

Laser Interstitial Thermal Therapy

Effective: April 1, 2024**Next Review:** December 2024**Last Review:** February 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Laser interstitial thermal therapy (LITT) involves the introduction of a laser fiber probe to deliver thermal energy for the targeted ablation of diseased tissue. The goal of therapy is selective thermal injury through the maintenance of a sharp thermal border, as monitored via the parallel use of real-time magnetic resonance (MR) thermography and controlled with the use of actively cooled applicators. In neurological applications, LITT involves the creation of a transcranial burr hole for the placement of the laser probe at the target brain tissue. Probe position, ablation time, and intensity are controlled under MRI guidance. LITT has been proposed as a less invasive treatment option for patients with neurological conditions compared to surgery.

MEDICAL POLICY CRITERIA

- I. Laser interstitial thermal therapy (LITT) may be considered **medically necessary** for the treatment of refractory epilepsy when both of the following Criteria (A. and B.) are met:
 - A. There is documentation of disabling seizures despite use of two or more antiepileptic drug regimens (i.e., medically refractory epilepsy), and

- B. There is a well-defined epileptogenic focus of seizure propagation in the temporal lobe or hypothalamus accessible by LITT.
- II. Laser interstitial thermal therapy (LITT) is considered **investigational** for all other neurological indications, including but not limited to the treatment of refractory epilepsy when Criterion I. is not met and for the treatment of primary or metastatic brain tumors or radiation necrosis.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Medical records related to:
 - History and physical/chart notes including those documenting disabling seizures
 - Conservative treatment provided, including documentation of two or more antiepileptic drug regimens
 - Documentation of well-defined epileptogenic focus of seizure propagation in the temporal lobe or hypothalamus *that is accessible by LITT.*

CROSS REFERENCES

1. [Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy of Intracranial, Skull Base, and Orbital Sites](#), Surgery, Policy No. 213
2. [Focal Laser Ablation of Prostate Cancer](#), Surgery, Policy No. 222

BACKGROUND

LASER INTERSTITIAL THERMAL THERAPY

Laser interstitial thermal therapy (LITT) involves the introduction of a laser fiber probe to deliver thermal energy for the targeted ablation of diseased tissue. Thermal destruction of tissue is mediated via DNA damage, necrosis, protein denaturation, membrane dissolution, vessel sclerosis, and coagulative necrosis.^[1] The goal of therapy is selective thermal injury through the maintenance of a sharp thermal border, as monitored via the parallel use of real-time magnetic resonance (MR) thermography and controlled with the use of actively cooled applicators.^[2] In neurological applications, LITT involves the creation of a transcranial burr hole for the placement of the laser probe at the target brain tissue. Probe position, ablation time, and intensity are controlled under MRI guidance.

The majority of neurological LITT indications described in the literature involve the ablation of primary and metastatic brain tumors, epileptogenic foci, and radiation necrosis in surgically inaccessible or eloquent brain areas.^[2] LITT may offer a minimally invasive treatment option for patients with a high risk of morbidity with traditional surgical approaches. The most common complications following LITT are transient and permanent weakness, cerebral edema, hemorrhage, seizures, and hyponatremia.^[3] Delayed neurological deficits due to brain edema are temporary and typically resolve after corticosteroid therapy. Contraindications to MRI are

also applicable to the administration of LITT.

REGULATORY STATUS

In August 2007, the Visualase™ Thermal Therapy System (Medtronic; formerly Biotex, Inc.) received initial marketing clearance by the FDA through the 510(k) pathway (K071328). In January 2022 (K211269), the system (software version 3.4) was classified as a neurosurgical tool with narrowed indications for use, including "to ablate, necrotize or coagulate intracranial soft tissue including brain structures (for example, brain tumor, radiation necrosis and epileptic foci as identified by non-invasive and invasive neurodiagnostic testing, including imaging) through interstitial irradiation or thermal therapy in medicine and surgery in the discipline of neurosurgery with 800 nm through 1064 nm lasers." The device is contraindicated for patients with medical conditions or implanted medical devices contraindicated for MRI and for patients whose physician determines that LITT or invasive surgical procedures in the brain are not acceptable. Data from compatible MRI sequences can be processed to relate imaging changes to relative changes in tissue temperature during therapy. The Visualase™ cooling applicator utilizes saline.

In April 2013, the NeuroBlate® System (Monteris Medical) received initial clearance for marketing by the FDA through the 510(k) pathway (K120561). As of August 2020, the system is indicated for use "to ablate, necrotize, or coagulate intracranial soft tissue, including brain structures (e.g., brain tumor and epileptic foci as identified by non-invasive and invasive neurodiagnostic testing, including imaging), through interstitial irradiation or thermal therapy in medicine and surgery in the discipline of neurosurgery with 1064 nm lasers" (K201056). The device is intended for planning and monitoring of thermal therapy under MRI guidance, providing real-time thermographic analysis of selected MRI images. The NeuroBlate® system utilizes a laser probe with a sapphire capsule to promote prolonged, pulsed laser firing and a controlled cooling applicator employing pressurized CO₂.

On April 25, 2018, the FDA issued a safety alert on MR-guided LITT (MRgLITT) devices with a letter to healthcare providers stating that the FDA is currently evaluating data suggesting that potentially inaccurate MR thermometry information can be displayed during treatment which may contribute to a risk of tissue overheating and potentially associated adverse events, including neurological deficits, increased intracerebral edema or pressure, intracranial bleeding, and/or visual changes. Several risk mitigation strategies were recommended. In an updated letter released on November 8, 2018, risk mitigation recommendations specific to the Visualase™ and NeuroBlate® systems were issued.

EVIDENCE SUMMARY

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the

intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PRIMARY OR METASTATIC BRAIN TUMORS

Clinical Context and Therapy Purpose

The purpose of MRgLITT is to use a focused thermal therapy technique to ablate primary or metastatic brain tumors and to avoid potential complications associated with alternative surgical interventions.

Review of Evidence

Systematic Reviews

Alkazemi (2023) published a systematic review of comparative and descriptive studies (excluding case reports) assessing the evidence for LITT in primary and metastatic brain tumors. A total of 45 studies (n=826) were included. Lesions were categorized as high-grade gliomas (n=361), low-grade gliomas (n=116), metastatic brain tumors (n=337), or nonglial tumors (n=15). The majority of studies offered LITT for patients with inaccessible or deep tumors (n=12), after failed radiosurgery (n=9), or were nonspecific (n=12). One-year progression-free survival (PFS) was 19.6% (95% confidence interval [CI] 11.3% to 29.0%, $I^2=0\%$) in high-grade gliomas, 16.9% (95% CI 11.6% to 24.0%, $I^2=0\%$) in grade 4 astrocytomas, and 51.2% (95% CI 36.7% to 65.5%, $I^2=0\%$) in brain metastases. One-year overall survival (OS) was 43.0% (95% CI 36.0% to 50.0%, $I^2=7.6\%$) in high-grade glioma, 45.9% (95% CI 37.9% to 54%, $I^2=0\%$) in grade 4 astrocytomas, 93.0% (95% CI 42.3% to 100%, $I^2=\text{not applicable}$) in low-grade gliomas, and 56.3% (95% CI 47.0% to 65.3%, $I^2=\text{not applicable}$) in brain metastases. The incidence of major procedure-related adverse events (AEs) was 30% (95% CI 27% to 40%) with a 16% incidence (95% CI 12% to 22%) of major or minor neurological deficits. This study is limited by lack of comparator data.

Viozzi (2021) published a systematic review of data from 11 studies (n=111) of patients treated with LITT for newly diagnosed glioblastoma reported in 11 studies.^[4] All included studies were conducted in the US predominantly (81%) using the Neuroblate system. Median OS ranged from 4.1 to 32 months and PFS from 2 to 31 months. No randomized studies were identified for inclusion. All studies had serious or critical risk of bias, and the quality of evidence was graded as very low according to the GRADE criteria. The mean complication rate was 33.7%. No quality-of-life outcomes were reported. The low quality of available evidence regarding LITT for newly diagnosed glioblastoma precluded the author's ability to draw conclusions regarding the net impact of the technology on health outcomes.

Alattar (2019) published a systematic review of stereotactic laser ablation (SLA, also known as LITT) for the treatment of brain metastases recurring after radiosurgery.^[5] Thirteen publications were included. Median survival ranged from 5.8 to 19.8 months. About two-thirds of treated

lesions showed post-ablation expansion of contrast-enhancing volume and fluid-attenuated inversion recovery volume, which reached up to three times the pre-operative lesion volume, typically resolved within six months. Median hospital stay was one to two days (range one to five days), and most treated patients were discharged home (range 59.5% to 100%). The incidence of SLA-related permanent neurologic injuries was <10%. The most common complications were hemorrhage, thermal injury causing neurologic deficit, and malignant cerebral edema.

Chen (2021) published a systematic review and meta-analysis of retrospective studies and case series investigating the efficacy of LITT for brain metastases with in-field recurrence or radiation necrosis following treatment with stereotactic radiosurgery (SRS).^[6] A meta-analysis of 14 studies (470 patients with 542 lesions) was performed. The overall 12-month local control rate ranged between 56.0% and 84.7% with a pooled rate of 69.0% (95% CI 60.0% to 76.7%, $I^2 = 50.584\%$, $p=0.048$) and pooled overall survival of 17.15 months (95% CI 13.27 to 24.8). Among 153 recurrent brain metastasis lesions across five studies, the 12-month local control rate was 59.9% (95% CI 47.9% to 70.9%). Among 75 radiation necrosis lesions across four studies, the 12-month local control rate was 76.3% (95% CI 65.0% to 84.8%). Thus, LITT provided more favorable local control efficacy in patients with radiation necrosis compared to those with brain metastasis recurrence. No significant difference in median overall survival at one year was determined between radiation necrosis and brain metastasis groups (66.5% vs. 66.8%, $p=0.978$). Survival outcomes were not stratified by pathology and safety outcomes were not reported. Compared to previously reported estimates for surgical resection with a local control rate ranging from 62% to 93% and a median overall survival of 8.7 months, the authors concluded that LITT demonstrates comparable local control but a more satisfactory survival benefit. The analysis is limited by study heterogeneity, small sample sizes, and the lack of a standardized definition for local disease control.

A systematic review by Montemurro (2020) evaluated data on LITT in the treatment of recurrent glioblastoma and included data from 17 studies ($n=203,219$ LITT sessions).^[7] The median age was 57.4 years (65.8% male). Treatment location was most commonly frontal lobe (29%), followed by temporal (23.9%), parietal (21.4%) and occipital lobes (2.6%). Thalamus, corpus callosum and cerebellum also were treated (23.1%). Morbidity was 6.4% with a median hospital stay of 3.5 days. The most common complications were seizures (2%), motor deficits (1.5%), wound infection (1.5%), transient hemiparesis (1%) and hemorrhage (0.5%). All patients underwent adjuvant chemotherapy after treatment. The median PFS and the median OS after laser interstitial thermal therapy was 5.6 months and 10.2 months, respectively. The median OS from diagnosis was 14.7 months.

A meta-analysis by de Franca (2020) evaluated LITT as a therapy for brain tumors compared to SRS based on data from 25 studies.^[8] Patient populations included patients with brain metastasis and recurrent glioblastoma multiforme. A significant improvement in median overall survival was observed in patients treated with LITT compared to SRS among patients with brain metastasis (12.8 versus 9.8 months, $p<0.02$) and was associated with a 15% reduction in risk of adverse events overall. The authors concluded that "there is no evidence that LITT can be used as a treatment of choice when compared to SRS," and note specifically there is a "lack of systematic data that were reported in our pooled studies." The authors do indicate the use of LITT may have a role in lowering the risk of adverse events. The analysis was limited by inclusion of heterogeneous populations, small number of patients treated with LITT ($n=39$), and a lack of reporting on prior treatments. Patients treated with SRS varied in their degree of

radiosensitivity and prior radiation exposure, which may have influenced the higher rate of adverse events observed in this group.

A meta-analysis by Barnett (2016) compared LITT (eight studies with 77 patients) to open craniotomy (12 studies with 1,036 patients) for the treatment of high-grade gliomas in or near areas of eloquence, with a focus on adverse events.^[9] Proportions of major complications occurred in 5.7% (95% CI 1.8 to 11.6) and 13.8% (95% CI 10.3 to 17.9) of patients treated via LITT and craniotomy, respectively. Studies were rated at high risk of bias due to lack of randomization and blinding. The analysis was also limited by heterogeneous patient populations (e.g., age, Karnofsky score, recurrent vs. primary disease) and lack of reporting on health outcomes.

Comparative Observational Studies

Grabowski (2022) published a multicenter, retrospective study of patients undergoing treatment for biopsy-proven brain metastasis recurrence after stereotactic radiotherapy (SRT).^[10] Patients were stratified into three groups: planned LITT plus SRT (n=21), LITT alone (n=25), or repeat SRT alone (n=9). Mean patient age was 60 years (range 37 to 86) and median follow-up duration was 7.3 months (range 1.0 to 30.5). No patients in the LITT plus SRT group received prior surgery or WBRT, compared to 20% and 28% treated with LITT alone and 11% and 56% treated with SRT alone (p=0.05 and 0.01, respectively). Median time to index lesion progression for LITT plus SRT, LITT alone, and repeat SRT alone was 29.8, 7.5, and 3.7 months, respectively (p=0.022). A univariate analysis found a significantly increased risk of tumor progression among patients receiving prior surgery (hazard ratio 5.33, 95% CI 1.41 to 16.93, p=0.007). The authors noted that future prospective studies are required to validate these findings.

Fadel (2022) retrospectively reviewed an institutional database to identify patients with unifocal, lobar, surgically accessible recurrent glioblastoma who were treated with LITT or resection between 2013 and 2020.^[11] Of 744 patients identified, a LITT cohort of 17 patients was compared with 23 surgical patients. Baseline characteristics were similar between groups except for average lesion size, which was smaller in patients treated with LITT (4.37 cm³ vs. 7.54 cm³, p=0.017). Overall survival (14.1 vs. 13.8 months, p=0.578) and PFS (3.7 vs. 3.3 months, p=0.004) were not significantly different between groups. Significantly shorter hospital stays were observed in patients treated with LITT (2.2 vs. 3.0 days, p=0.004).

Mohammadi (2019) conducted a multicenter retrospective review of survival outcomes in patients with deep seated newly diagnosed glioblastoma treated with upfront MRgLITT prior to chemo/radiotherapy (n=24, median age of 54 years, 50% male) compared to a matched cohort of biopsy-only patients (n=24, median age of 64 years, 58% male).^[12] Patients were matched based on age, gender, tumor location (deep versus lobar), and tumor volume. Median follow-up was 9.3 months (range 2 to 43 months) and 14.7 months (range 2 to 41 months) in LITT and biopsy-only cohorts, respectively. Overall median estimates of overall survival and progression-free survival in the LITT cohort was 14.4 and 4.3 months compared to 15.8 and 5.9 months for the biopsy-only cohort. Age <70 y and tumor volume <11 cm³ were identified as favorable prognostic factors for overall survival. The study was limited by its retrospective design, lack of randomization, small sample size, and short follow-up durations. Additionally, concurrent chemotherapy and radiotherapy regimens were not specified.

Single-Arm Studies

The Laser Ablation of Abnormal Neurological Tissue Using Robotic NeuroBlate System (LAANTERN) registry is an ongoing industry-sponsored, multicenter, multinational prospective registry of the NeuroBlate device enrolling patients with primary and metastatic brain tumors, epileptic foci, and movement disorders (NCT02392078). Rennert (2019) reported procedural safety outcomes for the first 100 patients enrolled in the LAANTERN registry (42% male, 86% white), including 48 and 34 patients with primary or metastatic intracranial tumors, respectively.^[13] The majority of patients (81.2%) had undergone prior surgical or radiation treatment and received LITT for a single lesion (79%). The average length of intensive care and overall hospital stays were 38.1 and 61.1 hours, respectively. A total of 11 adverse events among nine patients were observed. Five adverse events were attributed to energy deposition from laser ablation, including neurological deficits (n=2), postoperative seizures (n=2), and delayed intraparenchymal hemorrhage (n=1). One mortality occurring within 30 days of laser ablation was reported and was not attributed to LITT.

Kim (2020) reported 12-month survival and quality of life outcomes among 223 patients enrolled in the LAANTERN registry with primary (n=131) or metastatic (n=92) brain tumors who received treatment with the NeuroBlate device.^[14] The majority of patients with primary tumors had high-grade glioma (n=90) and patients with metastatic disease had recurrent tumors (n=43) or radionecrosis (n=34). The one year estimated overall survival rate was 73% (95% CI 65.3% to 79.2%), which was not found to be significantly different between primary or metastatic tumors (74.6% vs. 70.7%, respectively). Quality of life assessments with the Functional Assessment of Cancer Therapy - Brain (FACT-Br) questionnaire did not meet the criteria for a clinically meaningful change (>10%) and EQ-5D questionnaires indicated an overall decline of 0.1 points from baseline. A subgroup analysis of LAANTERN data published by de Groot (2022) focused on new (n=29) and recurrent (n=60) cases of IDH wild-type glioblastoma.^[15] Median OS was 9.73 months (95% CI 5.16 to 15.91) for newly diagnosed patients and 8.97 months (95% CI 6.94 to 12.36) for recurrent patients. Median OS in newly diagnosed patients receiving post-LITT chemo/radiation was 16.14 months (95% CI 6.11 to not reached).

Ahluwalia (2018) reported results from the multicenter, prospective Laser Ablation After Stereotactic Radiosurgery (LAASR) study, which assessed the efficacy and safety of LITT as salvage treatment in patients with radiographic progression after SRS for brain metastasis.^[16] Forty-two patients were enrolled, including 20 patients with recurrent brain tumors, 19 patients with biopsy-proven radiation necrosis, and three patients with no diagnosis. PFS rates for patients with recurrent tumors was 54% at 12 weeks and 62% at 26 weeks. Corresponding OS rates were 71% at 12 weeks and 64.5% at 26 weeks. Of four tumor lesions that received total ablation, 3/4 achieved a complete response, compared to 0/8 that received subtotal ablation. Patient Karnofsky performance, quality of life, and neurocognitive scores did not change significantly over the duration of survival. Overall, 35/42 (83%) patients developed adverse events, including five cases of immediate LITT-related neurological complications and 14 surgery-related adverse events.

Patel (2016) conducted a retrospective analysis of patients who underwent MRgLITT with the Visualase system at a single center in the United States between 2010 and 2014.^[17] The majority of patients (87/102) were treated for intracranial tumors. Fourteen (13.7%) developed new neurological deficits following treatment, of which nine achieved complete resolution within one month, one achieved partial resolution within one month, two had no resolution at most recent follow-up, and two died without resolution of symptoms. The authors concluded

that LITT, albeit minimally invasive, must be used with caution as unintended thermal damage to critical and eloquent structures may occur despite MRI guidance.

Section Summary: Primary or Metastatic Brain Tumors

Evidence for the use of LITT in primary or metastatic brain tumors includes systematic reviews and meta-analyses, one retrospective matched-cohort study (in newly diagnosed glioblastoma comparing LITT to biopsy only), and several single-arm studies. Overall survival estimates ranged from 12.8 to 14.8 months. Among patients with metastatic tumors receiving LITT following prior SRS, overall survival rates have ranged between 72% and 76% at six months and between 63% and 65% at 12 months. In a more heterogeneous population of patients with primary and metastatic brain tumors who received LITT, 12-month OS rates were slightly lower in patients with brain metastases (56.3%) and high-grade glioma (43.0%) than other analyses. Systematic reviews comparing LITT to open craniotomy with resection or SRS suggest a reduced incidence of adverse events with LITT; however neurological deficits attributable to LITT-induced thermal damage have been observed despite concurrent MRI guidance. Studies are limited by high risk of bias, predominantly retrospective designs, small sample sizes, and population heterogeneity, with study subjects varying by performance status, lesion volume and location, extent of prior therapies, and extent of ablation. Prospective comparative studies in well-defined and -controlled patient populations are required to assess net health outcomes.

RADIATION NECROSIS

Systematic Reviews

The meta-analysis published by Chen (2021), described previously, included 168 (35.7%) patients with radiation necrosis (RN) who received LITT following prior treatment with SRS.^[6] The local control rate for patients with RN at 6 and 12 months was 83.1% (95% CI 68.4% to 91.8%) and 66.8% (95% CI 49.1% to 80.8%), respectively, and was more satisfactory compared to patients with recurrent brain metastasis. OS was 83.1% versus 69.2% at six months and 66.8% versus 66.5% at 12 months for RN and recurrent brain metastasis groups, respectively. Pre-ablation biopsy, which can accurately diagnose RN, was not routinely performed in all analyzed studies, highlighting a major limitation of this meta-analysis given that it can be quite challenging to accurately distinguish RN from brain metastases based on radiographic evidence alone.

Palmisciano (2021) published a systematic review and meta-analysis of bevacizumab versus LITT for the treatment of RN in patients with brain metastases previously treated with radiotherapy.^[18] Eighteen studies were included for analysis, including 143 patients treated with bevacizumab and 148 treated with LITT. Compared to LITT, a higher proportion of patients treated with bevacizumab experienced symptomatic improvement (73.3% vs. 60.8%) and ability to wean off steroids (66.7% vs. 44.1%), but these differences were not significantly different between groups ($p=0.187$, $I^2=54.8%$, and $p=0.614$, $I^2=25.5%$, respectively). At 18 months, median OS was significantly higher for patients treated with LITT (46.4% vs. 25%, $p=0.038$, $I^2=73.7%$). Rates of adverse events were similar between bevacizumab (14.7%) and LITT (12.2%) cohorts. This analysis is limited by inclusion of primarily retrospective studies, heterogeneous study populations and treatment centers, and limited patient-level data.

Comparative Observational Studies

Sankey (2022) published a multicenter, retrospective study of SRS-treated patients with brain metastases who developed biopsy-proven RN who were treated with LITT (n=57) or medical management (n=15).^[19] Median follow-up was 10.0 months (range 4.2 to 25.1 months). There was no significant difference in median OS (15.2 vs. 11.6 months, p=0.60) or freedom from local progression (13.6 vs. 7.06 months, p=0.40) in LITT or medical management cohorts, respectively. Patients were able to discontinue steroid therapy earlier in the LITT cohort at a median of 37 versus 245 days (p<0.001). The authors note that prospective trials should be designed to validate the utility of LITT for radiation necrosis, including its impact on steroid-induced morbidity.

Sujjantararat (2020) conducted a retrospective chart review comparing outcomes for patients with biopsy-confirmed RN treated with LITT (n=25) or bevacizumab (n=13) at a single center between 2011 and 2018.^[20] The LITT group had a significantly longer OS compared to bevacizumab (median 24.8 versus 15.2 months, p=0.003). Time to local recurrence was not statistically significant between groups (p=0.091) but trended longer in the LITT cohort. Among 13 patients with pre-treatment symptoms in the LITT group, nine (69%) achieved symptom relief. Among 11 patients with pre-treatment symptoms in the bevacizumab group, four (36%) achieved symptom relief. No significant difference was noted between groups for the ability to wean off concurrent steroids. Given that only 50% of lesions treated with LITT were symptomatic compared to 80% of lesions treated with bevacizumab, the authors suggest that LITT treatment may be more successful before radiation necrosis lesions become symptomatic. The study is limited by its retrospective design, small sample size, and population heterogeneity.

Hong (2019) conducted a single-center retrospective chart review of patients treated with LITT or craniotomy for previously irradiated brain metastasis, including 42 patients with recurrent brain tumors and 33 patients with RN.^[21] Among the 33 RN patients, 15 received craniotomy and 18 received LITT, of which 20% and 38.9% received adjuvant post-operative bevacizumab, respectively. No significant differences for mean length of hospital stay, symptom improvement, ability to wean off steroids, or rate of perioperative complications were observed between LITT and craniotomy groups. Overall PFS for patients with RN was 73.2% and 86.7% at 24 months for patients treated with LITT and craniotomy, respectively. OS for patients with RN at 24 months was 64.6% for those receiving craniotomy and 63.2% for those receiving LITT. Study interpretation is limited by its retrospective nature and heterogeneity of prior and adjuvant treatments.

Single-Arm Studies

The LAASR study by Ahluwalia (2018), described previously,^[16] included 19 patients with biopsy-confirmed radiation necrosis who received LITT following prior treatment with SRS for brain tumors. PFS and OS survival was 100% and 91%, respectively, at 12 weeks, and 100% and 82.1%, respectively, at 26 weeks. PFS was significantly higher at 12 weeks for patients with radiation necrosis compared to patients with recurrent tumors (p=0.016) but was not significantly different at 26 weeks (p=0.166). Similar trends were seen for OS in patients with radiation necrosis at 12 weeks (p=0.02) and 26 weeks (p=0.09). Thirty percent of subjects were able to stop or reduce steroid usage by 12 weeks after surgery. For patients with RN, regardless of whether a lesion was totally or subtotally ablated, LITT resulted in close to 100% lesion control and >80% survival at six months. No significant differences in Karnofsky performance status, quality of life, or neurocognitive scores were detected between subgroups.

Section Summary: Radiation Necrosis

Evidence on the use of LITT in patients with radiation necrosis includes one meta-analysis, two nonrandomized comparative studies, and one single-arm study. Studies have reported improved local control and survival outcomes in patients with radiation necrosis compared to those with brain metastases. One study comparing LITT to bevacizumab suggested that LITT treatment may be more successful among patients before radiation necrosis lesions become symptomatic. One study comparing LITT to craniotomy did not report significant survival differences between groups. One retrospective study of patients treated with LITT or medical management reported earlier steroid discontinuation with LITT but no significant differences in median OS or freedom from local progression. Studies are limited by retrospective designs, small sample sizes, population heterogeneity, and unclear relevance, as symptomatic status was not consistently reported. Prospective comparative studies in well-defined and -controlled patient populations are required to assess a net health outcome.

DRUG-RESISTANT EPILEPSY

Systematic Reviews

Barot (2022) published a systematic review with meta-analysis of outcomes following LITT for the treatment of drug-refractory epilepsy, comparing outcomes between temporal, extratemporal epilepsies and hypothalamic hamartoma.^[22] Twenty-eight studies (n=559) were included. The overall prevalence of Engel class I outcome was 56% (95% CI 0.52% to 0.60%). Hypothalamic hamartomas patients had the highest seizure freedom rate of 67% (95% CI 0.57% to 0.76%) and outcome was overall comparable between mesial temporal lobe epilepsy (mTLE) (56%, 95% CI 0.50% to 0.61%) and extratemporal epilepsy (50%, 95% CI 0.40% to 0.59%). The postoperative adverse event rate was 19% (95% CI 0.14% to 0.25%) and the most common adverse event was visual field deficits. The reoperation rate was 9% (95% CI 0.05% to 0.14%), which included repeat ablation and open resection.

Marathe (2021) conducted a systematic review and meta-analysis comparing open surgical resection, SRS, LITT, and radiofrequency ablation (RFA) in drug-resistant mTLE.^[23] Forty-one publications were included in the analysis, including 19 studies on open surgery, 11 on LITT, four on RFA, and seven on radiosurgery. The pooled seizure-free rate per person-year was 0.72 (95% CI 0.66 to 0.79) with trans-sylvian selective amygdalohippocampectomy (sAHE), 0.70 (95% CI 0.64 to 0.77) with anterior temporal lobe resection (ATL), 0.60 (95% CI 0.49 to 0.73) with transcortical sAHE, 0.59 (95% CI 0.53 to 0.65) with LITT, 0.50 (95% CI 0.34 to 0.73) with SRS, and 0.38 (95% CI 0.14 to 1.00) with radiofrequency ablation. The authors concluded that while there is no evidence to suggest that LITT is less effective than open surgical resection in the short term, long-term data are lacking and an RCT comparing LITT to open surgical methods is needed. Additionally, reporting of secondary neuropsychological and treatment-related morbidity outcomes is inconsistent and lacks standardization.

Kohlhase (2021) published a meta-analysis evaluating outcomes and complications following temporal lobe MRgLITT, RFA, and conventional surgical approaches (i.e., ATL or sAHE) for the treatment of drug-refractory mTLE.^[24] Forty-three studies (13 MRgLITT, 6 RFA, and 24 surgery studies) of 554, 123, 1,504, and 1,326 patients treated by MRgLITT, RFA, ATL, or sAHE, respectively, were included in the review. Engel Class I (Engel-I) outcomes were achieved after MRgLITT in 57% (315/554, range 33.3% to 67.4%), RFA in 44% (54/123, range 0% to 67.2%), ATL in 69% (1,032/1,504, range 40% to 92.9%), and sAHE in 66% (887/1,326, range 21.4% to 93.3%). No significant difference in seizure outcome between MRgLITT and

RFA (Q=2.74, p=0.098) was found, however, ATL and sAHE were both superior to MRgLITT (ATL: Q=8.92, p=0.002; sAHE: Q=4.33, p=0.037) with better outcomes in patients at follow-up of 60 months or more. The rate of major complications was 3.8% for MRgLITT, 3.7% for RFA, 10.9% for ATL, and 7.4% for sAHE; none of these frequencies were statistically significantly different. While the severity of cognitive impairment was not evaluated across treatment groups directly, the authors note that cognitive impairment following intervention appears to increase with the invasiveness of the respective intervention. The authors conclude “patients undergoing MRgLITT may experience fewer major complications compared to ATL or sAHE and might have a more beneficial neuropsychological outcome.”

Kerezoudis (2021) published a meta-analysis aimed at quantifying the relationship of LITT ablation volume with postoperative outcomes in temporal lobe epilepsy.^[25] A total of 13 studies (551 patients) were analyzed. Meta-regression of seizure freedom rate for the overall cohort and mesial temporal sclerosis subset (n=384) was performed adjusting for overall ablation volume as well as percentage of hippocampal and amygdala ablation. Overall seizure freedom rate was 58% (95% CI 54% to 62%) and was not significantly associated with total ablation volume (p=0.42), hippocampal ablation (p=0.67), or amygdala ablation (p=0.33). Seizure freedom rate for patients with mesial temporal sclerosis was 66% (95% CI 58% to 74%) and was also not found to be significantly associated with total ablation volume (p=0.15), hippocampal ablation (p=0.73), or amygdala ablation (p=0.43). Overall complication rate was 17% (95% CI 13% to 22%).

Wang (2021) published a systematic review of data on LITT, SRS, radiofrequency thermocoagulation (RF-TC), and focused ultrasound for the treatment of mTLE.^[26] Data from 19 publications were included with 1094 patients (LITT: 434, SRS: 81, RF-TC: 402, cortico-amygdalohippocampectomy (CAH): 153, and selective amygdalohippocampectomy (SelAH): 24). At six months postoperatively, LITT (9/19) Engel I outcomes ranged from 52% to 80%. Seizure freedom was similar between LITT studies and to rates achieved by CAH and SelAH, however, no direct comparisons were available. Common complications included transient postprocedure headaches (LITT: 0.4% to 27%, SRS: 15% to 70%, and RF-TC: 23%) and visual field deficits (LITT: 3% to 40%, SRS: 34% to 50%, and RF-TC: 2% to 5%).

Brotis (2021) conducted a meta-analysis to estimate the efficacy of LITT for mTLE.^[27] Sixteen retrospective case series published between 2012 and 2019 representing 575 patients (range 1 to 231) were identified. Overall, seizure freedom was achieved in 54.7% (95% CI 50.6% to 58.8%, I²=18.7%) of patients undergoing LITT with a median follow-up duration of 18 months (IQR 12 to 26 months). Sensitivity analyses yielded similar results. Four studies representing 150 patients indicated that the prevalence of Engel Class IA outcomes decreased with time, estimated at 64.2%, 46.9%, and 42.4% at 12-, 24-, and 36-month follow-up, respectively. The overall quality of evidence was regarded as 'very low' according to GRADE recommendations, with only four studies included more than 20 patients. The authors concluded that while mTLE resective surgeries are invasive and irreversible, they offer better seizure control rates, with previously reported seizure-free rates ranging from ranging from 60% to 90% for mTLE.

Grewal (2019) published a meta-analysis comparing MRgLITT versus SRS for medically intractable temporal lobe epilepsy.^[28] A total of 19 studies published between 2008 and 2018 representing 404 patients (range 5 to 58) were identified, including nine retrospective studies on LITT (n=239). The overall seizure freedom rate was not found to be significantly different between LITT (50%, 95% CI 44% to 56%) and SRS (42%, 95% CI 27% to 59%; p=0.39), nor was it significantly different for patients with lesional conditions (62%, 95% CI 48% to 74% vs.

50%, 95% CI 37% to 64%, $p=0.23$). While LITT was associated with a significantly lower procedural complication rate (20% vs. 26%, $p=0.06$), reoperation rates were not significantly different (15% vs. 27%, $p=0.31$). The authors noted that the quality of evidence was low and that large-scale comparative studies directly comparing LITT and SRS are required to validate findings.

Xue (2018) reported postoperative outcomes for MRgLITT in the treatment of drug-resistant epilepsy.^[29] Sixteen nonrandomized studies published between 2014 and 2018 representing 269 patients (range 5 to 30) were included in the meta-analysis. The prevalence of Engel Class I, II, III, and IV outcomes was 61%, 12%, 16%, and 15%, respectively. The prevalence of postoperative complications was 24% (95% CI 16% to 32%). Interpretation of outcomes is limited by small study size and short follow-up durations (range 7 days to 51 months).

Comparative Observational Studies

Hale (2019) reported postsurgical outcomes in 26 pediatric patients with insular epilepsy treated with LITT ($n=14$) or open resection ($n=12$).^[30] Mean follow-up was 2.43 years. Engel Class I outcomes were achieved in 43% of patients treated with LITT compared to 50% who underwent open insular resection at one year post-surgery. Postoperative complications occurred in six patients treated with LITT and seven patients treated with resection, all of which resolved within three to four months. The authors conclude that further studies are needed to determine the noninferiority of LITT with respect to resection in terms of complication rates and seizure freedom, especially in cases of cortical dysplasia that may involve extensive regions of the brain.

Petito (2018) published a retrospective, single center analysis of 100 consecutive neurosurgeries performed between 2013 and 2015 in patients with drug-resistant epilepsy, representing 33 LITT procedures and 21 open resections with mean follow-up durations of 21.7 and 21.3 months, respectively.^[31] A discrete lesion was radiographically identified in 85% of patients treated with LITT and 65% of patients treated with resection. The mean post-operative hospital length of stay was significantly shorter for LITT compared to resection (1.18 versus 3.43 days, $p=0.0002$). Patients treated with resection were significantly younger, with a mean age of 35.4 years ($p=0.001$). At 12 months, seizure freedom was achieved in 56.3% (95% CI 39.3% to 71.8%) and 60% (95% CI 38.7% to 78.12%) of patients treated with LITT and resection, respectively ($p=0.79$). Among patients with focal lesions, the seizure freedom outcomes were not significantly different between groups ($p=0.21$). For non-lesional patients, LITT treatment trended towards a better outcome, but did not achieve statistical significance ($p=0.05$). Study interpretation is limited by small sample size, retrospective analysis, and population heterogeneity.

Single-Arm Studies

Esmaeili (2023) published a prospective observational study of consecutive LITT-treated patients with drug-resistant epilepsy from 2013 to 2021.^[32] The primary outcome was sudden unexpected death in epilepsy (SUDEP). There were four SUDEP cases among 135 patients over a median duration of 3.5 years (range 0.1 to 9.0) for an estimated SUDEP incidence of 8 per 1,000 person-years. Among a historical control group, the incidence of SUDEP was estimated to be 2 per 1,000 person-years in patients who underwent resection surgery and 6.1 per 1000 years in patients who did not receive surgical intervention but were candidates. Thus, LITT-treated patients had significantly higher SUDEP incidence compared with surgery ($p=0.02$), but similar rates compared with those without intervention ($p=0.55$).

Kanner (2022) conducted a retrospective review of long-term seizure and psychiatric outcomes among patients who underwent LITT for drug-resistant mTLE between 2013 and 2019 at a single academic center.^[33] Forty-eight patients (mean age 43 years) were identified with a mean follow-up duration of 50 ± 20.7 months (range 18 to 81). Engel class I outcomes were achieved in 29 (60.4%) subjects and 11 (22.9%) reported one to three seizures per year. The seizure-freedom rate was 77.8% among patients with 24-month follow-up which decreased to 50% among patients with >61-month follow-up data. Seizure freedom was associated with mesial temporal sclerosis, no pre-treatment focal to bilateral tonic-clonic seizures, and no psychopathology in the last follow-up year. Mood and/or anxiety disorders were identified in 30 (62.5%) of patients pre-surgery, of which 19 (62%) remitted following LITT.

Landazuri (2020) reported one-year outcomes following LITT of epileptogenic foci with the NeuroBlate system in patients with drug resistant epilepsy enrolled in the previously described LAANTERN registry study by Rennert (2019).^[13, 34] Engel Class I outcomes were achieved in 27/42 (64.3%, 95% CI 48.0% to 78.5%) patients at one year. No significant difference was observed in patients with mTLE (70.8%) versus other etiologies. Five adverse events were reported, with one categorized as serious. Median baseline QOLIE-31 was 51.7 (range 8.7 to 77.3). Median scores increased by 14.1 points reflecting a 72.4% improvement (95% CI 52.8% to 87.3%) in quality-of-life measures. However, the total score change was not statistically significant ($p=0.217$). Seizure worry and social functioning sub-scores were considered statistically significant ($p=0.0219$ and $p=0.0175$, respectively). The authors note that the primary success of LITT remains in well localized lesions/localizations, such as those seen in mTLE/mesial temporal sclerosis, cortical dysplasia, and hypothalamic hamartoma.

Wu (2019) published the results of a multicenter, retrospective cohort study of 234 patients with drug-resistant mTLE who underwent LITT between 2011 and 2017.^[35] At both one and two years after LITT, 58% of patients achieved Engel I outcomes. Engel I outcomes were associated with ablations involving more anterior, medial, and inferior temporal lobe structures, which tended to involve greater amygdalar volume. Presence or absence of hippocampal sclerosis did not have a significant effect on seizure outcomes. Overall, Engel I or II outcomes were achieved by 76.9% patients at the time of last follow-up. A total of 42 complications were observed in 35 patients, of which 34 persisted at last follow-up.

Section Summary: Drug-Resistant Epilepsy

The evidence for the use of LITT in drug-resistant epilepsy includes several large systematic reviews ($n>500$ patients treated with LITT) and meta-analyses, nonrandomized comparative studies, and single-arm studies. Meta-analyses have reported seizure freedom rates ranging from 50 to 61% and six months postoperatively, Engel I outcomes have been observed between 52% to 80%. Nonrandomized studies comparing outcomes following LITT to open resection or radiofrequency ablation have reported comparable outcomes in patients with drug-refractory mTLE. A subsequent meta-analysis concluded that while there is no evidence to suggest LITT is less effective than open surgical resection in the short term, long-term data are lacking. Total quality of life scores reported in the ongoing LAANTERN registry study increased by 72.4%, however this change did not reach statistical significance ($p=0.2173$).

PRACTICE GUIDELINE SUMMARY

AMERICAN ASSOCIATION OF NEUROLOGICAL SURGEONS

In September 2021, the American Association of Neurological Surgeons (AANS) and

Congress of Neurological Surgeons (CNS) Joint Section on Tumors issued a position statement regarding the use of LITT for brain tumors and radiation necrosis.^[36] The statement concludes that "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 [newly diagnosed glioblastoma multiforme (GBM), recurrent GBM, and primary or recurrent brain metastases.] 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."

AMERICAN SOCIETY OF SURGICAL ONCOLOGY, SOCIETY FOR NEURO-ONCOLOGY, AND AMERICAN SOCIETY FOR RADIATION ONCOLOGY

In 2021, the American Society of Clinical Oncology (ASCO) issued a joint evidence-based guideline on the treatment of brain metastases with the Society for Neuro-Oncology (SNO) and the American Society for Radiation Oncology (ASTRO).^[37] The guideline stated that "no recommendation can be made for or against laser interstitial thermal therapy (Type: informal consensus; Evidence quality: low; Strength of recommendation: none)."

AMERICAN SOCIETY FOR STEREOTACTIC AND FUNCTIONAL NEUROSURGERY

In September 2021, the American Society for Stereotactic and Functional Neurosurgery (ASSFN) issued a position statement on the use of LITT in drug-resistant epilepsy.^[38] The statement recommends consideration of MRgLITT as a treatment option when all of the following criteria are met:

- "Failure to respond to, or intolerance of, at least 2 appropriately chosen medications at appropriate doses for disabling, localization-related epilepsy AND
- Well-defined epileptogenic foci or critical pathways of seizure propagation accessible by MRgLITT."

CONGRESS OF NEUROLOGICAL SURGEONS

The Congress of Neurological Surgeons (CNS) guidelines for the treatment of adults with metastatic brain tumors (2019) state that "there is insufficient evidence to make a recommendation regarding the routine use of laser interstitial thermal therapy (LITT), aside from use as part of approved clinical trials."^[39]

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for central nervous system cancers (v.1.2023) states that MRgLITT "may be considered for patients who are poor surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases, radiation necrosis, and recurrent glioblastoma." (Category 2B)^[40]

SUMMARY

Studies comparing laser interstitial thermal therapy (LITT) to open resection or

radiofrequency ablation have found comparable outcomes in the treatment of drug-resistant epilepsy. In addition, there is evidence that this treatment approach may be associated with fewer major complications and improved cognitive outcomes than open approaches. Evidence-based clinical practice guidelines recommend LITT for the treatment of drug-resistant epilepsy when criteria are met. Therefore, LITT for the treatment of drug-resistant epilepsy may be considered medically necessary when there is documentation of disabling seizures despite use of two or more antiepileptic drug regimens (i.e., medically refractory epilepsy) and there is a well-defined epileptogenic focus of seizure propagation in the temporal lobe or hypothalamus. The evidence for the use of LITT for all other neurological indications is limited by retrospective designs, small sample sizes, and population heterogeneity. In addition, neurological deficits attributable to LITT-induced thermal damage have been observed despite concurrent MRI guidance. The evidence is insufficient to determine that the use of LITT results in an improvement in the net health outcome for these patients. Therefore, LITT is considered investigational for all other neurological indications, including but not limited to treatment of primary or metastatic brain tumors or radiation necrosis.

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CODES

Codes	Number	Description
CPT	61736	Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; single trajectory for 1 simple lesion
	61737	Laser interstitial thermal therapy (LITT) of lesion, intracranial, including burr hole(s), with magnetic resonance imaging guidance, when performed; multiple trajectories for multiple or complex lesion(s)
	64999	Unlisted procedure, nervous system
HCPCS	None	

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