperative Stimulation Mapping in Neurosurgery for Anesthesiologists—Part 1: The Technical Nuances

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Abstract

Brain mapping has evolved tremendously in the past decade, fueled by advances in functional neuroimaging technology in neuro-oncology and epilepsy surgery. Despite this, wide anatomic-functional interindividual variability and intraoperative brain shift continue to challenge neurosurgeons performing surgery within or near eloquent brain regions. As such, intraoperative direct cortical and subcortical stimulation mapping remains the gold standard for localizing eloquent brain regions with precision for a safe and tailored resection. Intraoperative stimulation mapping (ISM) allows for maximizing the extent of resection while minimizing postoperative neurological deficits, resulting in better patient outcomes. Understanding the technical nuances of ISM is imperative for the anesthesiologist to provide better anesthetic management tailored to the surgery and stimulation mapping planned. A comprehensive search was performed on electronic databases to identify articles describing intraoperative cortical and subcortical mapping, language, and motor mapping. In the first part of this narrative review, we summarize the salient technical aspects of ISM and the common neurophysiological tasks assessed intraoperatively relevant to the anesthesiologist.

Keywords
- direct electrical stimulation
- intraoperative stimulation mapping
- awake craniotomy
- language mapping
- motor mapping

Introduction

Advances in neurosurgical techniques have significantly improved overall survival and quality of life in patients with low-grade glioma[1] and medically refractory epilepsy.[2] A lesion within or adjacent to an eloquent brain region poses a unique challenge for neurosurgeons, as maximal resection conflicts with the preservation of neurological functions. The wide interindividual anatomical and functional variability of eloquent areas and the limitations of current preoperative functional brain imaging technologies reinforce the need for real-time intraoperative mapping techniques to enable safe and tailored resection.[3–5] As such, despite almost a century of clinical application, direct electrical cortical stimulation (DES) in awake patients remains the gold standard for intraoperative brain mapping of the eloquent cortex due to its high precision and reliability in identifying functional cortical and subcortical structures during resection. In the first part of this narrative review, we summarize the principles, techniques, and applications of intraoperative

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stimulation mapping (ISM) in neurosurgery relevant to anesthesiologists and the common tasks assessed intraoperatively.

Methods

A comprehensive electronic search was performed in the following databases from their inception to June 2023: PubMed, Embase, Cochrane, Scopus, Web of Science, and Google Scholar. The literature search was performed using specific keywords: intraoperative stimulation mapping, brain mapping, intraoperative cortical or subcortical mapping, motor mapping, language mapping, awake craniotomy (AC), and asleep mapping. Articles were screened and included if it described the technical aspects of intraoperative brain mapping either during glioma surgery or epilepsy surgery, neurophysiological tests done during intraoperative mapping, and patient outcomes after brain resection guided by ISM. Articles that described extraoperative mapping and AC without ISM were excluded.

Intraoperative Stimulation Mapping

Brief History of Direct Electrical Stimulation of the Brain

Direct Electrical Stimulation (DES) of the human cortex was pioneered by Robert Bartholow in 1874 in a patient with an exposed cortex secondary to basal cell carcinoma that demonstrated contralateral motor responses.[6] Several clinicians then used it to delineate eloquent parts of the brain, most notably by Penfield in 1937 with his famous description of motor and sensory homunculi.[7] In the 1970s, George Ojemann further revolutionized cortical mapping in the modern era by improving the understanding of cortical stimulation responses and recording single neurons' activity in awake patients.[8] His innovation in ISM enabled accurate language mapping, resulting in a marked reduction in aphasia after epilepsy surgery. Before the 1990s, DES was performed primarily in awake patients due to the inconsistent cortical response elicited in patients under general anesthesia (GA). In 1993, Taniguchi et al proposed a high-frequency stimulation paradigm in humans for cortical mapping which they found to be effective in triggering distal muscle contraction in patients under GA.[9] This became the scientific basis for current motor mapping under GA. The mapping of the subcortical tract was first described by Skirboll et al in 1996 in a case series of glioma resections.[10] Thereafter, with a deeper understanding of the white matter tracts and advancement of functional imaging modalities, cortical and subcortical mapping are frequently used together during ISM in neurosurgery.[4,11–18]

The Physical Basis of Direct Electrical Stimulation of the Brain

Electrical stimulation induces a passive increase in the membrane potential of stimulated neurons at the cathodal level, which leads to antegrade or retrograde propagation of an action potential. Once the threshold potential is reached, it is followed by synaptic conduction within the physiological subcircuit of interest.[19] Neurons are preferentially activated at the level of the initial segment of axons and nodes of Ranvier, which have the highest density of sodium channels in the neuron.[20,21] Increases in stimulation intensity increase the density of activated axons in proximity to the electrode tip and the distance of activated axons through transsynaptic activation of sites connected to the stimulation site.[22–24] Preclinical studies have shown that single cortical DES evokes an action potential followed by long-lasting inhibition suggesting that stimulation of cortical afferents disrupts the propagation of cortico-cortical signals beyond the first synapse.[25] A comprehensive discussion of the biophysical and mathematical principles underlying DES is beyond the scope of this article and can be found elsewhere.[26]

Stimulation Paradigms

Two primary stimulation paradigms form the basis of functional mapping protocols used in contemporary neurosurgery.[27] The traditional DES technique, also known as the Penfield technique, uses low-frequency (LF) stimulation (50–60 Hz) via a bipolar stimulator probe (►**Fig. 1**) with two electrodes 5 mm apart, delivering biphasic square waveform pulses of alternating anodal and cathodal polarity. LF stimulation induces positive mapping responses (motor and speech) in current intensity range between 2 and 7 mA in an awake patient, but higher current intensities (7–16 mA) are required for motor mapping under GA.[28–30]

The second technique, or the Taniguchi technique, employs high-frequency (HF) stimulation (250–500 Hz), monophasic square waveform pulses, delivered as a train of five pulses (range between 4 and 9 pulses) via a monopolar (most commonly) or bipolar probe (►**Fig. 1**).[28,31] The current intensity needed to produce a positive mapping response (motor and speech) in awake conditions ranges between 2 and 7 mA, and higher current is required for motor mapping under GA (5–15 mA).[28–30] The electrical field distribution differs by the stimulation probe used. The monopolar probe emits a radial homogenous electrical field, while the bipolar probe delivers a more focused inter-tip electrical field.[32] A bipolar probe with LF stimulation increases the focality, but requires an increase in current intensity.[33] A specialized monopolar suction stimulator has recently allowed dynamic mapping via concurrent subcortical stimulation and tumor resection (►**Fig. 2**).[34,35] The salient differences between both stimulation paradigms are summarized in ►**Table 1**.

Physiological Responses to Direct Electrical Stimulation of the Brain

DES can generate either a positive or negative physiological response depending on the brain region being stimulated, the characteristics of the stimulating current, the local organization of the neuronal circuit, and the use of anesthetics and antiepileptic medications.[6,25,36] Positive physiological responses to stimulation include involuntary movement, vocalization, paresthesia, and phosphenes. On the contrary, negative responses cause interruption of tasks

Fig. 1 Common stimulation probes used during intraoperative stimulation mapping: (**A**) monopolar ball-tip probe; (**B**) monopolar flat-tip probe (used for simultaneous resection); and (**C**) bipolar probe.

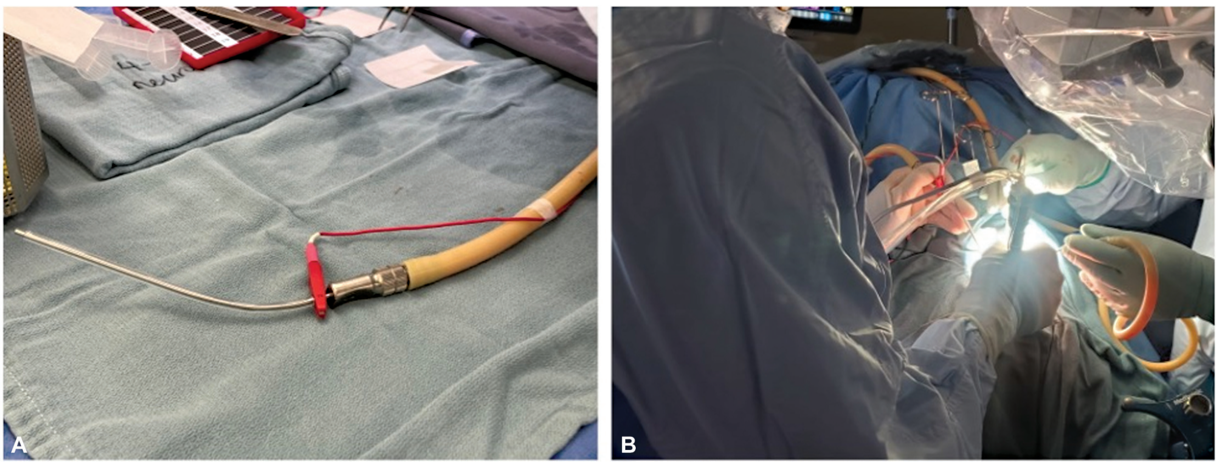

Fig. 2 (**A**) Monopolar stimulator (red cable) attached to metal suction tip via a metal clip (red); (**B**) used by surgeon intraoperatively for continuous dynamic mapping during resection.

Table 1 Comparison of stimulation paradigms used during intraoperative stimulation mapping

	Low-frequency (LF)	High-frequency (HF)
Frequency	50–60 Hz	250–500 Hz
Pulse form	Biphasic	Monophasic
Probe used	Bipolar	Monopolar or bipolar (less common)
Number of pulses	N/A	Train of 5 pulses (range between 4 and 9 pulses)
Current intensity		
Awake Asleep (motor mapping)	2–7 mA 7–16 mA	2–7 mA 5–15 mA
Current spread direction	Focused inter tip spread	Homogenous radial spread
Pulse polarity	N/A	Anodal for cortical Cathodal for subcortical
Others	Used primarily for language mapping Less effective for asleep motor mapping Ineffective in high-risk patients: infiltrative tumors and long-standing seizures Higher risk of inducing seizures	Provides information on distance to CST (1 mA = 1 mm rule) during subcortical mapping

Abbreviations: CST, corticospinal tract; mA, milliampere; N/A, not applicable.

such as speech arrest, anomia, alexia, memory deficit, and disturbances of other higher cognitive processes.[19,37,38] These responses are used to establish a map of functionally essential areas of the cortex and subcortical tracts to guide resection. This terminology should not be confused with the terms "positive mapping" and "negative mapping," where positive mapping refers to the situation in which functionally important sites are identified after a positive or negative physiological response to stimulation. On the other hand, negative mapping is the situation where no functional sites are identified in the mapped area, which is then presumed noneloquent.[38–40]

A false negative is the nonidentification of a critical eloquent brain region, potentially leading to resection and permanent postoperative neurological deficits. This may be secondary to inadequate stimulation settings, inappropriate neurophysiological tests (for the area being resected), or stimulation during a postepileptic refractory phase.[19] The possibility of false negatives should be considered after negative mapping before initiating resection. Nonetheless, negative mapping is safe with strict adherence to established stimulation protocols allowing tailored craniotomies.[11,38–40] False negatives can also be minimized by optimizing the intraoperative tasks selected based on preoperative functional assessment combined with functional imaging.[19]

On the other hand, false positive is the mischaracterization of a noneloquent region as eloquent, potentially leading to premature cessation of resection. Several factors may cause this, including patient fatigue due to the long duration of functional evaluation (typically 2 hours or more), stimulation-induced partial seizures, axonal propagation of stimulation to remote structures, or identification of eloquent structures that could be functionally compensated following resection owing to brain plasticity mechanisms. False positives may be inherent in DES, primarily through the activation of remote structures, and should be considered a possibility during intraoperative decision-making following positive stimulation.[19] If false positives are caused by patient fatigue, repeat tests may be performed after a period of rest, and by limiting the duration of assessment. The use of intraoperative electrocorticography recording to detect after discharges (ADs) may reduce false positives from a stimulation-induced partial seizure. ADs are rhythmic transient epileptiform activity induced by DES that persists after the termination of the stimulus. AD results from stimulation of hyperexcitable tissue, which may overlap with an epileptogenic focus.[41] AD is also used to select the lowest appropriate stimulus intensity to reduce the incidence of intraoperative seizure.[38,41] The mapping threshold and AD thresholds may vary between individuals and between different brain regions in one individual.[36]

Neurophysiological Tests during Intraoperative Stimulation Mapping

Language and motor mapping are the two main neurophysiological modalities tested during ISM-guided resection of the eloquent brain regions. Tasks chosen depend on the location of the lesion and the surgical resection planned.[29,30] Language mapping is commonly employed during epilepsy surgery as most epileptogenic lesions are near language areas, and this requires an awake patient for speech assessment intraoperatively. In the case of a brain tumor within or near eloquent regions, a combination of motor and speech mapping may be used depending on the tumor site, thus requiring an awake patient during ISM-guided resection. However, if only motor mapping is planned for a perirolandic tumor, this may be done under GA. Recently, two small studies looked at the feasibility of mapping language areas under GA. A case series examined the feasibility of mapping the motor speech area using electromyography (EMG) recordings of the laryngeal muscles.[42] While another study found that the preservation of language was possible via cortico-cortical evoked potential mapping of the arcuate fasciculus under GA.[43]

Language Mapping

Most patients planned for intraoperative speech mapping would have a preoperative language assessment performed by a neuropsychologist or speech therapist to assess their baseline language production, comprehension, and language deficits. These tests vary by institution; some examples are the Boston Diagnostic Aphasia Examination (BDAE), Boston Naming Test (BNT), Aachen Aphasia Test, and the Dutch Linguistic Intraoperative Protocol (DuLIP).[4,44–46] Intraoperative tasks include picture naming, counting, text reading, sentence completion, word repetition, spelling, text writing, and language syntax.[4,39] Tasks chosen depend on the location of the lesion or tumor, the patient's baseline performance, and local institutional protocol.[30] The most common language task is picture naming, where the patient is asked to begin each answer with the phrase *"This is a …"* before naming the object in the picture shown to them to separate pure aphasia from anomia. Preoperative evaluation also serves the purpose of training patients with the stimulus material. For example, in the picture naming task, pictures that patients do not recognize are removed from intraoperative testing.[47]

There is limited literature regarding assessment of bilingual and multilingual patients intraoperatively. A recent systematic review reported seven studies of which cortical mapping was performed in multilingual patients with brain tumor. Heterogeneity was noted in the location and number of language areas identified intraoperatively.[48] A multilingual picture naming test (MULTIMAP) was recently developed for mapping of eloquent brain regions intraoperatively to address the previous shortcomings of lack of standard tests for different languages.[49]

During cortical mapping, the stimulation intensity is started at 2 mA and progressively increased by 0.5 mA to a maximum of 6 mA or 1 mA below which evokes an AD potential. Each site is stimulated at least three times and is considered a positive site when speech arrest, anomia, or alexia occur during at least 2 out of 3 stimulation trials.[38,39] Subcortical language tracts are also mapped during surgical resection in awake patients with similar stimulation paradigms.[12] Other cognitive functions that may be tested in awake patients during surgery include visuospatial functions, sensory modalities, memory, calculation, and other higher cognitive tasks. However, protocols for these other modalities are less well-established than language testing.[50–52]

Traditionally, the LF stimulation paradigm was used for language mapping using a bipolar probe. More recently, HF stimulation through a monopolar probe has been shown to be a safe and effective technique for language mapping in awake patients.[53,54] The distance between the resection margin and the closest positive language site strongly predicts the evolution of postoperative language deficits, making language mapping an essential tool to help preserve language functions.[55]

Motor Mapping

Most patients requiring intraoperative motor mapping are for resections of tumors or lesions within or adjacent to the motor cortex (also known as the Rolandic cortex) or motor pathways (corticospinal tract, CST).[11,34,56–63] Several other brain regions also play a crucial role in modulating motor responses; these are the premotor region and the supplementary motor area.[64,65] Cortical or subcortical DES of the motor area would produce involuntary overt movement or muscle activity detected by EMG. The use of EMG in asleep conditions also allows the detection of impending seizures.[31,66]

Both stimulation paradigms can be used for cortical and subcortical motor mapping; LF stimulation with a bipolar probe, or HF stimulation with a monopolar probe.[67,68] However, both paradigms have distinct differences under awake and asleep conditions (refer ►**Table 1**).[28,29] The HF stimulation technique triggers a time-locked compound motor action potential response with measurable amplitudes and latencies, in contrast to the sustained muscle contraction caused by classical LF stimulation.[33] HF stimulation induces motor evoked potentials (MEP) when applied over the primary motor cortex or subcortically, and the use of continuous EMG recording (►**Fig. 3**) allows the use of lower stimulation intensities with increased sensitivity to identify motor pathways compared with visual inspection of overt movement, and thus favorable for use under GA.[31,66,69,70] LF stimulation paradigm is ineffective during cortical and subcortical mapping under asleep conditions in patients with infiltrative tumors, long history of seizures, and is prone to cause seizures. Thus, LF is not the preferred paradigm for this subset of patients for motor mapping under GA.[31] Monopolar HF stimulation has been associated with a lower incidence of intraoperative seizures.[33,53,71] Additionally, patients with epilepsy mapped with HF stimulation under GA do not suffer from more stimulation-induced seizures than nonepileptic patients.[72] With monopolar HF stimulation, anodal stimulation is best used on the cortical surface, while cathodal stimulation is optimal in subcortical tissue.[59,70]

Furthermore, monopolar HF subcortical MEP stimulation allows determination of the distance to the CST with a simple rule that 1 mA of stimulation intensity to elicit an MEP response resembles a 1-mm distance to the CST.[56,59] Different motor thresholds (MTs) have been suggested to define the limits of resection, with subcortical MT of 3 mA generally considered safe, with a chance of inducing a permanent deficit of less than 2%.[58,61,73] In addition, continuous dynamic mapping of the motor tracts can be performed during tumor resection by integrating the monopolar stimulator into the suction tip (►**Fig. 2**) and gradually reducing the current intensity as resection becomes closer to the CST.[58] Cortical and subcortical DES motor mapping may also be combined with direct cortical MEP monitoring generated using a subdural electrode strip over the motor cortex, and transcranial MEP, recently termed "triple motor mapping." This combination method may improve the safety of

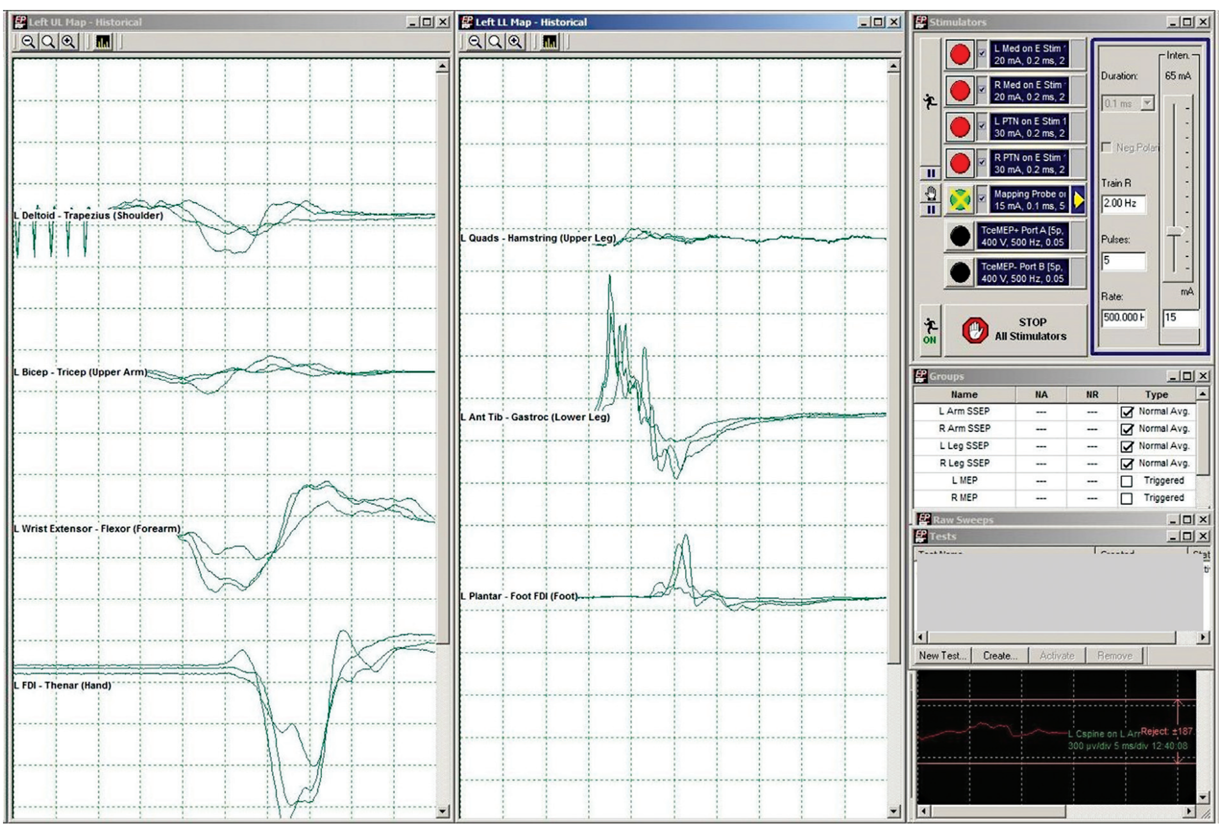

Fig. 3 Intraoperative direct electrical stimulation (DES) during asleep motor mapping: Electromyographic (EMG) recording of evoked motor evoked potential (MEP) during DES in hands and legs with high-frequency (HF) stimulation paradigm (train of 5, 500 Hz, 15 mA). FDI, first dorsal interosseous muscle.

resection by alerting the surgeon of proximity to the CST before irreversible changes in MEP occur.[34,57,73–76] Somatosensory evoked potential phase reversal is another technique where the central sulcus is identified for localization of the primary motor cortex during surgery to guide mapping.[77,78]

Since the introduction of the HF paradigm for direct cortical motor mapping by Taniguchi et al in 1993,[9] more resections involving perirolandic tumors have been performed under GA with comparable outcomes to AC.[79,80] However, Rossi et al reported that a significant portion of patients undergoing glioma resection under GA developed hand apraxia after surgery.[81] This led to the development of more advanced motor tasks that can be evaluated during AC. Tasks to assess the nonprimary motor areas and sensory-motor integration are the repetitive arm flexion-extension movement[82,83] and the hand-manipulation task.[52,81,83,84]

Importance of Intraoperative Mapping in Neurosurgery

Variability of Eloquent Area Localization

Preoperative functional mapping is helpful in defining structures at risk of intraoperative damage when planning surgical resection of an intracranial lesion[85] using techniques such as functional magnetic resonance imaging,[86,87] diffusion tensor imaging,[88] positron emission tomography,[87] transcranial magnetic stimulation,[89] and magnetoencephalography.[90,91] Many studies have demonstrated complex neural connectivity and interindividual anatomical and functional variability in the sensory and motor representation of healthy individuals and those with brain lesions.[4,5,36,92–95] For example, language sites identified with ISM are often smaller in area than the classically defined Broca and Wernicke areas but are very variable in localization.[3] Even without an underlying identifiable anatomic lesion, patients with epilepsy show a wider distribution of language areas on language mapping, extending well beyond the classic Broca and Wernicke areas.[96] This variability poses a challenge for neurosurgeons planning resection of tumors adjacent to presumed eloquent brain, since anatomical landmarks alone may not be sufficient to determine the eloquence of a specific brain region.

Furthermore, brain shift during surgery either from physical factors (related to navigation hardware), surgical factors (use of retractors, cerebrospinal fluid, or tissue loss during surgery), or biological factors (tumor type or location, and use of mannitol to reduce intracranial pressure) may render imaging-guided mapping less effective for intraoperative surgical resection.[97] Brain tumor progression also leads to functional reorganization over time, which may complicate resection guided by imaging only.[98–102] Thus, ISM combined with preoperative functional neuroimaging increases the precision of identifying critical cortical and subcortical structures for preservation during surgery.[88,103–107]

Outcome Evidence for Intraoperative Stimulation Mapping

Previous retrospective studies have shown that ISM-guided resection has been associated with a greater extent of resection (EOR), less delayed neurological deficits,[40,60,108] and extended survival[109] compared with resection under GA without ISM. In glioma surgery, a greater EOR correlates with improved patient outcomes, including survival in low-grade and high-grade tumors.[110–118] Gross total resection (GTR) of gliomas compared with subtotal resection is associated with improved overall survival, progression-free survival, and seizure control.[119,120]

The GLIOMAP study, the first international multicenter propensity-matched cohort study, reported similar results that AC with ISM resulted in fewer late neurological deficits (26% vs. 41%), longer overall survival (17 vs. 14 months), and longer median progression-free survival (9 vs. 7.3 months).[121] Two recent meta-analyses concluded that ISM use during glioma surgery was associated with a higher rate of GTR, longer median overall survival, lower postoperative complications,[122] and shorter hospital stay.[123]

Conclusion

ISM is the standard of care to guide the resection of lesions within or adjacent to eloquent brain tissue. Despite technological advancements in functional neuroimaging, the wide anatomo-functional variability and intraoperative brain shifts confound the precision of real-time resection of the eloquent regions. ISM-guided resection has been proven to result in better seizure control, reduced postoperative deficits, and improved survival. LF and HF are the two stimulation paradigms utilized for DES, with distinct differences in their physical properties and outcomes during awake and asleep conditions. Language and motor are the two primary neurophysiological modalities assessed intraoperatively in neuro-oncological and epilepsy surgery. Understanding these technical aspects of ISM and the neurophysiological tests employed enables the anesthesiologist to provide an anesthetic that may complement the procedure planned.

Conflict of Interest
None declared.

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