Chapter 10

Techniques to Improve the Extent of Brain Tumor Resection — Awake Speech and Motor Mapping, and Intraoperative MRI

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Additional information is available at the end of the chapter

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1. Introduction

It has long been believed by many neurosurgeons that maximizing tumor resection improved patient outcome for patients with high-grade gliomas. Over the past decade the impact of maximizing tumor resection has been clearly shown to be a favorable prognostic factor in the treatment of many types of brain tumors in clinical studies [1-11]. This holds true not only for GBM and other high-grade gliomas but also for lower grade lesions as well [11-13]. In addition, complete tumor resection has also been long known to be potentially curative for many "benign" intracranial lesions such as meningiomas and pituitary tumors with much higher rates of progression free survival for these types of lesions when complete resection has been performed [14].

Even for the most experienced surgeon visual inspection and surgical judgment are not enough to determine when complete resection has been obtained [3,15,16]. Too little resection increases the chances for earlier recurrence and disease progression and overly aggressive resection leads to an increased risk of potential neurological and cognitive deficits. As a result of this many technological advances have been developed to try to assist the surgeon with determining when complete resection has been obtained. These developments included intraoperative ultrasound, frame based and frameless navigation systems, intraoperative MRI, and intraoperative fluorescence with 5-aminolevulinic acid (5-ALA).

In addition, the utilization of awake mapping procedures also allows surgeons to maximize tumor resection by enabling them to monitor the patient's neurological status (motor or speech) throughout a resection. This real-time feedback enables surgeons to maximize tumor resection in lesions near eloquent cortex while minimizing the development of neurological deficits [17].

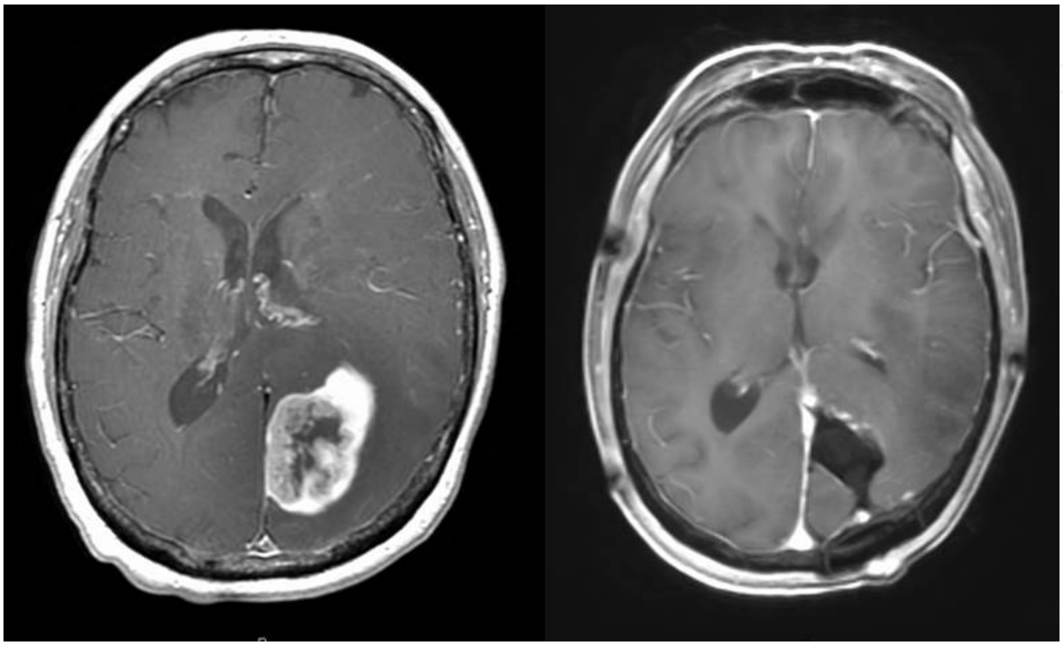

Figure 1. T1 Weighted post contrast preoperative and intraoperative MRI scans illustrating complete resection of a left parietal GBM

2. Literature review of positive prognostic effect for extent of resection (EOR)

One of the original studies to clearly show a survival advantage for extent of resection was a large retrospective endeavor by LaCroix and the MD Anderson Group [1]. They showed a survival advantage for extent of resection greater than 90% and an even greater advantage when resection was over 97%. A 2012 review by Sanai found five studies which used volumetric imaging to compare pre and postoperative MRIs for the EOR of contrast enhancement for patients undergoing surgical treatment of primary GBM. Three of these studies showed a survival advantage of between 2-8 months for patients undergoing complete resections compared to subtotal resections [18]. He also found that seventeen out of twenty eight nonvolumetric studies also found a survival advantage for extent of resection on univariate analysis [18]. Fourteen of these twenty eight studies also performed multivariate analysis to attempt to control for patient age, KPS and other factors. All fourteen of these papers found extent of resection to be a positive prognostic factor using this type of analysis [18].

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In 2011 Sanai et al. [2] published a retrospective review evaluating extent of resection from a retrospective series of 500 consecutive newly diagnosed GBM patients treated at the University of California San Francisco Brain Tumor Center. Not only did they find a survival advantage based on extent of resection; but they also showed that a resection threshold greater than 78% was associated with a significant survival advantage. Although this study was retrospective in nature, the large patient volume adds significantly to its importance and illustrates that even in cases where complete resection may not be deemed safe that a significant debulking of greater than 78% likely conveys a survival advantage versus less aggressive resections [2].

Finally Marko et al. [19] recently published another retrospective review of 721 primary GBM patients treated at MD Anderson. They used an Accelerated Failure Time computer modeling system to evaluate the effects of various parameters on patient outcome. They once again showed a significant survival advantage for patients based on extent of resection. Unlike previous studies they felt that there was an advantage across all levels compared to biopsy alone and therefore felt that surgery should not be withheld based on preoperative assumptions of only obtaining a subtotal resection. In addition, they also showed the strength of such systems in reliably modelling outcome based on numerous patient and treatment parameters and suggest possible uses for this system in determining personalized outcome models as well as more appropriately stratifying patients for future clinical studies [19].

3. Elderly patients with GBM

At many institutions older patients with GBMs are not treated as aggressively as their younger counterparts. Part of this problem is associated with higher rates of medical comorbidities which may make more aggressive surgical interventions riskier. However, another bias is the belief that elderly patients will not tolerate more aggressive procedures and subsequent adjuvant treatments. Osvald et al. [20] performed a retrospective review of a large prospectively collected database to evaluate the impact of patient age on treatment. They found that 72% of patients younger than 65 were treated with resection vs. 55% of the older patients ($p<0.001$). Elderly patients had lower KPS and significantly more medical comorbidities. However, of the patients undergoing resection there was no statistical difference in the percent that had gross total resection when the two groups were compared. Elderly patients had a significantly decreased overall survival (9.1 months vs. 14.9 months), but subgroup analysis of patients undergoing resection showed no difference in overall survival based on age (13.0 months for elderly vs. 13.3 months in younger patients) [20].

Grossman et al. [21] evaluated the effect of age on a group of patients undergoing awake craniotomy for high-grade gliomas. They found perioperative morbidity (3.3% vs 0.59%) as well as length of stay (6.6 vs 4.9 days) higher in the elderly group (age >65 years). The EOR was not significantly different between the two groups (77.25 vs 81.9%).

4. Recurrent GBM

The value of extent of resection for patients with recurrent GBM is even more difficult to determine. Part of the issue in evaluating these patients is secondary to the bias created in evaluating patients who are candidates for surgery, as less than 30% of patients are typically deemed candidates for additional surgery. Factors in determining surgical eligibility include patient performance, tolerance to previous treatments, patient wishes, and tumor factors such as timing, size and location of recurrence [2,22-26].

Subgroup analysis of the Lacroix [1] paper showed a survival advantage for patients with recurrent GBM who had maximal tumor resection at time of recurrence. In addition Bloch et al. [7] evaluated the importance of extent of resection at the time of repeat surgery on a group of 107 patients who underwent multiple resections at USCF. They found that if patients had gross total resection at time of initial surgery than the extent of resection at recurrence did not affect outcome; however, in patients who had subtotal resections at time of initial surgery than the extent of resection at time of recurrence did impact overall survival. In addition, they found that in patients who had an initial subtotal resection had a complete resection at recurrence than there was no difference between them and patients who had complete resection initially and were candidates for additional surgery regardless of extent of resection [7].

Oppenlander et al. [22] published results of 170 patients who were treated with recurrent GBM at Barrow Neurological Institute. They found a distinct survival advantage based on an extent of resection of 80% or greater in these patients. The median interval between initial and subsequent surgery was 8.6 months (range 1.1-93.1 months) [22]. While these data do once again show level 3 data of a survival advantage for these patients it is important to approach this subgroup of patients with great care. First of all, early recurrence (less than 4-6 months) should be approached with great hesitancy. Many of these patients harbor "treatment effect" or pseudo-progression which can be managed medically in most of these patients. Secondly patients who have true progression in this very short time frame often have very aggressive tumor subtypes and are likely to progress despite further surgical interventions. My personal practice is to typically withhold additional cytoreductive surgery in patients who have disease progression prior to 6 months unless surgery is planned as a salvage intervention for symptom management in an otherwise healthy individual, for tissue diagnosis, or to obtain tissue for enrollment in a clinical trial. Finally, the incidence of wound healing and neurological complications is much higher in this patient population. The Barrow group [22] reported preoperative motor and language deficits in 33 and 31% respectively. Additionally they found new or worsened deficits in 19% and 13% postoperatively at one week which only decreased to 15% and 9% at one month [22]. These lesions are not curable and thus patient quality of life is of paramount importance. Every effort should be made to minimize neurological worsening in this patient population and thus judicious evaluation should be performed when determining who is a candidate for additional cytoreductive surgery.

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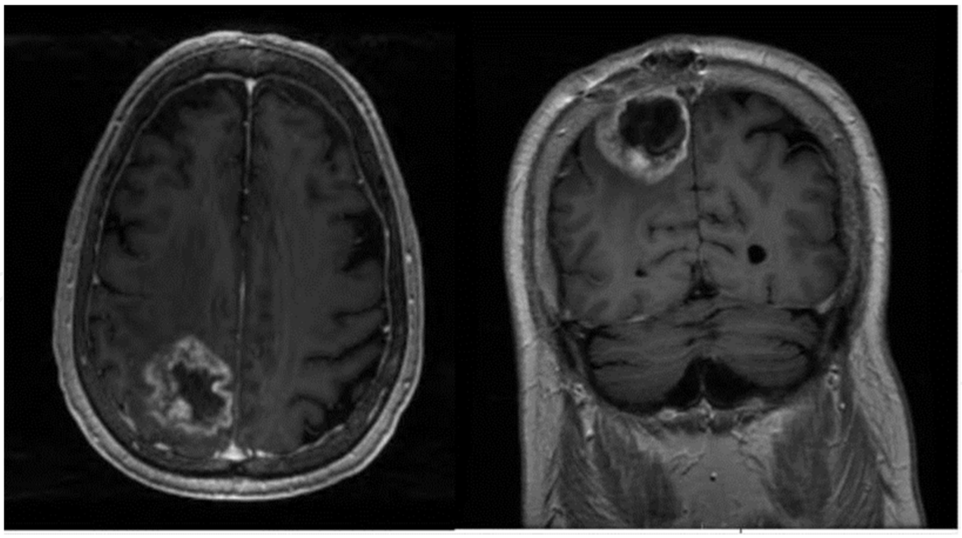

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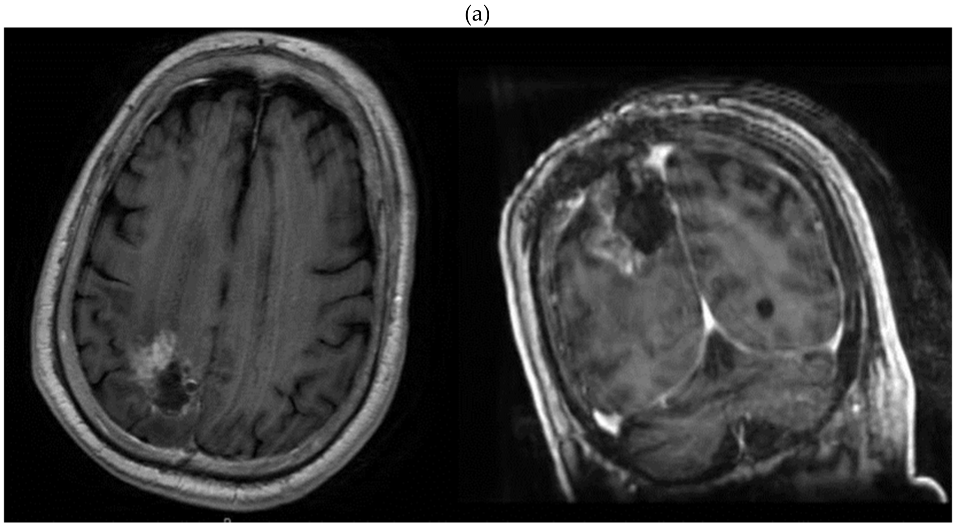

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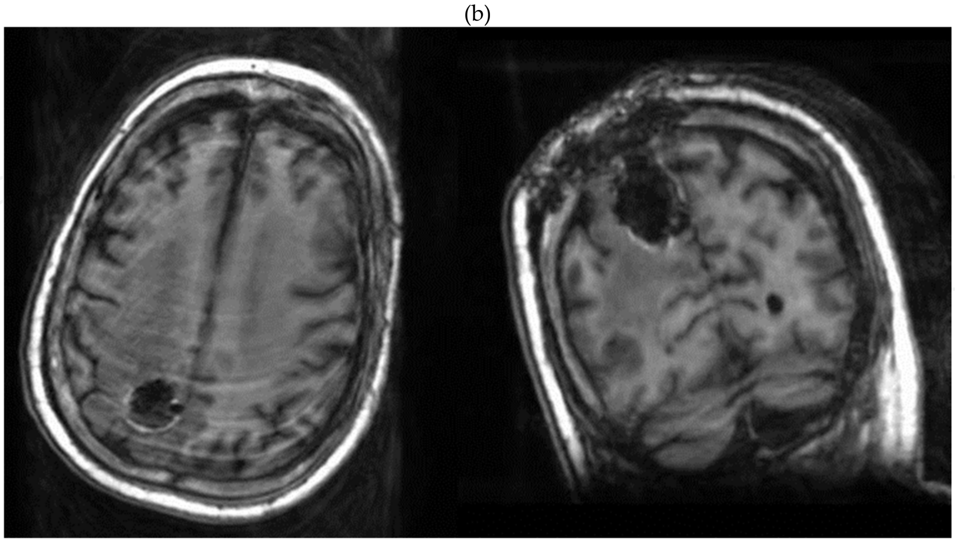

(c)

Figure 2. Post contrast axial and coronal T1-weighted images of recurrent GBM, A. Preoperative; B. First intraoperative (showing residual tumor along the lateral wall); C. Second intraoperative MRI scans

5. Low grade gliomas

Once again in Sanai's 2012 review [18] he found three papers which evaluated EOR for low grade gliomas using volumetric analysis and all three of these showed a significant increase in 5 year survival. He also reviewed eight nonvolumetric studies and once again found an advantage in five year survival in 7 of these 8 studies. Five year survival was shown to increase from 50-70% in cases with subtotal resection to 80-95% in total resections.

Several recent studies have also shown that increasing the extent of resection in low grade gliomas may also decrease the rate of malignant transformation in these tumors. Typically only pilocytic gliomas and other infrequent subtypes such as Ganglioglioma can be cured with complete surgical resection. For the remainder of these lesions recurrence and often progression to a higher grade lesion is the norm. Smith et al. [11] in their review of 216 low grade lesions found that increased EOR was associated with increased malignant progression free survival (MPFS). However, Snyder et al [12] reviewed the impact of EOR on overall survival and MPFS in 93 pure grade II oligodendrogliomas treated at their institution. They found that an increased EOR was associated with an improved OS but did not influence the rate or timing of progression in these patients as MPFS was not influenced by EOR [12].

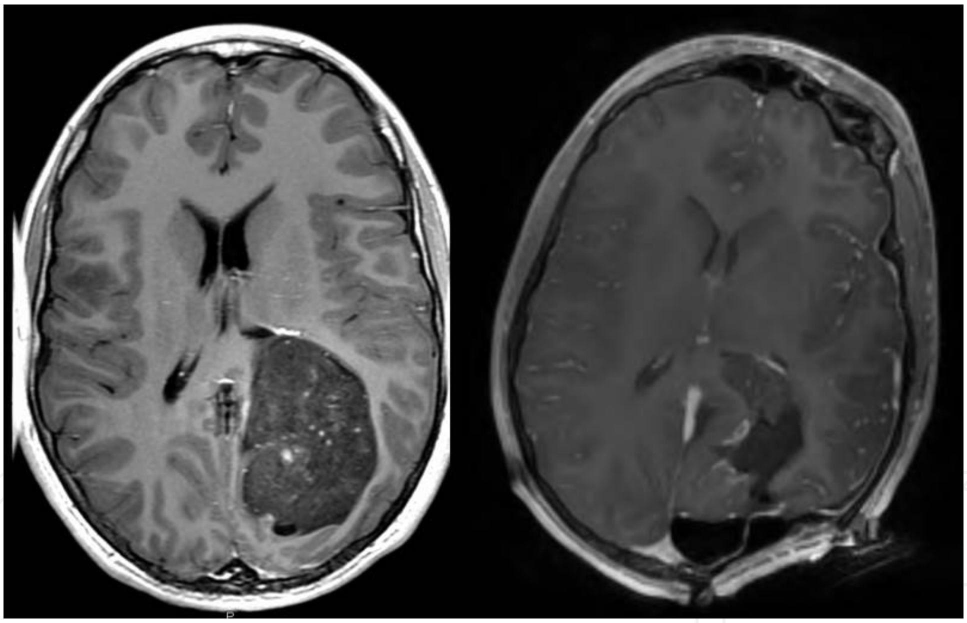

Figure 3. Axial T1-weighted preoperative and intraoperative scans showing low-grade non-enhancing tumor with residual tumor positioned next to atrium on intraoperative scan, that was subsequently resected.

6. Methods to increase extent of resection

Despite the growing body of evidence leaning towards significant survival advantage in both low and high grade gliomas, complete resection is often only obtained between 17-47% of cases

[1,27-33]. Numerous intraoperative adjuncts have been trialed to help increase the EOR in these procedures. Intraoperative frameless navigation is a mainstay in most North American Brain Tumor Centers. This technology which is based on a preoperatively obtained imaging set has been shown to be ineffective in increasing the EOR in a prospective randomized trial [34]. Upon opening the dura and proceeding with CSF drainage and tumor resection considerable brain shift can occur which makes the information obtained from preoperative datasets inaccurate (figure 4)[35].

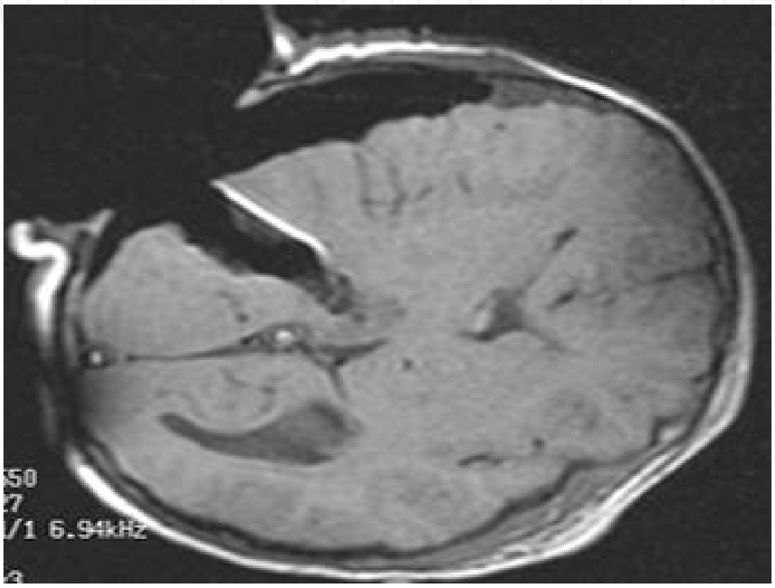

Figure 4. Axial T1 weighted intraoperative MRI scan illustrating the extreme degree of brain shift that can occur with opening the dura, drainage of CSF and tumor resection.

Orringer et al. [27] evaluated patient and tumor characteristics that might effect EOR in GBM patients. Interestingly they found that based on postoperative MRI scans complete resection was obtained in only 17% of cases despite the surgeon's belief that GTR had been obtained based on intraoperative assessments. They also found that larger tumors, lesions touching the ventricles and lesions in or near eloquent cortex were associated with lower extent of resection [27]. Of the 17 cases where complete resection was felt to be possible based on blinded review of two experienced surgeons this was only obtained in four patients (23%)[27]. This study clearly shows that the surgeon's impression alone is not enough to maximize tumor resections for these patients.

6.1. Ultrasound

Ultrasound was introduced as a surgical tool in the 1960s. This technology which typically utilized low frequencies was extremely limited secondary to poor image resolution and cumbersome intraoperative probes. The sensitivity and specificity of findings was limited especially for highlighting small tumor remnants or differentiating tumor from edematous brain. In addition, it was even more difficult to differentiate tumor from surrounding normal brain in low grade gliomas [36,37]. However, newer developments in ultrasound technology; with the use of higher frequency devices, has created a recent resurgence in this technology. New smaller light-weight probes can be placed within a resection cavity and give a much better spatial resolution of surrounding areas. The use of higher frequencies improves image resolution however this has a tradeoff of lower tissue penetration [38]. Serra et al. [38] performed a retrospective review of 22 patients with high grade lesions (mixed pathology) who they felt to be good candidates for gross total resection based on preoperative imaging findings. High frequency intraoperative ultrasound was used for all patients. They found that 21 of the 22 patients had gross total resection of the enhancing lesion on postoperative imaging; however, as the study was retrospective they were unable to determine how many patients underwent additional imaging based on ultrasound findings.

6.2. Fluorescence guided resections

5-aminolevulinic acid (5-ALA) is an orally administered pro-drug which is metabolized intracellularly to protoporphyrin IX which gives off a red-violet fluorescent signal to blue light. This agent preferentially accumulates in certain tumor types and thus can be used to help differentiate tumor from normal surrounding brain tissue [39]. The oral agent is administered 3 hours prior to surgery and then the operative field can be intermittently interrogated for evidence of fluorescence throughout the procedure by switching back and forth between white and blue light on the operative microscope.

Several prospective studies have been performed evaluating the benefits of 5-ALA in patients undergoing surgical resection of high-grade gliomas [39]. Stummer et al [40] performed a phase IIIa prospective study evaluating the impact of this technology on patients with high-grade gliomas. The study was terminated early because interim analysis showed a significant benefit in the study arm. Gross total resection was seen in 65% of patients in the 5-ALA arm vs. 36% in the control group [40]. The utility of this technology only seems beneficial in patients with high-grade lesions as significant accumulation has not been shown to occur in low grade gliomas [41,42].

6.3. Intraoperative MRI

Intraoperative MRI (iMRI) was first used in Boston in the mid 1990's. Since then numerous revisions and variations of the technology have been performed. While significant expansion in the number of centers with this technology has occurred in the past decade, cost is still the limiting factor. The current technology can be divided into two categories based on magnet strength. Low field systems such as the original 0.5 Tesla GE Signa SP (GE Medical Systems, Milwaukee, WI) the 0.12 Tesla Odin Polestar table mounted system (Odin Technologies, Yokneam, Israel); versus high-field systems which consist of 1.5 or 3.0 Tesla magnets. The high-field systems all require cessation of the surgical procedure for imaging. Two subgroups exist in this category. One in which the magnet is moved from a storage facility into the operating theater via an overhead crane system (IMRIS Inc., Winnipeg Canada) and the other in which the patient is moved from the operating theater into an adjacent ferrous free imaging zone (figure 5). This use of this technology allows for intraoperative imaging for evaluation and confirmation of the anticipated surgical results. In addition, it also allows for intraoperative updating of the navigation system to offset the changes that result from tumor resection and brain shift. Each system has its own advantages and tradeoffs in terms of cost, ease of use and image resolution [43].

Figure 5. Various Intraoperative MRI concepts (clockwise from top left: GE Signa SP double doughnut, IMRIS mobile ceiling mounted system (scanner moves to patient), GE hybrid OR concept (inset shows close up of scanner; patient moves to scanner), Odin table mounted system.

I [44] previously reviewed the results for treatment of GBM using the older GE Signa SP system at Norton Healthcare (Louisville, KY) and found that additional surgical resection was performed in 71.4% of cases based on intraoperative imaging results. The average EOR in this patient group was 93.7% and was limited secondary to tumor location and vascular anatomy in cases where EOR was less than 95%. Numerous other authors have shown the value of such systems in increasing EOR [15,16,45-50].

Senft [6] performed a randomized controlled study looking at the utility of iMRI for treatment of gliomas. All patients were felt to be candidates for complete resection based on preoperative imaging findings. Patients were randomized to undergo surgery with conventional microsurgical techniques vs iMRI using the Odin Polestar system. In the study group the use of iMRI led to additional tumor resection in 33% of patients with 96% of patients in the iMRI group obtaining complete resection vs 68% in the control arm. Six month progression free survival was 67% in the iMRI group compared to 36% in the control arm ($p<0.05$).

Roder et al. [51] compared a group of 117 patients treated with iMRI (IMRIS Visius System) vs. a control arm treated with microsurgical techniques plus 5-ALA in some patients. 5-ALA was used in 70% of iMRI patients and 60% of patients in the control arm. Complete tumor resection was seen in 74% of the iMRI group vs 34% for the conventional group. Subgroup analysis of the control group showed that complete resection in the conventional group increased to 45% and mean residual volume decreased for patients who had 5-ALA fluorescence as part of their procedure.

These studies all show a significant advantage for the use of this technology not only for high-grade gliomas as outlined above but also for low-grade gliomas and pituitary tumors [16,43,52-54]. However, despite the use of this technology complete resection is sometimes still not possible. This can be secondary to tumor location in or near eloquent cortex, tumor adjacent to the ventricle or tumor extending into deep or midline structures or associated around major vascular structures[27,35,55,56]. Image interpretation during intraoperative procedures can also lead to its own challenges. Tissue can become distorted and damaged secondary to surgical trauma. This can lead to a disruption of the blood-brain barrier and thus increased contrast enhancement. In addition, blood products and air in the surgical cavity can also distort the imaging findings [35,43,44]. Finally the administration of contrast agents for preoperative navigational studies the morning of surgery can also affect intraoperative imaging results. As a result of these issues we routinely review all intraoperative imaging scans alongside an experienced neuroradiologist in the iMRI control room during all procedures. Intraoperative scans are directly compared to preoperative studies and when necessary any areas of questionable residual tumor are directly investigated after the new dataset is downloaded to the navigation system. Careful review of the imaging findings are necessary as overly aggressive resections can lead to increased risk of new neurological deficits.

7. Awake mapping techniques

Regardless of the surgical techniques used for tumor resection the goal for extensive tumor removal must always be tempered with the potential risk of inducing new or worsened neurological injuries, as the patients postoperative neurological status is strongly correlated with overall outcome. For lesions located in or near motor or speech centers intraoperative mapping via electro-cortical stimulation can effectively identify these eloquent areas.

Newer developments in preoperative imaging such as functional MRI (fMRI) and diffusion tensor imaging based fiber tracking (DTI-FT) can help to grossly localize the location of eloquent cortex and their corresponding deep white matter tracts; however the accuracy of exact localization is more reliably determined with intraoperative cortical and subcortical

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mapping techniques [57-64]. A meta-analysis of over 8000 patients who underwent craniotomy for resection of intracranial glioma showed that patients who underwent intraoperative mapping had a greater than two fold reduction in permanent neurological deficits [65].

Motor mapping can be performed either with the patient awake or under general anesthesia (without muscle paralysis) while speech mapping requires the use of an awake anesthesia technique at least during the mapping portion. Remifentanil and propofol or dexmetomidate infusions are often used for these procedures as they have very short half-lives [17,55]. The use of longer acting narcotics should be minimized as patients can become agitated and uncooperative with the over use of sedatives or narcotics. In addition an extensive local field block of all regional nerves with a combination of a short and long-acting local anesthetic also helps significantly with patient comfort and cooperation [17]. Patient selection is of paramount importance as patients with severe edema, or significant pulmonary or airway issues may not tolerate such a procedure. Time should be taken with the patient preoperatively to address and concerns and thus minimize anxiety as well as to prepare the patient for their involvement for the procedure. Complete details regarding the anesthesia for this technique are available elsewhere [17,55]. I prefer to conduct all of my mapping procedures with an awake technique regardless of whether speech function is being interrogated as having the ability to converse with the patient and readily assess their neurological function is as important as localizing the area of eloquent cortex. I have my anesthesiologist or operating room nurse regularly assess the patients motor function throughout tumor resection, if speech cortex is involved we routinely employ the assistance of a trained speech and language therapist who also assists the patient in carrying on a conversation during tumor resection after mapping and stimulation have been completed.

Mapping is routinely performed using a bipolar stimulation probe with 5 mm spacing between the electrodes. Stimulation is performed at increasing amplitudes until a positive result in encountered or after discharges are seen on electrocorticography or a upper threshold limit is reached. The use of surface EEG is of great importance as it can minimize the risk of generalized seizure activity induced by the stimulation and can verify that the stimulation system in functioning adequately. A constant current generator is used to provide square biphasic wave pulses for 1-4 seconds at 60Hz frequency (figure 6) [17,55,66]. Unlike epilepsy surgery where positive stimulation results are almost always obtained the growing trend among tumor surgeons is to perform smaller more tailored craniotomies for these cases. In these instances negative stimulation results (with appropriate artifact on surface recordings) can be interpreted as absence of eloquent tissue [18]. Most authors recommend keeping a border of at least 0.8-1.0 cm of tissue between resection site and any site showing positive stimulation results [17,18,55,66].

Subcortical stimulation can be performed using the same equipment and settings. The surgeon must frequently alternate between deep white matter tract stimulation and tumor resection. Resection is continued until either positive stimulation results are obtained or complete tumor resection has been achieved. Higher rates of postoperative neurological deficits have been shown in cases where positive motor stimulation is obtained during subcortical mapping, likely secondary to manipulation in close proximity of these pathways [55,67].

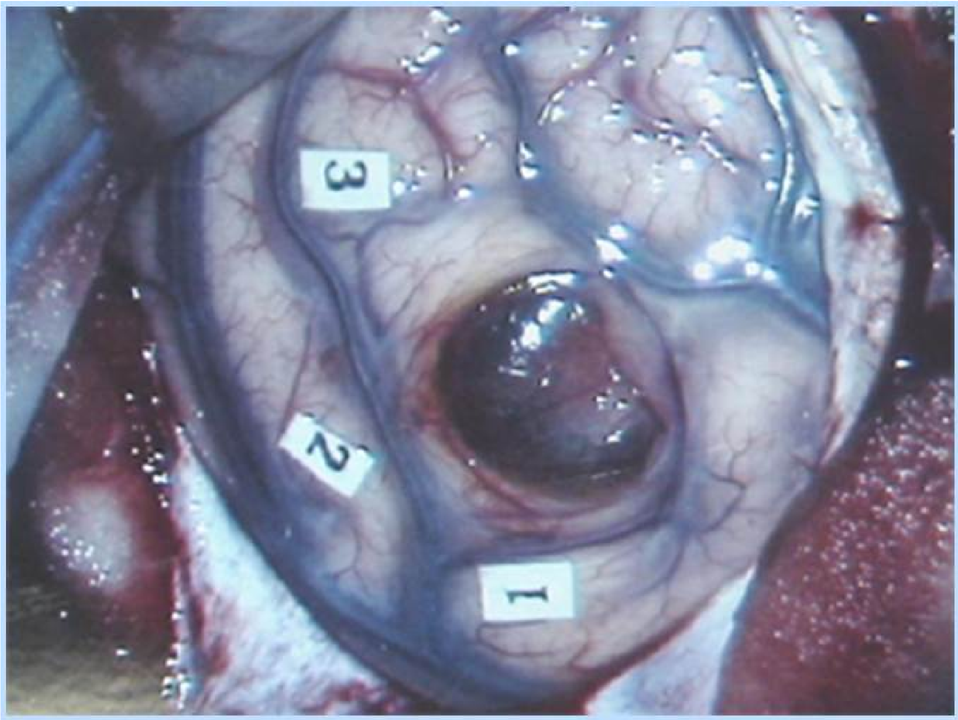

Figure 6. Picture of intraoperative mapping case; #1 corresponds to area of lower extremity stimulation, #2 hand stimulation, #3 face stimulation, lesion is seen just anterior to #2 on surface of the brain.

In appropriately selected patients awake mapping procedures can be performed safely with minimal patient anxiety or discomfort. The information obtained from mapping and intraoperative neurological assessment allows the surgeon to make a well informed decision regarding the safety of continued resection vs. the risk of inducing new neurological deficits (figure 7).

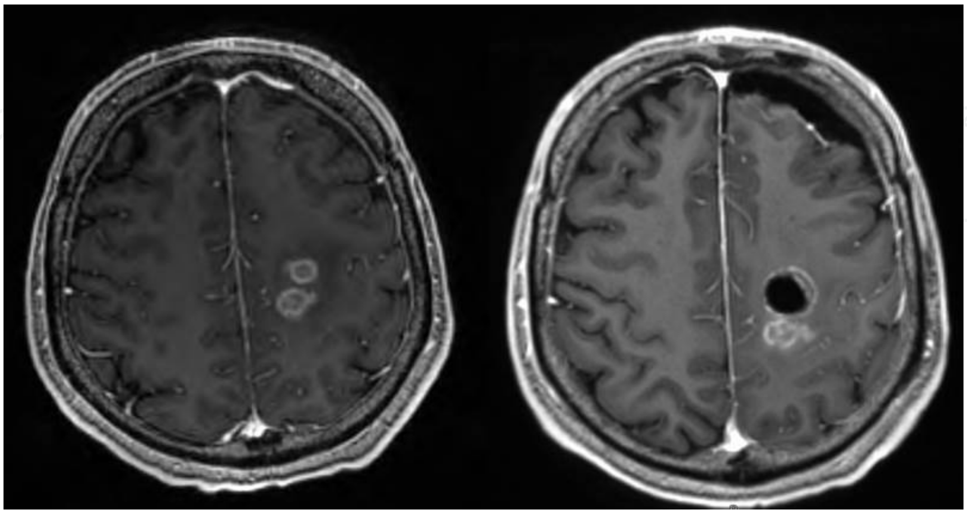

Figure 7. Preoperative and intraoperative axial T1-weighted post contrast scans; subcortical stimulation was positive along the lateral and posterior border of the resection cavity thus a portion of the tumor was not resected.

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8. Conclusion: Combining technologies to obtain maximal safest results

I and several other authors have had experience combining several of these advanced technologies together for the treatment of high risk patients undergoing treatment of intracranial gliomas [44,45,56,68]. Select patients with lesions near or in eloquent cortex can undergo awake mapping procedures with frequent neurological assessment to ensure the absence of generating new neurological deficits. Intraoperative imaging can be performed once maximal tumor resection has been performed to verify that the anticipated results have been obtained (figure 8). If significant residual tumors remains than the surgeon can immediately determine whether further resection is deemed safe and continue with additional tumor removal while constantly assessing the patients function or evaluating subcortical stimulation results. In cases where the patient may be sedated but not intubated than transport of the patient into the scanner does carry additional risks as the anesthesiologist has even more limited access to the patient and their airway during imaging; however, I am unaware of any serious complications as a result of performing iMRI on a mildly sedated non-intubated patient.

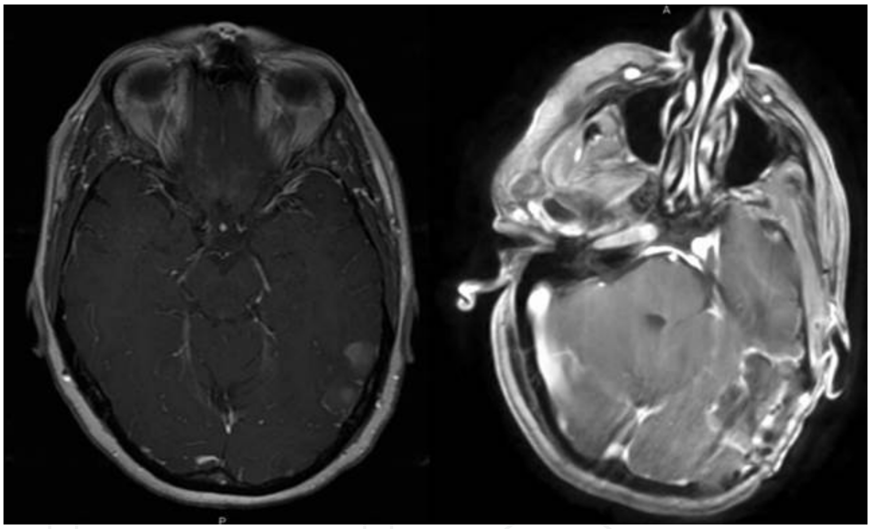

Figure 8. Preoperative and intraoperative axial T1-weighted post contrast images showing complete resection of a posterior left temporal lesion that was removed using an awake mapping technique in the intraoperative MRI.

One of the main drawbacks of the current high-field iMRI systems is the time required for patient transport and scanning. For a majority of our cases we conduct only a single intraoperative scan, typically if any residual tumor exists than further resection is performed based off of updated neuronavigation results. In a minority of cases, typically those with large volumes of residual tumor on the first scan, than a second confirmatory scan is performed. The use of 5-ALA plus iMRI in patients with high-grade gliomas can further decrease the need for additional scans. By maximizing the EOR based on the intraoperative fluorescence findings, there is a higher likelihood of satisfactory results on the first scan, thus eliminating the need for subsequent imaging. Any small or deep areas of residual tumor not appreciated with 5-ALA can be seen on the iMRI images and resected with updated neuronavigation [51].

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