# Intra-operative Imaging Techniques During Surgical Management of Gliomas

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## Abstract

The goal of glioma surgery is to maximize tumor removal while preserving existing function. Intra-operative imaging techniques play an important part in achieving this goal. This article surveys those techniques and discusses the indications, advantages, and drawbacks of each. Structural techniques such as intra-operative magnetic resonance imaging (MRI), ultrasound, diffusion tensor imaging, and 5-aminolevulinic acid staining offer anatomic information. Functional techniques such as functional MRI, magnetoencephalography, and transcranial magnetic stimulation provide information about the functionality of brain regions. When incorporated into a frameless stereotactical neuronavigation system, these modalities increase both the efficacy and safety of glioma surgery by allowing the surgeon to achieve the most extensive and safe resection possible.

The goal of glioma surgery is to maximize tumor resection while preventing a new post-operative neurologic deficit. For both low- and high-grade gliomas, increased extent of resection correlates with improved progression-free survival as well as with overall survival.[1–5] While some features of brain tumors can be visualized, in general, most aspects of infiltrative gliomas cannot be clearly seen by direct vision, thus making it difficult to evaluate when the resection is complete. Furthermore, identifying deeper structures in the trajectory of resection is critical to preserving subcortical white matter tracts and blood vessels. For these reasons, recent advances have made intra-operative imaging a cornerstone of modern glioma neurosurgery.

Neuroimaging techniques fall into two broad groups: structural and functional. Techniques such as frameless stereotaxy, intra-operative magnetic resonance imaging (MRI), ultrasound, diffusion tensor imaging (DTI), and 5-aminolevulinic acid (5-ALA) staining provide anatomic and structural information, helping to identify normal structures and tumoral regions. Functional techniques such as functional MRI (fMRI), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS) yield information about the functionality of given brain regions. Typically, functional imaging data are acquired pre-operatively and applied intra-operatively. Depending on the technique, navigational data are acquired either pre-operatively or intra-operatively, and applied intra-operatively. This article discusses both categories of neuroimaging, since they both have intra-operative applications and are critical to the successful management of gliomas.

## Frameless Stereotaxy

Frameless stereotactical neuronavigation systems are the mainstay of modern image-guided neurosurgery.[6] Introduced in the 1980s, frameless stereotactical neuronavigation allows the surgeon to navigate in three dimensions within the anatomy of a specific patient in real time, making use of images that are acquired pre-operatively (see *Figure 1*). This technique depends on accurate co-registration between the patient and the scan. An infrared emitter and receiver system records the coordinates of each of the fiducial points on the patient's head or the head shape in 3D space with respect to a reference arc next to the head. The software then calculates the position of the patient in space and co-registers the patient to the scan. Thereafter, touching the probe anywhere on or in the patient's head will cause the neuronavigational system to display the relevant slices of the scan, with a crosshair indicating the position of the probe tip.

Frameless stereotactical neuronavigation has greatly improved the accuracy and safety of glioma surgery. It effectively allows a resection to be carried up to its safe margin. In so doing, this technique has been shown to improve the extent of resection and to reduce post-operative deficits.[7–10] Additionally, it enables the surgeon to tailor craniotomies with greater accuracy, allowing for smaller exposures, shorter incisions, and reduced morbidity.[11] Finally, as stated previously, frameless stereotactical neuronavigation forms the platform by which pre-operative functional imaging data may be applied intra-operatively.

## Figure 1: A Frameless Stereotactical Intra-operative Navigation System Display



## Figure 2: High-field Pre-operative, Intra-operative, and Post-operative Magnetic Resonance Imaging Scans of Patients Undergoing Awake Craniotomy with Language Mapping



*The blue arrows depict additional areas of tumor that were identified and resected after intra-operative magnetic resonance imaging. Source: Leuthardt et al., 2011.[13]*
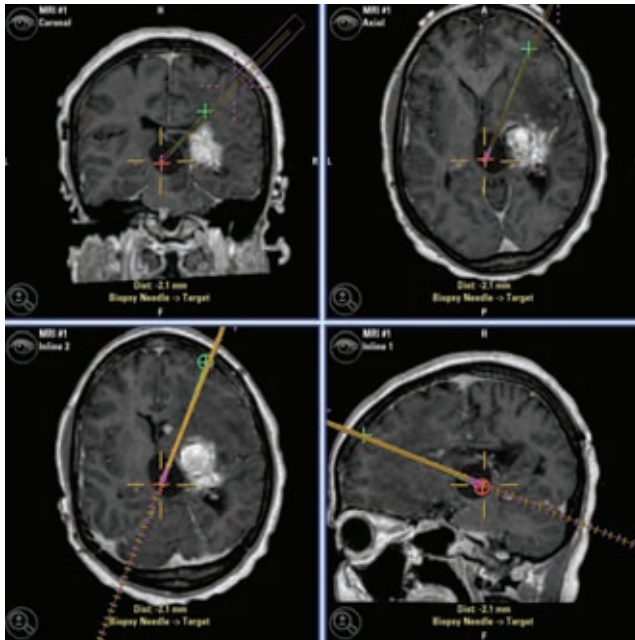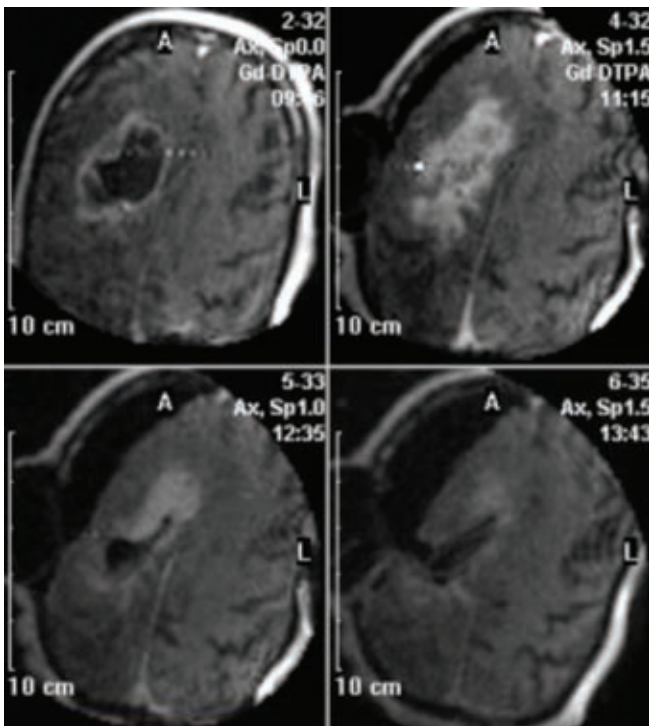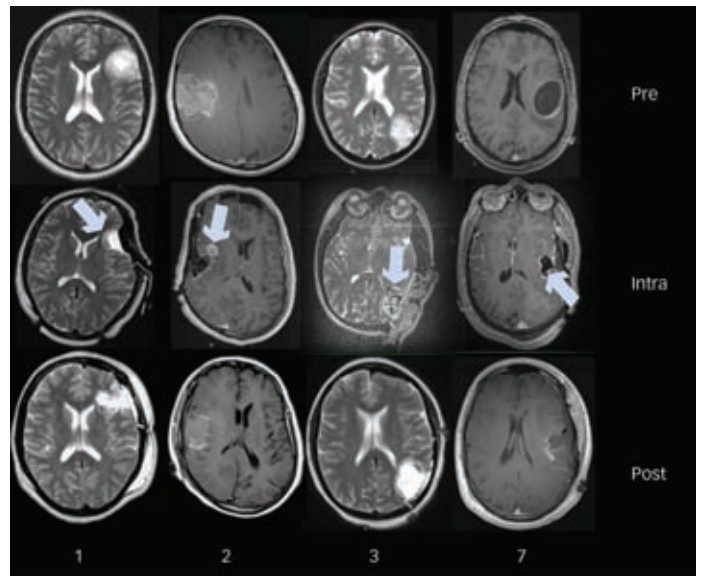
## Figure 3: Low-field Intra-operative Magnetic Resonance Imaging Scans of a Patient Undergoing Resection of Glioma



*The resection cavity is evident in the right frontal region. Image courtesy of Pieter Kubben, MD, Maastricht University Medical Center, AZ Maastricht.*

## Figure 4: Intra-operative Ultrasound of a Cystic Glioma



*The ultrasound image is co-registered to a magnetic resonance imaging scan using a frameless stereotactical navigation system.*
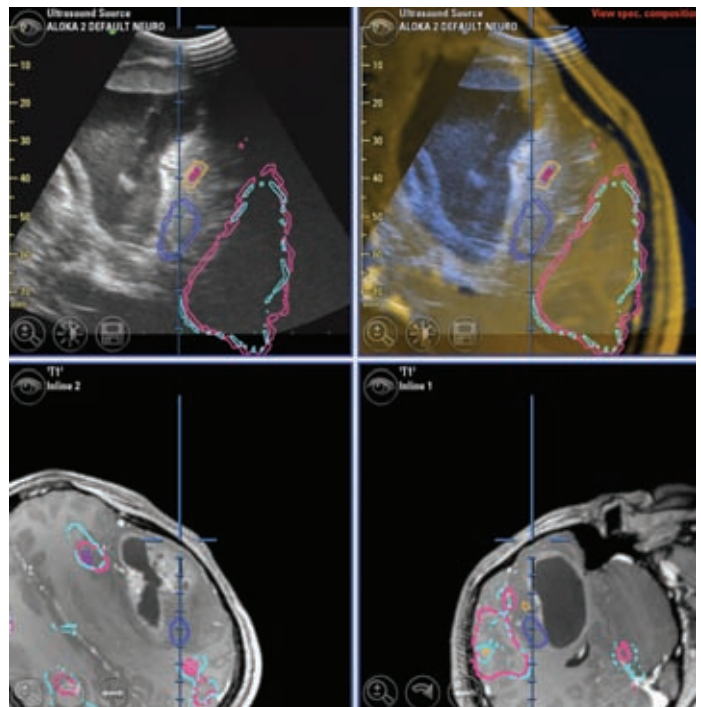
Frameless stereotactic neuronavigation does have limitations, which fall into two categories overall. The first consists of poor co-registration between the scan and the patient, usually from non-optimal fitting of the pre-operative MRI and intra-operatively acquired landmarks. Even a few millimeters of shift in the location of the reference markers from positioning the patient can introduce problems in co-registration. Another limitation stems from intra-operative brain shift or edema. While these limitations are of concern, newer methods such as intra-operative

## Figure 5: Resection of a Glioma that Has Been Labeled with 5-Aminolevulinic Acid
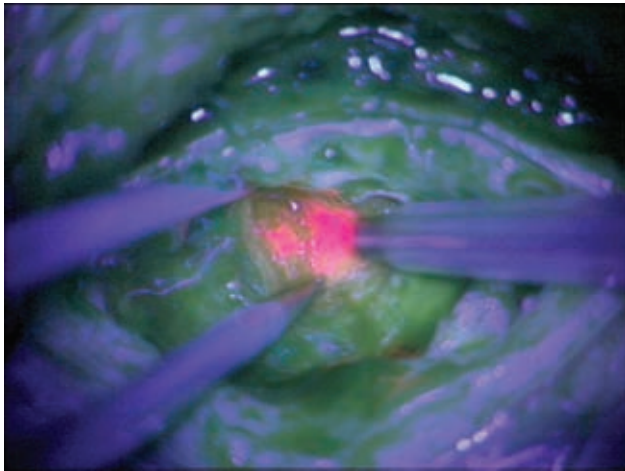


*Under the fluorescent lighting of the operating microscope, the malignant tissue is centrally located and glowing with an apparent deep pink color.*

## Figure 7: Diffusion Tensor Imaging Tractography in a Patient with Glioma



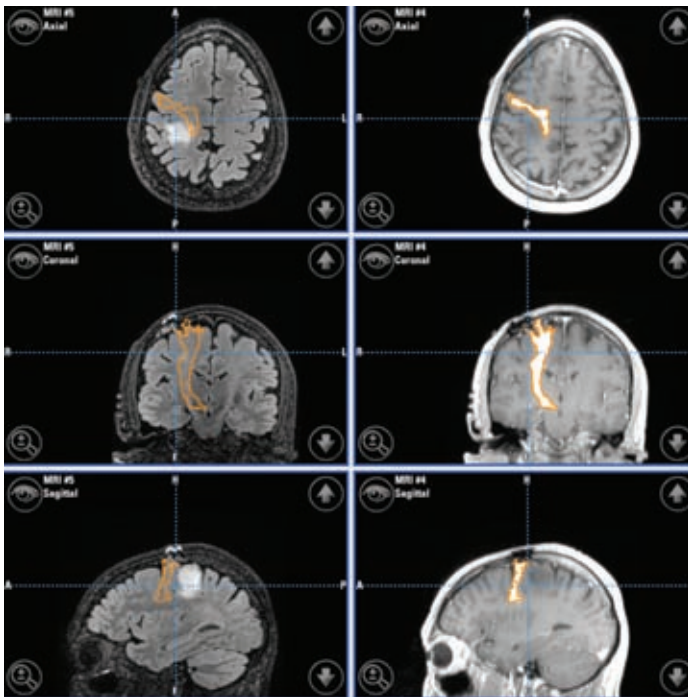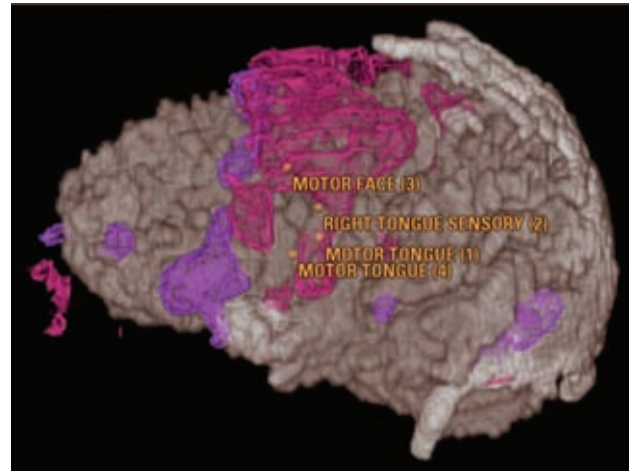*The regions highlighted in orange correspond to descending corticospinal fiber tracts. The tractography has been integrated with a neuronavigational system for intra-operative use.*

## Figure 6: Functional Magnetic Resonance Imaging of Motor and Pre-motor Areas



*Intra-operative direct cortical mapping results are overlaid on the 3D volume. The motor region defined by functional magnetic resonance imaging (fMRI) is more extensive than that defined by direct cortical mapping; this lack of specificity makes fMRI unsuitable for the intra-operative identification of eloquent cortical regions.*

## Figure 8: Example Magnetoencephalograph of Somatosensory Stimuli to the Right Lip and Right Index Finger
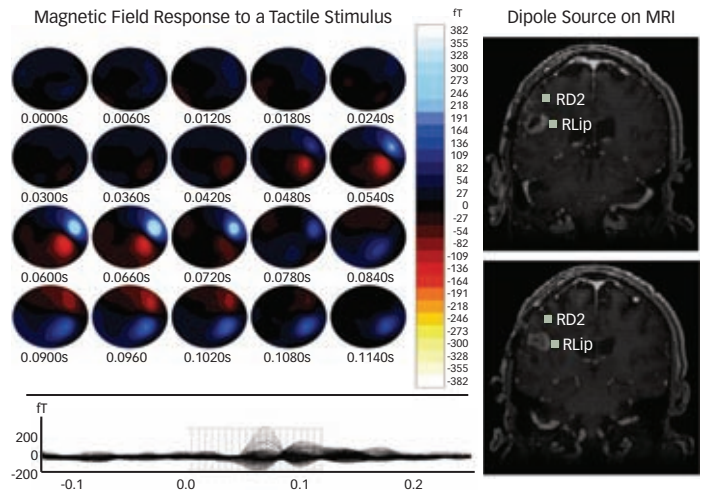


*Multiple stimulus trials are performed for each site and cortical magnetic fields are recorded. The trials are averaged and a single dipole is reconstructed for each site using the least-square fit method. The resulting dipoles are then displayed on a co-registered, T1-weighted post-gadolinium coronal magnetic resonance slice.*
*RD2 = right index finger; RLip = right lip.*

MRI and intra-operative ultrasound (IUS) are being developed to address these issues.

## Intra-operative Magnetic Resonance Imaging

As its name suggests, intra-operative MRI refers to the acquisition of the MRI using a specialized scanner in the operating room itself.[12] High-field intra-operative MRI usually functions at 1.5T or greater and yields high-resolution scans (see *Figure 2*). These units are bigger and often require that the surgical suite be designed for rapid, easy transport of the patient to the scanner for image acquisition, such as with a motorized table that is continuous with the bore of the scanner. Low-field scanners usually function at or below 0.5T and are less expensive than the high-field scanners (see *Figure 3*). Although these images are of lower resolution, the machines are smaller and may thus be moved over a stationary patient.[13]

Intra-operative MRI can confer great advantages in glioma surgery.[14,15] First, it allows for the most accurate navigational co-registration because the scan is performed after the patient has been positioned for surgery. Fiducial markers are unnecessary and only the external reference marker

## Figure 9: Example Case of a 46-year-old Right-handed Woman with a Left Fronto-temporo-insular Low-grade Glioma
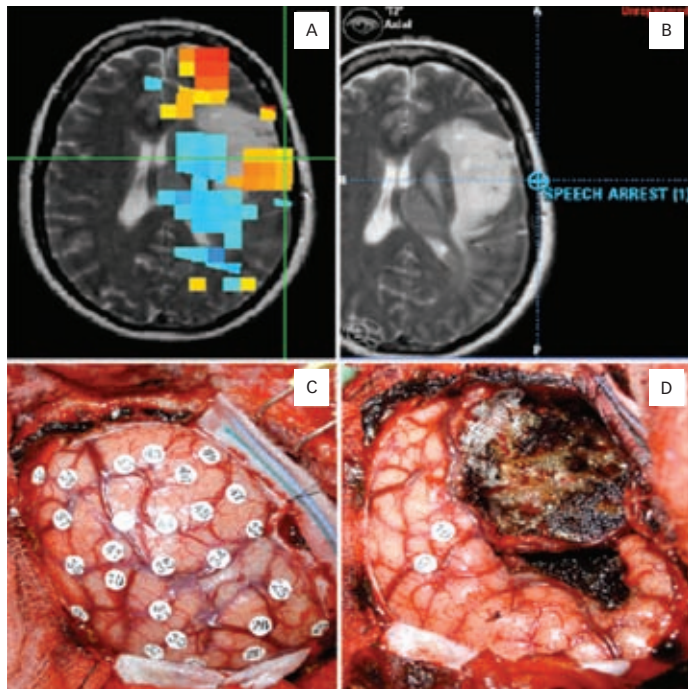


*A: Magnetoencephalography analysis showing increased cortical connectivity values posterior to the tumor in the posterior frontal operculum (indicated by the orange and yellow regions marked by the green cross). B: Intra-operative neuronavigation image indicating the area where speech arrest was elicited during direct cortical mapping, marked by the blue cross. Comparison of images A and B revealed good correlation between the area of speech arrest and an area of increased cortical connectivity. C: Intra-operative photograph taken before tumor resection; #9 and #10 mark the area of speech arrest. D: Intra-operative picture after tumor resection. The temporal and insular components of the tumor have been removed; the functional language points identified (marked with the numbers 9 and 10) have been preserved.*

is required. Second, intra-operative MRI allows the surgeon to evaluate the extent of resection using a gadolinium contrast agent if desired, and to continue to remove any residual tumor if found. In traditional glioma surgery, this interim assessment is impossible; the surgeon must finish the case and the post-operative scan is completed the next day. Third, if brain shift occurs during surgery, an interim intra-operative scan can provide updated imaging data that accurately reflect the current anatomy.

Intra-operative MRI has been shown to improve surgical outcomes.[14–16] In comparison with traditional methods, it improves the extent of resection[17–19] in both low-grade[2,20] and high-grade[16,21] gliomas, and has been shown to reduce the size of residual tumor in the case of subtotal resection.[22] In a randomized controlled trial, patients undergoing surgery for contrast-enhancing gliomas with intra-operative MRI had a significantly higher rate of gross total resection than those in the control group.[23]

Despite the mounting evidence that glioma surgery with intra-operative MRI leads to better surgical outcomes, there are as yet no clear data that it leads to increased progression-free or overall survival. Although further studies will likely demonstrate these advantages, the cost of this technology is still an obstacle to its widespread adoption beyond tertiary referral centers.

## Figure 10: Motor Map of the Precentral Gyrus Generated with Transcranial Magnetic Stimulation
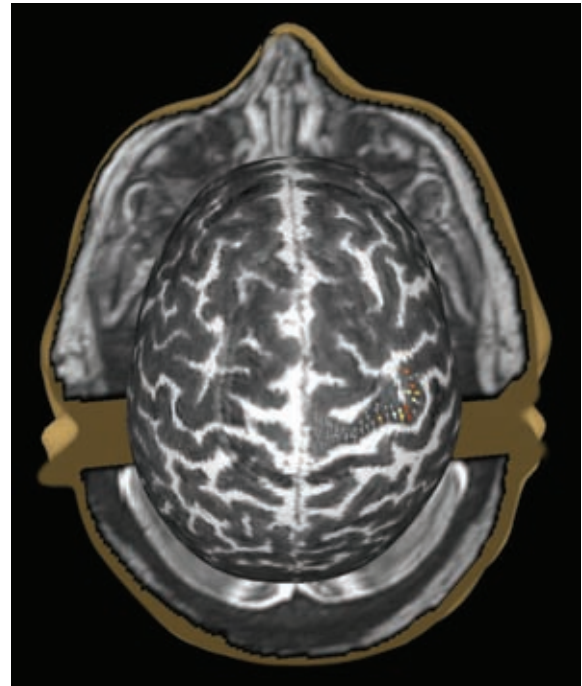


*Variably colored pins indicate the amplitude of motor-evoked potentials in the abductor pollicis brevis during the mapping procedure.*

### Intra-operative Ultrasound

IUS is a modality that has been employed by neurosurgeons for decades. First discussed in the 1970s, IUS has been used intracranially for tumor localization, tumor biopsy, cyst drainage, and navigational guidance of ventriculo-peritoneal shunts.[24] The advantages are many: IUS, like MRI, uses no ionizing radiation; unlike MRI, ultrasound units are relatively inexpensive, portable, and quick to use; finally, IUS can be used by the surgeon directly without the need for additional personnel (see *Figure 4*).

In the last decade, IUS techniques have become more suited to neurosurgical procedures.[25] In particular, 3D ultrasound is increasingly able to localize lesions within the brain parenchyma.[26,27] Because IUS has the ability to resolve small anatomic structures, such as the small vessels on the cortical surface, it can be used to achieve highly accurate co-registration in a frameless stereotactical neuronavigation system.[26] Similarly, IUS can be used for intra-operative re-registration of an existing MRI to account for brain shift.[27] Despite these advantages, there are limitations to this technique. IUS is not optimal for deep lesions because of their distance from the probe. Additionally, it does not allow for as much tissue differentiation as other modalities, such as intra-operative MRI. Finally, IUS requires experience on the part of the user to be able to take and interpret IUS images successfully.

### 5-Aminolevulinic Acid

5-ALA is a small-molecule precursor that causes certain types of cancerous cells to synthesize or accumulate fluorescent porphyrins.[28–31] One such porphyrin, protoporphyrin IX (PPIX), specifically accumulates in glioma cells. PPIX, when illuminated with a violet-blue (375–440 nm)

light, emits a red fluorescence which can be viewed through a 455 nm long-pass filter. In effect, it makes glioma cells directly visible under the operating microscope (see *Figure 5*). 5-ALA is administered as an oral solution from six to 24 hours prior to surgery. Intra-operatively, the tumor is resected using standard techniques. As the pseudo-margins of the tumor are approached, fluorescence within cells may be used as one indicator that further resection is warranted.

Thus far, results with 5-ALA have been promising. It improves the extent of resection.[32,33] In one study, it increased the rate of complete resection of the enhancing portion of glioblastoma multiforme from 36 to 65 %; the 5-ALA patients also doubled their progression-free survival.[34] In another study, patients receiving 5-ALA had median residual tumor volumes of 0 cm compared with 0.5 cm in the conventional group.[35] In that study, however, patients receiving 5-ALA were more likely to have short-term neurologic deficits than control patients. This increased temporary morbidity is likely a result of the extended resections: 5-ALA does not differentiate between eloquent and non-eloquent tissue, so the resection must not be extended to the limits of fluorescence without consideration of functional pathways. Again, in this trial patients with complete resections had longer survival and time to neurologic progression.

## Pre-operative Imaging—Integration with Intra-operative Navigation

Since its advent in 1991, fMRI has become the dominant technique for functional brain imaging. It uses the blood-oxygen-level dependence (BOLD) signal, which is a reflection of the changing levels of oxyhemoglobin and deoxyhemoglobin in functionally active brain regions. fMRI is limited by relatively poor temporal resolution (several seconds). It is a safe, non-invasive method that allows for whole-brain coverage, including the ability to examine activity in deep structures. Importantly, the widespread availability of MR scanners has made the technique easy to adopt across the medical field. In patients with brain tumors, fMRI has been used to identify sensorimotorcortex (see *Figure 6*), but other modalities such as DTI and TMS (see below) are proving to be more accurate for this purpose. Currently, the use of fMRI to delineate regions associated with specific language tasks (i.e. word repetition, word reading, and object naming) is in the experimental stage. Similarly, language lateralization with fMRI is a subject of continuing research and is rapidly reaching equivalent sensitivity and specificity to Wada testing.[36]

DTI is another MR-based technique used to measure the diffusion of water molecules in tissue. Because water molecules tend to diffuse preferentially along densely myelinated white-matter tracts, DTI can accurately trace white-matter tracts, a process known as tractography. In this modality, regions of interest that are presumed to be functionally connected are selected (i.e. primary motor cortex and cerebral peduncle). The algorithm then calculates the most likely pathway connecting those

regions (see *Figure 7*). DTI can be performed on most modern MRI scanners. DTI-based tractography is commonly used to define the pyramidal tract[10,37–39] and, to a lesser extent, language[40] and visual pathways[41,42] in patients with lesions in proximity to eloquent cortical and subcortical areas.

MEG measures tiny magnetic fields outside of the head that are generated by neural activity. Because it measures these fields directly, MEG offers excellent temporal resolution (<1 ms). Furthermore, magnetic fields are unimpeded by biological tissue, so MEG recordings offer an undistorted signature of underlying neural activity. MEG scanners, however, are expensive and relatively rare, so MEG is less widespread than MR-based techniques. MEG studies are useful for localization of sensory, motor[43] (see *Figure 8*), and language regions (see *Figure 9*).[44] They are also used to localize seizure foci, which is often helpful in the management of epileptogenic tumors such as oligodendrogliomas.

TMS is a technique that uses an externally applied, highly focused, brief magnetic pulse that is of sufficient strength to induce a depolarization in the underlying neuronal units. Depending on the frequency and location of the pulse, it can either cause neuronal excitability or have a temporary lesion effect. Navigated TMS, in which the magnetic pulses are guided by a co-registered, pre-operative MRI scan, allows for highly accurate mapping of the motor system (see *Figure 10*). TMS is frequently used in the management of peri-Rolandic tumors, where the pyramidal tract is at highest risk of disruption from surgical resection.

Each of these four modalities can offer valuable information in the pre-operative period, assisting in planning of the surgical approach, delineating the location of the tumor with respect to eloquent brain regions, and informing pre-operative discussions with patients regarding expected risks and post-operative course. However, they are highly valuable intra-operatively as well. Each of these modalities can be co-registered to a structural MRI scan and uploaded to a frameless stereotactical intra-operative neuronavigational system. With the functional imaging data thus integrated into the intra-operative navigation, it becomes a powerful tool for identifying in real time those regions that have been pre-operatively identified with a given functional study. While these techniques lack the accuracy of direct electrocortical stimulation mapping (see *Figure 9c–d*), they are increasingly useful adjuncts in the operative management of gliomas.

## Conclusion

Intra-operative imaging is playing an increasing role in the surgical management of gliomas. Current techniques allow the surgeon to define functional brain regions, navigate accurately during the surgical resection, identify critical structures, and maximize the extent of resection while preserving function. As these modalities become increasingly refined and complex, a thorough understanding of their advantages and limitations will lead to better outcomes for patients. ■

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