Review

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Innovations in the surgical treatment of gliomas

Abstract: Gliomas are common brain tumors that have historically carried a dire prognosis with few useful treatment options. However, modern neurosurgical literature supports a strong role for aggressive surgical resection in some cases. Technical advances in neuroimaging and neuronavigation have changed the way surgeons approach these tumors, and intraoperative technology aimed at improving extent of resection without compromising safety has led to improved long-term results. Here, the authors review the state-of-the-art surgical approach to this challenging disease.

Keywords: Endoscopy; GBM; glioma; keyhole; minimally invasive.

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Introduction

The surgical treatment of glioma has long been a subject of little consensus. Historically, opinions on the role of surgery have ranged widely, with some conservative physicians proposing that obtaining tissue diagnosis and relieving life-threatening mass effect were the only valid indications for surgical intervention in these patients [29, 31]. Conversely, there have been a growing number of tumor surgeons arguing that maximal safe surgical resection provides patients with glioma improved quality of life and prognosis [4, 36].

Over the past decade, numerous authors have sought to define the role of surgical resection in glioma and to quantify its benefit. There is now a preponderance of evidence that suggests that patients who undergo a resection of 95%–99% of the tumor visualized on imaging have improved progression-free and overall survival [12, 19–21, 25, 35, 41, 42, 47]. The caveat repeatedly noted in this literature, however, is that patients who suffer surgical complications, including the development of new neurologic deficits, do not benefit from this aggressive approach. For these reasons, the goal of the modern neurosurgical oncologist is to achieve maximal tumor resection while minimizing the risk of surgical morbidity. The future of glioma surgery lies in efforts designed to achieve this goal.

Preoperative evaluation

A variety of preoperative studies may be employed to optimize surgical planning. Conventional magnetic resonance imaging (MRI) is used to visualize the lesion and surrounding normal structures. The evolution of MRI technology with higher field-strength magnets and higher resolution has enhanced the ability of the surgeon to assess a tumor’s relationship to critical structures within the brain. However, this information is purely anatomic. Newer technology focuses on providing relevant functional information to the surgeon planning his or her approach.

Functional MRI (fMRI) is one means of closely identifying the location of a tumor with respect to functional eloquent areas of the brain. fMRI signal is used to define task-driven regions of cortical activity in patients given a basic instruction requiring activation of motor or language areas. It is most frequently used in glioma patients as a tool to assess the proximity of the tumor margins to critical motor or speech areas, and may help the surgeon with preoperative planning and patient counseling regarding risks of postoperative deficits as depicted in Figure 1 [13, 53]. In some studies, fMRI has been shown to be as effective as intraoperative neuromonitoring in guiding surgical resection in patients with gliomas [44]. While fMRI is a powerful tool, accurate results require close concentration by a relaxed and interactive patient, which can be a challenge in some patients with gliomas. This has constrained the widespread use of fMRI in the brain tumor population [41].

Diffusion tensor imaging (DTI) or tractography has grown in popularity as a means of analyzing the subcortical anatomy of critical fiber tracts that are often distorted by the presence of a mass lesion. DTI does not require patient interaction during the exam subsequently it is better tolerated than fMRI in some cases. Resulting images display the anatomic locations of fiber tracts relative to the lesion and are particularly useful when planning the
resection of a tumor that involves the sensorimotor cortex and its descending pathways. This information has been shown to increase the extent of resection (EOR) in glioma patients [17]. Increasingly, DTI has been employed as a method of mapping subcortical language pathways preoperatively, though this method may not yet be as reliable as intraoperative stimulation [22, 54]. DTI may also help detect brain invasion, but caution must be exercised in interpreting this result as DTI is limited in its ability to differentiate tumor infiltration from vasogenic edema [3, 15].

**Surgical planning and approach**

When approaching a presumed glioma, a surgeon carefully weighs the need for exposure with the risk of morbidity. In the modern era of neurosurgery, this means performing the resection with the minimal amount of normal tissue exposed while ensuring that the operation is safe and the exposure is adequate to allow a maximal resection. Thus, this “minimally invasive” approach will look different for every tumor, and, in fact, may look different for every surgeon. Experience and comfort level will dictate the amount of exposure required by an individual surgeon, but the guiding principle should be minimally invasive [45].

The “keyhole concept” in neurosurgery, pioneered by Axel Perneczky, describes the notion that even large, deep-seated intracranial lesions can be reached through a small craniotomy [49]. The concept was recently quantitatively validated in a cadaver study comparing the keyhole supraorbital exposure of the skull base to those of larger
traditional approaches [2]. It is important to note that in some cases exposure of the entire lesion requires subtending various angles of approach during the course of resection [30]. Use of this technique to approach gliomas results in smaller incisions, less tissue disruption, and less exposure of normal brain [8, 30, 32, 45]. Correspondingly, patients may experience less wound complications, pain, and recover from surgery more quickly [9]. This is particularly important in patients who anticipate starting adjuvant therapy shortly after recovery. With proper patient selection, gross total resection of low and high grade gliomas can be obtained through appropriate use of this technique as illustrated in Figure 2.

In some cases, use of the operating microscope is adequate for visualization of a tumor approached through a minimally invasive craniotomy. In other cases, however, the surgeon may find it difficult to illuminate deep tissue adequately or may find some corners of the resection cavity inaccessible. In these cases, use of a rigid neuroendoscope with or without angled instruments can provide superior illumination and close inspection of the tumor bed [30, 33]. Liberal use of the neuroendoscope is an important adjunct to the minimally invasive approach as it has been shown to increase the EOR [9].

Preoperative planning for any brain tumor resection requires careful analysis of the surface anatomy to develop the optimal trajectory of approach. Intraoperative frameless stereotactic navigation is a critical component of that process and a mainstay of the modern neurosurgical operating room. Current systems can provide sub-millimeter anatomic accuracy in many settings allowing surgeons to minimize the size of their exposure. Current efforts are aimed at merging this fixed anatomic data with functional imaging studies obtained preoperatively, including both fMRI and DTI [38]. In this way, the surgeon can better map key eloquent structures before and during the case, even in the anesthetized patient.

Frameless navigation systems have been shown repeatedly to improve extent of resection in patients with glioma, but their weakness is that they are static. Over the course of an operation, brain shift and removal of tumor or CSF leads navigation systems to become increasingly inaccurate. Future adaptations will aim at modifying the displayed image to account for these factors in real time [18].

**Intraoperative tools**

During the course of a tumor resection, there are additional tools a surgeon may use to improve the EOR or

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**Figure 2** Example of a minimally invasive approach leading to successful resection of a glioblastoma multiforme. (A) Preoperative magnetic resonance imaging (MRI) with arrows indicating the extent of deep exposure that can be achieved through the planned craniotomy. (B) Postoperative MRI demonstrating an excellent resection result obtained through a keyhole opening (C).
delineate important normal anatomy. Intraoperative MRI (ioMRI) is highly regarded in this respect in some neurosurgical centers. Use of ioMRI in patients undergoing resection of gliomas has been shown to increase EOR in some studies [23, 28, 39, 40, 46, 52]. As high-field scanners have been designed for this purpose, imaging quality has improved and scan time has shortened to make this process more feasible in many cases. However, the challenges and cost of building a dedicated ioMRI suite with the required instruments and equipment has remained a major barrier to using this technology on a more widespread basis. In a systematic literature review published in 2011, Kubben et al. effectively defined the issues inherent to interpreting the role of this technology in treatment of patients with high grade gliomas [16]. They concluded that the current evidence was insufficient to demonstrate a survival advantage in patients who undergo resection of a glioma using ioMRI rather than conventional frameless navigation techniques. Until such data is available, surgeons will continue to weigh the costs and benefits of adding such a program to their centers.

Another surgical adjunct aimed at improving EOR is the use of the compound 5-aminolevulinic acid (5-ALA). Given orally prior to surgery, 5-ALA is a pro-drug that leads to intracellular accumulation of protoporphyrins IX (PpIX) in tumor cells of most high grade gliomas. This compound then emits red fluorescence when excited by blue light. Fluorescence can be detected under the operating microscope and can be useful in detecting residual foci of tumor along the borders of the resection cavity [10, 26, 34, 43, 48]; 5-ALA has been studied in a multicenter phase III trial and was shown to improve EOR in high grade gliomas [42]. However, it has little role in the treatment low grade gliomas and other non-enhancing tumors and the surgeon must take care not to overlook satellite lesions that may not clearly fluoresce [7, 11].

One potential application for the 5-ALA technology lies in fluorescence-guided robotic tumor resections. Liao et al. have described their attempts at merging MRI and intraoperative fluorescence data to guide a robotic laser photocoagulation system [24]. Future applications of this technology may allow surgeons to ablate tumor tissue with absolute precision, reducing the damage to adjacent normal brain. Robotic technology has increasingly been applied to the problems of brain tumor treatment, and several centers are currently studying the safety and feasibility of robotic biopsies and resections of gliomas in human subjects [6].

While ioMRI and 5-ALA are tools aimed largely at improving EOR, the practice of intraoperative functional mapping during awake craniotomy is geared towards minimizing morbidity. It is well documented that patients who develop a neurologic deficit after resection of a glioma have a worse prognosis, even in cases of excellent EOR. For that reason, some surgeons advocate the use of intraoperative stimulation of presumed eloquent tissue prior to resection to limit the risk of new deficit [37]. This process has been demonstrated to be a very reliable indicator of the patient’s postoperative neurologic outcome. However, as functional imaging has become progressively more advanced, some have argued that studies such as preoperative DTI have eliminated the need for awake surgery. While the topic is still debated, most authors currently recommend awake subcortical mapping of language pathways rather than DTI [5, 22, 54]. For motor and sensory pathways, growing evidence indicates that the two modalities are likely equivalent. As awake surgery with functional mapping can be difficult for the patient and challenging for the surgical team, efforts to optimize functional imaging and make awake procedures less necessary will likely continue in the near future.

The role of surgeons in future research

If advances in the understanding of the molecular biology of glioma have focused on one theme, it is that glioma is a heterogenous disease characterized by a variety of molecular perturbations and clinical phenotypes. As our understanding of the pathways involved in the development and progression of glioma becomes clearer, it is increasingly evident that a single therapy or intervention is unlikely to be appropriate for all patients. For that reason, it is important that surgeons consider how they manage patient tissue. Many neurosurgical centers maintain tissue banks, where excess tumor tissue is stored and used for a variety of research pursuits. Those stores of tissue will become increasingly important as new questions about the origins and treatment of gliomas arise. As surgeons, acting as stewards of these collections, it is one way to ensure that future therapies are available.

In the coming years, surgeons may play additional roles in the adjuvant treatment of patients with gliomas. Already, personalized vaccines may be made to act against a patient’s own tumor cells, and clinical trials measuring the efficacy of such an approach are underway worldwide. In most cases, enrollment in these trials must occur preoperatively so that tissue can be collected and
stored at the time of surgery. In addition, emerging therapies employing nanotechnology will likely involve direct inoculation of the tumor cavity with therapeutic agents at the time of resection [1, 14, 27, 50, 51]. For all these reasons, modern glioma surgeons must be particularly mindful of the emerging treatment options available and must play a role in developing new therapeutic protocols.

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