Laser Ablation for Cerebral Metastases

Evan Luther, MD[a,b,*], Samuel Mansour, BS[c], Nikolas Echeverry, BS[c], David McCarthy, MSc[a,b], Daniel G. Eichberg, MD[a,b], Ashish Shah, MD[a,b], Ahmed Nada, MD[a,b], Katherine Berry, MD[a,b], Michael Kader, MD[a,b], Michael Ivan, MD[a,b,d], Ricardo Komotar, MD[a,b,d]

KEYWORDS

• Brain metastasis • Laser interstitial thermal therapy • Laser ablation • Metastases • Brain tumor • Neuro-oncology • Oncology • Minimally invasive surgery

KEY POINTS

- Laser interstitial thermal therapy is an effective salvage therapy for treatment refractory brain metastases.
- Local progression-free survival and overall survival rates varied widely among studies but seem to be comparable with radiation therapy and/or craniotomy for recurrent brain metastases.
- Complication rates are low with only 5.26% risk of developing any permanent neurologic sequelae.
- Future prospective, randomized studies are necessary to determine if laser interstitial thermal therapy is an effective primary therapy for brain metastases.

INTRODUCTION

Laser interstitial thermal therapy (LITT) is a minimally invasive surgical alternative for neuro-oncology patients deemed poor candidates for open resection. The technology delivers laser light through a stereotactically navigated fiber optic probe to create thermal damage, leading to cellular death within the target lesion. Although LITT has become increasingly used as an adjunct treatment for gliomas, dural-based lesions, and even radiation necrosis, most neuro-oncologic studies evaluating the use of LITT have focused on the treatment of cerebral metastases.[1–3] A systematic review of the available literature is provided to concisely summarize the current indications, results, and limitations of laser ablation in cerebral metastases. A brief overview of the technology and case examples are also provided.

SYSTEMATIC REVIEW OF THE AVAILABLE LITERATURE

The systematic review was performed in accordance with the PRISMA guidelines. Relevant articles were found via the following electronic databases: MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews.

Eligibility Criteria and Study Selection

Only peer-reviewed articles evaluating the use of LITT in the management of metastatic lesions to the brain published after January 1, 2000 were included. Articles in which subjects undergoing LITT for brain metastases were only a subgroup of a larger cohort were also included as long as the majority of the results for brain metastases could be interpreted separately from their

[a] Department of Neurosurgery, University of Miami Miller School of Medicine, Miami, FL, USA; [b] Department of Neurological Surgery, University of Miami/Jackson Health System, Lois Pope Life Center, 2nd Floor, 1095 Northwest 14th Terrace, Miami, FL 33136, USA; [c] Florida Atlantic University Charles E. Schmidt College of Medicine, 777 Glades Road, Boca Raton, FL 33431, USA; [d] Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA

* Corresponding author. Department of Neurological Surgery, University of Miami/Jackson Health System, Lois Pope Life Center, 2nd Floor, 1095 Northwest 14th Terrace, Miami, Fl 33136.
E-mail address: evan.luther@jhsmiami.org

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nonmetastatic counterparts. Case reports and studies in which LITT was used exclusively for lesions other than brain metastases were excluded. Studies not written in English, not performed on human subjects, and review articles that did not include their own patient subset were all excluded. The PRISMA flowchart is shown in Fig. 1.

Data Collection Process

The following search string was used to identify relevant articles: (LITT) OR ("laser interstitial thermal therapy") OR ("stereotactic laser ablation") AND (metastases OR metastatic OR metastasis). The language (English) and publication date (01/01/2000–12/31/2020) filters were used in all searches. The search yielded 213 articles and 7 additional articles were located using the references of the articles initially located via the database search. After duplicate articles were removed, 198 remained. After further screening and elimination of irrelevant articles, 14 were found to meet all the inclusion criteria and were included in this qualitative analysis.

Data Analysis

The 14 articles were critically evaluated and the data regarding LITT for metastatic lesions were compiled. Variables included study size, patient

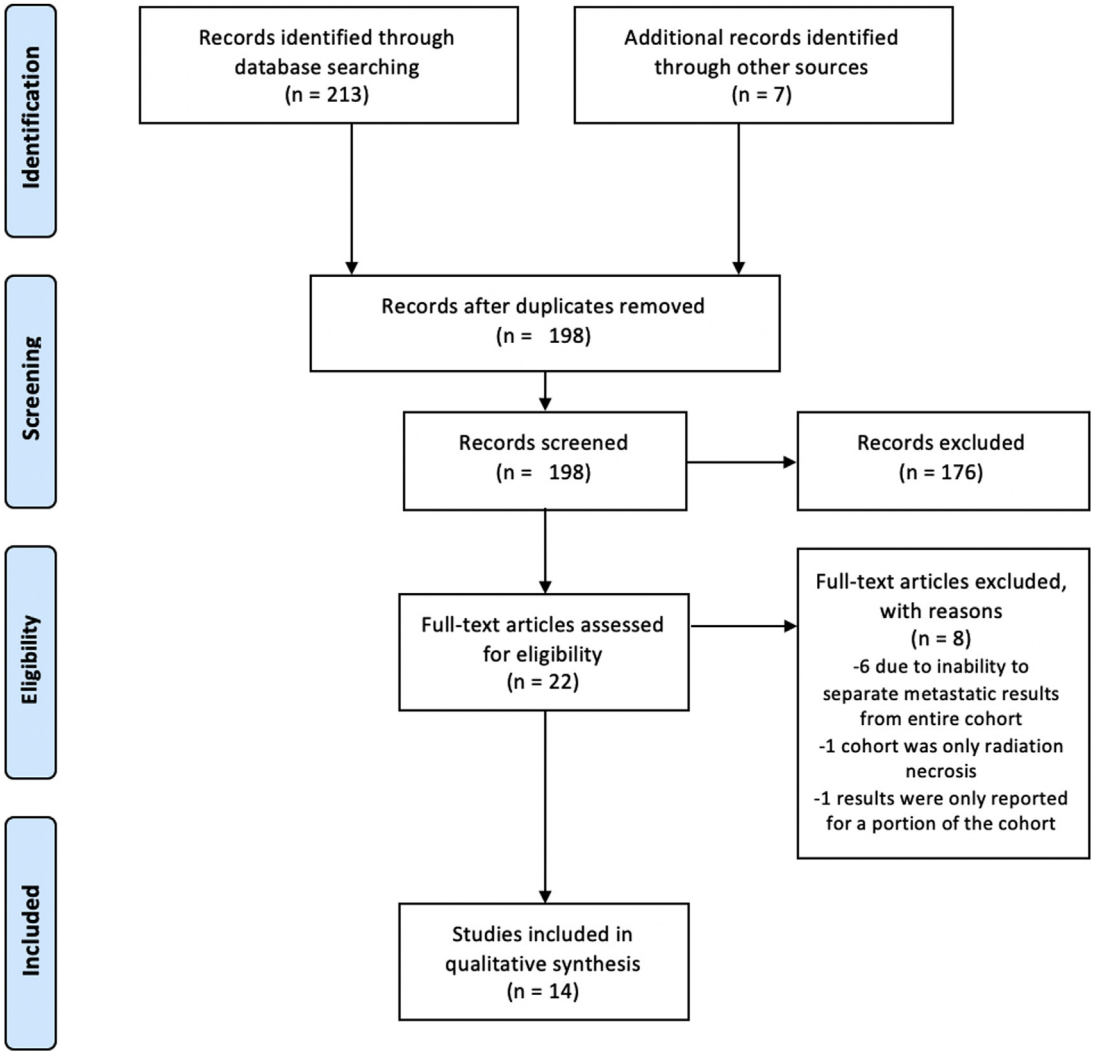

Fig. 1. PRISMA flowchart of the systematic review. Data added to the PRISMA template. (*Adapted from* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group [2009]. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7):e1000097) under the terms of the Creative Commons Attribution License.)

demographics, size/location, extent of ablation, patient outcomes, and periprocedural complications. The results of these variables were compiled and reported as either a sum total, a percentage of the pooled results, or a weighted average, as applicable. Included articles did not uniformly report every variable evaluated in this analysis and, as such, the reported results are based on aggregate data from the subgroup of articles in which the variable in question was both available and consistent.

Study Demographics, Indications for Laser Interstitial Thermal Therapy, and Ablation Volumes

In total, 228 cases of LITT were reported for the treatment of cerebral metastases. In the subset of articles for which the total number of patients was available, 156 patients underwent 203 LITT procedures. Demographic data for each study including patient age, gender, lesion size, extent of ablation, and primary indication for LITT is available in **Table 1**.[1,4–16] Ten articles reported the mean patient age and the weighted average age within this subset was 58.86 years. Eleven articles reported patient sex, of which 68.92% were female.

The most frequently stated primary indication for performing LITT was prior treatment failure (98.25% of all lesions). Other primary indications for LITT included patient preference (1.32%) and LITT as an initial treatment (0.44%). Other secondary indications for LITT included lesions deemed as poor surgical or radiation candidates (10.09%) or a deep-seated location (14.92%). The criteria for poor surgical candidates, deep or inoperable lesions, and recurrent or refractory disease were not universally congruent throughout the included studies. However, prior treatment failure was frequently defined as previously failed stereotactic radiosurgery (SRS) or craniotomy and most studies defined a poor surgical candidate based on advanced age and the presence of multiple medical comorbidities that would preclude the patient from undergoing a large surgery under general anesthesia. Deep or inoperable lesions were most frequently defined as an area deemed inappropriate for open surgical resection owing to either close proximity to eloquent areas, deep brain structures, or crossing hemispheres or lobes. LITT as an initial treatment, defined as LITT before standard of care, typically occurred because of the study design.

Lesion-Specific Data

The median pre-LITT lesion size and extent of ablation were available for a majority of the included studies and can be found in **Table 1**. The average median preoperative lesion size and extent of ablation were 16.22 cm^3 and 97.04%, respectively. Data regarding lesion location and primary pathology were available in 11 of the included articles. Therefore, the rest of the analysis in this section is restricted to this subgroup. Lesion locations were categorized as either lobar, deep, or within the posterior fossa. Approximately 80% of all lobar lesions were in the frontal, temporal, and parietal lobes and all of the deep lesions were found in either the thalamus or basal ganglia. Posterior fossa lesions comprised 18.45% of all brain metastases treated with LITT. The 3 most common primary pathologies for the metastatic lesions were lung and breast cancer followed by melanoma. Specific data regarding lesion locations and primary pathology types can be found in **Table 2**.

Post-Laser Interstitial Thermal Therapy Lesion Progression, Overall Survival, and Follow-Up

The median overall survival and time to local disease recurrence for brain metastases treated with LITT were provided in only a minority of the included studies and were not uniformly reported when available. As a result, it was not possible to accurately calculate aggregate outcomes data across all the studies. The median length of follow-up was available in 9 studies. The average median follow-up for this subset of patients was 12.12 months. Details regarding patient outcomes can be found in **Table 3**.

Laser Interstitial Thermal Therapy Perioperative Adverse Events

Perioperative adverse events were available for every included study and are displayed in **Table 4**. The overall perioperative adverse event rate across all studies was 18.42%. However, the majority of these adverse events resolved over time resulting in an overall complication rate at last follow-up of only 5.26%. The most frequently experienced adverse event was a new postoperative neurologic deficit or complaint. Some were as serious as aphasia or paresis, whereas others were as benign as a headache; the majority resolved with expectant and/or medical management regardless of severity. Other less common adverse events included symptomatic cerebral edema, postablation seizures, intracranial hemorrhage, infection, hydrocephalus, probe misplacement, metabolic derangements, and cerebrospinal fluid leak.

Table 1
Demographic data, lesion size and extent of ablation

Study, Year	No. of Patients	No. of Lesions	Mean Age (y), (IQR)	No. of Females	Primary Indication for LITT	Median Preoperative Lesion Size (cm^3), (Range)	Median EOA (%), (IQR)
Carpentier et al,[14] 2008	4	6	58.25 (50–73)	3	Prior treatment failure	N/A	N/A
Carpentier et al,[8] 2011	7	15	54[a]	N/A	Prior treatment failure	N/A	N/A
Hawasli et al,[10] 2013	5	5	59 (57–61)	3	Prior treatment failure	6.6 (5.2–9.9)	100 (98.3–100.0)
Ali et al,[5] 2016	23	26	59.13 (51.0–68.5)	16	Prior treatment failure	4.9 (0.4–28.9)	87.4 (73.9–97.5)
Wright et al,[13] 2016	1	1	63[a]	0	Prior treatment failure	14.2[a]	92[a]
Kamath et al,[11] 2017	N/A	25	N/A	N/A	Prior treatment failure	N/A	94[a]
Beechar et al,[6] 2018	36	50	N/A	20	Prior treatment failure	5.05 (0.54–23.31)	N/A
Borghei-Razavi et al,[7] 2018	3	3	68 (65.5–73.0)	1	Patient preference	2.01 (1.05–13.26)	100 (100–100)
Maraka et al,[12] 2018	1	1	N/A	N/A	Initial treatment	101.48[a]	100[a]
Eichberg et al,[9] 2018	4	4	54.25 (46.25–62.5)	1	Prior treatment failure	2.55 (1.1–7.2)	100 (97.05–100.00)
Shah et al,[1] 2019	36	45	60 (27–75)	30	Prior treatment failure	4.3 (0.6–28.0)	100 (88–100)
Ahluwalia et al,[4] 2019	20	20	N/A	14	Prior treatment failure	N/A	N/A
Traylor et al,[16] 2019	8	8	60.88 (36–79)	7	Prior treatment failure	4.91 (0.33–7.52)	100 (100–100)
Eichberg et al,[15] 2019	8	19	53.75 (26–69)	7	Prior treatment failure	N/A	N/A

N/A signifies either that the variable was not reported, unable to be separated from the rest of the study cohort, or reported in a matter incongruent with the majority of the other studies.

Abbreviations: EOA, extent of ablation; IQR, interquartile range.

[a] IQR/range unavailable or unable to be reported for the subset in question

Table 2
Lesion locations and primary pathology

	Location	No. of Lesions	% Total	Pathology	No. of Lesions	% Total
Lobar	Frontal	65	38.7	Lung	56	33.5
	Parietal	20	11.9	Breast	48	28.7
	Temporal	16	9.5	Melanoma	29	17.4
	Occipital	14	8.3	Colorectal	10	6
	Parieto-occipital	5	3	Gynecologic	6	3.6
	Frontoparietal	4	2.4	Sarcoma	5	3
	Insular	2	1.2	Bladder	2	1.2
	Cingulate	1	0.6	Esophagus	2	1.2
Deep	Thalamus	7	4.2	Renal	2	1.2
	Basal ganglia	3	1.8	Prostate	1	0.6
Posterior fossa		31	18.5	Other[a]	6	3.6

[a] Other signifies either a carcinoma of unknown origin or that the study did not specify the primary tumor origin.

SURGICAL PROCEDURE FOR LASER ABLATION

LITT is a minimally invasive neuro-oncologic technique that uses focused laser light, delivered through a fiber optic probe housed within a sterile catheter, to thermally ablate a variety of intracranial lesions (Fig. 2).[1,2] The trajectory of the catheter is planned using stereotactic neuronavigation and is typically selected so that the fiber traverses the longest axis of the lesion while avoiding injury to any critical anatomic structures. A multiarticulated precision aiming device, or PAD, is then positioned over the entry site along the planned trajectory to provide support as the catheter is advanced into the lesion (Fig. 3). Using a stab incision, a small burr hole is then made through the skull. The laser probe is subsequently inserted through the PAD and then advanced stereotactically through the burr hole along the designated trajectory into the lesion.[1,2] The probe is then fixed into position

Table 3
Patient outcomes and follow-up

Study	Median Time to Local Recurrence (mo)	Median Overall Survival (mo)	Median Length of Follow-up (mo), (IQR)
Carpentier et al,[14] 2008	3	N/A	3
Carpentier et al,[8] 2011	3.8[a]	17.4[a]	N/A
Hawasli et al,[10] 2013	2.85	4.2	4.2 (1.9–5.8)
Ali et al,[5] 2016	N/A	N/A	5.05 (3.32–10.90)
Wright et al,[13] 2016	–	–	13.07[b]
Kamath et al,[11] 2017	N/A	17.2	9.8[b]
Beechar et al,[6] 2018	10.5	N/A	1.82 (0.25–4.50)[c]
Borghei-Razavi et al,[7] 2018	7.5	N/A	N/A
Maraka et al,[12] 2018	N/A	N/A	N/A
Eichberg et al,[9] 2018	–	–	10.5 (9.25–14.25)
Shah et al,[1] 2019	55.9	16.9	7.6 (3.4–17.2)
Ahluwalia et al,[4] 2019	N/A	N/A	N/A
Traylor et al,[16] 2019	N/A	N/A	N/A
Eichberg et al,[15] 2019	9	N/A	54 (23.4–49.4)

N/A signifies either that the variable was not reported, unable to be separated from the rest of the study cohort, or reported in a matter incongruent with the majority of the other studies.
Abbreviations: IQR, interquartile range; –, no event occurred during the follow-up period.
[a] Values reported as a mean.
[b] Values reported as median only without IQR.
[c] Values reported as median and range.

Table 4
LITT perioperative adverse events

Study	Adverse Events (n, %)	Complication Type						No. at Last Follow-Up
		Neurologic	Edema	Seizure	ICH	Infection	Other[a]	
Carpentier et al,[14] 2008	0 (0)	–	–	–	–	–	–	–
Carpentier et al,[8] 2011	4 (26.67)	2	–	–	1	–	1	–
Hawasli et al,[10] 2013	2 (40)	2	–	–	–	–	–	–
Ali et al,[5] 2016	5 (19.23)	3	1	–	–	–	1	1
Wright et al,[13] 2016	1 (100)	1	–	–	–	–	–	1
Kamath et al,[11] 2017	5 (20)	1	1	2	–	–	1	1
Beechar et al,[6] 2018	16 (32)	16	–	–	–	–	–	7
Borghei-Razavi et al,[7] 2018	1 (33.33)	1	–	–	–	–	–	–
Maraka et al,[12] 2018	1 (100)	–	1	–	–	–	–	–
Eichberg et al,[9] 2018	0 (0)	–	–	–	–	–	–	–
Shah et al,[1] 2019	2 (4.44)	–	–	1	–	1	–	–
Ahluwalia et al,[4] 2019	3 (15)	2	–	–	1	–	–	2
Traylor et al,[16] 2019	0 (0)	–	–	–	–	–	–	–
Eichberg et al,[15] 2019	2 (10.53)	–	–	–	–	1	1	–

Abbreviation: ICH, intracranial hemorrhage.
[a] In descending order, the other complications are as follows: probe misplacement, transient hydrocephalus, hyponatremia, and transient cerebrospinal fluid leak.

with a bone anchor to prevent any future dislodgement (Fig. 4). Intraoperative MRI is then used to ensure proper placement of the laser probe. Once the catheter is confirmed to be intralesional, the system is activated, allowing the probe to deliver near-infrared laser light to generate temperatures sufficient to coagulate tumor foci. Fig. 5 displays a cross-sectional view of the catheter during ablation. The bone anchor provides coaxial stability and the cap lock limits any further longitudinal probe movement. The catheter has 2 channels with the inner channel containing the fiber optic core and the outer channel containing a continuously circulating coolant to prevent unwanted damage to the tissues along the catheter trajectory. The fiber optic core is attached to a diffuser at the tip of the probe that allows the laser light to be concentrically delivered to the lesion. Real-time MRI thermography is concurrently performed to ensure the lesion receives adequate thermal exposure while simultaneously preventing injury to the normal surrounding parenchyma (Fig. 6).[2]

Generating temperatures of 40°C to 90°C at the site of the lesion, the lasers are fired in pulsatile doses of 10 to 15 W each in intervals lasting from 30 seconds to 3 minutes with a total ablation time of 10 to 30 minutes.[2] Pulsatile thermal dosing is essential because prolonged administration at therapeutic temperatures has been shown to lead to coagulative necrosis of the adjacent normal parenchyma.[17] At the level of the tissue, absorption of the laser light results in heat production, which is then distributed throughout the

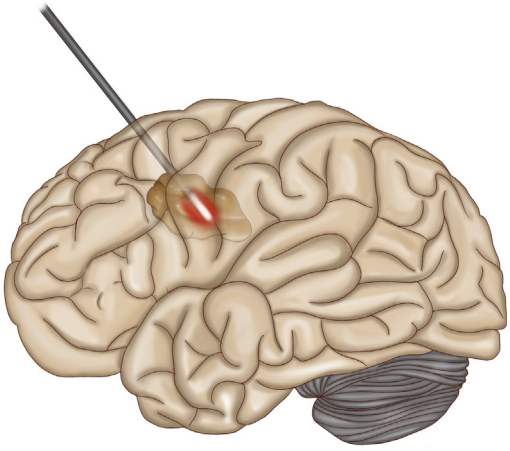

Fig. 2. Illustration demonstrating placement of the LITT catheter into a deep-seated intracranial lesion.

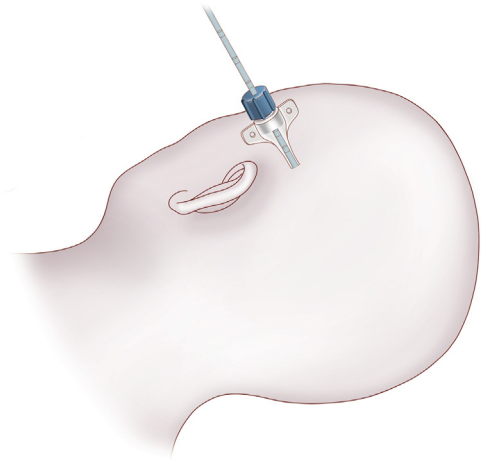

Fig. 4. LITT catheter secured to the skull with a plastic bone anchor after precision aiming device-assisted placement of the fiber optic probe.

lesion and is further facilitated by local blood flow.[18] At temperatures of 42°C to 45°C, cells become highly susceptible to thermal damage and further increases in temperature can result in cell death at much shorter time intervals.[2] Additionally, if temperatures surpass 60°C, rapid coagulation necrosis can occur from the induction of mitochondrial and nuclear damage.[19] Intraprocedural LITT temperatures are typically restricted to less than 90°C at the probe tip and less than 50°C at the periphery of the ablation zone because temperatures of more than 100°C have been shown to lead to irreversible damage to the surrounding extralesional brain and place the patient at greater risk of developing tissue vaporization, which can decrease the effectiveness of the ablation and potentially cause elevated intracranial pressures.[2] Continuous cooling of the portions of

Fig. 3. Precision aiming device and neuronavigation wand positioned along the planned trajectory for the LITT catheter.

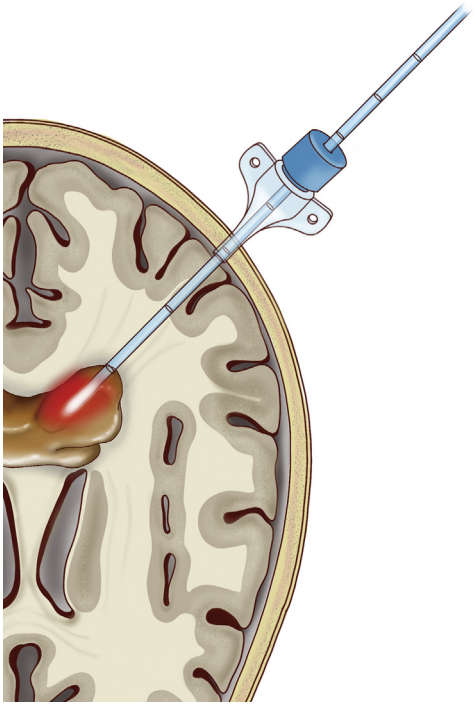

Fig. 5. Cross-sectional view of the LITT catheter during ablation.

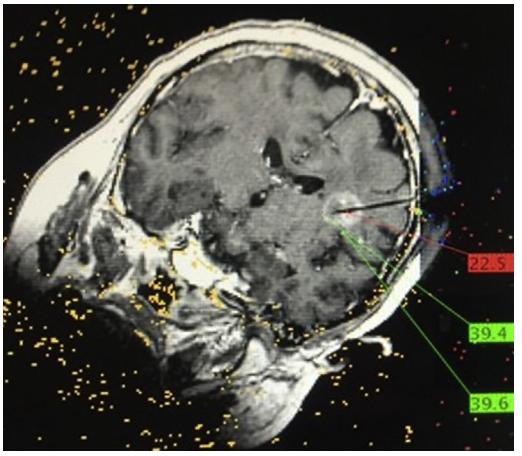

Fig. 6. Intraprocedural MR thermography provides a real-time heat map of the concentric tissues surrounding the probe.

the probe not in direct contact with the target lesion further decrease the possibility of iatrogenic thermal injury of healthy brain tissue.[2] Once the entirety of the planned ablation zone reaches 50°C, ablation is considered complete and the probe is removed. The wound is typically closed with a single absorbable suture. Postoperatively, a repeat MRI is frequently performed to confirm the extent of the ablation.[20,21]

Available Laser Interstitial Thermal Therapy Platforms

Two LITT platforms have been approved by the US Food and Drug Administration for intracranial use and are commercially available: the Neuroblate Laser Ablation System (Monteris, Inc., Minneapolis, MN) and the Visualase Thermal Therapy System (Medtronic, Inc., Dublin, Ireland). Both systems function very similarly and can be integrated with most MRIs. The main differences between the 2 systems are that the Neuroblate system produces a 12 W, 1064 nm beam and is cooled using CO_2 gas, whereas the Visualase system operates at 15 W, 980 nm, and uses circulating saline for cooling.[2]

Case Example

A 70-year-old woman with a past medical history of metastatic ovarian cancer to the left cerebellum underwent surgical excision followed by SRS to the resection cavity. Fifteen months later, the patient developed recurrence of the lesion on surveillance MRI (Fig. 7A). Owing to her radiation history, she was not eligible for repeat radiosurgery, given the lesion's proximity to the brainstem. Given the location and history of prior craniotomy, the patient was treated with LITT. A total ablation was achieved (Fig. 7B) and the patient has remained recurrence free at last follow-up over 6 years after the procedure.

DISCUSSION

Current Applications of Laser Interstitial Thermal Therapy in Brain Metastases

Although SRS and/or craniotomy have been considered the first line of therapy for metastatic brain tumors, LITT has been increasingly used over the last decade as either a primary therapy or an alternative to repeat resection or radiation for these lesions.[2] SRS-associated complications, including the development of radiation necrosis, have been observed in approximately 14% of patients at 1 year and this risk is known to only increase with further radiation treatments.[3,22–25] Furthermore, craniotomy is not always a viable alternative when the risk of neurologic injury or a perioperative adverse event is thought to be high. Comparatively, LITT offers more direct access to most noncortical intracranial lesions and, as such, does not confer as high of a risk of secondary damage to the healthy surrounding parenchyma when compared with open surgical

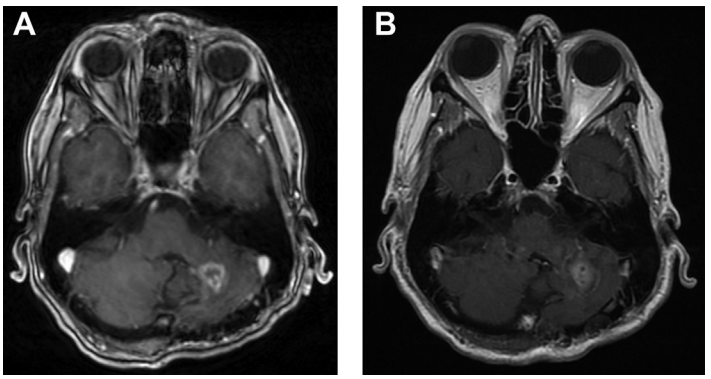

Fig. 7. (*A*) T1-weighted MRI demonstrating recurrent ovarian metastasis in the left cerebellum. (*B*) Post-LITT T1-weighted MRI demonstrating total lesional ablation.

resection or repeat SRS.[2,26] For brain metastases, LITT is most frequently used in lesions that are resistant to, or recur after, initial treatment.[7,10–12] Lesion locations deemed inaccessible via open surgery is another common indication for using LITT, with surgical inaccessibility typically defined as either close proximity to deep or eloquent structures or because open resection conferred unacceptably high morbidity.[2,3] The majority of metastatic lesions treated with LITT were lobar; more specifically, frontal with deep and posterior fossa ablations accounting for only a small percentage of the lesions reported. This likely represents surgical selection bias. Because the trajectory of the LITT catheter must avoid any important anatomic structures, surgeons will likely only offer LITT to patients in which a safe trajectory can be selected. This finding, coupled with the fact that brain metastases tend to occur more often at the cortical grey–white interface, likely explains why lobar lesions were more commonly ablated than deep or posterior fossa lesions.

Laser Interstitial Thermal Therapy for Radiation Necrosis

Although this review did not focus on the use of LITT in radiation necrosis, an overview of the topic is warranted given that it is often seen as a long-term complication of SRS in brain metastases. Briefly, radiation necrosis is a non-neoplastic inflammatory process that is thought to occur secondary to persistent free radical formation after radiation-induced cellular death. It can occur months to years after a single radiation treatment and can be very difficult to manage. Currently, treatments for radiation necrosis are limited, with either surgical resection or corticosteroids considered the mainstays of treatment. However, given the risks associated with both surgical intervention and prolonged steroid use, their efficacy is limited.[2] Interestingly, in patients with radiation necrosis, LITT has shown to cause long-term decreases in lesion size and symptomatology.[2,27–31] Given that patients with metastatic disease are often sicker and less able to handle the rigors of open surgery, LITT offers a viable alternative to resection of the radiation necrosis lesion.[1]

Perioperative Adverse Events Associated with Laser Interstitial Thermal Therapy in Cerebral Metastases

Among the studies reviewed, we found an overall perioperative adverse event rate of 18.42% with the majority (~66.67%) being composed of new-onset neurologic deficits or complaints. The severity of the neurologic symptoms ranged from aphasia or paresis to headaches and imbalance. Symptomatic cerebral edema and postoperative seizures were the second most frequently reported adverse events after LITT. More than two-thirds of these adverse events resolved over time, leading to an overall complication rate of 5.26% at the last follow-up. Although the upfront risk of LITT may be greater than that seen in radiation therapy, the overall complication rate seems to be similar to that seen in craniotomy for recurrent metastatic disease. This finding suggests that LITT can be a safe and effective alternative to radiation or resection in the management of treatment-refractory metastases.[3,32–39] This can be especially true when the patient has already received high cumulative radiation doses or craniotomy is considered exceptionally high risk.

Overall Survival and Local Disease Progression in Laser Interstitial Thermal Therapy: Brain Metastases

The median overall survival ranged from 4.2 to 16.9 months in the available studies for patients undergoing LITT for cerebral metastases. However, it should be noted that the majority of the included studies did not provide enough necessary data to calculate a true aggregate median overall survival.[1,11] Despite this fact, the range of median overall survival seems to be comparable with those seen in craniotomy or radiation therapy.[22,40] This finding may support assertions by previous studies that suggest that LITT is similarly efficacious in providing overall survival benefit when compared with typical treatment measures.[2]

Unfortunately, the median time to local disease recurrence could not be calculated across all the included studies because insufficient data were available; a majority of the articles did not stratify local recurrence rates by pathologic diagnosis. The median time to local recurrence ranged from 2.85 to 55.9 months in the available results. This large variability in local progression free survival is likely the result of 2 different yet dependent variables: pre-LITT lesion size and extent of ablation. Several studies have now demonstrated that total ablations increase time to local recurrence in lesions treated with LITT.[4,31] However, larger lesions are more difficult to completely ablate and thus require more thermal energy to do so. This increase in energy requirements may ultimately lead to adverse effects and clinical progression of the lesion, despite undergoing complete ablation.[41] Further studies are necessary to determine how to optimize energy delivery to lesional tissue via LITT.

Limitations

Given the highly variable reporting of various outcome measures, the time to local disease recurrence and overall survival could not be compiled to calculate meaningful aggregate results across the cohorts. Furthermore, because the majority of the included articles were case-control studies or retrospective analyses, inclusion criteria were not universally consistent, which can thus introduce significant selection bias. As a result, further research in the form of prospective, randomized, controlled trials are necessary to produce enough adequate data to truly compare LITT with traditional first-line therapies.

SUMMARY

LITT is an effective therapy for the management of recurrent or refractory metastatic brain tumors, but is still considered a salvage therapy when repeat radiation or craniotomy is thought to confer too much risk. Although LITT carries slightly more upfront risk than SRS, it still can provide a minimally invasive option for various surgically inaccessible lesions. Further trials are needed to assess the relative efficacy of LITT in the management of cerebral lesions compared with standard therapies.

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DISCLOSURE

M. Ivan, MD is a consultant for Medtronic. The other authors have nothing to disclose.

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