Stereotactic Laser Ablation of Glioblastoma

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KEYWORDS

• Laser interstitial thermal therapy • LITT • Stereotactic laser ablation • SLA • Glioblastoma • GBM

KEY POINTS

- Over the past decade, laser interstitial thermal therapy (LITT) has emerged as a valuable surgical tool that allows for glioblastoma (GBM) cytoreduction in deep-seated and/or eloquent lesions that are otherwise inoperable.
- When compared with frequently used treatments for GBM, current literature suggests that LITT compares favorably in terms of outcomes, complication rates, preservation of quality of life, and cost-effectiveness when adequate extent of ablation is achieved.
- Given its minimally invasive nature, current research is focused on LITT's potential to disrupt the blood-brain barrier and induce immunomodulatory effects. Clinical trials are currently being conducted using LITT in combination with other therapies, such as immunotherapy, to investigate these phenomena.
- Because no randomized controlled trials have been performed, well-designed, prospective trials are needed to further define the utility and outcomes of LITT for GBM.

INTRODUCTION

Laser interstitial thermal therapy (LITT) is a minimally invasive surgical procedure that uses a laser probe inserted through a burr hole to deliver optical radiation and thermal damage to intracranial lesions.[1] Although the modern concept of using a stereotactically introduced, intracranial laser probe to deliver thermal damage was first formalized in the 1980s and used experimentally in clinical practice shortly thereafter, limitations inherent to the technology of the time prevented its widespread adoption.[2–4] In recent decades although, improvements in equipment such as laser probe design and cooling, stereotactic targeting hardware, and real-time thermography have allowed neurosurgeons to effectively and safely deliver targeted treatments.[5] These key advancements have increased the clinical deployment of LITT as a management option for a variety of neurosurgical pathologies, including gliomas, brain metastases, and radiation necrosis, as well as some indications outside the neuro-oncology sphere, such as epilepsy.[6,7] This review aims to describe the current state of the technology, operative technique, and periprocedural practices, as well as summarize the data regarding outcomes and future directions in the use of LITT for treating glioblastoma (GBM).

SURGICAL METHODOLOGY

Laser Interstitial Thermal Therapy Systems

There have been 2 widely used and Food and Drug Administration (FDA)-approved systems for LITT: the Medtronic Visualase (Medtronic; Minneapolis, Minnesota) and the Monteris NeuroBlate (Monteris; Plymouth, Minnesota) systems (Fig. 1). Both systems rely on the principle of selective transmission of laser energy with resultant interstitial

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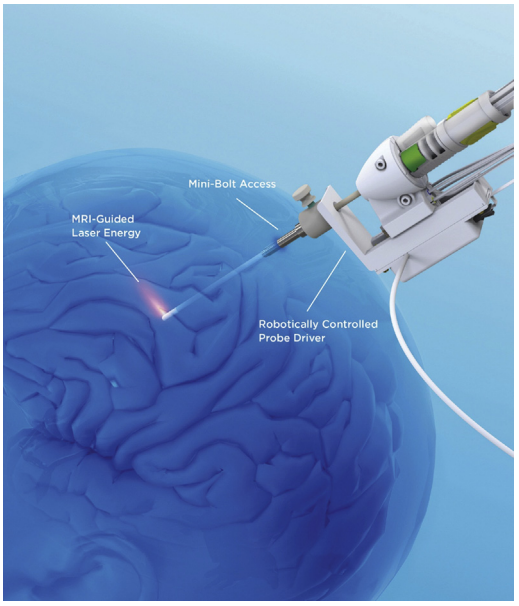

Fig. 1. The NeuroBlate system for stereotactically targeted treatment of intracranial lesions, including GBM. (Used with permission. © 2020 Monteris Medical.)

hyperthermia and tissue ablation based on the Arrhenius equation.[8] The Visualase system uses a liquid saline–cooled, 15W 980 nm diode laser with a 1 cm omnidirectional tip. Emission at 980 nm allows for a higher water absorption coefficient and therefore faster heating of affected tissue and less tissue penetration, allowing for sharper delineation between zones of thermal injury.[9,10] The Visualase system allows operators to set temperature limit points at zones within the affected tissue, usually set at 90°C at the tip of the probe and 50°C at the periphery of the lesion, to prevent carbonization and vaporization of the treated tissue. On initiation of the laser, fast-spoiled gradient-recalled echo (GRE) images are obtained, and test 3 to 4 W pulses are administered to determine the exact location of the 1-cm laser-emitting distal tip of the probe.[6,11,12] The Monteris system uses a 12 W neodymium-doped, yttrium aluminum garnet (Nd:YAG) diode laser with an emission of 1064 nm, which is cooled by gaseous carbon dioxide and has both omnidirectional and directed, side-firing tips.[6,13,14] Emission at 1064 nm allows for greater tissue penetration and therefore greater ablation volumes in regions of high blood perfusion. Use of the side-firing directional tips, although decreasing rate of tissue heating, allows for greater sculpting of thermal injury zones and conformation to tumor margins.[9,10] Monteris systems also have both 3.2 and 2.1 mm probes, allowing for tailoring of treatment plans.[15]

Laser Interstitial Thermal Therapy Procedure

Before the initiation of the procedure, patients undergo contrast-enhanced, T1-weighted volumetric MRI scans for planning and stereotactic navigation, with further imaging depending on tumor location (eg, diffusion tensor imaging [DTI] and functional MRI for characterization of white matter tracts and eloquent cortex).[16–18] Trajectories for biopsy/treatment are planned on neuronavigation software, with an ideal trajectory traveling down the long axis of the targeted lesion while avoiding sulci, vascular structures, and eloquent white matter tracts.[17,19]

The patient is induced under general anesthesia and fixed to the table using an MRI-compatible, 3-point cranial fixation device. Scalp fiducials are registered, a frameless stereotactic guidance system is aligned to the predefined trajectory, and biopsy specimens are obtained for histopathologic diagnosis.[20] Using the same trajectory, the hollow bolt is screwed into the skull for precise passage of the laser. In Monteris systems, the 142-mm lower profile Monteris MiniBolt can be used for single passes, whereas the 197 mm Monteris Axiis frame is required for multiple trajectories instead of using several MiniBolts.[17] The laser probe is then attached to the frame and introduced into the tumor along the planned trajectory. The patient is then further draped, the MRI bore is brought into the operating theater (or the patient is taken to an MRI suite if intraoperative MRI is not available), and a scan is performed confirming the location of the probe.[14] The final position of the probe tip is optimized using the probe driver, and in Visualase setups, 3 to 4 W test pulses administered under continuous image acquisition confirm distal tip location.[18–20] The laser probe output is increased to treatment dosages, and the therapy commences. Throughout the lasing portion of the procedure, GRE MRI sequences are continually obtained at roughly 8-second intervals for acquisition of thermometry data.[21] The images are deconvoluted, displayed at the Visualase or NeuroBlate workstation, and allow for near real-time monitoring and manipulation of laser output, ablation depth, or in the case of NeuroBlate side-firing tips, directionality of thermal damage (**Fig. 2**).

The extent of thermal damage and ablation (EOA) is calculated by an algorithm incorporating temperature and time and is displayed as thermal damage threshold (TDT) lines. Yellow TDT lines indicate regions of tissue exposed to 43°C for 2 minutes, blue TDT lines indicate regions exposed to 43°C for 10 minutes (or higher temperatures for shorter durations), and white TDT lines indicate regions exposed to 43°C for 60 minutes (see

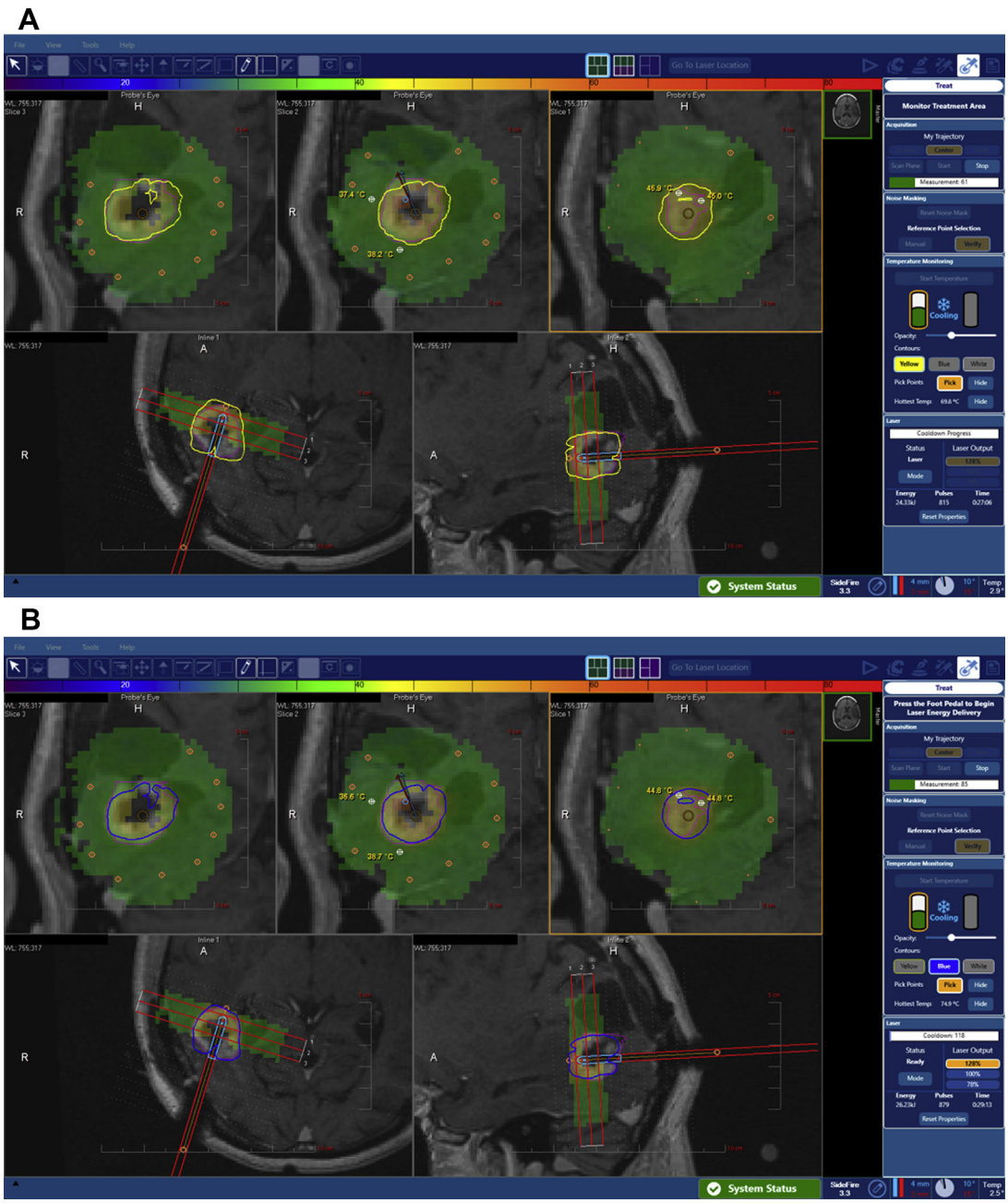

Fig. 2. Intraoperative view from LITT workstation during treatment of a right-sided tumor. The operator is able to manipulate the laser's depth and directionality to conform energy delivery to tumor boundaries (*pink line*). (*A*) Example of a yellow TDT line (defined as the tissue exposed to 43°C for 2 minutes) and (*B*) a blue TDT line (43°C for 10 minutes). (Used with permission. © 2020 Monteris Medical.)

Fig. 2).[14,22] In preclinical studies, tissue within white TDT lines suffered 100% death within 48 hours, whereas tissue outside of the yellow TDT line boundaries demonstrated no irreversible damage.[19] Tumor volumes within the blue TDT lines have been associated with necrosis, whereas volumes inside the yellow line have been associated with apoptosis.[23] Recent histopathologic analysis demonstrated 3 concentric zones of cellular architecture radiating outward from the thermal source. The innermost zone 1 harbors necrotic cells, the middle zone 2 has a rim of granulation tissue, and the outermost zone 3 contains viable tumor cells, although these zones have not

been specifically linked to the intraoperative visualized TDT lines.[24] Treatment zones typically stop enlarging about 15 seconds after ceasing of laser activity.[19]

Although most of the tumors in several series (more than 80%) have been successfully treated using one trajectory, larger or more irregular lesions may require multiple trajectories in a single procedure (up to 3 trajectories in a single setting).[17,25] On completion of treatment, the MRI, laser probe, and stereotactic frame are removed, and closure is performed similar to a standard stereotactic biopsy. Postoperatively, patients are placed on dexamethasone to mitigate edema and monitored in a neurosurgical step-down or intensive care unit overnight. In many institutions, a postprocedure MRI is performed on the day after surgery to assess the EOA, extent of edema, and serve as the new baseline for monitoring progression.[17] Postoperative MRIs demonstrate 5 zones of tissue damage post-LITT: the probe track itself, a central zone centered at the laser probe tip that has foci of hemorrhage on susceptibility weighted imaging, a peripheral zone corresponding to the treated tissue, a thin rim surrounding the peripheral zone, and the peritumoral edema.[26] With larger tumors that have undergone LITT, some centers have attempted to mitigate postoperative swelling with minimal-access craniotomies and debulking of thermally treated tumors, although this not routinely performed.[27–29] Patients are typically discharged from the hospital within 1 to 2 days on a rapid steroid taper, with monitoring MRIs typically performed 1 to 2 months postprocedure and every 2 to 4 months subsequently (**Fig. 3**).[30]

DISCUSSION

Current Evidence

The first use of the Nd:YAG laser system to treat brain tumors in humans came in 1990 when Sugiyama and colleagues[3] reported on the outcomes of 5 patients. However, formal FDA approval for the modern LITT systems (ie, NeuroBlate and Visualase) would not come until decades later. Since then, publications reporting outcomes data in GBM have steadily increased, which will be summarized hereafter.

Outcomes in newly diagnosed glioblastoma

Although there are numerous case series reporting on the outcomes of patients with GBM treated with LITT, most of the early literature did not stratify the outcomes by upfront versus recurrence or glioma World Health Organization (WHO) grade. Because of this, higher-quality outcomes data on nGBM treated upfront with LITT was very sparse until 2019, when Mohammadi and colleagues[31] published the first and largest multiinstitutional retrospective cohort study. In it, 24 patients with nGBM were treated initially with LITT followed by concurrent chemoradiation therapy (CRT) and were compared with a matched control group who underwent biopsy-only followed by CRT, with median follow-up times of 9.3 months (2–43) and 14.7 months (2–41), respectively. Most of the patients receiving LITT had deep-seated GBMs or were not good candidates for standard microsurgical resection. The 2 groups had similar characteristics, including age, sex, and location (including the thalamus in ~30% of each group). Contrast-enhancing tumor volume (CETV) and Ki-67 was similar between the 2 groups (LITT group with mean CETV of 9.3 cc); however, the biopsy-only group had more favorable molecular markers with respect to IDH1 and MGMT methylation status. There was no statistically significant difference in the median progression-free survival (PFS) and overall survival (OS) between the overall LITT and biopsy groups: PFS: 4.3 versus 5.9 months (P = .94), OS: 14.4 versus 15.8 months (P = .78).[31] Of note, the landmark trial by Stupp and colleagues in nGBM reported a median OS of 15.8 months with a complete/partial resection followed by CRT and a 9.4-month OS in those with biopsy plus CRT. Therefore, Mohammadi and colleagues's[32] biopsy-only group seems to have above-average outcomes, and this may be partially explained by the favorable molecular markers in that group. However, when LITT patients were stratified by EOA, those with favorable EOA had improved (lower) disease-specific PFS and OS cumulative incidence at 12 months compared with those with biopsy only (disease specific progression free survival, confidence interval [CI]: 25% vs 63%, P = .05; DSOS CI: 25% vs 31%, P = .03).[33–35] The effect of EOA will be discussed in further detail in a later section.

Other smaller studies have published on LITT as a primary treatment of nGBM. Shah and colleagues[36] reported in 2019 on 11 patients with nGBM who underwent LITT as a primary treatment of deep-seated tumors (median depth 60.4 mm [range 46.2–68.2]). Mean CETV for their cohort was 6.8 cc (1.2–127.0), and mean EOA was 98%. They report a median PFS of 31.9 months and a median OS of 32.3 months. Other studies from 2012 to 2016 with between 2 and 16 patients with nGBM each reported on patients treated with upfront LITT for newly diagnosed high-grade gliomas (nHGGs), showing much shorter average PFS of between 2.0 and 5.1 months (range 2.0–23) and a median OS of

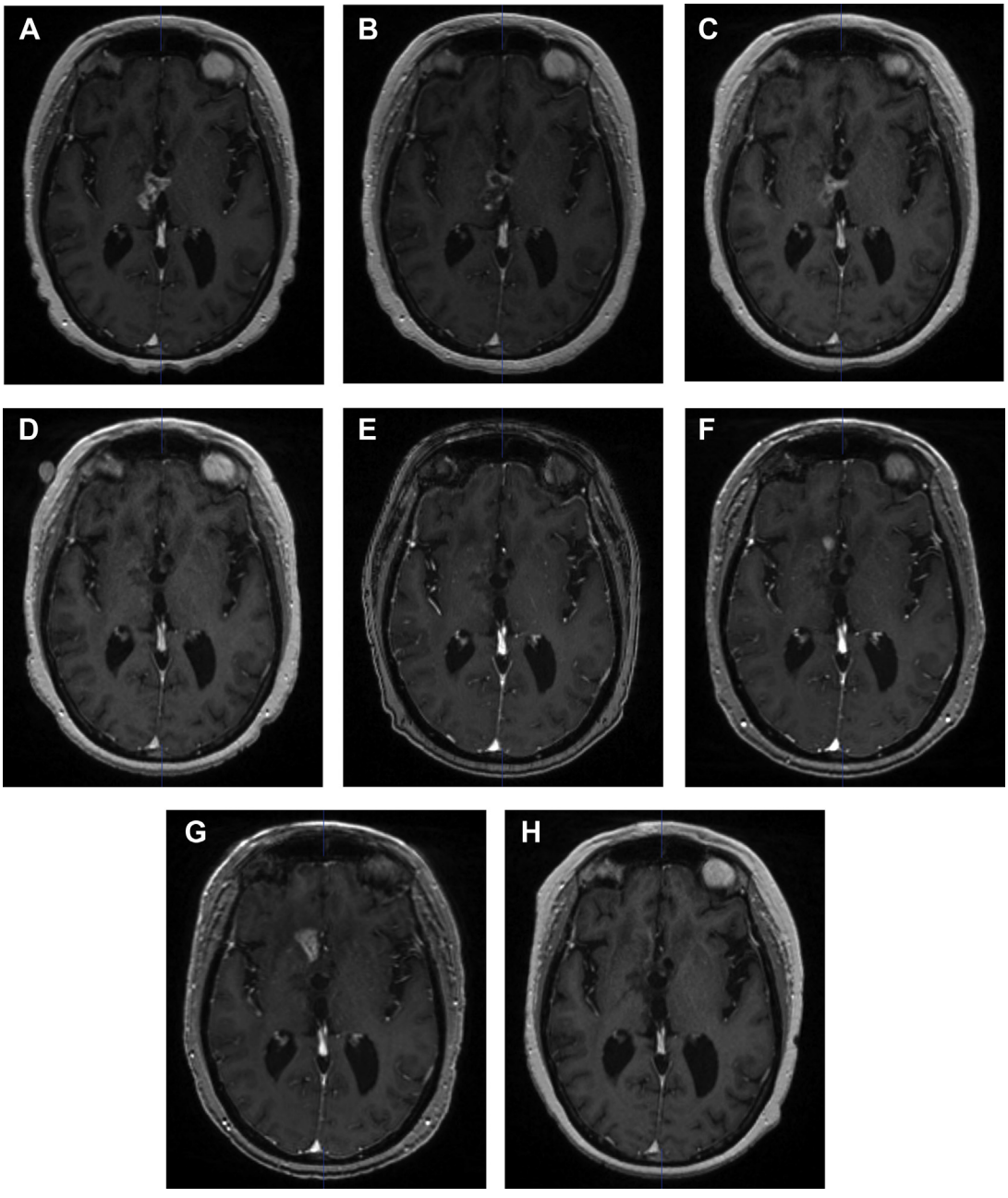

Fig. 3. A 54-year-old patient treated with LITT for recurrent GBM of the right thalamus. Contrast-enhanced, T1-weighted MR images at (*A*) preoperative, (*B*) immediate postoperative, (*C*) 2-, (*D*) 5-, (*E*) 7-, (*F*) 10-, (*G*) 12-, and (*H*) 14-month time points, showing the radiographic evolution of the LITT-treated lesion. The lesion recurred at an adjacent site within the corpus callosum, which was then treated with stereotactic radiosurgery (*F–H*). The patient survived 18.7 months from the time of LITT treatment.

14.2 months (range 0.1–23) in a small meta-analysis of these data.[14,27,30,37–41] The limited sample sizes, lack of consistent availability of EOA, retrospective nature, and outcomes variability limit the interpretability of these data. Therefore, given the evidence to date, LITT has not been established as a first-line therapy for nGBM in most of the cases. Well-designed, prospective trials should be undertaken to assess LITT's impact as an upfront treatment of nGBM, specifically in those for whom surgical resection is infeasible.

Outcomes in recurrent glioblastoma

Compared with LITT for nGBM, a greater number of studies have reported on their outcomes in patients with rGBM.[25,42] One of the earliest publications (first in human study) using a modern LITT system for rGBM was performed by Sloan and colleagues[19] in 2013 from a phase I, thermal dose-escalation trial. Ten patients were included in their initial study, with a mean CETV of 6.8 cc ± 5 and mean EOA of 78% +/− 12%. The median OS was 10.4 months (range 2.0–25.2), with 3 patients improving neurologically, 6 remaining stable, and 1 worsening.[19] Given these promising results, multiple case series were subsequently published; however, as mentioned previously, many studies did not stratify their outcomes by nGBM versus rGBM, or WHO grades 3 versus 4, limiting the interpretability of the data.[43]

More recent studies have stratified their outcomes data by recurrence status, such as the one by Thomas and colleagues[30] in 2016. This paper describes their experience with 13 patients with rGBM undergoing LITT. The mean age was 49 years, with a mean time from diagnosis of 16 months. Sixty-two percent of lesions were located in eloquent areas, and 69% were multifocal, with an average CETV of 14.6 cc. This group had a median PFS of 5 months and a median OS of greater than 7 months from LITT, as 7/13 patients were still alive at the time of publication.[30]

In 2019, Shah and colleagues[36] analyzed outcomes in 14 patients treated with LITT for rGBM. Their patients had a mean age of 54 years and median preoperative CETV of 3.8 cc (range 0.5–15.8). All lesions were considered deep seated and were treated to a median EOA of 87.5% (range 77.0%–99.5%). The investigators report a median PFS of 5.6 months and OS of 7.3 months. Similarly in 2019, Kamath and colleagues[44] reported on their center's outcomes in 41 patients with rGBM treated with LITT, with 35 of them on their first recurrence. Median PFS was 7.3 months (95% CI 5.1–8.9, range 0–32) and median OS was 11.8 months (95% CI 8.6–13.8, range 0–34.2). When calculated from time of the initial GBM diagnosis, their OS was 22.3 months (95% CI 16.2–26.8).

No study has directly compared LITT versus other treatment modalities for rGBM in a prospective format, requiring other literature to derive outcomes from comparator cohorts. A recent study with 299 patients with rGBM reported median OS of 3.1 months for best supportive care, 7.3 months for systemic therapy, and 11 months for reresection followed by adjuvant treatment, with no statistically significant difference found between systemic therapy and reresection groups when controlling for multiple confounders.[45] For the patients receiving systemic therapy and reresection, median PFS was 4.3 months and 9.0 months, respectively. Given the deep-seated nature of many of these rGBM lesions treated with LITT, the current LITT outcomes compare favorably with frequently used treatments for rGBM such as systemic therapy and reresection. Head-to-head trials are needed to further clarify the utility and outcomes with LITT for rGBM.

Preservation of quality of life and functional status

Although LITT has often been presented as a more minimally invasive, less morbid alternative to craniotomy, high-quality prospective data supporting that belief has been lacking until recently. The Laser Ablation of Abnormal Neurologic Tissue Using Robotic NeuroBlate System (LAANTERN) Study is an ongoing, prospective, multicenter registry enrolling patients undergoing treatment with the NeuroBlate system. Its outcome data include cognitive, functional, and quality of life (QoL) metrics, among others, with the first report of these data only recently published for 223 patients with brain tumors.[42] Of these 223 patients, 90 had HGGs, with an estimated survival rate of 59% at 12 months (95% CI 55%–79%). A mean Karnofsky Performance Score (KPS) change of −5.4 points ± 11.7 was seen at the 1-month follow-up compared with baseline KPS (86.2 ± 11.8), which stabilized from the 1-month score until the 12-month time point, where a median decrease of −13.2 points compared with baseline was seen ($P < .0001$). Fifty-one percent of patients had no change or an improvement in their KPS at 6 months. Within the Functional Assessment of Cancer Therapy-Brain data looking at social, emotional, and functional well-being, there was no clinically meaningful changes (>10% of instrument range) seen at the 1-, 3-, 6-, or 12-month time points when compared with baseline. In the EuroQol 5-dimensional questionnaire, improvements were seen in the subscores for mobility, self-care, and usual activities, and scores for pain/discomfort, anxiety/depression, and visual analogue scale were stable.[42] These data suggest that on average, QoL remains stable both in the immediate and long-term post-LITT period and that improvements can be seen in patient mobility, self-care, and ability to participate in usual activities.

Other quantitative measures of the minimally invasive nature of the procedure were also reported in the 2020 LAANTERN data.[42] Mean blood loss for primary tumor cases was minimal at 7.0 ± 18.3 cc and total procedure time averaged

198.8 ± 91.1 minutes. Most of the patients were discharged to home after the procedure (83.2%, with 10.7% discharged to rehab and 1.5% to a nursing facility) following a median 33.8-hour hospital length of stay (LOS, range 20–695). Of note, it has been reported in multiple studies that the procedure length and LOS tend to decline as providers become more familiar with the procedure and the patients' clinical course post-LITT.[25,28]

Complication rates

The complication rate from open surgery and stereotactic biopsy for GBM has historically ranged from 4.5% to 13% and 5% to 7% in large cohorts of patients, respectively.[42,46] Recent publications have shown that the LITT complication profile is comparable with these results, especially when considering the difficult-to-access/deep-seated nature of many of the LITT-treated tumors. Barnett and colleagues[47] performed a meta-analysis comparing proportions of major complications between LITT (n = 79) and craniotomy-treated (n = 1036) patients with HGGs in or near areas of eloquence. The results showed a reduction in major complication rates for LITT compared with craniotomy (5.7% [95% CI: 1.8–11.6] vs 13.8% [95% CI: 10.3–17.9], respectively).[47] In 100 consecutive procedures from 2013 to 2018, Shah and colleagues[36] reported a complication rate of 4%, which included superficial wound infections, seizures, and a transient facial palsy. In the 223 patients reported in the 2020 LAANTERN results, 1.8% of patients experienced an LITT/surgery-related serious adverse event, with the same percentage having readmission within 30 days.[42] In Kamath and colleagues,[25] they report a complication rate of 15.5% overall, with morbidities such as cerebral edema, seizures, hydrocephalus, hyponatremia, and infection seen. Their study also included 2 mortalities—one related to hemorrhage after treatment, whereas the second was due to equipment contamination leading to fulminant Enterobacter meningitis. In the 136 patients who received LITT more recently from 2015 to 2018, Shao and colleagues[28] reported a permanent neurologic deficit rate of 4.4%, no hemorrhages necessitating evacuation, no infections, and a 1.5% 30-day mortality rate. Each of these complication rates were reduced when compared with those in an earlier cohort of 96 patients receiving the procedure in 2011 to 2014 at the same center, which may reflect refined patient selection and/or improvements in operator technical proficiency over time. Taken as a whole, these recent data suggest that LITT has a comparable or favorable safety profile to that of craniotomy and stereotactic biopsy in appropriate-use scenarios for GBM.

Cost-effectiveness of laser interstitial thermal therapy

Research has also focused on the cost-effectiveness of LITT. Leuthardt and colleagues[48] compared acute care costs (inpatient care + aftercare) of LITT versus craniotomy for primary tumors at an academic medical center in year 2015 costs. They found that patients receiving LITT had a significantly shorter hospital LOS and were more likely to be discharged home compared with craniotomy. When looking at primary tumors alone and difficult-to-access primary tumors, there was a trend toward reduced costs with LITT compared with craniotomy, although this did not reach statistical significance.[48] Adding to this literature, Voigt and Barnett performed a cost-effectiveness analysis from a societal perspective in patients with HGG treated with LITT.[46] When compared with other treatments, they found an incremental cost/life year gained (LYG) of $29,340 when using LITT, significantly less than the international threshold value of $32,575/LYG and the US threshold value of $50,000/LYG.

Technical Considerations to Improve Outcomes

Complete lesion coverage

The benefits of resection over biopsy in GBM have been well documented in the neurosurgical literature, as well as the improvements in PFS and OS seen with a higher extent of resection/lower postoperative residual CETV.[33,35,49] Analogous to this, multiple studies have now reported on the importance of maximizing LITT EOA to the blue/yellow TDT lines, with smaller lesions being associated with higher EOA, and higher EOA being predictive of lower disease-specific PFS and OS (see **Fig. 3**).[14,20,31,36] These findings have been replicated across LITT systems, and EOA calculations can be performed with both of the major systems available currently.[31,36]

Shah and colleagues[36] identified an EOA cutoff of 85% to be a significant predictor of longer disease-specific PFS for both nGBM and rGBM (P = .006) using the Visualase system. In patients with nGBM treated with the NeuroBlate system, Mohammadi and colleagues[31] were able to identify 3 prognostic groups that correlated with PFS: favorable—≤0.025 cc of CETV within the yellow-blue TDT transition zone; intermediate—greater than 0.025 cc of CETV in the transition zone and greater than 90% tumor coverage by the blue TDT line; and unfavorable—greater than 0.025 cc and less than 90% tumor coverage by the blue TDT line.[31] These groups were then associated

with lower incidence of disease-specific PFS and OS on multivariate analysis. Additionally of note, a systematic review found that LITT is associated with a higher EOA than the extent of resection able to be obtained by craniotomy in GBM lesions located in eloquent or difficult-to-access locations.[47] These findings highlight the importance of maximizing EOA and the utility of LITT in attaining a high EOA with lesions in challenging locations.

Fiber tracking

In an attempt to improve outcomes and minimize neurologic deficit complications, fiber tracking (DTI sequences) has been used successfully in LITT planning. In a group of patients operated on between 2011 and 2015, volume of overlap between the corticospinal tracts (CSTs) and TDT lines were identified that were associated with postoperative motor deficits (PMDs), and cutoff points were determined that provided optimal sensitivity (92%–100%) and specificity (80%–90%).[50] These overlap volumes for the yellow, blue, and white TDT lines equated to 0.103, 0.068, and 0.046 cc, respectively, indicating that PMDs can result from even a minimal overlap of the CSTs and TDT lines.[50] Recently published outcomes comparing the early (2011–2014) versus recent (2015–2018) LITT-treated cohorts revealed a statistically significant reduction in PMDs in the recent cohort (4.4% vs 15.5%, $P = .005$) after routine utilization of fiber tracking in planning.[28]

Future Directions

Laser interstitial thermal therapy, the blood-brain barrier (BBB), and chemoradiation

The BBB is a known impediment to delivering systemically administered chemotherapies in high concentrations to the tumor microenvironment. As LITT induces changes to the perilesional vasculature, Leuthardt and colleagues[16] investigated the disruption of the BBB after LITT through dynamic contrast-enhancement brain MRI and measurements of neuron-specific enolase.[43] They report that disruption of the BBB occurs immediately and peak permeability occurs ~1 to 3 weeks after LITT, returning to normal by 4 to 6 weeks.[16] These pilot data were analyzed in conjunction with a clinical trial investigating the delivery effects and efficacy of early versus late administration of post-LITT doxorubicin in patients with rGBM, as the minimally invasive nature of LITT allows early administration of chemotherapy with minimal impact on wound healing (NCT01851733).

In addition to the effects on the BBB and chemotherapies, there are implications with LITT and radiotherapy. As hyperthermia is known to radiosensitize cells, Man and colleagues[51] investigated the effects of preradiotherapy hyperthermia on glioma stem cells (GSCs) and the PI3K/AKT pathway, which is aberrantly regulated in more than 40% of GBM and is associated with poor patient prognosis. GSCs treated with radiation alone exhibited increased AKT activation, but the addition of hyperthermia before radiotherapy reduced AKT activation and impaired GSC proliferation, an effect that was further enhanced by treatment with a PI3K inhibitor.[51] These preclinical data show the potential combined effects of LITT and other conventional treatment strategies.

Laser interstitial thermal therapy and immunotherapy

Hyperthermia has been found to improve both the innate and adaptive antitumor immune response via several mechanisms, including the release of tumor antigen-dense exosomes with increased tumor antigen presentation; induction of immune-stimulating heat-shock proteins expression; increased cytokine and chemokine production resulting in attraction of and enhanced activity of antigen-presenting cells, cytotoxic T cells, and natural killer cells; and vessel dilation with BBB disruption and increased perfusion permitting greater immune surveillance.[43,52,53] And this effect is not limited to the treated lesion, as multiple animal models in various types of cancers have demonstrated that lesions near or distant to the treatment area shrank or were stable after LITT was performed (abscopal effect).[54–59] These tumors were found to have a significant increase in CD3+ T cells at the tumor-host interface of both ablated and distant tumors, among other immunomodulatory effects. Although more comprehensive data with regard to immunophenotypic changes in the tumor microenvironment exists in other types of ablation techniques and cancer models, several studies have reported favorable preclinical results using hyperthermia via LITT in conjunction with immunotherapies to improve the body's immune response to gliomas.[52] For example, nanoparticle-enhanced thermal ablation paired with anti-PD-L1 immunotherapy improved survival and enabled rejection of tumor rechallenge in a murine model of GBM.[60] At least 2 clinical trials are currently underway investigating the outcomes of combinatorial LITT + immunotherapy for rGBM (NCT03341806: LITT + avelumab; NCT03277638: LITT + pembrolizumab). The field awaits the results of these trials expectantly, both from a clinical outcomes standpoint and any experimental aims examining the systemic immune alterations

in patients, as well as those within the tumor microenvironment.

Nanoparticles

Given the importance of maximizing EOA, researchers have investigated the uses of nanoparticles to act at "lightning rods" to increase the diameter of ablation and specificity for the tumor. Chongsathidkiet and colleagues[61] showed that plasmon-activated gold nanostars have selective tumor uptake and expanded the tumor-conforming zone of cytotoxic edema in a murine model of GBM.[60] In phantoms containing the gold nanostars, blue TDT line coverage expanded to 3.8 cm in diameter from 2.0 cm, with faster heating, higher temperatures, and more homogenous temperature zones attained.[60,61] Development of additional novel techniques to increase LITT coverage area and tumor specificity could confer significant improvements in LITT-related outcomes in GBM.

SUMMARY

The previous decade has seen an expansion in the use of LITT for a variety of pathologies. Although LITT has been used for both nGBM and rGBM, these systems have developed a niche in treating deep-seated, difficult-to-access lesions, where open resection is otherwise infeasible. Improvements in patient outcomes and reductions in complications have stemmed from advances in operative technique to maximize EOA and minimize damage to nearby critical fiber tracts. In appropriately selected patients, LITT outcomes for GBM seem comparable or favorable to that of craniotomy and/or stereotactic biopsy in recent literature. And given its immunomodulatory effects, ability to alter BBB permeability, and potential synergism with chemotherapies and immunotherapies, multiple trials using LITT are currently underway to advance the treatment options and improve outcomes for patients with this near-uniformly fatal disease.

DISCLOSURE

A.M. Mohammadi is a consultant for Monteris Medical, Inc. The other authors have nothing to declare.

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