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# Role of Laser Interstitial Thermal Therapy in the Management of Primary and Metastatic Brain Tumors

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## Opinion statement

Laser interstitial thermal therapy (LITT) is a minimally invasive treatment option for brain tumors including glioblastoma, other primary central nervous system (CNS) neoplasms, metastases, and radiation necrosis. LITT employs a fiber optic coupled laser delivery probe stabilized via stereotaxis to deliver thermal energy that induces coagulative necrosis in tumors to achieve effective cytoreduction. LITT complements

surgical resection, radiation treatment, tumor treating fields, and systemic therapy, especially in patients who are high risk for surgical resection due to tumor location in eloquent regions or poor functional status. These factors must be balanced with the increased rate of cerebral edema post LITT compared to surgical resection. LITT has also been shown to induce transient disruption of the blood–brain barrier (BBB), especially in the peritumoral region, which allows for enhanced CNS delivery of anti-neoplastic agents, thus greatly expanding the armamentarium against brain tumors to include highly effective anti-neoplastic agents that have poor BBB penetration. In addition, hyperthermia-induced immunogenic cell death is another secondary side effect of LITT that opens up immunotherapy as an attractive adjuvant treatment for brain tumors. Numerous large studies have demonstrated the safety and efficacy of LITT against various CNS tumors and as the literature continues to grow on this novel technique so will its indications.

## Introduction

The term "laser" is an acronym for light amplification by stimulated emission of radiation and is commonplace in current jargon but was a novel device introduced in 1960. Since that time, lasers have been used for numerous medical applications including treatment of melanoma, prostate cancer, lung cancer, brain cancer, and epilepsy. The first report using a laser to induce hyperthermic injury to a tumor was by Bown in 1983 [1]. Next, an early in-human report using lasers for treating brain tumors was published in 1990 [2]. The authors used a Nd-YAG (neodymium-doped yttrium aluminum garnet) laser to treat five patients. All patients reportedly had radiographic resolution of their tumors. Although promising, the technique failed to gain traction due to inability to monitor the temperature produced by the laser. But in the early 2000s, advancements in imaging technology allowed for improved capacity to monitor thermal response of tissues in near real time. Henceforth, the technique of laser interstitial thermal therapy (LITT) was born. This review will discuss the surgical technique employed to perform LITT, its safety and mechanisms of tissue destruction, its role in the treatment of brain tumors, and its utility in amplifying response to adjuvant therapy.

# Existing systems

The two leading LITT systems available in the USA are the Visualase (Medtronic, Minneapolis, MN) and NeuroBlate (Monteris, Plymouth, MN). The first published trial using one of these novel systems was by Carpentier et. al. in 2008 [3]. In this publication, four patients with brain metastases were treated with LITT. The procedure was well tolerated and led to no tumor recurrence in 90 days. The first clinical trial using NeuroBlate in patients with recurrent glioblastoma was by Sloan et. al. in 2013 [4]. The median survival in this group of ten patients was 316 days, which represented a marked improvement compared to no therapy.

# Technique

## Patient selection

The primary consideration for choosing which patients would benefit from LITT involves excluding patients better suited for surgical resection. Surgical resection is the standard of care for most brain tumors regardless of histology or recurrence status. However, some tumors are surgically inaccessible. Specifically, deep-seated (e.g., basal ganglia, thalamic or periventricular) tumors are often considered inoperable. Additionally, LITT is minimally invasive with a smaller incision (< 1 cm), thereby making this an attractive option for patients with significant comorbidities or wound healing concerns.

Patients who are good candidates for LITT have tumors that are accessible using existing stereotactic techniques. Specifically, some stereotactic frames struggle to access low-lying tumors including those in the posterior fossa. Additionally, there needs to be a relatively "safe" approach to the tumor that will not compromise eloquent brain. The extent of thermal injury that LITT can deliver is roughly a 3-cm ellipse. Tumors larger than 3 cm can be treated with LITT using multiple trajectories for the laser, although this approach increases the risk of post-operative symptomatic cerebral edema. Patients should also have an adequate baseline functional status, defined by Karnofsky Performance Score (KPS) > 60. Patients with poor functional status may benefit from LITT but there is a paucity of published data in this group. Due to the importance of MR thermometry for LITT, a LITT candidate must be capable of undergoing MRI based on body habitus and preexisting metallic implants.

## Surgical technique

There is significant variation among institutions for the technique used to perform LITT. Our institutional method has been previously published by Laurent et. al. and entails pre-operative trajectory planning using MRI [5]. For the NeuroBlate system, a trajectory through intact skull is necessary for placement of the titanium bolt that directs the laser probe. Therefore, pre-operative planning in patients who have had prior craniotomies usually also requires a head CT to ensure that the planned trajectory avoids the edge of a bone flap or previous titanium plate. The biopsy and NeuroBlate bolt placement are performed using frame-based stereotaxis and monitored anesthetic care (MAC). However, many institutions use general anesthesia. The headring is removed and the patient is then transitioned to MRI where the probe driver and laser are inserted into the NeuroBlate bolt. Treatment is delivered using the NeuroBlate software and one final MRI is obtained prior to removal of the laser and bolt. Postoperatively, the patients are monitored in the post-anesthesia care unit prior to being transferred to the neurological floor. The majority of patients are discharged the next day with close follow-up in neurosurgery clinic. Patients are commonly treated with

corticosteroids to treat or prevent post-LITT cerebral edema. In patients in whom immunotherapy is being utilized after LITT, corticosteroids are avoided or used sparingly to minimize their immunosuppressive effects.

# Mechanism of action

## Direct tissue effects

The basic premise of LITT is that a laser delivery probe is placed using stereotaxis into the tumor bed. This probe utilizes an optical fiber connected to a diode laser to deliver light energy in the form of 1064 nm photons which are absorbed by tissue chromophores [6, 7]. When these chromophores relax from their excited state, thermal energy, via molecular motion, is released. The optimal range of heating is from 42 to 100 °C [8]. This amount of thermal energy is sufficient to cause thermal injury, namely coagulation, but not vaporization of tissues. The primary issue with vaporization is generation of gas which impairs heating of surrounding tissues and could raise intracranial pressure to a dangerous level. The thermal dose (cumulative equivalent minutes at 43C or CEM43) sufficient to cause tissue necrosis and irreversible cell death in the brain is anywhere from 10 to 60 min [9]. Using the Arrhenius equation, this information can be used to extrapolate the time needed to induce tissue necrosis at other temperatures [10]. The thermal response of the tissues is monitored in real-time utilizing an MRI scanner. Factors that affect how the heat spreads through the tumor include tissue consistency, thermal conductivity, and proximity to "heat sinks" such as the ventricles, other CSF spaces and blood vessels which shunt heat away from the treatment zone. The temperature can be approximated using the proton density, $T_1$ and $T_2$ relaxation times, diffusion coefficient, or proton resonance frequency [10]. Both the NeuroBlate and Visualase systems have proprietary software that can be used to calculate the thermal dose zones.

As stated, the effect of thermal therapy on tissues is coagulation of proteins. This includes irreversible damage to proteins in the cell membrane, cytosol, nucleus, and mitochondria leading to eventual necrotic cell death [11]. In addition, there are delayed effects of thermal injury including apoptosis and ischemia [12]. An interesting single-patient case-report described the histologic findings after administration of LITT in a patient with glioblastoma who experienced progressive symptoms requiring en bloc resection 2 weeks later [13]. The thermal-treated tumor contained 3 separate zones: the central acellular necrotic zone; the intermediate granulation tissue zone with numerous macrophages; and the peripheral zone with viable cells (Fig. 1).

## Effect on adjuvant therapy

In addition to the direct cytoreduction from tissue necrosis, LITT also affords other therapeutic benefits for the treatment of brain tumors. Specifically, LITT has been demonstrated to disrupt the blood–brain barrier

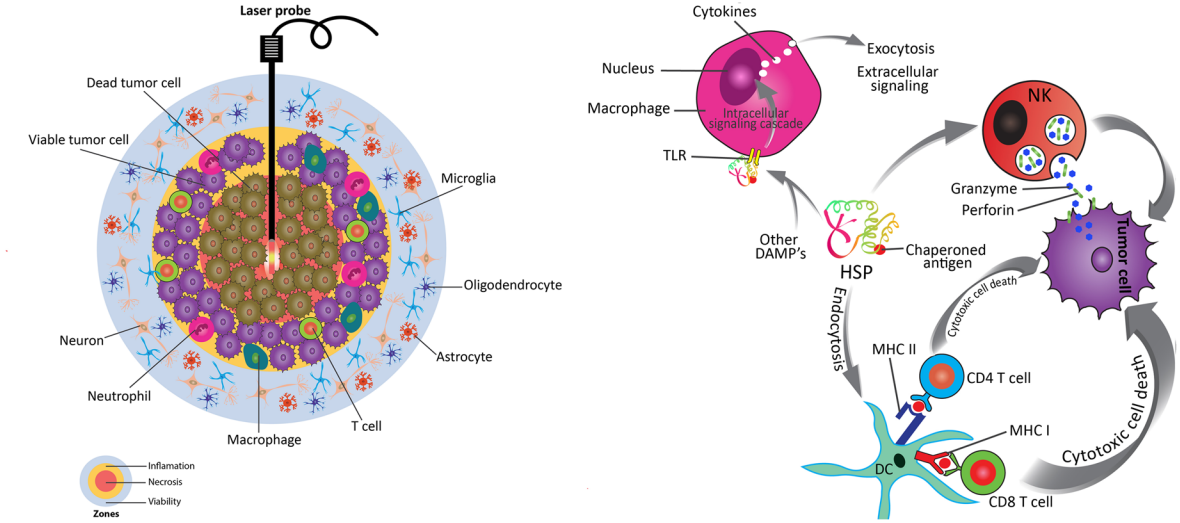


**Fig. 1** Depiction of cellular changes that occur as a result of LITT

(BBB), improve the efficacy of immunotherapy, and increase sensitization to ionizing radiation. The BBB is composed of endothelial cells that form tight junctions to protect the brain from the systemic circulation; however, it is often a hindrance to CNS delivery of chemotherapy and immunotherapy. Using dynamic contrast enhanced MRI to estimate the degree of BBB disruption through the vascular transfer constant ($K^{trans}$) of gadolinium, Leuthardt et. al. (2016) conducted an elegant analysis of LITT-induced peritumoral BBB disruption as a part of a clinical trial testing the ability of LITT to increase CNS delivery and efficacy of the BBB-impermeable chemotherapy drug doxorubicin in recurrent glioblastoma (GBM) [14]. The peritumoral BBB disruption post LITT was corroborated by the concurrent increase in serum levels of brain-specific enolase. These results further confirmed that the disruption of the BBB immediately following LITT lasted for at least 6 weeks post ablation, which has the potential to allow use of chemotherapeutics that are otherwise ineffective for brain tumors due to their poor BBB penetration. In the same study, the LITT-doxorubicin combination resulted in a significant improvement in overall survival compared to historical controls treated with LITT alone or bevacizumab, a standard biologic agent for recurrent GBM [15•]. A recent publication has further elucidated the effect on the BBB post LITT. The authors demonstrated that in a murine model, LITT decreased tight junction integrity and increased brain endothelial cell transcytosis leading to leaking of molecules as large as immunoglobins [16].

Hyperthermia has also been shown to lead to increase cytokine response, systemic leaking of tumor antigens and improved penetration of immune cells, presumably due to the disrupted BBB and the hyperthermia-induced immunogenic cell death, thereby improving efficacy of natural tumor immune response and engineered immunotherapies

[17–19]. In response to hyperthermic stress, heat shock protein (HSP) expression is greatly increased [20]. HSPs serve as molecular chaperones facilitating protein folding to prevent protein aggregation and mediate activation of inflammatory pathways that often ensue after a hyperthermic shock, including increasing the cytotoxicity of natural killer (NK) cells in an MHC class I-dependent fashion, and promoting antigen presentation to both CD4 + and CD8 + T lymphocytes via MCH class II and class I (Fig. 1) [21–25]. Not unexpectedly, recruitment and activation of immune cells to the ablated tumor has specifically been demonstrated in response to LITT. In a murine hepatic tumor model, LITT increased recruitment of CD8 + T cells to the tumor microenvironment [26, 27].

Additionally, hyperthermia can activate the innate immune response via release of damage-associated molecular patterns (DAMPs) including HSPs, nuclear proteins, and nucleic acids, cellular matrix proteins such as glycans, fibronectin, and heparan, as well as others [28]. DAMPs bind to a variety of pattern recognition receptors including TLR2 and TLR4 to mediate production of proinflammatory cytokines (Fig. 1) [29, 30].

Through these aforementioned mechanisms, LITT is postulated to enhance efficacy of immunotherapy. This was first demonstrated in melanoma, which is immunologically "hot" yet still able to resist immunotherapy. Specifically, LITT with adjuvant ipilimumab which is a CTLA-4 inhibitor leads to a durable cure in one patient [31]. In a murine glioma model, a poorly immunogenic tumor type, thermal ablation synergized with immune checkpoint blockade significantly improved overall survival [32].

Lastly, it is well established that hyperthermia leads to tissue radiosensitization [33–36]. The mechanism behind this effect is related to hyperthermia-associated impaired cellular signaling and DNA repair [35, 37]. For example, base excision repair at the religation step was shown to be severely impaired due to hyperthermia leading to a high mutational burden that eventually triggers apoptosis [34]. In glioma cells specifically, prior hyperthermic treatment at 45 °C for 60 min sensitized tumor cells to subsequent radiation [38], likely by decreasing AKT activation leading to cell death [37].

In summary, LITT induces hyperthermia which is capable of directly killing cells via coagulative necrosis. For cells that survive the direct hyperthermic assault, they are at risk of destruction by the immune system due to damage to the BBB, activation of the innate immune response via DAMPs, and stimulation of the adaptive immune response via HSP-mediated MCH-dependent cytotoxicity. These physiologic changes result in increased efficacy of chemotherapy, immunotherapy and radiation.

## Safety

Although generally well tolerated, LITT carries risk of certain complications. Due to the commercial availability of LITT and selection bias on the part of surgeons and patients, there has never been a large randomized clinical trial comparing LITT to surgical resection that would permit direct comparison of safety metrics. So, all comparisons are based on retrospective reviews

which have inherent selection bias. The primary complications observed are symptomatic cerebral edema, worsening neurologic deficit, hyponatremia, infection, intracranial hemorrhage, and death. It is important to consider that the expected progression of intracranial neoplasms includes neurologic worsening and eventual death. For this reason, it is often difficult to discern if peri-procedural deaths are related directly to the procedure. In the literature, we identified two deaths that were definitively not related to disease progression—one of meningitis and one of malignant cerebral edema [39, 40]. In the first report of using the NeuroBlate system by Sloan et. al., of ten patients, three had worsening neurologic deficit 14 days after LITT [4]. This resolved in two patients but persisted for one patient. The rate of neurologic worsening in roughly 30% of patients is similar to other publications [41, 42, 43•]. In contrast, the LAANTERN (Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System) is a multi-center prospective trial that followed 233 patients who underwent LITT. This trial did not report minor worsening in neurologic exam but stated the rate adverse events was 10.7% and that of serious adverse events was only 1.8% [44••]. To reconcile these differences, it is important to consider the 7 years that elapsed between these publications and that the safety of a technique often improves with continued experience and evolution of the technology. Shao et. al. demonstrated in a cohort of 238 patients who underwent LITT that early neurologic deficits and mortality decreased significantly over time from 15.5% and 4.1% to 4.1% and 1.5% respectively [45••]. The acute post-operative neurologic worsening post-LITT is often due to a transient increase in cerebral edema. These changes are often mild and can be minimized by treating smaller lesions and utilizing corticosteroids or hypertonic saline post-operatively. Moreover, the NeuroBlate system has three different laser output settings. Using a lower laser output setting results in slower thermal ablation with the theoretical reduced risk of symptomatic cerebral edema. Additionally, some centers employ tubular or endoscopic surgical resection following LITT for larger lesions to reduce the morbidity associated with cerebral edema[46, 47]. The rate of surgical site or deep wound infection following LITT is exceedingly low. Many series have no instances of infection and in a series of 100 patients enrolled in the LAANTERN trial, only one had an infection [48]. To put these numbers in perspective, the rate of neurologic deficit and mortality following craniotomy is 13–30% and 0.5–3% respectively [49, 50]. The rate of infection following craniotomy is 4–10% [51–56]. So, although LITT does portend surgical risk, it is demonstrably safer than craniotomy.

## Cost

A concern when adopting a new therapy, in addition to safety and efficacy, is cost. LITT is associated with short hospital stays, an average of 33.4 h in one large retrospective analysis [44••]. Likewise, the length of ICU admission was only 18.8 h on average and the rehospitalization rate was only 1.8%.

These factors all contribute to favorable cost profile of LITT. Leuthardt et. al. revealed that the cost of LITT is less than that of craniotomy for patients with brain metastases [57•]. This calculation considered procedure, in-hospital, and post-discharge costs. Since most patients treated with LITT are discharged the day after treatment, the hospital costs are generally lower than patients who undergo a craniotomy. For patients with high grade glioma, Voigt and Barnett modeled the cost of LITT and demonstrated that LITT procedures are cost effective and well below the USA threshold value for added cost per life years gained [58].

# Applications

## Metastases

The first published application of LITT for brain tumors in the USA was for brain metastases in 2008 by Carpentier et. al [3]. This small pilot clinical trial used LITT to treat four patients with metastatic brain tumors who had already undergone radiation and chemotherapy. The primary goal of this small study was to demonstrate safety of the procedure. The study concluded that the procedure was well tolerated and led to gradual radiographic decrease in tumor volume. In a follow-up study in 2011, the authors reported treatment of fifteen tumors in seven patients [59]. At 30-month follow-up, most lesions were radiographically stable, and the median survival was 19.8 months. One patient died from systemic disease, two died from other untreated intracranial metastases, and only one died from recurrence of a treated tumor. Since these early initial reports, there have been numerous small series of LITT for brain lesions including metastases, primary brain tumors, and radiation necrosis [39, 60, 61]. However, these studies fail to distinguish efficacy for brain metastases and primary brain tumors.

The next large study (laser ablation after stereotactic radiosurgery or LAASR) was published in 2018 by Ahluwalia et. al. [62•] reporting on the use of LITT in a larger cohort, including 20 patients with recurrent metastatic disease after stereotactic radiosurgery (SRS). Progression-free survival and overall survival were 54% and 71% respectively at 12 weeks. Although the benefit of LITT in treating brain metastases that grow after SRS is that LITT is effective for both tumor cytoreduction and radiation necrosis, patients who have symptomatic cerebral edema with growing brain metastases will have faster resolution of their edema with surgical resection [63]. In comparing LITT to surgical resection, a 2019 retrospective chart review series evaluated 42 patients treated for brain metastases that recurred after radiation [64••], of whom, 26 underwent craniotomy and 16 received LITT. Overall and progression-free survival at 1- and 2-year follow-up was similar between the two groups. In summary, LITT has been shown to be safe and effective in the management of recurrent brain metastases.

The types of metastatic cancers that have been treated with LITT include lung cancer (small cell, non-small cell, and mesothelioma), breast cancer, melanoma, colon cancer, colorectal cancer, osteosarcoma, renal cell

carcinoma, urothelial cancer, prostate cancer, ovarian cancer, and germ cell tumors [61, 62•, 64••, 65–67]. In 2019, Jermakowicz et. al. demonstrated that the thermal doses delivered by LITT to brain metastases may be overestimated by conventional methods. This means that the thermal dose actually delivered is lower than what is expected which may lead to disease recurrence [68]. Theoretically, certain tumor histologies may be more sensitive to hyperthermic therapy. However, definitive data supporting this notion is currently lacking and is an important research question to address with future studies on LITT.

## Glioblastoma (GBM)

For newly diagnosed GBM, LITT is a secondary option if surgical resection is not feasible [69]. Thomas et. al. (2016) compared the characteristics of eight patients who underwent LITT for primary GBM to those of thirteen patients who underwent LITT for recurrent GBM [70]. The patients with newly diagnosed GBM tended to be older, had larger tumors, and were more likely to be IDH wild type. The median overall survival for the patients with newly diagnosed GBM was unfortunately only eight months despite adjuvant temozolomide and radiation. In 2019, Mohammadi et. al. compared 24 patients with newly diagnosed GBM who underwent upfront LITT to a matched cohort who underwent biopsy alone [71]. Both groups received adjuvant temozolomide and radiation. The median overall survival for the LITT group was 14.4 months compared to 15.8 months in the biopsy only group. The authors note that the survival in the biopsy only group is significantly higher than the literature but offer no explanation for the phenomenon. Of note, more patients in the biopsy group had IDH mutations (10% vs 0%) and MGMT methylations (50% vs 30%) which may have led to the unexpectedly increased survival. For the patients that underwent LITT, multivariate analysis indicated that extent of ablation, tumor volume, and age correlated with overall survival.

A recent systematic review by Viozzi et. al. summarizes the existing data on LITT for newly diagnosed GBM [72]. The review analyzed 11 publications from 2013 to 2020. The authors recognize that all the studies are subject to selection bias. The median overall survival ranged drastically from 3.3 to 32.3 months. The lowest median overall survival reported was based on 13 patients with thalamic tumors, nine of which were glioblastoma. Unfortunately, two patients died in the peri-operative period from an intracranial hemorrhage, which likely confounded the median overall survival. As a result, the authors of this cohort suggested avoiding treating thalamic tumors > 3 cm with LITT. In contrast, the longest median overall survival occurred in group of eleven patients all treated by the same surgeon [73]. These patients all had newly diagnosed GBM that was considered unamenable for resection. Ten patients had tumors in the frontal, parietal, or temporal lobes only one tumor was thalamic. No perioperative complications were reported. The stark contrast between these two studies suggests that for patients with newly diagnosed GBM undergoing LITT, the location of the tumor may affect overall response and survival.

In 16 patients with recurrent GBM (rGBM) treated with LITT, Schwarzmaier et. al. (2006) reported a median survival of 11 months after LITT [74], which was comparable to survival after salvage SRS in rGBM [75]. Similarly, Sloan et. al. in 2013 also reported a median survival of 10.5 months in ten patients with rGBM treated with LITT [4]. In one of the largest series to date consisting of 41 patients with rGBM treated with LITT, the median survival post LITT was 11.8 months [76]. A systematic review published in 2020 found 17 studies encompassing 203 patients with rGBM treated with LITT [77••]. The median overall survival post LITT was 10.2 months. The median overall survival from initial diagnosis was only 14.7 months and the median progression-free survival was 5.6 months. They report that this represents a similar survival from the time of recurrence compared to patients who undergo craniotomy. The rate of complications was 6.4% with seizures, hemiparesis, wound infection, and hemorrhage being the most common. There were no LITT-related mortalities. However, this analysis had a large selection bias and a study directly comparing surgical resection and LITT in patients with rGBM will be necessary to determine the true differences in survival outcomes.

In summary, although craniotomy is still the standard treatment for newly diagnosed and recurrent GBM, LITT offers a viable option for inoperable tumors or when patient characteristics favor a more minimally invasive approach. Although there have not been any prospective randomized trials comparing LITT to craniotomy, retrospective data suggests similar survival and morbidity between the two treatment modalities.

## Radiation necrosis

Cerebral radiation necrosis is a complication of radiation treatment estimated to occur in 5–10% of patients [78]. The primary risk factors for development of radiation necrosis are related to the dose and type of radiation delivered. Radiation necrosis presents as neurologic or radiographic changes and usually occurs within one year of treatment although delayed presentations can occur. Symptoms can be treated with dexamethasone, hyperbaric oxygen therapy, and bevacizumab [79]. Although not in and of itself typically lethal, the symptoms can be debilitating and the need for prolonged steroid treatment can cause systemic complications. There are two instances where LITT may be utilized to treat radiation necrosis: First, when the symptoms are not responsive to medications or in patients for whom the medications are not well tolerated; and second, in the event that it is unclear if radiographic changes represent disease progression or radiation-induced changes [80].

The first case report using LITT for radiation necrosis was in a patient with a metastasis who was symptomatic despite medical therapy and was not a candidate for surgical resection [81]. The intervention was successful with the patient having improved symptoms and radiographic improvement at the 7-week follow-up. The patient was also able to be weaned from steroids.

Another small case-series demonstrated safety in ten patients with radiation necrosis secondary to treatment to brain metastasis or glioblastoma [82]. In this cohort, the 6-month survival was 77.8% and the 1-year survival was 64.8%. Another favorable finding was that 8 of 10 patients were able to be weaned from dexamethasone following a 2-week postoperative course. In 2014, Rao et. al. published a series of sixteen patients who had either radiation necrosis or tumor recurrence [80]. Pathology was not obtained at the time of LITT so it is difficult to draw conclusions from this cohort. However, the authors hypothesized that the actual histology at the time of LITT had little effect on overall outcome. The overall survival at 24 weeks was 57%. The next large study to differentiate radiation necrosis from tumor recurrence was by Ahluwalia et. al. in 2018 [62•], in which 19 patients who developed biopsy proven radiation necrosis after radiation treatment of brain metastasis achieved an overall survival rate at 12 weeks of 100% and at 26 weeks of 82.1% without significant decline in cognition or quality of life after treatment.

A retrospective comparison of LITT to craniotomy in patients with radiation necrosis after radiation treatment of cerebral metastasis demonstrated that progression free survival and overall survival in patients undergoing LITT for radiation necrosis were significantly better than those with tumor recurrence [64••]. Of note, for patients with histologically confirmed radiation necrosis, overall survival rates post LITT were 94.4%, 73.8%, 73.8%, and 63.2%, as compared to post resection rates of 100%, 93.3%, 71.8%, and 64.6% at 6, 12, 18, and 24 months, respectively.

More recently, a 2020 retrospective review on LITT administered to 20 patients with radiation necrosis secondary to glioblastoma or metastasis. The mean overall survival in this group was 14.3 months. Interestingly, radical ablation (ablation larger than the area of enhancement) led to the lowest risk of disease progression. Additionally, nine patients were able to be weaned from their preoperative steroids. Only four patients experienced a complication, one each with a new neurologic deficit, a seizure, a CSF leak, and a pulmonary embolus. In conclusion, numerous retrospective analyses have demonstrated that LITT is an effective treatment modality for radiation necrosis.

## Other primary brain tumors

LITT has been investigated for treating other surgically inaccessible primary brain tumors including high-grade gliomas, chordomas, meningiomas, solitary fibrous tumors, and low-grade gliomas including infiltrating gliomas, pilocytic astrocytomas, ependymomas, and subependymal giant cell astrocytomas [60, 73, 83]. As with metastases, certain tumor types and locations may be more sensitive to thermal ablation. Dural-based lesions such as meningiomas and solitary fibrous tumors and meningiomas in general as compared to other tumor types have significantly lower percent extent of ablation, with the average extent reaching only 80% in one series [73, 83]. Further research on this topic is required to establish clear guidelines.

**Table 1 Actively recruiting clinical trials incorporating LITT (information obtained from clinicaltrials.gov)**

| Trial Name | Principle Investigator(s) (Institution) |
|---|---|
| Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN) | Leuthardt (Washington University School of Medicine) |
| LITT and Pembrolizumab in Recurrent Brain Metastasis (TORCH) | Rahman, Tran (University of Florida) |
| MK-3475 in Combination With MRI-guided Laser Ablation in Recurrent Malignant Gliomas (PROGRESS) | Campian, Tran (Washington University School of Medicine, University of Florida) |
| LITT Followed by Hypofractionated RT for Newly Diagnosed Gliomas | Mishra (University of Maryland) |
| LITT Followed by Hypofractionated RT for Recurrent Gliomas | Mishra (University of Maryland) |
| Laser Interstitial Thermotherapy (LITT) Combined With Checkpoint Inhibitor for Recurrent GBM | Sloan (Case Western) |
| Expedited Laser Interstitial Thermal Therapy + Chemoradiation For Newly Diagnosed High Grade Gliomas | Yu (Cleveland Clinic) |
| Avelumab With Laser Interstitial Therapy for Recurrent Glioblastoma | Hormigo (Mount Sanai) |
| MR-guided LITT Therapy in Patients With Primary Irresectable Glioblastoma | Ter Laan, Viozzi (Netherlands) |

## Active clinical trials

Despite the growing evidence of clinical benefits of LITT, there are still many remaining questions regarding how this therapy is compared across different tumor types and to other treatment modalities. Additionally, it is currently unclear if LITT may be particularly beneficial in conjunction with certain systemic therapies. Table 1 summarizes current ongoing clinical trials using LITT.

## Conclusion

LITT utilizes photons generated from a stereotactically implanted laser to thermally ablate tumors and other abnormal cerebral tissue. LITT works by inducing coagulative necrosis to the abnormal tissue as well as disrupting the peritumoral BBB that potentially increases efficacy of cytotoxic chemotherapy, immunotherapy and radiotherapy. Several studies have demonstrated safety and efficacy in using this novel approach for brain metastases, radiation necrosis, and primary brain tumors. We expect as surgical experience improves and more patients are treated with LITT that this modality will become a mainstay as a valuable treatment strategy for CNS tumors.

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## Declarations

**Conflict of Interest**

Kaitlyn Melnick declares that she has no conflict of interest.David Shin declares that he has no conflict of interest.Farhad Dastmalchi declares that he has no conflict of interest.Zain Kabeer declares that he has no conflict of interest.Rahman: PI of the TORCH study (NCT04187872) studying LITT and PD-1 blockade for recurrent brain metastases. Sponsored by Monteris Medical. Dr. Rahman receives no direct funding for this study.Tran: David D. Tran has received research funding from Sarepta, Novocure, Lacerta Therapeutics, Merck, Novartis, Monteris Medical, Tocagen, Advanced BioScience Laboratories (ABL), and Stemline Therapeutics; has received compensation from Novocure and Monteris Medical for participation on medical advisory boards; has received reimbursement for travel expenses from Novartis; and has the following patents pending:* "Inhibiting Prostaglandin E Receptor 3 Resensitizes Resistant Cells to TTFields".* "Methods for Reducing Viability of Cancer Cells by Activation of the STING Pathway with TTFields".* "AAV capsid variants targeting human glioblastoma stemlike cells" (licensed to Lacerta Therapeutics).* "Core Master Regulators of Glioblastoma Stem Cells".* "Methods for Targeted Treatment and Prediction of Patient Survival in Cancer".* "Methods for Cancer Screening and Monitoring by Cancer Master Regulators Markers in Liquid Biopsy".* "Immunotherapy for Direct Reprogramming of Cancer Cells into Immune Cells/Antigen Presenting Cells/Dendritic Cells".* "GeneRep and nSCORE: Method and Apparatus for Improved Determination of Node Influence in a Network".Ghiaseddin: Ashley P. Ghiaseddin has received research funding from Orbus Therapeutics and has received compensation from Novocure and Monteris Medical for participation on medical advisory boards.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance


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## Publisher's Note