Laser Interstitial Thermal Therapy for Glioblastoma: A Single-Center Experience

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BACKGROUND: **Surgical resection has been shown to prolong survival in patients with glioblastoma multiforme (GBM), although this benefit has not been demonstrated for reoperation following tumor recurrence. Laser interstitial thermal therapy (LITT) is a minimally invasive ablation technique that has been shown to effectively reduce tumor burden in some patients with intracranial malignancy. The aim of this study was to describe the safety and efficacy of LITT for recurrent and newly diagnosed GBM at a large tertiary referral center.**

METHODS: **Patients with GBM receiving LITT were retrospectively analyzed. Overall survival from the time of LITT was the primary end point measured.**

RESULTS: **There were 69 patients identified for inclusion in this study. The median age of the cohort was 56 years (range, 15–77 years). Median tumor volume was 10.4 cm^3 (range, 1.0–64.0 cm^3). A Kaplan-Meier estimate of median overall survival for the series from the time of LITT was 12 months (95% confidence interval 8–16 months). Median progression-free survival for the cohort from LITT was 4 months (95% confidence interval 3–7 months). Adjuvant chemotherapy significantly prolonged progression-free survival and overall survival ($P < 0.01$ for both) in the cohort. Gross total ablation was not significantly associated with progression-free survival ($P = 0.09$).**

CONCLUSIONS: **LITT can safely reduce intracranial tumor burden in patients with GBM who have exhausted other adjuvant therapies or are poor candidates for conventional resection techniques.**

INTRODUCTION

Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumor.[1] Despite the multitude of treatment options available, patients have a median survival of 12–15 months under the current standard of care.[2] While surgery is generally considered the mainstay of treatment for patients with surgically accessible GBM, local and distant intracranial recurrence is common. A management conundrum arises with intracranial recurrence, as some studies suggest that reoperation is beneficial only in select patients.[3,4] Additionally, factors such as age and functional decline are contraindications for additional resections. The advent of laser interstitial thermal therapy (LITT) for tumor ablation provides a potentially viable salvage therapy for patients with recurrent or newly diagnosed disease inaccessible to conventional surgical approaches.[5-7] The use of magnetic resonance thermography has made the clinical application of LITT possible by allowing for thermographic feedback, minimizing damage to adjacent neural structures.

Descriptive studies are emerging to support the use of LITT for a number of neurosurgical disorders from the ablation of epileptogenic foci to the reduction of intracranial tumor burden.[8-10] Although the results of the various studies to date have used different methodologies for quantifying the efficacy of LITT, they have generally shown this technique to be effective for reducing tumor burden in patients

Key words
- Glioblastoma
- Laser interstitial thermal therapy
- Overall survival
- Progression-free survival

Abbreviations and Acronyms
GBM: Glioblastoma
GTR: Gross total resection
LITT: Laser interstitial thermal therapy
MRI: Magnetic resonance imaging
OS: Overall survival
PFS: Progression-free survival

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with metastatic and primary tumors.[11-13] In patients with GBM, prior reports have described successful application of LITT for unresectable tumors, though these studies have generally been small and heterogeneous, making statistical interpretation difficult[7,14] with the exception of a few larger studies.[15] We have previously described our experience and operative technique with LITT for a smaller cohort of recurrent and newly diagnosed GBM.[7] In the present study, we examined the outcomes of LITT in a much larger series of patients with newly diagnosed and recurrent GBM and defined its impact on the disease process.

MATERIALS AND METHODS

Study Design, Setting, and Participants

A retrospective review was conducted of a consecutive series of patients treated with LITT at a large academic center for histopathologically confirmed GBM between 2013 and 2017. This study was performed under an institutional review board–approved protocol in compliance with institutional regulations with regard to the study of human subjects. Consent was obtained for all described procedures. Patient demographic, clinical, radiologic, and genetic data were recorded from the electronic medical record. All LITT operations described in this article were performed by the senior author (SSP) and coauthor (GR).

Study Variables

The following variables were extracted from the medical records: age, sex, date of histopathologically confirmed GBM diagnosis, treatment modalities used before LITT, primary versus secondary GBM status, tumor location, *IDH* mutation status, local recurrence after LITT, and date of last follow-up. Karnofsky performance scale (KPS) score and a detailed neurological examination were recorded before and after LITT. Recurrent GBM tumors were previously resected, while newly diagnosed tumors had not received any operative intervention. Primary GBM was defined as World Health Organization grade IV on original diagnosis, while secondary GBM progressed from a lower World Health Organization grade (II–III). Deep-seated tumor location was ascribed to lesions by the treating surgeon as lesions that could result in significant morbidity as a result of surgery (basal ganglia or other midline or paramedian tumors). Overall survival (OS) was defined as the time from LITT to death or censored at date of last follow-up in the electronic medical record if death was not reported. Progression-free survival (PFS) was defined as the time from LITT to local progression or censored at date of last magnetic resonance imaging (MRI) evaluated using our institution's advanced brain tumor imaging protocol if local progression was not reported. Local progression was determined using the Response Assessment in Neuro-Oncology (RANO) criteria for high-grade glioma applied by a team including a neuroradiologist and neurosurgeon at our institution.[16] Complications were classified as either neurological or medical. Neurological complications included any persistent or new motor or speech deficit present at 30 days after LITT.

Operative Technique

Operations described in this article were performed at our institution in an intraoperative MRI suite with a Siemens Espree 1.5T open bore scanner (Siemens Healthineers, Erlangen, Germany). The NeuroBlate (Monteris Medical, Winnipeg, Manitoba, Canada) and Visualase (Medtronic, Minneapolis, Minnesota, USA) systems were used for LITT delivery. Though our initial experience was with the Visualase system, we have since adopted the NeuroBlate system as the primary ablation delivery system because of its better conformity and treatment plans for lesion ablation. Details regarding the technique used have been described in a previous study by our group.[7] Enhancing margins of every tumor were treated to 43°C for 10 minutes corresponding to the blue thermal damage threshold line in the NeuroBlate system, which is sufficient to induce cell death.[17] Depending on the geometry of the lesion, either the side-fire or the diffusion tip was used in the NeuroBlate system. With the aid of the NeuroBlate software, thermal damage was assessed in real time by magnetic resonance thermography. Preoperative diffusion tensor imaging was used to identify anatomic (white matter) constraints of ablation. The imaging changes over time for a GBM lesion treated with LITT in our cohort are shown in **Figure 1**.

MRI Volumetric Analysis

All patients underwent preoperative brain MRI followed by brain MRI after LITT along with follow-up imaging every 2–3 months after LITT. All planning volume data were extracted from the iPlan workstation (Brainlab, Munich, Germany). Tumor volumes were calculated preoperatively by a neuroradiologist at our institution using the iPlan workstation on previously obtained T1 postcontrast sequences. The lesion margins on preoperative MRI represented the enhancing tumor, while the enhanced margins on posttreatment MRI represented the ablation volume. Single, three-dimensional volume measurements of each lesion were taken and verified by the lead surgeons. The volume not covered was calculated intraoperatively in the iPlan workstation by superimposing the ablation cavity volume over the preoperative tumor volume using the image fusion function in iPlan. Gross total ablation was defined by <1 cm^3 of tumor not covered by the ablation radius corresponding to the blue thermal damage threshold line in the NeuroBlate magnetic resonance thermography suite.

Statistical Analysis

All statistical analysis was completed in R using the survival package.[18] Kaplan-Meier estimates of OS and PFS were calculated. Groups were compared with a log-rank (Mantel-Cox) test. Multivariate predictors of OS were assessed by using the Cox proportional hazards model set to 95% confidence and reported with hazard ratios and confidence intervals. A P value <0.05 was considered significant for all analyses. Age (>55 years vs. ≤55 years), sex, *IDH* status, recurrent status, primary versus secondary GBM, tumor location (deep-seated vs. non–deep-seated), tumor volume, gross total ablation, post-LITT chemotherapy, and post-LITT radiotherapy were analyzed by Kaplan-Meier (log-rank).

RESULTS

Patient and Tumor Characteristics

Table 1 summarizes patient demographics and tumor characteristics. There were 69 patients analyzed in the study.

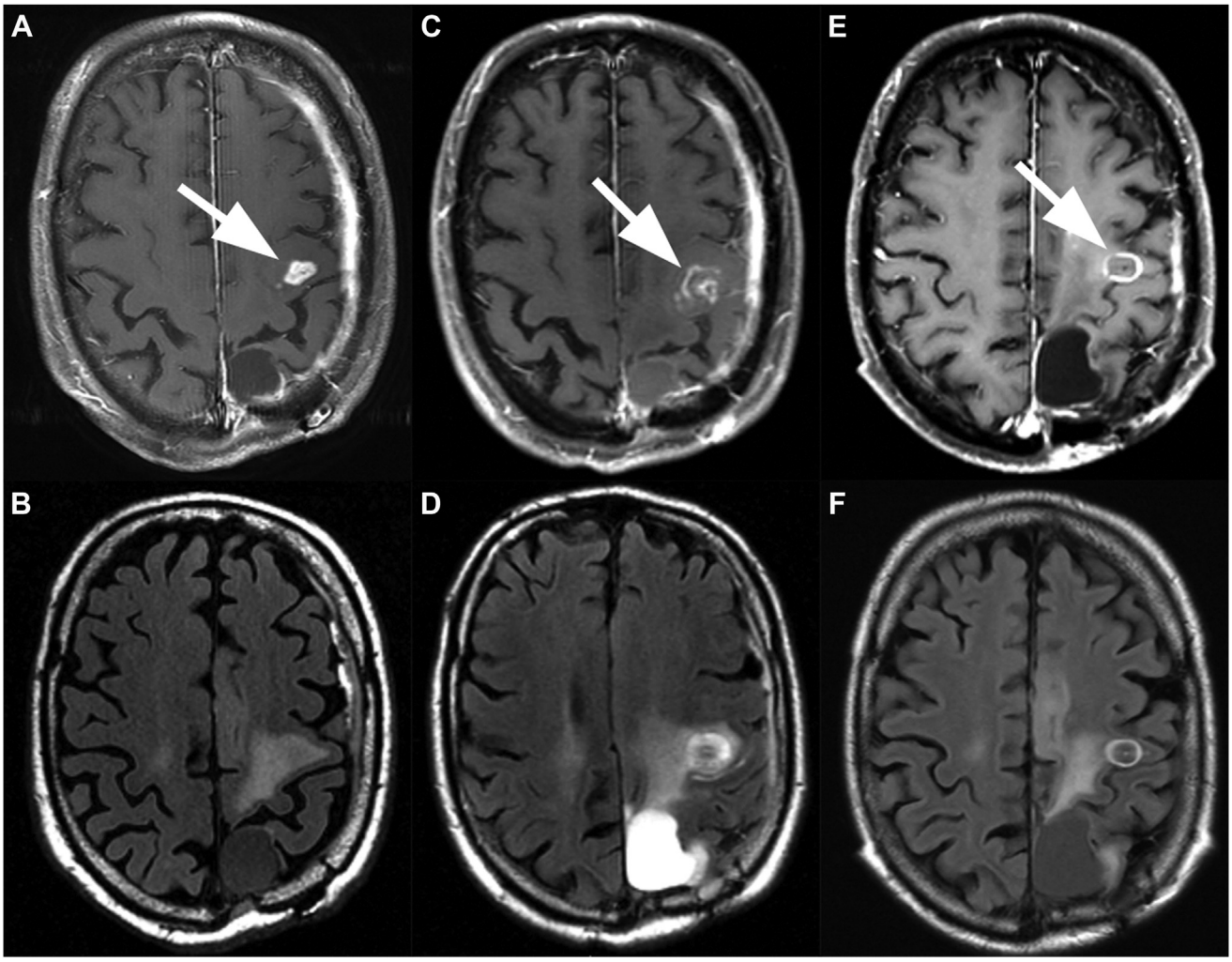

Figure 1. T1-weighted post-contrast (**A**) and fluid attenuated inversion recovery (FLAIR) (**B**) magnetic resonance imaging (MRI) revealing left posterior frontal enhancing glioblastoma (*white arrows*) and surrounding edema before laser interstitial thermal therapy (LITT). T1-weighted postcontrast (**C**) and fluid attenuated inversion recovery (**D**) imaging after LITT delineating the ablation cavity with marginal eggshell enhancement and persistent edema consistent with post-treatment change. T1-weighted post-contrast (**E**) and FLAIR (**F**) imaging obtained 6 months after LITT revealing a stable ablation cavity.

The median age of the cohort was 56 years (range, 15–77 years). Median tumor volume was 10.4 cm^3 (range, 1.0–64.0 cm^3). Median volume uncovered by the radius of ablation was 1.31 cm^3 (range, 0–41.2 cm^3). Median hospital stay was 2 days (range, 0–47 days). Figure 2 illustrates 3 cases of GBM treated with LITT.

Predictors of OS and PFS

A Kaplan-Meier estimate of median OS for the cohort from the time of LITT was 12 months (95% confidence interval 8–16 months). Similarly, the median PFS was 4 months (95% confidence interval 3–7 months) (Figure 3). Adjuvant chemotherapy was found to significantly prolong PFS ($P < 0.01$) and OS ($P < 0.01$). Women were observed to have a significantly longer OS than men from the time of LITT ($P = 0.01$). Conversely, sex had no effect on PFS ($P = 0.85$). Younger patients (≤55 years old) had a slightly increased OS from the time of LITT, although this was not significant on log-rank test ($P = 0.08$). Age (>55 years vs. ≤55 years) was not a significant predictor of PFS ($P = 0.75$), however. *IDH* status was not a significant predictor of OS ($P = 0.81$) or PFS ($P = 0.83$). Recurrent GBM (vs. newly diagnosed) was not predictive of OS ($P = 0.81$) or PFS ($P = 0.35$). Primary GBM (vs. secondary) was also not predictive of OS ($P = 0.89$) or PFS ($P = 0.32$). Tumor location (deep-seated vs. non–deep-seated) was not predictive of OS ($P = 0.87$) or PFS ($P = 0.96$). Tumor volume (>10 cm^3 vs. <10 cm^3) was not predictive of OS ($P = 0.99$) or PFS ($P = 0.82$). Gross total ablation of the tumor was not predictive of OS ($P = 0.39$) and not significant for prolonging PFS ($P = 0.09$). The addition of adjuvant radiotherapy after LITT was observed to significantly

Table 1. Patient Characteristics

Characteristic	Number (%)
Age	
>55 years	39 (56.5)
≤55 years	30 (43.5)
Sex	
Female	26 (37.7)
Male	43 (62.3)
GBM diagnosis	
Newly diagnosed	20 (29.0)
Recurrent	49 (71.0)
IDH status*	
Wild-type	48 (87.3)
Mutant	7 (12.7)
TP53†	
Wild-type	45 (73.8)
Mutated	16 (26.2)
EGFR†	
Wild-type	50 (82.0)
Mutated	11 (18.0)
MGMT†	
Unmethylated	51 (83.6)
Methylated	10 (16.4)
Prior GTR‡	
Yes	37 (75.5)
Subtotal	12 (24.5)
Tumor location	
DST	27 (39.1)
Non-DST	42 (60.8)
Tumor volume	
>10 cm^3	35 (50.7)
<10 cm^3	34 (59.3)
Gross total ablation	
Yes	28 (40.6)
No	41 (59.4)
Post-LITT chemotherapy	
Yes	47 (68.1)
No	22 (31.9)
Post-LITT radiotherapy	
Yes	19 (27.5)
No	50 (72.5)
Complications	
Neurological	17 (24.6)
Medical	10 (14.4)

GBM, glioblastoma; GTR, gross total resection; LITT, laser interstitial thermal therapy; DST, deep-seated tumor.
*IDH status available only for 55 patients.
†Mutation data available only for 61 patients.
‡Recurrent GBM in 49 patients.

prolong PFS ($P = 0.03$), but not OS ($P = 0.11$). Figure 4 illustrates statistically significant and near-significant relationships with OS and PFS based on univariate analysis. Multivariate predictors of OS are summarized in Table 2.

Complications

Of the 69 patients in the series, 24% ($n = 17$) were observed to have permanent neurological complications; 65% ($n = 45$) had no previous motor deficits, while 35% ($n = 24$) had a preexisting motor deficit. Of the patients who had a preexisting motor deficit, 13 had persistent worsened motor deficit. Overall, 4 patients had a new persistent motor deficit related to the procedure (Figure 5). Most patients, however, continued to improve, and this did not preclude them from restarting their adjuvant treatments. Overall, speech deficits were observed in 11 of 69 patients with a variable response to steroids, and all deficits resolved by 30 days after LITT.

Medical complications were observed in 14% of the cohort ($n = 10$). These included new-onset seizures observed in 4 patients after LITT; 1 case was refractory to antiepileptic medications. Three patients experienced impaired cognition in the follow-up period. Other medical complications ($n = 6$) included urinary tract infection, pneumonia, hyponatremia, pulmonary embolism, and acute kidney injury. Complications are summarized in Table 3.

Serious complications leading to death were observed in 2 patients with butterfly GBM treated with LITT. One patient with a butterfly GBM treated with bilateral LITT probes was observed to have decreasing consciousness and worsening oxygen saturation leading to hospice transfer on post-LITT day 13 and ultimately death 7 days later. Another patient who received bilateral LITT probes to a butterfly GBM within the splenium was noted to have hyponatremia on follow-up. This was ultimately diagnosed as syndrome of inappropriate antidiuretic hormone secretion and progressively worsened on repeat follow-up despite treatment with conivaptan and salt repletion. The patient died 3 months after surgery owing to progression of the underlying malignancy.

DISCUSSION

Background

Current management strategies for GBM involve gross total resection (GTR) followed by systemic chemotherapy and adjuvant

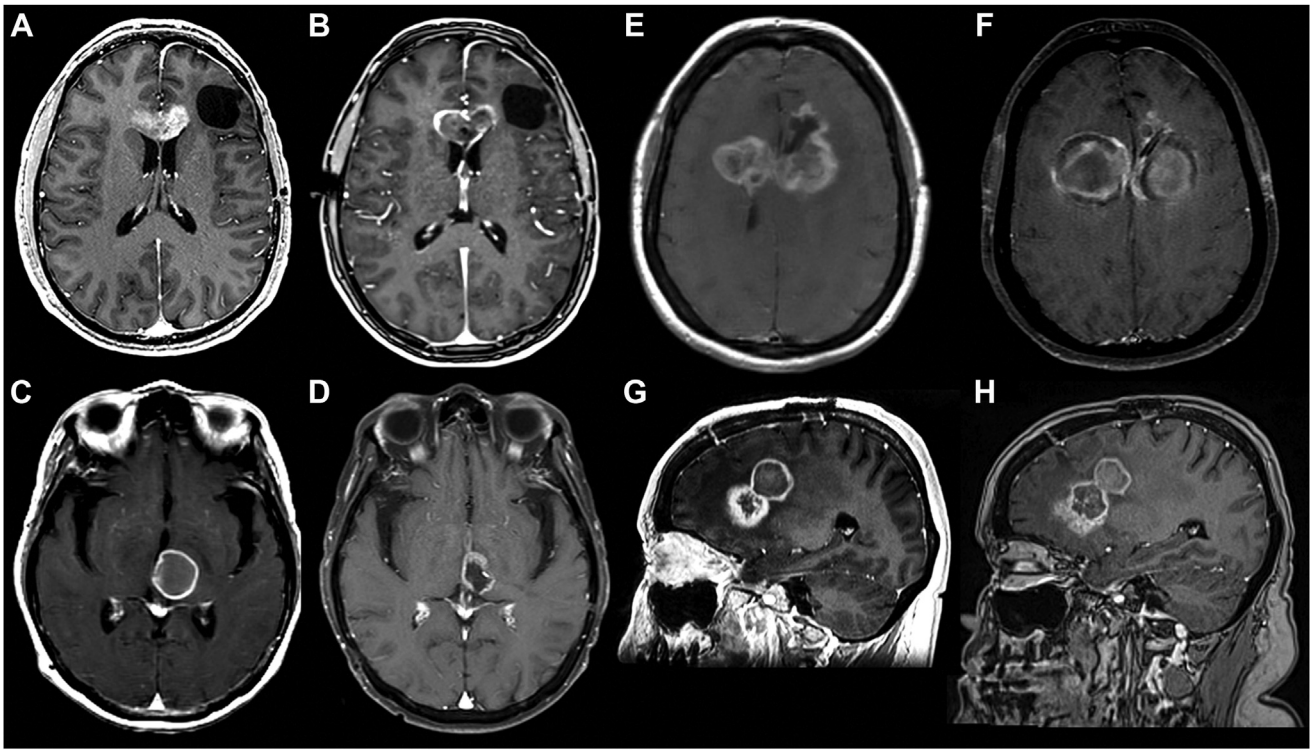

Figure 2. Three illustrative cases of laser interstitial thermal therapy (LITT) for glioblastoma (GBM). (**A** and **B**) Axial T1-weighted post-contrast magnetic resonance imaging (MRI) before (**A**) and after (**B**) LITT of an *IDH* wild-type butterfly GBM treated with bilateral ablation probes. Post-LITT Karnofsky performance scale for this case was 100. (**C** and **D**) Axial T1-weighted post-contrast imaging before (**C**) and after (**D**) LITT for an *IDH* wild-type left thalamic GBM. Following ablation, the patient was able to tolerate chemotherapy and radiation well. (**E**–**H**) Imaging of a patient with irregular *IDH* wild-type GBM treated with 2 iterations of bilateral LITT probes who survived 4 years from the first ablation procedure with aphasia. Axial (**E**) and sagittal (**G**) T1-weighted post-contrast scans before LITT and axial (**F**) and sagittal (**H**) scans after LITT are shown.

radiation. In circumstances where resection is unattainable owing to tumor location in eloquent or deep-seated regions, patients are typically managed nonoperatively with chemoradiation and consequently experience worse outcomes.[19] For these patients, LITT provides a therapeutic alternative to GTR, allowing for a reduction in tumor burden with potentially less collateral damage to adjacent eloquent cortex or white matter. Additionally, current evidence suggests that less than a third of GBM lesions are amenable to GTR, further indicating a need for alternative cytoreductive techniques.[20] Over the last 3 decades, a growing number of studies have reported on the efficacy of LITT in the management of primary intracranial tumors.[14,21-27] However, fewer studies have investigated the utility of this technique for GBM specifically.[7,11,14,26-35] Previous reports of LITT for GBM are summarized in Table 4.

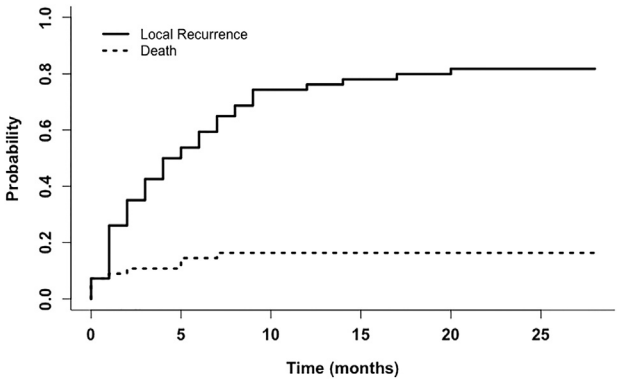

Figure 3. Curves delineating the cumulative incidence functions for death and local recurrence.

Key Results and Interpretation

Our study is one of the largest single-institution cohort studies to assess the efficacy of LITT for GBM and underscores the results of smaller, previously published cohort studies. Additionally, the majority of patients returned home on post-LITT day 1 or 2. This underscores the importance of this minimally invasive technology especially when these patients have no other meaningful treatment options. Additionally, LITT can break down the peritumoral

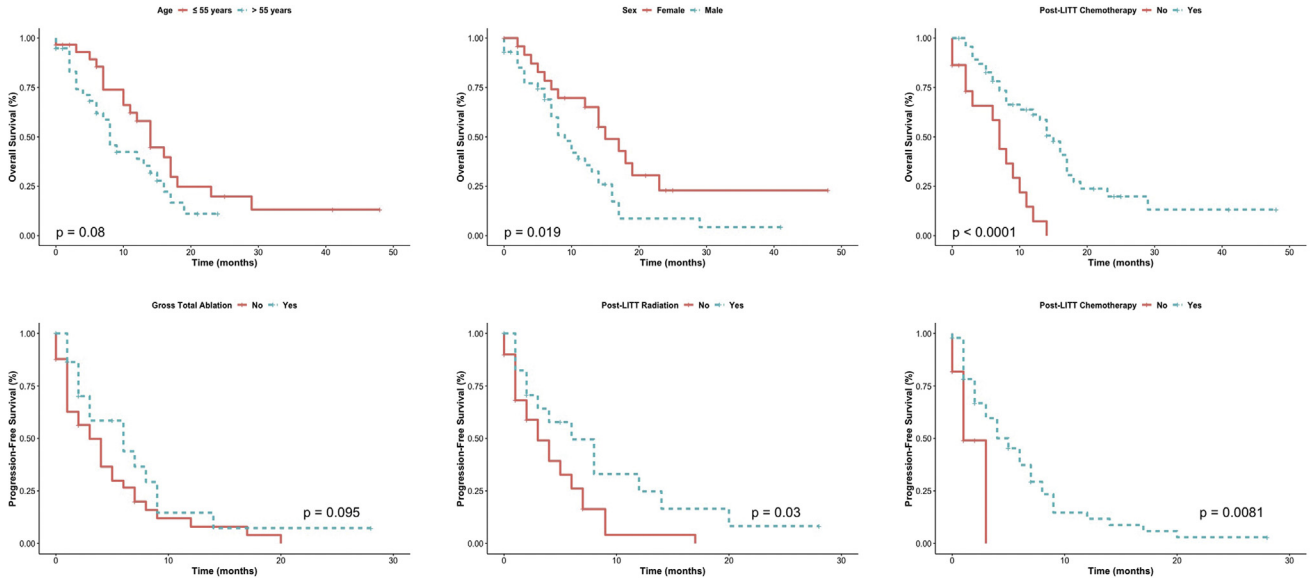

Figure 4. Kaplan-Meier analysis for variables predictive of overall survival and progression-free survival. *P* values from the log-rank tests are reported on each respective curve.

blood-brain barrier,[34] facilitating the delivery of adjuvant chemotherapy to the tumor site. There are some thoughts that an optimal time for chemotherapy administration would be after LITT.[36]

Table 2. Cox Multivariate Analysis for Predictors of Overall Survival

Group	Hazard Ratio (95% CI)	*P* Value
Age	1.03 (1.00—1.06)	0.05*
Sex, male versus female	2.40 (1.01—5.67)	0.05*
Recurrent versus newly diagnosed	1.20 (0.33—4.44)	0.78
Primary versus secondary	1.00 (0.24—4.24)	0.99
Pre-LITT KPS score	1.01 (0.97—1.05)	0.75
Tumor volume	1.00 (0.97—1.04)	0.97
Deep-seated tumor, yes versus no	0.99 (0.44—2.23)	0.99
Gross total ablation, yes versus no	0.79 (0.28—2.23)	0.65
IDH status, mutant versus wild-type	1.01 (0.24—4.37)	0.98
Post-LITT chemotherapy	0.28 (0.07—1.13)	0.07
Post-LITT radiotherapy	0.61 (0.20—1.84)	0.38

CI, confidence interval; LITT, laser interstitial thermal therapy; KPS, Karnofsky performance scale.
*Statistically significant.

Our study provides additional insight into the efficacy of post-LITT adjuvant therapies such as chemotherapy and radiotherapy. Our findings suggest that the use of chemotherapy and radiotherapy in the adjuvant setting significantly prolongs OS and PFS.[37] This follows a similar study at our institution showing significantly prolonged time to local recurrence with adjuvant systemic therapy following LITT for brain metastases.[10] However, it is important to note that this may be due to selection bias in that patients without other treatment options may have other factors contributing to their poor prognosis. Specifically, patients who received LITT as a salvage therapy exhausted most adjuvant chemotherapy options. Additionally, women treated in our cohort were observed to have a longer OS from the time of LITT, which reflects previous reports of sex differences in GBM.[38]

As seen from our data, this technology is not free of complications. However, a majority of patients treated with LITT were able to continue with adjuvant therapy, as the neurological deficits in most cases were transient. The higher incidence of complications also speaks to the eloquent and deep location of tumors that this technology can be applied to when other treatments have been exhausted or contraindicated. Specifically, neurological deficit in the post-LITT course reflects the proximity of critical white matter structures to the primary tumor, rather than the procedure itself. From our experience, we believe that LITT can provide a benefit in these preselected patients. There are 2 potential ways to mitigate the risk of complication. One option is to overlay diffusion tensor imaging maps during treatment to better inform the extent of ablation. Another option is to initiate ablation

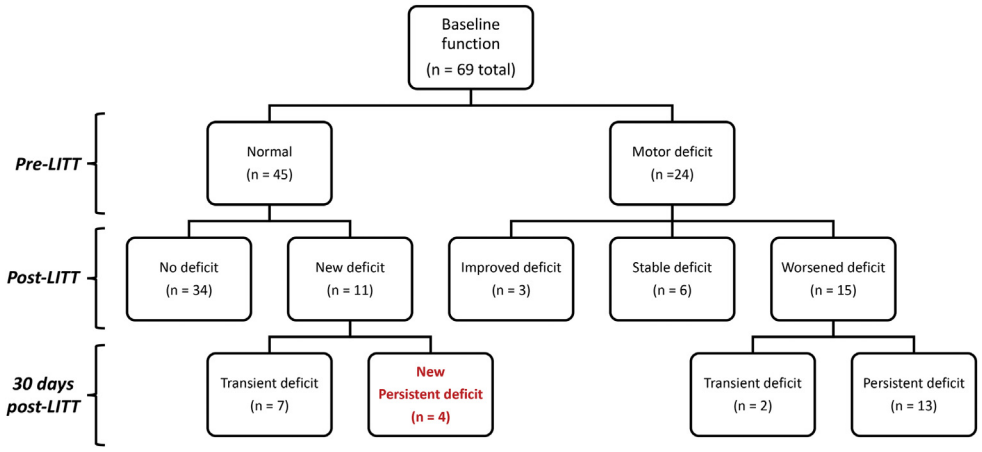

Figure 5. Motor deficits observed after laser interstitial thermal therapy (LITT).

at a lower setting and observe the heat distribution in the lesion before increasing the power. In our experience, we tend to see more rapid dispersion of heat in necrotic tumors.

Limitations

This study is limited by the retrospective nature of data collection. Additionally, surgical resection of the lesion was contraindicated in all patients in the cohort. This introduces a selection bias, which can skew the significance of downstream analysis. Another limitation is the small sample size in which recurrent, *IDH* wild-type GBMs are overrepresented, which can potentially confound outcome analysis. Although we originally attempted to stratify subsets by *IDH* status wherever possible, our sample size did not allow us to make any meaningful conclusions based on analysis of only patients with recurrent, *IDH* wild-type GBM. Further, the volumetric data extracted from preoperative plans merged with post-LITT imaging is prone to error, particularly when calculating the volume of tumor not covered by the ablation cavity, as brain shift can occur intraoperatively. Despite these limitations, the median OS of the recurrent cases in our series was comparable to those for cohorts with recurrent GBM receiving repeat surgical resection and provides further evidence for the utility of LITT in this patient population.[39]

Table 3. Complications 30 Days After Laser Interstitial Thermal Therapy

Complications	Number (%)
Total	69 (100)
Neurological complications	
Total	17 (24)
Persistent new/worsened motor deficit	17 (24)
Persistent new/worsened speech deficit	0 (0)
Medical complications	
Total	10 (14)
Seizures	4 (6)
Urinary tract infection	1 (1)
Pneumonia	1 (1)
Acute kidney injury	1 (1)
Pulmonary embolism	1 (1)
Hyponatremia	2 (3)

CONCLUSIONS

Treatment of GBM not amenable to GTR poses a challenge for clinicians to manage. Our results suggest that LITT may confer a survival benefit over nonoperative management of newly diagnosed GBM; however, larger studies are needed for this relationship to be established.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Jeffrey I. Traylor: Writing - original draft, Writing - review & editing, Data curation, Formal analysis. **Rajan Patel:** Writing - review & editing, Data curation. **Matthew Muir:** Writing - review & editing, Data curation. **Dhiego Chaves de Almeida Bastos:** Data curation, Methodology, Formal analysis, Writing - review & editing. **Visweswaran Ravikumar:** Formal analysis. **Carlos Kamiya-Matsuoka:** Writing - review & editing. **Ganesh Rao:** Writing - review & editing. **Jonathan G. Thomas:** Data curation. **Yvonne Kew:** Data curation. **Sujit S. Prabhu:** Conceptualization, Writing - review & editing, Methodology.

Table 4. Previous Reports of Laser Interstitial Thermal Therapy for Glioblastoma Multiforme

Reference	Number of Patients	Overall Survival (months)	LITT Delivery System
Reimer et al., 1998[28]	1	NR	NR
Leonardi et al., 2001[26]	6	9	NR
Schulze et al., 2004[27]	5	NR	NR
Schwarzmaier et al., 2006[29]	16	7	NR
Carpentier et al., 2012[30]	4	10	Visualase
Jethwa et al., 2012[31]	6	NR	Visualase
Hawasli et al., 2013[32]	10	11	NeuroBlate
Sloan et al., 2013[11]	10	11	NeuroBlate
Mohammadi et al., 2014[33]	24	NR	NeuroBlate
Thomas et al., 2016[7]	21	7	NeuroBlate + Visualase
Leuthardt et al., 2016[34]	14	NR	NeuroBlate
Kamath et al., 2019[14]	54	11.5	NeuroBlate
Mohammadi et al., 2019[35]	24	NR	NeuroBlate
Shao et al., 2020[15]	104	13.6	NeuroBlate
Current study, 2021	69	12	NeuroBlate + Visualase

LITT, laser interstitial thermal therapy; NR, not reported.

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