Intracerebral laser interstitial thermal therapy followed by tumor resection to minimize cerebral edema

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OBJECTIVE Laser interstitial thermal therapy (LITT) is used in numerous neurosurgical applications including lesions that are difficult to resect. Its rising popularity can be attributed to its minimally invasive approach, improved accuracy with real-time MRI guidance and thermography, and enhanced control of the laser. One of its drawbacks is the possible development of significant edema, which contributes to extended hospital stays and often necessitates hyperosmolar or steroid therapy. Here, the authors discuss the use of minimally invasive craniotomy to resect tissue ablated with LITT in attempt to minimize cerebral edema.

METHODS Five patients with glioblastoma multiforme prospectively underwent LITT followed by resection. The LITT was performed with the aid of an MR-compatible skull-mounted frame in the MRI suite. Ablated tumor was then resected via small craniotomy by using the NICO Myriad system or cavitron ultrasonic surgical aspirator. Postoperative management involved dexamethasone administration slowly tapered over several weeks.

RESULTS The use of resection following LITT, as compared with open resection or LITT alone, did not extend the hospital stay except in 1 patient who required 3-day inpatient management of edema with a trapped ventricle. No new neurological deficits were encountered, although 1 patient developed seizures postoperatively. No increase in infection rates was identified.

CONCLUSIONS Resection of ablated tumor is a viable option to reduce the incidence of neurological deficits due to edema following LITT. This approach appears to mitigate cerebral edema by increasing available volume for mass effect and reducing the tissue burden that may promote an inflammatory response.

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KEY WORDS laser therapy; LITT; ablation; brain tumor; cerebral edema

LASER interstitial thermal therapy (LITT), originally proposed in 1983, is used as a minimally invasive technique for the treatment of difficult-to-resect intracranial lesions such as tumors, radiation necrosis, and epileptic foci in eloquent brain or deep nuclei and white matter.⁵ It has also become a viable option for select patients who would otherwise be unsuitable surgical candidates because of comorbidities or anesthesia risks.¹ Given its minimally invasive nature, LITT is an appealing tool for neurosurgeons under the appropriate circumstances. The long-term efficacy of LITT is currently under investigation in multiple applications including the treatment of primary and secondary tumors, and it appears to be a

promising therapy for high-grade gliomas since associated survival has ranged from 6.9 to 30 months in various studies.^{2,4} One of the drawbacks of using LITT is the development of significant cerebral edema,¹² which in patients harboring larger lesions can require prolonged courses of steroids and can be significant enough to warrant hyperosmolar therapy, extending hospital stays or even causing hospital readmissions. Steroid therapy most often manages edema effectively; however, symptomatic edema following LITT can be so severe that it requires decompressive surgery to manage it or, according to anecdotal reports (Barnett GH, presentation to Kansas City Neurology and Neurosurgery Society, 2015), results in se-

ABBREVIATIONS CUSA = cavitron ultrasonic surgical aspirator; GBM = glioblastoma multiforme; LITT = laser interstitial thermal therapy; MRgLITT = MRI-guided LITT; TDT = thermal damage threshold.

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rious neurological deficit or even death.^{3,12} We discuss our approach in managing larger lesions with LITT followed by planned minimally invasive craniotomy for resection of the ablated tissue.

Methods

Patient Selection

Among 34 patients undergoing LITT for tumor ablation, 5 underwent subsequent prospectively planned resection. All 5 patients were preoperatively evaluated with standard 3-T MRI per current brain tumor imaging guidelines, and all had glioblastoma multiforme (GBM). Laser interstitial thermal therapy was prospectively selected independent of the current study using a combination of factors including site operability, patient risk factors, previous treatments received, and patient preference. The University of Kansas Medical Center Institutional Review Board approved this study, and individual patient consent was received in each case. Three surgeons (P.J.C., R.B.C., and K.E.) performed LITT on patients between July 2014 and May 2016 using MRI-guided laser treatment after laser probe placement by one of 2 stereotactic methods discussed below.

Laser Probe Placement and MRI-Guided Laser Treatment

Two methods of stereotactic guidance were used throughout our patient series. Earlier cases involved stereotactic localization of the planned trajectory in the operating room by using the Brainlab Curve system. The Monteris AXiiiS tripod was mounted on the skull, and a twist drill was placed along the appropriate trajectory through the Brainlab VarioGuide. An MR-compatible Monteris intracranial bolt was placed, and the patient was transferred to the MRI suite for LITT. More recently we have placed the twist drill hole in the MRI suite by utilizing a proprietary MR-compatible ClearPoint system (MRI Interventions). After an appropriate trajectory for the laser probe is determined, a self-adhesive fiducial grid is placed over the approximate entry site (SmartGrid, MRI Interventions). Planning MR images are obtained to determine the entrance site. The ClearPoint frame is then affixed to the skull, and a series of scans are obtained to determine x, y, and pitch and roll adjustments to match the projected trajectory. An MR-compatible hand drill is used to create a twist drill hole through the frame, and the dura is punctured. If a confirmatory biopsy is needed, an MR-compatible biopsy needle is used at this time. The Monteris bolt is then placed, and the robotic driver system is mounted on the bolt. The NeuroBlate laser probe (Monteris) is then inserted. Predetermined trajectories are chosen to maximize tumor volume coverage with thermal damage threshold (TDT) lines while minimizing coverage of thermal therapy to nonneoplastic tissue.

In all cases the TDT lines are monitored on the Monteris workstation with image processing for real-time thermometry. Our chosen thermal dosage volumes include those previously described by Sloan et al.¹² A white TDT line indicates exposure to 43°C cumulative equivalent for 60 minutes. A blue TDT line indicates exposure to 43°C cumulative equivalent for 10 minutes. A yellow TDT line indicates exposure to 43°C cumulative equivalent for 2

FIG. 1. **Left:** Preoperative axial MR image obtained in a patient with a right thalamus GBM. **Right:** Postoperative axial MR image obtained after LITT and resection of the GBM.

minutes. As others have done, we attempted to cover as much of the tumor as possible with the blue TDT line.

Given our experience with and literature supporting the occurrence of cerebral edema,^{3,12} we now plan to resect ablated tissue in a minimally invasive manner in selected cases. Parameters in determining debulking include tumor volume with or without surrounding preoperative edema indicated by FLAIR hyperintensity in locations that may either preclude open surgery because of morbidity or have detrimental effects due to swelling. Laser interstitial thermal therapy plus minimally invasive resection is considered when tumor volume is at least 10 cm³ with significant surrounding edema, when tumors are located in the deep white matter, basal ganglia, and/or thalamus, and when swelling may cause hydrocephalus (for example, near the aqueduct of Sylvius). The resective process involves a return to the operating room from the MRI suite, where a small craniotomy is performed. Thin self-retaining retractor blades or tubular retractors are used to hold a small 1.5- to 2-cm path into the ablated tissue. Resection adjuncts such as the NICO Myriad device (NICO Corp.) and cavitation ultrasonic surgical aspirator (CUSA; Integra) were used in our cases.

Postoperatively patients were managed with a steroid, typically dexamethasone beginning at 6 mg every 6 hours with a slow taper for 2–3 weeks. Patients are usually discharged within 48 hours unless concern over swelling or medical comorbidities necessitates a longer hospital stay. Antibiotic prophylaxis is administered perioperatively, preferably cefazolin every 8 hours for up to 24 hours if a patient is still in the hospital. Clinic follow-up is completed in a manner similar to that for patients undergoing standard tumor resection. Imaging examples obtained before and after LITT and resection in a patient with a right thalamus GBM are shown in Fig. 1.

Results

All 5 cases were performed for a diagnosis of GBM, which was confirmed by pathological analysis; 1 case was a recurrent GBM. Preoperative and postoperative management along with patient demographics and tumor characteristics in these cases are summarized in Table 1. Preop-

TABLE 1. Summary of data on 5 patients with GBM treated with LITT plus resection

Case No.	Diagnosis	Location	Tumor Vol (cm ³)	Previous Tx	Steroid Taper Duration	LOS (days)	30-Day Readmission	Postop Infection	Instrument	Follow-Up
1	GBM	Rt frontal/corpus callosum	147.7	None	22 days	2	No	No	CUSA	Postop seizure; no deficits; stable at 2 mos
2	GBM	Rt thalamus	36.3	None	UK*	4	No	No	NICO	Stable; began RT & TMZ
3	GBM	Rt thalamus	54.8	None	UK*	9	No	No	NICO & CUSA	Required postop sodium management; currently in IRF
4	GBM	Rt thalamus	49.0	STR/biopsy	UK*	2	No	No	UK†	Stable; began RT & TMZ
5	GBM	Rt frontotemporal-corona radiata	59.6	Resection	UK*	4	No	No	CUSA	Stable; began RT & TMZ

IRF = inpatient rehabilitation facility; LOS = length of stay; RT = radiation therapy; STR = subtotal resection; TMZ = temozolomide; Tx = treatment; UK = unknown.

* Exact duration of steroid taper was unknown because patient was followed up by another provider (neurooncologist) and/or because they began RT after LITT.

† Information unknown due to lack of documentation in the chart.

erative tumor volume and associated edema ranged from 36.3 to 147.7 cm³.

Inclusion of a post-LITT mini-craniotomy with resection of ablated tissue did not extend the hospital stay in a significant manner as compared with that following routine open craniotomy or LITT alone. None of the patients sustained any new deficits due to the LITT or the postablative resection. Two adverse events were encountered including a postoperative seizure, which was controlled with antiepileptic medications, and a trapped lateral ventricle related to cerebral edema, which required 3 days of hypertonic saline. There were no postoperative infections, nor have there been any infections in any of the 34 patients who underwent LITT for tumor at our institution despite steroid therapy or other immunosuppression due to chemotherapy.

The manner of tumor resection varied and was based on surgeon preference. Both the NICO Myriad device and CUSA were used in this study. The ablated tissue ranged from soft, avascular, and bloodless to a somewhat firm and rubbery texture. The return to the operating room for resection necessitated an increase in total operating time as compared with the time required for cases without resection, which was to be expected. There were no 30-day readmissions for our 5 cases.

Discussion

Laser interstitial thermal therapy is viewed as a cytoreductive technique, and its effects are immediate as opposed to the weeks it can take other alternatives such as radiosurgery to have an effect on tissue.² The technique utilizes thermal energy to generate cellular changes in the target foci. Heating to 43°C for 60 minutes will cause protein denaturation, destruction of membrane lipids, and enzyme activation, resulting in irreversible damage of tissues.^{6,12} These tissues are selectively targeted using the innate differences in thermal conductive properties between pathological and normal tissues.¹⁰

In recent years, LITT has become a suitable option for several types of difficult cases. Multiple advances such as the development of MR thermography, enhanced laser control,⁶ and real-time visualization of temperature changes in pathological and normal tissues¹⁰ have increased the appli-

cability of LITT with fewer complications. In a retrospective analysis of patients who underwent MRI-guided LITT (MRgLITT) for glioma, recurrent metastasis, radiation necrosis, and epilepsy between 2010 and 2014, the average length of stay was 1.8–3.6 days.⁹ The average hospital stay commonly varies depending on postoperative complications and the severity of resultant edema.^{8,12,13}

Laser interstitial thermal therapy is especially useful in GBM, which exhibits a higher level of heat absorption than low-grade gliomas.⁶ Several early studies involving patients with GBM treated with LITT have shown increased survival, which correlated with the degree of ablation, ranging from 6.9 to 30 months.^{2,7} In a study of 24 patients with GBM, Mohammadi et al. reported a median of 5.1 months of progression-free survival post-LITT.⁷ Mohammadi and Schroeder presented 10 patients with recurrent GBM treated with the highest thermal dose to achieve better survival.⁸ Sloan et al. described 10 patients with recurrent GBM who underwent ablation via LITT, which resulted in a median survival time of 316 days, median progression-free survival of more than 30%, and only 2 patients who sustained long-term neurological complications post-LITT.¹² Jethwa et al. described 20 cases of brain tumors, 6 of which were GBM.³ Only 1 GBM patient experienced excessive edema from the use of 3 laser probes simultaneously.³

Radiologically there is immediate disruption of the blood-brain barrier and subsequent neovascularization following LITT; additional findings have included peripheral enhancement and restricted diffusion outside the initial borders of the treated tumor.² Opening of the blood-brain barrier has exciting potential for adjuvant chemotherapy for brain tumors. In addition to this opening of the blood-brain barrier, damaged cells release signals that trigger surrounding tissues to produce proinflammatory mediators as a means of tissue repair.¹¹ Thus, although LITT reduces viable tumor cells, this inevitably produces a surrounding region of edema that peaks at 3–4 days post-LITT.³ Standard treatment for this edema has been steroid therapy and occasionally hyperosmolar therapy.^{8,10,12,13}

Larger lesions treated with LITT can present a problem via the anticipated increase in tissue volume with the edema that typically follows LITT. Jethwa et al. treated this

edema with a steroid taper over 2–4 weeks.³ In another study, 4 mg of intravenous corticosteroids every 6 hours was administered postoperatively to control edema.⁸ In most cases, steroids have been successful in managing the edema; however, on rare occasions, edema cannot be treated with medication alone. Jethwa et al. described a case in which hemispherectomy was required due to malignant edema following thermoablation of a large glioblastoma.³ Sloan et al. noted edema ranging from undetectable to moderate to severe (with midline shift).¹² Two patients in their series developed toxicity (deficits) related to LITT but both improved with steroids.¹²

In our series we elected to use LITT plus minimally invasive resection in cases in which tumor volume was at least 10 cm³, with significant tumor in regions that might lead to hydrocephalus (for example, near the aqueduct of Sylvius), and/or in locations that might otherwise preclude safe complete resection such as deep white matter, basal ganglia, thalamus, or corpus callosum. With these criteria we hoped to achieve beneficial, precise, thermal cytoreductive effects and blood-brain barrier opening with LITT while reducing the burden of apoptotic tissue to minimize the amount and effects of swelling in these regions and to achieve this without the morbidity of open tissue resection.

The limitations of this study include its small number of cases. We continue to use this technique in selected cases in which the larger tumor and/or edema volume might portend problems with postablation swelling. Note that the mean volume of tumor plus associated edema was 69.48 cm³. While the small craniotomies were similar and the resections proceeded with minimal disturbance of adjacent tissue, the method of resection varied slightly. The application of surgical adjuncts such as stereotactically directed, trocar-based tubular retraction systems may further improve the approach in this resective technique.

Conclusions

Intracranial edema postthermoablation may require additional medical or surgical therapy to avert neurological deterioration. We propose a method of planned resection of ablated tissues to minimize the development of edema. We believe this technique potentially confers 2 benefits: 1) resection decompresses the ablated region, allowing room for cerebral edema and tissue expansion, and 2) it reduces the amount of apoptotic and necrotic tissue and therefore reduces the downstream effects of cytotoxic edema and the inflammatory response. Although this has not been proven on a cytological level in our series, the results in this small series have been positive in terms of symptoms, outcomes, length of stay, and readmission rate.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Camarata. Acquisition of data: Camarata, Smith, Ebersole, Chamoun. Analysis and interpretation of data: Pisipati, Smith, Shah, Ebersole, Chamoun. Drafting the article: all authors. Critically revising the article: Camarata, Pisipati, Smith, Shah, Chamoun. Reviewed submitted version of manuscript: Camarata, Pisipati, Smith, Shah.

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