

## The role of intraoperative magnetic resonance imaging in glioma surgery

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### Abstract

For patients with gliomas, the goal of surgery is to maximize the extent of tumor resection while avoiding injury to functional tissue. The hope is to improve patients' survival and maintain the highest quality of life as possible. However, because of the infiltrative nature of gliomas these two goals often oppose each other so a compromise must be met. Many tools have been developed to help with this challenge of glioma surgery. Over the past two decades, intraoperative-magnetic resonance imaging (iMRI) has emerged as an increasingly important modality to enhance surgical safety while providing the surgeon with updated information to guide their resection. Here the authors review the studies that demonstrate a positive correlation between extent of resection (EOR) and overall survival (OS), although the data is clearer in patients with low-grade gliomas (LGG) and still somewhat controversial in those with higher-grade tumors. We will then review some of the studies that support the role of iMRI and how it has impacted glioma surgery by increasing the EOR. The value of iMRI usage in regards to overall patient outcome can be extrapolated through its effect on EOR. Overall, available data support the safe use of iMRI and as an effective adjunct in glioma surgery.

**Key Words:** Extent of resection, high-grade glioma, intraoperative magnetic resonance imaging, low-grade glioma

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### INTRODUCTION

The surgical resection of gliomas has been a challenge since the beginning of modern neurosurgery. Before the development of modern neuroimaging, diagnosing these intrinsic tumors was difficult and usually occurred when the patient developed advanced symptoms. The natural history of these tumors was progressive neurological decline and death, with increased rapidity in higher grades such as WHO grades III and IV. Therefore, the strategy adopted by many was biopsy for histological

diagnosis followed by radiation therapy, and more recently, chemotherapy. Debulking was reserved for those with significant mass effect to prevent early herniation but did not affect their overall survival.

The advent of computed tomography and, later, magnetic resonance imaging (MRI), made it possible to diagnosis intrinsic tumors much more easily and earlier on in the disease process. MRI greatly improved noninvasive detailed visualization of brain structures and its pathological conditions over previous modalities. Surgeons now became increasingly confident to resect more tumor with the

knowledge of the exact location of the tumor and its relation to critical normal structures that may be nearby. This was in hopes of improving EOR while minimizing morbidity from iatrogenic injury to functional areas.

As MRI technology rapidly improved, this modality was adopted for use in the operating room. With the development of iMRI systems, imaging has been brought into the operating room and can be performed at any point during a surgical procedure. The goal is to provide updated images for neuronavigation to correct for brain shift and help guide the resection of gliomas where boundaries between tumor and normal brain can be vague. However, this technology has not been universally adopted because of the high costs of iMRI devices and the learning curve necessary to integrate this into practice without significant increases in operative time. Thus, it may not be clear whether this technology is justified and provides clinically significant benefits from its usage.

Here we review some major studies looking at iMRI and its impact on glioma surgery. There is, more or less, a consensus that more complete resections does delay recurrence and increase survival. Therefore, we will highlight the studies that have looked at how iMRI has affected the EOR. We will also review some of the newer studies that have tried to directly correlate iMRI use and patient outcomes. We feel the evidence is compelling that iMRI is an important tool in glioma surgery.

## DEVELOPMENT OF INTRAOPERATIVE MAGNETIC RESONANCE IMAGING

### Initial design

The first intraoperative MRI (iMRI) unit for neurosurgery was developed at the Brigham and Women's Hospital in collaboration with General Electric (Milwaukee, WI).<sup>[20]</sup> This initial prototype was a low-field unit and featured a 0.5-T magnet in an open “double donut” design.<sup>[27]</sup> This allowed the neurosurgeons to stand between the coils for access to the patient, positioned and fixed inside the scanner. In 1996, Black *et al.* first reported the use of this new technology for brain tumor resection.<sup>[1]</sup> Over a period of 1 year, 60 patients underwent craniotomies, including 49 for gliomas. They demonstrated that iMRI can be safely used during tumor resection and provides useful updated images throughout the operation. In about a third of their cases, intraoperative imaging revealed residual tumor even though gross total resection was thought to have been achieved per surgical judgment.

This initial design did pose some challenges to its users. The space between the coils was 56 cm, limiting surgeon access to the operative field. In addition, the patient position is somewhat fixed and limited inside the tube of the magnet. Finally, a whole new set of MRI compatible equipment had to be made to accommodate being used

inside the magnetic field, such as the instruments, head holder, drill, and operating microscope—even scalpels.<sup>[20]</sup> Despite these limitations, this original design remains the truest concept of iMRI, in which imaging, surgical, and stereotactic spaces are one. And more importantly, this paved the road for future developments in iMRI technology.

### Subsequent models

Newer iMRI designs were then developed in hopes to improve usability, using different compromises from the original concept. Mobile iMRI units were constructed to allow the unit to be moved away from the patient when not in use. Alternatively, other designs were based on fixed iMRI units where the patient would be moved to and from the scanner. These two concepts would allow full access to the patient, matching traditional operative ergonomics. In addition, separating the patient from the iMRI allowed “regular” ferromagnetic instruments to be used. With mobile units, non-MRI compatible instruments could be moved out of the field when the iMRI was brought in. In the case of fixed iMRI units, the operative zone is usually placed outside the 5 Gauss line so that non-MRI compatible instruments are not affected by the magnetic forces.

An early example of the “fixed” design is the Hitachi AIRIS II unit (Hitachi Medical Corp., Tokyo, Japan) first used at the Mayfield Clinic.<sup>[2]</sup> Basically, this was a “twin OR design” that consisted of a 0.3-T unit housed in an iMRI room with an adjacent conventional operating room. At any time during surgery, the patient in the conventional room can be moved through a sterile corridor to the iMRI room for scanning. If additional resection was needed, it could be done in either room. The Mayfield Clinic group showed that patient movement did not compromise patient safety or surgical sterility.

### Ultra-compact low-field model

Another unique design was an ultra-compact iMRI unit, the PoleStar (Odin, Israel/Medtronic, Louisville, USA). This was a 0.12-T unit designed to fit underneath the head of the patient's bed. The magnet gantry can be raised intraoperatively up to the patient's head for a scan.<sup>[6]</sup> This unit was designed with the ideal concept in mind.—that is, the goal was to unite the operative space, imaging space, and stereotactic space as much as possible. The compact design of the PoleStar allows for full surgeon access to the operative field. Also, the receiving coils can be draped out of the sterile field, remaining in position from before surgery throughout the procedure. It requires no patient movement to the iMRI, let alone to a different room. This eliminates the need to undrape and redrape patients, as is typically needed when the iMRI is housed out of the OR itself. Finally, the PoleStar allows for real-time imaging and guidance during stereotactic procedures.<sup>[6]</sup> Despite the low strength of the magnet,

it provides adequate images most of the time.<sup>[29]</sup> Still, this unit's major drawback is the low magnet strength, which prevents the acquisition of diagnostic quality images, or of obtaining "advanced" sequences such as for angiography, spectroscopy, or diffusion weighting as will be described later.

### High-field units

1.5-T high-field iMRI units have been developed to maintain the quality of images while decreasing susceptibility to radiofrequency interference. Contrary to previous low-field designs that were meant for the iMRI to adapt to an operating room, these systems were meant to utilize "off the shelf" MRI units and integrate a sterile operating room into a MRI suite. These designs include immobile units such as the Philips Gyroscan (Philips Medical Systems, Best, The Netherlands),<sup>[8]</sup> the Siemens Magnetom (Siemens AG, Erlangen, Germany),<sup>[34]</sup> and the mobile IMRIS (Magnex Scientific, Abingdon, Oxon, UK) iMRI.<sup>[37]</sup> The first two systems utilize a moving operating room bed that moves into the magnet while the latter places the iMRI on a ceiling mounted track to allow the magnet to move to the patient. Although such systems come at higher costs, these high-field units do provide diagnostic image quality and the ability to acquire the advanced sequences noted above.

Ultra high-field 3-T MRI units have also been adopted for use in the operating room. Hall *et al.* at the University of Minnesota were the first to describe their experience with 3T iMRI in neurosurgery. They performed one craniopharyngioma drainage and reservoir placement, five brain biopsies, and two craniotomies in their Intera fixed 3.0-T unit (Philips Medical Systems, Best, the Netherlands). They successfully achieved their goals in all 8 cases and concluded that ultra-high field iMRI is just as safe as their 1.5-T experience.<sup>[7]</sup>

Recently, Pamir *et al.* reported their series of using 3-T iMRI in LGG surgery, their results will be discussed later on. Their system is a "twin-room" design; the operating room is adjacent to the iMRI room, which houses a fixed 3-T Siemens Magnetom Trio unit (Siemens AG, Erlangen, Germany). The patient is sterilely transported between rooms using a specially designed "floating" table. When the iMRI is not in use in surgery, it is used for outpatient diagnostic imaging through a separate entrance. Thus, its usage as an iMRI and a diagnostic MRI helped justify their high cost system.<sup>[22]</sup>

## DOES EXTENT OF RESECTION AFFECT OUTCOME IN PATIENTS WITH GLIOMAS?

Many factors in glioma surgery can make a complete resection difficult. Both LGGs and high-grade gliomas (HGGs) are infiltrating tumors that do not have distinct borders. At the periphery it can be difficult to distinguish

between tumor and normal brain making surgical injury a risk if the tumor involves functional areas. Thus, as the surgeon gets closer to the perceived edge, this uncertainty may be approached conservatively and tumor may be left behind to avoid injury. The question is does pushing the EOR to its maximum, which may increase chances of new neurological deficits, have any long-term benefits? Can a gross total resection (GTR) change the natural history of the disease process? To answer these questions, we look at the literature on gliomas and consider LGGs and HGGs separately because of their different natural histories.

### Extent of resection on low-grade gliomas

From the 1970s through the 1990s, there were many small series by various groups who published their data on the surgical treatment of LGG patients. Conclusions varied greatly, thus at this time there was at best class III evidence on the management of this entity.<sup>[3,12]</sup> Keles *et al.* from the UCSF group published a review of the studies looking at the prognostic effect of EOR on outcome during this time period. They included only the adult studies with statistical analysis included, hoping to be able to infer what the most beneficial treatment is for these patients. They did notice a trend in the literature over time that shifted with more articles being published favoring extensive resection. After narrowing the literature down according to their criteria, their main conclusion from five studies was that there was increasing evidence favoring extensive resection in LGGs.<sup>[12]</sup>

In 2008, the UCSF group published their own large series of LGG patients, management and outcomes. They retrospectively reviewed 216 patients who had primary resections of hemispheric LGGs. Their purpose was to correlate EOR with long-term outcome. They were able to show that in patients who had achieved at least 90% EOR by volumetric analysis, OS increased as compared to <90% EOR. Five and 8-year OS was increased by 21% and 31%, respectively, when greater than 90% EOR was achieved. Also, after adjusting for other factors, such as age, Karnofsky Performance Score (KPS), tumor subtype, and location, EOR was a statistically significant predictor of OS.<sup>[33]</sup> This was the first recent study that gave strong evidence in favor of maximal EOR to improve survival in patients with LGGs.

That same year, McGirt *et al.* from Johns Hopkins looked at their own series of LGGs as well. In their study, they analyzed 132 patients who underwent primary resections of LGGs. They qualitatively grouped the EOR into GTR, near total resection (NTR), and subtotal resection (STR). Their results showed a statistically significant advantage of GTR versus STR. The 10-year median OS for GTR, NTR, and STR was 76, 57, and 49%, respectively. They also looked at median time to tumor progression for GTR, NTR, and STR which was 7.0, 4.0, and 3.5 years,

respectively. Hence this study also provided strong evidence for maximizing EOR in patients with LGGs.<sup>[18]</sup>

### Extent of resection in high-grade gliomas

The Radiation Therapy Oncology Group in 1993 published a large series of patients with glioblastoma to find prognostic factors in their survival. One of the factors they looked at is EOR by comparing biopsy only, partial resection, and total resection. From their analysis of 645 patients, they found that total resection yielded a median survival of 11.3 months as compared to 6.6 months in the biopsy only group. Even partial resection yielded 10.4-month median survival. This large-scale study proved that resection had a significantly beneficial effect even for glioblastomas.<sup>[32]</sup>

Another large qualitative study to answer this question was published by McGirt *et al.* from the Johns Hopkins group. They retrospectively reviewed 946 cases, of which 549 were primary resections and 400 were revision resections. They categorized the EOR into three qualitative categories: gross total resections, NTR, and STR. They found that in primary resections of GBM, the median survival for GTR, NTR, and STR was 13, 11, and 8 months, respectively. They even found statistical difference in revision resections which showed median survival for GTR, NTR, and STR of 11, 9, and 5 months, respectively.<sup>[19]</sup>

To address this question quantitatively, Lacroix *et al.* from the M.D. Anderson Cancer Center performed an analysis of their experience with patients with glioblastoma. They performed univariate and multivariate analyses to determine prognostic factors in this group of patients. Their results showed that a resection of 98% or more of a patient's tumor yielded a significant increase in survival. A resection greater than 98% was an independent prognostic variable associated with longer survival in all groups through multivariate analysis. Median survival was 13 months, as compared to 8.8 months in those who did not achieve a 98% EOR.<sup>[16]</sup>

Sanai *et al.* from UCSF recently performed a retrospective analysis of 500 newly diagnosed glioblastoma patients looking at EOR on survival. They performed volumetric manual segmentation to assess varying EORs. Their results showed that resection of greater than 78% can lengthen survival and the effect continues to increase as EOR increases. After multivariate analysis and recursive partitioning analyses, EOR greater or equal to 95% made the strongest significance in predicting survival, throughout all groups. The median survival equalled 14.5 months.<sup>[26]</sup> This was also validated in earlier studies by the same UCSF group specifically looking at anaplastic astrocytomas. In this group of patients, it was also shown that the volume of residual disease and the volume of residual contrast enhancing tumor were predictive of time to progression and OS, respectively.<sup>[11]</sup>

Finally, even analysis of specific subgroups of patients has yielded similar results. Many surgeons may be less than enthusiastic about glioma resections in the elderly because of the perception that this subgroup has increased surgical morbidity and mortality. Ewelt *et al.* from Germany posed an interesting question. They retrospectively analyzed 103 glioma patients that were greater than 65 years of age to see if EOR affects outcome in this specific population.<sup>[4]</sup> They split this population into three groups: biopsy alone, partial resection, and complete resection. They found that both PFS and OS increased with greater EOR. Median OS was 2.2 m, 7.0 m, and 13.9 m in biopsy alone, partial resection, and complete resection groups, respectively. Thus, a strong direct association between EOR and median survival is seen even in the elderly.

Therefore, it is evident that there has been a paradigm shift over the last 20 years. The recent data regarding management of patients with low-grade gliomas support maximizing EOR, which decreases the time to malignant transformation, lengthens progression-free survival (PFS), and improves OS. With respect to HGGs, the growing literature also supports safe maximal resection as well in order to increase survival.<sup>[25]</sup>

### DOES IMRI AFFECT EXTENT OF RESECTION IN PATIENTS WITH GLIOMAS?

Stereotactic frameless neuronavigation is often used to assist surgical planning in glioma surgery. It can be used to help define the location of the tumor and identify anatomic landmarks indicative of functional areas. However, surgical navigation that relies only on pre-operative images can also pose a challenge to the surgeon. As tumor is resected, brain shift inevitably occurs, thereby rendering "conventional" navigation inaccurate. This is especially magnified with deformation from retraction, effects of gravity, and loss of cerebrospinal fluid.<sup>[24]</sup> These factors can make it difficult to ascertain the extent of resection even for the most experienced surgeons. The ability to update navigation based on intraoperative images should be one of the key features of any iMRI system.<sup>[1]</sup> In addition, of course, iMRI provides lesion resection control as well as the opportunity to visualize an intracranial hematoma or other such complication before the patient has left the operating room. For the purposes of this discussion of the impact of iMRI on the management of patients with gliomas, the resection control feature probably is the most relevant. The validity of this feature has been tested and analyzed since the beginning of iMRI use by looking at data such as need for further resection after intraoperative imaging, EOR, and GTR rates.

One of the earliest studies assessing iMRI was by Knauth *et al.* from the University of Heidelberg. They looked at

38 patients who underwent 41 surgeries for resection of HGG. Every patient underwent a scan with their low-field 0.2-T iMRI when the surgeons felt they had a complete resection. They found only 36.6% of their cases showed no residual enhancement on the iMRI scan. The rest of the patients needed and underwent continued resection. Early post-operative MRI showed no enhancement in 75.6% of patients. This was a statistically significant finding, which implied that the GTR rate increased from 36.6 to 75.6% with the use of iMRI.<sup>[14]</sup>

Around the same time, Bohinski *et al.* from Mayfield Clinic reported their experience with iMRI-guided surgery of patients with gliomas. Procedures were done in a low-field 0.3-T iMRI. With respect to LGGs, they found that in 4/10 patients iMRI detected residual tumor, 3 of which went on to GTR.<sup>[2]</sup> In their HGG group of 30 patients, 16 patients had iMRI scans that revealed residual, resectable tumor. Out of those, 12 went on to achieve GTR. So for this group, iMRI increased the GTR rate from 47 to 70%. Combining all patients, they conclude that 47% achieved the surgical goal as assessed with iMRI and 53% showed residual tumor that led to additional resection. Postoperative MRI confirmed that all had achieved the desired final EOR.

A study utilizing high-field iMRI was conducted by Hatiboglu *et al.* from the M.D. Anderson Cancer Center. This was a prospective study aimed to address EOR specifically. They reported 44 craniotomies for patients with glioma. The surgical team performed volumetric analysis by manual segmentation to quantify the degree that 1.5-T iMRI increases EOR in glioma surgery. A unique aspect of this study is that during the intraoperative scan, the surgeons filled out a questionnaire about their perceived EOR and their impression as to whether they had achieved their surgical goal. This was in attempt to correct for any bias towards early intraoperative scanning that may skew the statistics. They found that 47% underwent additional resection after review of iMRI scans. In patients with enhancing tumor, median EOR increased from 84 to 99% after the use of iMRI. In those with nonenhancing lesions, the median EOR increased from 63 to 80%, although this was not statistically significant due to small sample size. The overall median EOR for all comers increased from 76 to 96% after iMRI use. Finally, 52% of all patients who had gross total resections were because of additional resection after iMRI scanning.<sup>[9]</sup> This study is one of the few to attempt to quantify the effect of iMRI on EOR using volumetry by manual segmentation, whereas most previous studies are based on post-operative qualitative interpretation.

Pamir *et al.* describe their experience with LGGs utilizing 3 T iMRI. Over the course of 3 years, they performed 56 LGG resections with iMRI. After the first intraoperative

scan, 37.5% of cases had unexpected residual tumor. Almost half of these, 47.6%, patients were able to achieve a GTR after additional resection. Thus, the use of their 3-T iMRI increased GTR's from 31 patients to 41 patients, corresponding to a 17.9% increase.<sup>[22]</sup>

There may be some doubt that ultra-low field iMRI has the resolution to affect glioma surgery the same way higher field units can. In fact, the only randomized, controlled trial of iMRI-assisted vs. conventional surgery for contrast enhancing gliomas was recently published by Senft *et al.*, who worked with the 0.15-T iMRI. This is perhaps the strongest evidence to date demonstrating an advantage of using iMRI. After a screening and exclusion process, they had 24 patients randomized to iMRI group and 25 patients in the conventional surgery group. Analysis of their data revealed that 96% of the iMRI group achieved GTR while only 68% in the conventional group. They were also able to demonstrate that GTR lengthened PFS to statistical significance. It increased from 98 days to 226 days in incomplete resection vs. complete resection, respectively.<sup>[30,31]</sup>

A retrospective analysis of the senior author's experience was done comparing the EOR of low- and HGGs in patients who had surgery with or without iMRI using the 0.15-T PoleStar N-20 (Medtronic, Louisville, USA). Volumetric analysis was done on images acquire before, during, and after surgery. In patients with high-grade tumors there was a trend (37% vs. 12%,  $P = 0.08$ ) for a higher likelihood of GTR when iMRI was used. In the low-grade glioma group, iMRI-guided surgery led to a mean EOR of 93%, as opposed to 79% in the non-iMRI group ( $P = 0.035$ ).<sup>[28]</sup>

A systematic review based on 12 published studies was done by Kubben *et al.* looking at the effect of iMRI on EOR, quality of life, and/or survival.<sup>[15]</sup> These studies all showed that iMRI added some benefit either in the form of GTR rate, EOR, or median survival. They concluded that the 12 studies provide at best level 2 evidence that iMRI is effective in increasing EOR, enhancing quality of life, and prolongs OS. However, the authors did note the limitations in the current literature regarding these questions. There is a lack of consensus on how EOR is best measured. In the studies that use qualitative categorization of EOR, the definitions vary from study to study. Even in reports that used quantitative volumetric manual segmentation, there could be inter-observer variances during the segmentation process. Finally, the majority of the studies are retrospective cohort studies. Randomized, prospective studies such as that noted above by Senft *et al.*<sup>[30,31]</sup> would provide the best evidence of the benefits of iMRI-guided surgery.

Despite these limitations in the literature, there is growing evidence that iMRI is effective in increasing EOR and maximizing GTR rates. Numerous groups using

various commercially available iMRI units of different magnet strengths have showed this benefit.

## IMRI INTEGRATION WITH OTHER SURGICAL TECHNIQUES

iMRI like other surgical tools in the end, is just a tool and must be tempered by surgical judgment. There are many techniques in the tumor surgeon's armamentarium to gather as much information to make the surgery safer. With iMRI being only one of these tools, it is imperative that these techniques be seamlessly integrated. As iMRI experience grows, groups have begun to study the combinations of the various established methods to answer this question.

### Intraoperative neurophysiology

A standard method of monitoring functional cortex is intraoperative cortical mapping. Using cortical strip electrodes to measure somatosensory-evoked potentials (SSEP), phase reversal can be recorded to locate the central sulcus and thus the primary motor and sensory cortices. Direct cortical and subcortical stimulation also can be done to ensure integrity of the corticospinal pathway.<sup>[13]</sup> Hatiboglu *et al.* describe their experience with 38 patients who underwent intraoperative monitoring in conjunction with iMRI during glioma surgery.<sup>[10]</sup> They reported successful recording of SSEPs in 90% and direct stimulation in 45% of their patients. Median EOR was 97% for this study group. Persistent deficits remained more than 6 months in 8% of patients, which is in line with other published rates where iMRI is not used.<sup>[7]</sup> They concluded that intraoperative cortical mapping and its equipment can be safely used in the iMRI environment and can aid in minimizing permanent postoperative deficits.

### Awake cortical mapping

For tumors that involve areas of the brain needed for language, the best means of monitoring function during intra-axial surgery remains awake cortical language mapping.<sup>[21]</sup> MR images only provide anatomic information and functional MRI can be misleading especially when there is vascular dysregulation from tumor mass or edema. Awake cortical mapping provides direct functional information of a specific brain region of interest. However, combining an awake craniotomy in an iMRI suite can be challenging. Patient comfort, appropriate sterile draping and re-draping, and airway access are some of the problems that may compromise overall safety.

Parney *et al.* from the Mayo Clinic describe a case where they combined awake language mapping and iMRI for the resection of an anaplastic astrocytoma.<sup>[23]</sup> This patient's preoperative functional MRI (fMRI) revealed bilateral frontal and temporal lobe activation for speech. Therefore

it was not clear based on the fMRI where the speech center was located. As a result the patient underwent an awake craniotomy for language mapping in their iMRI suite. Awake cortical mapping revealed a single, critical area for speech. With this knowledge, they performed an appropriate anterior lobectomy. Because of brain shift, their neuronavigation became inaccurate and thus they needed to rescan. They were able to visualize the residual tumor and re-register their neuronavigation. At the end, they achieved a 90% resection and the patient remained neurologically intact.

Leuthardt *et al.* described their experience with a series of 12 patients who underwent combined awake cortical mapping and iMRI with their 1.5-T IMRIS system (Magnex Scientific, Abingdon, Oxon, UK) for glioma surgery. After successful cortical mapping, intraoperative imaging revealed residual tumor in 11 of the 12 patients. Six of those patients underwent additional resection to achieve gross or near total resections. The remaining 5 patients did not have further resection because of eloquence in the residual tumor.<sup>[17]</sup>

Weingarten *et al.* from the National Institutes of Health described their 10 patients who underwent awake cortical mapping and iMRI with their 1.5-T unit.<sup>[39]</sup> After awake mapping and resection, iMRI scan was performed to assess for residual tumor. Nine cases revealed residual tumor, and 2 of these 9 were deemed unsafe for continued resection due to mapping results. The remaining 7 underwent continued resection. Six of these 7 achieved a GTR and the one could achieve GTR due to mapping results. Overall, they achieved a 70% GTR rate. Three patients had temporary new postoperative deficits, but all resolved with steroids. Their series illustrate nicely how both techniques allowed them to perform a maximal EOR while avoiding injury utilizing mapping data.

These three reports illustrate how awake cortical mapping can be seamlessly integrated with iMRI technology to enhance surgery of tumors in eloquent areas. More importantly, the patients were reported to have tolerated this combined surgery well.

### Stereotactic neuronavigation with tractography and subcortical stimulation

Another example of the merits of high-field iMRI which can provide more sophisticated data includes the work from M.D. Anderson Cancer Center combining three tools: iMRI tractography, neuronavigation, and subcortical stimulation. Gasco *et al.* report a case where they used intraoperative tractography, obtained from their 1.5-T iMRI, and subcortical stimulation to monitor the descending corticospinal tracts.<sup>[5]</sup> A monopolar probe was registered with their BrainSuite frameless neuronavigation system (BrainLAB, Heimstetten, Germany) to allow using the probe for navigation while simultaneously performing subcortical stimulation. The functional images for

navigation can be updated and monopolar probe re-registered after intraoperative scanning. Using the combination of iMRI functional data, neuronavigation, and electrophysiologic data, they were able to achieve a GTR in their patient with a peri-rolandic GBM.

### 5-Aminolevulinic acid-induced fluorescence

Another tool becoming increasingly utilized for HGG resection is 5-aminolevulinic acid (5-ALA) (Cosmo Bio Co, Ltd, Tokyo, Japan) induced fluorescence. The basis for this technique is that malignant tissue synthesizes and accumulates fluorescent porphyrins after administration of 5-ALA.<sup>[36]</sup> By using violet-blue excitation, the fluorescence can be selectively seen with an operating microscope fitted with the appropriate filter. This fluorescence visualization is then used to guide malignant tumor resection. This technique was validated in a phase III clinical trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC). Patients with malignant gliomas were randomized to conventional white light surgical resection and 5-ALA induced fluorescence-guided surgery. They demonstrated that the rate of achieving GTR increased from 36% to 65% when using 5-ALA induced fluorescence.<sup>[35]</sup> They also looked at 6 month PFS between the two groups. Their results yielded 41% vs. 21% PFS at 6 months in the 5-ALA group and white light group, respectively. So the EORTC concluded that the use of 5-ALA is safe, increases rates of GTR and prolongs PFS.

One study coming from Tokai University in Japan looked at combining the use of iMRI and 5-ALA as surgical adjuncts. Tsugu *et al.* retrospectively compared results from 4 groups: resection of 5-ALA fluorescence-positive gliomas with and without iMRI and resection of 5-ALA fluorescence negative gliomas with and without iMRI.<sup>[38]</sup> Their results yielded increased GTR rates when iMRI was used, although the increase was very small in 5-ALA positive gliomas. Thus, they concluded that even though 5-ALA is very effective at achieving gross total resections, iMRI can provide additional benefit with regards to satellite lesions or T2 abnormalities where direct visualization of 5-ALA fluorescence is not possible.

## CONCLUSIONS

Although there is no class I, large-scale, prospective randomized trial to fully answer this question, the experience gained over the last 20 years has provided compelling evidence that EOR lengthens time to progression and median survival in both low and HGGs. Therefore, a maximal resection while avoiding neurological injury is the preferred surgical goal in these patients. iMRI has become an increasingly important tool in augmenting surgical judgment in order to help achieve the maximal EOR during tumor surgery. It has been proven to be safe and aids the visualization of occult

residual tumor. Additionally, advanced imaging techniques are available with high-field iMRIs that provide intraoperative data such as fiber tracking and functional images which can increase the safety of surgery. Further experience will help determine if these benefits over low-field iMRIs outweighs the added acquisition time of such data and the increased costs of high-field systems. Finally, iMRI has been shown to be successfully used in conjunction with other important techniques, such as awake cortical mapping and 5-ALA fluorescence guided microsurgery, and will be an important complement to help achieve the highest levels of EOR while minimizing neurologic injury.

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