



An analysis of functional outcomes following laser interstitial thermal therapy for recurrent high-grade glioma

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OBJECTIVE Laser interstitial thermal therapy (LITT) is an emerging tool for treating a variety of focal brain lesions, including recurrent high-grade glioma (HGG). While the efficacy and uses of LITT have been well studied, the impact of this treatment on patient functional outcomes has not been analyzed in detail. This study sought to better define the role of LITT in treating patients with recurrent HGG, examining which patients exhibit good functional outcomes after LITT, and to determine risk factors for worsening neurological function.

METHODS The medical records of patients treated with LITT for recurrent HGG at a single tertiary care center were retrospectively reviewed. Functional status was assessed using the Karnofsky Performance Scale (KPS). Demographic, clinical, and radiological data were examined for associations with change in KPS score assessed 4–6 weeks following surgery.

RESULTS Forty-seven patients were included in the study with histopathologically confirmed recurrent HGG. The mean age was 57 years, and 21 (45%) patients were female. The pre-LITT KPS scores were as follows: 100 in 4 (9%) patients, 90 in 15 (32%) patients, 80 in 10 (21%) patients, 70 in 13 (28%) patients, and 60 in 5 (11%) patients. Overall, 59% of patients showed a stable or improved KPS score after undergoing LITT. Tumor volume was the sole predictor of decreased KPS score after LITT. Notably, tumor location including eloquent location, preoperative KPS score, and other comorbidities were not independently associated with change in functional status.

CONCLUSIONS The majority of patients undergoing LITT for recurrent HGG had a favorable functional outcome at the initial follow-up visit. The treated tumor volume was inversely and independently associated with post-LITT functional outcome. This information may help guide patient selection and treatment optimization in the setting of LITT-based approaches for recurrent HGG.

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KEYWORDS glioma; laser interstitial thermal therapy; LITT; KPS

HIGH-GRADE gliomas (HGGs) frequently recur despite combined surgical, radiation, and chemotherapy treatments. In the setting of recurrence, the goal of care for HGG patients is to maximally remove tumor components, reduce mass effect and the need for antiedema therapies (e.g., dexamethasone), and maintain or improve neurological function. Unfortunately, only a small percentage of patients with a recurrent HGG are

candidates for re-resection because of the tumor location, concerns for wound healing, risk of prolonged recovery, and other factors.

Laser interstitial thermal therapy (LITT) is an emerging minimally invasive neurosurgical approach for treating various intracranial lesions such as primary and metastatic tumors, radiation necrosis, and epileptic foci.^{1–3} LITT ablation generally involves passing a laser probe through one

ABBREVIATIONS EOA = extent of ablation; HGG = high-grade glioma; KPS = Karnofsky Performance Scale; LITT = laser interstitial thermal therapy; mFI = 5-item modified frailty index.

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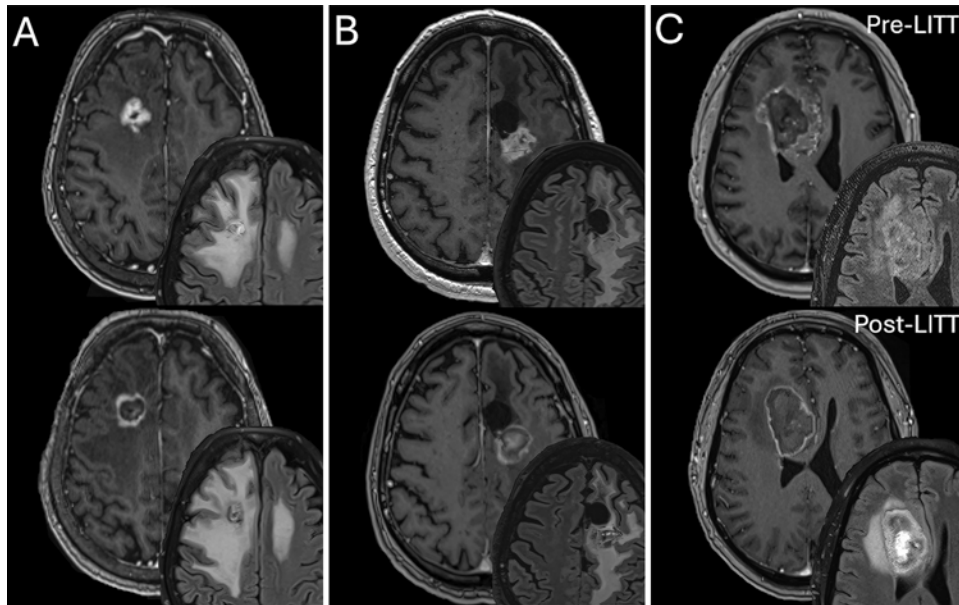


FIG. 1. Upper Row: Preoperative T1-weighted contrast-enhanced MR images demonstrating small (A), moderate (B), and large (C) recurrent frontal glioblastomas. **Lower Row:** Postoperative T1-weighted contrast-enhanced MR images showing a rim of enhancement along the edges of each ablation. The **bottom right insets** demonstrate the corresponding T2-FLAIR MR images.

or more cranial burr holes along preplanned trajectories and delivering energy with real-time thermal imaging (e.g., MR thermography) to monitor the treatment. Delivering energy into the target tissues can lead to coagulative necrosis, blood-brain barrier opening, and/or activation of heat response elements.⁴⁻⁶

One of the main advantages of LITT lies in its minimally invasive nature, making it an additional therapeutic option for patients with deep-seated lesions, with or without the addition of stereotactic biopsy.^{7,8} Studies have shown that LITT is effective and confers a survival benefit compared with biopsy alone in deep-seated lesions and comparable survival to the combination of open surgery and chemoradiation therapy in select glioblastoma patients.⁹⁻¹¹ The small incision size also requires shorter healing times, facilitating the initiation of adjuvant therapies and reducing the hospital stay and cost of care.¹² Studies have noted that patients undergoing LITT have mixed changes in functional status postprocedurally,¹³⁻¹⁵ and a detailed analysis of which patients see a benefit has yet to be performed. Furthermore, the intrinsic difference between LITT ablation and surgical debulking may limit the generalizability of previous studies.

In order to advance the balanced and effective clinical implementation of LITT, there continues to be a need and opportunity to optimize patient selection and treatment delivery. In this study, we analyze a series of 47 consecutive LITT treatments for recurrent HGG to systemically examine associations between treatment and patient-specific parameters with functional outcomes.

Methods

This study was approved by the University of Maryland School of Medicine Institutional Review Board, and

patients were identified through the electronic medical record. Given the retrospective nature of this study, individual patient consent was not required.

Patient Selection

We retrospectively reviewed the medical records of all patients receiving LITT at the University of Maryland Medical Center from February 2019 through November 2023 who underwent elective treatment of intra-axial tumors. Those with histopathologically proven recurrent HGG were included in this study.

Surgical Technique

Preoperative T1-weighted, T2-weighted, and contrast-enhanced T1-weighted MR images were used for surgical planning and image guidance (Fig. 1A). Patients were taken to the operating room, where stereotactic biopsies were obtained prior to LITT, and the treatment proceeded upon confirmation of pathology. LITT was performed using the NeuroBlate system (Monteris Medical). Real-time MR thermometry was used to estimate the regions receiving thermal doses ≥ 2 cumulative equivalent minutes at 43°C (CEM₄₃) and ≥ 10 CEM₄₃, with a goal of heating as much of the enhancing region to at least 10 CEM₄₃ as safely possible (Fig. 1B). CEM₄₃ is a thermal dose metric derived from a normalizing method that converts the various time-temperature exposures applied into an equivalent exposure time.¹⁶ Postprocedure imaging was acquired to evaluate ablation volumes (postoperative rim of enhancement) and potential complications (Fig. 1C).

Data Acquisition

Demographic, clinical, radiological, and histopatho-

logical data were extracted from the electronic medical record. Demographic data included patient age, sex, comorbidities, Karnofsky Performance Scale (KPS) score as determined by an attending physician, and any previous treatments for the intracranial tumor. Comorbidities were assessed using the modified frailty index of five relevant conditions (mFI-5), a metric that predicts postoperative complications after brain tumor resection.¹⁷ The number of trajectories used was recorded in the operative report. Radiographic reports interpreted by a board-certified neuroradiologist were used to determine the tumor location and multifocality. Eloquent locations were defined as primary somatosensory, motor, speech, and visual cortex.¹⁸ Histopathological diagnosis was attained from the pathology report of the pre-LITT biopsy. Treatment duration, energy delivered, and power used were acquired from the Monteris NeuroBlate workstation.

Image Processing

Three-dimensional masks of each intracranial mass were created within Brainlab Elements. Tumor volume and minimum depth of the lesion from the cortical surface were recorded based on preoperative T1-weighted, T2-weighted, and contrast-enhanced T1-weighted MR images. Tumor volume encompassed by the rim of enhancement on postoperative contrast-enhanced T1-weighted MR images was divided by the total tumor volume to yield the extent of ablation (EOA) as a percentage. Preoperative midline shift was assessed using established methods on stealth sequence MRI performed the morning of LITT.

Assessment of Functional Outcome

Functional outcome was assessed by examining the change in KPS score before and after LITT. The postoperative KPS score was calculated as the greatest KPS score at follow-up visits within 8 weeks of LITT. This outcome was dichotomized into patients whose KPS score was stable or improved versus those whose KPS score decreased. Changes in the need for corticosteroids were examined in the peri-LITT period by comparing steroid dose on admission with that at follow-up within the global period.

Statistical Analysis

Variables of interest were analyzed using generalized linear and logistic regression models to determine their influence on continuous and discrete outcomes, respectively. An alpha level of 0.05 was used to indicate statistical significance. Analyses were performed in R statistical software version 4.1.0 (R Foundation for Statistical Computing).

Results

Patient Cohort

LITT was performed in 47 consecutive cases from 2019 to 2023 to treat recurrent HGG. The patient cohort consisted of 21 women and 26 men with a mean age at surgery of 57 ± 14.2 years. Functional status was evaluated with the KPS preoperatively. More than one-third of patients presented with a score of 90 or higher.

TABLE 1. Baseline characteristics of patients with recurrent HGG

	Value
Total no. of pts	47
Age, yrs	57 ± 14.2
Sex	
Female	21 (45)
Male	26 (55)
KPS score	
100	4 (9)
90	15 (32)
80	10 (21)
70	13 (28)
60	5 (11)
Change in KPS score	
Worse	17 (36)
Stable	19 (40)
Improved	9 (19)
Time to KPS assessment, wks	4 (1.7–6.4)
mFI-5*	1 (0–2)
Previous treatment	
Surgery	47 (100)
Chemotherapy	36 (77)
Radiation therapy	37 (79)
Preop steroid use	19 (40)

Pt = patient.

Data are given as number of patients (%), mean \pm SD, or median (IQR).

* The mFI-5 is a measure of a patient's most significant comorbidities and ranges from 0 to 5. Points consist of hypertension, type 2 diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, and reduced functional capacity.

All patients underwent tumor resection prior to LITT treatment. The majority of patients also received previous radiation therapy (79%) and completed a full regimen of chemotherapy (77%). Five patients had progressive disease from residual tumor after a subtotal resection and received LITT before starting chemoradiation therapy (Table 1). Three patients did not undergo surgery followed by chemoradiation therapy due to an inability to tolerate the side effects of these treatments (e.g., temozolomide-induced thrombocytopenia).

All patients were treated for recurrent HGG. Thirty-five (74%) of these were glioblastoma and 3 (6%) were grade 4 *IDH*-mutant astrocytoma. LITT treatments for grade 3 glioma comprised a smaller proportion of this cohort, with 5 (9%) grade 3 astrocytomas and 3 (4%) grade 3 oligodendrogliomas. One-quarter of these tumors were multifocal, and nearly half spanned at least two lobes. The median tumor volume was 12.8 cm³ (IQR 5.5–21.5 cm³), and the median tumor depth was 8.7 mm. These tumors created mass effect as evidenced by the median midline shift (2.2 mm, IQR 1.4–3.1 mm) (Table 2).

The median treatment duration was 91.5 minutes with a median energy delivery of 28.8 kJ. Twenty-four (51%) patients received LITT using one laser trajectory, 16 (34%) patients required two trajectories, and 7 (15%) patients required three. The EOA assessed on postoperative imag-

TABLE 2. Tumor type, location, and geometry

	Value
Tumor type	
Glioblastoma	35 (74)
Astrocytoma grade 4 <i>IDH</i> mutant	3 (6)
Astrocytoma grade 3	5 (11)
Oligodendroglioma grade 3	3 (6)
Gliosarcoma	1 (2)
Laterality	
Lt	22 (47)
Rt	22 (47)
Midline	3 (6)
Tumor location	
Frontal	22 (47)
Temporal	14 (30)
Parietal	11 (23)
Occipital	2 (4)
Periventricular	2 (4)
Basal ganglia	1 (2)
Thalamic	1 (2)
Corpus callosum	3 (6)
Cerebellar	0
Brainstem	0
Eloquent tumor location	18 (38)
Multilobar tumor	18 (38)
Multifocal tumor	11 (23)
Tumor vol, cm ³	12.8 (5.5–21.5)
Tumor depth, mm	8.7 (3.2–16.3)
Midline shift, mm	2.2 (1.4–3.1)

Data are given as number of patients (%) or median (IQR).

ing was 87.9% ± 12.0% of the total preoperative volume (Table 3).

Factors Associated With Functional Outcome

Of the 47 patients included in this study, 28 had stable or improved functional status during the period considered (median 30 days after LITT, IQR 12–45 days) (Table 4). Seventeen patients exhibited a worse postoperative functional status, and 2 patients were lost to follow-up and did

TABLE 3. LITT treatment parameters

	Value
Treatment duration, mins	91.5 (60.0–130.5)
Energy delivered, kJ	28.8 (12.9–39.8)
Trajectories utilized	
1	24 (51)
2	16 (34)
3	7 (15)
EOA, %	87.9 ± 12.0
Postablation residual, cm ³	0.75 (0.25–1.95)

Data are given as median (IQR), number of patients (%), or mean ± SD.

TABLE 4. Changes in KPS score after LITT

	Value
Stable KPS score	19 (40)
Improved KPS score	9 (19)
10 points	5 (11)
20 points	4 (9)
Worse KPS score	17 (36)
10 points	4 (9)
20 points	7 (15)
>20 points	6 (13)
Preop KPS score of pts w/ stable or improved status	
100	3 (6)
90	15 (32)
80	5 (11)
70	3 (6)
60	2 (4)
Preop KPS score of pts w/ worse status	
100	3 (6)
90	3 (6)
80	5 (11)
70	5 (11)
60	1 (2)
KPS assessment post-LITT, days	30 ± 21

Data are given as number of patients (%) or mean ± SD.

not have postoperative KPS scores recorded. There was no difference in preoperative KPS scores between these groups (p = 0.824).

Of the 17 patients showing a decline in KPS score after LITT, 5 demonstrated a new focal neurological deficit. The remaining 12 patients had reduced function due to nonfocal causes.

Regression analysis was performed to identify potential associations with postoperative functional status. Patient factors including age, preprocedure KPS score, and significant medical comorbidities as measured by the mFI-5 did not correlate with postablation function (Table 5). Tumor volume was negatively associated with postablation KPS score (p = 0.0387), although eloquent tumor location, multifocality, and mass effect did not show any relationship with this outcome. Likewise, no intraprocedural factor, including EOA, number of trajectories used, or volume of any postablation residual tumor, showed a correlation with patient functional status.

Tumor volumes were then binned to determine an implementable cutoff for these results. There were 34 patients with tumors < 20 cm³, 6 with tumors 20–40 cm³, 4 with tumors 40–60 cm³, and 3 with tumors > 60 cm³. Dichotomizing tumor volume at 20 cm³ showed a significant difference in change in KPS score postprocedure (β = 11.9, 95% CI 1.482–22.31; p = 0.026). Further stratification to compare a cutoff at 10 cm³ did not generate a significant result (p = 0.967). Logistic regression demonstrated a 4.2 times greater odds of achieving a stable or improved KPS score for tumors < 20 cm³ (p = 0.0497) with an area under the curve of 0.6345, positive predictive power of 70.59%, and negative predictive power of 63.64% (Fig. 2B and C).

TABLE 5. Bivariate regression of KPS score showing that tumor volume is negatively associated with post-LITT functional status

	ρ (95% CI)	p Value
Pt characteristics		
Age, yrs	-0.1267 (-0.4120 to 0.1586)	0.3756
Preop KPS score	0.1126 (-0.2863 to 0.1680)	0.6023
mFI-5	0.0079 (-0.02152 to 0.01030)	0.4805
Tumor characteristics		
Eloquent location	0.0046 (-0.0151 to 0.0037)	0.2266
Tumor vol, cm ³	-2.576 (-0.7553 to -0.0211)	0.0387
Multifocal	0.0041 (-0.0068 to 0.0097)	0.7251
Midline shift, mm	0.0224 (-0.0442 to 0.0463)	0.9644
Treatment parameters		
EOA, %	0.1171 (-0.3677 to 0.1050)	0.2686
No. of trajectories	0.0071 (-0.0268 to 0.0017)	0.0821
Postablation residual, cm ³	0.0414 (-0.1388 to 0.02841)	0.19

Boldface type indicates statistical significance.

TABLE 6. Corticosteroid usage before and after LITT

	Value
Pts not requiring steroids before LITT	
New steroid requirement	13 (46)
Remained off steroids	15 (54)
Pts requiring steroids before LITT	
Increased dose	9 (47)
Continued pre-LITT dose	3 (16)
Reduced dose	5 (26)
Discontinued	0 (0)
Insufficient follow-up data	2 (11)

Data are given as number of patients (%).

status (KPS score: 78 ± 11 vs 89 ± 7 , $p = 0.049$), and had more preexisting midline shift (1.6 ± 1.5 mm vs 3.3 ± 2.7 mm, $p = 0.046$). Of the 13 patients who required prolonged steroid usage, 5 were unable to discontinue corticosteroids before the end of life. The remaining 8 patients were able to wean off of steroids 69 ± 23 days postprocedure.

An additional 19 patients had been on steroids prior to receiving LITT: 9 required an escalated dose after the procedure, 3 continued their pre-LITT dose, and 5 were able to decrease their dose. Two patients did not have adequate follow-up data during the global period. Those requiring an increased steroid dose after undergoing LITT had a lower pre-LITT steroid dose (3.4 ± 2.4 mg daily vs 9 ± 6.2 mg daily, $p = 0.025$), greater midline shift (3.9 ± 2.5 mm vs 1.5 ± 1.5 mm, $p = 0.032$), and greater EOA ($94\% \pm 6\%$ vs $87\% \pm 5\%$, $p = 0.023$). Seven of these patients were able

Effect of LITT on Corticosteroid Requirements

Changes in the need for corticosteroids are presented in Table 6.

Twenty-eight patients did not require steroid treatment prior to LITT, and 15 of these patients were able to continue weaning off of steroids after the procedure, whereas the other 13 patients demonstrated a new need for steroids to achieve symptomatic relief. Patients with a new steroid requirement were older (62 ± 12 years vs 49 ± 14 years, $p = 0.017$), had lower preoperative functional

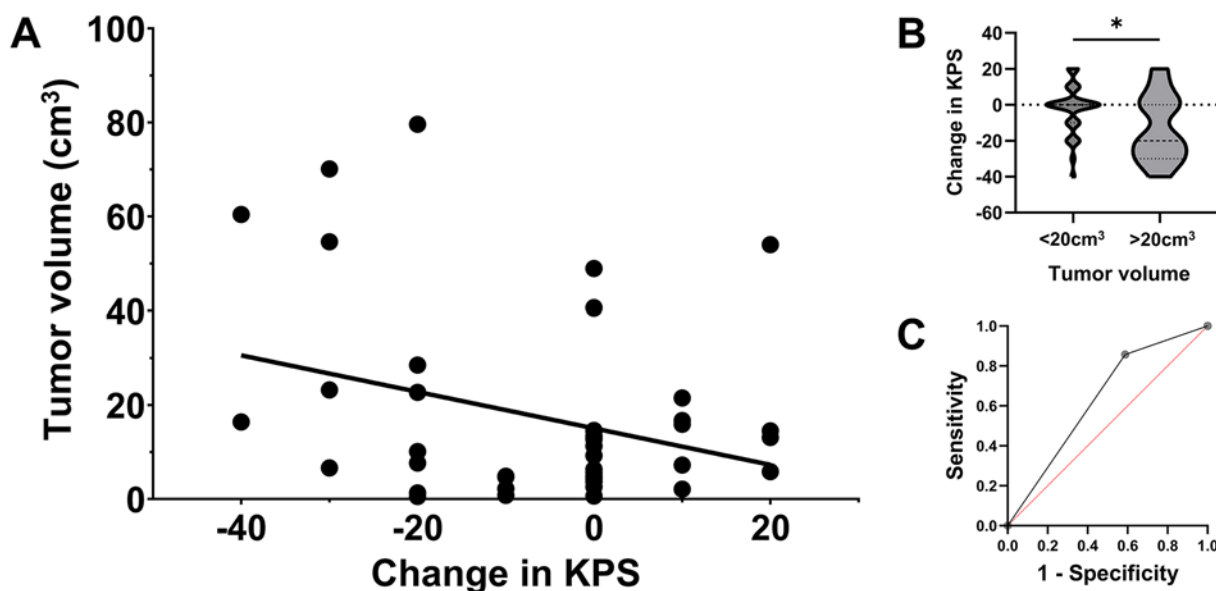


FIG. 2. A: Graph showing that tumor volume is negatively associated with change in KPS score after LITT for recurrent glioma ($\beta_1 = -0.2464$, $R^2 = 0.0956$; $p = 0.0387$). **B:** Violin plots demonstrating that tumor volumes < 20 cm³ have significantly more stable KPS scores after LITT than tumors of greater volume ($p = 0.0372$). * $p < 0.05$. **C:** Area under the curve plot of tumor volume < 20 cm³ as a predictor of stable and improved post-LITT KPS scores.

to discontinue steroids before succumbing to their disease, a mean of 151 ± 72 days after receiving LITT, which was significantly longer than the group of patients who did not take steroids prior to LITT ($p = 0.033$). Neither tumor volume nor EOA was associated with time to steroid freedom ($R = 0.197$ [$p = 0.334$] and $R = 0.184$, [$p = 0.368$], respectively).

Discussion

In this study, perioperative functional outcomes were examined in patients who underwent LITT for recurrent HGG. While multiple prior studies have characterized clinical and technical factors affecting the efficacy of LITT,^{9,10,19–24} there are still several postoperative functional outcomes that have yet to be analyzed to improve patient selection. This is especially relevant for recurrent HGG, in which the preoperative and predicted postoperative neurological function are important considerations in surgical recommendations.

Nearly two-thirds of patients in this series exhibited stable or improved function 1 month after undergoing LITT for recurrent HGG. Of these patients, the majority exhibited a stable postoperative KPS score, while 9 improved. Seventeen patients experienced worsening functional capacity after undergoing LITT. In comparison, functional outcomes in the Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN) study showed a gradual decline in KPS score following LITT for both primary and metastatic tumors.²⁵ However, because of a ceiling effect, the magnitude of functional decline was often greater than the benefits obtained by local ablation. As a consequence, patients with stable and improved function in the LAANTERN study were likely not reflected in the mean KPS score changes.

We found that tumor volume is significantly associated with postablation functional outcome. Specifically, patients with larger tumors were less likely to have stable or improved KPS scores after LITT. A linear relation was noticed between tumor volume and change in KPS score as demonstrated by regression analysis. Given their collinearity with tumor volume, treatment duration and energy delivered were not examined in the final linear regression. Tumor volumes were stratified to determine a practical cutoff associated with good functional outcome. We found that patients with recurrence of tumor $< 20 \text{ cm}^3$ in volume were more than four times as likely to avoid postoperative functional decline than those with larger tumors. Notably, there was a population of patients who did experience a worsening in their functional status after LITT. As these tumors were larger, although not statistically significant, they spanned into adjacent lobes. This may add weight to the converse of our above finding: large, morphologically irregular tumors may be better candidates for re-resection if the patient is in suitable condition for open surgery and has mass effect–related symptoms.

Interestingly, no other tumor-related factors such as eloquent location were related to post-LITT functionality, supporting the observation that LITT is suitable for ablating tumors even when they abut eloquent cortices.²⁶

Extent of resection has been heavily studied in the

glioma literature, and a significant association has been reported with increased risk of neurological morbidity.²⁷ In contrast, the results shown here demonstrate no association between EOA and KPS score after treatment. Other groups have put forth the idea of safe, supramarginal ablation, and the effect of this technique on functional outcome may warrant further investigation.^{22,28}

No patient-related factors, including age, comorbidities, and preoperative KPS score, were associated with functional outcomes. This finding is opposed to the current literature for open resection in which a lower preoperative KPS score predicts worse functional outcomes.^{29–31} Instead, this finding adds to the evidence shown in direct comparisons between LITT and open surgery that suggests a role for LITT in patients with low baseline functional status.²⁶

Nearly half of the patients in this study demonstrated a new or increased need for corticosteroids after undergoing LITT. This is not surprising given that LITT has been shown to open the blood-brain barrier, a property that is under investigation to augment drug delivery.^{4,32,33} Leuthardt et al. found that the blood-brain barrier was disrupted for weeks following LITT for recurrent glioblastoma, with some patients demonstrating elevated vascular permeability for as long as 70 days after the procedure.³⁴

In this cohort of recurrent HGG, those with greater midline shift were more likely to require an escalation in corticosteroid use after LITT. This is likely a result of cytotoxicity induced by LITT without directly alleviating mass effect. While LITT ultimately led to greater steroid independence in a study of patients with radiation necrosis and brain metastasis,³⁵ our disparate results likely reflect a biological difference in the primary brain tumor's response to thermal ablation. These findings may reflect a need for more directed cerebral edema management in the post-LITT period.

There are several limitations to this study. This cohort represents a single institution's patient population that was selected for LITT with potential sampling bias. Our patient population harbored various pathologies with differing previous treatments, although this may make our cohort more reflective of a neurosurgeon's oncological practice in general. As these patients had different pathologies, we do not report survival data. We did not assess the effect of LITT on long-term functional status; however, given the nature of recurrent glioma, this is certain to decline with enough time. The level of evidence for our findings is limited by the retrospective nature of our study. The limited sample size limits the power and generalizability of the statistical analyses.

Conclusions

In this study of 47 consecutive patients undergoing LITT for the treatment of adult recurrent HGG, the majority had a favorable functional outcome and tumor volume was inversely associated with post-LITT functional outcome. Those patients with a treated tumor volume $< 20 \text{ cm}^3$ were significantly more likely to maintain or experience improvement in their neurological function after LITT. This information may help guide patient selection

and treatment optimization in the setting of LITT-based approaches for recurrent HGG.

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Disclosures

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Author Contributions

Conception and design: Woodworth, Mishra, Motta, Ksendzovsky. Acquisition of data: Woodworth, Wilhelmy, Serra, Mishra. Analysis and interpretation of data: Woodworth, Wilhelmy, Serra, Chen, Mishra, Rodrigues, Badjatia, Motta. Drafting the article: Woodworth, Wilhelmy, Serra, Mishra, Badjatia. Critically revising the article: Woodworth, Mishra, Rodrigues, Badjatia, Ksendzovsky. Reviewed submitted version

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