Practical Application of Preoperative and Intraoperative Cortical Mapping in Surgery

Sepehr Sani, Carter S. Gerard,
and Richard W. Byrne

Core Messages and Summaries for the Clinician

1. While anatomical and functional imaging are helpful in localizing the relationship of lesions to eloquent cortical regions, the high temporal and spatial resolution of cortical mapping during resection render this technique the gold standard for ensuring maximal extent of safe resection of intrinsic brain tumors and epileptogenic lesions.
2. The key to success of cortical stimulation mapping is its rigorous and consistent methodological application throughout the operation and in between operations.
3. Despite high temporal and spatial resolution, cortical stimulation mapping has limitations that may lead to a more limited resection.

Introduction

While concrete knowledge of classical anatomic descriptions of cortical language and motor locations is mandatory for each neurosurgeon, in many cases it is not sufficient for localizing eloquent cortices. Even in the normal brain, language function localization can be highly variable [1–6]. Further distortion of eloquent cortex can occur due to nearby pathology including tumors, epileptogenic foci, or vascular lesions [7–9]. Although the uses of neuronavigation and functional neuroimaging have improved localization, these techniques only reveal areas that are involved in language or motor function, but not critical to it. While intraoperative cortical stimulation mapping was first described over 80 years ago [10], it remains the gold standard for in vivo identification of eloquent cortex allowing the neurosurgeon to maximize resection while minimizing risk to the patient [11–13].

Indications

When evaluating patients for cortical stimulation, preoperative imaging is reviewed and the pathology can be classified into three groups: presumed eloquent location, near-eloquent location, and non-eloquent location. We define topographic regions of the brain with presumed

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S. Sani, M.D. (✉) • C.S. Gerard, M.D.
R.W. Byrne, M.D.
Department of Neurosurgery, Rush University
Medical Center, 1725 W. Harrison Ave. Ste. 855,
Chicago, IL, 60612, USA
e-mail: Sepehr_Sani2@rush.edu;
Carter_Gerard@rush.edu;
Richard_W_Byrne@rush.edu

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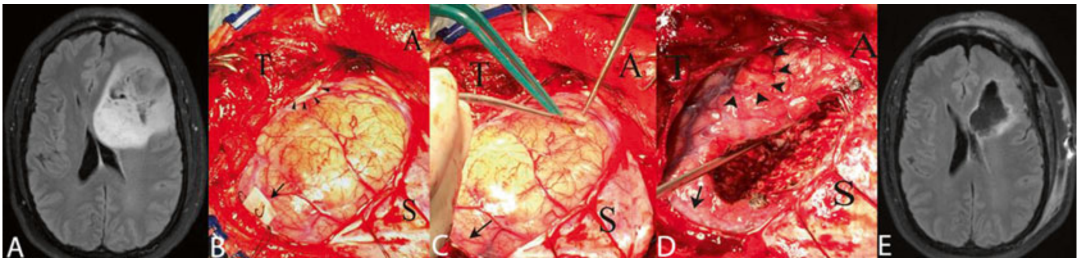

Fig. 1 (**a**) Shows a well-defined left frontal lesion with involvement the dominant frontal operculum (language) and posterior frontal cortex (motor). (**b**) After mapping, language (*small arrows*) and motor (*large arrow*) areas are marked. (**c**) The resection is begun away from eloquent cortex and taken toward functional areas. (**d**) The final resection was taken within 5 mm of motor cortex and was stopped when the patient developed new subtle language deficits. (**e**) Postoperative MRI shows a small area of residual tumor involving white matter beneath Broca's area corresponding to the intraoperative finding. *A* anterior, *T* Temporal, *S* Superior, *Arrowheads*—Broca's expressive language area; *Arrow*—primary motor hand area

eloquence similar to previously published studies [14–20] and includes the primary sensorimotor cortex of the pre- and postcentral gyri, Wernicke's area (posterior portion of the superior temporal gyrus and the inferior parietal lobule), Broca's area (inferior posterior dominant frontal lobe), the calcarine visual cortex, the basal ganglia, internal capsule, thalamus, and the white matter paths of each. If any part of the lesion is found to infiltrate these regions (Fig. 1a) it is regarded as being located in presumed eloquent brain; if it approaches, but does not clearly involve these regions it is considered near eloquent and if it is situated in a separate anatomic location it is considered non-eloquent.

The classification of a lesion as located in eloquent, near-eloquent (E), or non-eloquent (NE) brain has ramifications for the operative strategy used. While lesions distant from eloquent anatomic structures do not require further preoperative functional investigation, it is prudent to consider preoperative functional imaging in lesions involving eloquent and near eloquent brain to help define the critical structures within the proposed operative field. Patients with pathology within the areas considered to be eloquent or near eloquent cortex may benefit from intraoperative cortical stimulation. If language mapping is required a patient must be without major dysphasia or confusion (Table 1), and have the ability to tolerate an awake craniotomy.

Table 1 Relative contraindications for awake craniotomy

- Uncooperative patient
- Pediatrics—<10 years old
- Extreme obesity
- Airway concerns
- Extreme mass effect (consider staging)
- Significant dysphasia

Integrating with Functional Imaging

While the use of functional MRI allows the surgeon to better assess the relationship of a lesion to eloquent cortex, there are considerable limitation, especially when mapping language areas. Several recent studies have shown relatively reliable motor cortex mapping when compared to intraoperative stimulation [1, 21–23]. However, while fMRI has largely replaced Wada test for language lateralization, fMRI does not allow for precise localization of language which is reflected by the wide range of reported results in the literature. A review of five studies showed language mapping sensitivity from 59 to 100 % and specificity from 0 to 97 % when compared to intraoperative stimulation [2, 24]. Various authors have used newer noninvasive technologies for anatomic mapping such MEG and TMS [25–28]. Advanced preoperative functional imaging may serve two important purposes:

1. Neuroplasticity may induce migration of functional activity to other neighboring regions in tumor-infiltrated brain, which is why minimal or no neurological deficits are seen in some patient with slow growing low grade gliomas. Thus a better understanding of the true functional eloquence of the anatomically eloquent region under investigation is gained. This finding has redefined the term "eloquence" and indeed resulted in a greater number of tumors being resected that were previously considered as being part of anatomically eloquent cortex.
2. It enables the surgeon to understand the most dangerous regions of the tumor with regard to neurological morbidity and estimate the extent of safe resection prior to the operation [29–31]. This can aid discussions with the patient and multidisciplinary care-providers considering adjuvant and neoadjuvant treatment options.

Preoperative Preparation

The Patient

In preparation for surgery, a thorough understanding of the patient's baseline neurocognitive status is needed. We consider formal neuropsychological evaluation of patients with lesions involving or near the speech cortex. Often there are "silent" deficits present preoperatively that may go unnoticed [32]. Furthermore, identification of cognitive deficits may guide the resection approach and extent irrespective of pure motor or language findings in addition to monitoring postoperative recovery [33, 34].

The cornerstone of a successful cortical mapping assisted resection is patient cooperation in the awake setting. This is particularly important in language mapping. During the preoperative clinic visit, a detailed rehearsal and review of expectations during the awake portion of the operation can be very helpful in allaying patient anxiety and ensuring a cooperative patient (Table 2).

Table 2 Preoperative evaluation for awake craniotomy

• Medical evaluation
• ICP control—dexamethasone, mannitol
• Anticonvulsant
• Speech, motor evaluation
• Consider fMRI, DTI (cases where mapping may fail, subcortical cases)
• Image guidance MRI
• Anesthesia evaluation and discussion of expectation

If language mapping is anticipated, preoperatively the patient is extensively counseled on the nature of intraoperative testing and undergoes a baseline language evaluation as follows: the patient is asked to count from 1 to 50, name objects seen on a computer generated slide show, read single words projected on a computer screen sequentially, repeat complex sentences, and write words and sentences on paper. Language deficits are classified as anomia when the patient is unable to name an object but able to repeat sentences and has fluent speech . Alexia is defined as retention of the ability to write spell, but with reading errors. Aphasia may be expressive, receptive, or mixed. Mild language errors such as paraphasic errors are not considered in resection planning. Patient should have 80 % language comprehension preoperatively in order to be considered for awake speech mapping.

Equipment

The following is a listing of the standard material and equipment used at the senior author's institution for cortical and subcortical brain mapping during resection operation:

(a) Image guidance for anatomical localization and verification.
(b) Electroencephalographic (EEG) monitoring of cortical surface by placement of an electrode strip or grid on the cortical surface to monitor after-discharges during stimulation.
(c) Appropriate EEG cables and strips or grids. 1–2 six contact strips are placed adjacent to the stimulated area.

(d) Cortical stimulation probe and box with power source verified (e.g. Ojemann Cortical Stimulator (Radionics Corp., Burlington, MA) or another commercially available probe).
(e) Counted and linked map tags for cortical identification during mapping.
(f) Cold saline or Ringer's solution for irrigation to abrogate an induced seizure during stimulation.
(g) Neuropsychological assessment team with naming cards for speech mapping.
(h) Dedicated and experienced neuroane sthesiologist.

Anesthetic Considerations

For general anesthesia, a routine cranial neuroanesthesia protocol is followed. Pharmacological paralysis and high concentrations of inhalation anesthetic agents are avoided. In awake craniotomy cases, the following regimen is employed: Before incision, midazolam (2 mg; avoided if EEG to be recorded) and fentanyl (50–100 mcg) are administered. During surgery, either propofol (50–100 mcg/kg of body weight per minute; avoided if EEG to be recorded) or dexmedetomidine (0.2–0.7 mcg/kg/h) and remifentanil (0.05–0.2 mcg/kg/min) are given. Local anesthesia is given along the Mayfield pin sites as well as a circumferential scalp field block. A mixture of 0.5 % lidocaine, 0.25 % Marcaine (bupivacaine hydrochloride), and epinephrine (1/200,000) are used. Once the craniotomy is performed, intradural injections along either side of the middle meningeal artery are given in cases involving the middle fossa. Anesthetic agents are discontinued at this time until mapping is completed. Painful portions of the operation, such as early portions of the exposure and dural opening are managed by sedation, patient reassurance, and transient increase in propofol infusion rate. In cases that require additional sedation, supplementary boluses of propofol (0.5 mg/kg) are given and the infusion rate may be increased to 125 mcg/kg/min. Nausea or vomiting can be controlled with intravenous droperidol (1.2–2.5 mg) or metoclopramide (5–10 mg). The patient is asked to hyperventilate before dural opening. Once mapping is complete, sedatives are restarted. Intraoperative seizures due to cortical stimulation have been reported in up to 24 % of cases [35, 36]. Epilepsy patients are at particularly increased risk of intraoperative seizures due to decreased anticonvulsant levels. These seizures, whether focal or general, are usually transient and can be suppressed by application of local ice-cold Ringer's solution and a bolus of intravenous propofol (1 mg/kg) [37]. If airway control is of concern, tracheal intubation may be necessary.

Preparations and Positioning

Patient comfort is paramount in cortical mapping operations, Often during longer operations in an awake patient, hip or neck pain can cause more discomfort than the actual surgery. Extra padding of all pressure points is essential. The neck position should look comfortable. Side positioners should be placed on both sides along with safety straps and the patient should be securely taped to the bed. Wrists should be secured with restraints. The drapes need to be elevated to allow direct visualization for seizures, airway concerns, testing such as object naming, and to avoid claustrophobia.

After positioning, monitors are attached, an indwelling urinary catheter is inserted, and oxygen delivery via nasal cannula is provided. Usually the semilateral position is preferred using a padded roll for back support. The semisitting position may be needed for some cases involving motor or sensory cortex. Medications such as mannitol and dexamethasone, as well as antibiotics are given prior to making the incision.

Craniotomy Considerations

The draping is performed accordingly to allow the anesthesiologist and examiner the full view of the patients face as well as contralateral arm and

Table 3 Intraoperative troubleshooting

• Apnea
• Coughing
• Swelling
• Low level after discharge
• Seizure

leg for intraoperative monitoring of the patient's neurologic and respiratory status (Table 3). A localized craniotomy is performed using standard neurosurgical technique with the assistance of neuronavigation. A tailored craniotomy is preferred, including the underlying lesion or seizure focus, along with exposure of surrounding areas. The patient remains under heavy sedation until the craniotomy is complete. Ideally the patient awakens as the dura is opened. Pain upon awakening can be addressed with local anesthetic. Often pain is related to the temporalis muscle which is difficult to block. Releasing traction on the muscle can relieve pain.

In case of an occipital focus, a generous craniotomy is preferred with exposure of the occipital, occipital-parietal, and posterior temporal language areas for testing. After the durotomy, neuronavigation is used to identify the cortical margins of the lesion. Expected locations of the central sulcus and sylvian fissure are also identified. All margins and landmarks are labeled on the cortical surface.

Stimulation Mapping

Somatosensory Evoked Potential Recordings

Evoked potential recording can be used to localize the central sulcus [38, 39]. This is particularly helpful in cases in which underlying lesions have distorted normal anatomy. The technique is performed by placing an electrode strip perpendicular across the proposed location of central sulcus. A contralateral suprathreshold median nerve stimulation is made, an N20 wave is recorded over the hand somatosensory cortex, and a phase reversal is observed across the fissure. This process is performed several times as the strip is moved along the sensory-motor cortex. Recording is usually begun 3–4 cm above the sylvian fissure medial. Two or three recordings are usually needed to localize the central sulcus. The hand region is the most readily identifiable area and is generally localized to 4–6 cm above the sylvian fissure. Once identified, the sulcus is labeled accordingly and the strip is removed. Continuous SSEP or motor evoked response can be continued through the operation. Evoked potential recording can be performed in the awake patient or under general anesthesia.

Electrocorticography

In patients with intractable epilepsy, electrocorticography may be used in order to identify the abnormal interictal spikes. It may be helpful to have a neurophysiologist or epileptologist with neurophysiology expertise in the operating room for recording interpretation. An electrode grid is laid over the cortical area of interest and several minutes of electrocortical activity are recorded. Areas with abnormal interictal spikes are marked [18]. Surgical resection of these areas depends on their functional importance based on motor or language mapping. Electrocorticography is also employed in monitoring of after-discharges during sensorimotor or language mapping as described in the succeeding section.

Sensorimortor Stimulation

Cortical mapping begins with a function check by stimulating the temporalis muscle, if exposed, and confirming visual contraction. If no contraction is seen up to 10 mA of stimulation, a systemic check is done (cable connections, paralytic levels, stimulation parameters, battery, etc.) It is important to remember that the bipolar stimulators are designed to be used in only five cases and are then replaced in order to avoid potential disconnection. The localization of pre- and postcentral gyri are confirmed by direct cortical stimulation after identification with evoked potentials. Detailed somatotopic mapping is also possible with cortical stimulation. This technique is used when the lesion or seizure focus is close to or involves sensorimotor locations. Stimulation is performed using an Ojemann Cortical

Stimulator (Radionics Corp., Burlington, MA). Primary sensory cortex is mapped with the patient awake. Stimulation parameters of 1–2 mA initially, with a frequency of 60 Hz and a pulse duration of 1 ms are used. Cortical patches of 1 cc are stimulated sequentially with rest periods between stimulations. The probe is applied to the cortex for 3 s duration and the patient is asked to report the onset and location of any perceived paresthesias. Stimulation starts in the suprasylvian portion of the sensory gyrus and advanced superiorly, thereby sequentially identifying the tongue, lip, and hand sensory areas. If the operation is being performed under general anesthesia, only motor mapping is possible [18]. Stimulation parameters remain the same, but usually a higher threshold of initial stimulation is used (3–6 mA). Stimulation intensity increases until contralateral movement is observed by the anesthesiologist or the examiner. Amplitudes greater than 10 mA are not recommended in motor cortex stimulation. Stimulating different areas in sequence rather that immediately adjacent areas, and using pauses of at least 10 s between stimulations may reduce the risk of intraoperative seizures. Congruent with sensory mapping, stimulation is initiated in the suprasylvian region in 1 cm patches and moves superiorly along the gyrus until somatotopic mapping of tongue, lips, thumb, hand, and arm are obtained sequentially. If mapping of motor leg region is needed, stimulation is given through a strip electrode that is inserted in the interhemispheric fissure. Seizures, focal and general, can occur during motor mapping and have been reported in up to 24 % of cases [35, 36]. They are usually transient. Application of ice cold Ringer's solution for 5–10 s is often effective at breaking the seizures. A bolus of intravenous propofol (1 mg/kg) [37] can also be given as adjunct to stop the seizure. Areas stimulated are labeled by the linked map tags that are connected to the surgical drapes. A picture may be taken at the end of mapping and the tags are removed.

Language Mapping

Language mapping is done in the awake patient when the lesion involves the dominant perisylvian frontotemporal region. Preoperative language evaluation and counseling has been described earlier in this chapter. Intraoperative language mapping is not useful in patients with significant language deficits. Intraoperatively, Broca's area is identified by stimulation induced speech arrest. Mapping is initiated at stimulation parameters of 1.5–3 mA, frequency of 50–60 Hz, and pulse duration of 1 ms. Once identified, cortical patches of 5 mm are stimulated sequentially with rest periods between stimulations. The probe is applied to the cortex for 1–3 s and the patient is monitored. Each cortical patch is tested up to three times. Electrocorticography is monitored to determine the threshold for after-discharges. It is important to keep all stimulation below this threshold and meticulously monitor for after-discharges as they can produce false localizing results during mapping and may lead to a clinical seizure. For each site, the patient can be tested for counting errors, object naming errors, and word reading errors as they are presented on naming cards. A cortical area is considered positive for language function if the patient is unable to count, name objects, repeat words, or read words in two out of three stimulations [40]. Positive sites are labeled by sterile labels on the cortex (Fig. 1b) and marked using neuronavigation. It is also important to move to a different area of the cortex after completing stimulation in order to prevent summation and subsequent seizure activity. Usually no more than 25–30 sites are tested around the intended resection site to delineate the positive language areas. All positive language areas, vascular supplies, and white matter connections must be preserved during resection with a margin of 1 cm [41–44]. In anterior temporal resections of the dominant hemisphere, resections within 2 cm of a positive language area, particularly stimulation-induced anomia, will produce a mild but identifiable general language deficit observed on an aphasia battery administered 1 month after the operation [45].

If all tested areas are negative for language errors and the mapping team is confident in the equipment and technique (stimulating up to after-discharge), wider cortical exposure is not necessary and the resection can be carried out based on delineated margins of the lesion or seizure focus. The cortical incision is made in a "silent" area first and resection is carried out (Fig. 1c). Subcortical stimulation may be performed to preserve essential white matter. This typically requires higher levels of stimulation. Once mapping is completed, additional anesthetic agent may be given for patient comfort. It may be difficult to distinguish the mechanism of speech arrest during stimulation of the inferior prefrontal cortex as this area is intimately involved in both language and motor function. Speech arrest can be attributed to a stimulus disturbance of language function or arrest of motor activity. Indeed a combined language and motor function in these cortical areas has been suggested [46, 47]. These areas, when encountered, should be marked as eloquent cortex and preserved, as their resection will lead to postoperative language deficits.

Stimulation Pitfalls

Although identification of the eloquent areas of cortex by stimulation mapping is considered the gold standard, this technique is not without limitations. Indeed a positive cortical finding during stimulation may reflect retrograde activation of another area through network activity. Another issue is that an area that is found to be positive by stimulation may be redundantly represented (whether as a function of the original network or due to plasticity secondary to the underlying pathology) and hence amenable to resection.

Another issue worthy of mention is negative mapping. This technique has been reported as an alternative to positive mapping with the advantage of a more limited craniotomy, exposure, and operative time [19, 48–50]. This technique is of great value for the experienced practitioner. However, the caveat lies in the potential for false negative findings in less experienced centers. Technical issues, suboptimal patient cooperation, or insufficient levels of stimulation can skew negative mapping results and result in resection of potentially eloquent areas. Furthermore, in operations involving seizure foci or lesions (such as low grade glioma) that do not have visible anatomical borders, the extent of resection is defined by the borders of positive mapping, not negative mapping. In most cases, however, negative mapping is adequate for safe resection in and around eloquent centers, and remains a significant advance in clinical management.

Subcortical Stimulation Mapping

Once resection continues past the cortical surface, it is possible and sometimes necessary to continue stimulation mapping. Subcortical stimulation mapping (SSM) refers to stimulating the descending (or ascending in case of primary sensory cortex) white matter network tracks that connect various cortical structures to each other to deep nuclei as well as stimulation of the basal ganglia or thalamic areas. The technique is the same as cortical mapping but stimulation parameters are generally higher than cortical mapping. The resection is carried out incrementally using anatomic landmarks and neuronavigation, with frequent confirmation by SSM before proceeding to the next area. It should be emphasized that subcortical white matter tracks are as eloquent as the cortical structures (Fig. 2). Preservation of theses essential tracks is especially challenging due to the poorly defined borders of subcortical anatomy and the tendency of adjacent pathology to distort the expected trajectory of the white matter.

Surgical Endpoints

The goal of stimulation mapping is to allow the surgeon maximal extent of resection with preservation of neurological function. Upon completion of mapping, resection starts from the least eloquent area and proceed to the most eloquent area. In the awake patient, continued motor and speech assessment will alert the surgeon to any new deficits. These assessment should increase in frequency as needed as the operation proceeds toward mapped eloquent areas.

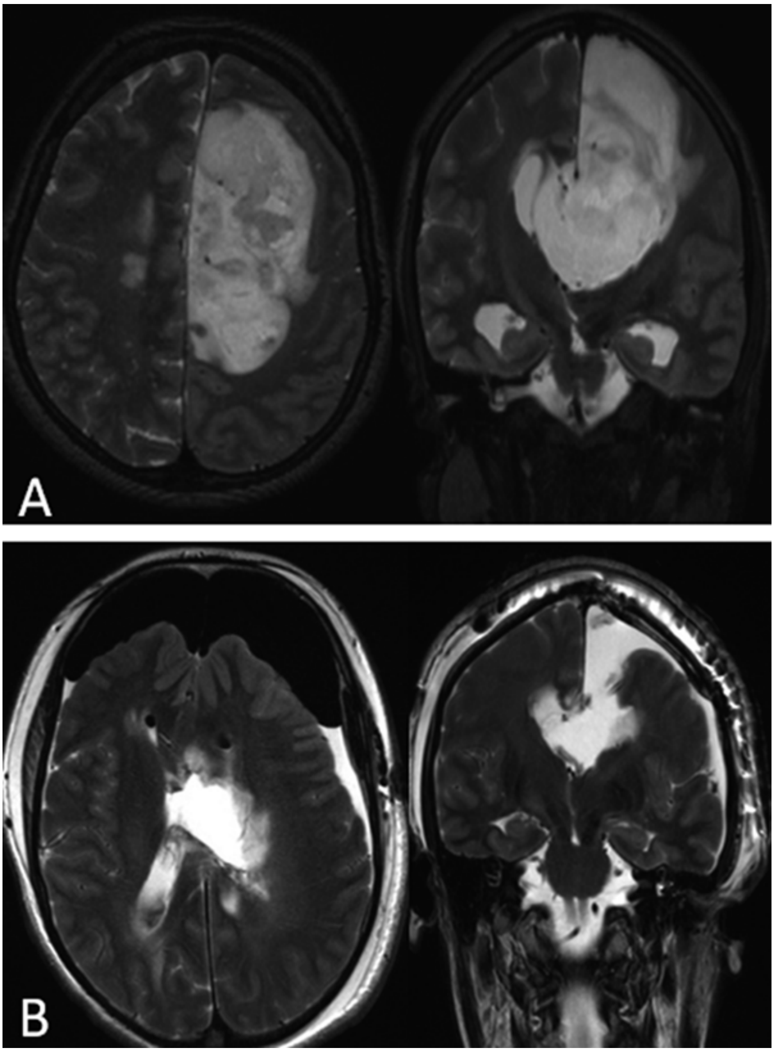

Fig. 2 A 29-year-old female presented with progressive headaches, nausea, and right-sided weakness is found to have a large left frontal-parietal lesion. MRI reveals a lesion expanding F1 with extension into the lateral and third ventricle (**a**). Due to involvement of the supplemental motor area and the significant mass effect, the surgery was performed asleep with stimulation. After cortical mapping, resection began anteriorly and proceeded posteriorly. The resection was stopped when subcortical stimulation produced leg activity at 6 Ma. Pathology was consistent with diffuse astrocytoma, WHO grade II and postoperative imaging showed significant improvement in mass effect (**b**). The patient initially developed a supplementary motor syndrome that completely resolved 6 weeks postoperatively

Resection involving motor cortex or subcortical areas should stop at least 1 cm from identified eloquent areas [51]. Resection can be continued to the pre or post central sulcus if there are clearly identified and white matter is spared. Low grade gliomas often respect gyri. The tumor can expand gyri, pushing into presumed functional areas without infiltrating. They appear to occupy eloquent regions, but often only displace. They can then be identified by counting the gyri. It has been the senior author's experience that stopping the resection when the patient's motor examination is 3/5 or mild dysphasia will result is an intact patient at 6 weeks follow up unless there is a vascular injury or descending white matter has been interrupted. Alternatively for continuous motor mapping a six contact strip can be placed on the precentral gyrus for continuous motor stimulation mapping. Continuous, repeated assessment of an awake patient while operating in or near eloquent cortex remains the safest way to maximize resection and preserve function. When operating around language areas, resection should stop 1 cm from any identified speech area or if there is any change in language testing (Fig. 3).

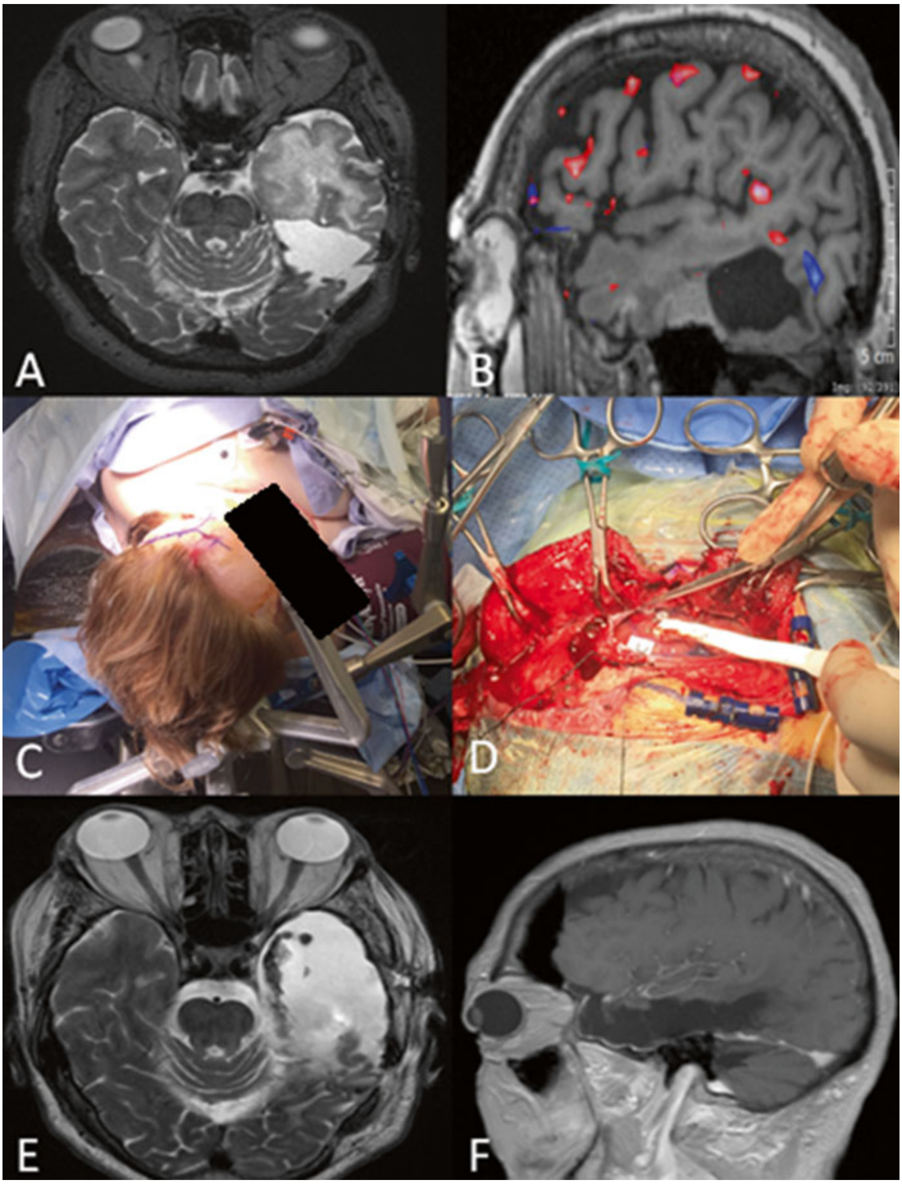

Fig. 3 A 63-year-old female with a history of left temporal anaplastic oligodendroglioma with 1p/19q deletions s/p resection 10 years earlier presents for evaluation due to radiographic progression on serial imaging (**a**). Functional MRI showed bilateral speech with activity at the superior posterior border of the existing resection cavity (**b**). The patient was taken to the OR for awake craniotomy for speech mapping (**c**). Intraoperative speech mapping produced arrest during inferior parietal stimulation (**d**). The surgery was completed without development of deficits. Postoperative imaging showed a gross total resection of the tumor, including 8 cm of dominant temporal lobe (**e**, **f**)

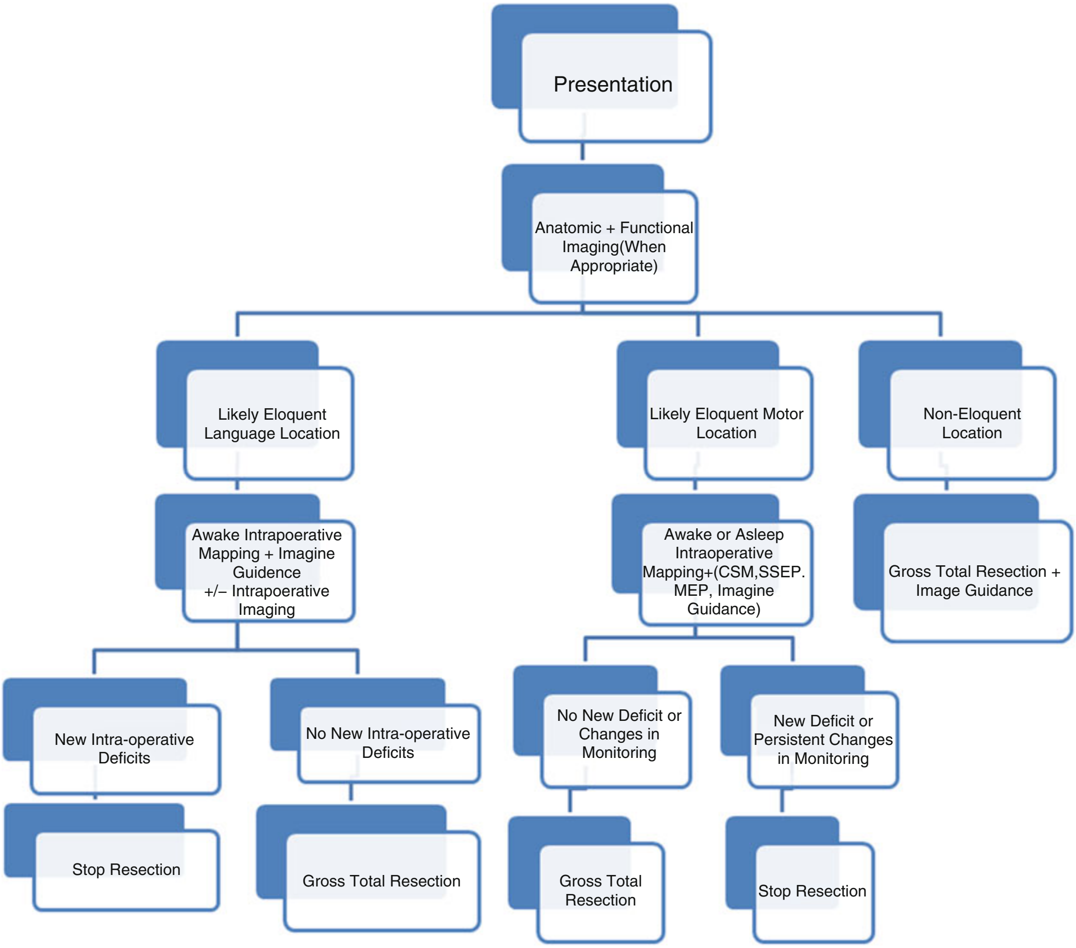

Fig. 4 Shows the treatment paradigm for patients with focal intracranial lesions who require surgical intervention

Summary Algorithm

Shown below (Fig. 4) is a summary of the algorithm used at the senior author's institution to aid in communicating the surgical paradigm for treatment starting with diagnosis of an intracranial lesion.

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