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Fluorescence Guidance and Intraoperative Adjuvants to Maximize Extent of Resection

Safely maximizing extent of resection has become the central goal in glioma surgery. Especially in eloquent cortex, the goal of maximal resection is balanced with neurological risk. As new technologies emerge in the field of neurosurgery, the standards for maximal safe resection have been elevated. Fluorescence-guided surgery, intraoperative magnetic resonance imaging, and microscopic imaging methods are among the most well-validated tools available to enhance the level of accuracy and safety in glioma surgery. Each technology uses a different characteristic of glioma tissue to identify and differentiate tumor tissue from normal brain and is most effective in the context of anatomic, connectomic, and neurophysiologic context. While each tool is able to enhance resection, multiple modalities are often used in conjunction to achieve maximal safe resection. This paper reviews the mechanism and utility of the major adjuncts available for use in glioma surgery, especially in tumors within eloquent areas, and puts forth the foundation for a unified approach to how leverage currently available technology to ensure maximal safe resection.

KEY WORDS: 5-aminolevulinic acid (5-ALA), Fluorescence-guided surgery (FGS), intraoperative MRI (iMRI), Raman microscopy

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Maximizing extent of resection (EOR) both at the time of initial diagnosis and recurrence is associated with increased progression-free survival (PFS) and overall survival (OS) in glioma patients.[1-7] There are several factors that limit EOR including the difficulty in distinguishing between normal brain tissue and tumor-infiltrated brain and colocalization with eloquent structures.[5,8] The recent decades have seen substantial innovation in techniques and technology to enable maximal safe resection in glioma surgery. Preoperative planning based on strong fundamentals of anatomy, physiology, and, increasingly, connectomics[9,10] is the cornerstone of ensuring maximal safe resection.

ABBREVIATIONS: 5-ALA, 5-aminolevulinic acid; **BBB,** blood-brain barrier; **CEUS,** contrast-enhanced ultrasound; **EOR,** extent of resection; **FLAIR,** fluid-attenuated inversion recovery; **GBM,** glioblastoma multiforme; **GTR,** gross-total resection; **ICG,** indocyanine green; **IOUS,** intraoperative ultrasound; **LGG,** low-grade glioma; **MRI,** magnetic resonance imaging; **OS,** overall survival; **PFS,** progression-free survival; **PpIX,** protoporphyrin IX; **SRH,** stimulated Raman histology

However, in this review we aim to focus on the evidence behind clinically available tools designed to ensure maximal safe resection, especially in eloquent regions of the brain. We also touch on experimental approaches that may yield improvements in tumor visualization in the future. Our review culminates in a case presentation as a means of demonstrating how modern imaging tools and techniques can be integrated to support sound and effective surgical decision-making during resection planning, tumor debulking, and margin verification. We envision this review as a resource for neurosurgeons looking to incorporate current technologic advances to achieve optimal to achieve optimal outcomes in the treatment of glioma patients.

FLUORESCENCE-GUIDED SURGERY

Differentiating tumor from adjacent noninfiltrated brain has vexed neurosurgeons since the early days of tumor resection. Over 70 yr ago, Moore et al[11] proposed the use of fluorescein to better localize intracranial neoplasms. In

1982, Murray et al[12] laid the foundation for using fluorescence to guide EOR in their series of 23 cases in which all biopsies of fluorescent tissue contained neoplastic tissue or necrotic debris and 95% of unstained margin specimens were negative for tumor. However, fluorescence-guided surgery (FGS) was not widely adopted until Stummer et al[13] reported a randomized clinical trial examining the impact of 5-aminolevulinic acid (5-ALA) in the setting of high-grade glioma (HGG) surgery in 2006. Their study showed a 29% absolute increase in EOR with 65% of patients undergoing complete resection with 5-ALA compared to 36% with white light and 20% increase in 6-mo PFS when using 5-ALA-guided resection compared to white-light standard resection. This study demonstrated the beneficial effect of 5-ALA on EOR and was one of the clearest demonstrations of the impact of EOR on PFS in HGG.

5-ALA MECHANISM OF ACTION AND CLINICAL IMAGING

5-ALA is a building block in the heme synthesis pathway that is naturally converted to protoporphyrin IX (PpIX), a fluorescent molecule that accumulates in glioma tissue due to local disruption of the blood-brain barrier (BBB) and increased PpIX synthesis by tumor cells. PpIX fluorescence appears red within the tumor core and pink at the margins where there are lower concentrations of PpIX. 5-ALA is most effective in HGG patients since PpIX tends to accumulate in malignant tissue.[14] For this reason, the FDA approved 5-ALA as an "optical imaging agent indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during surgery."[15,16] Fluorescence is most notable when observed under violet-blue light. An appropriate microscope must be secured with the capacity to excite PpIX in the 375 to 410 nm range and observe red emission from 620 to 710 nm. To maximize fluorescence during surgery, the working distance between light source and patient should be minimized with a working angle such that as much of the cavity can be illuminated by the excitation signal as possible.

5-ALA PATIENT SELECTION

The wording of the FDA label implies that the surgeon should first apply imaging criteria to build reasonable "suspicion" that the patient is harboring HGG. The most reliable way to predict tumor fluorescence in a given patient is through an evaluation of clinical and radiographic factors.

Clinical Factors

Differences in the pathophysiology of low- vs high-grade gliomas account for variability in clinical presentation, as does tumor location. Low-grade gliomas (LGGs) are more likely to present with seizures, especially those that are refractory to medical management. LGGs are more likely in children and young adults with a peak incidence in the 40s. HGGs are more common in older patients where 64 yr of age is the average age at presentation.[17]

Radiographic Factors

Magnetic resonance imaging (MRI) is the principal method used in the presurgical assessment and diagnosis of glioma. Standard MRI sequences (T1, T2, postcontrast T1) are typically sufficient in predicting tumor grade based on (1) contrast enhancement, (2) central necrosis or cyst formation, generally present in HGG, and (3) perilesional edema and mass effect.

5-ALA AS A MEANS OF INFORMING SURGICAL DECISION MAKING DURING SURGERY

The best application of 5-ALA in a given patient varies based on tumor depth, size, and proximity to eloquent cortex. The application of 5-ALA in HGG surgery generally falls into the following 3 scenarios:

1. Identification of the surface presentation of a tumor: While densely infiltrated and necrotic HGG tissue has an appearance that is distinct from the normal brain, infiltrating regions of an HGG are increasingly difficult to delineate as tumor concentration falls. Specifically, fluorescence can be utilized to identify the ideal corridor for cortical access to ensure that a minimum amount of healthy cortex is sacrificed. Selection of cortical access is crucial when a tumor is located near an eloquent area.
2. Perhaps the most valuable application of 5-ALA is in visualizing areas of tumor-infiltrated brain that would otherwise be undetectable. Surgical approaches for margin delineation with 5-ALA vary with some surgeons electing to use fluorescent conditions to remove as much tumor as possible while other surgeons choosing to perform the majority of the tumor debulking under white light, employing fluorescence at the end of the resection to visualize otherwise undetectable tumor remnants.
3. Identification of the most malignant regions of a heterogeneous HGG in the setting of biopsy or resection: The selection of fluorescing tissue is a reliable means of ensuring that the most aggressive portions of the tumor have been collected.

Nuances of 5-ALA-Guided Surgery and Emerging Technologies to Improve Visualization

Although efforts are underway to develop imaging systems that allow visualization of PpIX fluorescence under bright-field conditions, currently available microscopes require substantial darkening of the operative field. The main drawback of operating under dark-field conditions is that the visualization of anatomic landmarks and key neurovascular structures is compromised.

Consequently, in many cases, a surgeon must alternate between bright- and dark-field conditions to realize the full benefit of 5-ALA fluorescence.

Several techniques are employed due to the need for switching back and forth between bright-field and dark-field conditions. While under white light conditions, surgeons can memorize a map of no-go zones including areas containing critical blood vessels or hemorrhagic regions and supplying vessels can be preemptively coagulated. Bleeding cannot be easily addressed under dark-field conditions and, as such, a moderate degree of bleeding is tolerated.

In theory, PpIX fluorescence can be quenched or photobleached by prolonged exposure to blue light. As a result, portions of the tumor that are exposed to blue light conditions may fluoresce initially but lose their fluorescence over time. Photobleaching is largely a surface phenomenon, however and removal of a few cell layers of a photobleached area using suction can expose brightly fluorescent tissue. Notably, though published data are not yet available, several manufacturers are developing systems to enable visualization of 5-ALA under bright-field conditions.

5-ALA is highly specific for the detection of brain tissue infiltrated by malignant glioma. While FGS is a tool to help surgeons identify tumor tissue, false positives and false negatives occur in clinical practice. Sensitivity and specificity in dense HGG tissue are commonly reported at above 90%.[18] A variety of studies focusing on the use of 5-ALA for in glioma surgery have reported sensitivities of 21% to 95% and specificities of 53% to 100%, respectively.[19-23] The wide variability in reported sensitivity and specificity is likely related to variability in study design as well as biological factors.

A false negative result occurs with 5-ALA when glioma is present but fluorescence is not observed. Rigorous evaluations of tumor cell content in nonfluorescing tissue have unequivocally demonstrated that roughly 10% of biopsies in brain harboring glioma infiltration do not fluoresce.[24] Up to 88% of nonfluorescent samples contained tumor on the border of resection cavities.[25]

Presumably a critical number of tumor cells must be present to produce visible fluorescence. Handheld spectroscopic methods have been proposed to identify lower levels of PpIX in areas with lower tumor cell density.[26-30] Spectroscopic methods may also be used to identify fluorescence using the characteristics of PpIX. Using this technique, sensitivity can be increased to 72% while maintaining a specificity of 95%, with an accuracy of 88%.[29] In one study by Valdés et al, quantitative fluorescence was performed using an intraoperative probe that used a spectrometer and its data to calculate the concentration of PpIX in resection tissue. Quantitative fluorescence can increase the sensitivity of PpIX from 47% in conventional fluorescent imaging to 84%, but there is an associated decrease in specificity from 100% to 92%.[27] While promising, further translational work is required to bring tools to lower the threshold of 5-ALA detection into clinical practice.

OTHER FLUOROPHORES

Though not specifically approved for use in glioma surgery, indocyanine green (ICG) has also been used as a means of enhancing EOR during glioma resection. ICG is a hydrophobic cyanine dye that binds to plasma proteins and typically remains in intravascular spaces and is commonly used in angiography and cerebrovascular surgery.[31] ICG can be administered intraoperatively to distinguish hypervascular tumor remnant from normal tissue after initial debulking.[32,33] ICG can also be administered preoperatively to help surgeons visualize glioblastoma multiforme (GBM) tissue 6 to 48 h after administration, correlating with T1 post contrast enhancing tissue.[34,35] At higher concentrations, it can illuminate gliomas due to disruption of the BBB, lack of lymphatic drainage, and hypoxic tumor microenvironment with a sensitivity of 98% and specificity of 45%.[34]

Fluorescein was the first fluorophore used in FGS. Under a 560-nm wavelength fluorescent light source, gliomas appear bright yellow during intraoperative administration of fluorescein. It has been used to enhance EOR and improve rates of gross-total resection (GTR) in glioma resection.[36-38] Fluorescein has a sensitivity and specificity of 75% to 97% and 75% to 100% respectively for identifying tumor containing tissue.[23,39] Fluorescein can also be used in conjunction with 5-ALA in order to improve the background illumination to better identify tumor. When used together, the tumor fluoresces orange to red with PpIX whereas surrounding edematous tissue and normal brain fluoresces green.[40,41]

FUTURE DIRECTIONS

Neither ICG nor fluorescein is considered a tumor-specific fluorophore as they lack a molecular target. There are now multiple agents in development that would add to the armamentarium of FGS that are more targeted. Tozuleristide is a protein/fluorophore conjugate that uses ICG as the fluorescent molecule bound to chlorotoxin that allows the conjugate to bind selectively to solid tumors.[42] Early clinical studies have shown high specificity for tozuleristide, but follow-up data have been lacking.[43]

Cancer-selective alkylphosphocholine analogs conjugated with a green or near-infrared fluorophore (CLR1501 and CLR1502 respectively) were also being explored as 5-ALA was being developed. These compounds accumulate in tumor cell membranes due to their increased number of lipid rafts.[31] In one 2015 study, CLR1501 and CLR1502 were able to exhibit tumor to brain fluorescence ratio similar to or greater than 5-ALA.[44] Furthermore, fluorescently labeled antibodies are currently being investigated. Cetuximab-IRDye800, an antibody against EGFR commonly overexpressed in GBM, has also been proposed as an intraoperative adjunct.[45]

Notably, FGS alone also does not provide anatomic or functional guidance when trying to prevent postoperative deficits. As such, when resecting tumors in proximity to eloquent

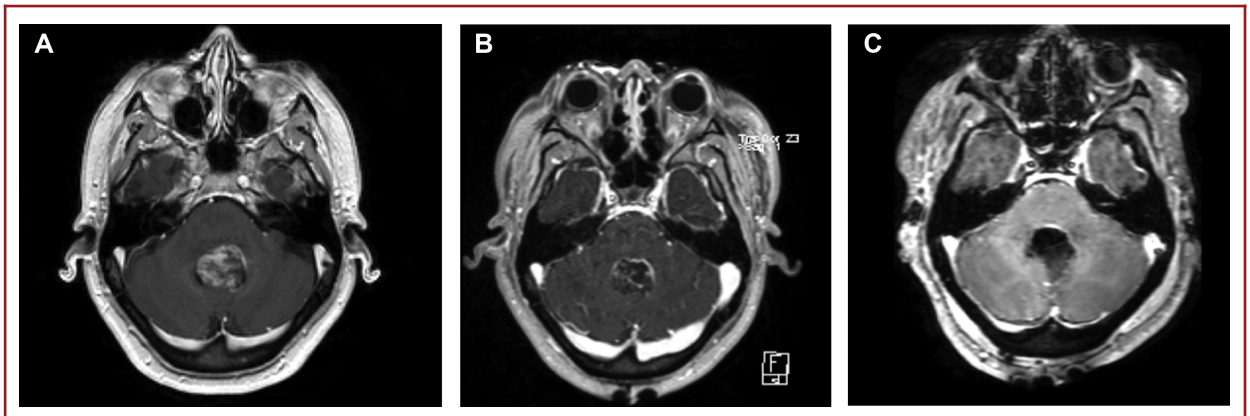

FIGURE 1. *The use of iMRI in the resection of an anaplastic ependymoma of the fourth ventricle: The preoperative image* **A** *demonstrates a contrast-enhancing mass in the fourth ventricle. After GTR is achieved, an MRI is obtained intraoperatively revealing residual-enhancing tissue within the fourth ventricle* **B**. *Based on the intraoperative image, further resection is carried out until all enhancing tissue is removed from the fourth ventricle* **C**.

brain, FGS is frequently used in conjunction with intraoperative imaging techniques and/or neuromonitoring to further enhance EOR while preventing postoperative neurological deficits.[46-51]

IMAGING TECHNOLOGIES FOR OPTIMIZING EOR

Intraoperative MRI

MRI has long been used to assess surgical candidates, plan for surgery, integrate neuronavigation systems, and evaluate EOR postoperatively by providing anatomic information on the lesion being resected. Radiologic characteristics of gliomas, such as enhancement on the T1-postsequence for HGG and T2 or fluid-attenuated inversion recovery (FLAIR) sequence hyperintensity for LGG, are used to evaluate the EOR and residual tumor volume on postresection scans. Intraoperative MRI (iMRI) was developed in the 1990s to update neuronavigation systems and evaluate EOR intraoperatively.[52,53]

When iMRI is utilized, residual tumor can be detected in 65% to 94% of cases, and of those cases, 22% to 68% undergo continued resection based on those images (Figure 1).[54-57] Sensitivity and specificity to detect residual tumor have been estimated as 50% to 75% and 100%, respectively.[19,20] Ultimately, iMRI increases the EOR and, for tumors amenable to GTR, results in a rate of GTR of 38% to 100%.[5,6,54,55,58,59]

The highest quality evidence supporting the use of iMRI comes from a prospective study by Senft et al[60] in which 58 patients were randomized to receive conventional surgical resection or surgical resection with iMRI guidance. In the iMRI group, the rate of complete resection was 96% while the rate of complete resection in the control group was 68%. Additionally, patients who underwent complete resection of glioma had a longer PFS.

iMRI is particularly useful in eloquent regions because it has the capacity to identify residual tumor, assist with planning further resection based on anatomic landmarks, and update neuronavigation systems during surgery to account for intraoperative brain shift. While iMRI enhances EOR in glioma resection, it is not accessible to all surgeons or institutions and can add about 1 h or more of time spent in the operating room. iMRI can be used in conjunction with FGS to evaluate for residual tumor and enhance EOR and can lead to a rate of GTR of up to 100% in lesions amenable to complete resection.[19,46,48] Notably, the use of FGS and iMRI independently have been shown to be superior to just conventional neuronavigation alone in achieving GTR.[61]

Ultrasound

While intraoperative MRI may not be widely accessible, intraoperative ultrasound (IOUS) is almost always available and is considered an inexpensive surgical adjunct. It provides real-time visualization of tumor with information on surrounding anatomy. Gliomas appear hypoechoic on IOUS, and this characteristic can be a reliable method to navigate towards core tumor during resection.[62] IOUS can also be integrated with neuronavigation systems to adjust for up to 67% of brain shift during surgery to provide more accurate neuronavigation and result in a safer resection.[63] In a study by Sweeney et al,[64] IOUS was used to evaluate for residual tumor after resection with stereotactic neuronavigation. GTR was achieved in 75% of cases with intended GTR. IOUS has a sensitivity and specificity of 50% to 80% and 100%, respectively.[20,64] In practice, IOUS is an accessible and easy surgical adjunct that can be used to identify core tumor. However, this technology is user-dependent and has lower sensitivity for determining residual tumor than other intraoperative adjuncts, though this can be improved with contrast-enhanced ultrasound (CEUS).

As early as 2005, CEUS was being investigated during resection of brain tumors to facilitate intraoperative navigation.[65,66] It is an ultrasound modality that can be used in addition to typical B-mode and color Doppler ultrasound that highlights

vasculature and perfusion patterns with the injection of an ultrasound contrast agent. It enables differentiation of normal tissue from tumor and artifact, can help with intraoperative surgical planning, and ultimately improve EOR.[67,68] Compared to IOUS, CEUS shows an improvement in imaging quality of up to 50%.[69] In a series of 10 GBM resections by Prada et al,[70] CEUS was able to accurately identify contrast-enhancing residual tumor tissue in subtotal resections with histological confirmation. CEUS has even been combined with 5-ALA to improve EOR in GBM resection when compared to using either method alone.[71] In contrast to 5-ALA that only shows fluorescence on the surface, CEUS can demonstrate both superficial and deep vascular structures. Ultimately, CEUS provides advantages compared to IOUS in identifying tumor margins and improving EOR while being cost-effective and safe. However, CEUS has limitations including interobserver variability and need for additional training. Furthermore, inconsistency of flow within tumor vessels may affect the accuracy of CEUS and the lack of vascularization in lower grade tumors limits its utility in the resection of LGGs.[72]

INTRAOPERATIVE BRAIN MAPPING AND MONITORING

While this topic is reviewed in depth elsewhere in this series, the interface of other intraoperative adjuncts with mapping will be briefly discussed. Given that the goal of brain tumor surgery is maximal safe resection, neurosurgeons are charged with determining the limits of the tumor and whether or not the tumor can be fully removed without damaging adjacent structures that are important from a neurophysiologic standpoint. Monitoring and mapping is the only intraoperative adjunct that can directly assess functional status of tissue being considered for resection. Brain mapping can identify "no go" zones of eloquent tissue to ensure predictable neurologic outcomes for brain tumor surgery. By providing more robust real-time feedback about the safety of an aggressive resection, mapping can increase the rate of EOR.[73] Specifically, mapping gives surgeons the confidence to approach tumor margins that are close to or overlapping with eloquent areas. In some cases, due to plasticity within the nervous system, brain mapping provides safe access to tumor through tissue that would be predicted to be eloquent. Mapping as an adjunct is limited by the baseline status of the patient. Specifically, mapping is limited by patient participation during surgery, which can be compromised by preoperative deficits (either aphasia or weakness), language barriers, or other cognitive deficits.

Used in conjunction with FGS and imaging, mapping can be used to increase the safety of aggressive tumor resection in eloquent areas. Intraoperative monitoring with the use of FGS has been shown to be safe while allowing for GTR of tumors at risk of being in eloquent areas on preoperative imaging with GTR of up to 64% to 74% of these lesions.[47,49,50] Similarly, the use of iMRI during awake craniotomies has shown a rate of GTR of up to 70% to 89% with mean rate of new permanent neurological deficit of 10% and could help limit new deficits compared to use of iMRI alone.[74-77]

THE ROLE FOR MICROSCOPIC IMAGING IN MAXIMIZING EOR

At its core, the goal of brain tumor surgery is to safely remove as many neoplastic cells as possible. Fluorescence, ultrasound, and iMRI are invaluable tools to indirectly estimate where neoplastic cells have infiltrated the brain but they lack the ability to directly visualize tumor cells on a microscopic scale.

A handful of technologies, 2 of which have recently become available for clinical use, now offer surgeons the ability to rethink the concept of cytoreduction by offering direct visualization of tumor cells.

Zeiss has recently released the Convivo system, a handheld microscopic device that provides low-resolution images of cellular architecture in the operative field in situ. The ability to distinguish amongst various types of tumor using handheld confocal microscopy has been reported, and some investigators hypothesize that the device can be used for margin analysis in glioma surgery, though robust data to support this theory have not been reported.

Multimodal handheld devices are also being investigated including an optical cancer detection system using Raman spectroscopy, intrinsic fluorescence spectroscopy, and diffuse reflectance spectroscopy.[23,26,78,79] These technologies were combined into one handheld probe, and, in a series of 15 patients undergoing resection of cranial tumors including metastasis and grade 2-4 glioma, cancer could be detected with an accuracy of 97%, sensitivity of 100%, and specificity of 93%.[79] Larger series using this multimodal device will be required for clinical implementation. Handheld spectrosopic devices may ultimately impact EOR but clinical data supporting this hypothesis have not yet emerged.[30]

Stimulated Raman Histology

In partnership with Invenio Imaging Inc, a team led by Orringer and colleagues developed the NIO imaging system, a portable imaging system for executing stimulated Raman histology (SRH) in the operating room. SRH, an ex Vivo technology, produces virtual H&E images of tissue specimens in minutes at the bedside without the need for tissue processing, sectioning or staining (Figure 2).[80-84] Ji and colleagues[85] demonstrated that SRH could be used to visualize human brain tumor infiltration that would otherwise be invisible. SRH is capable of identifying infiltrating tumor even at low tumor density and is also able to differentiate between areas of little to no tumor infiltration (<25%) and areas of high tumor infiltration (>75%).[86] In addition, SRH has been shown to reveal diagnostic features of human brain tumors in over 300 patients.[83,87]

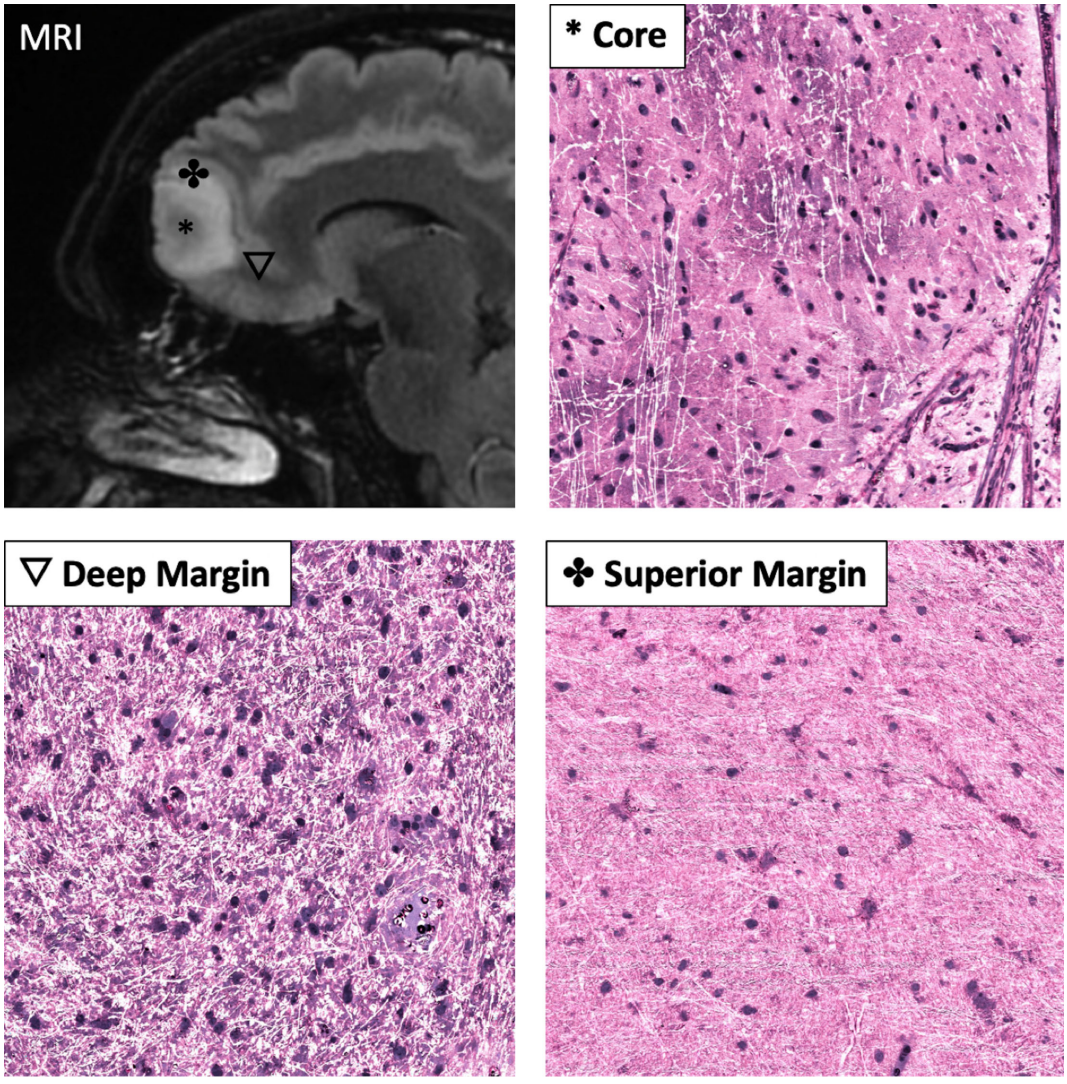

FIGURE 2. *The use of SRH to evaluate the cellularity of glioma margins. A patient with a left frontal pole glioma underwent the MRI shown here and was taken to the OR. 3 × 3 mm biopsies were removed and evaluated in minutes at the bedside with SRH. Tissue taken from the core (*) reveals a hypercellular infiltrating glioma intermixed with axons, which appear as linear "white" elements. All visible and MRI detectable tumor was removed. Sampling of the deep margin (∇) revealed hypercellular white matter and suggested that further resection was required to fully resect all infiltrated tissue in this area. Sampling of the superior margin (✤) revealed mildly gliotic cortex with normal cellularity without evidence of tumor infiltration. No additional resection was required or carried out at the superior margin.*

Consequently, SRH is most useful in rapid tumor diagnosis and in the detection of otherwise invisible tumor, especially at tumor margins. While proof-of-concept data have been presented that demonstrate the ability of SRH to visualize very low levels of glioma infiltration encountered over the course of an operation, rigorous demonstration of how best to use rapid bedside microscopic data to ensure maximal, safe resection is still forthcoming.

In the meantime, published evidence on the performance of SRH supports the use of the technology for detecting tumor infiltration in a manner that can halt resection when histologically normal tissue is encountered in the course of resection and support further resection when dense tumor is encountered in noneloquent regions. In addition, because it delivers data concordant with gold-standard histology, SRH can be used to verify the results of other imaging modalities where specificity and sensitivity are lacking. For example, in a resection cavity margin where iMRI, ultrasound, or fluorescence suggests the presence (or absence) of tumor, or if they offer conflicting results, SRH can provide a quick and reliable assessment of the degree of microscopic tumor infiltration.

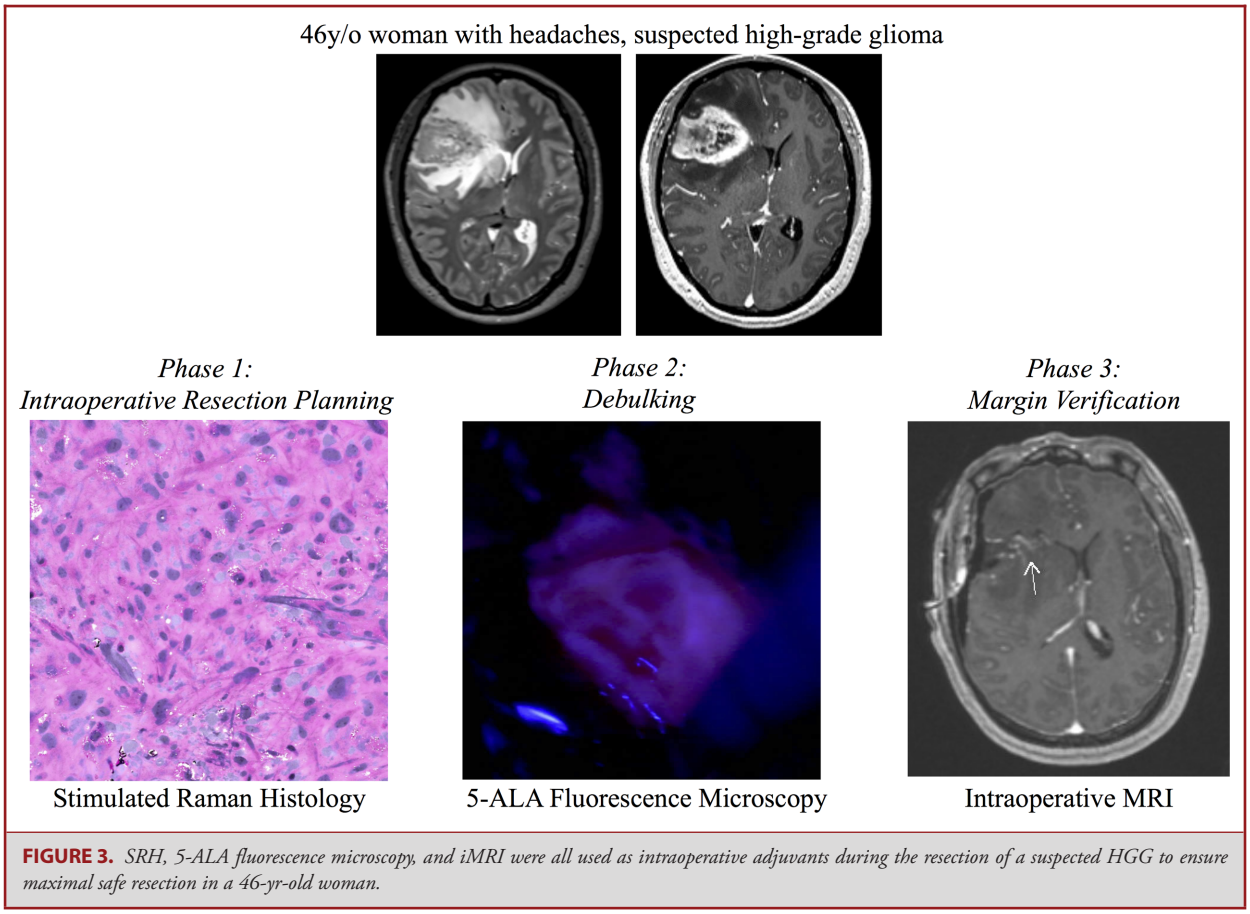

FIGURE 3. *SRH, 5-ALA fluorescence microscopy, and iMRI were all used as intraoperative adjuvants during the resection of a suspected HGG to ensure maximal safe resection in a 46-yr-old woman.*

CASE ILLUSTRATION

A 46-yr-old-woman presented with progressive headache, nausea, vomiting, and facial droop. MRI revealed a 6-cm right frontal, rim-enhancing centrally necrotic mass with perilesional edema. Resection was advised. In cases like this one, EOR is one of the major prognostic factors. We typically break down our implementation of various adjuvants to ensure optimal resection by 3 main phases of tumor resection: (1) intraoperative resection planning, (2) tumor debulking, and (3) defining surgical endpoints (Figure 3).

Resection Planning

With respect to intraoperative resection planning, the first consideration is ensuring the approach to the tumor does not involve eloquent cortical or subcortical structures and that key neurovascular structures are not at risk. In this case, we determined that awake mapping was not necessary but we prepared for subcortical motor mapping and used continuous motor-evoked potentials given the proximity of the corticospinal tracts at the posterior margin of the tumor. SRH is also utilized as soon as lesional tissue is encountered to ensure that the tumor is indeed a surgical lesion as resection would be terminated if the histologic appearance was consistent with lymphoma or a non-neoplastic etiology. In this case, hypercellularity, necrosis, glial processes, and microvascular proliferation observed with SRH were all consistent with the suspected diagnosis of HGG. Ultrasound is also an essential imaging adjunct at this phase of the operation, mainly used in our practice to ensure the cranial access to the lesion is appropriate and to understand the relationship of the tumor to key cerebral landmarks such as the ventricular system.

Tumor Debulking

During tumor debulking, 5-ALA fluorescence microscopy was essential in this operation. We had a high level of confidence that the tumor would be high grade, and therefore fluoresce, given its enhancement with MRI contrast administration, central necrosis, and perilesional edema. We aim to respect the pseudocapsule of a tumor whenever possible. 5-ALA guidance can provide additional cues to the appropriate maintenance of a pseudocapsule during dissection allowing for uniform and swift tumor debulking. During debulking, continuous assessment with navigation and periodic motor-evoked potentials ensured that the margins of resection did not veer too posteriorly into corticospinal pathways.

TABLE. The Advantages and Limitations of Different Intraoperative Adjuncts Used to Maximize Safe Resection

Adjuncts	FGS	iMRI	IOUS	Mapping
Advantages	Helps to delineate tumor from normal brain Direct visualization of tumor during surgery	Whole organ scale imaging Provides updated neuronavigational data Clinical gold standard for evaluating extent of resection	Readily available and low cost Adjust for brain shift in real time Can identify superficial and deep tumor	Functional assessment of eloquent tissue prior to and during resection Reduces risk of postoperative neurological deficit
Limitations	Sensitivity at tumor margins and in LGG Some fluorophores required dark-field conditions Superficial imaging modality	Increases surgical time Unavailable in many surgical centers Residual tumor and surgical artifact may be challenging to differentiate	User dependent with interobserver variability Lower sensitivity for residual tumor	Use may be limited in patients with preoperative deficits Anesthetic must be tailored to mapping modality Specific expertise and team required for successful implementation

Defining Surgical Endpoints

We relied on an inspection of the tumor cavity with 5-ALA fluorescence microscopy to verify the margins of the resection cavity. Ultrasound was also used to ensure there is no evidence of gross residual tumor. It is also our practice to utilize iMRI to verify EOR. In this case, iMRI revealed residual tumor in the posterior and superior margins of the resection cavity prompting further resection. 5-ALA microscopy was utilized to help detect the residual tumor as identified by iMRI. Following resection of residual tumor, SRH was used to verify there was no evidence of dense tumor, with the understanding that there are likely to be some residual tumor cells in all glioma margins.

SUMMARY

Modern neurosurgical oncologists have a large armamentarium of adjuncts designed to ensure maximal safe resection. Each adjunct has unique advantages and limitations (Table). Maximal safe resection is most likely to be achieved when knowledge of anatomy can be combined with radiographic and microscopic imaging techniques. Often more than one intraoperative adjunct is necessary to safely maximize EOR. Neurophysiologic mapping, based on relevant anatomic and connectomic principles, is the only adjunct that provides a functional assessment of tissue surrounding a lesion and, consequently, should be applied whenever possible.

Generally, we recommend selecting the adjuncts considering how they would be used during the tumor resection in conjunction with neuronavigation and neurophysiologic mapping. During the resection planning stage, we commonly employ ultrasound, SRH, and, in some cases, fluorescence microscopy. During debulking, we rely heavily on fluorescence microscopy to augment neuronavigational data to assess EOR. Finally, to define surgical endpoints, we utilize iMRI, fluorescence microscopy, and SRH—all interpreted in the context of neurophysiologic mapping data. In conclusion, while they may add complexity to the surgical workflow, modern technologic adjuncts enable surgeons achieve a level of accuracy in glioma surgery that has not been previously possible.

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Disclosures

Dr Stummer reports consultant and lecture activities for Carl Zeiss Meditech, Photonamic, Medac, and NXDC. Dr Orringer is a consultant for NXDC and Stryker instruments. He is also a medical advisor and shareholder of Invenio. Dr Orillac has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors provide a timely review of surgical adjuncts to maximize extent of resection of gliomas. Safe maximal resection of gliomas provides our patients the best possible outcomes. The use of fluorescence-guided surgery (FGS), intraoperative MRI/ultrasound, microscopic imaging methods, and intraoperative brain mapping are mainly discussed. The present-day neurosurgical oncologist needs to understand the role of each of these intraoperative tools and how each can help in their decision making during surgery. Ultimately, the neurosurgeon needs to continue utilizing tools for intraoperative visualization of tumor and identification of critical tracts in order to preserve neurologic function but permit maximal resection. This is a balance that needs to be kept in mind at all times.

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