Editorial

Advances in surgical approaches in glioblastoma (GBM)

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Glioblastomas (GBM) remain the most common primary intracerebral neoplasm, comprising 15% of all primary central nervous system (CNS) tumors and 46% of all malignant CNS and brain tumors (1). While the prognosis for patients with GBM is undeniably grim, advances in the primary treatment modalities consisting of chemotherapy, radiation, and surgery have gradually improved the overall and progression-free survival. In particular, although GBM is not curable with surgery, gross total or near gross total resection does offer survival advantages compared to subtotal resection or biopsy alone (2,3). As such, maximizing extent of resection (EOR) while preserving neurological function has long been an important goal in surgery. To this end, recent advances in surgical techniques and adjuncts have improved the care of patients, lessening morbidity while extending survival. This editorial will briefly summarize recent advances in surgical techniques in the neurosurgeon's armamentarium in the care of GBM patients.

Perhaps the most significant recent advance in the surgical care of patients has been the development and application of the intraoperative magnetic resonance imaging (iMRI). It provides near real-time imaging of the brain during surgery, allowing the surgeon to assess for EOR, thus eliminating the risk of need to return to surgery because of inadequate resection. In addition, the iMRI also provides for correction of brain shift due opening of the cranial vault, loss of cerebrospinal fluid, cerebral edema and tumor resection. The first clinical use of iMRI was described by Dr. Black and colleagues at the Brigham and Women's Hospital in the 1990s (4). The earliest versions of iMRIs were quite difficult to use, as they severely limited the working area while also requiring dedicated MRI-safe surgical instruments (4). More recent iMRI configurations consist of a surgical table outside of the MRI which then moves into the iMRI scanner or the scanner itself moves on a track to encompass the surgical field, thus essentially eliminating the prior workflow disadvantages. The benefit of iMRI in aiding EOR has been well-demonstrated and has also been associated with improvement in progression-free and overall survival, as would be expected with an increased EOR (5,6). As a result, there has been gradual adoption of this technology, especially at specialized neuro-oncology centers.

With the availability of real-time MRI imaging, there has been development of new surgical techniques which utilize the capabilities of iMRI beyond simply increasing EOR. For example, laser interstitial thermal therapy (LITT) has become an increasingly popular surgical treatment modality in the last decade for patients with a variety of intracranial pathologies including gliomas, metastases, radiation necrosis and epilepsy. With LITT, a small laser fiberoptic probe ensheathed in a cooling catheter is stereotactically inserted into the tumor via a twist drill hole in the skull. An infrared laser is then used to heat the surrounding tissue, thus producing cell death through thermal coagulation. Prior research had used lasers to deliver heat to surrounding structures, but were hampered by the inability to finely control and monitor the ablation (7). Through the use of MR thermometry as well as the surrounding cooling catheter, the heat produced can be controlled exquisitely and monitored in near real-time, which allows for fine control of the ablation while sparing adjacent, possibly eloquent, brain tissue (8). There are currently two commercially available systems, Medtronic Visualase (Minneapolis, MN, USA) and Monteris NeuroBlate (Plymouth, MN, USA). There are slight differences in wavelength used (Visualase—980 nm; NeuroBlate—1,064 nm) as well as different cooling

techniques (Visualase—saline; NeuroBlate—CO_2), which results in differences in the heating characteristics. The NeuroBlate system has the capability to produce larger ablation (up to 3–4 cm in diameter) (9) while the Visualase system produces faster heating and possibly a more sharply delineated ablation zone, though at the expense of a smaller ablation (about 2 cm in diameter) (10). Both systems rely on the contrasting optical characteristics of the tissue to be ablated as compared to the surrounding more normal brain tissue. As a result, relatively conformal tissue ablations can be performed. In addition, adjacent natural heat sinks such as cisterns and sulci can be used to protect adjacent eloquent brain structures (11).

There has been a rapidly growing body of literature examining the use of LITT for GBM, both in the newly diagnosed and recurrent setting. Although it remains to be seen if there are survival advantages compared to open craniotomy, it seems to be a relatively safe technique (12). Although there can be size limitations to the lesions which can be treated due to the worsened mass effect that can be seen with these procedures from a predictable increase in cerebral edema, most patients tolerate this procedure quite well and are usually able to discharged after a short hospital stay of 1–2 days. Also, because of the relatively smaller incision and less concomitant tissue disruption associated with open craniotomy, patients tend to recover faster. As a result, LITT has become an increasingly popular technique in the United States, now offered at more than 100 centers. Currently only available in North America, both companies are actively seeking regulatory approval in Europe and Asia.

Along with LITT, focused ultrasound is another relatively new surgical technology which takes advantage of the real-time imaging offered by iMRI. Focused ultrasound employs a hemispheric phased array transducer combined with a cooling helmet to deliver acoustic energy to structures within the brain, which is then finely controlled with MR thermometry. Current technology has overcome barriers to therapeutic adoption of ultrasound such as attenuation of ultrasonic energy by the skull and prior inability to visualize and control the delivery of the heat to tissues. Depending on what settings are used and if "microbubbles" are employed, focused ultrasound can exert a number of differing effects, including: thermal ablation, acoustic cavitation, and immunomodulation. Similar to LITT, the lesion is targeted with the goal of coagulative necrosis. When "microbubbles" are used, the rapid expansion and contraction of the microbubbles causes mechanical lysis of the tissue. This method enhances local heating and it is theorized that lethal and surrounding sublethal heating combined with the mechanical lysis can cause permanent or transient damage to the blood-brain barrier, potentially increasing the delivery of chemotherapy locoregionally. In addition, the microbubbles can potentially be loaded with tumor antigens, thus possibly enhancing the host anti-tumor response. As of yet, experimentation has been limited to case series and pre-clinical studies, but this remains an exciting, relatively non-invasive, potentially effective treatment for GBM (13).

In this vein of less invasive surgical approaches, the cranial access needed for more traditional open resections is lessening through the use of novel surgical technologies. Furthermore, tumors which were previously considered unresectable due to deep location or proximity to adjacent eloquent structures have increasingly become more amenable to resection. By using advanced imaging techniques, such as diffusion tensor imaging (DTI), surgical approaches can be tailored to minimize damage to overlying eloquent structures such as critical white matter tracts. As computing power has increased, DTI fiber tracking has become increasingly automated, thus decreasing barriers to routine adoption. Moreover, surgical adjuncts which improve the visualization of GBMs such as fluorescein and 5-aminolevulenic acid (5-ALA) allow surgeons to more easily see the tumor, thus enhancing the ability of the surgeon to more completely resect the tumor while protecting the adjacent more normal tissue. In the case of fluorescein, the surgery is guided by resecting tissue in which the fluorescein has extravasated. This is akin to seeing the leaky vessels associated with contrast enhancement seen in GBMs (14). In contrast, 5-ALA works through a metabolic mechanism, whereby 5-ALA is taken up preferentially by tumor cells and converted to protoporphyrin-IX, a hemoglobin precursor which fluoresces under a 405-nm blue light (15). Although these two drugs work in different methods, both effectively enhance visualization of the tumor mass, thus increasing EOR (14,16). Either drug is probably more cost effective than an intraoperative MRI as it only requires the use of a special filter attached to a microscope. Indeed, because of its efficacy, 5-ALA has essentially become the standard of care in Europe and has recently garnered the FDA approval in the United States as well.

In the end, no matter how complete a resection has been performed, even a supramaximal resection, GBMs inevitable recur. Simply speaking, GBM is by its nature surgically incurable disease. Nonetheless, beyond the relatively minor

survival benefit associated with a more complete EOR, there are additional benefits that can be accrued with an open resection. For instance, there have been multiple trials using viruses to target GBM. Currently, direct injection into the tumor or resection cavity is the only effective means of delivering virus to the tumor. Various clinical studies have employed this method to deliver viral agents to the tumor with encouraging results (17,18). As a result, viral treatments for GBM have been a popular avenue of research recently. Treatment strategies using tumor tissue to create vaccines have been researched as well. Two Phase II clinical studies (NCT00045968 and NCT01814813) recently completed accrual and the tumor community is eagerly awaiting results of these trials.

In this era of precision medicine, more and more effort has been focused on tailoring treatment to a patient's tumor specific characteristics. Obtaining tissue is still the gold standard for making diagnosis and allows for genetic and proteomic testing by which targeted agents may be selected for a tumor's specific set of characteristics. As such, chemotherapy trials for GBM have increasingly used agents which target a specific genetic abnormality, of which only a minority of GBMs may express this derangement. This underscores the continuing importance of surgery, even in this era of less and less invasive treatments. Furthermore, early phase clinical studies have increasingly employed a "phase 0" strategy, in which chemotherapy is administered prior to surgery. Open surgical resection is then performed and the tissue yielded can then be tested for drug penetration and its effects on the tumor cells. The drug is then continued after surgery to assess for safety and efficacy. By employing this rational strategy, it is hoped that the pace of drug development and assessment may be hastened.

Even in this modern era of increasingly minimally invasive treatments, surgery continues to play a critical role in the treatment paradigm of GBM patients. Surgeons have become less insulated as they have increasingly adopted advanced imaging techniques to aid with surgery. In addition, the surgeon's role in the medical treatment of GBM has become greater as well, as seen in the case of viral treatments and tumor vaccines. In the future, we are likely to see further integration of surgery into the overall treatment algorithm for patients with GBM.

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Footnote

Conflicts of Interest: The author serves as a consultant for Medtronic and Monteris.

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