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## Current role of laser interstitial thermal therapy in the treatment of intracranial tumors

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## Current Role of Laser Interstitial Thermal Therapy in the Treatment of Intracranial Tumors

### Abstract

Laser interstitial thermal therapy (LITT) is gaining popularity in the treatment of both primary and secondary intracranial tumors. The goal of LITT is to deliver thermal energy in a predictable, controlled, and minimally invasive fashion. It can be particularly valuable in patients with recurrent tumors who, due to previous radiation or surgery, may have a potentially higher risk of wound breakdown or infection with repeat craniotomy. Deep-seated lesions that are often inaccessible through open approaches (thalamus, hypothalamus, mesial basal temporal lobe, brainstem) may also be suitable targets. The experience and data published thus far on this modality is limited but growing. This review highlights the use of LITT as a primary treatment method in a variety of intracranial tumors, as well as its application as an adjunct to established surgical techniques.

**Keywords:** Brain metastasis, brain tumor, laser ablation

### Introduction

The concept of laser interstitial thermal therapy (LITT) for tumors has existed since the late 1970s. Technical limitations of appropriate laser systems, lack of accurate targeting of desired treatment areas, and the inability to monitor the thermal effects produced were some of the reasons limiting the widespread application of this technique. In 1983, Bown *et al.* reported the use of a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser in an experimental brain tumor model achieving focal tissue coagulation.<sup>[1]</sup> Several animal studies followed by clinical trials recognize the viability of LITT in treating intracranial tumors, and in 1990, Sugiyama *et al.* first reported the use of LITT in treating brain tumors.<sup>[2]</sup> Multiple subsequent studies explored its utility in brain tumor ablation.<sup>[3-10]</sup> Despite the availability of magnetic resonance thermography (MRT), a lack of sophisticated laser probes with in-built cooling systems and unavailability of intraoperative magnetic resonance imaging (MRI) prevented this modality from gaining widespread usage. With advances in technology, the last decade has seen a resurgence in interest in the use of the technique.

Two systems are currently approved by the US Food and Drug Administration (FDA) for intracranial application: Monteris NeuroBlate (Monteris, Plymouth, Minnesota-First approved in 2009) and the Medtronic Visualase (Medtronic, Minneapolis, Minnesota). The NeuroBlate uses a CO<sub>2</sub> cooled Nd: YAG laser with a 1064-nm wavelength while the Visualase uses a saline-cooled diode laser with a 980-nm wavelength.<sup>[11,12]</sup> The two systems differ slightly in their degree of tissue penetration with the NeuroBlate system being able to achieve slightly larger ablation volumes. Both systems employ a fiberoptic catheter placed under stereotactic guidance through which light energy is delivered to the target tissue in the form of thermal energy. The thermal energy causes protein denaturation, melting of membrane lipids, vessel sclerosis, and coagulation necrosis, which occurs at 60C, while apoptosis is triggered between 43C and 60C. Based on the optical characteristics of the normal brain parenchyma and pathological tissue, the lesion created can be conformed to the boundaries of the target lesion. Following LITT, three zones can be identified on MRI. The innermost zone is the zone of coagulation necrosis, the second (peripheral) zone also has nonviable

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tissue with increased interstitial fluid, and the outermost zone is the marginal zone consisting of edematous but viable surrounding brain parenchyma.<sup>[13]</sup>

The goal of this modality is to deliver thermal energy in a predictable and controlled fashion. This has been possible with MRI thermography providing real-time imaging cues, which allows optimal heating of the target tissue without significant char formation or unintended normal tissue destruction. A small scalp incision and burr hole provide access to deep-seated lesions, which would otherwise be difficult to reach through a traditional open craniotomy.<sup>[14,15]</sup>

### Role in Primary Brain Tumors [Table 1]

Newly diagnosed high-grade gliomas (HGGs), specifically the World Health Organization (WHO) Grade IV gliomas, have a dismal prognosis. Depending on age, preoperative Karnofsky Performance Scale, and extent of resection on initial surgery, overall survival (OS) is best estimated at 12–16 months. Similarly, recurrent HGGs have a poor prognosis overall, an estimated 39 weeks for anaplastic astrocytomas, and 30 weeks for grade IV gliomas.<sup>[16]</sup> Several therapies have been tested for recurrent HGGs, including repeat craniotomy for cytoreduction, chemotherapeutic trials of repeat temozolomide, bevacizumab, gliadel wafer implantation, and more recently the approval of tumor treating fields.<sup>[17]</sup> With open surgery for recurrent lesions, the risk of wound complications may be higher and access to deep-seated lesions may present a challenge. This is where LITT may have a role in appropriately selected patients.<sup>[15]</sup> Han *et al.* showed that while laser ablation is minimally invasive (less blood loss, less pain, early resumption of adjuvant treatment) it is not particularly beneficial when it comes to larger or amorphous lesions.<sup>[18]</sup> When such lesions are present, there is a need for multiple probes and repositioning, which will add to the duration of the surgery and the invasiveness of the procedure.

Several of the early reports on the use of LITT were on patients with recurrent HGG. In 1998, Reimer *et al.* presented their experience of four patients with recurrent high-grade gliomas who were palliatively treated with LITT.<sup>[10]</sup> After LITT, all patients were clinically stable at 6 months with good local tumor control. In 2002, Leonardi *et al.*, presented their work on 24 patients (seven low-grade gliomas, eleven anaplastic astrocytomas, six grade IV gliomas) with mean survival times of 34, 30, and 9 months, respectively.<sup>[19]</sup> Meantime to progression after LITT for the three histological subgroups were 16 months, 10 months, and 4 months, respectively. In 2005 and 2006, Schwarzmaier *et al.* published their initial experience with a total of eighteen patients with recurrent grade IV glioma.<sup>[11,20]</sup> In their initial report, survival times of 16 and 20 months was noted in two patients. In a subsequent report of sixteen patients, the survival time of 11.2 months was seen, significantly longer compared with historical

controls. Compared to other treatment combinations, these were rather promising results for recurrent HGG.

In 2012, Jethwa *et al.*, from the United States (US) and Carpentier *et al.*, from France reported their experiences with the Visualase system.<sup>[21,22]</sup> In the series from the US, twenty patients were included of which seven had recurrent or newly diagnosed HGG. One patient in this group had malignant cerebral edema following the procedure requiring a decompressive hemicraniectomy. In the series from France, four patients were included with recurrent grade IV gliomas, and all of them achieved complete lesional ablation. The median progression-free survival (PFS) was 1 month, and the median OS was 10 months.<sup>[21,22]</sup>

In 2013, Sloan *et al.* reported their outcomes of ten patients with recurrent grade IV glioma in a phase I safety analysis, and noted a median OS of 10.5 months.<sup>[23]</sup> Three patients had new or worsening neurological deficits after the procedure, of which two were transient. One of the patients had a vascular injury resulting in a pseudoaneurysm, which was subsequently treated by endovascular means.

Similarly, Hawasli *et al.* reported their initial experience in 2013.<sup>[24]</sup> It included eleven patients with newly diagnosed or recurrent HGGs out of the total study population of seventeen patients. In this patient cohort, progression within the observation period (0.1–11.2 months) was seen in five of the eleven patients. Recurrence-free survival for recurrent HGG was noted to be 8.4 months, slightly higher than recurrent tumors treated with bevacizumab. The small patient number, however, does not allow one to generate any meaningful conclusion. Two of the glioma patients had postoperative transient neurological deficit, while one died from meningitis.

Mohammadi *et al.*, in their report from 2014, enrolled 34 patients with HGG who underwent LITT with the Neuroblate system.<sup>[25]</sup> This was a retrospective, nonrandomized study with a heterogeneous patient population. Sixteen patients with a new diagnosis, and eighteen patients with recurrent HGG were included. A 68% 1-year survival rate and 5.1-month median PFS rate was noted. Significant morbidity was associated with the procedure, with 13 of 34 patients having a neurological complication. Twenty-three patients had recurrences after a median of 7.2 months of follow-up; five within the treatment field, twelve at the periphery, five were outside the enhancing volume but within 2 cm, and one was remote. Importantly, a higher percentage of contrast-enhancing tumor ablation was associated with increased survival (9.7 vs. 4.6 months,  $<0.05$  cm<sup>3</sup> of tumor remaining). This study signifies that the cytoreductive effect of hyperthermia can be considered equivalent to surgical debulking.

In 2016, Leuthardt *et al.* treated twenty patients with recurrent HGGs.<sup>[26]</sup> An interesting aspect of this report was the testing of the level of brain-specific enolase as a marker

**Table 1: Studies on role of laser interstitial thermal therapy in primary brain tumors**

Study	Number of patients	Reported outcomes/complications	System used
Reimer <i>et al.</i> , 1998 <sup>[9]</sup>	4	LITT as palliative treatment. All clinically stable at six months with good local control	Neodym-YAG laser
Leonardi <i>et al.</i> , 2002 <sup>[17]</sup>	24 (7 LGGs, 11 AAs 6 GBMs)	Mean survival time with LITT: 34, 30, and 9 months, respectively	Nd-YAG laser
Schwarzmaier <i>et al.</i> , 2005 <sup>[10]</sup>	2 (Recurrent GBMs)	Survival time after the diagnosis of recurrence was 16 and 20 months respectively (four times longer than the natural history of the disease)	Nd-YAG laser
Schwarzmaier <i>et al.</i> , 2006 <sup>[18]</sup>	16	Median survival increased to 11.2 months	Nd-YAG laser
Jethwa <i>et al.</i> , 2012 <sup>[19]</sup>	20	Complications: One case each of insertion related hemorrhage, diabetes insipidus and metabolic derangement, significant cerebral edema requiring decompressive craniectomy, and inaccurate registration missing the target lesion	Visualase system
Carpienter <i>et al.</i> , 2012 <sup>[20]</sup>	4	Median PFS=1 month. Median OS=10 months Complications: One transient supplementary motor area syndrome, one epileptic seizure, and one CSF leak	Visualase system
Sloan <i>et al.</i> , 2013 <sup>[21]</sup>	10	Ten patients with recurrent GBM. Median OS=10.5 months Complications: Three patients with new or worsening neurological deficits. One patient with a vascular injury resulting in a pseudoaneurysm	Neuroblate system
Hawasli <i>et al.</i> , 2013 <sup>[22]</sup>	11 (HGGs)	Eleven patients with newly diagnosed or recurrent HGGs: Five of eleven patients had progression. PFS for recurrent HGG=8.4 months. Complications: Two patients had postoperative transient neurological deficit, while one died from meningitis	Neuroblate system
Mohammadi <i>et al.</i> , 2014 <sup>[23]</sup>	34 (HGG)	Thirty-four patients with HGG, Median PFS=5.1 months. 68% 1-year survival rate Complications: Seven cases of worsening preoperative neurological deficits, one case of new seizure, one case of postoperative hyponatremia, one case of bilateral DVT, and two cases of infection	Neuroblate system
Leuthardt <i>et al.</i> , 2016 <sup>[24]</sup>	20 (recurrent HGGs)	Two cases of radiological progression seen within 10 weeks of LITT	Neuroblate system
Thomas <i>et al.</i> , 2016 <sup>[25]</sup>	8	Eight newly diagnosed GBMs: median PFS=2 months, median survival=8 months Thirteen recurrent GBM: median PFS=5 months, median survival >7 months	Visualase and neuroblate system
Barnett <i>et al.</i> , 2016 <sup>[26]</sup>	79	Comparison between LITT (79 patients) and Craniotomy (1036 patients). 5.7% chance of major complication in LITT compared to 13.9% for traditional craniotomy	
Mohammadi <i>et al.</i> , 2019 <sup>[27]</sup>	48 (24 LITT, 24 biopsy only)	Comparison of LITT with biopsy only patients. Median PFS=4.3 months and 5.9 months, respectively. Median OS: 14.4 months and 15.8 months respectively Complications: Six cases of worsening neurological deficits, one case of DVT, and twenty cases of moderate to severe intratumoral bleeding	Neuroblate system

GBMs – Glioblastoma Multiformes; HGGs – High-grade gliomas; LITT – Laser interstitial thermal therapy; PFS – Progression-free survival; OS – Overall survival; DVT: Deep vein thrombosis, LGGs: Low grade gliomas, AAs: Anaplastic astrocytomas

of blood-brain-barrier disruption, postulated to enhance drug delivery. In this patient cohort, no peri-procedural complications were noted. Late clinical and radiological follow-up was not recorded, although two cases of radiological progression were seen within 10 weeks of LITT. Thomas *et al.* recently published their series that included eight patients with newly diagnosed grade IV glioma and thirteen patients with recurrent disease.<sup>[27]</sup> This study is unique as it assessed the molecular status of the newly diagnosed grade IV group (greater proportion had IDH wild-type GBMs). In this group, the median PFS and median OS was 2 and 8 months, respectively. Radiographic involution of the tumor was not seen in any patient. In the thirteen patients with recurrent disease, five

had a demonstrable response with concurrent radiographic shrinkage of the tumor following ablation. Median PFS was 5 months, and the median OS was >7 months.

In a recent systematic review, open craniotomy for new or recurrent HGG in eloquent or deep-seated areas, and minimally invasive laser ablation technique were assessed head to head.<sup>[28]</sup> Eight LITT studies with seventy-nine patients and twelve craniotomy studies, including 1,036 patients, were identified by the authors. Meta-analysis demonstrated the extent of an ablation of 85.4% ± 10.6% with brain LITT versus extent of resection of 77.0% ± 40% with craniotomy. Analysis of complications revealed 5.7% (95% confidence interval [CI]: 1.8–11.6)

chance of major complication in the LITT procedure versus 13.8% (95% CI: 10.3–17.9) for traditional craniotomy. This study was obviously limited by the low number of reported patients in the LITT group, making a direct comparison rather difficult.

In 2018, Mohammadi *et al.* reported the efficacy of laser ablation followed by standard chemo/radiotherapy for newly diagnosed grade IV glioma.<sup>[29]</sup> They also compared the results of laser ablation therapy ( $n = 24$ ) to a matched cohort of patients who underwent only biopsy ( $n = 24$ ) followed by chemo/radiotherapy. Overall, the median estimate of OS and PFS in the laser ablation cohort was 14.4 and 4.3 months compared to 15.8 and 5.9 months for biopsy only cohort. They concluded that maximum tumor coverage by laser ablation followed by chemo/radiotherapy is an effective treatment modality, particularly for patients with high-grade gliomas who are either unsuitable for aggressive surgery or choose not to undergo standard resection.

### Role in Metastatic Lesions [Table 2]

In the landmark study by Patchell *et al.*, surgical resection of a single focal metastatic lesion with adjuvant whole-brain radiotherapy (WBRT) was shown to reduce local recurrence rates to 10% after 1 year.<sup>[30]</sup> This study was a paradigm shift in the standard of care for brain metastases. Currently, surgical resection, focal radiosurgery and/or WBRT, and systemic chemotherapy specific to the tumor type is utilized.<sup>[31]</sup> However, for certain deep-seated metastatic lesions or recurrent disease, surgery or repeat radiation may not be an option.

In 2008, Carpentier *et al.*, published their pilot clinical trial of LITT with real-time MRI in focal intracranial metastatic lesions, which were resistant to standard therapy.<sup>[32]</sup> As a follow-up to this in 2011, the same group reported their outcomes in phase I trial of seven patients receiving 15 treatments for breast and lung adenocarcinoma metastases. Tumor size in these patients did not exceed 30 mm. No major complications were noted in this series. Mean PFS was noted to be  $3.8 \pm 1$  month.

There was a difference between the fully treated subset and the partial treatment group. Median OS was estimated to be 17 months.<sup>[33]</sup> Hawasli *et al.*, in their 2013 report also included five metastatic lesions.<sup>[24]</sup> Two patients had transient postoperative deficits. Out of the five patients, three had good local disease control, whereas the other two had central and systemic disease progression. Most recently, Chaunzwa *et al.*, presented the results of a multi-center retrospective study in which thirty patients with metastatic lesions were included. Good local control was noted at 6 months, reaching 93%. Twenty-four lesions were biopsied, however only five of these revealed tumor four of which required a salvage craniotomy. The rest were consistent with radiation necrosis (RN).<sup>[34]</sup>

Another recent multicenter study by Ali *et al.*, in 2016 showed the use of LITT in postradiosurgery recurrence of metastatic lesions.<sup>[35]</sup> Twenty-six lesions in twenty-three patients who recurred after stereotactic radiosurgery (SRS) were treated with ablation. Nine lesions progressed despite treatment (35%). All cases of progression occurred in lesions with <80% ablation, whereas stability was achieved in those with  $\geq 80\%$  ablation. Five lesions were treated with a combination of laser ablation followed 1 month later by adjuvant SRS (5 Gy daily  $\times$  5 days). No disease progression was observed in these patients despite an ablation efficiency of <80%. This may suggest an augmented effect of laser ablation with SRS, or simply efficacy of the SRS itself, which has been shown to be effective up to three or more times in the same lesion.<sup>[36]</sup>

### Role in Posttreatment Radiation Necrosis

Most treatment regimens for intermediate and high-grade brain tumors require some form of radiation therapy as part of the treatment armamentarium. RN can occur as a result, and in certain cases, it can be severe enough to cause local mass effect and significant edema. It can also mimic tumor progression that may require resection through craniotomy, or repeat radiation, which may exacerbate the issue. The incidence of posttreatment RN has been reported to be as high as 50% with 16–22 Gy treatment dose.

**Table 2: Studies on role of laser interstitial thermal therapy in metastatic tumors**

Study	Number of patients	Reported outcomes/complications	System used
Carpentier <i>et al.</i> , 2008 <sup>[32]</sup>	4 (6 lesions)	Gradual and steady decrease in lesion volume with no tumor recurrence within thermal ablation zones	Visualase system
Carpentier <i>et al.</i> , 2011 <sup>[33]</sup>	7 (15 lesions)	Mean OS: 17.4+/-3.5 months. Mean PFS: 3.8+/-1.0 months. No major complications noted.	Visualase system
Hawasli <i>et al.</i> , 2013 <sup>[24]</sup>	5 (Mets)	Median OS: 5.8 months. Two patients had transient postoperative deficits	Neuroblate system
Ali <i>et al.</i> , 2016 <sup>[35]</sup>	23	Lesions in which <80% ablation was achieved, 35% of these progressed Complications: Three patients had transient hemiparesis, one developed hydrocephalus, and one required emergency hemicraniectomy	Visualase and neuroblate system
Chaunzwa <i>et al.</i> , 2017 <sup>[34]</sup>	30	OS: 52.3% at 6 months, 26.1% at 12 months, 21.8% at 18 months, and 16.3% at 30 months	Neuroblate system

PFS – Progression-free survival; OS – Overall survival

Few therapeutic options are available for the treatment of this problem. Steroids temporarily alleviate the situation but are not a viable long-term solution. Vitamin E and pentoxifylline have been tested, and recently a trial of intra-arterial bevacizumab has been initiated (LIBERTI, Dashti *et al.*).<sup>[37,38]</sup> LITT has shown to have some promising effects as well. Laser ablation for RN targets not only the necrotic mass but also the peri-necrotic region, which is the bed of vascular endothelial growth factor (VEGF) production. RN becomes symptomatic largely due to perilesional edema. This is driven by VEGF production, leading to disorganized angiogenesis. The obliteration of this peri-necrotic region leads to an effective ablation. In the first description of this application, Rahmathulla *et al.* included a margin of 0.5 cm around the lesion and achieved good control.<sup>[39]</sup> Rao *et al.* in 2014 published their report of fifteen treatments in fourteen patients for previously treated metastatic disease, with either symptomatic recurrence or radiographic recurrence.<sup>[40]</sup> The lesions were considered to be either RN or metastatic disease, as no tissue diagnosis differentiating between the two was obtained before laser ablation. Good local control was achieved in twelve patients, with two requiring surgical resection after the failure of LITT. The median PFS was 37 weeks, and OS was 57%. The tissue pathology did not reveal any tumor cells in these two patients, indicating RN. In 2016, Smith *et al.*, in their series of 25 patients with biopsy-confirmed RN (four of whom were later found to have high-grade glioma on craniotomy) showed the safety of LITT and possibly achieving local control of the RN.<sup>[41]</sup>

In 2018, Ahluwalia *et al.*, published a multicenter prospective study of LITT ablation in patients with radiographic progression after stereotactic radiosurgery for brain metastases.<sup>[42]</sup> Forty-two patients were included: 19 with biopsy-proven RN, twenty with the recurrent tumor, and three with no diagnosis. Twenty-seven patients (64%) had complete data for the 12 weeks follow-up, while sixteen patients (38%) had complete data for the full 26 week follow-up. Of the data available the local PFS for the group was 74% at 12 weeks and through the last follow-up. When comparing the two groups based on pathology, they found local PFS was statistically different at 12 weeks (100% for RN vs 54% for tumor;  $P = 0.016$ ) but not at the last follow-up beyond 12 weeks (91% for RN vs. 62% for tumor;  $P = 0.166$ ). OS for the whole group was 86.5% at 12 weeks and 72.2% at 26 weeks. For RN patients, OS survival was 100% at 12 weeks and 82.1% at 26 weeks. Despite positive results, the utility of this technique in improving OS quality of life remains to be determined definitively.

### Role in Recurrent Dural Based Lesions

For recurrent meningiomas, standard therapy is re-operation or conformal radiotherapy. Chemotherapeutic options have been tried with limited efficacy. With these recurrent

lesions, laser ablation may hold some value. Ivan *et al.*, in their series of five patients harboring previously resected and radiation, now recurrent convexity meningiomas and a solitary fibrous tumor, showed reasonable local control in three out of five cases with short term follow up.<sup>[43]</sup>

### Role in Pediatric Brain Tumors

Laser ablation has not been used extensively in children harboring brain tumors. Tovar-Spinoza, in their report from 2016, described their experience with eleven children harboring twelve lesions.<sup>[44,45]</sup> The pathologies included six pilocytic astrocytomas, one ependymoma, one medulloblastoma, two choroid plexus xanthogranulomas in one patient, one subependymal giant cell astrocytoma (SEGA), and one ganglioglioma. Six patients received LITT as first-line therapy. Tumor volume decreased in the first 3 months after ablation and continued to decrease by the 4–6 month follow-up. Two patients experienced postablation complications: transient right leg weakness in one patient, and transient hemiparesis, akinetic mutism, and eye movement disorder in the other. It is important to note that the intraventricular lesion was safely treated in this group of patients. Similarly, Dadey *et al.* also noted safe ablation of SEGAs in two patients in their report.<sup>[46]</sup> The first patient had recurrent disease, which was treated successfully with LITT. In the second patient, obstructive hydrocephalus was noted with tumor growth, prior to treatment with LITT. The patient was treated with robot-guided LITT and a ventriculostomy for the resolution of hydrocephalus, resulting in good tumor control on subsequent imaging.

### Other Neurosurgical Applications of Laser Interstitial Thermal Therapy

#### Chronic pain

Lesions in the cingulate gyrus have often been used for pain management in terminally ill cancer patients and in the management of psychiatric patients. In 2015, Patel *et al.* published their experience with MRI guided LITT in three patients with chronic refractory cancer-related pain who underwent bilateral anterior cingulotomy.<sup>[47]</sup> These patients had failed multiple medication trials and interventions. The median preoperative pain severity (PSS) and pain interference score (PIS) were 7,7 (range: 7.5-9.3) and 9.9 (range: 9.7–10.0), respectively. Postoperatively the median PSS and PIS were 1.6 (range 1.0 2.8) and 2.0 (range 0.3–2.6), respectively. There was a significant reduction in pain medications requirement for all three patients in the follow-up period, and no adverse effects were encountered in the procedure.

#### Spinal metastasis

Metastatic spinal disease is a source of significant morbidity in cancer patients.<sup>[48]</sup> An ideal minimally invasive surgical approach to spinal metastasis would achieve local tumor

control, allow for fast recovery, minimize postoperative pain and morbidity, and curtail delays in initiating or interrupting systemic therapies directed to the primary tumor. In 2015, Tatsui *et al.*, retrospectively reviewed 11 patients at their institute, all with spinal metastasis from histologies considered to have an unfavorable response to conventional external beam radiation therapy.<sup>[49]</sup> All patients underwent spinal laser interstitial thermal therapy (SLITT) with the Visualase laser system. The mean preoperative Visual Analog Scale (VAS) for pain was 6.8, while the VAS postoperatively at 30 and 60 days was 4.27 and 2.8, respectively. The mean preoperative VAS was significantly higher than the VAS 30 days postoperatively ( $P = 0.035$ ) and 60 days postoperatively ( $P = 0.01$ ). Furthermore, the mean thickness of the epidural tumor decreased significantly from 8.82 mm (95% CI 7.38–10.25) prior to treatment to 6.36 mm (95% CI 4.65–8.07) on the 2 months follow-up images ( $P = 0.0001$ ). They concluded that SLITT can be used as an alternative to separation surgery in patients without neurological deficits prior to spinal stereotactic radiosurgery.

### Epilepsy surgery

Up to a third of epilepsy patients have seizures refractory to medical treatment. In patients with well-localized drug-resistant epilepsy (DRE), surgical resection of the epileptogenic zone (EZ) is highly effective with the overall quality of life benefits.<sup>[50]</sup> Magnetic resonance-guided laser interstitial thermal therapy (MRgLITT) is an increasingly popular surgical option for DRE because it provides minimally invasive access anywhere in the brain with minimal disruption to overlying white matter and cortex. Curry *et al.*, retrospectively reviewed the use of MRgLITT on five pediatric epilepsy patients whose seizures failed to improve from medical management with at least two anti-epileptic drugs.<sup>[51]</sup> Postoperatively all patients remained without complications and were seizure-free at follow-up evaluations ranging 2–13 months. These results showed a significant potential for MRgLITT to offer a minimally invasive technique for ablation of epileptic foci.

### Eloquent region pathologies

Intracranial lesions in functional areas of eloquence pose a challenge for surgical resection. In 2019, Kuo *et al.* presented their series of five pediatric patients with intracranial lesions in eloquent areas.<sup>[52]</sup> Clinical presentations included intractable epilepsy, hemiparesis, and aphasia by entities, including tumor, dysplasia, and RN. Postoperatively, all patients improved clinically and remained stable through follow-up. Furthermore, in 2020 Easwaran *et al.*, presented the case of an 11-year-old boy with a growing left insular mass determined to be WHO grade II diffuse astrocytoma.<sup>[53]</sup> After the initial resection, the patient underwent laser ablation due to recurrence. At both 1- and 6-month follow-up the patient remained stable and seizure-free. For intracranial lesions involving the

eloquent cortex, open resection presents as a challenge and LITT can be used as a potentially effective option.

### Discussion

LITT can be a valuable tool in patients harboring recurrent tumors who have a potentially higher risk of scalp breakdown or infection with repeat craniotomy due to previous radiation or surgery. Deep-seated lesions which are inaccessible (thalamus, hypothalamus, mesial basal temporal lobe, brainstem, etc.) may also be suitable targets. LITT has shown some efficacy as an alternative to open craniotomy for deep-seated metastatic lesions and recurrent gliomas, however, it is yet to be tested in a comparative large-scale study. Similarly, for newly diagnosed HGG or easily accessible metastatic lesions, there is limited evidence to support its use as a first-line treatment. Despite the minimally invasive approach (small skin incision and bone opening) the hyperthermia created can result in unwanted side effects, which be mitigated via open craniotomy approaches.<sup>[25]</sup> In addition to the above-mentioned tumor types, other tumor types which are considered inoperable, such as bi-hemispheric corpus callosum gliomas (butterfly lesions) may be an entity where combined with stereotactic biopsy for tissue diagnosis, LITT can play a role in achieving cytoreduction and thus improve the efficacy of adjuvant therapy. Use of fiber tractography and in certain cases angiography to better delineate the vascular anatomy can be helpful in planning targets and minimizing damage to adjacent white matter tracts and neurovascular structures.

Combination therapy with LITT, followed by craniotomy through minimally invasive trans tubular or trans-sulcal approach, is an intriguing prospect. In the majority of reports, LITT has been used in isolation, and craniotomy for the lesion has been necessitated only if there has been malignant cerebral edema requiring decompression or if the tumor continues to show mass effect and associated symptoms requiring resection.<sup>[21,34,35]</sup> It is also important to understand that LITT has traditionally been used thus far for tumors <3 cm diameter and its use in larger tumors has been limited due to risk to adjacent vessels, white matter tracts, ventricular system and to prevent the induction of malignant edema. It does, however, raise the question that if these risks are all there and craniotomy will be attempted anyway, why perform laser ablation initially? Combining the two modalities appears to be similar to the treatment strategy for arteriovenous malformations and for certain skull base lesions, where preoperative embolization readily reduces the arterial inflow, thereby making the surgical resection less challenging. Laser ablation can be effective in coagulating the tumor and changing the consistency, which may allow a complete resection via a minimally invasive trans-sulcal tubular approach rather than a larger craniotomy.<sup>[54,55]</sup> In this approach, the laser ablation acts as the actual cytoreduction therapy akin to maximal safe cytoreduction through open craniotomy, whereas the craniotomy is to reduce the mass

effect from the ablated tissue in large tumors. Wright *et al.* noted that in ten patients treated with LITT and subsequent craniotomy, the tumor was current jelly-like and avascular when accessed using a trans tubular approach, making the operation much less involved.<sup>[55]</sup>

Some of the studies mentioned above have shown significant prolongation of OS and PFS for recurrent glioma patients, which may be tied in with the genetics and molecular markers of those tumors. It remains to be seen whether primary GBM compared to secondary GBM, with or without certain genetic mutations, would behave differently in comparison to each other.<sup>[56]</sup> Similarly, metastatic lesions of different origins may respond in a varied fashion to thermal ablation. LITT is a promising tool but will require extensive testing in a randomized control trial setting to understand the indications and effectiveness of this method before it is accepted as a standard of care. Currently, one trial is underway to assess LITT for pediatric central nervous system tumors.<sup>[57]</sup> Results are expected for another trial that finished recruiting in 2014 for the treatment of metastatic brain tumors.<sup>[58]</sup>

Direct costs associated with laser ablation, including imaging and anesthesia, are estimated at about \$56,127 versus \$50,447 for a craniotomy.<sup>[18]</sup> The time to perform either procedure is also comparable. However, variables such as team and surgeon experience, availability of relevant equipment, and ease of access to neuroimaging modalities can have a bearing. In 2016, Barnett *et al.* presented the value of using LITT in patients with high-grade gliomas where maximal safe resection is not feasible.<sup>[59]</sup> They compared the overall costs in employing either LITT or standard of care treatments recommended by the National Comprehensive Cancer Network (NCCN) guidelines. At the time of the study, in the US cost-effectiveness ratios of <\$50,000/life year gained (LYG) was considered a good value, while internationally, it was considered to be at 30,000€ (or \$32,575 in US dollars)/LYG (or at \$2714/month survival gained). They concluded that it would cost an additional \$2445 for every month of survival gained in using LITT versus current treatment, but for HGGs residing in or near eloquent areas, which may require major open operations, LITT appeared to be cost-effective. The LAANTERN study noted similar findings.<sup>[60]</sup> It also postulated that quality of life measures are likely improved in patients undergoing LITT compared to open craniotomy, due to the minimal invasiveness of the procedure. With low rates of complications and safety profile similar to a needle biopsy, it is possible that the volume of tissue ablation achieved would be similar to resection via craniotomy, therefore providing equivalent cytoreduction, similar survival outcomes, and improved quality of life.

## Conclusion

LITT is gaining traction as one of the many tools currently available to neurosurgeons for the treatment of

intracranial tumors. Despite accumulating evidence to suggest its efficacy and safety, particularly in the treatment of recurrent or deep-seated gliomas and metastatic lesions, open craniotomy techniques remain standard of care. The prospect of combining LITT with minimally invasive craniotomy techniques is exciting. Cost may be a prohibitive factor, especially in developing countries.

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## Conflicts of interest

There are no conflicts of interest.

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