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Review Article

The Ethical Dilemma in the Surgical Management of Low Grade Gliomas According to the Variable Availability of Resources and Surgeon Experience

Abstract

Low grade gliomas (LGGs) affect young individuals in the prime of life. Management may alternatively include biopsy and observation or surgical resection. Recent evidence strongly favors maximal and supramaximal resection of LGGs in optimizing survival metrics. Awake craniotomy with cortical mapping and electrical stimulation along with other preoperative and intraoperative surgical adjuncts, including intraoperative magnetic resonance and diffusion tensor imaging, facilitates maximization of resection and eschews precipitating neurological deficits. Intraoperative imaging permits additional resection of identified residual to be completed within the same surgical session, improving extent of resection and consequently progression free and overall survival. These resources are available in only a few centers throughout the United States, raising an ethical dilemma as to where patients harboring LGGs should most appropriately be treated.

Keywords: *Gliomas, intraoperative, magnetic resonance imaging, neuronavigation, supratotal resection, surgeon experience, survival, technology*

Marshall Norman Lahiff[1,2], Michael George Zaki Ghali[3,4]

[1]School of Law, University of Miami, [2]Walton Lantaff Schoreder and Carson LLP, Miami, Florida, [3]Department of Neurological Surgery, Houston Methodist Hospital, Houston, Texas, [4]Department of Neurobiology and Anatomy, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA

Introduction

Approximately 1600 cases of low grade gliomas (LGGs) are diagnosed annually in the pediatric population and 5000 cases in adults.[1,2] The natural history of LGG follows a course that is ultimately fatal with mean age at diagnosis of approximately 41 years.[3] This age is often the most productive part of life, often with a spouse and children involved. Therefore, treatment decisions are extremely important, since outcomes critically impact on the patient's quality of life[4-6] and poor decisions could putatively have significant ramifications to the individual and family. We will thus perform a thorough review of the literature in order to evaluate the argument that patients harboring LGGs should receive multidisciplinary treatment at centers capable of providing all the surgical adjunctive resources facilitating preoperative and intraoperative determination of tumor structure properties,[7-19] relationship to eloquent cortical structures[20-23] and white matter tracts,[24-27] and completeness of extirpation, in order to safely maximize the extent of resection.[6,28-44] If this is true, it should pose an ethical dilemma regarding where, and by which surgeon, the operation is most appropriately performed.[45]

Supratotal and Maximal Safe Resection of Low Grade Gliomas

The optimal treatment of LGGs remains controversial and the most appropriate management of these tumors is not entirely clear, though a plethora of studies have made significant strides and efforts in order to precisely elucidate ideal therapeutic strategies.[1,2,5,25,29,31-34,36,38,40,41,43,46-58] For symptomatic LGGs in noneloquent parenchyma, there is general agreement that an aggressive resection proves ideal,[4,6,28,35,37,38,41,43,44] but for lesions that are asymptomatic, slow-growing, and/or located in eloquent cortex, the optimal management strategy remains disputed, with conservative[58] or surgical therapy[1,4,5,45,47,49] alternatively appropriate. Multiple therapeutic paradigms exist in order to effectively manage these lesions,[47] including observation (clinical and imaging

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Address for correspondence:
Prof. Michael George Zaki Ghali,
Department of Neurosurgery Surgery, Houston Methodist Hospital, 6560 Fannin Street, Houston, TX 77030, USA.
E-mail: mgzghali@gmail.com

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surveillance) alone,[59] biopsy and observation, biopsy and radiotherapy, extirpation resection[60] without or with neoadjuvant chemotherapy (e.g., temozolomide)[29,38] followed by observation, surgical resection followed by radiotherapy,[52] and laser interstitial thermal therapy.[56,61]

While earlier studies had supported observation as an equally viable alternative to surgical resection,[59] a subsequent study carried out in Norway demonstrated significantly greater 5 year overall survival (74%) in patients with diffuse LGG following resection compared to observation (60%).[60] Moreover, recent evidence suggests upfront maximal safe resection (MSR) not only alters the natural history of the disease, but also additionally improves overall survival and malignant progression-free survival, as well as seizure control.[4,30,35,41,44,60,61-64] Furthermore, authors have described supratotal resection, whereby maximal resection is extended to include a rim of radiographically and grossly normal tissue, a strategy having become an attractive concept well demonstrated to improve outcomes.[4,6,44]

Surgical Resources Maximizing the Resection of Low Grade Gliomas

Based on the aforementioned studies, and if the recent data are correct, a maximal/gross total or supratotal resection should be the goal in patients with LGGs in order to optimize clinical outcomes.[4,6,28,35,37,38,41,43,44] The natural history of LGGs may be significantly improved with a more aggressive or even a supratotal resection.[4,6,44] An oncofunctional balance must be made, wherein eloquent parenchyma is preserved in order to prevent deficits,[39,65] while achieving a maximal resection in order to improve overall survival.[6] In order to reliably obtain these goals safely, especially in regions adjacent to eloquent cortex, use of numerous preoperative and intra-operative modalities proves requisite (Tovar Spinoza *et al*., 2016).[4-6,39,44,61] Preoperative resources include functional magnetic resonance imaging (MRI) to evaluate functional cortex,[20-23] WADA testing to evaluate speech dominance, and diffusion tensor imaging and fiber tractography in order to accurately locate deep fiber tracts [Figure 1].[24-27] The intraoperative adjunct armamentarium includes neuronavigation,[21,66] awake craniotomy with intraoperative cortical and subcortical mapping,[8,10,11,14,15,23,67] intraoperative tumor staining dyes (e.g., 5-delta-aminolevulinic acid) to delineate tumor from normal brain,[68-71] and intraoperative MRI to detect tumor residual following initial resection,[7-19] all of which prove useful alone or in combination to facilitate MSR of diffuse low grade and high grade gliomas.[4,6,32-34,39,44] Additionally and indispensably, the surgeon's experience operatively and with the foregoing modalities is highly variable and arguably critical in determining the degree of MSR achievable and optimizing patient outcomes, a general principle in neurological[69-71] and general[75-79] surgery. Critically, this may bear significant medicolegal implications as well, since surgeon inexperience accounts for approximately 40%–60% of factors contributing to medical error, resulting in malpractice cases.[80,81]

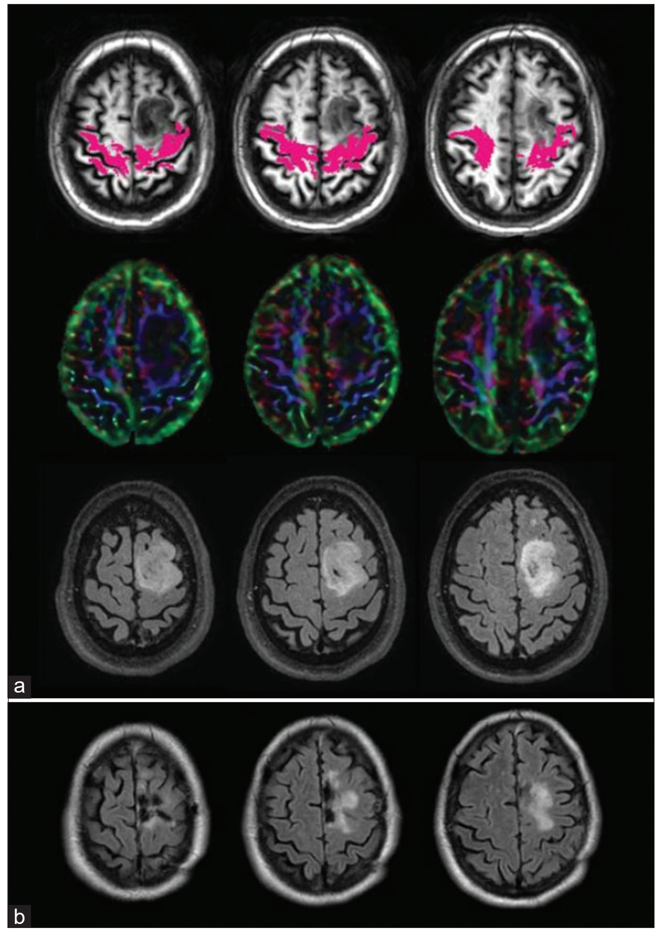

Figure 1: Diffusion tensor tractography of a patient with left frontal oligodendroglioma. (a) The tumor infiltrates the left corticospinal tract (magenta) throughout its precentral gyral and centrum semiovale extents. Upper panel: Axial T1 weighted magnetic resonance imaging (MRI) sequences demonstrate left frontal oligodendroglioma. The location of the corticospinal spinal tracts (magenta) is determined by diffusion tensor tractography and superimposed on the axial T1 weighted MRI. Middle panels: Color maps demonstrate decreases in fractional anisotropy resulting from left frontal oligoglioma. Lower panels: Axial fluid attenuated inversion recovery MRI sequences indicate the location of the left frontal oligodendroglioma. Volumetric analysis determines the oligodendroglioma occupies a space of 29 cm^3. (b) Axial fluid attenuated inversion recovery magnetic resonance imaging sequences performed postoperatively evidence residual within the area of deep fascicular infiltration. Corticospinal tract involvement precludes safely achieving a supratotal resection and predicts worse outcomes following operative intervention. Modified with permission from Figure 1 of Castellano *et al*.[27]

Surgeon Experience and Patient Outcomes

The importance of surgeon experience on survival and functional outcomes cannot be overemphasized. Improved outcomes for complex surgical problems are consistently correlated with surgeon experience and hospital volume in both neurological[45,72,73] as well as general[75-79] surgery, especially for more complex and challenging pathologies.[74,82] For instance, greater surgeon experience correlates with reduced mortality in laparoscopic major hepatectomies,[83] reduced postoperative complications and mortality following laparoscopic colorectal operative intervention,[84] enhanced recovery of urinary continence following robotic-assisted radical prostatectomy,[85] higher endocrinological cure rates for transsphenoidal resection of pituitary adenoma,[74] reduced postoperative corneal edema following cataract surgery,[86] reduced postoperative mortality following pancreaticoduodenectomy,[82] reduced postoperative complications following laparoscopic cholecystectomy,[87] and fewer complications following shoulder arthroplasty and hemiarthroplasty.[88]

Conclusions

Neurosurgical outcomes obtained in the treatment of low grade gliomas are significantly facilitated by the use of awake craniotomy with cortical stimulation mapping, neuronavigation guided craniotomy, surgical approach, and microsurgical tumor removal, diffusion tensor imaging to identify the relationship of eloquent white matter tracts with respect to the tumor, intraoperative magnetic resonance imaging to guide tumor resection and determine extent of resection prior to closure of craniotomy, and d-aminolevulinic acid staining to distinguish between tumor tissue and normal cerebral parenchyma (Duffau, 2017, 2018, 2019; de Leeuw and Vogelbaum, 2019; Dimou *et al*., 2019; D'Souza *et al*., 2019).[89-95] Since diffuse LGGs bear fatal consequences which can be facilely delayed with optimal and ideal treatment, an ethical dilemma becomes clearly evident. This dilemma is present in the United States of America and throughout the world.[28] Despite the extensive evidence arguing in favor of, and supporting, more aggressive and earlier resection in order to improve outcomes, LGGs are treated at a variety of facilities across the world and the United States of America without these operative resources or surgeon experience to optimize the ultimate outcome for the patient due to limited availability. In third world nations with facilities lacking all, or the majority, of these resources, it may be ethical to operate on LGGs when the differential outcome may otherwise be fatal to this young population. However, in the United States of America, which spends close to 18% of its gross domestic product on healthcare, with amply equipped facilities and experienced surgeons readily available nationally, a dilemma arises as to whether it is ethical to operate on these lesions without the aid and benefit of these resources. Further studies rigorously evaluating the survival advantage conferred by the use of each of these surgical adjuncts and resources will critically inform this heated debate.

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Conflicts of interest

There are no conflicts of interest.

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