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REVIEW ARTICLE

Cerebral microcirculation in glioblastoma: A major determinant of diagnosis, resection, and drug delivery

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Abstract

Glioblastoma (GBM) is the most common primary brain tumor with a dismal prognosis. Current standard of treatment is safe maximal tumor resection followed by chemotherapy and radiation. Altered cerebral microcirculation and elevated blood-tumor barrier (BTB) permeability in tumor periphery due to glioma-induced vascular dysregulation allow T1 contrast-enhanced visualization of resectable tumor boundaries. Newer tracers that label the tumor and its vasculature are being increasingly used for intraoperative delineation of glioma boundaries for even more precise resection. Fluorescent 5-aminolevulinic acid (5-ALA) and indocyanine green (ICG) are examples of such intraoperative tracers. Recently, magnetic resonance imaging (MRI)–based MR thermometry is being employed for laser interstitial thermal therapy (LITT) for glioma debulking. However, aggressive, fatal recurrence always occurs. Postsurgical chemotherapy is hampered by the inability of most drugs to cross the blood-brain barrier (BBB). Understanding postsurgical changes in brain microcirculation and permeability is crucial to improve chemotherapy delivery. It is important to understand whether any microcirculatory indices can differentiate between true recurrence and radiation necrosis. LITT leads to peri-ablation BBB opening that persists for several weeks. Whether it can be a conduit for chemotherapy delivery is yet to be explored. This review will address the role of cerebral microcirculation in such emerging ideas in GBM diagnosis and therapy.

KEYWORDS
5-ALA, brain drug delivery, brain tumor, contrast enhancement, EOR, GTR, indocyanine green, intraoperative MRI, laser interstitial thermal therapy

1 | INTRODUCTION

High-grade gliomas (HGGs), including Glioblastoma (GBM), are the most common primary malignant brain tumor in adults.[1] Despite intense research over the last 50 years, the survival of patients with HGG, a group comprising WHO grade III and IV malignant glioma tumors, continues to be poor.[2,3] The current standard of care consists of surgery followed by external beam radiotherapy (EBRT) and temozolomide (TMZ).[4] For GBM, the most common malignant glioma, the median survival is 14–16 months with a 2-year survival rate of about 30% following standard of care treatment.[5,6] With maximal cytoreductive surgery consisting of resection of the contrast-enhancing lesion up to 98%, survival can

Abbreviations: 5-ALA, 5-aminolevulinic acid; ADC, apparent diffusion coefficient; BBB, blood-brain barrier; BTB, blood-tumor barrier; DCE-MRI, dynamic contrast-enhanced MRI; DSA, digital subtraction angiography; DWI, diffusion-weighted imaging; EBRT, external beam radiotherapy; EOR, extent of resection; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma; GTR, gross total resection; HGG, high-grade glioma; iCEUS, intraoperative contrast-enhanced ultrasound; ICG, indocyanine green; ICG-VA, ICG-videoangiography; iMRI, intraoperative MRI; iUS, intraoperative ultrasound; LITT, laser interstitial thermal therapy; MRI, magnetic resonance imaging; NPV, negative predictive value; PFS, progression-free survival; PPV, positive predictive value; TIFP, tumor interstitial fluid pressure; TMZ, temozolomide; WHO, World Health Organization.

be increased by approximately six months in both primary and recurrent conditions.[7,8] Unfortunately, the prognosis is particularly poor; progression inevitably occurs, with 6-month progression-free survival (PFS) of 5–15%. Limiting treatment options, nearly all other approved and experimental drugs have shown no positive effects in glioma therapy. Molecular and genetic analyses have led to better disease stratification, but not to effective therapies.[9,10] Maximal resection of contrast-enhancing tumor followed by radiation and chemotherapy according to the Stupp protocol (EBRT/TMZ followed by metronomic TMZ) until evidence of recurrence is the only approved first line of treatment for newly diagnosed GBM. Indices of survival being directly proportional to the extent of resection (EOR), efforts are ongoing to maximize the surgeon's ability to identify the tumor margins during resection.[11]

GBM is highly vascularized tumors demonstrating angiogenesis and vascular co-opting to derive blood supply and energy to their proliferating and infiltrative regions. Thus, brain microvasculature plays a crucial role in sustaining GBM and, as a result, is also a therapeutic target.[12-17] Angiogenesis leads to leaky vasculature compared to the normal brain microvasculature that exhibits extremely low permeability to most blood-borne substrates. This property has been exploited in identifying tumor margins via gadolinium-based, T1 contrast-enhanced MRI.[18,19] With the absence of radiation and excellent soft tissue contrast, MRI is the preferred technique for brain tumor visualization for its localization.[20] Delineation of tumor boundaries is a pre-surgical necessity because tumors in or near eloquent regions, for example, Broca's area, require additional precautions during surgery. In addition, extravascular gadolinium contrast provides the most efficient approach that can be repeated over time to identify changing tumor margins due to disease progression or treatment. Recently, MRI has been supplemented with other tracer techniques that further enhance real-time tumor visualization during surgery and aid in maximal cytoreductive resection. Fluorescent 5-aminolevulinic acid (5-ALA)[21] and indocyanine green (ICG)[22] are examples of such intraoperative tracers that are approved for clinical use. In addition, intraoperative ultrasound (iUS) and its variation viz., intraoperative contrast-enhanced US (iCEUS) provide other methods for glioma visualization during surgery.[23]

Several other intraoperative brain tissue visualization and evaluation techniques such as Raman spectroscopy, optical coherence tomography, neurophysiological monitoring, stereotactic navigation, functional MRI, whole brain tractography, and diffusion tensor imaging are also employed to aid in efficient tumor debulking while sparing the normal brain tissue.[24,25] However, this review will focus on techniques that are primarily reliant on glioma microvascular flow (for delivering tracers), BBB/BTB permeability alterations (facilitating extravasation of contrast agents and fluorescent tracers), or endothelial metabolic alterations (aiding in preferential tracer accumulation in tumor).

2 | MAGNETIC RESONANCE IMAGING

MRI has the highest degree of fidelity in the diagnosis of GBM and is widely used for identifying the location and size of brain tumors. Thus, it is the imaging modality of choice to localize the presence of a suspected or confirmed GBM because of its sensitivity to soft tissue contrast, as well as to tumor-induced mass effect.[26] Hydrogen nucleus/water proton in body fluids and tissues is the MR active nucleus and used in clinical MRI. Since water exhibits high signal intensity on T2-weighted images, and GBMs have high levels of free water, T2-weighted images are used to visualize them. Conventional techniques employed for vascular imaging include spin echo and gradient echo sequences. In general, spin echo imaging uses radiofrequency pulse combinations at 90° and 180° pulses of inflowing protons. Gradient echo sequences are usually acquired with an initializing radiofrequency pulse followed by a refocusing gradient pulse, both at a given flip angle. These sequences can be supplemented with pre-saturation or gradient moment rephasing to visualize the flowing protons as either signal void (black blood imaging) or signal enhancement (bright blood imaging). They also provide excellent contrast between the tissue and the vessels and, thus, can be used to visualize vascular patency and any occlusions. Despite the utility of T2 imaging in tumor visualization, there are pathological conditions in which even the high T2 hyperintensity may be insufficient for accurate tumor detection. Although T1-weighted imaging shows higher signal-to-noise ratio in fat, tumor water demonstrates low signal intensity on T1. Enhancement agents (contrast agents) are then introduced to selectively affect the T1 and T2 relaxation times in tumors to facilitate accurate tumor detection. Use of MR contrast agents provides an additional level of vascular information. Unlike computed tomography contrast agents wherein the enhancement is directly due to the concentration of the agent used, in MRI the effects of the contrast agent used are measured. The most commonly used MRI contrast agents are gadolinium chelates.

MRI findings usually demonstrate an embedded mass with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. It is also characterized by irregular blood flow, internal cystic areas, areas with hemorrhagic foci (high T1 signal intensity), necrosis, peri-tumoral vasogenic edema, and significant mass effect such as ventricular compression, typical of space-occupying tumors. However, conventional MRI is limited in its ability to determine type and grade of brain tumors, but advanced MRI techniques, such as perfusion weighted imaging, may provide more physiologic information, potentially including glioma grading.[27] In addition, diffusion-weighted imaging (DWI) and its derivative apparent diffusion coefficient of water (ADC) are often used as surrogate markers of treatment response and tumor cellularity.[28] It has also been shown that dynamic contrast-enhanced MRI (DCE-MRI) data can be processed to produce sophisticated, quantitative, model selection maps of tumor segmentation based on vascular function in both preclinical models and clinical cases of GBM.[29,30] Recently, several novel dynamic contrast-enhanced (DCE) MRI biomarkers to measure tumor interstitial fluid pressure (TIFP), peri-tumoral flux and tumor cellularity have been described in preclinical models.[31-33]

The multi-planar structural data acquired by conventional MRI using T1-weighted, T2-weighted, and gadolinium-enhanced

sequences play a central clinical role in diagnosis, grading, and in monitoring treatment effects. It also has some limitations regarding the biological specificity of the underlying signals. T2-weighted dependent signal hyperintensity is dominated by tissue water content, and traditional T1 contrast enhancement reflects a non-specific increase in BBB permeability. Invasive and infiltrative GBM components not accompanied by edema or BBB opening can evade detection by proton MRI. Diagnosis can be further confounded by treatment-induced effects that somewhat limit the prognostic capacity of this type of imaging. Although gadolinium contrast is almost always used to measure T1-weighted contrast, the use of such agents is contra-indicated in cases with compromised kidney function.[34] Poor renal clearance of gadolinium in these cases is related to the development of nephrogenic systemic fibrosis or nephrogenic fibrosing dermopathy. Iron-based, blood pool contrast agents such as ferumoxytol can be an alternative under such circumstances. Compared to the lower average molecular weights of gadolinium-based contrast agents (eg, Magnevist = 938 Da), ferumoxytol has a molecular weight of 731 kDa.[35] Its large size confers ferumoxytol with imaging advantages like prolonged blood pool phase and delayed intracellular uptake.[36] Its long duration of intravascular space occupancy allows acute, high-resolution imaging of vascular space and delayed imaging of BBB disruption. In addition, studies have suggested that a combination of gadolinium and ferumoxytol imaging can assist in differentiating between radiation necrosis and pseudo-progression in recurrent GBM.[37] However, it needs to be noted here that use of ferumoxytol as a MR contrast agent is considered as off-label use. Other research has shown that tumor microvascular quantification using MRI-based vessel size imaging can be potentially of use in noninvasive grading of glioma severity[38] and, based on ADC alterations, in determining isocitrate dehydrogenase (IDH) mutation status.[39] Specific point mutations of the genes encoding IDH 1 or 2 suggest GBMs that are associated with a more favorable outcome. Thus, determining IDH mutation status has important implications in glioma prognosis.[40]

Due to its preferred status as the imaging modality of choice in GBM diagnosis, it is not surprising that intraoperative MRI (iMRI) has found applications in GBM surgery. It was first used by Black et al. in 1997 to treat intracranial lesions.[41] Since then it has become a part of the neurosurgical instrumentation to determine the presence of residual tumor. One of the great advantages of iMRI is that it compensates for changes in brain morphology after craniotomy and dural opening that can make relating to pre-surgical tumor loci difficult. Improvements in image quality and the availability of new MR sequences have co-evolved with the use iMRI. iMRI is also used during surgery to update contrast-dependent neuronavigation to confirm tumor tissue shift due to cerebrospinal fluid loss and debulking.[11] Its utility is evident by data from studies that have compared EOR in cases that were iMRI-aided to those that were not. The addition of iMRI increased EOR from about 58% to 71% in one study.[42] Gross total resection (GTR) also increased with the addition of iMRI. Another study reported that GTR and overall survival were better and postsurgical complications were lower after iMRI-aided tumor debulking.[43] Thus, despite the high cost, iMRI has become an indispensable tool in glioma surgery due to its ability to identify GBM vascular features and tumor tissue status.[25]

3 | 5-AMINOLEVULINIC ACID

5-ALA is a prodrug preferentially metabolized by glioma cells that allows direct, real-time visualization of pathologic tissue through fluorescence under 400–410 nm blue light.[21] Its exact mechanism is unclear, but via heme metabolic pathways tumor cells preferentially accumulate the fluorescent reaction product protoporphyrin IX than in the surrounding normal cells. Although not directly reliant on glioma microvascular flow or permeability abnormalities, endothelial proliferation in glioma is presumed to play a major role in tumor-specific accumulation of 5-ALA. The European Medicines Agency officially authorized 5-ALA for use in glioma in 2007 and it was approved in the United States in 2017. The prodrug is usually given orally at least 4–6 h before surgery to achieve peak tumor accumulation. However, 5-ALA alone does increase EOR by itself while also increasing PFS. A phase II randomized trial showed that traditional white light microscopy-based resection achieved 6-month PFS of 21% compared to 41% in 5-ALA-based resection.[44] Significantly more EOR and PFS was also achieved with the use of 5-ALA (18 months and 97%) compared to white light (6 months and 85%) in another study.[45] It can also be used in conjunction with iMRI with contrast enhancement. When used in combination, 5-ALA can help localize MRI-invisible tumor tissue that is associated with an intact BBB. Thus, the two techniques are mutually complementary and augment EOR when used together. Therefore, experts recommend using 5-ALA in conjunction with iMRI (Figure 1) which increases EOR significantly.[21] In support of this, 5-ALA alone led to total resection in 46% of cases, whereas the addition of iMRI resulted in total resection in 74% of the cases.[42] With its ease of application, ability to seamlessly combine with iMRI and high tumor-specificity, 5-ALA is considered the gold standard in intraoperative glioma visualization.

4 | INDOCYANINE GREEN

Indocyanine green videoangiography (ICG-VA) is a near-infrared range fluorescent marker used for intraoperative real-time assessment of flow in cerebrovascular surgery.[22] ICG has a positive patient safety profile and is well tolerated in clinically required doses. It provides high spatial and temporal resolution and is extensively used in visualizing cerebral aneurysm repair and vessel grafting. ICG is given as an intravenous injection and binds to plasma proteins and remains intravascular. With a plasma half-life of 3–4 min, repeat bolus injections of ICG can be made for continuous vessel monitoring. ICG binds to plasma proteins and turns into a blood pool agent with a short half-life despite its small size (775 Da). This feature facilitates repeated injections at quick intervals to visualize the temporal phases of microvascular flow, viz., arterial, capillary and a

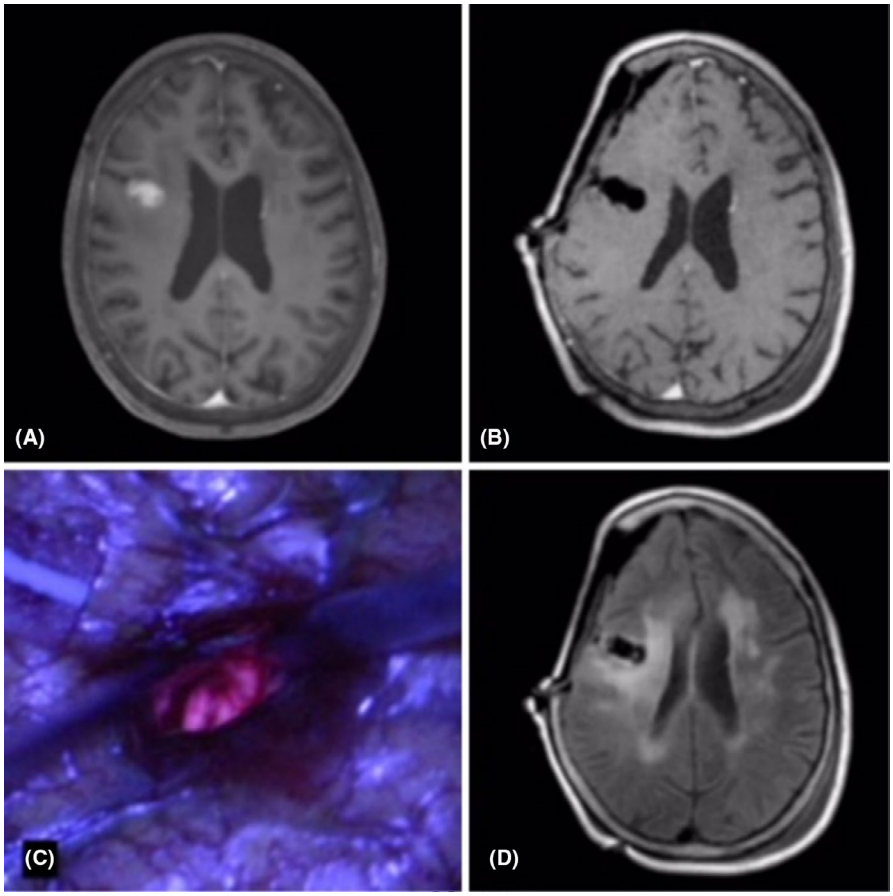

FIGURE 1 (A) Preoperative MRI T1+ gadolinium contrast (Magnevist) depicting right frontal contrast-enhancing lesion. (B) Intraoperative MRI T1+ contrast depicting gross total resection of all enhancing tissue. (C) View through operative microscope with blue light demonstrates residual fluorescence, though not as avid as the majority of the tumor. (D) Intraoperative MRI T2 fluid-attenuated inversion recovery (FLAIR) sequence, likely representing residual non-enhancing lower grade tumor cells. (Reproduced with permission from:Haider SA et al. *Journal of Neuro-Oncology*. 2019;141(3):507–515. https://doi.org/10.1007/s11060-018-03061-3)

combined arteriovenous phase due to dye recirculation. In its basic use, ICG-VA provides low cost, useful, real-time qualitative and quantitative information regarding cerebral blood flow in the visual field. The addition of digital subtraction angiography (DSA) enhances ICG-VA capability, but is an expensive, labor-intensive procedure.[22] ICG is often used in transplantation surgery to test the patency of grafted blood vessels, in repairing brain aneurysms and to visualize ischemic regions during such procedures. However, its application in the study of the vascular pathophysiology in central nervous system tumors and its potential utility in their surgical management is still limited. Recently, however, several studies are exploring ICG-VA as a tool in brain tumor resection. One study examined the feasibility of ICG-VA in 71 brain and spinal tumor subtypes, including 14 cases of glioma.[46] This study included the addition of a novel FLOW 800 algorithm integrated with the surgical microscope. This algorithm calculates fluorescence intensities in the exposed areas based on the average arbitrary intensity units detected by the camera and reconstructs maps of maximal fluorescence intensities and of delay times, producing semiquantitative cerebral blood flow estimates. It was noted that pre-surgical imaging helped plan the surgery and postsurgical imaging aided in estimating local hypoperfusion and associated risks. Several patients received multiple ICG injections with no apparent negative side effects. The ability of ICG to bind to plasma proteins and remain intravascular in normal blood vessels has been exploited in a "Second Window ICG" technique for GBM resection that utilizes the inherently increased permeability of the tumor vasculature. A high dose of ICG was delivered ~24 h before surgery, leading to extravasation and accumulation of the tracer within the tumor allowing real-time intraoperative tumor identification to optimize surgical resection.[47] It was observed that ICG accumulation in tumor tissue was stable between 6 and 48 h after administration allowing a broad timeframe for surgical planning. ICG-VA has been also used to identify the venous drainage pattern and collateral circulations during tumor resection for possible venous sacrifice to predict and minimize the potential side effects.[46] Larger clinical trials that include survival and quality of life measures are needed to make the ICG-VA technique, as well as its potential combination with iMRI, more widely applicable in GBM resection.

5 | FLUORESCEIN AND INTRAOPERATIVE CONTRAST-ENHANCED ULTRASOUND

Fluorescein has been found to be useful in glioma surgery due its accumulation in tumors with increased vascular permeability.[48] It resembles the MR contrast agents in this respect, but requires sophisticated intraoperative fluorescence microscopy for its localization. Although under clinical trials, but currently not approved by Food and Drug Administration in the United States, fluorescein has been shown to increase tumor debulking in GBM with 83% GTR in the fluorescein group (n = 47) compared to 55% in the non-fluorescein group (n = 33); this efficacy was also seen in median survival

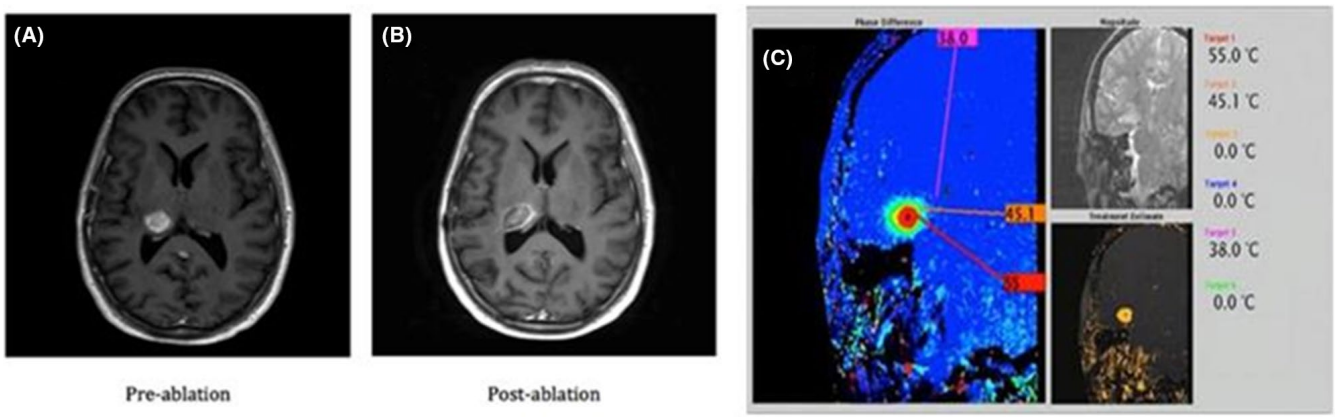

FIGURE 2 Pre- (A) and post-laser ablation (B) MR images in recurrence in left thalamic GBM. Note the peri-ablation gadolinium contrast enhancement in B. The panel (C) shows the temperature map from MR thermometry. The intraoperative MR thermometry map was used to precise definition of ablation margins and to spare maximum possible, normal peri-tumoral brain tissue. This image was generated while using a Visualase LITT system (Medtronic, Inc., Minneapolis, MN). It uses a saline-cooled diode laser with a near-infrared (980 nm) wavelength. This wavelength has a high water absorption coefficient, which produces rapid heating and a sharply delineated ablation zone. Note the minimally distorted skull and brain anatomy in 2A and 2B compared to images in Figure 1B,D

time, with 46 and 34 weeks for the fluorescein and non-fluorescein groups, respectively.[49] Better GTR under fluorescein-guided GBM resection was also reported by Neira JA et al.[50] If and when approved, fluorescein can provide another tumor vascular permeability-based, intraoperative tracer in GBM resection.

We note here that although both 5-ALA and fluorescein are fluorescent, there are some important differences between them. Fluorescein is seen primarily as a marker for contrast leakage so it can act as a surrogate for contrast enhancement. 5-ALA is a metabolic marker. This is borne out by the fact that while the positive predictive value (PPV) for fluorescence is very high (essentially 100%), the negative predictive value (NPV) is very low (more like 20%). This is reflective of the both local and diffuse nature of gliomas with high-grade (high fluorescence) tumor in the area of contrast enhancement, whereas the non-fluorescent areas will still have tumor tissue, but in lower concentration and lower grade.

Ultrasound is a low cost, portable imaging modality with a long history of successful applications in various organ systems. iUS is reported to be useful in brain and spinal tumor surgery and assists in increasing GTR and EOR.[51] Increased survival (11.9 as opposed to 9.6 months) was found after retrospective analysis in one study.[52] Notably, Jakola et al reported that the use of iUS was associated with better quality of life in glioma patients.[53] The efficacy of iUS can be improved by using iCEUS. This technique uses microbubbles injected intravenously just before beginning the imaging procedure and increases EOR as well as provides a better detailed picture of tumor-associated microvasculature.[23] In a prospective study of 10 patients, these authors observed that the use of CEUS before, during, and after surgery helped in tumor localization, maximizing GBM resection. The iCEUS images could be superimposed over preoperative MR images for confirmation and resected tumoral areas were confirmed by histopathology for the presence of tumor tissue. In addition, the contrast enhancement progression allowed visualization of arterial macrovessels within the lesion with a rapid venous phase composed of multiple veins aiming toward the periventricular zone.[23] With confirmation by larger cohort studies, iCEUS can be a valuable tool in GBM surgery and tumor vascular visualization.

6 | LASER INTERSTITIAL THERMAL THERAPY

Recently, laser interstitial thermal therapy (LITT) has emerged as a minimally invasive technique to treat brain tumors.[54-59] Through the use of MR thermometry, tumor ablation can be tracked in real time, thus obtaining precise margins with prompt recovery and minimal surgical side effects when compared to traditional techniques.[60-63] Accordingly, this technique is often used for recurrent brain tumors and for primary tumors in locations where conventional techniques might leave the patient with profound disability. In the post-LITT period, the rim of tissue around the ablation periphery is reported to develop a relatively long-lasting (several weeks) and localized BBB breakdown, as evidenced by a characteristic rim contrast enhancement on post-ablation T1-weighted MRI.[64,65] LITT is reliant on iMRI for laser fiber insertion into the tumor core and for monitoring the extent of ablation in real time. It also has the advantages of being minimally invasive (a small burr hole made for the laser fiber in contrast to a craniotomy for traditional resection), quicker recovery time and shorter hospital stay for the patient. With the absence of craniotomy and dural opening, tissue shifts due to cerebrospinal fluid loss are also minimized and the iMRI is likely to have a greater degree of agreement with pre-surgical scans in determining glioma debulking limits.

LITT is increasingly being used for cytoreductive surgery in recurrent glioma. It relies on a stereotactically guided laser probe to deliver

heat in a controlled manner and ablate the surrounding tumor tissue (Figure 2A,B). Uniquely, LITT uses MR thermometry which allows the expansion of the ablation to be closely monitored in real time (Figure 1C), thereby sparing surrounding brain tissue.[66] Of particular importance, MRI after LITT demonstrates post-contrast enhancement in the periphery of tissue ablation zones. Within the ablation zone, the tissue undergoes coagulative necrosis, which is thus impermeable, as evidenced by the lack of contrast enhancement in the core. However, the temperature achieved (about 40–43°C) in the perilesional zone is not high enough to cause cell death, but does result in disruption of the BBB (Figure 2B). LITT is also the GBM cytoreductive procedure with a specific, relatively long-lasting effect on peri-tumoral BBB permeability. This raises the question as to whether LITT breaks down the BBB sufficiently to deliver chemotherapy agents in useful concentrations to the surrounding brain. Available published reports are supportive. For instance, in a rodent model, heating by a Nd-Yag laser resulted in increased diffusion of Evans blue (a fluorescent dye often used to visualize BBB breakdown) and paclitaxel in the vicinity.[67] Similarly, in microwave-induced hyperthermia in monkeys, a ring of contrast enhancement appeared on MRI, confirmed as disruption of the BBB by extravasation of Evans blue.[68] Other studies have examined methods for BBB disruption, for example, radiofrequency ablation to cause local heating of brain tissue[69]; more recent studies using lasers have demonstrated transient disruption of the BBB in an animal model[70] and after LITT in humans.[65]

7 | GLIOMA DRUG DELIVERY

Even in cases of surgical resection with maximal removal of the contrast-enhancing lesion, infiltrative tumor cells reside in the peripheral margin. However, the BBB, which functions to protect the brain from foreign substrates, is mostly intact following surgery. Nearly 98% of small molecule drugs and all large molecule drugs do not cross the BBB.[71-74] Thus, inadequate drug delivery to the brain is a major limiting factor in the treatment of HGG.[9,75] Several different approaches are being tried to enhance drug delivery to the brain.[76] They include transient opening of the BBB via infusion of hyperosmotic mannitol,[77] focused ultrasound,[78,79] Trojan horse approach via endothelial transferrin receptors[74] and ultrashort pulsed laser.[80] A promising clinical treatment is osmotic BBB opening using intra-arterial mannitol infusion.[81] A bolus of mannitol is infused via either internal carotid or vertebral artery to transiently and unilaterally open the BBB for chemotherapy delivery in this technique. It has been successfully used in the treatment of primary central nervous system lymphoma and other brain tumors with intraoperative monitoring to confirm BBB opening.[82] Yet, drug delivery to a large number of primary, recurrent and metastatic brain tumors to achieve durable response remains a challenge.[76,83-85] There is benefit to circumventing the BBB as demonstrated by the therapeutic effects of inserting carmustine-impregnated polymer wafers (Gliadel) into the surgical cavity.[86,87] LITT-induced transient BBB opening observed in GBM assumes significance in furthering such efforts to overcome the BBB for effective glioma drug delivery.

8 | PERSPECTIVE

It is now recognized that just like a combination of treatments for GBM, also needed is a combination of multimodal, intraoperative imaging techniques to achieve as complete a tumor resection as safely possible. Several such techniques that exploit the microvascular alterations in GBM are available and are being continually optimized for intraoperative applications. The techniques described above utilize GBM vascular flow, permeability or other functional alterations to assist in intraoperative visualization for increasing resection efficacy. However, more research needs to be done for a better understanding of the relationship between the tumor and surrounding normal brain tissue, microcirculation and their interactions to develop technologies and tracers with high specificity and sensitivity. In addition, standardization of image acquisition and analysis techniques for various MRI parameters needs to be achieved for efficient monitoring of resection as well as treatment efficacy and their inter-institute comparisons.[88] For instance, note the effects of bevacizumab on GBM. The drug led to acutely decreased contrast enhancement, but that did not represent true tumor response. The decrease represented lowered BBB/BTB permeability and potentially the switch of the tumor growth pattern to an infiltrative, non-enhancing phenotype.[89] The recently described DCE-MRI parameters that represent several, inter-dependent, concurrently measured parameters may be of help in resolving such false-positive results.[30] Drug delivery to gliomas remains a challenge. A greater understanding of permeability alterations and vascular adaptation changes in tumoral and peri-tumoral cerebral microvasculature is crucial to overcome this obstacle to effective treatment.

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CONFLICT OF INTEREST

TNN declares no conflicts of interest. IYL has consulting agreements with Medtronic, Inc., Minneapolis, MN, USA, and Monteris Medical, Inc., Plymouth, MN, USA.

DATA AVAILABILITY STATEMENT

Data presented in Figure 1 of this manuscript are from the senior author's own previous publication available on public domain. Data in Figure 2 are unpublished and available as part of the data repository in the Department of Neurosurgery.

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