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Chapter

# Laser Ablation for Gliomas

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## Abstract

Laser interstitial thermal therapy (LITT) is a novel minimally invasive neurosurgical procedure in which laser light is delivered through a stereotactically positioned probe to an intracranial lesion for controlled thermal ablation of the pathological tissue. LITT is considered for patients who are poor candidates for open surgical resection due to (1) location of lesion (e.g., deep-seated or near critical structures), (2) history of intracranial interventions or medical comorbidities that increase surgical risk, or (3) lesion refractoriness to prior conventional therapies. The use of LITT was initially limited by concerns over off-target thermal damage; however, recent advances in magnetic resonance imaging-based thermal imaging have enabled real-time monitoring of tissue ablation dynamics, thereby improving its safety profile. Accordingly, the past two decades have seen a rapid expansion in the use of LITT for a variety of intracranial pathologies, including neoplasms, radiation necrosis, and epilepsy. This chapter focuses on the novel application of LITT to both newly diagnosed and recurrent glioblastoma multiforme (GBM). We first review the technological developments that enabled the safe use of LITT for GBM. We then review recent evidence regarding the indications, outcomes, and limitations of LITT as a novel adjuvant treatment for GBM.

**Keywords:** LITT, laser, glioma, glioblastoma, astrocytoma, ablation

## 1. Introduction

### 1.1 Glioblastoma multiforme: standard-of-care and prognosis

World Health Organization (WHO) grade IV glioma (glioblastoma multiforme) is the most common and most lethal malignant primary brain tumor. The incidence in the United States is estimated to be 3.12 per 100,000 persons with a median age of 64 years at diagnosis [1]. Current standard-of-care guidelines for initial treatment for grade III or IV gliomas (high-grade gliomas (HGG)) are maximal safe surgical resection followed by adjuvant temozolomide chemotherapy and radiation [2]. Although standard-of-care treatment improves median survival from 3 months in untreated patients to 14.8 months, GBM remains a terminal diagnosis as tumors inevitably recur [2, 3]. There are few positive prognostic factors. In a minority of patients, certain tumor molecular phenotypes correlate with improved prognosis. For example, methylguanine methyltransferase (MGMT) promoter hypermethylation is associated with an increased median survival of 21.7 months. Isocitrate dehydrogenase 1 (IDH) mutation-positive tumors, especially in

combination with MGMT hypermethylation, also correlate with a survival benefit [4]. Other favorable prognostic factors include younger age at diagnosis, pre-treatment functional status, and extent of surgical resection of the tumor mass [5].

### 1.2 Rationale for use of LITT for glioblastoma

Recent studies have improved our understanding of how the extent of surgical resection impacts progression-free survival and overall survival for GBM patients [6, 7]. Although GBM is a diffusely infiltrative disease, gross total resection (GTR) is associated with increased progression-free survival and overall survival compared to subtotal resection (STR), which itself confers a survival benefit compared to biopsy alone [7]. Studies aiming to quantify a threshold extent of resection have concluded that a threshold at 78% resection of radiographic tumor is necessary to confer a survival benefit compared to radiation and chemotherapy alone [8–11]. Other recent studies have found an additional survival benefit from supra-total resection (i.e., resection beyond the contrast-enhancing tumor margins) to include any fluid-attenuated inversion recovery (FLAIR) abnormalities or a total right frontal or parietal lobectomy compared to GTR [12, 13]. These findings support the current standard-of-care guidelines for maximal safe surgical resection and reinforce the primary role of cytoreduction in GBM treatment.

However, some patients may not be able to undergo conventional open surgical resection. Factors contributing to this include medical comorbidities that increase surgical risk, low preoperative functional status, inability to tolerate general anesthesia, and history of radiation therapy or prior craniotomy that may impair wound healing and increase risk of postoperative neurological worsening [14]. Up to 40% of GBM tumors are considered surgically “unresectable” based on their location in deep or eloquent brain regions or adjacent to critical neurovascular structures [15]. Postoperative neurological deficits from injury to eloquent brain regions during open surgical resection are associated with reduced overall survival and functional status [16]. When open surgery is not an option, patients may simply receive a needle biopsy for diagnosis and chemoradiation. For these patients, laser interstitial thermal therapy is a minimally invasive alternative approach for cytoreductive intervention.

## 2. Laser interstitial thermal therapy: Principles and technological developments

### 2.1 Technological principles

LITT is a minimally invasive neurosurgical procedure that delivers laser light to an intracranial target to thermally ablate pathological tissue [17]. Laser light is a form of non-ionizing radiation and is emitted from a power source as a coherent beam of electromagnetic radiation. Laser light is delivered intracranially through a fiber optic ensheathed in a rigid laser probe that can be stereotactically inserted along a linear trajectory from a single skull entry point to the lesion. The primary mechanism of thermal damage occurs when laser light is absorbed by tissue water and hemoglobin molecules, causing excitation and release of heat. In LITT, laser light in the near-infrared range (980–1064 nm) is used to maximize tissue penetrance (up to 10 mm). Tissue heating to at least 43°C for several minutes is sufficient to cause irreversible tissue damage; heating to 60°C rapidly induces protein denaturation and damage to DNA and lipid membranes, resulting in coagulative necrosis [18]. At 100°C, tissue vaporization occurs, which can result in

increased intracranial pressure. Tissue charring at temperatures >90°C can also damage healthy brain and impair laser penetration to further target regions. Therefore, the ideal temperature range for thermal ablation is 50–90°C [19].

The first use of LITT in neurosurgery was reported in the early 1980s [20]; however, concerns were raised over how to limit thermal injury to pathological tissue only [21]. Although early LITT users could stereotactically position a laser optical fiber to the center of a lesion, they did not have an accurate method for measuring heat distribution throughout the target and to surrounding off-target areas. Two advances in LITT technology have improved its safety: (1) real-time magnetic resonance (MR) thermometry and (2) the development of commercially available LITT systems that successfully integrate MR thermometry data and enhanced control over laser energy delivery into a standard workflow.

MR thermometry was introduced in the 1990s as a way to monitor real-time changes in tissue temperature on an MR imaging sequence [22, 23]. T2-weighted MRI images are taken intraoperatively; changes in tissue temperature affect the water proton resonance frequency signal in a linear relationship and can be mapped onto pixels of the MRI image. The result is a heat damage map that can be updated throughout the procedure and used to guide the boundaries of laser ablation [24].

The NeuroBlate laser ablation system (Monteris, Inc.) and the Visualase Thermal Therapy System (Medtronic, Inc.) received Food and Drug Administration (FDA) approval in 2007 and 2009, respectively. These commercial LITT platforms use MR thermometry software that allows the surgeon to define a maximum temperature threshold at the periphery of the target lesion; surpassing this threshold automatically triggers laser shutdown to protect off-target regions [24]. The Visualase and NeuroBlate LITT systems also improved procedure safety in designing a cooling sheath to surround the laser fiber along the length of laser probe, thereby limiting thermal damage to the tip of the probe [18].

## 2.2 Overview of the LITT setup and workflow

The LITT setup consists of four components: (1) laser energy source, (2) laser applicator probe, (3) cooling mechanism, and (4) computer workstation with software for processing real-time MRI thermometry data and controlling laser energy delivery. The patient is induced under general anesthesia or monitored anesthesia care (MAC). In the operating room, the laser trajectory from a skull entry point to the target lesion is planned using standard neuronavigation (e.g., Stealth system, Medtronic Inc.) technology. The laser applicator probe is stereotactically positioned along this trajectory through a single burr hole at the entry point. The surgeon may opt to perform stereotactic needle biopsy prior to implantation of the applicator probe to obtain a histopathological diagnosis. The patient is then transferred to an MRI suite under anesthesia. Laser energy is delivered through the probe to the target lesion in controlled doses lasting several minutes each. Concurrent real-time MRI thermal imaging (MRTI) of the treatment region allows the user to adjust laser output parameters so that thermal ablation of the target is achieved while avoiding thermal damage to normal surrounding brain tissue. Following LITT treatment, the applicator probe is removed, and the small skin opening overlying the entry point is closed.

## 2.3 LITT system platforms and surgical technique

### *2.3.1 LITT system platforms*

The NeuroBlate system consists of a 12-Watt (W) pulsed-output 1064 nm wavelength neodymium-doped yttrium aluminum garnet (Nd-YAG) laser with a

side-firing laser probe design, allowing some control over the direction of ablation. Temperature at the tip is controlled with a $C0_2$ gas cooling mechanism with a built-in thermocouple for feedback control. The Visualase system consists of a 15 W 980 nm diode laser with diffusing-tip probe design. Within the probe, the laser fiber optic is ensheathed within catheter circulating cooled saline. Both systems have a computer workstation with software for MR thermal imaging analysis and control over laser treatment parameters [25]. The 1064 nm wavelength laser used in the NeuroBlate system allows for deeper tissue penetration and potentially larger ablation zone, while the Visualase 980 nm wavelength laser produces more efficient heating [9].

*2.3.2 Surgical procedure*

After the patient is induced under anesthesia, stereotactic registration is performed to plan laser probe trajectory. If a stereotactic headframe is used to set the laser probe trajectory, then a preoperative T1-weighted MRI with contrast and neuronavigation technology is used to plan the trajectory. If the surgeon is using a frameless setup for registration, then an initial computed-tomography (CT) head with fiducial markers is obtained; this is merged with preoperative T1-weighted MRI with contrast studies, and then registration proceeds using neuronavigation. Once registration is complete, a linear trajectory is planned connecting a single entry site at the skull to the lesion that avoids critical brain structures. A trajectory that is orthogonal to the skull surface in all three dimensional planes helps to prevent skiving during drilling and catheter placement and should be utilized. After image registration, the entry point is found with the navigation wand and marked. Local anesthetic is infiltrated at the scalp over the entry site. A precision aiming device and Stealth navigation wand are aligned along the planned trajectory. A 4-mm incision is made to bring the navigation wand tip onto the skull surface entry point. A small burr hole is made with a 3.2-mm drill bit. After the dura is punctured, a reducing cannula is used to pass a rigid stylet, which maintains alignment during placement of the plastic bone anchor. The plastic bone anchor is screwed into the skull with the rigid stylet as a guide. The laser probe is placed into the cooling catheter and fixed in place (**Figure 1**). The patient is then transported under sterile draping and with continued general anesthesia to the MRI suite, where a T2-weighted MRI imaging is then performed to confirm placement of the laser probe in the lesion.

The LITT system software is used to set maximum temperature thresholds of 90°C in the immediate ablation zone around the laser probe tip and 50°C at the target periphery to ensure tissue ablation throughout the target zone (**Figure 2A–D**). Additional maximum temperature thresholds are set in the normal parenchyma surrounding the lesion that, if reached, trigger automatic shutoff to avoid off-target tissue damage [19]. Under real-time MR thermography guidance, a 30–60-second, 3–4 W-test dose is administered to localize the distal end of the laser probe. Once localization of the laser probe to the target is confirmed, the lesion is treated with 10–15 W doses of laser light in 1–3 minute intervals. Ablation is considered complete when the region of tissue reaching 50°C is covered (**Figure 2E**). After ablation is complete, the LITT apparatus is removed through the burr hole craniotomy, and the skin is closed. Typical length of hospital stay is under 48 hours [19, 24, 26, 27].

Postoperative MRI imaging is typically obtained on the first day following LITT. On T1-weighted MRI with contrast, the thermal ablation zone has a thin enhancing rim with potential surrounding edema and enhancing residual blood products and protein coagulation [19]. Residual tumor remaining after subtotal ablation can be



**Figure 1.**
*Intraoperative setup for laser interstitial thermal therapy. The laser probe trajectory is planned under neuronavigation. The skin overlying the skull entry point is incised, a small burr hole is drilled, and a small incision in the dura is made. A cannula is inserted and used to guide the rigid stylet and bone anchor in the correct orientation along the planned trajectory.*

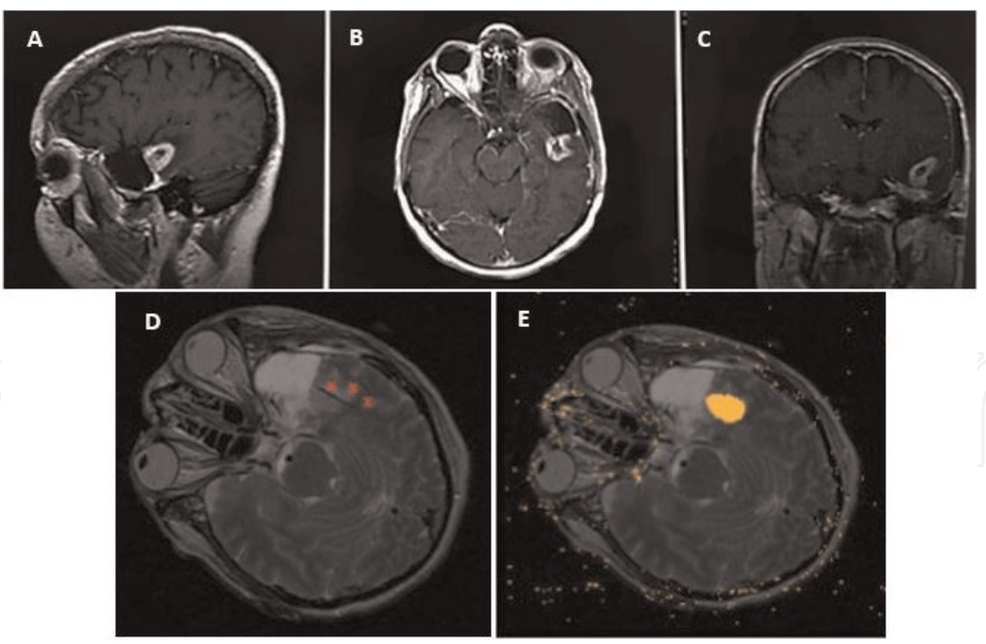



**Figure 2.**
*Representative results of MR thermometry, which acquires real-time temperature data for each pixel of an M2-weighted MRI image. Representative preoperative sagittal (A), axial (B), and coronal (C) T1-weighted MRI with contrast images are suggestive of high-grade glioma. In planning a course of LITT, markers for temperature thresholds to achieve ablation while avoiding off-target damage or tissue vaporization are set by the user (D). During LITT, a damage zone of tissue achieving temperatures sufficient for ablation is represented by orange pixels (E).*

detected on this first postoperative scan. The extent of ablation can be determined using volumetric analysis volume of the ablation zone postoperatively to the volume of the lesion on the preoperative MRI obtained for surgical planning [28].

Additional follow-up MRI studies are obtained 1–3 months postoperatively and then at longer intervals depending on clinical status, pathology, and radiology findings.

## 3. Patient selection

### 3.1 Indications

The development of commercially available stereotactic LITT systems that allow highly controlled delivery of laser light and real-time MRTI monitoring has enabled the routine use of the LITT. Currently, LITT is a treatment option for a variety of intracranial pathologies, including neoplasms (e.g., dural-based lesions, gliomas, metastases), epileptogenic foci (e.g., medial temporal sclerosis, focal cortical dysplasia), radiation necrosis, and chronic pain syndromes. The application of LITT to both newly diagnosed and recurrent gliomas has developed over the past decade; reports from initial institutional experiences demonstrate that LITT can be safely used for both supratentorial and infratentorial gliomas [28].

### 3.2 Criteria for patient selection

Identifying suitable candidates for LITT is important to ensure procedural safety and to optimize target lesion ablation. We propose that LITT is a viable alternative to open surgical resection in patients who meet the following criteria:

1. Lesion size of <3 cm diameter in any dimension. This size restriction reduces the risk of damage to critical brain regions.

2. The surgeon can reasonably predict to achieve an extent of ablation of at least 80%. This threshold is generalized from previous studies of the extent of tumor resection necessary to confer a significant survival benefit in open surgical resection [8–11].

3. Lesions that are inaccessible via conventional open surgery (e.g., lesions located adjacent to deep structures such as the basal ganglia, thalamus, splenium, etc., in eloquent motor or speech areas or near critical neurovascular structures).

4. Treatment refractory lesions (i.e., failure of previous craniotomy or radiation).

5. Patients with medical comorbidities, low preoperative functional status, or history of previous craniotomy/radiation therapy who are unable to tolerate prolonged anesthesia and blood loss or who are at high risk of surgical morbidity and impaired wound healing. Of note, patients should still have a preoperative functional status appropriate for a minimally invasive surgical procedure under anesthesia; in our institutional experience, patients are eligible if they have a Karnofsky Performance Score (KPS) of at least 70.

Therefore, LITT offers a minimally invasive cytoreductive therapy for patients with surgically inaccessible or treatment refractory tumors who would not benefit more from open surgical resection.

### 3.3 Illustrative case series

Here we present three cases of GBM tumors treated with LITT at our institution (University of Miami, Miller School of Medicine). Case 1 illustrates the use of LITT

for recurrent GBM. Case 2 demonstrates the use of LITT in treating primary GBM and the utility of performing stereotactic needle biopsy during the same operative setting to yield diagnostic information. In Case 3, we provide an example of subtotal ablation of a recurrent GBM tumor.

### *3.3.1 Case 1*

A 55-year-old gentleman with a 1-year history of GBM presented with focal nodular enhancement in the right temporal lobe on surveillance MRI. One year prior, he underwent surgical resection followed by temozolomide chemotherapy and radiation. Upon presentation to our surgical neuro-oncology service, the patient was asymptomatic; neurological exam was non-focal. Because of the surgeon's judgment that LITT would be able to achieve gross total ablation, the small size of the lesion, and the patient's history of treatment failure with surgical resection and chemoradiation, the patient was consented for LITT. After the stereotactic placement of the Visualase laser probe and confirmation of its location on intraoperative MRI imaging (**Figure 3A**), LITT was performed according to the following treatment parameters:

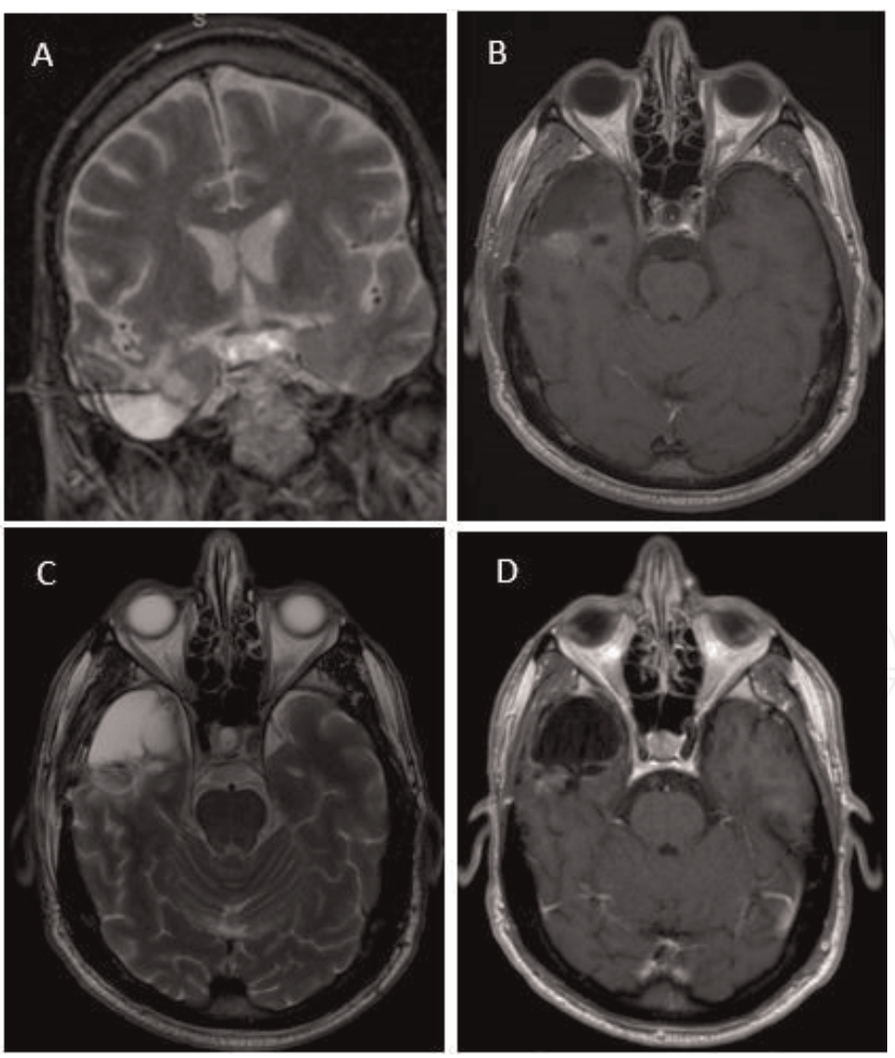



**Figure 3.**
*A 55-year-old gentleman presenting with asymptomatic GBM recurrence. Intraoperative T2-weighted sagittal MRI showing stereotactic placement of laser probe at target lesion (A). Postoperative day 1 of T1-weighted axial MRI with contrast demonstrates gross total lesion ablation; hyperintense signal most likely represents blood products (B) instead of residual tumor, as the same region does not enhance on T2-weighted MRI (C). At 22-months follow-up, T1-weighted axial MRI imaging with contrast showed the patient was recurrence-free (D).*

1. Test dose at 4 W for 7 seconds. Concurrent real-time MRI thermometry data confirmed total coverage of the target lesion.

2. Ablation dose at 10 W laser power for 3 minutes. Because MRI thermometry data confirmed target area ablation and ablation temperature threshold was reached (without reaching the maximum temperature threshold in off-target zones), the treatment was considered complete.

T1-weighted MRI on postoperative day 1 showed gross total (100%) lesion ablation (**Figure 3B** and **C**). The hyperintense signal in the tumor region represented blood products. On follow-up, the patient remained recurrence-free for over 2 years (26 months) (**Figure 3D**). The patient's family reported his death 3 months following tumor recurrence.

*3.3.2 Case 2*

A 60-year-old gentleman with progressive gait instability and confusion for 2 weeks and worsening headache for 2 days presented to the emergency department. MRI demonstrated a deep-seated left mesial temporal lobe lesion (**Figure 4A**). Due to the location of the lesion and progression of his symptoms, the patient was consented for stereotactic needle biopsy and LITT. In the operating room, a trajectory for the stereotactic biopsy needle and laser probe was planned, taking care to avoid critical cortical structures, ventricles, tentorium, arteries, and veins, targeting the center of the lesion volume (**Figure 4B**). To perform stereotactic needle biopsy, a preoperative and intraoperative computed-tomography scan was obtained using an O-Arm (Medtronic) to register and confirm intralesional biopsy. Two frozen cores of tissue were sent for pathological analysis, which confirmed the presence of necrotic brain tissue. Following biopsy, the laser probe was targeted to the lesion using neuronavigation with preoperative MRI registration. Follow-up T1-weighted MRI with contrast demonstrated gross total (100%) ablation (**Figure 4C**). At 1.4-year follow-up, the patient remains recurrence-free.

*3.3.3 Case 3*

A 58-year-old female with history of GBM initially diagnosed 2 years prior presented with focal recurrence in the left frontoparietal lobe on MRI imaging. The recurrence had recently been treated with stereotactic radiosurgery, after which the patient noticed new-onset right-hand weakness that did not improve with steroids.

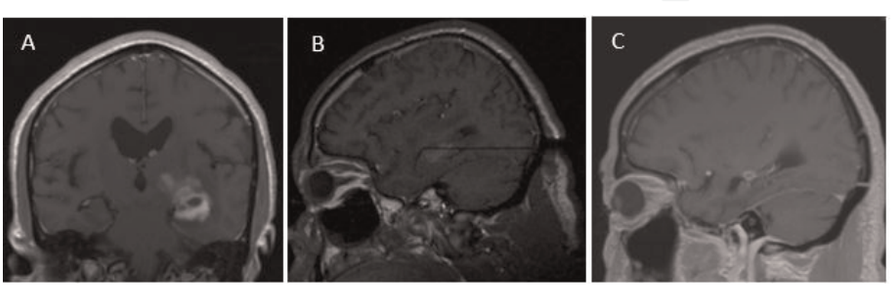



**Figure 4.**
*A 60-year-old gentleman found to have a new, deep-seated lesion on T1-weighted coronal MRI with contrast suspicious for glioma (A). Intraoperative T2-weighted sagittal MRI shows stereotactic positioning of the laser probe to access the lesion while avoiding critical brain structures (B). Postoperative T1-weighted sagittal MRI with contrast demonstrates gross total ablation of the lesion (C).*

Neurological exam was positive for 4/5 strength in the right hand, but was otherwise non-focal. MRI studies re-demonstrated the recurrence and extensive surrounding edema (**Figure 5A, B**). Because the lesion was small (2.0 cm maximum diameter) and failed both prior surgical resection and radiosurgery, the patient was consented for LITT. The patient was induced under general anesthesia, and a laser probe entry site and trajectory angle to the target lesion were planned using preoperative MRI imaging and Stealth neuronavigation (Medtronic, Inc.). The Visualase thermal therapy system laser probe was inserted stereotactically along the planned trajectory as described above (**Figure 5C**). The ablation procedure began with a test dose of laser energy at 3 W (20% of maximum power) for 3 minutes. Concurrent real-time MRI thermometry data was used to confirm target lesion coverage by the developing ablation zone. Next laser power output was increased to 7.5 W (50% maximum power) for 3 minutes, with successive 3-minute doses at 3 W stepwise increases in power. Once target area coverage was maximized and ablation temperature threshold reached (without reaching the maximum temperature threshold in off-target zones), the laser power was increased to 90% maximum power output for maximal ablation in 3-minute intervals. The final ablation zone was confirmed with MRI thermometry.

There were no complications. The patient was discharged the following day on a course of dexamethasone with steroid taper over 2 weeks. T1-weighted MRI with contrast on postoperative day 1 showed subtotal ablation of 70% of the pre-treatment volume (**Figure 5D**). Follow-up MRI imaging showed tumor recurrence at 9-week post-LITT (**Figure 5E**). The patient died 10 months following the procedure.

We present this case to illustrate how a subtotal ablation <80% may not be sufficient to confer a clinical benefit.

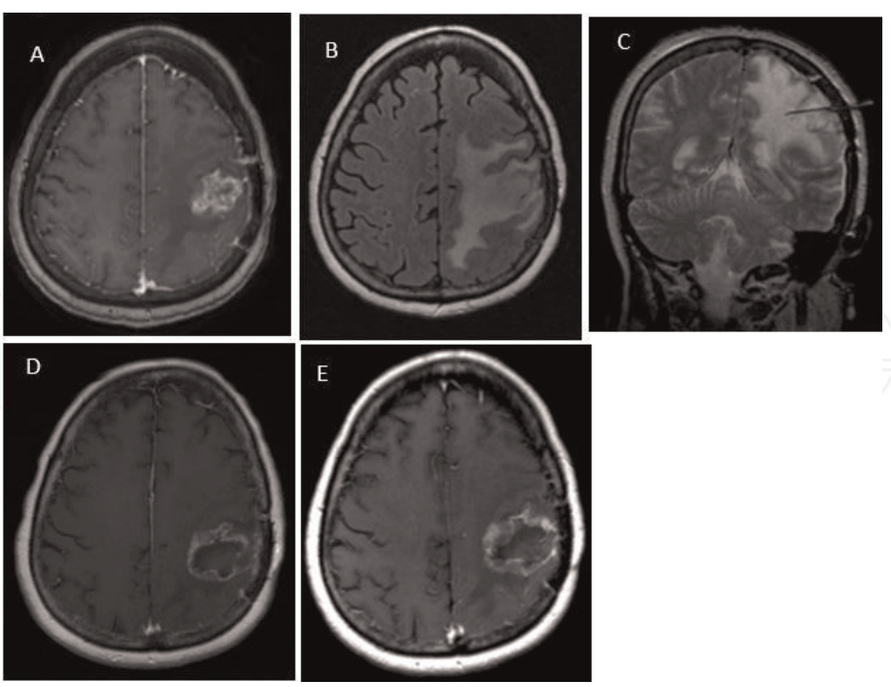



**Figure 5.**
*A 58-year-old female with left frontoparietal ring-enhancing lesion T1-weighted axial MRI with contrast suspicious for tumor recurrence (A) with surrounding peripheral edema on T2-weighted FLAIR sequence (B). Intraoperative sagittal T2-weighted MRI showing correct positioning of the laser probe to the lesion (C). Postoperative day 1 of axial T1-weighted MRI (D) demonstrates subtotal (~70%) thermal ablation of the lesion. Follow-up T1-weighted MRI with contrast approximately 9-week post-LITT demonstrates tumor progression (E).*

## 4. Clinical outcomes

The first case series reporting the use of LITT in gliomas were published in 1990 by Sugiyama et al., which described the successful total ablation of five deep-seated gliomas [37]. The advent of MRI thermography and the Visualase and NeuroBlate systems enabled institutional centers to publish data on larger case series over the past decade. These initial experiences provide valuable evidence supporting the safety and efficacy of LITT in select patient. In **Table 1** we present a comprehensive review of the literature of studies evaluating clinical outcomes in patients treated with LITT for either newly diagnosed or recurrent GBM tumors. To accurately represent the current use of LITT, only studies that included the use of real-time MR thermography are included in our review.

Abbreviations: M, male; F, female; NR, not reported; LITT, laser interstitial thermal therapy; STA, subtotal ablation; SupA, supra-ablation

## 5. Discussion

### 5.1 Current role of LITT in neurosurgery

The use of laser-based ablation technology in neurosurgery began with the treatment of movement disorders, chronic pain syndromes, and epilepsy. Technological advances over the past two decades in laser interstitial thermal therapy delivery platforms and real-time MR thermal imaging of tissue ablation dynamics have made LITT a viable minimally invasive therapy for a variety of intracranial and spinal lesions, including metastases, epileptogenic foci, radiation necrosis, dural-based lesions, and gliomas.

The advantage of LITT in treating gliomas includes:

1. Achieving cytoreduction in poor open surgical candidates: because laser light is delivered through a 1–3-mm diameter laser probe inserted through a single burr hole and dural opening, LITT reduces the risk of morbidity associated with craniotomy for surgical resection. This is especially relevant in GBM patients as the risk of neurological morbidity and poor wound healing or infection increases with repeat craniotomies and radiation therapy. The ability to tightly control the ablation zone using real-time MR thermography means that LITT is well suited for treatment of lesions in deep-seated locations or near critical structures.

2. Shorter procedure time and quicker recovery: the small incision required may result in fewer wound-healing complications, particularly in patients with impaired wound healing due to prior craniotomies or radiation therapy. Finally, a minimally invasive approach enables a quicker recovery and transition to continue chemotherapy or initiate another adjuvant therapy [26, 39].

3. The use of non-ionizing radiation: unlike ionizing radiation therapy, LITT thermal therapy can be used repeatedly without the risk of radiation necrosis [9]. Moreover, LITT can be used as a salvage therapy in treatment refractory tumors and may avoid increased risk of secondary malignancy-associated ionizing radiation [18].

4. Treatment of lesions that are inaccessible via open surgery: gliomas located in deep or eloquent regions of the brain (e.g., insula, thalamus, corpus callosum)

| Reference | # Cases | Newly-diagnosed or recurrent GBM lesions | Age, Gender | Location of lesion | LITT system used, Extent of ablation | Mean/median Recurrence-free survival; Overall survival |
|---|---|---|---|---|---|---|
| Schwartzmaier et al. 2005 [29] | 2 | Recurrent | 47 M<br>67 M | 1 Temporal<br>1 Parietooccipital | 1064 nm laser, STA | 1 recurrence; 13-16 months |
| Schwartzmaier et al. 2006 [30] | 16 | Recurrent | Median age 62, range 44-69, 10 men, 6 women | 3 Frontal<br>1 Frontoparietal<br>1 Frontotemporal<br>1 Temporal<br>1 Parietal<br>3 Parietooccipital<br>1 Corpus callosum<br>1 Parasagittal | 1064 nm laser; NR | 6.9 months; NR |
| Carpentier et al. 2012 [26] | 4 | Recurrent | 40-58 years, 3 men, 1 woman | 1 temporo-polar<br>1 corpus callosum<br>1 frontal<br>1 temporal | Visualase; SupA of 1 mm diameter or more | 1.25 months; 10 months |
| Jethwa et al 2012 [19] | 4 | Newly-diagnosed | Media n 60 years, range 56-81 | right frontal right frontal left temporal right midbrain | Visualase, NR | NR; NR |
| Hawasli et al., 2013 [31] | 6 | Newly-diagnosed | Media n 50 years, range 34-78,<br>6 men,<br>2 women | thalamus<br>left thalamus basal ganglia left thalamus right corpus callosum thalamus | Neuroblate; median 90.3% ablation | Recurrence in 3 of 6 patients at median 3.2 months (range 2.5-15 months); 3 of 6 patients alive at last follow-up, 3 of 6 patients died at median 1.7 months |
| Sloan et al. 2013 [27] | 10 | Recurrent | Media n 54 years, range 34-69.<br>8 men, 2 women | 2 temporal<br>1 temporoparietal<br>1 temporooccipital<br>3 parietal<br>3 frontal | NR | 10.5 months; |
| Mohammadi et al. 2014 [32] | 24 | Recurrent (14) and new (10) lesions | Media n age 56 (range 19-79), 38% female | 15 tumors in frontal lobe,<br>7 in thalamic region, 5 parietal,<br>5 temporal,<br>2 insular,<br>1 corpus callosum. | Neuroblate; Median ablation volume at yellow line: 98%, at blue line: 91% (includes non-GBM tumors included in study) | 5.1 months; 68% survival at 1 year |
| Thomas et al. 2016 [33] | 21 | Recurrent (13) and new (8) lesions | Mean age 49 years | 8 in eloquent regions (62%):<br>3 in motor cortex,<br>3 in speech,<br>1 temporal,<br>2 splenium,<br>2 cingulate,<br>2 insular | NeuroBlate; NR | 5 months; 7 months |

| Reference | # Cases | Newly-diagnosed or recurrent GBM lesions | Age, Gender | Location of lesion | LITT system used, Extent of ablation | Mean/median Recurrence-free survival; Overall survival |
|---|---|---|---|---|---|---|
| Shah et al., 2016 [34] | 7 | Newly-diagnosed | Mean age 59, 3 male, 4 female | 1 splenium<br>1 orbitofrontal<br>1 parieto- occipital<br>1 post. Cingulate<br>1. precuneus<br>1 Genu | Visualase; mean 98.5% | 14.3 months; 6 of 7 patients alive at last follow-up, 1 death at 14 months |
| Schroeder et al. 2014 [35] | 5 | Newly-diagnosed | Mean age 47 | | 94% | 11.5 months; NR |
| Kamath et al. 2019 [36] | 54 | Recurrent (41) and Newly-diagnosed (17) | Mean age 59 years | 14 frontal<br>8 temporal<br>9 parietal<br>1 occipital<br>4 pareito-occipital<br>4 temporo-parietal<br>8 corpus callosum<br>2 insular<br>8 thalamic | Neuroblate; 93.2% (yellow boundary), 88.0% (blue boundary) | 6.6 months; 11.5 months |

*Abbreviations: M, male; F, female; NR, not reported; LITT, laser interstitial thermal therapy; STA, subtotal ablation; SupA, supra-ablation.*

**Table 1.**
*Literature review of case series describing LITT for GBM (adapted from: [9, 38]).*

may increase open surgical risk to a degree that patients only receive stereotactic needle biopsy and adjuvant chemoradiation, thus losing the survival benefit associated with aggressive cytoreduction. Because LITT is delivered through a thin laser probe, lesions that are typically considered "surgically inaccessible" can now be treated with reduced risk of neurological morbidity [39].

The use of LITT for gliomas was initially limited to treating recurrences that failed conventional first-line therapies (i.e., surgical resection and adjuvant chemoradiation). Recently, LITT has been applied as a primary treatment for newly-diagnosed gliomas. Preliminary institutional experiences report local control and overall survival times of several months—over 1 year.

Patient selection is of critical importance in ensuring safe and effective use of LITT. To summarize, lesions should be <3 cm in diameter, in a region that can be accessed via a linear laser catheter trajectory without injury to critical structures and in patients who are able to tolerate a minimally invasive surgical procedure under anesthesia. In addition, the lesion should have identifiable margins such that at least 80% of the target area can be feasibly ablated with a roughly spherical ablation zone.

## 5.2 Limitations of LITT

The increasing use of LITT has revealed it to be an overall safe, well-tolerated procedure. The most common adverse events associated with the procedure include:

1. Intracranial hemorrhage: despite the use of neuronavigation and stereotaxy for trajectory planning, the laser probe may be malpositioned, resulting in injury to vessels and bleeding [40]. Estimates of overall rates of accurate implantation range from 85.7 to over 95%, with only three reported cases of resulting intracranial hemorrhage resulting from malpositioning [19, 40]. The risk of

hemorrhage may be reduced by obtaining a computed-tomography angiography (CTA) showing the location of critical vessels to avoid during laser trajectory planning.

2. Transient neurological deficit: neurological deficits such as weakness, hemianopsia, seizures, and dysphagia are often attributed to direct thermal injury to functional brain areas or cerebral edema. Estimates of transient neurological deficits have been reported to occur in 13–15% of patients [19, 40]. Permanent neurological morbidity is less common (5.6% of cases according to a recent literature review) [40]. Cerebral edema is frequently observed in the immediate postoperative period following LITT. A recent volumetric and time-course analysis found that edema volume has been shown to increase on average 41.5% immediately postoperatively, followed by a gradual decline resulting on average an 80.9% decrease in preoperative edema volume [28]. Although cerebral edema is common, it is unlikely to cause permanent neurological deficits and may be controlled with a course of steroids. Treatment of large (>3cm) lesions, use of multiple laser probes, or use of multiple laser trajectories is associated with a higher risk of significant cerebral edema [41].

Less common (<5% of all cases) complications include permanent neurological deficit, infection (e.g., ventriculitis, meningitis, or brain abscess), deep venous thrombosis, diabetes insipidus, hyponatremia, and intracranial hypertension. There is one reported case of gliosarcoma tumor seeding along the laser probe tract [27]. Finally, there are only two recorded deaths attributed to LITT in the literature, from postoperative meningitis and intracranial hemorrhage [32].

Our discussion of patient selection also reveals specific limitations of LITT. Multiple reviews cite a lesion size limit of 3 cm to reduce the chance of intracranial hypertension secondary to edema [18, 31]. As discussed previously, preoperative functional status, lesion accessibility by a laser trajectory, and anticipated extent of ablation are also factors that limit the use of LITT to particular lesions.

### 5.3 Future directions

In discussing complication rates, it is important to emphasize that LITT is a novel procedure, and so practitioners and institutions operate with a learning curve [18]. Recently, more institutional case series have proposed modifications to improve safety, for example, staging the treatment of larger (>3 cm) lesions to over multiple procedures to avoid morbidity or employing algorithms to optimize laser trajectory planning [42].

Along with further improvements in procedural safety, the future of LITT may lie in combination therapies to enhance tumor control and overall survival. Previous studies have shown that LITT induces a temporary increase in blood-brain barrier (BBB) permeability, which may offer a window of opportunity to deliver adjuvant chemotherapy more effectively [42, 43]. Another line of investigation is the use of gold nanoparticles, which may enhance tissue energy absorption and increase ablation efficacy [45].

Finally, future investigations will require prospective and randomized-controlled trials to evaluate the clinical outcomes of LITT compared to other therapies.

## 6. Conclusion

LITT is a novel adjuvant therapy for treatment of a wide variety of intracranial pathologies. In this chapter we review the evidence supporting the safety and

efficacy of LITT as a primary or adjuvant treatment for glioblastoma. Thus far, LITT is a safe, minimally invasive approach to cytoreduction in patients with gliomas that are poor open surgical candidates.

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## Conflict of interest

Michael Ivan is a consultant for Medtronic. The other authors have no financial, personal, or institutional interests in any of the materials, devices, or drugs described in this article. Laser ablation is the only Food and Drug Administration-approved procedure for the ablation of soft tissue.

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