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Original Article

Repeat laser interstitial thermal therapy for recurrent primary and metastatic intracranial tumors

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ABSTRACT

Background: Repeat craniotomy in patients with primary and metastatic brain tumors carries significant morbidity and can delay adjuvant treatments. Repeat laser interstitial thermal therapy (LITT) for recurrent disease has been described and could benefit patients with limited cytoreductive options. We aim to describe the indications, safety, and efficacy of repeat LITT for recurrent primary and metastatic intracranial tumors.

Methods: Patients undergoing repeat ablations for the same lesion were included in the study. We retrospectively analyzed 13 patients treated with 29 total LITT ablations.

Results: Eleven patients were treated for glioblastoma (GBM), while two had brain metastases. Eleven patients had LITT performed only 2 times, while three patients underwent three total iterations of LITT for disease recurrence. Median length of stay after the 1st ablation was 2 days, while the median length of stay after the 2nd ablation was 1 day. The median time to resuming adjuvant treatments after the 1st LITT was 11 days. The median time to resuming adjuvant treatments after the 2nd LITT was 28 days. Four patients after the 1st and 2nd LITT sustained deficits persisting through 30-day follow-up. The median progression-free survival among the GBM patients from the first ablation was 6.0 months, 3.2 months from the 2nd ablation, and 2.1 months from the 3rd ablation.

Conclusion: Recurrent tumors, especially GBM, can be safely treated using repeat LITT when surgery cannot be effectively performed. Our results indicate that patients tolerate the procedure well and have a meaningful survival given the salvage nature of the procedure.

Keywords: Brain metastases, Glioblastoma, Laser interstitial thermal therapy

INTRODUCTION

Laser interstitial thermal therapy (LITT) has emerged as a novel minimally invasive, cytoreductive technique that has been used for the treatment of newly diagnosed and recurrent gliomas, epileptic foci, as well as recurrent brain metastases and radiation necrosis.[1,3,18] The advent of magnetic resonance (MR) thermography which provides real-time temperature feedback has made possible the safe application of laser ablation to the central nervous system.[7] LITT has shown efficacy in the treatment of deep-seated malignant and epileptic lesions with minimal complications.[22] LITT has also been shown to be useful navigating the anatomical constraints of lesions in the posterior fossa, demonstrating limited complications, and a survival benefit in patients with no other viable surgical options.[5,26]

Patients with glioblastoma (GBM) on an average have 2–3 craniotomies performed over the lifetime of the disease. Each intervention carries significant morbidity and delays in restarting adjuvant treatments. Patients with recurrent lesions following LITT have few options. These tumors present a unique challenge; the location of the tumor or the comorbidities and poor prognosis of the patients usually exclude the possibility of re-resection.[6] No standard salvage treatment has emerged as the standard of care for these patients.[21] Chemotherapy, radiotherapy, targeted therapies, and immunotherapeutic options have been employed with limited success.[4,9-11,15,19] Because LITT is best suited for well-circumscribed lesions, the multifocal nature of many recurrent lesions following LITT usually precludes the possibility of repeat LITT. However, a small number of patients present with well-circumscribed recurrent lesions amenable to salvage repeat ablations. Furthermore, the minimally invasive nature of this approach enables for additional treatments with minimal morbidity with respect to conventional resection techniques. Herein, we describe our experience treating a cohort of patients who had repeat treatments with LITT after a local recurrence.

MATERIALS AND METHODS

Study design, setting, and participants

This study was performed under the auspices of an Institutional Review Board-approved protocol in compliance with institutional regulations on the study of human subjects. A retrospective search of the departmental database at our institution from January 2013 to January 2018 identified 13 patients who treated with repeat LITT for the same lesion. Characteristics for pre- and post-LITT outcomes are reported.

Operative technique

All procedures were performed in an intraoperative magnetic resonance imaging (MRI) suite with a Siemens Espree 1.5 T magnet (Siemens, Berlin, Germany). A preoperative MRI was obtained to plan the trajectory of the ablation probe using Brainlab iPlan software (Brainlab, Munich, Germany). A cannulated bolt was then inserted in the patient's skull under imaging guidance along the planned trajectory using the VarioGuide system (Brainlab) followed by insertion of the premeasured LITT1 probe. LITT procedures were performed by the senior authors with the NeuroBlate System (Monteris, Winnipeg, Canada) or the Visualase system (Medtronic, Minneapolis, Minnesota, USA). The NeuroBlate system was used on 11 patients, while the Visualase system was used on four patients. For two patients, a different system was used on each ablation. The details of our ablation technique have been described elsewhere.[25]

Follow-up, MRI, and volumetric analysis

All patients underwent brain MRI before the LITT procedure and follow-up imaging at regular intervals after treatment (usually every 2–3 months). Imaging sequences included T1-weighted precontrast and postcontrast (T1C+) and fluid-attenuated inversion recovery (FLAIR) MRI. The MRI data were exported to an iPlan workstation (Brainlab, Munich, Germany) from the electronic medical record. Using T1C+ MRI pre-LITT, immediately post-LITT, and at every follow-up, manual tumor segmentation was performed by a neuroradiologist to create a tridimensional volumetric measure. Similarly, manual segmentation of the edema was completed by a neuroradiologist, creating a tridimensional volumetric measure using FLAIR imaging data. On the preoperative scans, the tumor margin was the enhancing lesion. On the posttreatment scans, the margin was the ablation cavity. Single-volume measurements of each lesion and associated edema were calculated and verified by the senior author. The functional location of the lesions was classified per criteria described by Sawaya *et al.*[20] as Grade I (noneloquent), II (near eloquent), and III (eloquent).

Statistical analyses and data synthesis

Continuous variables were summarized with median and range; categorical variables, with frequency and percentage. Summary statistics were calculated for all variables. A Kaplan–Meier method was used to estimate overall survival (OS) and progression-free survival (PFS); survival curves were compared using a log-rank (Mantel-Cox) test. A Cox proportional hazards model with 95% confidence intervals was used to evaluate the difference in PFS between those patients who received post-LITT chemotherapy and those who did not. $P < 0.05$ was considered statistically significant for all analyses. Analyses were performed with SPSS 24 (IBM, Armonk, New York, USA). Graphs were constructed with the *ggplot2* (https://CRAN.R-project.org/web/packages/ggplot2/index.html) and *ggfortify* (https://CRAN.R-project.org/package=ggfortify) R packages.[24,27]

RESULTS

Patient and lesion characteristics are summarized in Table 1. Each ablation was performed for the same lesion as the previous ablation. The average extent of ablation for the contrast enhancing portion of the tumor for the first LITT procedure was 79%, 70% for the second, and 83% for the third. Seven of the patients had a gross total ablation (GTA) (>95% ablation) for their first ablation. Two of the patients had a GTA for their second ablation. All three patients undergoing a 3rd LITT had a GTA. The same trajectory was used for eight of the patients during the second ablation and two of the patients during the third ablation. Two patients

Table 1: Patient's demographics and clinical features at the time of LITT and in between procedures.

Type	Number	Percentage
Gender		
Male	6	46.2
Female	7	53.8
Age at the 1st LITT		
<60	9	69.2
>60	4	30.8
Functional location		
Eloquent	5	38.5
Near eloquent	3	23.1
Noneloquent	5	38.5
Histology		
GBM	11	84.6
Metastasis	2	15.4
Previous treatment		
Resection	10	76.9
Radiation	11	84.6
Chemotherapy	12	92.3
None	0	0
Treatment in between the 1st and 2nd ablations		
Chemotherapy	3	23.1
Radiation	3	23.1
None	9	69.2
Time for diagnosis to the 1st LITT		
<1 year	7	53.8
>1 year	6	46.2
Time in between the 1st and 2nd ablations		
<6 months	5	38.5
>6 months	8	61.5
Time in between the 2nd and 3rd ablations		
>6 months	0	0
<6 months	3	100
Complications after the 1st ablation		
Yes	4	30.8
No	9	69.2
Complications after the 2nd ablation		
Yes	5	38.5
No	8	61.5
Complications after the 3rd ablation		
Yes	1	33.3
No	2	67.7
Gross total ablation (ablation volume >95%)		
1st LITT	7	53.8
2nd LITT	2	15.4
3rd LITT	2	66.7

GBM: Glioblastoma, LITT: Laser interstitial thermal therapy

received adjuvant chemotherapy and radiation in between the 1st and 2nd ablation, while one patient received chemotherapy alone and one patient received radiation alone. Median time

from the first ablation to adjuvant treatment was 11 days. Seven patients received chemotherapy after the 2nd ablation and one patient received both chemotherapy and radiation after the 2nd ablation. Median time from the 2nd ablation to adjuvant treatment was 28 days.

GBM

Of the 11 patients with GBMs that underwent repeated ablations for the tumors with local recurrence, eight had repeat laser ablations, whereas three underwent three ablations. The majority of GBM patients were *IDH* wild type (*n* = 8). Most tumors were located in either the temporal (*n* = 4) or frontal lobes (*n* = 3). Median time from diagnosis to the first LITT was 8 months, from the first LITT to second, 6.9 months, and 7.9 months from the second ablation to the third, respectively. Before the first LITT treatment, nine patients received radiation, eight received chemotherapy, and 10 underwent resection. Median OS from time of diagnosis was 66.7 months (confidence interval [CI] 95% 23.4–110.1). OS of the cohort is represented by a Kaplan–Meier curve in Figure 1, while the PFS after each of the ablations is represented by Kaplan–Meier curves, as shown in Figures 1-3. Median PFS from the first LITT treatment was 6.0 months (CI 95% 4.1–8.0), from the second LITT 3.2 months (CI 95% 1.44–5.0), and from the third LITT 2.1 months.

Four patients (36%) experienced complications after the 1st LITT, 5 (45%) after the 2nd treatment, and 1 (33%) of the patients undergoing the 3rd LITT. The complications of all the patients after each ablation are summarized in Tables 2-4.

Metastases

Two patients underwent repeat ablations for brain metastases. One was a breast metastasis to the right temporal lobe and the other was a nonsmall-cell lung carcinoma (NSCLC) to the basal ganglia. The patient with the breast metastasis experienced no complications after either ablation and was alive with no recurrence at last follow-up, 5 years after the brain metastases diagnosis. The patient with the NSCLC metastasis also experienced no complications after either ablation and was alive with no recurrence at last follow-up, 6 years after diagnosis.

Complications

Four patients experienced complications after the first ablation, while five experienced complications after the second ablation. One of three patients experienced complications after the third ablation. Tables 1-3 describe the complications after each ablation. Only one patient who did not experience a complication after the first ablation experienced a complication after the second ablation. The same trajectory was used for this patient. Of the five

patients who had a postoperative complication after the first ablation, four had a complication after the second ablation. The one patient who had a complication after the third LITT also had a complication after the second LITT. Of the four patients who had complications after the first two ablations, two of them were worsening of the first postoperative deficit (weakness and aphasia), while the other two were new deficits. A different trajectory was used for five of the patients during the second ablation. For these five patients with different trajectories, none of them experienced a different complication profile during the 2nd ablation compared to the 1st.

DISCUSSION

LITT is an emerging therapy for the treatment of intracranial malignancy, particularly for deep-seated and recurrent lesions. The precise, minimally invasive application of the probe with stereotactic guidance has been associated with

Figure 1: Progression-free survival for glioblastoma patients after the 1st LITT treatment.

Figure 2: Progression-free survival for glioblastoma patients after the 2nd LITT treatment.

reduced cost and length of hospital stay for the treatment of intracranial tumors.[17] Because prior chemotherapy or radiotherapy does not preclude its use, LITT can be used as a salvage therapy for patients who would benefit from cytoreductive therapy but are not candidates for conventional open surgery. In addition, the qualities of LITT that contributes to its successful utility as a salvage therapy allow it to be repeated in cases of recurrence for ancillary local disease control.

Despite these attributes, there is a paucity of data to support the use of repeated laser ablation for control of either primary or metastatic brain tumors. The earliest in the literature was a 2012 study by Jethwa *et al.*[16] which described multiple LITT treatments for three separate patients in a total cohort of 20 patients receiving LITT for primary and metastatic intracranial malignancy. Of the three patients, no complications or deficits were observed in the initial LITT treatment phase, while one complication was observed after repeat LITT; metabolic derangements and diabetes insipidus resulting from thermal pituitary injury. The study did not report on the outcomes of the other two cases of repeat LITT. Another single-institution series of LITT by Hawasli *et al.*[13] reported one case of GBM that was originally treated with combined resection and chemoradiation followed by two iterations of LITT for subsequent recurrences. No permanent deficits or complications were observed with the initial or second laser ablation in this case with a hospital stay of 1 and 2 days, respectively. Finally, a 2019 study by Eichberg *et al.*[8] reported on a cohort of patients who underwent multiple iterations of LITT for brain metastases (*n* = 8) and GBM (*n* = 1). Of the nine total patients, one was treated with LITT in four sessions, six patients were treated with two LITT sessions, and two patients were treated with multiple lasers in a single session. Two complications were observed that were ultimately resolved without issue (cerebrospinal leak and
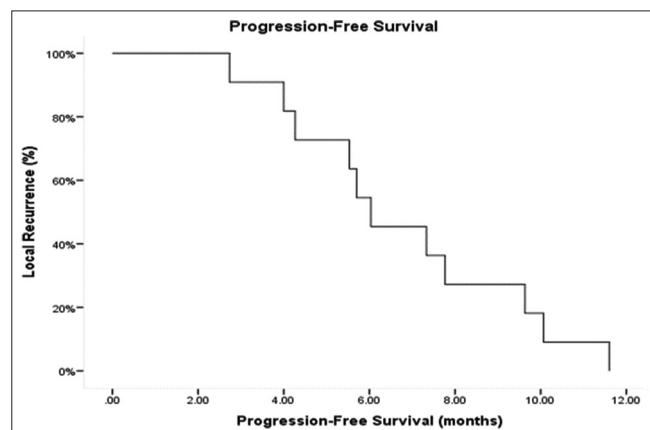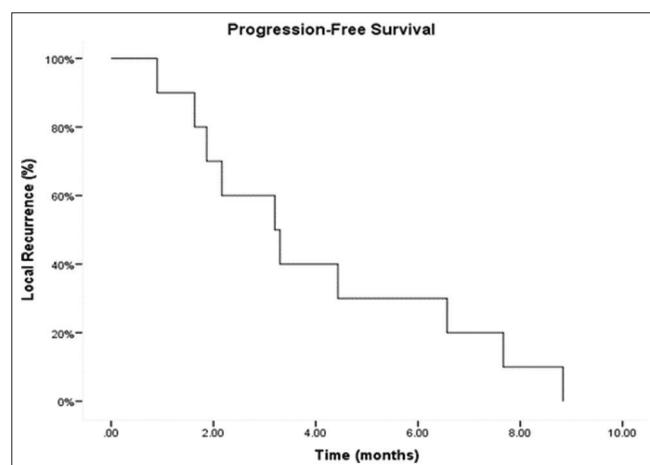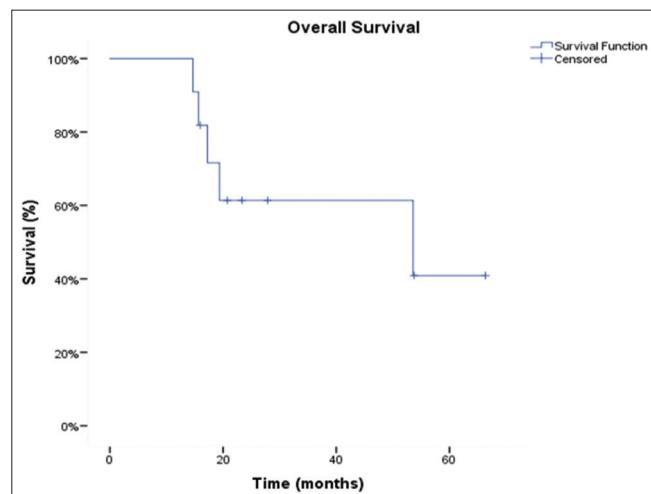

Figure 3: Overall survival of entire cohort from initial diagnosis.

Table 2: List of all complications after the first LITT.

#	Age	Pre-LITT KPS	Histology	Lesion location	Functional location	Tumor/ edema volume	Complication	Length of stay	Persistent neurological deficit at 1 month?
1	41	90	GBM	Left insula	Eloquent	9.44/26.9	None	1	N/A
2	50	60	GBM	Left temporal	Eloquent	13.70/100.2	Right-sided weakness	5	Yes
3	61	90	GBM	Left insula	Near eloquent	7.68/58.9	Aphasia	1	Yes
4	42	60	GBM	Right frontal	Noneloquent	0.74/45.60	None	1	N/A
5	42	100	GBM	Left insula	Near eloquent	21.10/73.10	None	1	N/A
6	42	100	GBM	Corpus callosum	Noneloquent	55.4/85	Aphasia	3	Yes
7	77	90	GBM	Right temporal	Noneloquent	5.15/19.2	None	2	N/A
8	40	90	GBM	Right temporal	Noneloquent	0.04/6.79	None	2	N/A
9	28	100	GBM	Right thalamic	Eloquent	22.70/42.00	None	2	N/A
10	32	100	GBM	Left frontoparietal	Eloquent	6.60/41	Right-sided weakness/ aphasia	4	Yes
11	72	80	GBM	Right temporal	Noneloquent	0.38/55.50	None	1	N/A
12	62	80	Breast metastases	Right cingulate gyrus	Near eloquent	2.38/17.93	None	1	N/A
13	50	90	NSCLC	Basal ganglia	Eloquent	7.33/71.42	None	2	N/A

LITT: Laser interstitial thermal therapy, GBM: Glioblastoma, NSCLC: Nonsmall-cell lung carcinoma

Table 3: List of all complications after the 2nd LITT.

#	Age	Pre-2nd LITT KPS	Histology	Lesion location	Functional location	Tumor/ edema volume	Complication after the 1st LITT	Complication after the 2nd LITT	Same approach from the 1st to 2nd LITT	Persistent neurological deficit at 1 month?
1	41	80	GBM	Left insula	Eloquent	15.4/72.3	None	None	Yes	N/A
2	50	80	GBM	Left temporal	Eloquent	18.0/49.0	R sided weakness	Expressive aphasia	No	N/A (no follow-up)
3	61	90	GBM	Left insula	Near eloquent	4.90/63.3	Aphasia	Worsened aphasia	No	Yes
4	42	80	GBM	Right frontal	Noneloquent	3.9/54.7	None	None	No	N/A
5	42	90	GBM	Left insula	Near eloquent	9.7/54.5	None	Aphasia	Yes	No
6	42	90	GBM	Bifrontal	Noneloquent	13.6/150.8	Aphasia	Worsened aphasia	Yes	Yes
7	77	80	GBM	Right temporal	Noneloquent	6.9/51.2	None	None	Yes	N/A
8	40	80	GBM	Right temporal	Noneloquent	27.3/66.5	None	None	Yes	N/A
9	28	90	GBM	Right thalamic	Eloquent	2/58.5	None	None	Yes	N/A
10	32	70	GBM	Left frontoparietal	Eloquent	2.25/11.6	Right-sided weakness	Worsened weakness	Yes	Yes
11	72	80	GBM	Right temporal	Noneloquent	7.2/65.9	None	None	Yes	N/A
12	62	80	Breast	Right temporal	Near eloquent	1.2/10.6	None	None	No	N/A
13	50	90	NSCLC	Basal ganglia	Eloquent	9.2/13.3	None	None	No	N/A

LITT: Laser interstitial thermal therapy, GBM: Glioblastoma, NSCLC: Nonsmall-cell lung carcinoma

Table 4: List of all complications after the 3rd LITT.

#	Age	Pre-3nd LITT KPS	Histology	Lesion location	Functional location	Tumor/ edema volume	Complication after 2st LITT	Complication after the 3nd LITT	Same approach from the 2st to 3nd LITT	Persistent neurological deficit at 1 month?
2	50	50	GBM	Left Temporal	Eloquent	18.0/49.0	Expressive aphasia	None	No	N/A
5	42	80	GBM	Left insula	Near eloquent	25.2/150.6	Aphasia	Gait abnormality	Yes	No
11	72	70	GBM	Right temporal	Noneloquent	2.7/65.9	None	None	Yes	N/A

LITT: Laser interstitial thermal therapy, GBM: Glioblastoma

superficial wound infection). The authors concluded LITT to be a safe and promising treatment modality, even in the context of repeat ablation.

The median PFS for the GBM patients in our study after each ablation was 6.0, 3.2, and 2.1, respectively. However, these results are difficult to interpret given the heterogeneous nature of the cohort. A previous study examining repeat craniotomies for recurrent GBM patients found PFS of 7.8, 6.0, and 4.8, respectively.[23] Given that most of the patients in our cohort already had at least one craniotomy, it makes the most sense to compare the PFS for the 2nd craniotomy to the PFS for the 1st LITT. This comparison shows identical PFS of 6.0 months. Given that these patients had no reasonable surgical alternatives, it is promising to find results comparable to the use of craniotomy, as similarly noted by Barnett *et al.* in a recent meta-analysis comparing LITT to craniotomy for high-grade gliomas.[2] For metastases, patients undergoing repeat resections experienced shorter OS but no differences in recurrence.[14] Both patients, in our study, were alive with no recurrence multiple years after undergoing repeat LITT.

The complication rate for this cohort was slightly higher after the second LITT. Reports from the literature cite similar postoperative neurological morbidity after repeat resection.[12] The small sample size, in contrast to the literature on repeat resections, makes it difficult to draw meaningful comparisons from our experience with repeat LITT. Remarkably, we observed no peri- or postoperative complications with repeat LITT for patients with no complications after initial ablation. In addition, none of the patients that received a different ablation trajectory during the 2nd ablation exhibited a different complication profile compared to the 1st ablation. These results seem to indicate that using different trajectories during repeat ablations does not increase or decrease risk for subsequent complications. Patients were able to receive adjuvant treatments despite post-LITT complications. Adjuvant treatments were typically started between 2 and 4 weeks after the ablation.

The results in this study should be interpreted in context of the salvage nature of the procedure. The patients selected for LITT in this study were not optimal surgical candidates. Across broad patient populations, LITT has not yet shown a significantly improved complication profile when compared to open craniotomy.[2] However, these studies involve extremely heterogeneous cohorts. It is our experience that for the right patient, LITT can offer a cytoreductive option that minimizes hospital stay and complication risk while expediting postprocedural adjuvant therapy.

Characteristics that excluded a craniotomy included medical comorbidities and depth and size of the tumor. For patients with medical comorbidities, LITT was chosen as a reasonable option to debulk the tumor while minimizing risk for medical complications associated with an open surgery and longer hospital stay. For patients with deep-seated tumors, LITT was chosen to preserve the access path tissue while still offering cytoreduction. For patients with small tumors, when craniotomy was determined not to justify the delay in adjuvant therapy, LITT was chosen to avoid delay starting chemotherapy. These are examples of the rationale used at our institution when selecting patients for LITT. Many patients exhibited a mixture of these characteristics.

The study is limited primarily by its small sample size and retrospective nature. Further, the variability in tumor histology and prior treatment obscures meaningful statistical analysis and conclusions. Future work should further stratify patient populations to study the efficacy and safety of LITT in specific patient subpopulations compared to open craniotomy. Despite these limitations, this study is the first of its kind to report on the safety of repeated LITT for GBM and brain metastases.

CONCLUSION

LITT is a burgeoning, minimally invasive approach for intracranial tumor ablation. The minimal morbidity associated with this technique allows it to be used safely for subsequent tumor recurrence and ablation, particularly in the context of GBM. Our study is the first to provide evidence

for the safety profile of a dedicated cohort of patients with GBM and brain metastases receiving repeat LITT for local recurrence. Additional matched cohort studies are needed to confirm the efficacy of this treatment modality.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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