Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Laser Interstitial Thermal Therapy for Neurological Conditions

Description/Background

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 achieved via DNA damage, necrosis, protein denaturation, membrane dissolution, vessel sclerosis, and coagulative necrosis.[1] The goal of therapy is selective thermal injury with 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 requires 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™ MRI-guided Laser Ablation System (Medtronic; formerly Biotex, Inc.) received initial marketing clearance by the U.S. Food and Drug Administration (FDA) through the 510(k) pathway (K071328). 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.

Medical Policy Statement

Laser interstitial thermal therapy is considered **established** for the treatment of epilepsy, radiation necrosis, glioblastomas and relapsed brain metastases, in individuals who meet the selection criteria.

Laser interstitial thermal therapy is considered **experimental/investigational** for all other neurological conditions.

Inclusionary and Exclusionary Guidelines

Inclusions:
Laser interstitial thermal therapy (LITT) is considered established in the treatment of refractory epilepsy when all of the following criteria are met:

- There is documentation of disabling seizures* despite use of 2 or more antiepileptic drug regimens** (i.e., medication-refractory epilepsy), AND
- There are well-defined epileptogenic foci accessible by LITT, AND
- A multidisciplinary team of physicians that includes at least 2 specialties (e.g., neurology, neurosurgery), after considering all possible treatments, agrees that LITT is the best treatment option for the patient.

*NOTE: disabling seizures can be defined as seizures that result in impairment or a loss of functional status.

**NOTE: antiepileptic drug regimens are defined as 2 tolerated and appropriately chosen and used antiepileptic drug schedules (as monotherapies or in combination) to achieve sustained seizure freedom.[17]
***NOTE: LITT should be performed by a neurosurgeon who has completed procedure-specific training in the use of a Food and Drug Administration (FDA) approved LITT ablation system and who has been granted hospital privileges to perform brain tumor surgery and LITT ablation procedures.[44]

1. Laser interstitial thermal therapy (LITT) is considered established for individuals who are poor candidates for craniotomy or resection when the following criteria are met:
   - Relapsed brain metastases, or
   - Radiation necrosis, or
   - Glioblastomas, AND

2. The treatment plan to use LITT has been agreed upon by a multidisciplinary team of physicians to include at least 2 specialists (e.g., neurosurgery, oncology) and after considering all relevant possible treatment approaches, is determined to be the best treatment option.

Exclusions:
Laser interstitial thermal therapy for epilepsy radiation necrosis, glioblastomas and relapsed brain metastases that does not meet the above criteria.

Laser interstitial thermal therapy is considered experimental/investigational for all other neurological conditions.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

61736 61737

Other codes (investigational, not medically necessary, etc.):

NA

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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 (RCT) 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 magnetic resonance (MR)-guided laser interstitial thermal therapy (LITT) 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.

The following PICO was used to select literature to inform this review.

Populations

The population of interest is individuals with primary or metastatic brain tumors that are inaccessible surgically or located in proximity to eloquent or radiosensitive areas. LITT is typically used when surgery is contraindicated due to a high risk of procedural morbidity and/or presence of comorbidities that preclude candidacy for open surgery. LITT may be preferred by individuals desiring a less invasive surgical alternative and its use has been explored in first-line, adjunct, and salvage settings.

Primary intracranial malignant tumors include gliomas, astrocytomas, malignant meningiomas, and primitive neuroectodermal tumors (ie, medulloblastoma, pineoblastoma). Treatment of primary brain tumors such as gliomas is more challenging, due to their generally larger size and infiltrative borders.

Intracranial metastases tend to have a smaller spherical size and noninfiltrative borders. Brain metastases occur frequently, seen in 25 to 30% of all individuals with cancer, particularly in those with cancer of the lung, breast, colon, kidney, and melanoma.

Interventions

The therapy being considered is laser interstitial thermal therapy (LITT), also known as stereotactic laser ablation. LITT is performed under real-time magnetic resonance imaging (MRI) guidance.

Comparators
The following therapies are currently being used to treat primary and/or metastatic brain tumors in select treatment settings: open surgical resection (e.g., craniotomy), stereotactic radiosurgery (SRS), radiotherapy (including whole-brain radiotherapy [WBRT]), and systemic therapies (e.g.,chemotherapy).

Outcomes
Primary outcomes of interest are overall survival (OS) and progression-free survival (PFS). Additional outcomes include local disease control, symptom improvement, functional outcomes, change in disease status, quality of life, and treatment-related morbidity. Follow-up duration of at least 2 to 3 years is of interest for survival outcomes in individuals with low-grade tumors. For individuals with tumors associated with a poor prognosis (e.g., recurrent glioblastoma), shorter follow-up durations may be appropriate.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with the 'best available evidence approach', within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews
Systematic review characteristics and survival outcomes are summarized in Table 1.

Pandey et al (2024) conducted a meta-analysis of 22 studies (N=206) that reported use of LITT for primary brain tumors (glioblastoma [n=185] and *IDH*-mutated astrocytoma [n=21]).[4,] Among patients with glioblastoma, OS was 9.3 months (range, 7.1 to 11.4 months) and PFS was 4.8 months (range, 2.0 to 7.9 months). Neurologic complications occurred in 10.3% and non-neurologic complications occurred in 4.8% of patients with glioblastoma. Among patients with astrocytoma, OS and PFS could not be determined due to a lack of data. Neurologic complications occurred in 33% and non-neurologic complications occurred in 8.3% of patients with astrocytoma.

Zhao et al (2024) performed a systematic review and meta-analysis of 8 studies (N=128) in patients with recurrent glioblastoma multiforme (rGBM).[5,] At 6 months, PFS was 25% (95% CI, 15% to 37%; I^2=53%) and OS was 92% (95% CI, 83% to 100%; I^2=0%). At 12 months, PFS was 9% (95% CI, 4% to 15%; I^2=24%) and OS was 42% (95% CI, 13% to 73%; I^2=67%). Complication rates were low overall, and most complications were mild to moderate in severity.

Alkazemi et al (2023)[6] 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 in patients with inaccessible or deep tumors (n=12), after failed radiosurgery (n=9), or were nonspecific (n=12). One-year 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 OS was 43.0% (95% CI, 36.0%-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=not applicable) in low-grade gliomas, and 56.3% (95% CI, 47.0% to 65.3%; I^2=not applicable) in brain metastases. Major procedure-related adverse events (AEs) were 30% (95% CI, 27% to 40%) with a 16% incidence (95% CI, 12% to 22%) of major or minor neurological deficits.

Chen et al (2021)[7] 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 SRS. 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=.048) and pooled OS of 17.15 months (95% CI, 13.27 to 24.8). Among 153 recurrent brain metastatic lesions across 5 studies, the 12-month local control rate was 59.9% (95% CI, 47.9% to 70.9%). Among 75 radiation necrosis lesions across 4 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 OS at 1 year was determined between the radiation necrosis and brain metastasis groups (66.5% vs. 66.8%; p=.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 OS 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.

de Franca et al (2020)[8] published a systematic review and meta-analysis of LITT as a therapy for brain tumors compared to SRS based on 25 studies. Patient populations included patients with brain metastasis and (rGBM). A significant improvement in median OS was observed in patients treated with LITT compared to SRS among patients with brain metastasis (12.8 vs. 9.8 months; p<.02) and was associated with a 15% reduction in risk of AEs overall. The authors concluded that "there is no evidence that LITT can be used as a treatment of choice when compared to SRS," but use of LITT may have a role in lowering the risk of AEs. The analysis was limited by inclusion of heterogeneous populations, the small number of patients treated with LITT (n=39), and a lack of reporting on prior treatments. In particular, patients treated with SRS varied in their degree of radiosensitivity and prior radiation exposure, which may have influenced the higher rate of AEs observed in this group.

Barnett et al (2016)[9] conducted a systematic review and meta-analysis comparing LITT (8 studies; 77 patients) to open craniotomy (12 studies; 1036 patients) for the treatment of high-grade gliomas in or near areas of eloquence, with a focus on AEs. 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.

Table 1. Systematic Review and Meta-Analysis Characteristics and Results

Study	Dates	Studies	Participants	N (Range)	Design	Duration	Survival Outcomes
Pandey et al (2024)[4]	To 2023	22	Patients with primary brain tumors (glioblastoma or IDH-mutated astrocytoma)	206 (2 to 29)	Noncomparative studies	NR	OS: Glioblastoma: 9.3 months (range, 7.1 to 11.4 months) Astrocytoma: NR
Zhao et al (2024)[5]	2001-2022	8	Patients with rGBM treated with LITT	128 (3 to 60)	Noncomparative studies	At least 6 to 12 mo	OS at 6 mo: 92% (95% CI, 83% to 100%; I^2=0%) OS at 12 mo: 42% (95% CI, 13% to 73%; I^2=67%)
Alkazemi et al (2023)[6]	To Oct 2021	45	Patients with primary or metastatic brain tumors undergoing LITT	826 (2 to 91)	RCTs; retrospective and prospective observational studies; case series	NR	OS at 1 year: 43.0% (95% CI, 36.0% to 50.0%; I^2=7.6%; p=.37; 12 studies) for high-grade glioma; 56.3% (95% CI, 47.0% to 65.3%; I^2=NA; p=.7; 5 studies) for metastatic brain tumors
Chen et al (2021)[7]	2011-2020	14	Patients treated with LITT for BM with in-field recurrence or radiation necrosis following treatment with SRS • Median age, 59.6 y (range, 23 to 90) • Male, 34.5% • Median KPS, 85 (range, 50 to 100) • Median pre-operative lesion volume, • 4.6 cm^3 (range, 0.2 to 38.9) • Radiation necrosis, 168/470 (35.7%)	470 (7 to 92)	Phase I-II nonrandomized; Prospective registry; Retrospective case-control; Retrospective case series	At least 6 to 12 mo	OS at 6 mo: 76.0% (95% CI, 1.4% to 80.0%; I^2=43.81%; p=.059) OS at 12 mo: 63.4% (95% CI, 52.9% to 72.7%; I^2=68.2%; p=.001)
de Franca et al (2020)[8]	2007-2017	25	Patients with BM or GBM treated with LITT or SRS • Mean age, 55.8 to 59.4 y • Median Karnofsky score, 70 to 87.5 • Mean tumor volume, 6.8 to 20.1 cm^3	BM: 12 (LITT); 1555 (SRS) rGBM: 27 (LITT); 232 (SRS)	Randomized controlled study (SRS); Prospective cohort studies; Retrospective studies	NR	Median OS: LITT: • BM: 12.8 mo • (range, 9.3 to • 16.3) • rGBM: 10.5 • (NA)[1] SRS: • BM: 9.8 mo (range, 8.3 to 9.9) • rGBM: 10.5 mo (range, 9.9 to 11.4)

Barnett et al (2016)[9]	1992-2014	20	Patients with recurrent or primary high-grade gliomas (WHO grade III or IV) in or near areas of eloquence treated with LITT or craniotomy, respectively • Mean age, 54.3 vs 45.6 (p<.00001) • Male, 64.2% vs 58.8% (p=.37) • Karnofsky score, 73.4 vs 78.4 (p=.0006) • Recurrent glioma, 68% vs 22% (p<.00001)	LITT: 67 Craniotomy: 522	Prospective cohort studies; Retrospective studies	NR	NR

BM: brain metastasis; CI: confidence interval; KPS: Karnofsky Performance Status; LITT: laser interstitial thermal therapy; NR: not reported; OS: overall survival; rGBM: recurrent glioblastoma multiforme; RCTs: randomized controlled trials; SRS: stereotactic radiosurgery; WHO: World Health Organization.
[1] Only 1 study result reported.

Comparative Observational Studies

Grabowski et al (2022)[10] published a multicenter, retrospective study of patients undergoing treatment for biopsy-proven brain metastasis recurrence after stereotactic radiotherapy (SRT). Patients were stratified into three groups: planned LITT plus SRT (n=21), LITT along (n=25), or repeat SRT along (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 along (p=.05 and .01, respectively). Median time to index lesion progression for LITT plus SRT, LITT alone, and repeat SRT alone was 29.8, 7.5, 3.7 months, respectively (p=.022). A univariate analysis found a significantly increased risk of tumor progression among patients receiving prior surgery (hazard ratio [HR], 5.33; 95% CI, 1.41 to 16.93; p=.007). The authors noted that future prospective studies are required to validate these findings.

Fadel et all (2022)[11] retrospectively reviewing an institutional database to identify patients with unifocal, lobar, surgically accessible recurrent glioblastoma who were treated with LITT or resection between 2013 and 2020. 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 cm^3 vs. 7.54 cm^3 ; p=.017). Overall survival (14.1 vs. 13.8 months; p=.578) and PFS (3.7 vs. 3.3 months; p=.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=.004).

Mohammadi et al (2019) conducted a multicenter retrospective review of survival outcomes in patients with deep seated newly diagnosed glioblastoma treated with upfront MR-guided LITT prior to chemo/radiotherapy (n=24; median age, 54 years; 50% male; 71% <70 years) compared to a matched cohort of biopsy-only patients (n=24; median age, 64 years; 58% male; 75% <70 years).[12] Patients were matched based on age, gender, tumor location (deep vs. 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 OS and PFS 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 years and tumor volume <11 cm3 were identified as favorable prognostic factors for OS. 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

Kaisman-Elbaz et al (2022)[13] Investigated the impact of the extent of ablation on the survival of patients with newly diagnosed glioblastoma treated with laser interstitial thermal therapy (LITT), analyzed a larger single-institutional cohort and found the extent of ablation significantly influenced patient survival. The findings suggest that maximizing the extent of ablation may improve survival outcomes for patients with glioblastoma undergoing LITT treatment.

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 et al (2020) reported procedural safety outcomes for the first 100 patients enrolled in the LAANTERN registry[14] The Laser Ablation of Abnormal Neurological Tissue using Robotic NeuroBlate System (LAANTERN) trial is an ongoing multicenter, non-randomized, prospective NeuroBlate LITT study. Several studies from the LANTERN trial have been published:

Kim et al (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.[15] Results from the ongoing LAANTERN registry demonstrate that LITT stabilizes and improves QoL from baseline levels in a malignant brain tumor patient population with high rates of comorbidities. Overall survival was better than anticipated for a real-world registry and comparative to published literature.

de Groot (2022)[52] studies revealed the median overall survival (OS) was 9.73 months for newly diagnosed patients and median post-procedure survival was 8.97 months for recurrent patients. Factors associated with improved survival were methylguanine-DNA methyltransferase (MGMT) promoter methylation, adjuvant chemotherapy within 12 weeks, and tumor volume <3 cc. The authors concluded that LITT offers an effective cytoreductive approach for patients with newly diagnosed and recurrent *IDH* wild-type glioblastoma. The authors stated its use in newly diagnosed patients who are followed by post-LITT chemoradiotherapy produces a median OS similar to that of patients treated with conventional surgical resection, thus making LITT a viable alternative in patients with inoperable tumors or those not amenable to resection.[15] The majority of patents with primary tumors had high-grade glioma (n=90) and patients with metastatic disease had recurrent tumors (n=43) or radionecrosis (n=34). The 1-yr estimated OS 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. In 2022, de Groot and colleagues published a subgroup analysis of LAANTERN registry data focusing on new (n=29) and recurrent (n=60) cases of IDH wild-type glioblastoma.[13] Median OS was 9.73 months (95% CI, 5.16 to 15.91) for newly diagnosed individuals and 8.97 months (95% CI, 6.94 to 12.36) for recurrent individuals. Median OS in

newly diagnosed individuals receiving post-LITT chemo/radiation was 16.14 months (95% CI, 6.11 to not reached).

Chan et al. (2023)[18] conducted a sub-study of 90 patients with one or more radiographically progressive brain metastasis with biopsy-proven radiation necrosis (RN) at time of LITT procedure, without evidence of tumor recurrence on pathology. LITT for radiation necrosis was not only again found to be safe and effective with low patient morbidity but was also a highly effective treatment for RN for both local control and symptom management (including seizures). In addition to averting expected neurological death, LITT facilitates ongoing systemic therapy (in particular immunotherapy) by enabling the rapid cessation of steroids, therapy by facilitating maximal possible survival of these patients.

Srinivasan et al. (2021)[19] summarized that laser interstitial thermal therapy (LITT) is a minimally invasive treatment for intracranial lesions entailing thermal ablation via a stereotactically placed laser probe. In metastatic disease, it has shown the most promise in the treatment of radiographically progressive lesions after initial stereotactic radiosurgery, whether due to recurrent metastatic disease or radiation necrosis. LITT has been demonstrated to provide clinical benefit in both cases, as discussed in the review below. With its minimal surgical footprint and short recovery period, LITT further provides advantages for patients who are otherwise high-risk surgical candidates or with lesions in difficult to access locations. Exploration of the current data on its use in metastatic disease will allow for a better understanding of the indications, benefits, and future directions of LITT for these patients Existing Studies Don the Use of Laser Interstitial Thermal Therapy (LITT) for Radiographically Progressive Metastatic Lesions After Stereotactic Radiosurgery.

Section Summary: Primary or Metastatic Brain Tumors
Evidence for the use of LITT in primary or metastatic brain tumors includes systematic reviews, meta-analyses and several nonrandomized comparative and single-arm studies. Overall survival estimates have ranged from 9.0 to 14.4 months in new or recurrent glioblastoma. Among with metastatic tumors receiving LITT following prior SRS, OS rates have ranged between 72% to 76% at 6 months and 63% to 65% at 12 months. In a more heterogenous 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 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 well-controlled patient populations are required to assess net health outcomes and have shown utility to support LITT for metastatic brain tumors.

Radiation Necrosis

Clinical Context and Therapy Purpose
The purpose of LITT is to use a focused thermal therapy technique to ablate regions of cerebral radiation necrosis in symptomatic individuals with an insufficient or intolerable response to medications, and to potentially avoid complications associated with alternative surgical interventions.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with symptomatic cranial radiation necrosis with insufficient response or intolerance to medication management. LITT is typically used when open surgery is contraindicated due to high risk of procedural morbidity and/or presence of comorbidities that precludes candidacy for open surgery.

Treatment-induced brain tissue necrosis (also referred to as cranial radiation necrosis or radionecrosis) is a serious delayed complication of cranial irradiation that typically develops after 1 to 3 years. Radiation necrosis is more likely to occur with high-dose fractionation and potentially with concurrent chemotherapy or use of radiosensitizers. The risk of radiation necrosis following SRS has been reported to be higher, with a steep dose-response relationship. Differentiating radiation necrosis from recurrent brain tumors via imaging can be difficult, as conventional structural MRI may reveal features that overlap with the typical radiographic appearance of high-grade primary or metastatic brain tumors. Biopsy may be required for a definitive diagnosis of radiation necrosis, particularly among individuals who are symptomatic or with worsening radiographic findings over time.

Symptoms of radiation necrosis are dependent on the location of the lesion and may include focal neurologic deficits or more generalized signs and symptoms of increased intracranial pressure. Seizures are observed in approximately 20% of individuals.

Interventions
The therapy being considered is LITT as an alternative to open craniotomy with resection and/or medication management. LITT is performed under real-time MRI guidance.

Comparators
The following therapies are currently being used to treat primary and metastatic brain tumors: surgical resection and medication management. Medications used in the management of radiation necrosis include corticosteroids and bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor.

Outcomes
Outcomes of interest are symptom improvement, medication use, quality of life, treatment-related morbidity, OS, and PFS. Follow-up duration of at least 2 to 3 years is of interest for survival outcomes.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Gecici et al (2024) conducted a systematic review and meta-analysis of 24 studies (N=547) that compared bevacizumab and LITT in patients with radiation necrosis.[16] Most of the included studies were retrospective. Symptomatic improvement or stability occurred in 87.7% and 71.2% of patients, respectively (p=.02). Radiologic improvement or stability occurred in 86.2% and 64.7%, respectively (p=.27). Steroid discontinuation occurred in 45% and 62.4%, respectively (p=.90). Heterogeneity for all comparisons was high (I^2>70%). Adverse event rates were similar between groups (11.2% vs. 14.9%; p=.66).

Vellayappan et al (2024) conducted a systematic review of treatments for radiation necrosis in patients who had previously undergone SRS.[17] The review was conducted on behalf of the International Stereotactic Radiosurgery Society. Of the 21 included studies, only 5 included LITT (n=151); one LITT study was prospective and the rest were retrospective. The pooled radiologic improvement/stability rate was 88% (95% CI, 82% to 93%) with LITT compared to 94% with bevacizumab. Symptom improvement was only reported in 2 studies and could not be pooled for analysis. Toxicity results were not consistently reported and no conclusions could be made. The authors concluded that the role of LITT is evolving and that prospective comparative studies are needed.

The meta-analysis published by Chen and coworkers (2021), described previously in Table 1, included 168 (35.7%) patients with radiation necrosis who received LITT following prior treatment with SRS.[7] The local control rate for patients with radiation necrosis 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. Overall survival was 83.1% versus 69.2% at 6 months and 66.8% versus 66.5% at 12 months for radiation necrosis and recurrent brain metastasis groups, respectively. Pre-ablation biopsy, which can accurately diagnose radiation necrosis, 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 radiation necrosis from brain metastases based on radiographic evidence alone.

Palmisciano et al (2021)[20] published a systemic review and meta-analysis of bevacizumab versus LITT for the treatment of radiation necrosis patients with brain metastases previously treated with radiotherapy. Eighteen studies were included for analysis, including 143 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=187; I^2=54.8% and p=.614; I^2=25.5%, respectively). At 18 months, median OS was significantly higher for patients treated with LITT (46.4% vs. 25%; p=.038, I^2=73.7%). Rates of AEs 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 et al (2022)[21] published a multicenter, retrospective study of SRS-treated patients with brain metastases who developed biopsy-proven radiation necrosis who were treated with LITT (n=57) or medical management (n=15). 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=.60) or freedom from local progression (13.6 vs. 7.06 months; p=.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<.001). The authors note that prospective trails should be designed to validate the utility of LITT for radiation necrosis, including its impact on reducing steroid-induced morbidity.

Sujijantarat et al (2020)[22] conducted a retrospective chart review comparing outcomes for patients with biopsy-confirmed radiation necrosis treated with LITT (n=25) or bevacizumab (n=13) at a single center between 2011 and 2018. The LITT group had a significantly longer OS compared to bevacizumab (median 24.8 vs. 15.2 months; p=.003). Time to local recurrence was not statistically significant between groups (p=.091) but trended longer in the LITT cohort. Among 13 patients with pretreatment symptoms in the LITT group, 9 (69%) achieved symptom relief. Among 11 patients with pre-treatment symptoms in the bevacizumab group, 4 (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 samples size, and population heterogeneity.

Hong et al (2019)[23] 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 radiation necrosis. Among the 33 radiation necrosis 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 radiation necrosis was 73.2% and 86.7% at 24 months for patients treated with LITT and craniotomy, respectively. Overall survival for patients with radiation necrosis 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.

Ashraf et al. (2018)[24] The study provides a comprehensive review of laser-induced thermal (LITT) in neuro-oncology, it discusses the application of LITT in treating various neuro-oncological conditions and examines its efficacy, safety , and potential complications. The review aims to provide insights into the current state of LITT in neuro-oncology and its role in improving patient outcomes.

Single-Arm Studies

The LAASR study, described previously [Ahluwalia et al (2019)],[25] included 19 patients with biopsy-confirmed radiation necrosis who received LITT following prior treatment with SRS for brain tumors. Progression-free survival and OS were 100% and 91%, respectively, at 12

weeks, and 100% and 82.1%, respectively, at 26 weeks. Progression-free survival was significantly higher at 12 weeks for patients with radiation necrosis compared to patients with recurrent tumors (p=.016) but was not significantly different at 12 weeks (p=.166). Similar trends were seen for OS in patients with radiation necrosis at 12 weeks (p=.02) and 26 weeks (p=.09). Thirty percent of subjects were able to stop or reduce steroid usage by 12 weeks after surgery. For patients with radiation necrosis, regardless of whether a lesion was totally, or sub totally ablated, LITT resulted in close to 100% lesion control and >80% survival at 6 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 meta-analyses, nonrandomized comparative studies, and a 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 report significant survival differences between groups. Studies are supported by retrospective designs, large sample sizes, population heterogeneity, and clear relevance, as symptomatic status is consistently reported.

DRUG-RESISTANT EPILEPSY

Clinical Context and Therapy Purpose
The purpose of LITT is to use a focused thermal therapy technique to ablate epileptogenic foci when seizures have become drug-resistant or medication-related adverse events are intolerable, and to potentially avoid complications associated with alternative surgical interventions.

The following PICO was used to select literature to inform this review.

Populations
The population of interest is individuals with drug-resistant or medication-intolerant epilepsy, defined as failure to achieve sustained seizure freedom despite adequate trials of 2 or more appropriately chosen and tolerated antiseizure medications, as specified by the International League Against Epilepsy (ILAE) Commission on Therapeutic Strategies consensus definition for drug resistant epilepsy.[23]

Epilepsy is diagnosed when an individual has unprovoked seizures. Primary seizure disorders include multiple subtypes that are recognizable by the degree and type of impairment of consciousness and motor capacity. Seizure disorders may be secondary to brain tumors or other space-occupying intracranial lesions such as congenital malformations, stroke, genetic syndromes, brain trauma, and cerebral infections. Mesial temporal lobe epilepsy (mTLE), also known as complex partial seizures, is a focal epilepsy syndrome. The epileptogenic foci may present in the hippocampus, amygdala, or parahippocampal gyrus. The most common non-traumatic or noninfectious etiology of mTLE is hippocampal sclerosis. The associated neuronal loss is a partial explanation for the difficulties in achieving satisfactory seizure control with antiepileptic medication. Approximately one-third of patients with epilepsy do not achieve adequate seizure control with antiepileptic drugs.

Patients with an identifiable seizure focus that can be targeted to achieve seizure freedom are primary candidates for epilepsy surgery, but individuals with multifocal or generalized epilepsy may also be considered.

Interventions
The therapy being considered is LITT as an alternative to open craniotomy with resection, SRS, or neurostimulation. LITT is performed under real-time MRI guidance.

Comparators
The following therapies are currently being used to treat medication-refractory epilepsy: open craniotomy with resection, SRS, vagus nerve stimulation, and responsive cortical neurostimulation. Surgical treatment may be considered in instances where seizures have proven refractory to medical management and when the frequency and severity of the seizures significantly diminish quality of life.

Outcomes
Outcomes of interest are symptom improvement, change in disease status, quality of life, hospitalizations, medication use, treatment-related morbidity, and disease-specific survival. Key outcome measures are summarized in Table 2.

Table 2. Epilepsy Outcome Measures

Outcome Domain	Outcome Measures
Symptom Improvement	Change in seizure frequency (>50% reduction considered clinically meaningful)
Change in Disease Status	Time to cessation of seizures; Postoperative outcome status, as measured by the **Engel classification**:[24] Class I: Free of disabling seizures Class IA: Completely seizure free since surgery Class II: Rare disabling seizures Class III: Worthwhile improvement Class IV: No worthwhile improvement
Quality of Life	QOLIE-89 or QOLIE-31 multi-scale questionnaires (higher scores indicate improved health outcomes); eligibility to drive
Treatment-related Morbidity	Neuropsychological and neurocognitive testing
Disease-specific Survival	Incidence of SUDEP

QOLIE: Quality of Life in Epilepsy questionnaire; SUDEP: sudden unexpected death in epilepsy.

Follow-up duration of at least 2 years is of interest to evaluate the effect of the procedure when compared to resection or neurostimulation. Rarely, a transient increase in seizure frequency and severity may be observed following surgical interventions. Therefore, time to cessation of seizures and proportion of patients with increased seizure frequency represent additional outcomes of interest.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Ekman et al (2024) performed a systematic review and meta-analysis of MR-guided LITT compared to temporal lobe resection in patients with drug-resistant mTLE.[29] Only cohort studies with a follow-up of at least 24 months were considered for inclusion (randomized trials were excluded). Of the 55 studies in the review, 14 studies assessed MR-guided LITT (n=534) and 41 studies assessed temporal lobe resection (n=4606). The primary outcome (seizure freedom, defined as the proportion of patients achieving Engel I status) was reported in 6 of the MR-guided LITT studies. A random effects model found that the proportion of patients with seizure freedom after MR-guided LITT was 57.1% (95% CI, 51.2% to 62.7%) versus 72.5% (95% CI, 65.6% to 78.5%) after temporal lobe resection (p<.01). The overall rate of complications was 6.5% (95% CI, 3.3% to 12.3%) after MR-guided LITT and 11.4% (95% CI, 7.4% to 17.2%) after temporal lobe resection (p=.15). There was no difference in major complications (2.7% vs. 2.0%, respectively; p=.54) but minor complications were more common with temporal lobe resection (9.9%) than with MR-guided LITT (4.1%; p=.04).

Hect et al (2023) conducted a systematic review of MR-guided LITT corpus callosum ablation for drug-resistant epilepsy.[30] Sixteen observational reports were included (N=85 patients). Seizure freedom at 6 months was evaluated in 53 patients and occurred at a rate of 18.87%. The rate of freedom from atonic seizures postoperatively was 46.28%. Overall, the rate in average number of seizures per day decreased by 80.12%. The complication rate was 12.94% and permanent neurologic deficits occurred in 4.71% of patients. The authors concluded that most patients experienced a meaningful decrease in seizure frequency and that LITT acceptable rate of complications.

Reese et al (2023)[26] A retrospective review of a multi-institution database was used to identify patients who underwent LITT between 2013-2022 for tumors located within the insula, thalamus, basal ganglia, and anterior perforated substance. The study investigated the association between laser interstitial thermal therapy (LITT) for deep-seated perivascular brain tumors and distal ischemia. It specifically examines whether LITT is linked to ischemic events in areas remote from the treated site. The findings suggest that LITT for such tumors is not associated with distal ischemia, providing valuable insights into the safety and efficacy of this treatment approach.

Barot et al (2022) published a systematic review and meta-analysis of LITT treatment outcomes among individuals with drug-resistant epilepsy of varying etiologies.[31] Twenty-eight studies representing 559 individuals were identified. The overall prevalence of Engel class I outcomes was 56% (95% CI, 52% to 61%). Highest seizure freedom rates were observed among individuals with hypothalamic hamartomas (67%; 95% CI, 57% to 76%). Comparable seizure freedom rates were observed between individuals with mTLE (56%; 95% CI, 50% to 61%) and extratemporal epilepsy (50%;95% CI, 40% to 59%). The overall rate of AEs was 19% (95% CI, 0.14% to 25%), of which visual field defects were most common.

Marathe et al (2021) conducted a systematic review and meta-analysis comparing open surgical resection, SRS, LITT, and radiofrequency ablation in drug-resistant mTLE.[32] Forty-

one publications were included in the analysis, including 19 studies on open surgery. 11 on LITT, 4 on radiofrequency, and 7 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 selective amygdalohippocampectomy (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(RFA). 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 et al (2021) performed a systematic review and meta-analysis to compare outcomes and complications from MR-guided LITT, (RFA), and conventional open surgery (ie, ATL or [sAHE]) in patients with drug-refractory (mTLE).[33] Forty-three studies were identified (13 LITT; 6 RFA; 24 conventional surgery) between 1995 and 2018. Meta-analytic estimates for the proportion of patients achieving Engel I outcomes were 34% (95% CI, 15% to 61%), 57% (95% CI, 53% to 61%), 65% (95% CI, 58% to 72%) and 69% (95% CI, 62% to 75%) for RFA, LITT, sAHE, and ATL, respectively. No significant difference in outcome was noted between LITT and RFA (p=.098), whereas significantly better outcomes were observed following conventional surgery with both sAHE (p=.0247) and ATL (p=.0113) compared to LITT. In a subgroup analysis of patients with follow-up duration ≥60 months, both ATL (p=.009) and sAHE (p=.043) resulted in significantly higher rates of Engel I outcomes compared to LITT. Among patients treated with LITT, significantly better outcomes were observed in patients with mTLE and hippocampal sclerosis (p=.0035). Overall complication rates were 14.1%, 17.5%, 31.3%, and 18.2% for LITT, RFA, ATL, and sAHE, respectively, with corresponding major complication rates of 3.8%, 3.7%, 10.9%, and 7.4%. However, meta-analysis revealed no significant differences concerning overall and major complication rates between procedures. The authors concluded that overall, patients treated with MR-guided LITT had a lower chance of achieving an Engel I outcome compared to those who received conventional surgery and that the presence of mesial hippocampal sclerosis might be a prognostic factor for a more favorable outcome with LITT.

Brotis et al (2021) conducted a meta-analysis to estimate the efficacy of LITT for mTLE.[34] 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 (interquartile range [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 4 studies including more than 20 patients. The authors concluded that while mTLE respective 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 et al (2019) published a systematic review and meta-analysis comparing MR-guided LITT versus SRS for medically intractable temporal lobe epilepsy (TLE).[35] A total of 19 studies published between 2008 and 2018 representing 404 patients (range, 5 to 58) were identified,

including 9 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=.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=.23). While LITT was associated with a significantly lower procedural complication rate (20% vs. 26%; p=.06), reoperation rates were not significantly different (15% vs. 27%; p=.31). The authors noted that the quality of evidence was low and that large-scale studies directly comparing LITT and SRS are required to validate findings.

Xue et al (2018) reported postoperative outcomes for MR-guided LITT in the treatment of drug-resistant epilepsy.[36] 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).

Hoppe and Helmstaedter (2018) reported postoperative outcomes for pediatric patients aged <18 years treated with LITT for drug-resistant epilepsy.[37] Twenty-five case series representing 179 patients were included in the review, with the majority of cases attributed to hypothalamic hamartomas (64.2%). Among published cases, the overall complication rate was 23.5% with a 3.4% rate of severe complications. Engel I seizure-free outcomes were achieved by 57.5% of patients across studies, including individuals with short follow-up (e.g., 1 month) and repeat treatments. No studies reported on cognitive outcomes on the basis of standardized psychometric measures. Overall, the authors concluded that the published evidence does not yet allow a scientific or clinical judgement on the utility of LITT for pediatric epilepsy surgery.

Comparative Observational Studies

Hale et al (2019) reported postsurgical outcomes in 26 pediatric patients with insular epilepsy treated with LITT (n=14) or open resection (n=12).[38] 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 1-year post-surgery. Postoperative complications occurred in 6 patients treated with LITT and 7 patients treated with resection, all of which resolved within 3 to 4 months. The authors concluded 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 et al (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.[39] 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 vs. 3.43 days; p=.0002). Patients treated with resection were significantly younger, with a mean age of 35.4 years (p=.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=.21). For nonlesional patients,

LITT treatment trended towards a better outcome, but did not achieve statistical significance (p=.05). Study interpretation is limited by the small sample size, retrospective analysis, and population heterogeneity.

Single-Arm Studies

Esmaeili et al (2023)[40] conducted a prospective observational study of consecutive LITT-treated patients with drug-resistant epilepsy from 2013 to 2021. The primary outcome was sudden unexpected death in epilepsy (SUDEP). There were 4 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 1000 person-years. Among a historical control group, the incidence of SUDEP was estimated to be 2 per 1000 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=.02) but similar rates compared with those without intervention (p=.55)

Kanner et al (2022)[41] conducted a retrospective review of long-term seizure and psychiatric outcomes among individuals who underwent LITT for drug-resistant mTLE between 2013 and 2019 at a single academic center. Forty-eight individuals (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 1 to 3 seizures per year. The seizure-freedom rate was 77.8% among individuals among individuals with 24-month follow-up which decreased to 50% among individuals 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 orders were identified in 30 (62.5%) of individuals pre-surgery, of which 19 (62%) remitted following LITT.

Landazuri et al (2020)[51] reported 1-year outcomes following LITT of epileptogenic foci with the NeuroBlate system in patients with drug resistant epilepsy enrolled in the previously described LAANTERN registry (see Rennert et al [2020]).[14] Engel Class I outcomes were achieved in 27/42 (64.3%; 95% CI, 48.0% to 78.5%) patients at 1 year. No significant difference was observed in patients with mTLE (70.8%) versus other etiologies. Five adverse events were reported, with 1 categorized as serious. Median baseline Quality of Life in Epilepsy Questionnaire (QOLIE-31) score 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=.2173). Seizure worry and social functioning sub-scores were considered statistically significant (p=.0219 and p=.0175, respectively). The authors noted that the primary success of LITT remains in well localized lesions/localizations, such as those seen in mTLE/mesial temporal sclerosis (MTS), cortical dysplasia, and hypothalamic hamartoma.

Holste et al. (2020)[42] summarized that Laser interstitial thermal therapy (LITT) is becoming an increasingly popular technique for the treatment of brain lesions. More minimally invasive that open craniotomy for lesion resection, LITT may be more appropriate for lesions that are harder to access through an open approach, deeper lesions, and for patients who may not tolerate open surgery. Methods:A search of the current primary literature on LITT for brain lesions on PubMed was performed. These studies were reviewed and updates on the radiological, pathological, and long-term outcomes after LITT for brain metastases, primary brain tumors, and radiation necrosis as well as common complications are included. Results: Larger extent

of ablation and LITT as frontline treatment were potential predictors of favorable progression-free and overall survival for primary brain tumors. In brain metastases, larger extent of ablation was more significantly associated with survival benefit, whereas tumor size was a possible predictor. The most common complications after LITT are transient and permanent weakness, cerebral edema, hemorrhage, seizures, and hyponatremia. Conclusions: Although the current literature is limited by small sample sizes and primarily retrospective studies, LITT is a safe and effective treatment for brain lesions in the correct patient population.

Wu et al (2019)[43] published the results of a multicenter, retrospective cohort study of 234 patients with drug-resistant mTLE who underwent LITT between 2011 and 2017. At both 1 and 2 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% of 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 systematic reviews and meta-analyses, nonrandomized comparative studies, and single-arm studies. Meta-analyses have reported seizure freedom rates ranging from 46% to 61% but are limited by heterogeneous study populations and follow-up durations. Nonrandomized studies comparing LITT to open resection have reported comparable outcomes in individuals with pediatric insular epilepsy and adult TLE. In one meta-analysis comparing LITT to RFA and conventional surgery, superior outcomes were noted with conventional surgery among individuals with 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 increased by 72.4%, but this change was not considered statistically significant (p=.2173). Prospective comparative studies in well-defined and controlled patient populations are required to assess a net health outcome and to identify patients most likely to benefit from LITT.

Summary of Evidence
For individuals who have primary or metastatic brain tumors who receive MR-guided LITT, the evidence includes systematic reviews and meta-analyses, and several nonrandomized comparative and single-arm studies. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Overall survival estimates have ranged from 9.0 to 14.4 months in new or recurrent glioblastoma. Among patients with metastatic tumors receiving LITT following prior SRS, OS rates have ranged between 72% to 76% at 6 months and 63% to 65% at 12 months. In a more heterogenous 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 stereotactic radiosurgery (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 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 well-

controlled patient populations are lacking. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic cranial radiation necrosis who receive MR-guided LITT, the evidence includes meta-analyses nonrandomized comparative studies, and a single-arm study. Relevant outcomes are OS, disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. 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 and one study comparing LITT to medical management did not report significant survival differences between groups. Studies are limited by retrospective designs, small sample sizes, population heterogeneity, and unclear relevance, as symptomatic status and steroid-related morbidity were not consistently reported. Prospective comparative studies in well-defined and well-controlled patient populations are lacking. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have drug-resistant epilepsy who receive MR-guided LITT, the evidence includes systematic reviews and meta-analyses, nonrandomized comparative studies, and single-arm studies. Relevant outcomes are disease-specific survival, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. Meta-analyses have reported seizure freedom rates ranging from 50% to 61% but are limited by heterogeneous study populations and follow-up durations. Studies comparing LITT to open resection have reported comparable outcomes in patients with pediatric insular epilepsy and adult temporal lobe epilepsy (TLE). In one meta-analysis comparing LITT to radiofrequency ablation (RFA) and conventional surgery, superior outcomes were noted with conventional surgery among patients with mTLE. A subsequent meta-analysis 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. Total quality of life scores reported in the ongoing LAANTERN registry increased by 72.4%, but this change was not considered statistically significant. For patients with medically-refractory epilepsy and well-defined lesions, studies suggest treatment with LITT may lead to freedom from seizures without the morbidity of temporal lobe resection. Laser interstitial thermal therapy has been considered as a minimally invasive option to surgical resection in patients with foci inaccessible with conventional surgery and in patients with drug resistant epilepsy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Association of Neurological Surgeons et al
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 laser interstitial thermal therapy (LITT) for brain tumors and radiation necrosis.[44] 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 Clinical Oncology et al
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).[45] 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.[46] The statement recommends consideration of MR-guided LITT (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."[47]

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for central nervous system cancers (v.3.2024) states that magnetic resonance (MR)-guided LITT "may be considered for individuals who are poor surgical candidates (craniotomy or resection). Potential indications include relapsed brain metastases radiation necrosis, glioblastoma." (Category 2B)[48] The guidelines additionally state that LITT “can be considered on a case-by-case basis for treatment of radiation necrosis in patients with a history of radiation therapy for primary brain tumor or metastatic disease. Consultation with adept neurosurgeons trained in LITT should be done when the procedure is considered.”

National Institute for Health and Care Excellence

In 2020, NICE published an interventional procedures guidance on the use of MR-guided LITT for drug-resistant epilepsy.[49] The NICE recommends that LITT should only be used with special arrangements, given serious but well-recognized safety concerns and low quality evidence for efficacy.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

In 1997, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage determination on the use of laser procedures, stating that "in the absence of a specific noncoverage instruction, and where a laser has been approved for marketing by the Food and Drug Administration, Medicare Administrative Contractor discretion may be used to determine whether a procedure performed with a laser is reasonable and necessary, and, therefore, covered."[50]

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT06161610	Randomized Clinical Trial of Efficiency and Safety of Recurrent High-Grade Glioma Treated by Laser Interstitial Thermal Therapy (REGALITT)	135	Sept 2027 (recruiting)
NCT06428045	Synergistic Treatment With Antiretrovirals and Laser Interstitial Thermal thErapy (STARLITE) for Unresectable High-Grade Gliomas: A Phase 1 Study	24	May 2029 (not yet recruiting)
NCT06341075	Real-World Study of Magnetic Resonance-guided Laser Interstitial Thermal Therapy for Patients With Drug-resistant Epilepsy	150	Mar 2026 (enrolling by invitation)
NCT02970448	Expedited Laser Interstitial Thermal Therapy and Chemoradiation for Patients With Newly Diagnosed High Grade Gliomas	45	Jan 2025 (recruiting)
NCT04181684	Pilot Study of Laser Interstitial Thermal Therapy Followed By Hypofractionated Radiation Therapy for Treatment of Recurrent Gliomas (GCCC 19140)	32	Dec 2026 (recruiting)
NCT04699773	Laser Interstitial Thermal Therapy Followed By Hypofractionated Radiation Therapy For Treatment Of Newly Diagnosed High-Grade Gliomas (GCC 20138)	32	Dec 2027 (recruiting)
NCT05124912 [a]	REMASTer: Recurrent Brain Metastases After SRS Trial	261	Oct 2028 (recruiting)
Unpublished			
NCT02844465[a]	Stereotactic Laser Ablation for Temporal Lobe Epilepsy (SLATE)	114 (actual)	Dec 2023

NCT05075850[a]	Patient Neuropsychological Outcomes After Laser Ablation (PENSAR)	250	Sept 2023

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Government Regulations

National:

National Coverage Determination (NCD): Laser Procedures 140.5
Effective Date of this Version: 05/01/1997

Medicare recognizes the use of lasers for many medical indications. Procedures performed with lasers are sometimes used in place of more conventional techniques. In the absence of a specific noncoverage instruction, and where a laser has been approved for marketing by the Food and Drug Administration, Medicare Administrative Contractor discretion may be used to determine whether a procedure performed with a laser is reasonable and necessary and, therefore, covered.

The determination of coverage for a procedure performed using a laser is made on the basis that the use of lasers to alter, revise, or destroy tissue is a surgical procedure. Therefore, coverage of laser procedures is restricted to practitioners with training in the surgical management of the disease or condition being treated.

Local:

There is no local coverage determination on this topic.

The 2025 CMS Physician Fee Schedule has fees listed for codes 61736, 61737.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Intensity Modulated Radiation Therapy (IMRT): Central Nervous System Tumors
Responsive Neurostimulation for the Treatment of Refractory Partial Epilepsy
Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 12/20/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/1/22	2/15/22		Joint policy established
5/1/23	2/21/23		Routine Maintenance (jf) added ref 9, 10,14,17,18,23, 24,32,36,42 Vendor Managed: NA
5/1/24	2/20/24		Routine Maintenance (jf) Vendor Managed: NA Ref Added: 4,11,16,17,22,24, 36,38,47,48 and 49 Edits to Description, MPS, inclusions and exclusions. Added in covering LITT for radiation necrosis, recurrent glioblastoma and relapsed brain metastases. Literature review
5/1/25	2/18/25		Routine Maintenance (jf) Vendor Managed: NA • Removed “and recurrent” in front of glioblastoma and added “s” after glioblastoma. o Edit to the MPS, inclusions and exclusions References added: 4,5,16,17,29,30

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: LASER INTERSTITIAL THERMAL THERAPY FOR NEUROLOGICAL CONDITIONS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered for indication of epilepsy; policy criteria apply. Non-covered for brain tumor.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.