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Review

Minimally Invasive Treatments for Glioblastoma: A Review of Current and Emerging Surgical Technologies

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Abstract

Glioblastoma (GBM) is malignant, primary intracranial neoplasm associated with poor outcomes. Maximal, safe cytoreduction remains an important component of effective treatment for patients with this disease; however, some patients are not candidates for resection due to comorbid status, tumor location, or other factors. In this review, we aimed to describe minimally invasive surgical techniques that are emerging as important tools for improving safety and efficiency in GBM cytoreduction, including for patients with previously unresectable lesions. Specifically, we aimed to describe the commercially available tubular retractor systems and describe the available data regarding the benefits, risks, and utility of these retractors for patients with GBM. Additionally, we aimed to describe laser interstitial thermal therapy (LITT) and its use in GBM, including a description of the mechanism of action, commercially available systems, the steps in surgical implantation, available outcomes data, and future directions for the technology in this context. Finally, we aimed to review the use of MRI-guided high-intensity focused ultrasound (MRgHIFU) in GBM, including a description of its mechanism and data regarding efficacy in GBM. The availability and use of tubular retractors, LITT, and MRgHIFU provide clinically effective alternative methods for

cytoreduction in GBM and are also emerging as important tools for the expansion of treatment to GBM that previously may have been classified as nonresectable. This review will assist in the development of an intimate knowledge of the use and utility of these techniques and is important for clinicians caring for patients with GBM.

Keywords
Tubular retractor systems; laser interstitial thermal therapy; LITT; MRI-guided high intensity focused ultrasound; MRgHIFU, glioblastoma; GBM; gliomas; minimally invasive surgery

1. Introduction

Gliomas are the most common malignant primary brain tumor. Previously, all grade 4 gliomas were designated glioblastoma (GBM), a diagnosis based upon histological features and molecular characterization [1]. However, the 2021 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) has changed the terminology and classification for grade 4 gliomas [2-4]. Lesions previously classified as GBM are now separated based upon IDH-status. IDH-mutant grade 4 lesions are designated astrocytoma, IDH-mutant, WHO grade 4 and IDH wild-type lesions are designated glioblastoma, IDH wild-type, WHO grade 4. The term GBM in this article will encompass both lesions since most of the studies included here utilized the prior classification schema.

The clinical presentation of a patient with a GBM is variable depending on lesion size, location, and comorbidity status, but common presenting symptoms include headache, seizure, or focal neurological deficit. MRI is the diagnostic modality of choice [5]. Prognosis is poor with overall survival (OS) ranging from 12-16 months and a 5-year survival rate near 5% with maximal treatment [5, 6].

The current standard of care for GBM consists of maximal safe surgical resection with adjuvant chemoradiation therapy as the initial treatment of the tumor [1]. Treatment for recurrent GBM may include repeat surgical resection, radiation, medical therapy, or a combination of these approaches and is typically individualized based on individual tumor and patient characteristics [7]. Numerous studies have demonstrated that increasing extent of resection is associated with significantly improved overall survival [8-11]. However, GBM in deep-seated or eloquent tissues may not be amenable to gross total resection via standard open surgical techniques due to significant risk to surrounding structures. Modern, minimally invasive surgical options to address these concerns are increasing in popularity and clinical practice. Herein, we aim to provide a comprehensive overview of these surgical options for GBM to include tubular retractor systems, laser interstitial thermal therapy (LITT), and MRI-guided high-intensity focused ultrasound (MRgHIFU) in order improve knowledge regarding these techniques since an understanding of all available treatment options for GBM is important for developing the most appropriate treatment strategy for an individual patient. This review is most applicable to clinicians that provide direct care to GBM patients such as neurosurgeons, oncologists, and radiation oncologists, but will also be of interest to other healthcare professionals who may interact with GBM patients so that prompt evaluation and appropriate referrals can be made.

2. Methods

We performed a literature search utilizing PubMed® and Google Scholar in order to identify relevant articles for our stated purpose. We performed a search utilizing combinations of the terms "Minimal Exposure Tubular Retractor system", "METRx", "BrainPath", "ViewSite Brain Access System", "VBAS", "tubular retractor", "glioma", "glioblastoma", "GBM", and "brain tumor" in order to identify all pertinent articles describing the use of tubular retractors in patients with GBM. Next, we performed a similar search for LITT utilizing combinations of the terms "laser interstitial thermal therapy", "LITT", "glioma", "glioblastoma, "GBM", and "brain tumor". Finally, we performed a search for MRgHIFU utilizing combinations of the terms "high-intensity focused ultrasound", "HIFU", "MRI-guided high-intensity focused ultrasound", "MRgHIFU", "glioma", "glioblastoma", "GBM", and "brain tumor". We extracted relevant articles within the search results to develop our review of each of the stated topics. All abstracts from search results were reviewed and selected based on perceived relevancy to the topic. We did not provide a comprehensive description of all published articles on each given topic. Instead, we aimed to compile appropriate articles to provide information for an informative review of the stated objectives.

3. Tubular Retractor Systems for Resection of Deep-Seated Lesions

3.1 Background and Advantages of Tubular Retraction

A major limitation to successful resection of deep-seated tumors is injury to normal tissues secondary to retraction or resection during surgery. Deep-seated lesions are difficult to visualize and historically have required significant retraction or resection of non-tumor brain to achieve adequate resection or access the tumor. Retraction was commonly achieved with flat, malleable handheld metal retractor devices. Although simple and effective, such retractors have been associated with significant ischemia to adjacent structures from focal pressure [12]. Laceration injuries are also possible if the edge of the retractor applies significant force to overlying brain tissue. Even small amounts of injury can be devastating depending on the location, so neurosurgeons have attempted numerous techniques to avoid such injury. These include dynamic intermittent retraction, gravity-dependent retraction, administration of osmotic agents for diuresis and brain relaxation, CSF drainage via direct suctioning and lumbar drainage, and hypothermia, among others. Despite such techniques, significant retraction on brain tissue to achieve meaningful resection of a deep-seated lesion is often unavoidable.

The use of tubular retraction systems is a surgical strategy aimed at diminishing some of the complications encountered with classical hand-held or fixed flat, malleable retractor systems. Specifically, these retractors distribute force evenly in a radial distribution over a larger volume of tissue than more traditional retraction methods, which minimizes focal parenchymal disruption and injury [13] (Figure 1). Additionally, these retractors create an operative corridor via smaller craniotomies to better visualize deep-seated lesions and can be combined with microscopic or endoscopic techniques to assist the surgeon in achieving safe and successful resection for deep-seated lesions in a minimally invasive fashion [14].

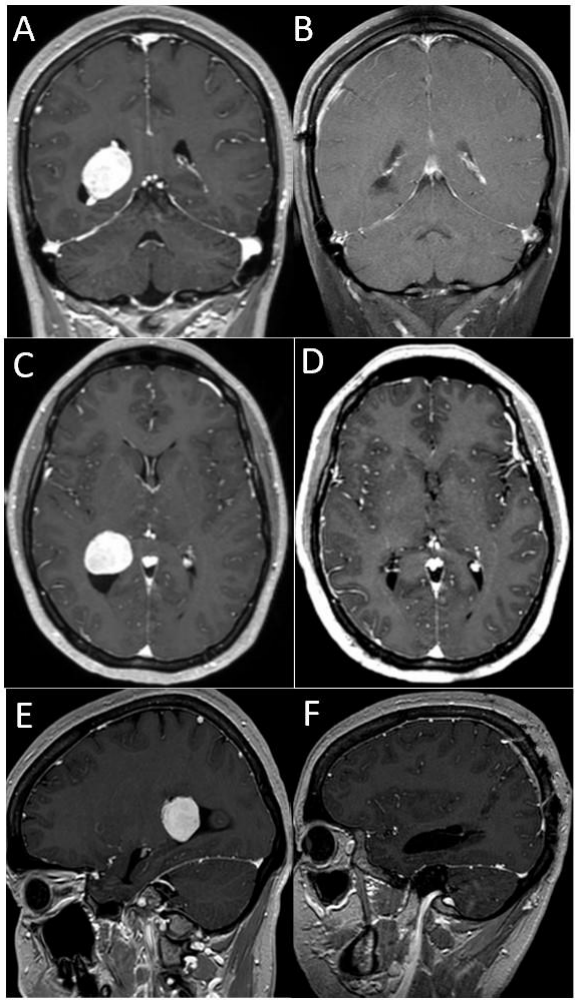

Figure 1 Resection of an intraventricular lesion utilizing BrainPath® from NICO corporation, Indianapolis, IN, USA. Post-contrast T1-weighted coronal (A), axial (C), and sagittal (E) sequences demonstrating a homogenously enhancing lesion with the atrium of the right lateral ventricle. Post-contrast T1-weighted coronal (B), axial (D), and sagittal (F) sequences demonstrating gross total resection of the lesion with minimal disruption of the cortical and subcortical tissue in the region adjacent to the lesion due to the use of a minimally invasive surgical strategy with a tubular retractor.

3.2 Commercially Available Tubular Retractor Systems and Use in Surgery for Patients with GBM

There are numerous tubular retractor systems currently available for cranial procedures. These include the BrainPath® system (NICO corporation, Indianapolis, IN, USA), the ViewSite Brain Access System™ (VBAS) (Vycor Medical Inc., Boca Raton, FL, USA), and the METRx™ system (Minimal Exposure Tubular Retractor System) (Medtronic, Minneapolis, MN, USA). The first two systems noted here have been specifically designed for use in intracranial procedures, whereas the METRx system was initially designed for use in spinal procedures but has since been adopted for use during cranial procedures.

3.2.1 BrainPath® System (NICO Corporation, Indianapolis, IN, USA)

BrainPath® is described as a parafascicular, transsulcal minimally invasive access system called MIPS (minimally invasive parafascicular surgery). It provides access to intracranial lesions including tumors, vascular lesions, hematomas, and cysts. The system includes a cannulation device with a tapered tip and diameter of either 11 mm or 13.5 mm (Figure 2). A plastic, hollow, transparent sheath overlies the cannulation device, which is left in place to create an operative corridor when the cannulation device is removed. Three sheath lengths are available in 11 mm diameter, while five are available in 13.5 mm diameter, which allows the surgeon to choose the most appropriate combination of diameter and length for a specific lesion. BrainPath is compatible with neuro-navigation systems for accurate sheath placement. Additionally, the plastic sheath can be locked in place so that the surgeon can use familiar bimanual techniques during resection (Figure 3).

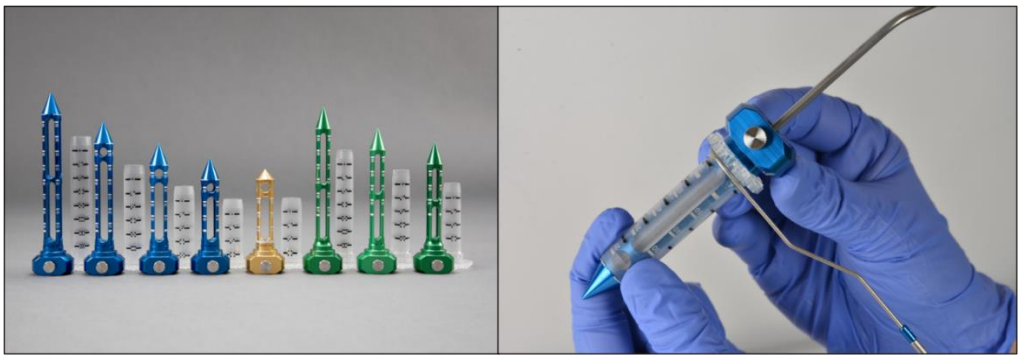

Figure 2 The BrainPath® system from NICO corporation, Indianapolis, IN, USA. Three sheath lengths are available in 11 mm diameter, while 5 are available in 13.5 mm diameter (A). The inner cannulator (blue device) can be combined with neuronavigation devices to aid in appropriate sheath placement, and the sheath can be fixed in place to allow for bimanual resection techniques, as shown here (B). *Images used with permission from NICO corporation*.

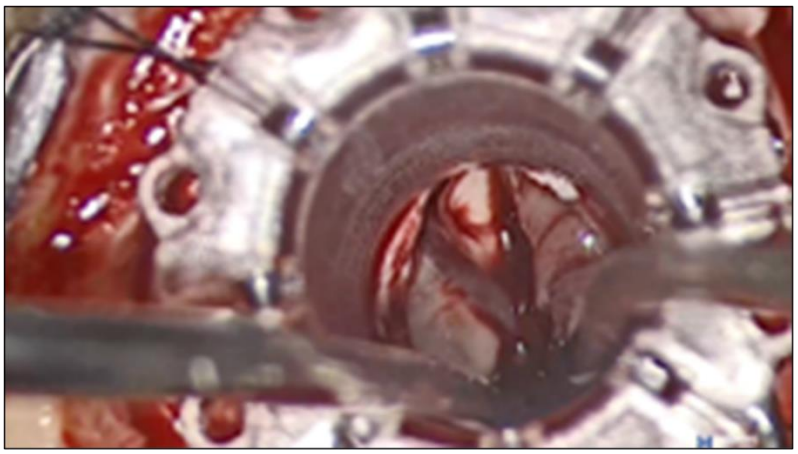

Figure 3 Bimanual resection technique with a BrainPath® restractor (NICO corporation, Indianapolis, IN, USA). A BrainPath® sheath is shown fixed in place allowing the surgeon to utilize multiple instruments simultaneously to assist with resection of a deep-seated lesion in a minimally invasive fashion. *Image used with permission from NICO corporation*.

There is a relative paucity of published data with regards to use of BrainPath® during resection of intracranial tumors, including GBM. Most data are limited to case reports or small case series. The largest series to date included 43 total tumor patients from a single institution, 15 of which were patients with GBM [15]. All patients harbored lesions in deep, subcortical locations. Data specific to the glioblastoma patients was not provided, but the author notes that obtaining gross total resection (GTR) of primary brain neoplasms was more difficult to obtain than for metastatic lesions, as evidenced by 65% and 95% GTR rates, respectively. Most complications occurred in patients with primary brain neoplasms, which included postoperative hemorrhage in 1 patient, new infarction in 1 patient, and new motor deficit in 5 patients. However, the author does note that the typical soft consistency of GBM combined with tubular retraction allows for improved ability to resect deep-seated GBM than more traditional techniques. Thus, BrainPath® may be useful in assisting the surgeon with at least partial resection of deep-seated lesions that otherwise may not be accessible through conventional methods due to risk of significant brain injury to surrounding structures such as white matter tracts.

Similarly, Iyer et al. described their experience with resection of deep-seated high-grade gliomas in 14 patients using the BrainPath® tubular retractor system [16]. Eleven of the 14 patients harbored GBM (3 patients had anaplastic astrocytoma). The most common tumor location was the thalamus with others adjacent to major white mater tracts or other deep nuclei structures. The authors were able to achieve 97% ± 1.2% GTR rates with over half of patients experiencing an improvement in Karnofsky performance Score (KPS) compared with the preoperative baseline.

3.2.2 ViewSite Brain Access System™ (VBAS) (Vycor Medical Inc., Boca Raton, FL, USA)

VBAS™ has similarities to BrainPath. There are two components: an introducer and an outer sheath, also known as the working channel. The introducer is longer than the working channel, acting as a dilator to assist with insertion of the device. The introducer does have a small opening that allows for drainage of blood or CSF upon insertion into the brain. The working channel is cylindrical and tapers towards the distal end. The proximal portion of the working channel can be attached to a fixed extension arm to allow the surgeon to perform bimanual resection techniques. As with BrainPath®, VBAS™ is compatible with neuro-navigation systems to assist with accurate lesion localization. There is a total of 14 VBAS sizes with unique length, width, and height dimensions allowing for access to a variety of lesions in different cerebral locations (Figure 4).

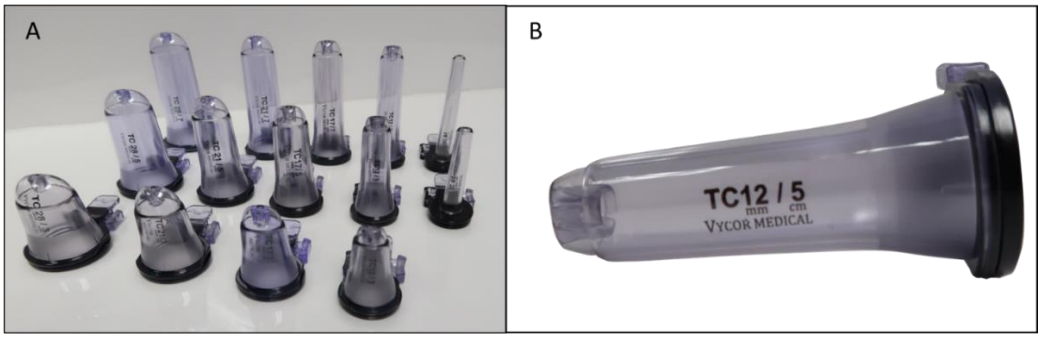

Figure 4 The ViewSite Brain Access System™ (VBAS) from Vycor Medical Inc., Boca Raton, FL, USA. There are 14 VBAS sizes with unique length, width, and height dimensions allowing for access to a variety of lesions in different cerebral locations (A). The introducer and outer working channel are shown (B). This system is also compatible with neuronavigation for accurate sheath placement and can be fixed in place to allow for bimanual resection techniques, similar to BrainPath. Images are used with permission from Vycor Medical Inc.

There are limited studies regarding the use of VBAS™ in assisting with resection of intracranial tumors, including GBM. Shapiro et al. performed a systematic review of the current literature regarding the use of VBAS for resection of deep-seated brain lesions including hematoma, brain tumors, colloid cyst, and foreign bodies [17]. A total of 106 patients were included in the review, 55 of which were tumor patients. The pooled gross total resection rate for the tumor patients was cited as 63%.

The combination of VBAS™ with other technology may also assist in resecting tumors in difficult locations. Akiyama et al. used VBAS™ for a series of 16 patients with brain tumors, 2 of which were GBM [18]. A fixed endoscope was utilized for improved lesion visualization and to allow for bimanual resection techniques. Partial resection was accomplished for one GBM and GTR for the other. No complications were noted for either tumor. Although no conclusions regarding outcomes were made based upon the data in this study, it did demonstrate that VBAS™ could be combined with endoscopic visualization to achieve adequate tumor visualization for accomplishing either biopsy or resection.

3.2.3 METRx™ System (Minimal Exposure Tubular Retractor System) (Medtronic, Minneapolis, MN, USA)

The METRx™ system was initially designed for use in spinal surgery, especially for microendoscopic discectomy. The system includes a series of metal dilators that are inserted in sequential fashion in a chosen trajectory from smallest diameter to largest diameter. A retractor tube is then inserted over the series of dilator tubes after a working channel with a large enough diameter for the indicated procedure has been made. An adjustable rigid arm is then attached to the proximal end of the retractor tube to provide hands-free retraction for the duration of the procedure. The dilators are then removed leaving only the working channel tube in place. The angle of the retractor can be adjusted with manipulation of the rigid arm system. The minimum available diameter is 14 mm and the largest is 26 mm (Figure 5). There are a variety of lengths available in

each diameter, again so the surgeon can choose the most appropriate combination for approach to the individual lesion.

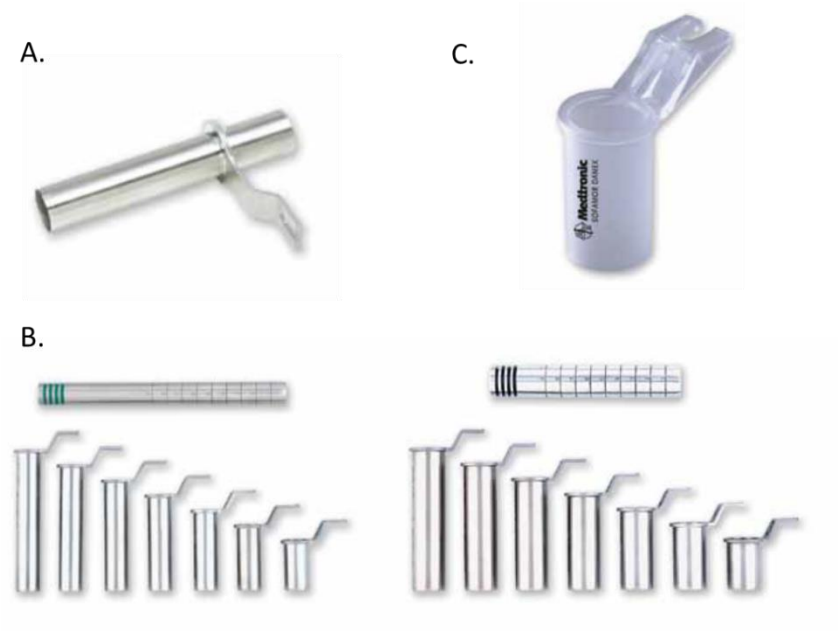

Figure 5 The METRx™ system (Minimal Exposure Tubular Retractor System) (Medtronic, Minneapolis, MN, USA). (A) A non-disposable tubular retractor that comes in various widths and lengths. (B) On the left, a 14.8 mm dilator and various length 16 mm diameter tubes are shown. On the right, a 20.8 mm dilator and various length 22 mm diameter tubes are shown. (C) A disposable tube that is available in various lengths. Images are used with permission from Medtronic.

Although this system was designed for use in spinal procedures, it has recently been applied for intracranial procedures. The METRx™ system was used for resection of deep-seated tumors in a series of 10 patients in one available study [19]. Two of these lesions were GBM located in deep right temporal and left parietal regions. The authors were able to achieve GTR of the lesions in both patients without any noted complications from surgery.

3.3 Complications Related to Use of Tubular Retractors in Intracranial Procedures

Despite the advantages of tubular retractor systems, there is still risk for injury to surrounding brain structures. Bander et al. utilized postoperative imaging to help visualize ischemic damage to surrounding tissue created by METRx™ tubular retractors [20]. The average DWI volume surrounding the retractor tract was 8.35 ± 3.05 cm^3. This suggests irreversible ischemic damage to brain tissues surrounding the retractor. No specific postoperative deficits were attributed to these changes in their series of 20 patients with deep-seated brain tumors. No formal comparisons between DWI volume changes using classic flat, malleable retractors and tubular retractors have been made; therefore, conclusions regarding reduction in brain tissue damage using tubular retractors cannot be made from this study alone. Other reported complications include contusions in the surrounding brain parenchyma, new or worsening focal neurological deficit related to tumor and retractor location, and cerebrospinal fluid leak, most of which are reported in case reports and

small case series [15, 21]. Further evaluation regarding complications related to tubular brain retractors for brain tumors in the setting of larger case series and, ideally, randomized controlled trails will be necessary.

3.4 Conclusions Regarding Tubular Retractor Systems

The use of tubular retractor systems in cranial neurosurgery is expanding due to their ability to target deep-seated lesions with reduced injury to the normal structures surrounding a lesion. Maximal safe resection is important for improving survival outcomes in GBM patients and these retractors may allow for improved cytoreduction in deep-seated lesions that have previously been unresectable due to concern for injury to surrounding structures. Furthermore, use of these systems for open biopsy allows for the possibility of increased specimen for molecular studies which are crucial for diagnosis and grading. Studies regarding their use for patients with deep-seated GBM are limited to small case series at this time but they do demonstrate some advantages over standard open surgical resection. Further study will be important to determine the ultimate effect these retractors have on patient survival.

4. Laser Interstitial Thermal Therapy (LITT)

4.1 Historical Perspective

LITT is a technique that utilizes the production of thermal energy to cause local tissue destruction. Initial applications for this therapy were in the treatment of liver and prostate cancers in the 1960s and 1970s. Its use was first expanded to human brain tumor patients in the 1990s after rat models demonstrated efficacy for reduction in size of cerebral lesions [22, 23]. Initial targeting methods utilized computerized tomography (CT), but more recent advances in surgical technique and MRI have improved the safety, accuracy and effectiveness of this therapy for intracranial lesions. Therefore, LITT is emerging as a minimally invasive alternative to open resection techniques in the treatment of a variety of neoplastic and nonneoplastic cerebral lesions, including GBM. A specific advantage is in application to lesions that are in difficult-to-reach or highly eloquent regions in which open surgical resection carries a high risk of postoperative neurological deficit. For example, Kuo et al. recently described the use of LITT in five pediatric patients presenting with epilepsy who were found to have lesions in sensorimotor or language areas [24]. More specific to GBM, Thomas et al. note that up to 40% of these lesions are considered unresectable based on location within eloquent tissue, so LITT may be helpful in targeting a large portion of previously non-surgically treated GBM due to its minimally invasive stereotactic implantation and the ability to monitor ablation in real time [25]. LITT has also been successfully applied for patients with recurrent lesions after failing surgical and radiation therapies, including GBM (11) [25-29].

4.2 Mechanism of Action and Application with MR-Thermography

LITT creates thermal energy from light energy absorption. Brain and other body tissues have a high-water content. The scattering coefficient in such a medium in the near-infrared range of light leads to good local tissue penetration and absorption of photons resulting in rapid heating of tissue via the release of thermal energy from breaking chemical bonds [30]. Specifically, oxyhemoglobin, hemoglobin, and water are the key absorbers in the near-infrared range. Hemoglobin molecules

tend to absorb photons maximally at the lower end of the range, whereas water does so at the higher end of the range. Local tissue absorption begins to diminish with wavelengths greater than approximately 980-1064 nm, which are commonly used wavelengths for LITT in brain tumor patients. LITT is used to heat targeted tissue to 43°C, which results in apoptosis and necrosis [31]. Since light penetrance and, therefore, the amount of light absorbed in a specific tissue reduces with distances further from the light source, a region of interest can be targeted for destruction.

MR-thermography is an MRI technique used to generate thermal maps throughout the duration of active ablation. This technique can measure tissue temperature to within 1°C with a spatial resolution of 1-2 mm based on the changes seen on various MRI sequences during ablation [32]. Temperature changes alter hydrogen bonds with surrounding molecules, which changes the resonance frequency of the proton in the hydrogen nucleus. The resonance frequency increases in a linear fashion with increasing temperatures allowing for thermal monitoring via MRI. Furthermore, T1 relaxation time can be used as water molecules have dipolar interactions with surrounding tissues, which creates a spin-lattice relaxation. The relaxation time is also a function of temperature, increasing with temperature rise. Finally, thermal energy creates random motion of water molecules, which increases at an exponential rate and creates MRI signal attenuation. This can be measured as a diffusion coefficient and used to create thermal maps. These thermal maps allow for the real time monitoring of temperature changes in the lesion and the normal surrounding brain tissue.

4.3 Imaging and Histological Characteristics of Tumor Tissue Exposed to LITT Ablation

LITT creates three “MRI zones” that are defined based upon imaging findings during treatment [33]. A central zone of T1 hyperintensity and T2 hypointensity represents the area immediately surrounding the LITT probe. The diameter of the central zone increases throughout the ablation as regions of cell death grow. A second region adjacent to the central zone is called the peripheral zone. This area is characterized by T1 hypointensity and T2 hyperintensity. There is a thin rim of enhancing tissue seen at the edge of the peripheral zone, which is thought to represent disruption of the blood-brain barrier. At the conclusion of the ablation, the central and peripheral zones together represent the area of treated lesion. A third zone is referred to as the perilesional zone, which is an area of reactive edema in viable brain tissue. This may appear similar to the peripheral zone on MRI but is separated from the peripheral zone by its rim of enhancing tissue. This is important as it signifies breakdown of the blood-brain barrier and the blood-tumor barrier [34]. Microscopic evidence of disruption to endothelial tight junctions and increased transcytosis into tumor tissue in animal models supports this hypothesis [35]. Furthermore, an increase in serum brain-specific enolase after thermal therapy supports breakdown of the blood brain barrier in human subjects [36]. This has important implications for drug delivery to cerebral lesions including GBM. In the delayed stage of treatment, defined as approximately 2 weeks to 6 months post-ablation, the central MRI zone gradually grows smaller as necrotic tissue is removed. The lesion in total grows smaller over the post-ablation period until there is only a small region of enhancement still seen on MRI. The perilesional zone typically resolves as edema improves with standard steroid therapy and watchful waiting over a 1-2 month period.

The histological analysis of a GBM specimen after LITT parallels the imaging findings described above. There are typically three zones of tissue destruction radiating concentrically from the LITT

probe, which correspond to MR-thermography values during the treatment phase [37]. The area immediately adjacent to the LITT probe is characterized by tissue necrosis, surrounded by a granulation tissue zone, and finally a peripheral rim of neoplastic cells These histological zones roughly correspond to the central zone, peripheral zone, and the perilesional zone seen on MRI, respectively.

4.4 LITT Systems and Implantation

4.4.1 Commercially Available Systems

There are currently two commercially available LITT systems in common use in the United States. These are the Medtronic Visualase® System *(Medtronic, Minneapolis, MN, USA)* and the Monteris NeuroBlate® System (Monteris Medical, Minnetonka, MN, USA). Each requires the stereotactic surgical implantation of a laser light probe and uses MR-thermography software to monitor temperature production in the lesion and surrounding tissues during ablation. Visualase® uses a catheter with a 1.65 mm diameter inserted through a bolt screwed into a 3.2 mm burr hole. A 980 nM continuous diode laser delivers light via a laser diffusing optical cable. The length of the cable is cooled with saline via an insulated chamber surrounding the cable circumferentially, other than the last 10 mm, which is left free from saline insulation. This is to avoid heating of tissue along the trajectory of the cable to the target lesion. The unprotected tip allows light to disperse into surrounding tissues and cause thermal damage as described earlier. In contrast, NeuroBlate® utilizes catheters that are 2.2 mm or 3.3 mm in diameter implanted via a similar bolt and burr hole. This system utilizes a 1064 nM pulsed diode laser. The cooling mechanism is similar but uses CO^2 instead of saline. A unique feature of this system is the ability to choose between the full-firing option, which releases laser light energy circumferentially at the probe tip as in the Visualase® system, or a side-firing option, which allows for directional laser light delivery. The treatment radius for both systems is 1-2 cm around the unprotected optical cable probe. The catheter may be advanced or retracted during the procedure to cover more tissue. This is done by hand with Visualase® whereas NeuroBlate® uses a robotic microdrive device to control catheter depth. For larger lesions, multiple catheters at different trajectories and/or depths can be implanted in order to adequately treat the lesion.

Each system utilizes proprietary MR-thermography software to generate dynamic thermal maps during active tissue ablation. Visualase® creates thermal damage estimates (TDE) appearing as yellow-orange overlays on MRI during ablation, which represent the estimated area of irreversibly injured tissue (Figure 6). The software allows the surgeon to essentially pin safety points around the lesion of interest to protect adjacent structures. The probe shuts off automatically to prevent damage to pinned structures if the temperature reaches a pinned safety point threshold. Other safety points with high temperature thresholds referred to as high safety points may be pinned around the cable probe tip. Temperatures near 90°C trigger system shut-down as higher temperatures may cause tissue vaporization and gas expansion, as well as charring/melting of the catheter tip. The NeuroBlate® software creates similar temperature maps in the form of thermal-damage-threshold (TDT) lines. White lines correspond to regions that are subjected to temperatures of at least 43°C for 60 minutes, blue lines to regions at 43°C for at least 10 minutes, and yellow lines to regions at 43°C for at least 2 minutes. Like Visualase® safety points, temperature pick points can be placed anywhere in the 3D ablation zone and appear as numerical values overlying specified

areas on MRI during ablation, which allows the surgeon to carefully monitor progress and determine if any surrounding tissue is experiencing high temperatures.

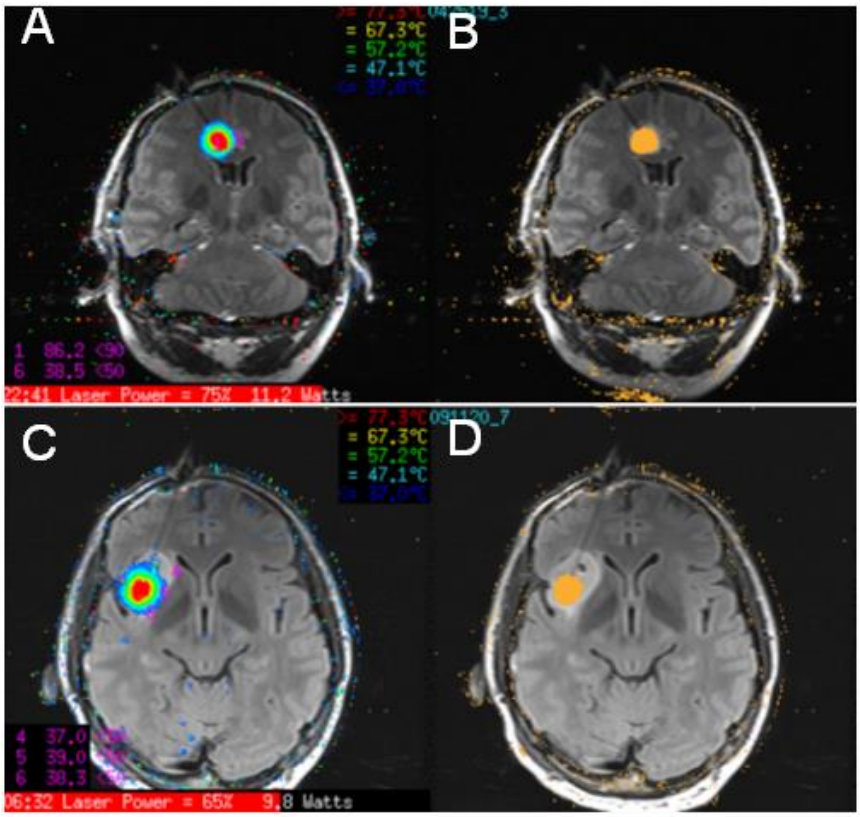

Figure 6 Thermal maps created during tumor ablation with the Medtronic Visualase® System *(Medtronic, Minneapolis, MN, USA)*. (A) Coronal images during thermal ablation of a biopsy-proven right frontal GBM at our institution demonstrate variable temperature zones around the laser probe tip with the hottest region noted in red at the center of the tumor where the probe has been implanted; (B) TDE map in coronal of the same patient; (C) Early thermal map in axial plane of a biopsy proven grade 2, IDH-1 mutated astrocytoma in the right insula; and (D) associated axial TDE map of the same patient.

4.4.2 LITT Surgical Procedure and Postoperative Care

There are a variety of methodologies for implanting the LITT probe using stereotactic methods. These include use of frame-based or frameless navigation techniques. Additionally, robot-assisted stereotaxy is especially useful when implanting multiple LITT probes with different trajectories in the same surgical setting.

The general steps at our institution for LITT utilizing Visualase® and a single probe are as follows:

Laser placement. An Integra® CRW headframe with localizer is placed in preoperative holding. The patient is then taken to a stand-alone CT scanner for a high-resolution head CT without contrast. This scan is merged with a previously obtained navigation MRI. After the CT scan, the patient is brought to the operating room, transferred to the operating table, and placed under general endotracheal anesthesia while the neurosurgical team plans a target, trajectory, and entry point.

After the patient has been intubated, lines and Foley catheter have been placed, the localizer is removed from the headframe which is then attached to the Mayfield adapter for immobilization. If frameless navigation is being used to supplement, the patient is registered with the frameless system software and fiducials. The proposed entry site is noted and marked on the patient's scalp. Next, the patient is prepared for surgery. Patients receive antibiotics and high dose dexamethasone.

The coordinates are verified with the arc system and phantom base on the back table. The frameless system is set up with the reference array in the sterile field. The entry site is confirmed. A small linear incision is made and carried down through the layers of the scalp using electrocautery. A 3.2 mm burr hole is made with the Stryker cordless driver with a drill stope set to pre-measured bone thickness. The dura is opened using electrocautery via a Bugbee electrode. The Visualase® bolt is placed in the burr hole and tightened appropriately. After calculating the appropriate depth and marking the fiber with a steristrip, it is then carefully inserted through the bolt and passed down to the target at the appropriate trajectory and depth based on preoperative targeting. We aim for the most distal point in the tumor for initial placement of the probe. The bolt is tightened gently to secure the laser probe into position but not crush it. Xeroform gauze is wrapped around the base of the bolt.

Ablation. The headframe is kept on the patient, and they are transferred from the operating room to the designated stand-alone MRI suite for the laser ablation portion of the procedure. A custom-made table adaptor for the headframe to attach to the MRI table is utilized to facilitate patient immobilization during transfer and the ablation procedure. After transfer into the MRI scanner, a preliminary scan prior to ablation is obtained to ensure appropriate probe placement in the target lesion. Next, protocol scans are obtained, and ablation begins with MR-thermography monitoring. The probe is pulled back by hand, if necessary, to cover more of the lesion. This process may be repeated several times until maximal tumor coverage has been obtained. Once ablation is complete, a final MRI is performed for assessment with sequences determined by the neurosurgeon. The patient is removed from the MRI scanner. The fiberoptic cable is removed, followed by the cranial bolt, and the incision is closed with a figure-of-eight stitch. The headframe is released from the headframe table adaptor, and the headframe is then removed. The patient is then transferred directly to the intensive care unit for extubation, close neurological monitoring, and blood pressure control. We typically continue dexamethasone in the postoperative period with a taper over 1-2 weeks depending on preoperative steroid use and amount of perilesional edema. The patient is typically transferred from the ICU to the neurosurgical ward on postoperative day number 1 and then discharged on postoperative day number 2-4.

4.5 Clinical Outcomes for Laser Interstitial Thermal Therapy in the Treatment of Glioblastoma

4.5.1 Introduction to LITT for GBM

The use of LITT in the treatment paradigm for GBM is expanding due to its numerous benefits including ability to target lesions in difficult areas, breakdown of the blood-brain and blood-tumor barrier to increase the effect of adjuvant therapies, and its minimally invasive nature. Publications regarding its use as both a primary therapy and as an adjunctive therapy to standard GBM treatment modalities have rapidly increased in recent years due to the above features.

For example, tumors in deep-seated, eloquent brain have historically been difficult to treat with conventional surgical methods due to the high-risk of post-operative morbidity. The cytoreductive ability of LITT for such deep-seated lesions was demonstrated in a small retrospective case series by Murayi et al. on a series of 9 consecutive thalamic GBMs [38]. LITT was the initial primary therapy for all but one of the lesions, which had previously undergone surgery followed by chemoradiation therapy. LITT was followed with adjuvant temozolomide and radiation in the Stupp protocol in all cases other than one, where no adjuvant therapy was given. There was an average reduction in tumor volume of 42.9% at 3-month follow-up demonstrating effective cytoreduction.

Pisipati et al. demonstrated the use of LITT in combination with open surgical resection of ablated tissue to reduce post-ablation edema [39]. Five patients with GBM underwent LITT immediately followed by mini craniotomy for tumor resection. This did not result in an increase duration of stay when compared with craniotomy for tumor resection alone or with LITT for tumor ablation alone. This did result in an increase in the total operative time when compared with LITT alone. The authors note that this technique may be particularly beneficial for lesions that are in locations which may lead to hydrocephalus secondary to edema as the goal of the technique is to reduce the total amount of apoptotic tissue after ablation thereby minimizing edema. No conclusions were made regarding the amount of postoperative edema when compared with craniotomy for resection or LITT for ablation alone.

4.5.2 LITT Effect on Survival Outcomes

There has been a recent increase in published data regarding outcomes for patient undergoing LITT both as a primary treatment for GBM and for recurrent GBM. One series of 25 GBM patients described outcomes for LITT-treated newly diagnosed and recurrent GBM separately [40]. Eleven of these patients harbored newly diagnosed GBM without any prior treatment. All except for one of the 11 lesions was cortical (1 thalamic GBM was included). The median extent of ablation in this group was 98% with a median PFS of 55.9 months and median OS of 32.3 months. The other 14 patients harbored recurrent GBM, all of which were cortical. The median extent of ablation was 87.5% with a median time-to-recurrence of 5.6 months and median OS of 7.3 months. No conclusions regarding the effect of extent of ablation on outcomes were made based on these data.

Mohammadi et al. similarly reported outcomes for LITT in GBM patients, but did demonstrate a survival benefit for increasing extent of ablation [41]. They performed a retrospective study on a group of 34 consecutive patients with high-grade glioma (24 GBM, 10 anaplastic astrocytoma) undergoing LITT for primary and recurrent tumor using the Monteris NeuroBlate® system. The median PFS for the group in entirety was 5.1 months, but the OS data were not available at the time of publication. Importantly, they analyzed the effect of TDT line coverage on clinical outcomes. The median blue TDT line coverage was 91% of the tumor volume, while median yellow TDT line coverage was 98%. Median PFS was 9.7 months in patients with <0.05 cm^3 of the total tumor volume remaining uncovered by yellow TDT lines versus 4.6 months for tumors with >0.05 cm^3 remaining uncovered by those lines. Similarly, PFS was better for patients with greater blue TDT line coverage. In patients with <1.5 cm^3 covered by yellow TDT lines, but not blue TDT lines, PFS was 7.6 months versus 3.3 months for those with >1.5 cm^3 discrepancy between the yellow and blue TDT line coverage. As noted earlier, the threshold for initiation of an apoptotic process that leads to tumor necrosis is near 43°C for 10 minutes. The results from Mohammadi et al. demonstrate that

increasing the volume of ablated tissue improves survival outcomes, which is like the improved survival resulting from greater extent of resection in patients undergoing open surgical resection of GBM lesions.

A meta-analysis on 25 newly diagnosed high-grade gliomas (21 GBM, 4 anaplastic astrocytoma) was performed by Ivan et al. in 2016 after a literature review of all retrospective studies, prospective studies, and case series regarding treatment of high-grade gliomas with LITT [42]. Lesions that had not undergone previous surgical or chemoradiation therapy were included in the analysis. The progression-free survival and overall survival for patients undergoing LITT for high-grade glioma was found to be 5.1 and 14.2 months, respectively. The authors note that these numbers are similar to other outcomes reported for high-grade glioma, and GBM in particular, undergoing standard open surgical resection with adjuvant chemoradiation therapy. With these results, it is again important to note that LITT may provide a viable route for cytoreduction in areas where open maximal surgical resection may carry very high risk of morbidity and mortality. Therefore, the therapy may be able to expand treatment to those who may otherwise not undergo therapy for GBM due to lesion location.

Kamath et al. also described their experience for a group of 58 patients with GBM treated with LITT, 17 of which had not undergone any previous treatment [43]. Tumors were located throughout the cerebrum, but most were lobar and nearly ¼ were frontal. The Monteris system was utilized. The blue TDT line coverage was 88.0% ± 14.2% and the yellow TDT line coverage was 93.3% ± 10.6%. PFS was 6.6 months overall (3.6 mo. for primary; 7.3 mo. for recurrent) and OS was 11.5 months overall (9.1 mo. for primary; 11.8 mo. for recurrent). No conclusion was made regarding the differences between outcomes in the primary versus secondary GBM patient groups, but the authors note that it is likely secondary to patient selection factors since LITT was chosen as the initial primary therapy in patients with GBMs in difficult locations, with more advanced age, and with poorer pre-operative functional status. Therefore, those patients began with a poorer prognosis. Importantly, the OS of 11.8 months for recurrent GBM treated with LITT in this cohort is approximately 2 months greater than published OS for recurrent GBM patients treated with bevacizumab alone [44] or bevacizumab and temozolomide in combination [45]. Importantly, however, previous studies have shown a survival benefit for increasing extent of resection in patients with recurrent GBM, again demonstrating the importance of cytoreduction in the treatment of these tumors [11, 46]. LITT may provide an alternative route for cytoreduction in patients with recurrent GBM, which may ultimately confer a survival benefit when compared with standard chemotherapy regimens in recurrent GBM similar to surgical resection for recurrent GBM. However, there have been no prospective, randomized comparisons amongst these treatment regimens, so no conclusion can be made at this time and further study is needed. Of additional interest in the study by Kamath et al. is the comparison among outcomes for LITT for lobar versus deep-seated lesions, which demonstrated no significant difference. The median PFS was 6.8 and 6.0 months for lobar and deep-seated lesions, respectively ($p = 0.68$). The median OS was 11.3 and 11.5 months for lobar and deep-seated lesions, respectively ($p = 0.44$). Therefore, LITT may be equally effective for treating GBM in varying cerebral locations. Again, further study is necessary before conclusions can be made.

Shao et al. performed a retrospective study on all patient's treated with LITT for brain tumor at their institution over a 10-year period [47]. This study included a total of 238 consecutive brain tumor patients, of whom, 104 harbored GBM. The authors analyzed the effect of lesion size on

survival outcomes. All high-grade astrocytomas (WHO grade III astrocytoma and GBM) were included in this analysis, but patients with lesions larger than >4 cm^3 had worse PFS and OS at 12, 18, and 24-month time points than those with lesions <4 cm^3. For GBM patients specifically, OS was 47%, 36%, and 29% at 12, 18, and 24-months, respectively. This study provides evidence for a potential drawback of LITT in the inability to treat larger lesions, which is likely secondary to the properties of light absorption and distribution in brain tissue that limits the treatment radius of the LITT catheter, as described earlier. Multiple LITT probes with different trajectories and targets in the same lesions might help to solve this problem, but there is also the possibility of increasing edema with larger areas of ablation. Further study regarding LITT in GBM of different sizes will help answer these questions.

Wright et al. treated 8 patients with GBM with MRI-guided LITT tumor ablation followed by immediate surgical resection of the ablated tissue [48]. All patient included in this study either had recurrent GBM or poor comorbid status resulting in a higher risk for open surgical resection. As with Pisipati et al., the goal was to reduce the amount of post-ablation edema by resecting ablated tissue immediately after the conclusion of LITT. The median tumor volume treated with TDT blue lines was 73% and median extent of resection of enhancing tumor was 92%. All patients received standard adjuvant chemoradiation. The median PFS was 9.3 months and median OS was 16 months in this small series, which are similar to published outcomes data for patients treated with standard maximal surgical resection and chemoradiation protocols [6]. Thus, LITT may be considered as part of a combined surgical strategy in selected patients.

Recent studies have also evaluated the utility of LITT in combination with immuno- and chemotherapies for recurrent GBM (rGBM). Use of check-point inhibitor therapy for recurrent GBM has been reported previously and did not demonstrate significant benefit compared with current standard GBM chemotherapies [49, 50]. However, Hwang et al. recently described the use of LITT in combination with pembrolizumab, an antibody check-point inhibitor targeting the PD-L1 membrane receptor found on tumor cells [51]. The goal was to use LITT for cytoreduction with the secondary benefit of BBB breakdown to improve delivery of the immunotherapeutic agent to tumor cells. The authors report on 3 patients with recurrent IDH-wild-type GBM treated with LITT and subsequent pembrolizumab. PFS was 7, 8, and 48 months, while OS was NR (alive at study publication), 12, and 40 months. Although this was a small sample size, these numbers were improved compared to previous data regarding surgical resection of a rGBM followed by check-point inhibitor therapy, with PFS and OS at 3.3 and 13.7 months, respectively, in that study [52]. Similar results were obtained in a series of 30 patients with rGBM treated with LITT followed by doxorubicin when compared with a historical cohort of patients treated with bevacizumab alone [53]. There was no improvement in PFS in this study, but OS was significantly improved compared to historical bevacizumab only control. These studies present data on small sample sizes and on patients with variable treatment and baseline characteristics. However, the data are important as they suggest a possible survival benefit using LITT in combination with adjuvant therapies for rGBM. Further study will be important to help elucidate the true utility of this treatment paradigm for this patient population.

Importantly, most study on LITT for GBM has not taken molecular findings into account, which are becoming increasingly important for treatment and prognostication. De Groot et al. recently provided the first publication analyzing outcomes from LITT for patients with specific molecular findings [54]. This study reviewed a total of 89 tumors undergoing LITT, 29 of which had previous

treatment. Data were collected from 14 centers as part of the LAANTERN prospective multicenter registry. All tumors were IDH wild-type. The authors demonstrated median OS of 9.73 months and 8.97 months for newly diagnosed and recurrent tumors, respectively. Additionally, median OS for patients with newly diagnosed tumors that underwent post-LITT chemoradiation was 16.14 months. The MGMT promoter methylation status was also evaluated and was associated with improved survival, which is a well-known feature of surgically treated GBM. The importance of molecular analysis in studies evaluating various treatments for GBM cannot be overstated as certain molecular features may result in variable tumor behavior and treatment response. Therefore, the study by de Groot et al. is an important framework for future study in LITT for GBM, which should incorporate molecular findings to help identify which patients may be candidates for LITT.

To the best of our knowledge, there are currently no randomized, prospective studies comparing outcomes in LITT versus conventional therapies for GBM. However, one recent retrospective study directly compared outcomes in patients with rGBM treated by LITT vs surgical resection [55]. A cohort of 17 patients with rGBm treated by LITT was compared with a historical cohort of 23 surgically treated patients. There were no statistically significant differences in baseline factors between the two groups of patients other than a slightly larger average lesion size in the surgically treated group. The median OS in the LITT treated group was 14.1 months and 13.8 months for the surgically treated group, which was not a significant difference. Additionally, the median PFS was 3.7 and 3.3 months for the LITT and surgical groups, respectively, which again was not statistically different. However, the patients in the LITT group did experience a shorter hospitalization. Larger randomized comparisons between LITT and surgical resection with incorporation of molecular findings will be important for informing future patient selection.

The currently available data suggest that LITT may provide a promising alternative to classical GBM surgical therapies, especially for GBM that are in difficult-to-treat regions and recurrent GBM lesions, but no conclusion can be made at this time regarding inferiority or superiority due to lack of head-to-head comparisons.

4.6 Complications from LITT for GBM

LITT provides a minimally invasive alternative to open surgical resection for GBM with the goal of providing maximal cytoreduction and minimizing complications. Transient postoperative neurological deficits, such as sensorimotor, language, or other neurological deficit depending on the location of the targeted lesion, is common and most often related to development of cerebral edema. Shao et al. noted that many patients experienced temporary motor deficits and that patients with these deficits tended to have larger areas of postoperative edema, although this was not statistically significant [47]. Maraka et al. evaluated 6 patients undergoing LITT and perioperative radiation therapy in order to characterize the effects of the combined therapy on cerebral edema [56]. Three of 6 patients included in the study were found to have worsened cerebral edema after LITT as evidenced with T2 and FLAIR changes on MRI. All these patients were treated with prolonged steroid therapy and 2 patients required treatment with bevacizumab due to steroid-refractory edema. Edema becomes an even greater concern for large lesions treated with LITT as these lesions already result in mass effect and there may be less room for the brain to compensate.

Permanent neurological deficit related to thermal damage is also possible. A retrospective review of 80 patients undergoing LITT for brain tumor (43 for high-grade glioma) evaluated postoperative neurological deficit in relation to corticospinal tract and TDT line overlap [57]. There were statistically significantly larger volumes of overlap with the corticospinal tracts and yellow, blue, and white TDT lines for patients with any postoperative (temporary or permanent) neurological deficit than those without postoperative deficit. This study demonstrates the importance of accurate fiberoptic catheter placement and close MR-thermography during ablation so that risk of injury to adjacent structures can be minimized.

Other general complications related to LITT for all indications include catheter malposition, arterial injury leading to acute brain hemorrhage, delayed tumor hemorrhage, seizure, infection, hyponatremia, and deep venous thrombosis [33, 42].

4.7 Developing Prognostication Tools in LITT for GBM

There are many horizons for research related to LITT for GBM due to its relatively recent application to the treatment of this disease process. One area of research is in prognostication for patients treated with this modality. Prognostication for patients with GBM is especially important due to the aggressive nature of the disease with low OS and PFS. One active area of prognostication research is the use of imaging for prediction of GBM recurrence after LITT. Recent analysis of post-ablation diffusion-weight imaging (DWI) sequences suggests that DWI may be able to predict specific locations for GBM recurrence [58]. The authors performed a retrospective review of 39 patients with GBM that had undergone LITT and postoperative MRI approximately 24 hours after ablation at a single institution. Thirty-six of 39 patients had radiographic evidence of GBM recurrence in follow-up. Analysis of the signal intensity in apparent diffusion coefficient (ADC) maps of the peri-tumoral region on the postoperative MRI scan demonstrated that regions of tumor recurrence had statistically significantly higher ADC intensity values than regions where recurrence did not occur ($1{,}391.3 \times 10^{-6}$ mm^2/s versus $1{,}012.7 \times 10^{-6}$ mm^2/s). Further study regarding the imaging characteristics of LITT-treated lesions may, therefore, provide prognostication data and assist clinicians with ongoing GBM surveillance and management for an individual patient in general.

Another area of research aimed at generating accurate prognoses for GBM patients after LITT is in monitoring the body's inflammatory response to LITT. Twenty-one patients underwent LITT for GBM in a single-center study [59]. A retrospective chart review was then performed in order to obtain neutrophil and lymphocyte counts preoperatively (on the day of surgery) and postoperatively (on the morning of postoperative day 1) to create the neutrophil-to-lymphocyte ratio (NLR). The postoperative NLR was compared to the preoperative NLR, giving a new value termed the delta-NLR. Patients with a larger delta-NLR tended to have a better OS. Therefore, monitoring the body's immunologic response to LITT therapy may provide insight into overall prognosis for an individual patient. Further studies with larger sample sizes and other measurements of immune response are necessary to determine whether immunologic parameters in the perioperative period will have lasting prognostic significance.

5. MRI-Guided High-Intensity Focused Ultrasound

5.1 Introduction to MRgHIFU

As seen with LITT, targeted thermal ablation provides an alternative route for cytoreduction in the treatment of GBM. Another emerging technique for thermal ablation is high-intensity focused ultrasound (HIFU), which can be combined with MRI localization for magnetic resonance guided HIFU (MRgHIFU). Historically, HIFU has been applied to the treatment of soft tissue cancers including liver, prostate, breast, and kidney malignancies [60]. In neurosurgical practice, MRgHIFU has been most commonly employed for the treatment of pain syndromes and movement disorders, but recent efforts have explored the application of this technique to the treatment to brain tumors, and particularly, to the treatment of GBM.

5.2 Physical Properties, Mechanism of Action, And Imaging Guidance of High-Intensity Focused Ultrasound

A concave ultrasound transducer is used to generate ultrasound waves that converge at a target, creating a high-intensity ultrasound field [60]. This high-intensity ultrasound field generates thermal energy at the site of convergence but does not heat tissue contacted by non-converged ultrasound beams. Therefore, a specific lesion can be targeted. Temperatures at the site of beam convergence can rapidly increase to more that 60°C, which is higher than temperatures sufficient to generate apoptosis and necrosis as seen with the LITT temperature thresholds discussed earlier. Thermal energy is created in a region measuring approximately 1-3 mm in diameter, although this can be adjusted depending on the specific acoustic parameters of the system used [61]. Aside from the thermal effect of HIFU, a mechanical effect is also seen. Ultrasound waves result in a cavitation effect on tissue immediately surrounding the region of convergence. This mechanical deformation can lead to further initiation of apoptotic processes.

Another important feature of this technique that has implications for its use for the treatment of GBM is its effect on breakdown of the blood-brain barrier. Early evidence suggests that the mechanical cavitation effect resulting from delivery of the ultrasound beams to a targeted region does result in blood brain barrier breakdown [62]. Additionally, as described with LITT, thermal energy has an effect on blood brain barrier breakdown, so delivery of thermal energy via targeted high-intensity ultrasound beams may result in localized breakdown at the brain-tumor interface [34]. This may allow for improved delivery of adjuvant chemotherapeutics to patients being treated for GBM.

A variety of targeting methods can be coupled with HIFU in order to accurately direct the creation of thermal energy in a lesion of interest [60]. However, MRI-guidance is of particular interest as it allows for thermal monitoring during the tissue ablation, similar to MR-thermography used during LITT tumor ablation. Additionally, MRI has superior anatomical resolution, which allows for accurate localization within targeted tissue.

5.3 MRgHIFU Procedure

There are a variety of procedural techniques that may be used to employ HIFU in the treatment of GBM. The major differentiator among protocols includes whether a window through the cranial

vault is created. Early studies of HIFU for use in cranial lesions utilized craniectomy prior to delivery of HIFU in order to eliminate the bony barrier; however, the use of lower frequencies with larger arrays and MRI-thermal monitoring with active scalp cooling has allowed for HIFU delivery through the skull without craniectomy in 1 small study [63].

There is no current standard protocol for HIFU ultrasound delivery for brain tumor patients, and specifically GBM patients, as reports related to cranial MRgHIFU are sparse and utilize individual procedural protocols in each study depending on whether or not a craniectomy is performed and depending on the specific system utilized for HIFU delivery. Promisingly, however, researchers are developing a procedure similar to LITT that may be employed for a minimally invasive use of HIFU, as described by MacDonell et al. [64]. In this "interstitial HIFU" or "catheter-based" technique, a HIFU probe would be implanted in stereotactic fashion via a burr hole craniectomy with MRI guidance. This would allow for precise ablation of a region of interest with the ability for thermal map monitoring during the ablation. This procedure has been successfully applied in a swine model. Continued development of this technique and ultimate application to humans may increase the utility of MRgHIFU in the clinical setting.

5.4 MRgHIFU for GBM

Ram et al. performed an early phase 1 safety and efficacy study regarding MRgHIFU on 3 patients with recurrent GBM [65]. Notably, patients in this study underwent craniectomy 7-10 days prior to ultrasound thermal ablation of the tumor due to concern for ultrasound wave penetration of the cranium. Ultrasound pulses were delivered to target in 12-20 second durations with thermal monitoring using MR-thermography throughout the procedure. Target temperatures were in the range of 60-90°C. Reduction in tumor volume was monitored with postoperative serial MRI scans. Response was seen in 2 of the 3 patients treated. The lack of response in the third patient was attributed to thermal energy absorption and dissipation by a dural substitute that was placed at the time of previous craniotomy for resection of the GBM. This patient died 10 months after undergoing MRgHIFU, but the other 2 patients were still alive at 33 and 38 months post-ablation (which was the time of study publication). This study demonstrated that MRgHIFU was feasible and provided evidence for efficacy in the treatment of GBM.

A subsequent phase I safety and feasibility study by McDonnald et al. on 3 patients with GBM demonstrated the ability to deliver ultrasound energy to intracranial tumor targets without the requirement of craniectomy [63]. All 3 patients had previously undergone chemoradiation therapy for GBM but did not undergo previous craniotomy or craniectomy for tumor resection. A focused ultrasound beam was targeted to the lesion and temperatures were monitored using MR-thermography. This did demonstrate a rise in tumor temperature to a maximum of 51°C over all ultrasound pulses delivered in all 3 patients. No thermal coagulation was generated in the targeted tissue, which the authors note was due to technical limitations of their instrumentation with inability to generate enough power to raise the temperature higher than 51°C. Since focused ultrasound is delivered in short bursts, unlike the longer duration of light energy delivery seen with LITT, a higher temperature threshold is needed to initiate the apoptotic process. Importantly, however, this study did demonstrate for the first time that ultrasound energy could be targeted and delivered to focal tissue within the skull without creating a defect in the skull.

At this time, further studies regarding the use of MRgHIFU for the treatment of GBM are limited. Further phase 1 clinical trials are currently enrolling patients for study regarding the use of MRgHIFU in the treatment of GBM, but conclusions surrounding its efficacy, safety, and overall place in the treatment paradigm of GBM cannot be made at this time due to this lack of information.

6. Conclusions

GBM continues to carry a poor prognosis despite modern advances in surgical techniques and chemoradiation therapy, especially for patients with deep-seated lesions, lesions in eloquent areas, or recurrent lesions. Tubular retractor system, LITT, and MRgHIFU are minimally invasive options that have emerged as new treatment strategies for GBM. There has been a recent increase in the literature regarding the use of all these techniques for intracranial lesions, including GBM. These techniques provide alternative and effective means of cytoreduction in GBM. Importantly, these techniques expand treatment options for patients with lesions that previously may have been considered nonresectable based upon location or patient comorbidity factors. Use of these techniques should be considered in the initial or recurrent treatment of GBM. Further study will continue to define the precise role of these techniques. The present review adds to the literature as a collated resource for clinicians of the background and mechanisms, indications, utility, efficacy, and future directions regarding the use of minimally invasive surgical techniques for the treatment of GBM.

Author Contributions

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