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ORIGINAL ARTICLE

Laser interstitial thermal therapy for newly diagnosed glioblastoma

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Abstract

Gliomas are the most frequent primary brain tumor in adults. Patients with glioblastoma (GBM) tumors deemed inoperable with open surgical techniques and treated only with chemo/radiation have a median overall survival of less than 9 months. Laser interstitial thermal therapy (LITT) has emerged as a cytoreductive alternative to surgery for these patients. The present study describes the outcomes of twenty patients with newly diagnosed, IDH wild-type glioblastoma treated with LITT. We retrospectively reviewed patients with newly diagnosed, unresectable GBM who underwent LITT at our institution. Progression-free survival (PFS) was the primary endpoint measured in our study, defined as time from LITT to disease progression. Results Twenty patients were identified with newly diagnosed, inoperable GBM lesions who underwent LITT. The overall median PFS was 4 months (95% CI = 2 — N/A, upper limit not reached). The median progression-free survival (PFS) for patients with less than 1 cm 3 residual tumor (gross total ablation, GTA) was 7 months (95% CI = 6 — N/A, upper limit not reached), compared to 2 months (95% CI = 1 — upper limit not reached) for patients with a lower GTA ($p = .0019$). The median overall survival was 11 months (95% CI = 6 — upper limit not reached). Preoperative Karnofsky performance score (KPS) less than or equal to 80 and deep-seated tumor location were significantly associated with decreased PFS (HR, .18, $p = .03$; HR, .08, $p = .03$, respectively). At the end of 1 month, only 4 patients (20%) experienced persistent motor deficits. LITT is a safe and effective treatment for patients with unresectable, untreated GBM with rates of survival and local recurrence comparable to patients with surgically accessible lesions treated with conventional resection. Careful patient selection is needed to determine if GTA is attainable.

Keywords Laser interstitial thermal therapy · Glioblastoma · Radiation necrosis · Neurological deficit · Deep-seated tumor

Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor, with a median survival of 15 months with current standard of care [13, 22, 23]. Up to 40% of GBM are not amenable to a gross total resection [6]. Thus, a significant number of patients are not eligible for surgical removal of their tumors, which has been shown to increase survival [10, 17]. Laser interstitial thermal therapy (LITT) has emerged as an ablative cytoreductive technique that can be used to treat GBM. Technological advances have allowed surgeons to use real-time magnetic resonance (MR)-thermography to monitor the ablation zone intraoperatively, minimizing damage to delicate surrounding structures [5, 24]. For some patients, LITT represents the only opportunity for tumor debulking before starting the standard of care chemotherapy and radiation. LITT was originally shown to be a safe and effective treatment for deep-seated brain metastases [4]. However, recent studies have investigated the efficacy and safety of LITT to treat GBM, showing a significant increase in LITT procedures since 2012 [8, 9, 24]. Previous studies have demonstrated the safety of this approach but the data concerning efficacy compared to standard of care alone is lacking [9, 22, 24].

In addition to debulking and cytoreduction, LITT has shown benefits through alternative mechanisms. Leuthardt

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et al. used dynamic, contrast-enhancement brain MRI to calculate the vascular transfer constant (Ktrans) in the peritumoral region to measure BBB permeability before and after laser ablation in patients with glioblastoma. The authors found that hyperthermia from LITT induced disruption of the peritumoral blood brain barrier (BBB). The permeability peaked within 1–2 weeks and resolved by 4–6 weeks, leading the authors to conclude that this time frame represents a therapeutic window of opportunity for enhanced delivery of systemic agents [11]. Another study of brain metastases patients found that the use of systemic therapy within 3 months after LITT was found to be negatively associated with local recurrence in multivariate analyses [1]. A study using a LITT mouse model found significantly disrupted BBB and blood tumor barriers (BTB) for up to 30 days after LITT. Large molecules such as human immunoglobulin extravasated through blood vessels and permeated laser treated brain tissue and tumors. These findings support the hypothesis that the disrupted BBB can facilitate immune penetration as well as increase delivery of systemic agents [16].

Regardless of the mechanism, LITT has emerged as an intriguing strategy for treating patients with lesions inaccessible to traditional resection. In the present study, we review our experience with newly diagnosed, inoperable GBM lesions treated with LITT. Patient characteristics, complication rates, and patient outcomes are reviewed as well as the volumetric response of the tumor and tissue edema over time after LITT.

Methods

Chart review and volumetric analyses

We retrospectively reviewed patients with newly diagnosed, inoperable GBM who underwent LITT at our institution. Institutional review board (IRB) approval was obtained with regard to the study of human subjects. Patients who were either diagnosed at the time of the procedure or those who had been diagnosed previously with biopsy sampling within 1 month of the LITT procedure and had not received any adjuvant radiation and/or chemotherapy treatments were considered "newly diagnosed" and eligible for this study. Preoperative clinical data that was collected including age, gender, tumor location, tumor volume, Karnofsky performance scale (KPS) score, *IDH1,* and other mutational status. Post-LITT data that were reviewed and collected included any new neurological deficits after LITT, time to clinical and/or radiographic progression, postprocedural chemotherapy and radiation regimens, and overall survival. Tumors were defined by location using criteria defined by Sawaya et al. [18]: non-eloquent (grade I), near-eloquent (grade II), and eloquent (grade III).

All patients underwent pre-operative brain MRI followed by a post-LITT brain MRI along with follow-up imaging at regular intervals after LITT treatment. Tumor volumes were determined using post contrast T1-weighted MR images before LITT. Single, three-dimensional volume measurements of each lesion were taken using the Brainlab iPlan workstation (Brainlab, Munich, Germany) using a segmentation algorithm employing Cavalier's principle. The blue TDT lines correspond with the ablation cavity in the post-LITT MR images and were used to overlay with the pre-LITT scan to calculate residual tumor volume. Residual tumor volume was divided by pre-LITT tumor volume to calculate percent of the tumor not covered by the ablation radius. Gross total ablation (GTA) was defined by less than 5% of the tumor volume not covered by the ablation radius. These measurements were then verified by the lead neurosurgeons. Edema volume was measured similarly using T2 fluid-attenuated inversion recovery (FLAIR) MRI sequences in the iPlan workstation.

Operative technique

Operations were performed in an intraoperative magnetic resonance imaging (iMRI) suite with a Siemens Espree 1.5-T bore scanner (Siemens, Berlin, Germany). The Neuroblate (Monteris, Winnipeg, Manitoba, Canada) and Visualase (Medtronic, Minneapolis, MN, USA) systems were used for LITT delivery. The Neuroblate system was used for 13 patients, while the Visualase system was used for seven patients. Due to our view that the Monteris system has superior computing algorithms, the Monteris system was used when possible. Details regarding the operative technique used have been described in a previous study by our group [24]. Enhancing margins of every tumor were treated to 43 °C for 10 min corresponding to the blue thermal damage threshold (TDT) line in the NeuroBlate system which is sufficient to induce cell death [19]. Depending upon the geometry of the lesion, either the side-fire or diffusion tip was used when using the Neuroblate system.

In the Visualase system, thermal damage was assessed with real time MRI scanning after a high temperature limit is set at 90 °C near the tip of the applicator. The low temperature limit is set at 47–50 °C at the borders of the target area or near critical structures in order to avoid unintended thermal damage. All lesions were treated to a target temperature of at least 46 °C throughout the volume of the lesion to ensure cell death. For larger lesions, a single probe was used and advanced or withdrawn for adequate coverage. In the cases in which tumors were irregularly shaped multiple probes were used. Multiple probes were used for five of the patients.

Statistical analysis

A Kaplan–Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). A log rank test was used to evaluate the difference in PFS between those who received a complete ablation and those who did not. A Pearson correlation test was used to evaluate associations between preoperative characteristics. A p-value < 0.05 was considered significant for all analyses. Analyses were performed using the statistical software SPSS V.24 (IBM Corp., Armonk, New York). Graphs were constructed with the *ggfortify* (https://CRAN.Rproject.org/package=ggfortify) packages in R. Locally weighted scatterplot smoothing (LOESS) were used for characterizing lesion and edema volume over time after LITT.

Results

Twenty patients were identified with newly diagnosed, inoperable GBM lesions who underwent LITT. Nine patients (45%) had tumors in eloquent locations, ten patients (50%) had tumors in near-eloquent locations, and one patient (5%) had a tumor in a non-eloquent location according to criteria defined by Sawaya et al. [18]. Median tumor volume was 11.34 cm^3. Six patients had tumors of the corpus callosum, eight patients had thalamic tumors, three patients had insular tumors, one patient had a temporal tumor, one patient had a basal ganglia tumor, and one patient had a parietal lobe tumor. Nineteen patients (95%) had a pre-LITT KPS greater than or equal to 70 and one had a KPS less than 70. Fourteen patients were IDH wild type, while six patients did not show molecular information in their chart.

Figure 1 shows the cumulative incidence function for death and local recurrence. The median PFS (4 months [95% CI = 2 — upper limit not reached]) for the cohort is summarized by Fig. 2, stratified by GTA. Ten patients (50%) had a GTA. median progression-free survival (PFS) for patients who received GTA was 7 months (95% CI = 6 — upper limit not reached), whereas the median PFS for patients with less than GTA was 2 months (95% CI = 2 — upper limit not reached) using the log rank test ($p = 0.0019$). Twelve patients had deep-seated tumors. Pre-LITT KPS less than or equal to 80 and deep-seated tumor location were significantly associated with decreased PFS (HR, 0.18, $p = 0.03$; HR, 0.08, $p = 0.03$, respectively). GTA was associated with significantly prolonged PFS ($p = 0.0019$) (Fig. 2). GTA was not significantly associated with increased overall survival ($p = 0.94$) (Fig. 3). We found that there was no correlation between tumor volume and a complete ablation using a Pearson correlation test ($r = 0.05$, $p = 0.84$). We also found no correlation between tumor volume and pre-KPS ($r = 0.13$, $p = 0.58$). Figure 4 shows the pre- and post-ablation MRIs of a patient who had a complete ablation (GTA). Figure 5 shows the pre- and post-ablation MRIs of a patient who had an incomplete ablation. Figures 6 and 7 demonstrate the volumetric response of the lesion volume and edema volume over time, respectively. Figure 6 demonstrates that most of the patients exhibited decreases in lesion volume by 30 days post-LITT. Seven patients (35%) had a length of stay greater than or equal to 5 days, while thirteen patients (65%) had a length of stay less than 5 days. Fifteen (80%) of patients received any type of adjuvant treatment. Thirteen patients (65%) received radiotherapy post-LITT, while 12 patients (60%) received post-LITT chemotherapy.

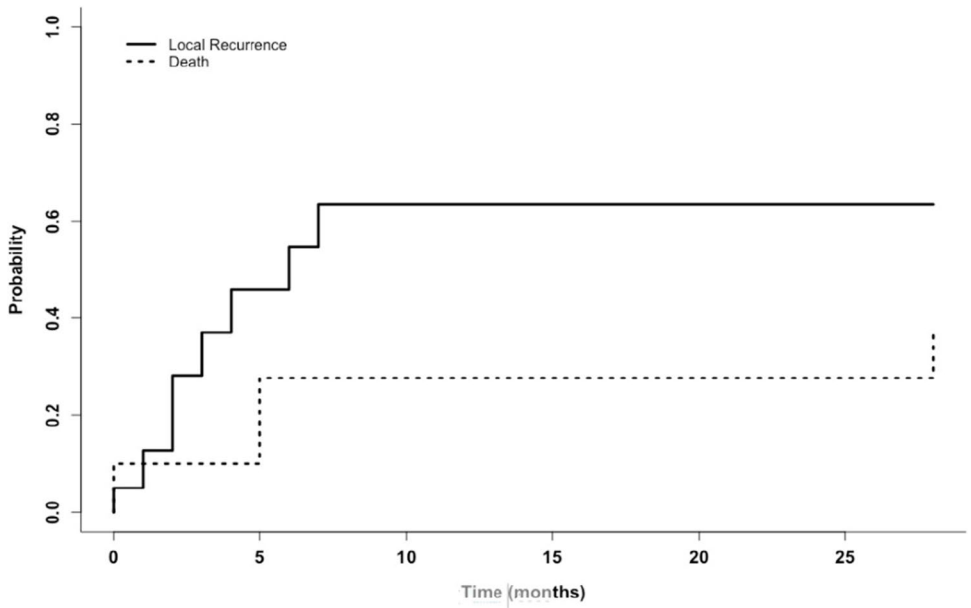

Fig. 1 Curves delineating the cumulative incidence functions for death and local recurrence

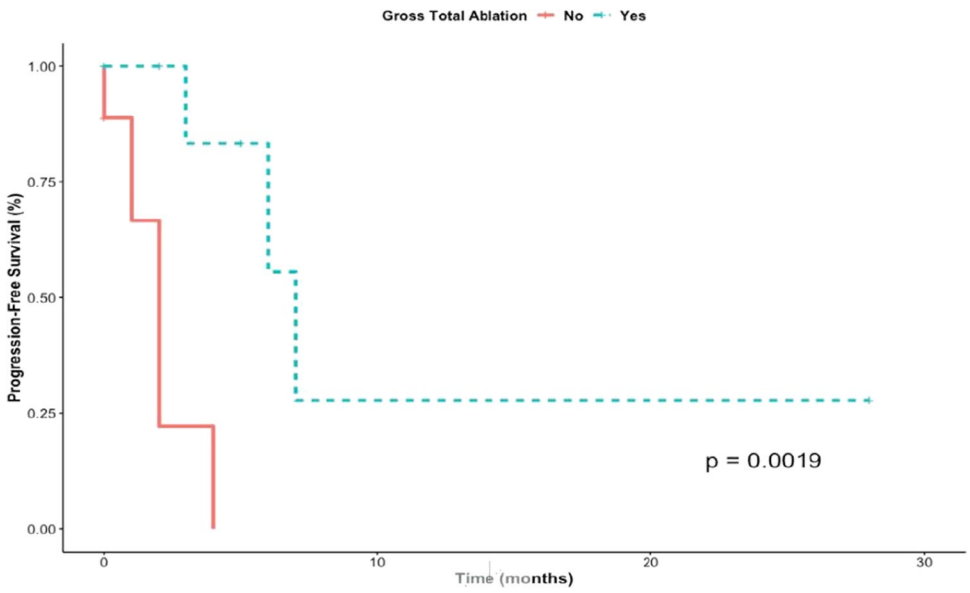

Fig. 2 Progression-free survival stratified with respect to GTA

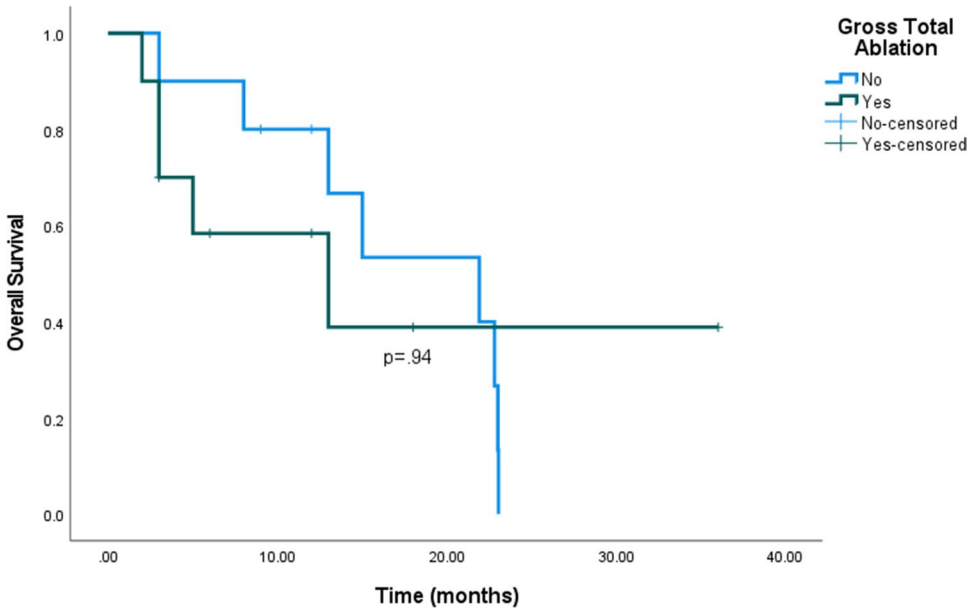

Fig. 3 Overall survival stratified with respect to GTA

Following LITT, 12 out of the 20 patients (60%) had a new or worsened motor deficit. This is not surprising given the proximity of the lesions to the eloquent cortical and subcortical structures. However, only 4 patients (20%) experienced symptoms lasting longer than 30 days. In each of these cases, the patients continued to improve with a KPS of 70 or more and went on to have adjuvant treatments. Two of the patients had postoperative medical complications, both of which were seizures (Tables 1 and 2). Figure 8 illustrates the complications with a deficit tree.

Discussion

Nearly 40% of GBM are not amenable to gross total surgical resection [6]. After surgeons have deemed a tumor inoperable, patients are generally relegated to chemoradiation. The advent of LITT has offered a viable cytoreductive option to debulk tumors located in unresectable locations [24]. Previous reports of treating newly diagnosed GBM with LITT have shown inconsistent results with respect to effects on OS and PFS, most likely due to the small

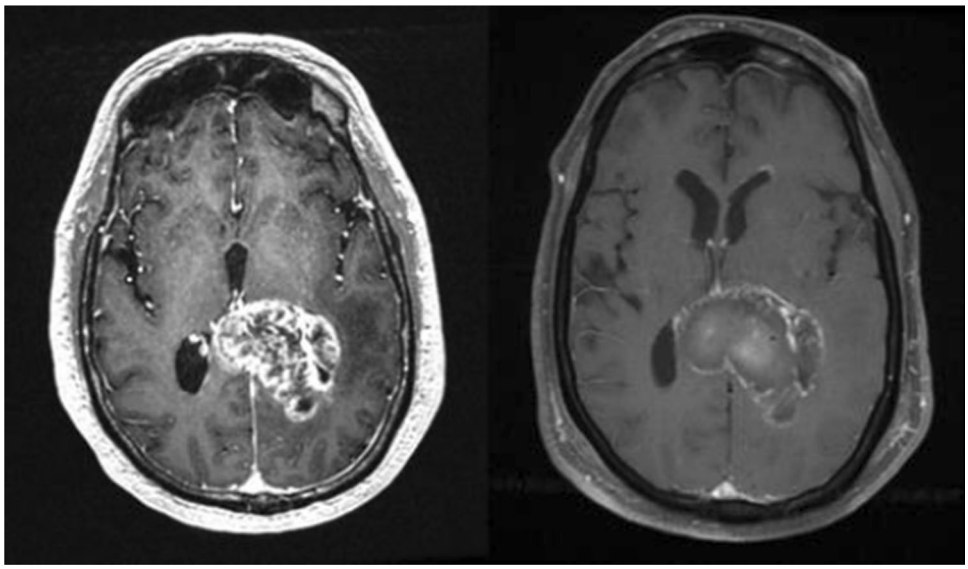

Fig. 4 Pre- and post-ablation MRIs of a complete GTA (left is pre-ablation, right is post-ablation)

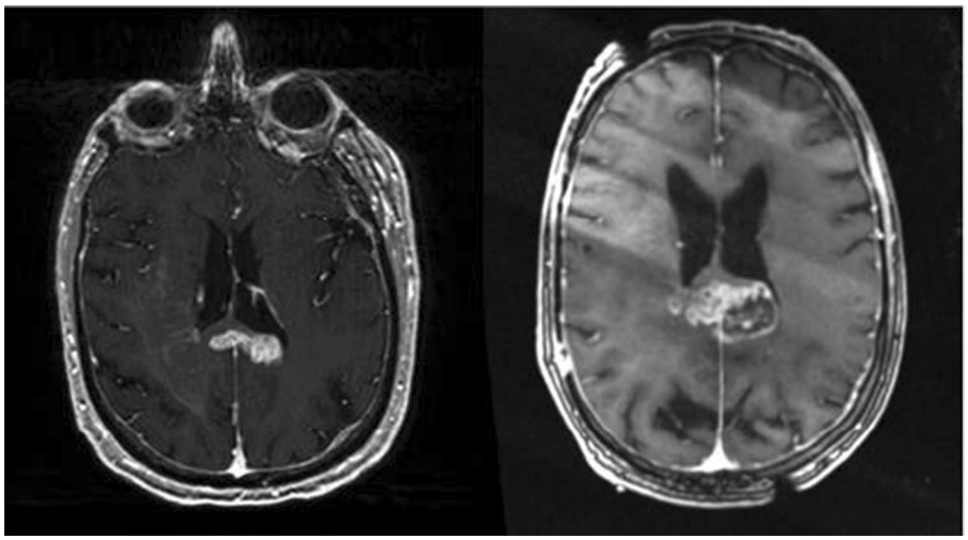

Fig. 5 Pre- and post-ablation MRIs of an incomplete ablation (left is pre-ablation, right is post-ablation)

patient cohorts [12, 21, 24]. A multi-institutional study reports a cohort of 24 patients, the largest to date. The authors compared the laser ablation group with a biopsy-only control group, finding no significant differences in OS or PFS. However, both the control and the laser ablation groups reported outcomes similar to reported literature for the Stupp protocol, which was the first to show a survival benefit for the addition of chemotherapy to radiation [12]. Kamath et al. published a cohort of over 50 glioma patients treated with LITT, with a subset of 17 newly diagnosed lesions. The study found similar PFS and OS to the Stupp protocol for the patients with newly diagnosed GBMs [9].

Previous reports of LITT used to treat newly diagnosed GBM are summarized in Table 3. Here, we report our experience with newly diagnosed, inoperable GBM treated with LITT. Median PFS for previous cohorts ranged from 2 to 5.1 months [12, 21, 24]. The median PFS for this cohort was 4 months (95% CI = 2 — N/A, upper limit not reached). We found a significant difference in PFS between patients with a GTA versus patients without a GTA (7 months vs 2 months respectively). These findings are consistent with evidence that a gross total resection (GTR) substantially improves progression-free survival [3]. Additionally, the overall survival rates of these patients are consistent with those treated with conventional GTR receiving the Stupp protocol [13, 23]. A possible confounder could be that patients with GTA had smaller tumors, enabling a larger extent of ablation. However, GTA was not shown to be associated with smaller tumor volumes using a Pearson correlation test. Pre-LITT KPS < 80 was also shown to be associated with decreased PFS, providing insight into the preoperative characteristics

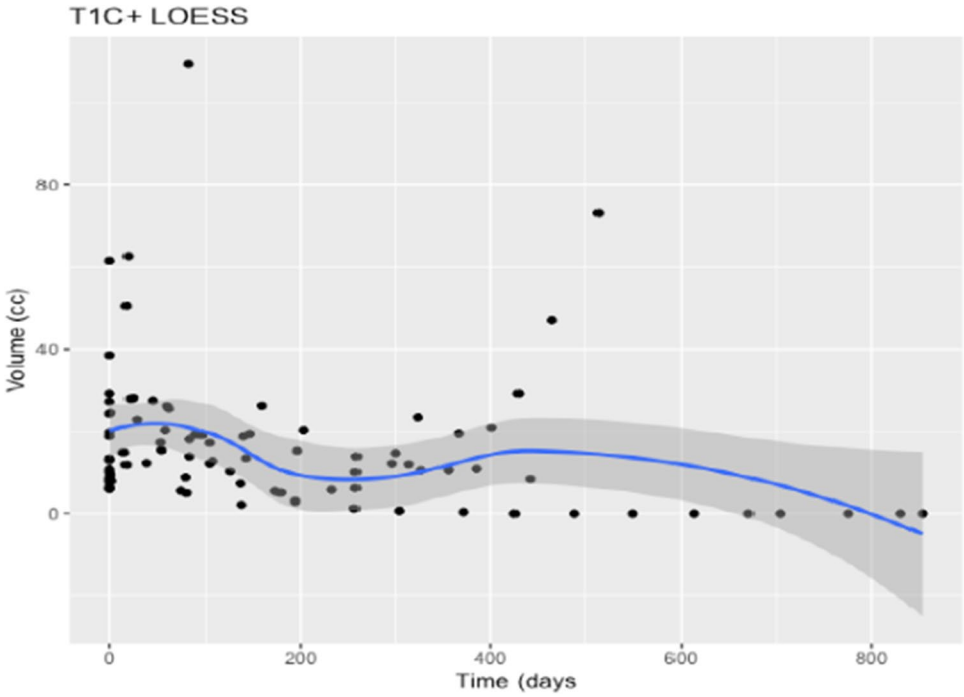

Fig. 6 Locally weighted scatterplot smoothing (LOESS) plot of tumor volume over time

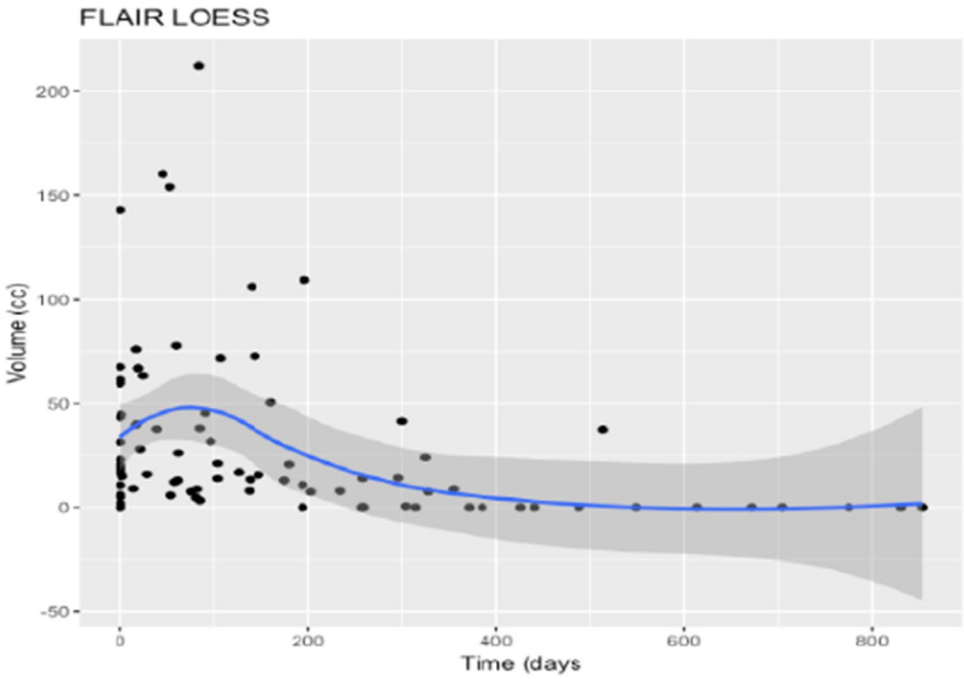

Fig. 7 Locally weighted scatterplot smoothing (LOESS) plot of edema volume over time

associated with a better outcome. This association was not confounded by tumor volume, as pre-LITT KPS and tumor volume were not shown to be associated with each other using a Pearson correlation test.

In this cohort of patients with newly diagnosed inoperable GBM, we examined the volumetric response of the lesion itself as well as cerebral edema after LITT. To our knowledge, this is the first volumetric analyses of patients with newly diagnosed GBM post-LITT. Immediately after the ablation, tissue begins to swell and cerebral edema increases exponentially and can result in temporary deleterious neurological sequela [15]. Volumetric analyses on brain metastases have shown that cerebral edema increases significantly in the initial perioperative period, sometimes making it difficult to ascertain treatment response. However, the edema begins to subside in most cases by about 3 months. The initial

Table 1 Patient's demographics and clinical features at the time of LITT

Type	Number	%
Gender		
Male	12	60.0
Female	8	40.0
Age		
< 60	11	55.0
> 60	9	45.0
Functional location		
Eloquent	9	55.0
Near eloquent	9	35.0
Non eloquent	2	10.0
Tumor size		
> 10 cm^2	11	55.0
< 10 cm^2	9	45.0
Gross total ablation		
Yes	10	50.0
No	10	50.0
IDH status		
Wild type	14	70.0
Mutant	0	0
N/A	6	30.0
Pre-LITT KPS		
≥ 70	19	95.0
< 70	1	5.0
Post-LITT KPS		
≥ 70	15	75.0
< 70	5	25.0
Previous treatment		
Radiation	4	20.0
Chemotherapy	3	15.0
None	16	80.0
Time for diagnosis to LITT		
< 6 months	16	80.0
≥ 6 months	4	20.0
Complications after LITT		
Yes	12	60.0
No	8	40.0
LOS after LITT		
≥ 5 days	7	35.0
< 5 days	13	65.0
Adjuvant treatments		
Yes	15	80.0
No	5	20.0
Post-LITT radiation		
Yes	13	65.0
No	7	35.0
Post-LITT chemotherapy		
Yes	12	60.0
No	8	20.0

edema pattern continues to subside over the first months after treatment, corresponding to improvements in neurological function. In our series, 60% of the patients had an initial neurological deficit, while that number decreased to 20% at the end of one month. This coincides with the observation that most complications also resolve within 3 months of the operation [2]. Volumetric analyses has also showed for brain metastases that lesion size measured by post-LITT T1 weighted MRIs initially increases but shows an overall decrease by about 6 months post-LITT [2].

Our patient cohort showed a similar increase in lesion volume immediately following the procedure to brain metastases treated with LITT [2]. However, most patients in this cohort started to exhibit decreases in lesion volume 30 days post-LITT. A previous study using LITT for brain metastases that have progressed post stereotactic radiosurgery (SRS) showed increases in lesion volume for up to 6 months [2]. Another volumetric analyses of heterogeneous recurrent intracranial tumors showed an increase in lesion size at time points varying between four and 11 weeks [14]. Some have speculated that the initial increase in lesion volume following LITT is due to the inflammatory response caused by the ablation [2]. The discrepancy in lesion volume observed between the newly diagnosed GBM cohort and previous cohorts could be due to the differences in radiation therapy timing. This cohort of newly diagnosed GBM patients received LITT before radiation, while patients from previous cohorts were already treated with radiation before LITT [1, 12]. The underlying swelling from radiation necrosis could have exacerbated the inflammatory response from the ablation.

Previous studies have shown that perilesional edema volume post-radiation or resection can predict both local and distant recurrence for brain tumors [7, 25]. Schoenegger et al. published a retrospective study showing that lower volumes of cerebral edema at the time of presentation are associated with better overall survival [20]. Because of the limited number of newly diagnosed inoperable GBM treated with LITT at our institution, we did not have an adequate cohort to quantitatively investigate the correlation of edema volume with recurrence. Future studies with a larger cohort should more rigorously investigate the association between post-LITT perilesional edema and tumor recurrence. A correlation between immediate post-LITT radiographic findings and tumor recurrence could guide further treatment.

We found comparable overall survival to patients receiving conventional resection and superior to the Stupp protocol of only chemotherapy and radiation. We found that patients who received a GTA had significantly shorter PFS. This finding illuminates the need to understand the factors leading to a GTA in order to optimize patient selection. Due to the limited nature of this cohort, we were unable to elucidate statistically significant predictors. However,

Table 2 List of all complications after LITT

#	Pre-LITT KPS	Lesion location	Functional location	Tumor volume	Complication	Length of stay	Neurological deficit at 1 month
1	100	Corpus callosum	Near eloquent	16.80	None	1	N/A
2	80	Corpus callosum	Near eloquent	8.10	Hemiparesis	10	New persistent[a]
3	60	Left insula	Near eloquent	3.62	Weakness	13	Persistent[b]
4	70	Left insula	Near eloquent	14.30	Weakness	26	Transient[c]
5	90	Corpus callosum	Near eloquent	40.30	None	2	N/A
6	90	Corpus callosum	Near eloquent	35.60	Weakness	5	Transient
7	90	Left thalamus	Eloquent	9.32	Weakness	4	Transient
8	90	Left thalamus	Eloquent	6.91	None	1	N/A
9	80	Corpus callosum	Near eloquent	27.30	Gait imbalance	30	Transient
10	100	Left thalamus	Eloquent	6.09	Dysarthria	3	Transient
11	90	Right thalamus	Eloquent	15.80	None	2	N/A
12	80	Left basal ganglia	Eloquent	37.90	Weakness	3	Transient
13	90	Left insular	Near eloquent	4.13	Weakness	21	Transient
14	90	Left thalamus	Eloquent	10.20	None	3	N/A
15	90	Right thalamus	Eloquent	20.50	None	1	N/A
16	70	Right temporal	Non eloquent	4.60	Weakness	1	Persistent
17	80	Left thalamic	Eloquent	5.37	None	1	N/A
18	80	Corpus callosum	Near eloquent	6.02	Weakness	1	Persistent
19	80	Right parietal	Near eloquent	14.18	None	1	N/A
20	80	Left thalamic	Eloquent	39.09	Weakness	47	Transient

[a]New post-LITT neurological deficit persisting past 1 month

[b]Worsened post-LITT neurological deficit persisting past 1 month

[c]New or worsened post-LITT neurological deficit subsiding before 1 month

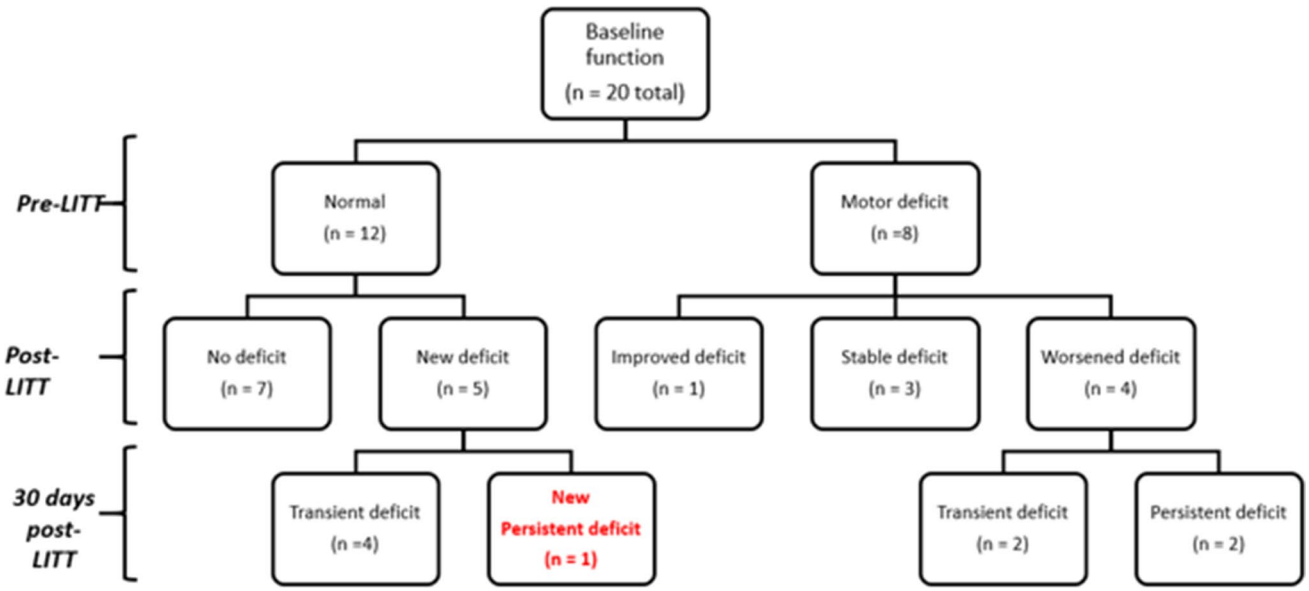

Fig. 8 Deficit tree

Table 3 Previous reports of using LITT to treat newly diagnosed GBM that report both PFS and OS for only newly diagnosed GBM patients

Author	LITT delivery system	N	PFS (months)	OS (months)
Hawasli et al. (2013)	Neuroblate	6	7.6	10.9
Thomas et al. (2016)	NeuroBlate	8	2	8
Kamath et al. (2017)	Neuroblate	23	5.9	11.4
Beaumont et al. (2018)	Neuroblate	9	3.4	18.2
Mohammadi et al. (2019)	NeuroBlate	24	4.3	14.4
Kamath et al. (2019)	NeuroBlate	17	3.6	9.1
Current Series (2021)	NeuroBlate/Visualase	20	4	11

the authors' experience has shown that tumor eloquence as well as large tumor volumes can limit the ability for a GTA. Future research should be guided towards characterizing the factors that predict gross total ablation.

Clinically relevant conclusions are difficult to make without matched cohorts or prospective clinical trials. Mohammadi et al. used a matched cohort to compare the outcomes of patients with newly diagnosed GBM treated with LITT to patients receiving only chemotherapy and radiation, finding no significant difference in overall survival or PFS [12]. This study had a total cohort of 24 patients from multiple institutions. Future studies should focus on selecting appropriate controls to make a single institutional comparison of outcomes for patients with newly diagnosed GBM treated with LITT.

Conclusion

LITT is a safe and effective alternative to conventional resection in patients with inoperable, newly diagnosed GBM. This cohort of patients showed comparable overall survival and progression-free survival to patients with surgically accessible GBM treated with conventional resection. Future studies should center around matched cohort studies as well as prospective clinical trials to determine clinical efficacy.

Abbreviations GBM: Glioblastoma; LITT: Laser interstitial thermal therapy; MR: Magnetic resonance; IRB: Institutional review board; KPS: Karnofsky performance scale; FLAIR: Fluid-attenuated inversion recovery; GTA: Gross total ablation; PFS: Progression-free survival; OS: Overall survival; GTR: Gross total resection; LOESS: Locally weighted scatterplot smoothing

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Declarations

Ethics approval and consent to participate Our study was approved by the institutional review board (IRB) at our institution with regard to the study of human subjects and consent was obtained for all described procedures.

Competing interests None of the authors have potential conflicts of interest with the material presented herein.

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