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Review Article

Surgical Management of Adult Glioma: A Contemporary Approach

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Abstract

Primary intrinsic brain tumors represent a significant cause of morbidity and mortality in the United States. Advancements in preoperative evaluation, intraoperative cortical and subcortical stimulation mapping, and emerging imaging modalities allow for earlier detection of tumors and more aggressive tumor resections while minimizing neurological morbidity. Interestingly, there is no general consensus in the literature regarding the efficacy of extent of glioma resection for improving patient outcome. Despite the lack of class I substantiation, mounting evidence suggests that more extensive surgical resection for glioma is associated with longer progression-free and overall survival for most patient populations. This evidence must be tempered by the requirement to treat each individual patient based on histological diagnosis and treatment goals.

Keywords: Glioma; Extent of resection; Oligodendroglioma; Astrocytoma; Oncology; Glioblastoma; 5-ALA; High-grade glioma; Low-grade glioma; Intraoperative MRI; Cortical stimulation mapping

Abbreviations

5-ALA: 5-Aminolevulinic Acid; DTI: Diffusion Tensor Imaging; EOR: Extent of Resection; fMRI: functional MRI; iMRI: intraoperative MRI; iUS: intraoperative Ultrasound; MRI: Magnetic Resonance Imaging; MRS: Magnetic Resonance Spectroscopy; MSI: Magnetic Source Imaging; RTOG: RPA Radiation Therapy Oncology Group recursive partitioning analysis; WHO: World Health Organization

Introduction

Despite their relative rarity, central nervous system neoplasms represent a significant morbidity and mortality burden in the United States. There were an estimated 23,130 new cases of primary intracranial tumors diagnosed in 2013, which were responsible for 14,080 brain tumor-related deaths [1]. Among patients younger than 20 years of age, brain tumors are the solid tumors found most frequently, and represent the second leading cause of cancer death. In the year 2000, 359,000 people were living with a diagnosis of primary brain tumor in the United States alone [2]. Median survival after diagnosis ranges from 6-8 years for those with low-grade gliomas (World Health Organization (WHO) grade II) and from 12-18 months for those with higher grade tumors (WHO grades III and IV) such as glioblastoma [1]. High-grade gliomas represent more than half of all adult primary intrinsic brain tumors [2].

Surgical resection is the foundation of treatment for most brain tumors [3]. Appropriate surgical intervention ranges from tumor biopsy followed by chemotherapy and radiation, to gross total resection. The most aggressive surgical strategies aim for maximal resection with preservation of neurologic function. Although a fundamental principle of neurosurgical oncology is that improved survival is related to greater tumor resection, this precept must be counterbalanced by the risk of functional deficit after a radical resection [4]. Surgical approach and treatment strategy depend on patient age, tumor location, mass effect, and the preoperative neurologic and medical status of the patient. Emerging innovations aim to improve anatomic, physiologic, and functional understanding of a tumor, its invasive margins and their relationship to surrounding functional areas. Evolving imaging and mapping technologies as well as state-of-the-art intraoperative techniques can maximize Extent of Resection (EOR) while minimizing associated procedure-related morbidity.

There is no class I evidence demonstrating a clear relationship between extent of tumor resection and progression-free and overall survival [5]. Only patient age, performance status, tumor histology, and certain genetic signatures such as IDH mutation and 1p19q deletion have been identified as reliable predictors of patient prognosis [6-9]. Understanding the importance of surgery and the role of EOR is critical for the treatment of both low- and high-grade gliomas.

Extent of resection in glioma surgery

Low-grade glioma: Among tumors of the central nervous system, there are 4 histological grades recognized by the WHO. Grade I tumors have minimal proliferative potential, circumscribed growth, and can be cured following surgical resection alone. Typical examples include pilocytic astrocytoma and subependymal giant cell astrocytoma, which are prevalent predominantly in children and, as such, will not be the primary focus of this article. WHO Grade II lesions include diffuse astrocytoma, pleomorphic xanthoastrocytoma, oligodendroglioma, and mixed oligoastrocytomas. These tumors have low mitotic activity; however, given their infiltrative nature, they have a tendency to recur. WHO grade III neoplasms, such as anaplastic astrocytoma, have histological evidence of anaplasia, increased cellularity, and tissue invasion. Glioblastoma is a WHO grade IV tumor and is the most common primary brain tumor in adults.

Over 20 studies have examined the relationship between EOR,

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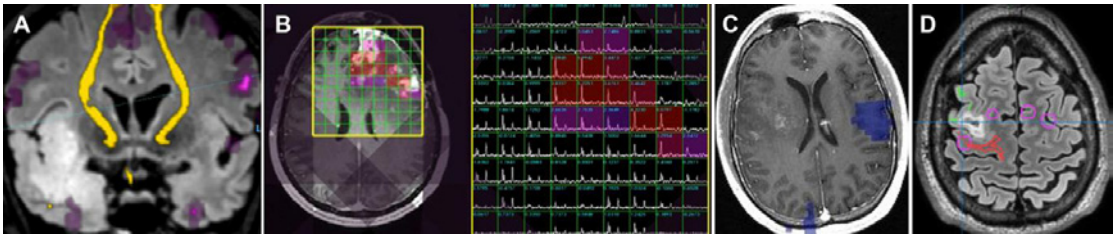

Figure 1: Imaging modalities such as fMRI, MRS, MSI, and DTI provide valuable information for both preoperative and intraoperative use. (A) fMRI reveals language activation sites in purple. (B) MRS identifies choline peaks adjacent to the necrotic core of a glioblastoma. (C) MSI similarly identifies activation of verb generation in blue. (D) DTI identifies corticospinal fibers running posterior and superior to longitudinal fasciculus fibers running lateral to the glioma.

survival, and time to malignant transformation among patients with low-grade glioma [8-27]. Of these studies, 5included volumetric analysis of tumor resection [9,10,13,24,28]. Results from 12 of the non-volumetric studies provided evidence to support EOR as a predictor of 5-year overall survival and 5-year progression-free survival. Three non-volumetric studies did not support EOR as a significant factor related to patient survival; however, these studies examined overall (not progression-free) survival. Four of the 5 volumetric studies for low-grade glioma demonstrated a statistically significant relationship between EOR and 5-year overall and progression-free survival.

One recent analysis of 190 patients with low-grade gliomas identified 91 patients (47.9%) that had greater than 90% of their tumor volume resected according to preoperative imaging [29]. The 5-year overall survival rate among these patients was 93%, compared to 84% for patients with a resected tumor volume between 70-89% [29]. Patients with an initial resection of 70% had a 5-year overall survival rate of 41% [29]. They define ΔVT2T1 as the volumetric difference between the T2- and T1-weighted Magnetic Resonance Images (MRIs) on preoperative tumor imaging [29]. This factor, along with EOR, are found to be the two strongest independent predictors for improving overall survival as well as for delaying tumor progression and malignant transformation in patients with low-grade glioma [29]. Our study employed a volumetric analysis of tumor volumes and further illustrates the positive impact of EOR on patient survival.

Many studies rely on the combined analysis of multiple low-grade glioma subtypes including astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. Though they have a similar natural history, these histological subtypes are distinct with respect to their molecular as well as clinical behaviour. Snyder et al. recently examined 93 patients who underwent surgery for the specific diagnosis of WHO grade II oligodendrogliomas [30]. The median EOR percentage was 85% and they found that EOR was associated with longer overall and progression-free survival [30]. However, greater EOR did not prolong the interval to malignant progression in patients with a 1p19q chromosomal co-deletion [30]. This suggests that while maximal safe resection is influential on clinical outcomes, each individual patient must be managed on a case-by-case basis.

High-grade glioma

Compared to low-grade gliomas, the value of EOR in patients with high-grade gliomas is robust but less dramatic. While it is known that surgery can achieve 10-year survival rates of nearly100% for patients with low-grade gliomas [31], evidence suggests maximal safe resection is an important factor for outcomes in patients with high-grade gliomas, albeit at different thresholds.

Thirty studies investigated the relationship between EOR and tumor progression along with survival in patients with high-grade gliomas [3,5,28,2-57]. Twenty-six studies employed a non-volumetric methodology. Of these, 16 demonstrated evidence that supports EOR as a predictor of both progression-free as well as overall survival. Four studies used volumetric analysis, with2demonstrating a significant survival advantage with greater EOR while 2 studies found no relationship.

A recent study by Chaichana et al. examined the effect of EOR on 259 patients with glioblastoma [58]. Median survival and progression-free survival were 13.4 and 8.9 months, respectively [58]. EOR was independently associated with survival, and the minimum EOR associated with a survival or recurrence benefit was 70% [58]. Furthermore, the maximum residual tumor volume for survival and recurrence advantage after surgery was 5 cm^3 [58].

Preoperative imaging

For decades, MRI has been the gold standard for detecting intracranial tumors. More recent advances in MRI technology, such as Functional MRI (fMRI), Magnetic Resonance Spectroscopy (MRS), Magnetic Source Imaging (MSI), and Diffusion Tensor Imaging (DTI) provide valuable information for preoperative planning (Figure 1). Proton MRS can detect metabolite levels in specific brain voxels and then makes a comparison to normal brain and standard metabolite levels [59]. MRS can provide physiologic as well as anatomic data. It has a diagnostic role in differentiating neoplastic processes versus inflammatory or demyelinating lesions [59]. Furthermore, MRS may separate active tumor versuspost-treatment effect [60]. The data from proton MRS also correlates with histopathologic data from tumor specimens. In 46 glioma patients with WHO tumor grades II-IV, higher choline and lipid peaks on preoperative imaging showed a significant positive correlation with nuclear density and Ki-67 proliferation index [61]. This information may be used to aid surgical decision-making with respect to guiding the surgeon's focus to the areas of most rapid growth within a tumor.

fMRI is another imaging tool that can be supportive in preoperative planning before glioma surgery. fMRI has evolved from initial language lateralization to specific language localization [62]. Additionally, fMRI is able to detect minute changes in tumor blood volume and metabolism coupled with neuronal activity in eloquent cortical regions during physiologic activation [63]. This information supports preoperative cortical and subcortical mapping of sites responsible for language function [64]. However, fMRI does have

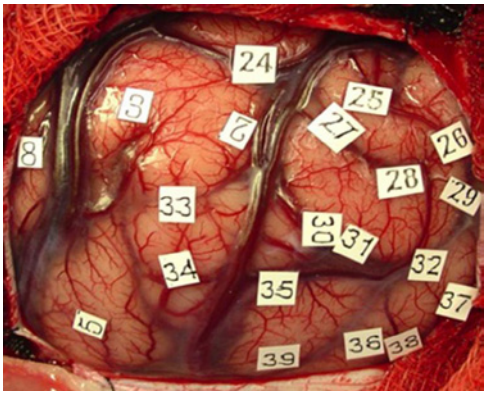

Figure 2: Direct cortical and subcortical stimulation mapping is the gold standard for identification of functional language and sensorimotor areas. Cortical mapping uses numbered markers placed at 1cm intervals for testing regions overlying and directly adjacent to the tumor.

limitations, as shown in a recent meta-analysis highlighting 9 studies of patients in whom fMRI was used as part of the evaluation of tumors in presumed functional cortex [65]. Sensitivities and specificities of fMRI, in comparison with intraoperative electrocortical stimulation as a gold standard, ranged from 59-100% and 0-97%, respectively [65-66]. Additionally, a study of 42 glioma patients who underwent pre-surgical mapping of the primary motor cortex with fMRI, revealed that blood oxygenation level-dependent fMRI signal is strongly related to tumor grade, volume, and distance to the activated focus. It is there for understood that these alterations may impair fMRI sensitivity [67]. MSI, similar to fMRI, combines temporal and spatial data from magneto encephalography with the anatomic specificity of MRI to create a functional map of human language and sensor motor function [68]. fMRI, in combination with anatomic information from conventional MRI, are useful adjuvant to direct stimulation mapping for the identification and preservation of functional areas.

DTI allows the study of white matter anatomy and structural connectivity [69]. In pre-surgical planning, DTI provides useful data about the local effect of a tumor on white matter structures [70]. A number of studies have examined the role of both DTI and fMRI in combination for pre-surgical planning in glioma patients. For instance, 2 recent trials studied the modification of surgical approach based on pre-surgical DTI and fMRI data. The use of this technology changed the surgeon's initial surgical approach in 16-21% of cases [71-72]. These findings are controversial; however, as other studies have found that preoperative DTI influenced surgical approach in only 1of 19 cases [73]. Overall, DTI in addition to fMRI, MSI, and MRS, provides important functional and anatomic data, which are useful during preoperative surgical planning but cannot be relied upon to accurately identify functional areas.

Cortical and Sub Cortical stimulation

Direct cortical stimulation was initially introduced by Horsley and later examined and implemented by Penfield for the identification and preservation of functional sites [74,75]. While language and motor mapping by direct cortical stimulation were originally employed in the context of epilepsy surgery, it has been accepted more recently in brain tumor surgery [76]. Stimulation depolarizes a focal area of cortex, which in turn evokes a response depending on the function

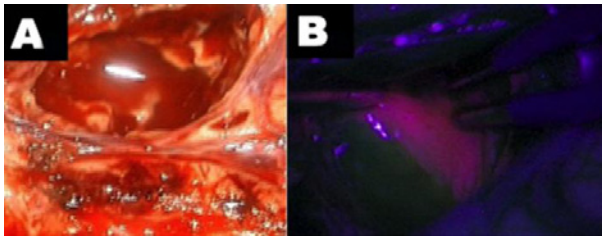

Figure 3: 5-ALA given 2-5 hours before surgery allows intracellular update of fluorescent porphyrins. (A) After corticectomy, white light microscopy. (B) Shows visible tumor, which is confirmed under violet-blue light as pink in color.

of the stimulated region [77]. Initially, large craniotomies were performed, allowing the surgeon to localize multiple "positive" sites that, when stimulated, evoke a language or sensorimotor response [78]. Resection then proceeds accordingly, avoiding these functional areas. Using this technique, wake craniotomies traditionally identify positive language sites in 95-100% of operations [77]. This paradigm is evolving, however, toward the use of smaller craniotomies to expose only the region surrounding the tumor. Cortical regions negative for sensor motor and language function now guide tumor resection.

The bipolar stimulation probes commonly used today have an estimated accuracy of approximately 5-6 mm [79,80]. This allows precise mapping during surgery, smaller craniotomies for tumor resection, and a more time-efficient neurosurgical procedure [78]. Direct cortical stimulation is used to map the cortex, beginning at a stimulus intensity of 1.5mA and increased to a maximum of 6mA. Each bipolar tip is 0.5 mm in diameter and is separated by a distance of 5mm [77]. The probe delivers biphasic pulses in 4-second trains at 60Hz [77]. During mapping, approximately 10-20 stimulation sites are marked with sterile numbers placed 1 cm apart (Figure 2) [77]. Continuous electrocorticography is used throughout the procedure to ensure that any functional changes in language are due to probe stimulation and not by more diffuse subclinical seizure activity [77]. Additionally, subcortical language mapping can be performed along subcortical white matter pathways [81,82]. Once negative sites are identified, resection can proceed safely.

There is significant variability in cortical and subcortical language organization [83-86]. The cerebral cortex and underlying white matter may also be infiltrated and distorted by glioma cells and localized mass effect. Multiple studies have found great individual variability in language sites responsible for speech arrest (Broca's area) between patients [87,88]. While typically the classic boundaries of Broca's area for motor speech are adjacent to face motor cortex, some studies have found boundaries several centimetres from the sylvian fissure [77]. Similarly, the temporal lobe's contribution to the perisylvian network language includes anomia, dysnomia, and alexia sites up to 9cm from the temporal pole [89]. Preoperative functional imaging, in combination with intraoperative cortical and subcortical mapping techniques, are necessary to detect and avoid functional language cortex and pathways during surgery [90]. One must proceed with caution when removing tumor from presumed functional areas, as it has been well-established that functional language and sensorimotor cells are often found within the tumor [91,92]. Even in patients with few neurologic symptoms preoperatively, it cannot be assumed

that a tumor is well-circumscribed and separate from functional pathways. The use of intraoperative stimulation is always necessary to avoid neurologic deficits [90,93]. The challenge in many cases is to maximize tumor resection while simultaneously minimizing risk of injury to vital cortical and subcortical structures.

Intraoperative imaging methods

Intraoperative MRI (iMRI): Intraoperative imaging such as iMRI, fluorescence-guided surgery, and ultrasound are useful adjuvants to direct stimulation mapping. iMRI was first introduced in themid-1980s using magnets with strengths of 0.5 Tesla or less in a double-doughnut system. Higher field strength systems, such as 1.5 to 3 Tesla magnets, now provide improved imaging [94]. The primary rationale for the use of iMRI is to provide anatomic detail and clarity in a dynamic surgical setting in order to mitigate a changing environment during surgery. These changes may include distortion of the brain parenchyma due to loss of cerebrospinal fluid, edema, or surgical manipulation of the tumor, all of which lead to "brain shift" [63]. Intraoperative brain shift changes the interpretation and comparison of neuronavigation when using preoperative images [63]. Therefore, iMRI provides updated anatomical detail during surgery as well as information regarding residual tissue of the indications for which iMRI-guided surgery has shown benefit, intra-axial tumors have produced some of the most striking data [10,95,96].

Several studies have reported added value of iMRI-guided surgery to improve EOR [63,69,97,98]. Most recently, a prospective randomized trial was performed that allocated 58 glioma patients to receive either surgery with iMRI, or conventional neurosurgical resection with neuronavigation. Gross total resection was achieved in 23/24 patients (96%) compared to17/25 patients (68%) in the conventional treatment group [98]. While this study provides level 1 evidence for the use of iMRI, the results suggest a median remaining enhancing tumor volume on postoperative imaging of 0.0 cm^3 in the iMRI group, compared to 0.03 cm^3 in the conventional treatment group [98]. However, there was no difference in progression-free survival between patients treated with the iMRI and conventional surgery using neuronavigation [98]. Whether or not this small difference in residual tumor volume justifies the added expense and intraoperative time is unknown.

A meta-analysis was recently performed to directly address the benefit of iMRI-guided surgery versus traditional neuronavigation for patients with high-grade glioma [63]. This retrospective analysis focused on primary outcome measures such as EOR and overall survival in 12 cohort studies. The authors concluded that the results support level 2 evidence suggesting that iMRI-guided surgery is more effective than conventional neuronavigation in improving EOR, enhancing quality of life, and prolonging survival after resection of glioblastoma [63]. There are a number of limitations to these studies, including heterogeneity with respect to WHO tumor grade and associated prognostic outcome. The meta-analysis did restrict its focus to high-grade gliomas, and it is unknown whether similar conclusions can be assumed when considering EOR with iMRI use in surgery for other tumor types. Another limitation is the assessment of EOR. Within the studies considered inthe meta-analysis, 5 different definitions for gross total resection are employed. Magnet field strength along with other factors related to MR technology may also influence the outcomes of surgery in cases where iMRI is used. Finally, a unique limitation to studying the value of iMRI is the inherent attribution bias associated with how surgeons change operative strategy when iMRI is available [63]. Neurosurgeons may tend to offer a more conservative initial resection, knowing that new and updated imaging information will become available along with the opportunity to continue tumor resection when iMRI is used during glioma surgery.

Aminolevulinic Acid (5-ALA) fluorescence-guided surgery: Fluorescence-guided surgery uses elective intracellular fluorescence to maximize EOR. 5-ALA is the most commonly used fluorescence agent in glioma surgery. 5-ALA is a natural biochemical precursor of hemoglobin that can be administered as a non-fluorescent prodrug [99]. When given, 5-ALA elicits synthesis and accumulation of intracellular fluorescent porphyrins in epithelial cells as well as rapidly dividing cancer cells, including glioma tissue [99]. Porphyrin fluorescence can be visualized with a confocal neurosurgical microscope or with appropriate short wavelength filters (Figure 3) [100].

In a study of 531 patients with intracranial tumors treated by 5-ALA-guided resection or biopsy, the highest percentage of 5-ALA-positive fluorescence was detected in 96% of glioblastomas, 88% of anapaestic gliomas, 40% of low-grade gliomas, and none of the WHO grade I gliomas [101,102]. There are few reported side effects of 5-ALA administration. In a study of 74 patients, the authors described 2 adverse drug reactions that included photo toxicity and generalized edema [103]. The utility of 5-ALA to aid in the visualization of residual tumor cells during resection of low-grade glioma is under investigation.

A recent randomized controlled study examined the use of 5-ALA versus conventional neurosurgical techniques both followed by radiotherapy in 322 glioma patients. Primary outcome measures included absence of contrast-enhancing tumor on postoperative MRI and 6-month progression-free survival on MRI [102]. Secondary endpoints were residual tumor volume, overall survival, neurologic deficits, and toxic effects. Gross total resection was performed in 90/139 patients (65%) assigned to 5-ALA compared to 47/131 patients (36%) treated with conventional surgery [102]. Patients receiving 5-ALA had 41% 6-month progression-free survival compared to 21% in the conventional treatment group [102]. There was no difference in adverse events or overall survival between groups. However, there was an influence of age on the degree of resection, confounding interpretation of the effect of EOR on survival. To clarify the issue, a Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) was performed to investigate the influence of pretreatment prognostic factors on EOR [104]. A total of 243 patients from the original 5-ALA study were re-stratified. Patients were allocated into RTOG-RPA classes based on Karnofsky Performance Scale score, age, neurologic condition, and mental status. These results demonstrated that patients with gross total resections had significantly longer survival times in RTOG-RPA classes IV and V, but not in RTOG-RPA class III patients, suggesting that the use of 5-ALA and its impact on EOR directly leads to increased overall survival in glioma patients.

The most recent study investigating the efficacy of 5-ALA

in glioma surgery is a retrospective analysis of 251 patients that underwent surgery with or without 5-ALA [105]. Gross total resection and progression-free survival at 6 months was significantly higher in patients treated with 5-ALA [105]. The complete resection rates in this study were 67% versus 45%, compared to 65% versus 36% in the original study by Stummer et al. [102,105]. Six-month progression-free survival was higher for both groups in this study (69% with 5-ALA and 48% without 5-ALA) compared to the Stummer et al. study (41% with 5-ALA and 21% without 5-ALA) [102,105]. Cumulative published data highlight the importance of fluorescence-guided surgery using 5-ALA for glioma resection. Long-term patient outcomes and the impact of fluorescence-guided surgery in patients with low-grade gliomas warrant further study.

Intraoperative ultrasound

Intraoperative Ultrasound (iUS) was first introduced to neurosurgery in the 1960s and has recently become more popular as an intraoperative adjunct for glioma surgery [106]. Image quality has improved with recent technologic advancements [107-109]. The utility of iUS in detecting intracranial tumors and guiding resection is now well-established [110-112]. However, limitations still exist including low sensitivity and specificity in detecting small and superficial tumor remnants [113]. It may also be difficult to distinguish tissue edema from tumor, particularly in low-grade gliomas [114]. Blood products may also obscure imaging. Higher frequency phased array ultrasound probes have improved radial and lateral resolution to approximately 0.5 mm and 1.0 mm, respectively [106]. Neuronavigation-based ultrasound techniques have made 3D image capture possible. In a retrospective analysis of 22 patients with high-grade gliomas, high-frequency ultrasound was used to image the resection cavity intraoperatively after tumor bulking [114]. Gross total resection was achieved in 21 patients (95.5%) on postoperative MRI [114]. The primary advantages of iUS include lower costs compared to iMRI or 5-ALA. iUS is more time-efficient than iMRI and requires no drug pre treatment as with 5-ALA. The primary disadvantage of iUS includes operator-dependent results [114]. Additional studies are needed to compare the efficacy of its use compared to other treatment modalities.

Conclusion

It is well-established in neurosurgical oncology that greater EOR correlates with improved patient outcomes in glioma patients. The degree to which this principle is true depends on many factors including tumor histology, genetics, and patient characteristics. In order to provide safe and effective treatment, a neurosurgeon must be able to synthesize clinical information and make decisions based on a risk-benefit spectrum that is unique to each patient. Emerging imaging technologies and advancements in intraoperative techniques continue to allow maximal tumor resections and improve surgical safety for glioma patients.

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