



American  
Association of  
Neurological  
Surgeons

---



Congress of  
Neurological  
Surgeons

# Position Statement on MR-guided Laser Interstitial Thermal Therapy (LITT) for Brain Tumors and Radiation Necrosis

Gene Barnett, MD, MBA

Eric Leuthardt, MD, PhD

Ganesh Rao, MD

Peter Fecci, MD, PhD

Andrew Sloan, MD

# Table of Contents

## Contents

Executive Summary .....	3
Purpose of the Statement.....	3
Importance of the CNS/AANS Statement .....	3
Indications for the use of LITT include the following criteria .....	3
Contraindications to LITT .....	3
Background and Supporting Literature.....	4
Prevalence of glioblastoma, brain metastases, and radiation necrosis .....	4
Medical and Surgical Management of Brain Tumors .....	4
LITT in Oncology .....	5
LITT procedure description .....	5
Efficacy of MR-guided LITT .....	6
Supporting Literature .....	7
Benefit of MR-guided LITT .....	11
Safety of MR-guided LITT .....	11
Future Investigations.....	12
Conclusion .....	12
References.....	13

## **Executive Summary**

### *Purpose of the Statement*

1. To provide an evidence-based, best-practice summary to guide health care providers in the use of MR-guided Laser Interstitial Thermal Therapy (LITT) in the management of newly diagnosed Gliomas/Glioblastoma (nGBM), Recurrent Glioblastoma (rGBM), Brain Metastases (Mets/rMets) and Radiation Necrosis.
2. To highlight literature evidence which describes the LITT procedure for use in achieving maximal safe cytoreduction for select patients.
3. To establish expert consensus opinion regarding LITT and to note areas requiring additional investigation based on the most recent peer reviewed published literature.

### *Importance of the CNS/AANS Statement*

1. Neurosurgeons are involved as part of a multidisciplinary team in the complex care and management of patients diagnosed with upfront and recurrent gliomas, recurrent brain metastases, and/or radiation necrosis. Guidance and recommendations from their associations and governing bodies are important in their decision-making processes.
2. Neurosurgeons are domain-specific experts in the comparative assessment of benefits, risks, and alternatives of procedures for the management of patients with gliomas, recurrent brain metastases, and/or radiation necrosis.

### *Indications for the use of LITT include the following criteria*

LITT is a neurosurgical tool FDA indicated for use to ablate, necrotize, or coagulate intracranial soft tissue, including brain structures (e.g., brain tumor, radiation necrosis and epileptogenic foci as identified by non-invasive and invasive neurodiagnostic testing, including imaging), through interstitial irradiation or thermal therapy in the discipline of neurosurgery with laser technology.

### *Contraindications to LITT*

1. Patients who have contraindications for MRI, including patients who may have contraindications due to implanted medical devices and are unable to undergo MRI.
2. Patients who the physician determines are not appropriate candidates for minimally invasive surgical procedures in the brain, including laser interstitial thermal therapy (LITT).

### *Basis for Recommendations*

1. There are numerous peer reviewed publications that demonstrate the safety and efficacy of the intracranial LITT procedure (see Efficacy of MR-guided LITT and Safety of MR-guided LITT). Intracranial LITT outcomes in both single and multi-center prospective and retrospective publications have demonstrated acceptable progression free survival (PFS) and overall survival (OS) for this patient population. Randomized control trials directly comparing LITT to open craniotomy or to radiosurgery in this patient population are unlikely to be performed due to lack of feasibility and patient/surgeon equipoise.

2. Intracranial LITT has favorable procedural recovery, including low rates of head pain, short length of stay (typically 1–2 days), short recovery time, low rates of rehospitalization, expedited wound healing and the potential to receive adjuvant treatments sooner than patients who undergo an open surgical resection.

3. NCCN (National Comprehensive Cancer Network) recently added LITT as a treatment option to their Central Nervous System Guiding Principles of Brain Tumor Surgery (BRAIN-B): MRI-guided laser interstitial thermal therapy (LITT) [Category 2B] LITT may be considered for patients who are not surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases and radiation necrosis.<sup>1</sup>

4. There is consensus that intracranial LITT should be considered as a potential option for patients with recurrent or progressive malignant tumor (primary or metastatic), lesion(s) inaccessible to surgical resection, or when the patient is unable to tolerate surgical resection due to medical comorbidities.

5. Intracranial LITT procedures are performed by highly trained neurosurgeons when the treatment plan to use LITT has been agreed upon by interdisciplinary oncology care teams after considering all relevant treatment approaches.

## **Background and Supporting Literature**

### *Prevalence of glioblastoma, brain metastases, and radiation necrosis*

Primary brain cancer remains relatively rare as compared to other primary cancer types.

Glioblastoma is the most common malignant primary brain tumor representing approximately 57% of all gliomas and 48% of all primary malignant central nervous system tumors. The overall prevalence of glioblastoma in the United States is 9.23 per 100,000 population.<sup>2</sup>

Brain metastases are the most common intracranial tumors in adults and are nearly 10 times more common than primary brain cancer. Approximately 100,000 (or more) people in the U.S. are diagnosed with brain metastases annually and about 20 to 40 % of people with cancer develop this complication.<sup>3</sup> As systemic treatments for other cancers (specifically breast and lung) have become more effective, metastases to the brain are becoming more common.<sup>4</sup> The majority of brain metastases are effectively managed (80%) by radiation as a first-line treatment; however, in up to 20% of cases tumors recur due to radio-resistant cancer types or treatment failure.<sup>5</sup>

Radiation-induced brain necrosis is a relatively uncommon but potentially severe adverse effect of whole brain radiotherapy and Stereotactic Radiosurgery (SRS) that occurs in approximately 5%–25% of patients.<sup>6</sup> Radiation necrosis generally occurs at 6 months to 2 years after radiation treatment and can range in severity from an incidental radiographic finding on magnetic resonance imaging (MRI) to debilitating neurologic symptoms or seizures.<sup>7</sup>

### *Medical and Surgical Management of Brain Tumors*

Newly diagnosed primary gliomas are generally treated through a process starting with maximal safe excision/cytoreduction of the lesion followed by a combination of radiation and chemotherapy.<sup>1,8</sup> These methods are intended to prolong survival, stabilize the disease, and to

prevent the progression of symptoms.<sup>9,10</sup> Recurrent gliomas can be treated with similar therapeutic combinations, although there is not consensus about standard of care for this patient population. Cytoreduction still continues to be an important component of treatment for these patients regardless of new or recurrent diagnosis.<sup>11</sup>

Open surgical resection is generally well-tolerated with a 30-day infection rate of 2.04%.<sup>12</sup> Unfortunately, many patients are unable to receive an open surgical resection as approximately 49% of tumors are located in deep regions of the brain or within eloquent (sensory/ motor/ memory) areas of the brain making it challenging or difficult to remove.<sup>11</sup> While craniotomy followed by chemo-radiation may provide improved local control in some patients, these therapies are not curative. In a study of glioblastoma patients, achieving  $\geq 98\%$  tumor resection only improved the average survival by about 4 months (from 8.8 months with  $< 98\%$  resection to 13 months with  $\geq 98\%$  resection).<sup>11</sup>

Personalized medicine delivered for tumor-specific molecular markers are a new hope for improving survival of those with primary and metastatic brain malignancies. However, while incremental improvements in patient outcomes have been achieved, survival outcomes still remain dismal for many of the most aggressive cancer types leaving an absence of a gold standard that will provide meaningful options for patients.<sup>1,13</sup>

### *LITT in Oncology*

Lasers have been used in neurosurgery for decades and the concept of MR-guided Laser Interstitial Thermal Therapy (LITT), initially termed “phototherapy”, to induce thermal tissue injury to tumors was first described in 1983 by Bown.<sup>14</sup> Magnetic resonance imaging (MRI)-guided laser ablation technology has been proposed as a minimally invasive means of treating brain tumors that are difficult to access or as an alternative to open craniotomy and radiation necrosis. LITT has been used in brain tumor ablations for over a decade.<sup>15</sup> The procedure involves stereotactic insertion of a fiberoptic laser probe into the target area followed by laser activation. Currently, the use of LITT for ablation of tumors has become a standard alternative to situations where open surgical resection would be considered (ex. gliomas,<sup>16–30</sup> metastases,<sup>31–37</sup> radiation necrosis<sup>33,38–41</sup>) and even in some circumstances where it is not considered (ex. tumor tissue that is challenging to access).<sup>19,23,27,42</sup>

### *LITT procedure description*

Magnetic resonance imaging (MRI)-guided laser ablation technology is a minimally invasive means of targeting brain lesions with low-profile access, such as with that of a cranial needle biopsy. In preparation for the procedure, a typical surgical work-up is performed to identify and confirm the target lesion. The LITT procedure is performed through stereotactic delivery of a laser probe into the target area, through a 1 cm incision, followed by laser activation, tissue heating, and ablation. Each individual laser pulse is directed to a different linear position and/or radial orientation of the target area. The MRI unit lets surgeons monitor the progress of the treatment as it is applied. The MRI signals are converted by the LITT system to measure temperature changes over time in and around the target area, enabling the physician to monitor

and adjust thermal progression as it occurs. This near real-time feedback guides the surgeon in precisely targeting the treatment, helping to eliminate some of the uncertainties of traditional surgical resection as well as the challenges of the older generations of LITT. This precise visualization is critical to ensure that only the intended target tissue, and not adjacent critical structures, are ablated.

### *Efficacy of MR-guided LITT*

The use of laser induced heating as a treatment modality is a known and accepted form of tissue ablation. MR image guided LITT has been used commercially in the U.S. for more than ten years in over 8,000 procedures at approximately 150 sites in the US. Over 2,200 patient experiences have been described in peer reviewed literature of LITT for upfront & recurrent primary and metastatic brain tumors and radiation necrosis (Pub Med search 2014-2020). This growing body of peer reviewed published literature describes LITT being used safely and effectively in patients with primary brain tumors (newly diagnosed and recurrent); brain metastases (recurrent), and for radiation necrosis. It achieves a cytoreductive effect via heat-induced killing that is comparable to resection when an open excision via craniotomy is not a viable option.<sup>43</sup>

With respect to open surgical resection, surgery followed by concurrent chemo/radiation therapy (Stupp protocol) is the typical course of treatment for patients with newly diagnosed high grade gliomas.<sup>8,44</sup> There are circumstances when gross total or even subtotal resection via craniotomy is not feasible; including patients with deep seated tumors, tumors adjacent to eloquent structures, or patients who are not candidates for open resection due to other comorbidities. When an open craniotomy resection is not feasible, LITT has been shown to be an effective treatment option in order to achieve maximal cytoreduction of the tumor prior to the administration of chemo and radiation.<sup>45</sup> According to Stupp et al., performing a biopsy only, without cytoreduction of the tumor, results in those patients faring the worst with respect to overall survival (9.4 months biopsy only vs. 13.5 months for partial surgical section).<sup>44</sup>

Procedurally, laser ablation is highly precise and when utilized by neurosurgeons it can be directed to avoid critical structures while obtaining the desired ablative coverage. LITT has been shown to achieve satisfactory ablative coverage of tumor tissue (>98%) which is linked to improved overall survival.<sup>27,28</sup> Multivariate analysis suggests that extent of ablation is the greatest predictor of lesion control as is also the case in craniotomy with respect to extent of resection.<sup>46</sup>

The LAANTERN study, the largest prospective multi-center outcomes publication to date for patients undergoing LITT for intracranial tumors, demonstrated that the overall survival rate 12 months post-LITT was 73% (CI 95% of 65.3% to 79.2%). This was noted to be equivalent to prior craniotomy studies in a similar population. Outcomes were comparable in patients with primary versus metastatic tumor.<sup>47</sup> KPS and QoL (as measured using the FACT-Br and EQ-5D) were shown to be stabilized for 6-12 months after LITT which was a better than expected result in this population. Following LITT, 83.4% of the patients discharged to home and the repeat hospitalization rate within 30 days of the LITT procedure was 1.8%.<sup>47</sup>

Long-term outcomes in brain tumor management post-LITT are impacted by many factors and have been described in several meta-analyses.<sup>17,22,48,49</sup> Many LITT studies in oncology highlight the long-term patient experiences as comparable, if not favorable, to those experienced after open resection.<sup>17,22,47</sup>

A listing of outcomes data in key cohort studies are summarized in **Table 1** and detailed in the **Supporting Literature** section.

**Table 1: Summary of outcomes experiences in oncology**

	<b>Progression free survival (PFS)</b>	<b>Overall survival</b>
<b>General Oncology Experiences</b> <i>Kamath<sup>50</sup>, Shah<sup>46</sup>, Kim<sup>47</sup></i>	Median PFS ranged from 7.7-31.9 months	Median of 11.7 months, 72% estimated survival at 1 year
<b>Brain metastases</b> <i>Bastos<sup>51</sup>, Hernandez<sup>52</sup>, Ahluwalia<sup>53</sup></i>	69.6%.-74% at 6 months	65.8%-72% at 1 year
<b>Glioblastoma</b> <i>Kamath<sup>54</sup></i>	Median PFS was 6.6 months	Median OS after the procedure was 11.5 mo.

### Supporting Literature

Kim AH, Tatter S, Rao G, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): 12-Month Outcomes and Quality of Life After Brain Tumor Ablation. *Neurosurgery*. Published online April 21, 2020:nyaa071. doi:10.1093/neuros/nyaa071

This publication represents the largest prospective, multi-center outcomes publication to date for patients undergoing LITT for intracranial tumors. Patients who chose to undergo LITT for treatment of their neurological disorder were prospectively accrued into this cohort and outcomes were obtained from analysis of obtained results. The 223 patient tumor cohort reflects the typical mix of tumor types indicated for laser ablation of the brain; high grade gliomas - upfront unresectable and recurrent, brain metastasis (primarily recurrent following SRS failure) and radiation necrosis. Overall survival at 12 months was 73% (CI 95% of 65.3% to 79.2%) which is equivalent to prior craniotomy studies in a similar population. No difference was seen in overall survival when comparing patients with primary versus metastatic tumor. KPS and QoL (as measured using the FACT-Br and EQ-5D ) were shown to be stabilized for 6-12 months after LITT which was a better than expected result in this population. 83.4% of the patients discharged to home and the repeat hospitalization rate within 30 days of the LITT procedure was 1.8%.

Shah AH, Semonche A, Eichberg DG, et al. The role of laser interstitial thermal therapy in surgical neuro-oncology: series of 100 consecutive patients. *Neurosurgery*. published online: 2019 (doi:10.1093/neuros/nyz424)

A cohort study of 91 patients (100 LITT procedures) underwent LITT to treat brain lesions;

including metastases (n = 45), newly diagnosed glioblastoma (n = 11), recurrent glioblastoma (n = 14), radiation necrosis (n = 20), and other (n = 10). The median TTR (Time to Recurrence) was 31.9 mo and median overall survival was 16.9 months. A survival benefit was noted in the nGBM group using biopsy + LITT compared to biopsy and chemoradiation alone. Median OS of nGBM patients in the biopsy + LITT group was 32.3 mo. Greater coverage of the ablated lesion predicted longer survival, indicating that OS-gain results are similar to those experienced with a gross total resection. All patients were discharged to home by postoperative day 2 and the complications rate was 4%, all of which were transient.

Bastos DC de A, Rao G, Oliva ICG, et al. Predictors of Local Control of Brain Metastasis Treated with Laser Interstitial Thermal Therapy. *Neurosurgery*. Published online September 20, 2019: nyz 357. doi:10.1093/neuros/nyz357

A cohort study of 61 consecutive patients with brain metastases (BM) who underwent LITT (5 newly diagnosed, 46 recurrences, and 31 radiation necrosis). The majority of the lesions had been previously treated with radiation (86.9%). Freedom from local recurrence for all lesions was 69.6% at 6 mo, 59.4% at 12 mo, and 54.7% at 18 and 24 mo. Patients with incompletely ablated lesions had shorter time to recurrence than those with completely ablated lesions, (median 6 mo vs median not reached respectively). Lesions with radiographic changes favoring tumor recurrence had shorter time to recurrence than radiation necrosis (RN) lesions (median 14 mo vs median not reached at 24 mo respectively). Patients receiving systemic therapy within 3 months of LITT had a longer time to local recurrence than those that did not receive systemic therapy within 3 months (median not reached vs median 6 mo respectively). Predictive factors of control rates in BM and RN patients after LITT are; extent of ablation, tumor recurrence, and systemic therapy within 3 mo after LITT.

Shao J, Radakovich NR, Grabowski M, et al. Lessons Learned in Using Laser Interstitial Thermal Therapy for Treatment of Brain Tumors: A Case Series of 238 Patients from a Single Institution. *World Neurosurgery*. 2020;139: e345-e354. doi: 10.1016/j.wneu.2020.03.213

A single institution retrospective review of 238 patients who underwent LITT for brain tumor over an 8-year period. Patient diagnoses consisted of glioma, radiation necrosis and brain metastases. Permanent motor deficits postoperatively decreased from 15.5% to 4.4% and 30-day mortality decreased from 4.1% to 1.5%. There was a clear correlation between tumor size and survival in HGG, smaller tumor volumes <4cc had improved OS and PFS compared to the larger counterparts (p<0.001 and p=0.015) which may be due to more favorable laser coverage. The review showed that the length of an operation decreased from an average of 6.6 hours to 3.5 hours. The authors note that 22% of cases remained complex enough to still required the use multiple trajectories for treatment. The study concludes that the efficiency and safety of LITT has improved over time and the



number of complications and mortality risk significantly decreased with minimal compromise to adjacent brain tissue.

Kamath AA, Friedman DD, Hacker CD, et al. MRI-Guided Interstitial Laser Ablation for Intracranial Lesions: A Large Single-Institution Experience of 133 Cases. *Stereotactic and Functional Neurosurgery*. 2017;95(6):417-428. doi:10.1159/000485387

A cohort study of 133 lesions undergoing LITT for brain tumors (glioblastoma (N=57), WHO grade I, II, and III glioma (N=26), and metastases (N=35), radiation necrosis (N=5), epilepsy (N=8) and other (N=2). Forty percent of lesions were deep and considered difficult to access. Results indicated low rates of procedural complications (6%) and that small lesions (3 cm or smaller in diameter) were less likely to have complications. Median progression-free survival (PFS) and overall survival (OS) for recurrent GBM were 7.4 and 11.6 months, respectively. When used as initial treatment in newly diagnosed GBM patients, median PFS and OS were 5.9 and 11.4 months, respectively. For metastases, OS was 17.2 months. Length of hospital stay also trended down over time, from an average of about 4 days in patients 1-50 to an average of about 2 days in patients 51-100. LITT is a safe and effective option for managing difficult-to-access lesions or surgically accessible lesions in properly selected patients.

Hernandez RN, Carminucci A, Patel P, Hargreaves EL, Danish SF. Magnetic Resonance-Guided Laser-Induced Thermal Therapy for the Treatment of Progressive Enhancing Inflammatory Reactions Following Stereotactic Radiosurgery, or PEIRs, for Metastatic Brain Disease. *Neurosurgery*. Published online May 31, 2018. doi:10.1093/neuros/nyy220

This publication represents a single center cohort study of 59 patients with brain metastases who underwent LITT after being shown to have a progressive enhancing inflammatory reaction (PEIR). PEIR can represent radiation necrosis, tumor progression, or both processes simultaneously. Patients were included if they were deemed poor candidates for additional radiotherapy (i.e. had a history of max radiation dosage). Symptomatic and asymptomatic patients were included. Primary histology included non-small cell lung carcinoma, breast, colon, renal cell carcinoma, melanoma, testicular, cervical, and small-cell lung carcinoma. At a median follow-up of 44.6 weeks post-LITT, the local control rate was 83.1% and most patients were weaned off steroids post-LITT. The authors concluded that LITT is an effective treatment for PEIRs after SRS for brain metastases.

Sujjantararat N, Hong CS, Owusu KA, et al. Laser interstitial thermal therapy (LITT) vs. bevacizumab for radiation necrosis in previously irradiated brain metastases. *J Neurooncol*. Published online June 29, 2020. doi:10.1007/s11060-020-03570-0

A case control study of 38 patients with brain metastases who developed radiation necrosis

after radiation treatment; 25 patients with biopsy proven radiation necrosis (RN) underwent LITT and 13 patients, with radiographic diagnosed RN, were treated with bevacizumab. Primary cancer diagnosis was lung, melanoma, breast, ovarian, renal cell, urothelial. The median time from radiation to treatment was longer in the LITT cohort (13 versus 6 months). The LITT cohort had a longer overall survival (median OS of 24.8 vs. 15.2 months for bevacizumab,  $p = 0.003$ ). The LITT cohort also had a longer time to intracranial local progression at last follow-up (median 12.1 months vs. 2.0 for bevacizumab) however, these differences were not found to be statistically significant ( $p=0.091$ ). LITT was shown to initially increase lesional volume compared to bevacizumab but this reversed in long term follow at 1 year with LITT leading to an overall lesional volume decrease and bevacizumab showing lesional volume increase ( $p=0.010$ ). This single institution study suggests that for patients with brain metastases and radiation necrosis, LITT can be a useful tool in extending OS and reducing overall lesional volume as compared to bevacizumab.

Ahluwalia M, Barnett GH, Deng D, Tatter SB, Laxton AW, Mohammadi AM, Leuthardt E, Chamoun R, Judy K, Asher A, Essig M, Dietrich J, Chiang VL. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg.* 2018 May 4;130(3):804-811. doi: 10.3171/2017.11. JNS171273. PMID: 29726782.

This multi-center prospective trial evaluated 42 patients with brain metastases who had evidence of radiographic progression following treatment with SRS. A biopsy was performed prior to the Laser Interstitial Thermal Therapy (LITT) procedure: 20 with recurrent tumor, 19 with radiation necrosis (RN) and 3 with non-diagnostic biopsies. Ablation data was available for 9 RN and 12 tumor regrowth patients. The lesions that received complete ablation (4 RN and 4 tumor) showed 100% and 75% complete response at 12 weeks respectively. Receiving a total ablation was shown to be a statistically significant predictor ( $p<0.001$ ) for achieving a complete response (CR). Local progression free survival (LPFS) at 26 weeks was shown to be 91% (RN) and 62% (tumor). Overall survival rates at 26 weeks were 82.1% for RN patients and 64.5% for tumor patients. This study also demonstrated that LITT can aid in stabilizing KPS (median KPS change =0), preserve both cognition and QOL, and was shown to have a steroid-sparing effect.

Chen, C., Guo, Y., Chen, Y., Li, Y., & Chen, J. (2021). The efficacy of laser interstitial thermal therapy for brain metastases with in-field recurrence following SRS: systemic review and meta-analysis. *International Journal of Hyperthermia*, 38(1), 273-281.

A meta-analysis that included 14 studies comprised of 470 patients total that looked at local control (LC) rate and overall survival (OS) of LITT for brain metastases after stereotactic radiosurgery (SRS). Studies were included in the analysis that evaluated (i) efficacy of LITT for in-field recurrence; (ii) used laser ablation; (iii) addressed intracranial radiation necrosis or brain metastasis (BM) recurrence after SRS – not spinal lesions; (iv) had more than 5 patients enrolled; (v) collected data on local control or OS. Of the 14

studies included, there were 9 retrospective case series, 2 retrospective case-control studies, one phase I clinical trial, one phase II clinical trial and one prospective registry study. The 12 month local control rate was found to be 69.0% (95% CI) and median OS of 17.15 months (95% CI). This was contrasted with surgical resection with the 12 month LC ranging from 62%-93% and OS of 8.7 months. LITT provided more satisfactory local control efficacy on RN than BM recurrence (76.3% vs. 59.9%,  $p=0.041$ ) at 12 months. This analysis concluded that LITT is an effective treatment option for patients experiencing in-field recurrence following SRS, with greater benefit seen on LC with RN than BM recurrence.

### *Benefit of MR-guided LITT*

Proposed benefits of MRI-guided laser ablation technology include low morbidity as is the case with many minimally invasive surgical procedures, faster recovery time, decreased wound-healing time, decreased hospital and intensive care stay, and the ability to access lesions not amenable to open surgery.<sup>47</sup> LITT has also been noted to be an alternative to craniotomy in patients with significant comorbidities and for whom open surgery would present increased risk. Patients undergoing LITT were shown to have a significantly shorter length of hospital stay and were more likely to be discharged home instead of a physical rehab or skilled nursing facility.<sup>55</sup> A 2016 study found that OS was improved with brain LITT versus current treatments by 3.07 months at an additional cost of \$7,508 (or \$29,340/LYG)<sup>23</sup>. This amount was significantly less than the current values of \$32,575/LYG and \$50,000/LYG for international and United States thresholds, respectively. As a result, the majority of academic neurosurgery centers are offering LITT as an option for both primary glioma and recurrent brain metastases, and patients are actively seeking this out as a validated and desirable treatment option. As LITT is minimally invasive, it may also be conducive to a more rapid initiation of adjuvant chemotherapy and/or radiotherapy following surgery when compared to open craniotomy.<sup>56</sup>

LITT is a compelling option for patients as it offers a method of minimally invasive, targeted thermal ablation of a lesion with minimal damage to healthy tissue.

### *Safety of MR-guided LITT*

There are two laser ablation systems cleared by FDA and available in the US that have been on the market for over ten years; Monteris NeuroBlate System and Medtronic Visualase System. NeuroBlate (Monteris) FDA 510(k) clearance initially in 2008 with updates in 2012, 2014, 2017, 2018, 2019, and 2020 and Visualase (Medtronic) FDA 510(k) clearance initially in 2007 with updates in 2008 & 2019.

The safety of LITT has been highlighted in multiple publications since 2008, including prospective multi-center studies and several retrospective cohort studies.<sup>15,51</sup> Complications of LITT include intracranial hemorrhage, neurological deficit due to thermal injury, operative site infection, increased cerebral edema, and increased seizure frequency<sup>57</sup>. Complication rates in LITT and craniotomy are greatly dependent on tumor characteristics (location and size).<sup>58</sup> A single center study evaluating LITT for treatment of brain metastases with evidence of progressive enhancing

inflammatory reaction (PIER) noted an initial complication rate of 25%, with the majority of patients improving with time and only 3.4% exhibiting permanent neurological deficits.<sup>52</sup>

Maximal safe resection via craniotomy is considered standard of care for primary gliomas and is used frequently for excision of secondary intracranial metastases. Maximal safe resection can be limited when tumor location is in or near areas of eloquence. Published literature indicates complication rates for open craniotomy at 15% or greater depending on location of tumor.<sup>22</sup> A systematic review and meta-analysis of LITT vs craniotomy for the treatment of high grade gliomas in areas of eloquence demonstrated major complication rates of 5.7% (95% CI) for LITT and 13.8% (95% CI) for craniotomy.<sup>22</sup>

### *Future Investigations*

Randomized controlled trials (RCT) comparing LITT to open craniotomy are unlikely to be performed in the future.<sup>59</sup> Laser ablation products are commercially available in US, Canada, and parts of Europe. Long term, post-market studies continue to be pursued in areas of research interest but RCTs are difficult to execute in this patient group.<sup>60</sup> There are feasibility and ethical concerns for a LITT vs craniotomy surgical study. There is evidence that only 21.3% of malignant glioma patients participate in clinical trials<sup>61</sup> and a 2018 paper estimated that only 8-11% of newly diagnosed glioblastoma patients enrolled in a clinical trial.<sup>62</sup> The reasons for this are numerous but include cognitive impairment or neurologic symptom burden of these patients, patient related cost and logistical restraints, and stringent participation eligibility in a terminally ill patient.<sup>63</sup> As well, the patient populations for LITT and open surgical resection differ; patients eligible for craniotomy will typically undergo an open surgical resection.

There is a current prospective, multi-center registry that includes data collection up to 5 years following LITT to evaluate safety, QoL, and procedural outcomes including local control failure rate, progression free survival, overall survival, and seizure freedom in up to 1,000 patients and 50 sites. This registry is intended to further understand the performance and utilization of laser ablation in current standard of care.

Another area of study is the cumulative effects of LITT plus other therapies. Early evidence suggests that additional effects of LITT can be exploited to enhance adjuvant therapies, e.g., blood-brain-barrier disruption, to facilitate entry of chemotherapy or immunotherapy agents.<sup>24,64,65</sup>

### *Conclusion*

LITT is an appealing option because it offers a method of minimally invasive, targeted thermal ablation of a lesion with minimal damage to healthy tissue. There is a growing body of evidence to demonstrate that LITT is an effective and well tolerated cytoreductive option for treatment of nGBM, rGBM, and Mets/rMets. Intracranial LITT is also an effective option for addressing radiation necrosis with an overall reduction in steroid dependence for these patients. Especially in instances where the therapeutic window is narrowed such that craniotomy is not a viable

option, LITT can play an important role in treatment for glioma or metastatic brain cancer. A multidisciplinary approach remains the cornerstone in the treatment of patients with brain tumors or radiation necrosis. It is important that physicians have discretion to exercise their clinical judgement when evaluating the most appropriate option for their patients' individual treatment plan.

## References

1. NCCN Guideline: NCCN Guidelines Version 1.2021, PRINCIPLES OF BRAIN TUMOR SURGERY, Guiding Principles [https://www.nccn.org/professionals/physician\\_gls/pdf/cns.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf).
2. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015. *Neuro-Oncol*. 2018;20(suppl\_4):iv1-iv86. doi:10.1093/neuonc/noy131
3. Memorial Sloan Kettering et al. Metastatic Brain Tumors & Secondary Brain Cancer <https://www.mskcc.org/cancer-care/types/brain-tumors-metastatic>.
4. Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res*. 2012;32(11):4655-4662.
5. Ali MA, Carroll KT, Rennert RC, et al. Stereotactic laser ablation as treatment for brain metastases that recur after stereotactic radiosurgery: a multiinstitutional experience. *Neurosurg Focus*. 2016;41(4):E11. doi:10.3171/2016.7.FOCUS16227
6. Lesueur P, Lequesne J, Barraux V, et al. Radiosurgery or hypofractionated stereotactic radiotherapy for brain metastases from radioresistant primaries (melanoma and renal cancer). *Radiat Oncol*. 2018;13(1):138. doi:10.1186/s13014-018-1083-1
7. Miyatake S-I, Nonoguchi N, Furuse M, et al. Pathophysiology, Diagnosis, and Treatment of Radiation Necrosis in the Brain. *Neurol Med Chir (Tokyo)*. 2015;55(1):50-59. doi:10.2176/nmc.ra.2014-0188
8. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *N Engl J Med*. 2005;352(10):987-996. doi:10.1056/NEJMoa043330
9. Sulman EP, Ismaila N, Armstrong TS, et al. Radiation Therapy for Glioblastoma: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Guideline. *J Clin Oncol Off J Am Soc Clin Oncol*. 2017;35(3):361-369. doi:10.1200/JCO.2016.70.7562
10. Nahed BV, Redjal N, Brat DJ, et al. Management of patients with recurrence of diffuse low grade glioma: A systematic review and evidence-based clinical practice guideline. *J Neurooncol*. 2015;125(3):609-630. doi:10.1007/s11060-015-1910-2

11. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95(2):190-198. doi:10.3171/jns.2001.95.2.0190
12. McCutcheon BA, Ubl DS, Babu M, et al. Predictors of Surgical Site Infection Following Craniotomy for Intracranial Neoplasms: An Analysis of Prospectively Collected Data in the American College of Surgeons National Surgical Quality Improvement Program Database. *World Neurosurg*. 2016;88:350-358. doi:10.1016/j.wneu.2015.12.068
13. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Central Nervous System Cancers Version 1.2015. NCCN.org.
14. Bown SG. Phototherapy of tumors. *World J Surg*. 1983;7(6):700-709. doi:10.1007/BF01655209
15. Carpentier A, McNichols RJ, Stafford RJ, et al. Real-time magnetic resonance-guided laser thermal therapy for focal metastatic brain tumors. *Neurosurgery*. 2008;63(1 Suppl 1):ONS21-28; discussion ONS28-29. doi:10.1227/01.neu.0000335007.07381.df
16. Lee I, Kalkanis S, Hadjipanayis CG. Stereotactic Laser Interstitial Thermal Therapy for Recurrent High-Grade Gliomas: *Neurosurgery*. 2016;79:S24-S34. doi:10.1227/NEU.0000000000001443
17. Ivan ME, Mohammadi AM, De Deugd N, et al. Laser Ablation of Newly Diagnosed Malignant Gliomas: a Meta-Analysis. *Neurosurgery*. 2016;79:S17-S23. doi:10.1227/NEU.0000000000001446
18. Pisipati S, Smith KA, Shah K, Ebersole K, Chamoun RB, Camarata PJ. Intracerebral laser interstitial thermal therapy followed by tumor resection to minimize cerebral edema. *Neurosurg Focus*. 2016;41(4):E13. doi:10.3171/2016.7.FOCUS16224
19. Wright J, Chugh J, Wright CH, et al. Laser interstitial thermal therapy followed by minimal-access transsulcal resection for the treatment of large and difficult to access brain tumors. *Neurosurg Focus*. 2016;41(4):E14. doi:10.3171/2016.8.FOCUS16233
20. Thomas JG, Rao G, Kew Y, Prabhu SS. Laser interstitial thermal therapy for newly diagnosed and recurrent glioblastoma. *Neurosurg Focus*. 2016;41(4):E12. doi:10.3171/2016.7.FOCUS16234
21. Tovar-Spinoza Z, Choi H. MRI-guided laser interstitial thermal therapy for the treatment of low-grade gliomas in children: a case-series review, description of the current technologies and perspectives. *Childs Nerv Syst*. 2016;32(10):1947-1956. doi:10.1007/s00381-016-3193-0
22. Barnett GH, Voigt JD, Alhuwalia MS. A Systematic Review and Meta-Analysis of Studies Examining the Use of Brain Laser Interstitial Thermal Therapy versus Craniotomy for the

Treatment of High-Grade Tumors in or near Areas of Eloquence: An Examination of the Extent of Resection and Major Complication Rates Associated with Each Type of Surgery. *Stereotact Funct Neurosurg*. 2016;94(3):164-173. doi:10.1159/000446247

23. Voigt JD, Barnett G. The value of using a brain laser interstitial thermal therapy (LITT) system in patients presenting with high grade gliomas where maximal safe resection may not be feasible. *Cost Eff Resour Alloc CE*. 2016;14:6. doi:10.1186/s12962-016-0055-2
24. Leuthardt EC, Duan C, Kim MJ, et al. Hyperthermic Laser Ablation of Recurrent Glioblastoma Leads to Temporary Disruption of the Peritumoral Blood Brain Barrier. *PLoS One*. 2016;11(2):e0148613. doi:10.1371/journal.pone.0148613
25. Sun XR, Patel NV, Danish SF. Tissue Ablation Dynamics During Magnetic Resonance-Guided, Laser-Induced Thermal Therapy. *Neurosurgery*. 2015;77(1):51-58; discussion 58. doi:10.1227/NEU.0000000000000732
26. Riordan M, Tovar-Spinoza Z. Laser induced thermal therapy (LITT) for pediatric brain tumors: case-based review. *Transl Pediatr*. 2014;3(3):229-235. doi:10.3978/j.issn.2224-4336.2014.07.07
27. Mohammadi AM, Hawasli AH, Rodriguez A, et al. The role of laser interstitial thermal therapy in enhancing progression-free survival of difficult-to-access high-grade gliomas: a multicenter study. *Cancer Med*. 2014;3(4):971-979. doi:10.1002/cam4.266
28. Sloan AE, Ahluwalia MS, Valerio-Pascua J, et al. Results of the NeuroBlate System first-in-humans Phase I clinical trial for recurrent glioblastoma: clinical article. *J Neurosurg*. 2013;118(6):1202-1219. doi:10.3171/2013.1.JNS1291
29. Galldiks N, von Tempelhoff W, Kahraman D, et al. 11C-Methionine positron emission tomographic imaging of biologic activity of a recurrent glioblastoma treated with stereotaxy-guided laser-induced interstitial thermotherapy. *Mol Imaging*. 2012;11(4):265-271.
30. Carpentier A, Chauvet D, Reina V, et al. MR-guided laser-induced thermal therapy (LITT) for recurrent glioblastomas. *Lasers Surg Med*. 2012;44(5):361-368. doi:10.1002/lsm.22025
31. Iyer A, Halpern CH, Grant GA, Deb S, Li GH. Magnetic Resonance-Guided Laser-Induced Thermal Therapy for Recurrent Brain Metastases in the Motor Strip After Stereotactic Radiosurgery. *Cureus*. Published online December 7, 2016. doi:10.7759/cureus.919
32. Fabiano AJ, Qiu J. Delayed failure of laser-induced interstitial thermotherapy for postradiosurgery brain metastases. *World Neurosurg*. 2014;82(3-4):e559-563. doi:10.1016/j.wneu.2014.06.007

33. Rao MS, Hargreaves EL, Khan AJ, Haffty BG, Danish SF. Magnetic resonance-guided laser ablation improves local control for postradiosurgery recurrence and/or radiation necrosis. *Neurosurgery*. 2014;74(6):658-667; discussion 667. doi:10.1227/NEU.0000000000000332
34. Fabiano AJ, Alberico RA. Laser-interstitial thermal therapy for refractory cerebral edema from post-radiosurgery metastasis. *World Neurosurg*. 2014;81(3-4):652.e1-4. doi:10.1016/j.wneu.2013.10.034
35. Torres-Reveron J, Tomasiewicz HC, Shetty A, Amankulor NM, Chiang VL. Stereotactic laser induced thermotherapy (LITT): a novel treatment for brain lesions regrowing after radiosurgery. *J Neurooncol*. 2013;113(3):495-503. doi:10.1007/s11060-013-1142-2
36. Carpentier A, McNichols RJ, Stafford RJ, et al. Laser thermal therapy: real-time MRI-guided and computer-controlled procedures for metastatic brain tumors. *Lasers Surg Med*. 2011;43(10):943-950. doi:10.1002/lsm.21138
37. Hawasli AH, Bagade S, Shimony JS, Miller-Thomas M, Leuthardt EC. Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. *Neurosurgery*. 2013;73(6):1007-1017. doi:10.1227/NEU.0000000000000144
38. Smith CJ, Myers CS, Chapple KM, Smith KA. Long-Term Follow-up of 25 Cases of Biopsy-Proven Radiation Necrosis or Post-Radiation Treatment Effect Treated With Magnetic Resonance-Guided Laser Interstitial Thermal Therapy: *Neurosurgery*. 2016;79:S59-S72. doi:10.1227/NEU.0000000000001438
39. Habboub G, Sharma M, Barnett GH, Mohammadi AM. A novel combination of two minimally invasive surgical techniques in the management of refractory radiation necrosis: Technical note. *J Clin Neurosci*. Published online October 2016. doi:10.1016/j.jocn.2016.09.020
40. Chan AY, Tran DKT, Gill AS, Hsu FPK, Vadera S. Stereotactic robot-assisted MRI-guided laser thermal ablation of radiation necrosis in the posterior cranial fossa: technical note. *Neurosurg Focus*. 2016;41(4):E5. doi:10.3171/2016.4.FOCUS1622
41. Rahmathulla G, Recinos PF, Valerio JE, Chao S, Barnett GH. Laser interstitial thermal therapy for focal cerebral radiation necrosis: a case report and literature review. *Stereotact Funct Neurosurg*. 2012;90(3):192-200. doi:10.1159/000338251
42. Khan AB, Matsuoka CK, Lee S, Rahman M, Rao G. Prolonged survival after laser interstitial thermal therapy in glioblastoma. *Surg Neurol Int*. 2021;12:228. doi:10.25259/SNI\_174\_2021
43. Mohammadi AM, Sharma M, Beaumont TL, et al. Upfront Magnetic Resonance Imaging-Guided Stereotactic Laser-Ablation in Newly Diagnosed Glioblastoma: A Multicenter Review



of Survival Outcomes Compared to a Matched Cohort of Biopsy-Only Patients. *Neurosurgery*. Published online November 23, 2018. doi:10.1093/neuros/nyy449

44. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459-466. doi:10.1016/S1470-2045(09)70025-7
45. Hong CS, Deng D, Vera A, Chiang VL. Laser-interstitial thermal therapy compared to craniotomy for treatment of radiation necrosis or recurrent tumor in brain metastases failing radiosurgery. *J Neurooncol*. 2019;142(2):309-317. doi:10.1007/s11060-019-03097-z
46. Shah AH, Semonche A, Eichberg DG, et al. The Role of Laser Interstitial Thermal Therapy in Surgical Neuro-Oncology: Series of 100 Consecutive Patients. *Neurosurgery*. Published online November 19, 2019:nyz424. doi:10.1093/neuros/nyz424
47. Kim AH, Tatter S, Rao G, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN): 12-Month Outcomes and Quality of Life After Brain Tumor Ablation. *Neurosurgery*. Published online April 21, 2020:nyaa071. doi:10.1093/neuros/nyaa071
48. Chen C, Guo Y, Chen Y, Li Y, Chen J. The efficacy of laser interstitial thermal therapy for brain metastases with in-field recurrence following SRS: systemic review and meta-analysis. *Int J Hyperthermia*. 2021;38(1):273-281. doi:10.1080/02656736.2021.1889696
49. Franca SA de, Tavares WM, Salinet ASM, Teixeira MJ, Paiva WS. Laser interstitial thermal therapy as an adjunct therapy in brain tumors: A meta-analysis and comparison with stereotactic radiotherapy. *Surg Neurol Int*. 2020;11:360. doi:10.25259/SNI\_152\_2020
50. Kamath AA, Friedman DD, Hacker CD, et al. MRI-Guided Interstitial Laser Ablation for Intracranial Lesions: A Large Single-Institution Experience of 133 Cases. *Stereotact Funct Neurosurg*. 2017;95(6):417-428. doi:10.1159/000485387
51. Bastos DC de A, Rao G, Oliva ICG, et al. Predictors of Local Control of Brain Metastasis Treated With Laser Interstitial Thermal Therapy. *Neurosurgery*. Published online September 20, 2019:nyz357. doi:10.1093/neuros/nyz357
52. Hernandez RN, Carminucci A, Patel P, Hargreaves EL, Danish SF. Magnetic Resonance-Guided Laser-Induced Thermal Therapy for the Treatment of Progressive Enhancing Inflammatory Reactions Following Stereotactic Radiosurgery, or PEIRs, for Metastatic Brain Disease. *Neurosurgery*. Published online May 31, 2018. doi:10.1093/neuros/nyy220
53. Ahluwalia M, Barnett GH, Deng D, et al. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg*. Published online April 2018:1-8. doi:10.3171/2017.11.JNS171273

54. Kamath AA, Friedman DD, Akbari SHA, et al. Glioblastoma Treated With Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy: Safety, Efficacy, and Outcomes. *Neurosurgery*. Published online August 22, 2018. doi:10.1093/neuros/nyy375
55. Leuthardt EC, Voigt J, Kim AH, Sylvester P. A Single-Center Cost Analysis of Treating Primary and Metastatic Brain Cancers with Either Brain Laser Interstitial Thermal Therapy (LITT) or Craniotomy. *Pharmacoeconomics - Open*. Published online November 3, 2016. doi:10.1007/s41669-016-0003-2
56. Holste KG, Orringer DA. Laser interstitial thermal therapy. *Neuro-Oncol Adv*. 2020;2(1):vdz035. doi:10.1093/nojnl/vdz035
57. Rennert RC, Khan U, Bartek J, et al. Laser Ablation of Abnormal Neurological Tissue Using Robotic Neuroplate System (LAANTERN): Procedural Safety and Hospitalization. *Neurosurgery*. Published online May 11, 2019. doi:10.1093/neuros/nyz141
58. Beechar VB, Prabhu SS, Bastos D, et al. Volumetric response of progressing post-SRS lesions treated with laser interstitial thermal therapy. *J Neurooncol*. Published online December 4, 2017. doi:10.1007/s11060-017-2694-3
59. Foroughi S, Wong H, Gately L, et al. Re-inventing the randomized controlled trial in medical oncology: The registry-based trial. *Asia Pac J Clin Oncol*. 2018;14(6):365-373. doi:10.1111/ajco.12992
60. Barbaro NM, Quigg M, Ward MM, et al. Radiosurgery versus open surgery for mesial temporal lobe epilepsy: The randomized, controlled ROSE trial. *Epilepsia*. 2018;59(6):1198-1207. doi:10.1111/epi.14045
61. Chang SM, Barker FG, Schmidt MH, et al. Clinical trial participation among patients enrolled in the Glioma Outcomes Project. *Cancer*. 2002;94(10):2681-2687. doi:10.1002/cncr.10536
62. Vanderbeek AM, Rahman R, Fell G, et al. The clinical trials landscape for glioblastoma: is it adequate to develop new treatments? *Neuro-Oncol*. 2018;20(8):1034-1043. doi:10.1093/neuonc/noy027
63. Lee EQ, Chukwueke UN, Hervey-Jumper SL, et al. Barriers to accrual and enrollment in brain tumor trials. *Neuro-Oncol*. Published online June 7, 2019:noz104. doi:10.1093/neuonc/noz104
64. Shin DH, Melnick KF, Tran DD, Ghiaseddin AP. In situ vaccination with laser interstitial thermal therapy augments immunotherapy in malignant gliomas. *J Neurooncol*. 2021;151(1):85-92. doi:10.1007/s11060-020-03557-x
65. Srinivasan ES, Sankey EW, Grabowski MM, Chongsathidkiet P, Fecci PE. The intersection between immunotherapy and laser interstitial thermal therapy: a multipronged future of

neuro-oncology. *Int J Hyperthermia*. 2020;37(2):27-34.  
doi:10.1080/02656736.2020.1746413