Laser Interstitial Thermal Therapy for Radionecrosis

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KEYWORDS

• Radiation necrosis • LITT • Review • Ablation • Outcome • Safety • Recurrence • Radiotherapy

KEY POINTS

- [For radionecrosis,] laser interstitial thermal therapy (LITT) might be more effective than medical therapy in prolonging survival and may reduce the risk of progression, help taper off steroids, and improve/resolve neurological symptoms.
- Although new imaging modalities exist, radionecrosis remains challenging to diagnose, and although biopsy may help to differentiate lesions it is subject to sampling bias.
- Lesion volume and surrounding edema may increase in the short-/medium-term following LITT, which is not progression but may worsen mass effect: LITT should be used with caution or be avoided in patients with large lesions or acute neurological symptoms.
- Initial increase in edema may require steroid use following LITT, but most patients can be weaned off steroids fast and thus net steroid use is reduced.
- Larger ablation volumes (even supralesional) may improve outcome and should be favored.

INTRODUCTION

Radionecrosis—Background, Definition, Incidence, and Pathophysiology

Brain tumors are usually treated by a combination of surgery, systemic therapy, and radiotherapy, the latter being particularly important in the management of brain metastases. Nowadays, stereotactic radiosurgery is often used as an alternative to whole-brain radiation therapy, in combination with surgery, or as a first-line treatment in nonacute life-threatening oligometastatic disease with lesions under 3 cm.[1] Unfortunately, similar to every treatment option, radiotherapy may cause short- and/or long-term adverse effects. Radiation necrosis (RN) is defined as a severe local tissue reaction occurring at least 3 to 12 months after radiotherapy, with an incidence that varies from 6.5% to 50% according to the modality of radiation, the total dose, the fractionation, the underlying pathology, and diagnostic methodology.[2] This incidence is documented between 14% and 15% for conventional modalities, between 4.7% and 9.2% for stereotactic radiosurgery for brain metastases, and up to 22.6% for large lesions (also stereotactic radiosurgery) or even 50% following brachytherapy.[2] Although the pathophysiology of RN is currently not completely understood, it is believed to be the result of a combination of initial vascular insult and subsequent brain parenchymal injury.[2] Both changes cause endothelial, microglial, neural, and tumoral cell damage, which produces reactive oxygen species and promotes apoptosis, fibrinoid necrosis, blood-brain barrier disruption, cerebral edema, and demyelination.

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Evaluation of Radionecrosis and Challenges

Patients suffering from RN may present with mild-to-severe cognitive and/or neurological deficits, symptoms of increased intracranial pressure, seizures, and rarely cerebral hemorrhage.[2,3] MRI features of RN include an increase in T2- fluid-attenuated inversion recovery (FLAIR) signal corresponding to edema, contrast leakage to surrounding normal brain tissue, decrease in regional cerebral blood volume, and increase in apparent diffusion coefficient.[3] Unfortunately, clinical presentation and radiological features of RN and tumor recurrence or progression following radiotherapy mostly overlap, which greatly complicates their distinction; this is a severe drawback for decision-making, given their contrasting treatment and prognosis. New imaging modalities such as magnetic resonance perfusion, magnetic resonance spectroscopy, PET, and single-photon emission computed tomography improve diagnostic accuracy but can be costly. Despite surgical risks and sampling bias, biopsy is still considered safe to confirm an RN.[2,4] An additional concern is that lesions following radiotherapy are often a combination of tumor cells and radiation injury, which complicates their classification/therapy and greatly increases the risk of sample bias. Recent recommendations aim to review as many characteristics as possible to identify the predominant component of the lesion instead of considering both mechanisms as complete separate entities.[3]

Therapeutic Options

Conservative treatment options for RN include corticosteroids, bevacizumab, hyperbaric oxygen, and anticoagulants.[5,6] Steroids can often rapidly improve symptoms, but they only confer symptomatic relief and may cause side effects or lower the efficacy of immunotherapy.[5] Bevacizumab was shown to improve the clinical symptoms of patients with RN and even to reduce lesion volume but is also associated with severe side effects and high costs.[5,6] For patients in need of urgent treatment or refractory to medical treatment, surgical resection remains of central importance, with the additional benefit of providing tissue samples. However, surgery is invasive, not well suited to deep-seated lesions, and normal brain tissue around the resection cavity may continue to cause necrosis even after complete resection.[6]

Laser Interstitial Thermal Therapy for Radionecrosis

In the last 10 years, laser interstitial thermal therapy (LITT) has increasingly been used to manage RN refractory to medical treatment. Because of its stereotactic precision and minimal invasiveness, LITT may reduce the risk of surgery and enable the targeting of difficult to access lesions by means of open surgery while still providing tissue sample and long-term reduction of edema and lesion volume. In the following article, the authors systematically report and discuss the available evidence relating to LITT for RN.

METHODS

To retrieve all reports of patient outcome following LITT for (suspicion of) RN, the authors conducted a structured literature search on Pubmed on 1st October 2022 with the terms (((radiation) AND (necrosis)) OR (radionecrosis)) AND ((LITT) OR ((laser) AND ((ablation) OR ((thermotherapy) OR ((thermal) AND (therapy)))))) NOT (animals[mesh] NOT humans[mesh]) and retrieved 207 records. They screened all titles/abstracts and/or full-texts and found 32 relevant studies. In addition, references of key articles were screened and 1 supplementary relevant article was found. All full-texts (n = 33) were retrieved, and all studies are summarized in **Table 1**.

RESULTS

Pioneering Studies

The first to describe the use of real-time MR-guided LITT for recurrent brain metastases following chemotherapy, radiotherapy, and radiosurgery were Carpentier and colleagues[7,8] in 2008, but patients with a suspicion of RN were excluded from their study. They published their final results in 2011 with no recurrence within the thermal ablation zone, a median survival of 19.8 months, and no serious adverse event (AE).[9] In 2012, Rahmathulla and colleagues[10] reported the first use of LITT for a biopsy-proven RN refractory to medical treatment in a patient with a history of non–small cell lung cancer with brain metastases treated with stereotactic radiosurgery. The patient, whose symptoms had been resistant to steroids for 6 months, was discharged within 48 hours of surgery and weaned from steroids within 7 weeks, with near complete neurological improvement. At that time, perilesional edema had nearly disappeared despite an increase in lesion size. Rahmathulla and colleagues hypothesized that LITT replaced endothelial proliferating cells and zone of disorganized angiogenesis with thrombosed vessels.

Clinical Outcomes

These results have led to multiple studies describing the use of LITT for RN or recurrent

Table 1
Summary of the available evidence

Authors	Center	Study Type and Purpose	n LITT/n LITT for RN	Progression (only for RN, if NOS)	Survival (only for RN, if NOS)	AE (for all Patients, including other diagnoses than RN, if NOS)	Comments	Lessons
Sankey et al,[34] 2022	• Duke University Medical Center • Cleveland Clinic	• Multicenter retrospective cohort study • LITT vs steroids alone for RN	57/57	Median PFS 13.6 mo	Median survival 15.2 mo	• Scalp burn secondary to drilling (n = 1) • Intraoperative desaturation leading to procedure prolongation (n = 1) • Seizure within 90 days (n = 7)	—	LITT significantly decreases time to steroid independence for RN following radiation for brain metastases as compared with medical treatment
Riviere-Cazaux et al,[19] 2022	Mayo Clinic: • Rochester • Phoenix • Jacksonville	• Multicenter retrospective • LITT for recurrent metastases/RN	23/13 (only 14 received biopsy)	81.8% with lasting local control until fu (mean fu time unknown)	Median survival 16 mo	• Mild transient language and cognitive/memory change (n = 2) • Left-sided visual loss and word-finding difficulty for 10 minutes (n = 1) • Mild visual symptoms with mild diplopia (n = 1)	Results provided for all cases (no subanalysis for biopsy-proven RN)	LITT was associated with sustained local control in most of the patients treated for radiographic progression after radiation of central metastases
Luther et al,[28] 2021	University of Miami Miller School of Medicine	• Single-center retrospective • Outcome for different LITT volumes for posterior fossa lesions	17/5	—	—	• Transient neurological deficits (n = 2)	No separate results for RN	Patients with radical ablation showed a greater decrease in perilesional edema and an improved functional status immediately and at last follow-up

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Authors	Center	Study Type and Purpose	n LITT/n LITT for RN	Progression (only for RN, if NOS)	Survival (only for RN, if NOS)	AE (for all Patients, including other diagnoses than RN, if NOS)	Comments	Lessons
Lanier et al,[23] 2021	Wake Forest School of Medicine	• Single-center retrospective • Outcome of LITT for RN	30/30	• 3 mo: 95.7% without progression • 6 mo: 90.9% • 9 mo: 90.9%	Median survival 2.1 years, 18 patients still alive at last fu	• Subacute edema (n = 1) • Intraparenchymal hemorrhage (n = 1)	2 patients with progression within 4 mo of treatment (salvageable)	LITT was safe and durably effective with only 2 recurrences; PRO showed no severe decline and stable well-being and functionality following LITT
Kaye et al,[18] 2020	Rutgers Robert Wood Johnson Medical School	• Single-center retrospective • Influence of LITT on neurological death for in-field recurrence of metastases after radiation	97 (70 patients)/ 97 recurrent metastases or RN	• 7 patients with local recurrence with a median time of 5.6 mo	• 24-mo cumulative incidence of death: 75.4% (36.9% non-neurologic, 30.8% neurologic, 7.7% unknown cause)	• New permanent neurological deficits (n = 3)	• No separate results for RN	Young patients with high baseline KPS and stable systemic disease had the best outcome after LITT
Bastos et al,[39] 2020	University of Texas MD Anderson Cancer Center	• Single-center retrospective • LITT for brain metastases	82 (61 patients)/ 31	Median time to local recurrence not reached at 24 mo	—-	• Medical (n =4) • Transient neurological deficits (n = 3) • Persistent neurological deficits (n = 8) • Technical issue with abandon of the procedure (n = 1)	—	Following LITT, tumor recurrence/new tumors had shorter time to recurrence as compared with RN
Ginalis & Danish,[17] 2020	Rutgers Robert Wood Johnson Medical School	• Single-center retrospective • LITT for patients between 65–74 y vs >75 y for intracranial tumors (including RN)	64 (55 patients)/ 40 recurrent metastases or RN	—	• 30-day survival 97.5%	• Inaccurate laser placement (n = 1) • Increased weakness (n =7) • Aphasia (n = 2) • Confusion due to edema (n = 1) • Cognitive deficits (n = 1)	No separate results for RN	LITT was safe for treatment of intracranial tumors and RN in geriatric patients

Luther et al,[29] 2020	University of Miami Miller School of Medicine	• Single-center retrospective • Outcome for different LITT volumes for RN	20/20	Mean PFS 5.8 mo	Mean survival 14.3 mo	• Transient altered mental status (n = 1) • Cerebrospinal fluid leak requiring surgical repair (n = 1) • Seizure (n = 1) • Pulmonary embolism (n = 1)	—	Larger ablation volumes (up to >200% of lesion volume) reduced perilesional edema, improved clinical functional status, and did not increase risk
Sujijantarat et al,[33] 2020	Yale University	• Single-center retrospective • LITT vs bevacizumab for RN	25/25	Median PFS 12.1 mo (range 0–64.6 mo)	Median survival 24.8 mo (range 6.0–89.0 mo)	• Confusion (n = 1) • Worsening of left-sided weakness (n = 1) • Seizure and bilateral deep vein thrombosis (n = 1)	—	LITT showed longer overall survival and better long-term lesional volume reduction than bevacizumab
Shah et al,[22] 2020	University of Miami Miller School of Medicine	• Single-center retrospective • Safety and outcome of LITT for intracranial tumors (including RN)	91 patients with 100 LITT/20	25% with recurrence, timing not known	Median survival 16.4 mo	• Transient facial palsy (n = 1) • Post-op seizure (n = 1) • Wound infection (n =2)	No adverse event in the RN group	LITT is safe in surgical neuro-oncology, extent of ablation predicted local control, extent of resection >85% predicted longer PFS (for all cases)
Shao et al,[40] 2020	Cleveland Clinic	• Single-center retrospective • LITT for patients treated before vs after 2014 for intracranial tumors (including RN)	238/50	—	—	• Temporary deficits (n = 68) • Permanent deficits (n = 25) • Seizures (n = 2) • Large hemorrhage (n = 26) • Hemorrhage requiring surgery (n = 3) • Infection (n = 3) • Death within 30 days (n = 6)	No separate results for RN	Efficiency and safety of LITT was improved since 2014

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Authors	Center	Study Type and Purpose	n LITT/n LITT for RN	Progression (only for RN, if NOS)	Survival (only for RN, if NOS)	AE (for all Patients, including other diagnoses than RN, if NOS)	Comments	Lessons
Hong et al,[41] 2020	Yale University	• Case report • LITT for RN following SRS for AVM	2/2	—	—	—	AVM obliteration was confirmed before the procedure	In both cases, LITT provided a rapid resolution/ stabilization of symptoms with decrease in edema
Kim et al,[25] 2020	14 centers from the LAANTERN registry[a]	• Multicenter prospective registry • LITT for intracranial tumors (including RN)	231 (223 patients)/34	—	• 1 mo: 94.1% • 3 mo: 91.1% • 6 mo: 87.8% • 12 mo: 71.1% • 24 mo: 71.1%	• 10.7% with AE • 1.8% with serious AE	—	There was no difference in the estimated OS between recurrent metastases and RN
Hong et al,[32] 2019	Yale University	• Single-center retrospective • LITT vs tumor resection for recurrent tumor after radiosurgery (recurrent metastases or RN)	34/18	• 6 mo: 87.8% without progression • 12 mo: 87.8% • 18 mo: 87.8% • 24 mo: 73.2%	• 6 mo: 94.4% • 12 mo: 73.8%–18 mo 73.8% • 24 mo: 63.2%	• Motor weakness (n = 3) • Hyperglycemia (n = 2) • Thrombocytopenia (n = 1) • Deep venous thrombosis (n = 1) • Dysphasia (n = 1) • Visual disturbance (n = 2) • Seizure (n = 2)	—	LITT showed a local control and capacity to wean off steroids similar as craniotomy and tumor resection for recurrent irradiated metastases and RN, but tumor resection was more effective to reduce neurological symptoms
Swartz et al,[42] 2019	University of Michigan Health System	• Single-center retrospective • LITT for intracranial tumors	13 (12 patients)/ 7	—	—	• Focal motor weakness (n = 4)	—	LITT was well tolerated and was effective in treating recurrent metastases/RN and to enable discontinuation of steroids

Hernandez et al,[16] 2019	Rutgers University	• Single-center retrospective • LITT for recurrent metastases or RN	74 (59 patients)	44.6 wk: 83.1%	—	• New or increased motor weakness (n = 9)	No separate data for RN	• LITT should be proposed before onset of symptoms, as patients on steroids preoperative are more likely to require steroids indefinitely, as well as to experience postoperative AEs • LITT showed a significant effect on the ability to wean off steroids
Rammo et al,[43] 2018	Henry Ford Hospital	• Single-center retrospective • Safety of LITT for RN	11 (10 patients)/ 11	—	• 6 mo: 77.8% • 12 mo: 64.8%	• Transient new neurological deficits (n = 3) • Worsening of seizures (n = 1) • Myocardial infarction (n = 1) • Pulmonary embolus after 1 mo (n = 1)	—	• LITT was relatively safe • Significant increase in ablation volume up to 1–2 mo, then decrease to less than original volume by 6 mo (69%)
Chaunzwa et al,[35] 2018	• Yale University • Cleveland Clinic • Washington University St Louis • Wake Forest Medical Center	• Multicenter retrospective • LITT for recurrent metastases or RN	30/19	Median PFS 6 mo	• 6 mo: 52.3% • 12 mo: 26.1% • 18 mo: 21.8% • 30 mo: 16.3%	• Intraoperative hemorrhage with no need for evacuation (n = 4) • 23% of neurological/medical complication • 20% of new neurological deficits	• No separate data for RN • 73.3% of patients stopped steroids at a median time of 4.5 wk • 48% saw improvement of their preoperative symptoms	• LITT for recurrent metastases/RN may be best suited for patients with large lesions, high functional status, and stable systemic disease • Good cell death coverage (ablation volume) improves outcome
Ahluwalia et al,[24] 2018	• Cleveland Clinic • Wake Forest University	• Multicenter prospective • LITT for recurrent metastases or RN	42/19	• 12 wk: 100% without progression • 12–26 wk (last fu): 91%	• 12 wk: 100% • 26 wk: 82.1%	• Complete hemiparesis (n =1) • Incomplete hemiparesis with hemineglect (n = 1)	—	LITT was shown prospectively to stabilize functional status, preserve quality

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Authors	Center	Study Type and Purpose	n LITT/n LITT for RN	Progression (only for RN, if NOS)	Survival (only for RN, if NOS)	AE (for all Patients, including other diagnoses than RN, if NOS)	Comments	Lessons
	• University of Kansas • Washington University • Thomas Jefferson University and Yale University					• Headache (n = 1) • The aforementioned AEs occurred following LITT for RN		of life and cognition, and reduce the need of steroids for recurrent metastases and RN
Borghei-Razavi et al,[27] 2018	Cleveland Clinic	• Single-center retrospective case series • LITT for posterior fossa tumors	8/2	Patient 1: • Increase in lesion volume of 20% 1 day postoperative • Decrease of 30% 6 mo postoperative Patient 2: • Increase of 164% • No other fu	—	• Hydrocephalus (n=1) • Wound infection (n = 1) • Abducens nerve palsy (n = 1) • Only one AE in patients treated for RN (hydrocephalus)	—	LITT was safe for posterior fossa lesions
Song & Colaco,[44] 2018	The Christie NHS Foundation Trust	• Case report • LITT for RN	2 (1 patient)/1	• Both lesions stable 30 mo after diagnosis of metastases (15 mo and 2 mo after LITT)	—	—	—	LITT was safe and effective for local control of RN
Beechar et al,[15] 2018	Baylor College of Medicine	• Single-center retrospective • Volumetric change of recurrent metastases or RN treated with LITT	50 (36 patients)/ 50 (recurrent metastases or RN)	• Median PFS 295 days (n = 3, range 269–538 days)	• Median OS not reached	• Neurological deficits (n = 16)	• 14 lesions with sustained increased volume following LITT • No separate data for RN	• LITT resulted in an immediate increase in edema and lesion volume, followed by a gradual decrease and symptom improvement • Smaller tumors are associated with a better response

Kamath et al,[45] 2017	Washington University School of Medicine	• Single-center retrospective • LITT for intracerebral lesions	133 (120 patients)/5 RN	—	—	• Edema requiring treatment (n = 3) • Hydrocephalus (n = 3) • Meningitis (n = 1) • Seizure (n = 5) • Hemorrhage (n = 1) • Hyponatremia (n = 3) • Mild confusion (n =1)	No separate results for RN	LITT was safe and effective in a variety of intracranial lesions
Habboub et al,[31] 2017	Cleveland Clinic	• Case report • Patient with RN who underwent LITT followed by minimal invasive tumor debulking	1/1	—	—	—	Steroids weaning over 2 wk	LITT may be used in combination with tumor debulking in patients with large RN
Torcuator et al,[14] 2016	Brigham and Women's Hospital	• Case report • LITT for recurrent metastases or RN	2/unknown	—	—	• Transient word-finding difficulty (n = 1) • Transient right leg weakness (n = 1) • Both due to increased edema around the lesion	• Results of biopsy unknown • Patient 1: initial increase in edema with word-finding difficulty, 22 wk fu with decreased lesion size and edema, neurological improvement and cessation of steroids • Patient 2: slight right leg weakness at 8 wk with increase in edema and lesion size	LITT was associated with an initial increase in lesion size responding to low-dose steroids
Smith et al,[21] 2016	Barrow neurological institute	• Single-center retrospective • LITT for RN	25/25	PFS: • 11.4 mo for metastases • 8.5 mo for grade 3 lesions (WHO) • 9.1 mo for grade 4 lesions	Mean survival: • 19.2 mo for metastases • 12.2 mo for grade 3 lesions • 13.1 mo for grade 4 lesions	• Initial increased left weakness (n = 2) • Increased foot weakness (n = 1) • Steroid-induced hyperglycemia (n = 1) • Headache (n = 1) • Fatigue (n = 1) • Seizure (n = 1)	• All biopsies showed no evidence of recurrent neoplasm • In 4 cases (glioblastoma), tumor resection was required and recurrent	• LITT caused an initial increase in tumor volume with a decrease in enhancement, followed by an eventual volume decrease in

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Authors	Center	Study Type and Purpose	n LITT/n LITT for RN	Progression (only for RN, if NOS)	Survival (only for RN, if NOS)	AE (for all Patients, including other diagnoses than RN, if NOS)	Comments	Lessons
						• Urinary retention and constipation (n = 1) • Asymptomatic catheter track hemorrhage (n = 1)	glioblastoma was found	almost all patients • LITT combined with needle biopsy may be subject to sampling error
Wright et al,[30] 2016	Cleveland Clinic	• Single-center retrospective • LITT immediately followed by minimally invasive, transsulcal resection	10/1 (with both recurrence and RN)	• No progression after 108 days	• Alive after 108 days	• Persistent mild neurological deficits (n = 1) • Transient mild neurological deficits (n = 1)		LITT may be used in combination with minimal invasive resection for difficult-to-access brain tumors
Patel et al,[13] 2016	Robert Wood Johnson University Hospital	• Single-center retrospective • LITT for various indications (including RN)	133 (102 patients)/37 (recurrent metastases or RN)	—	—	• Neurological deficits (n = 7) • Hemorrhage (n = 1) • Edema (n = 1) • Infection (n = 1) • Thermal injury (n = 1) • The aforementioned AEs occurred following LITT for recurrent metastases/RN	—	LITT resulted in few AEs that were mostly transient
Chan et al,[26] 2016	Medical College of Wisconsin	• Case report • Technical note about robot-assisted LITT for posterior fossa RN	1/1	2 mo: complete resolution of the lesion	—	—	Robot assistance was used because the trajectory was too low for arc-based stereotaxy	LITT using robot assistance in the posterior fossa was effective in inducing resolution of the lesion and improvement of symptoms

Fabiano and Alberico[12] 2014	University at Buffalo	• Case report • LITT for recurrent metastasis or RN	1/1	—	—	—	• Preoperative steroids with adverse effects (hyperglycemia, weight gain, muscle weakness) • Postoperative steroid weaning over 2 wk	LITT may help to reduce steroid need in patients with recurrent metastasis/RN
Rao et al,[11] 2014	Robert Wood Johnson University Hospital	• Single-center retrospective • LITT for recurrent metastases or RN	15 (14 patients)/ 15 (recurrent metastases or RN)	• 24 wk: 75.8% without progression • Median PFS of 37 wk	• 57% of survival median fu of 39 wk	• Asymptomatic hemorrhage (n = 1) • New left-sided weakness requiring steroids for 2 wk (n = 1)	• No distinction between recurrent metastases/ RN • 5 death of extracranial disease progression • 1 death of neurological progression elsewhere	LITT was effective and safe for patients with recurrent metastases/RN
Torres-Reveron et al,[20] 2013	Yale University	• Singe-center retrospective • LITT for recurrent metastases/RN	6/6	• 1 patient showed tumor growth after 3 mo and the tumor was resected	—	—	• 3 patients showed signs of tumor progression/recurrence on imaging, but all biopsies showed no tumor recurrence • All patients weaned of steroids by 2 mo postoperative • 1 patient died of progression of systemic disease within 1 mo	There was a discrepancy between results of imaging and histopathology
Rahmathulla et al,[10] 2012	Cleveland Clinic	• Case report • LITT for RN	1	—	—	• Word-finding difficulty and conduction dysphasia in the immediate postoperative period	• 7 wk fu: successfully weaned off steroids, near-total resolution for neurological symptoms	LITT was well tolerated and provided good edema and symptoms control

Abbreviations: AE, adverse events; AVM, arteriovenous malformation; fu, follow-up; IQR, interquartile range; LITT, laser interstitial thermal therapy; mo, months; NOS, not otherwise specified; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; RN, radiation necrosis; wk, weeks.

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tumors (mostly metastases), but the pathologies were usually not discriminated and often reported as a single entity, which hindered a better understanding of both entities.[7] Most of these studies reported promising results, as LITT for RN/recurrent metastases was considered safe, provided a good local control, enabled reduction/discontinuation of steroids, and/or reduced neurological symptoms.[11–19] Highlighting the difficulty to diagnose RN adequately, Torres-Reveron and colleagues[20] published a case series of 6 patients in which no biopsy showed evidence of tumor recurrence, whereas imaging was consistent with tumor recurrence/progression. Most interestingly, one lesion that had started regrowing after an initial decrease in size was eventually resected and diagnosed as tumor recurrence. The distinction between RN and tumor recurrence was even deliberately omitted by some investigators, as they considered that the treatment strategy could be effective regardless of the diagnosis.[11,16]

However, more recent studies tend to differentiate both pathologies, and there are multiple reports of the postoperative course of LITT for RN specifically. For example, Smith and colleagues[21] reported the results of 25 patients treated with LITT for RN following treatment of primary brain tumors and metastases. They observed a progression-free survival of 11.4 months for RN following metastases, 8.5 months for grade 3 lesions, and 9.1 months for grade 4 lesions. The corresponding mean survival was 19.2, 12.2, and 13.1 months. They reported 9 AEs (36%). In 4 cases (16%, all grade 4 lesions), tumor resection was needed after recurrence, which further highlights that stereotactic biopsy may be subject to sampling error. Later, in a subgroup of 20 patients who received LITT for RN, Shah and colleagues[22] reported a median overall survival of 16.4 months, with only 25% of the patients showing a recurrence of the lesion during the study period. They found no AE in the RN subgroup but reported a surprisingly low rate of AEs as compared with the rest of the literature (4,4%). Lanier and colleagues[23] also reported the results of LITT for 30 patients with RN, with 95.7% of patients showing no progression after 3 months, 90.9% after 6 months, and 90.9% after 9 months. The median survival was 2.1 years, with 18 patients (60%) still alive at the end of the study. They observed only 2 recurrences within 4 months, and 2 AEs (6.7%), with stable well-being and functionality measures postoperatively.

The first prospective study on this subject was published by Ahluwalia and colleagues[24] in 2018 who evaluated the outcome of LITT for recurrent metastases and RN following radiotherapy. They found a significant difference in the rate of absence of progression at 12 weeks (100% for RN vs 54% for recurrent metastases, $P < .001$), as well as survival at 12 weeks (100% for RN and 71% for recurrent metastases, $P = .02$). The difference in survival between both groups at 26 weeks was not statistically significant (82.1% for RN, 64.5% for recurrent metastases, $P = .09$). There were 3 AEs in the RN group (15.8%). Later, Kim and colleagues[25] published results from a multicenter prospective registry from which 34 patients had RN, with a survival of 94.1% after 1 month, 91.1% after 3 months, 87,8% after 6 months, and 71.1% after 24 months.

Further Applications and Comparison with Other Therapeutic Modalities

LITT for RN was shown to be safe and effective also in the posterior fossa,[26–29] and some investigators have reported good results for LITT combined with tumor debulking or resection.[30,31] Others have compared the safety and efficacy of LITT with alternative therapeutic modalities in retrospective studies. For example, Hong and colleagues[32] found that tumor resection was more effective to reduce neurological symptoms than LITT, but both interventions resulted in a comparable local control, ability to wean from steroids, and safety profile. They concluded that LITT should be considered in asymptomatic patients (or when neurological improvement is not the main purpose of the treatment) with difficult to access lesions, whereas craniotomy should be reserved for patients showing neurological symptoms and easily accessible lesions. Sujijantarat and colleagues[33] compared the outcome of LITT and bevacizumab and found that patients treated with LITT lived longer (median overall survival 24.8 months vs 15.2 months, $P = .003$), and although LITT usually resulted in an initial increase in lesional volume, the trend reversed after 1 year, as patients treated with LITT showed a median volume decrease of 64.7%, whereas those treated with bevacizumab showed a lesion volume increase of greater than 100% ($P = .01$). Finally, Sankey and colleagues[34] compared the effect of LITT and medical treatment (steroids) for biopsy-proven RN after stereotactic radiosurgery for brain metastases. They found that patients who underwent LITT were weaned from steroids more frequently (84% vs 53%, $P = .017$) and less patients developed radiographic progression in the LITT group (27% vs 5%, $P = .031$). They reported no major AEs, with a similar rate of seizure following LITT or biopsy alone.

Ablation Volume

Multiple studies have shown that good cell coverage is critical.[22,28,29,35] Chaunzwa and colleagues[35] reported a higher functional status for patients with recurrent metastases/RN and LITT volume of greater than 90% of lesion volume. Luther and colleagues[28,29] found that larger ablation volumes—most importantly supralesional ablation volumes—were more effective at reducing perilesional edema, improving functional status, and extending progression-free survival, while remaining safe even in the posterior fossa.

Volumetric Changes Following Laser Interstitial Thermal Therapy

Studies have shown that although some patients showed a rapid decrease in lesion size/edema, many were subject to an increase in size during the short-/medium-term period, with a subsequent decrease. Smith and colleagues[21] found that 2 months after LITT for RN, 74% of patients had an increase in lesion volume (mean relative increase 175%) and 26% a decrease (mean relative decrease of 38.7%). After 6 months, the trend was also for lesions to grow (66% with mean relative increase of 231.9%, 33% with a mean relative decrease of 26.2%). However, this trend was reversed after 12 months (44% with relative increase of 192%, 56% with relative decrease of 30.7%) and more dramatically after 24 months (17% with relative increase of 136.9%, 83% with a relative decrease of 49.1%). Beechar and colleagues[15] conducted a retrospective study to characterize volumetric changes following LITT for RN and recurrent metastases. Unfortunately, they did not provide separate results for patients with RN. They found an immediate increase in lesion size on T1 postcontrast imaging, with an eventual reduction in size after 6 months. FLAIR signal suggested perilesional edema was decreased after LITT in most of the patients, and this reduction was statistically significant after 6 months. Smaller tumors were associated with a better radiographic response.

Meta-Analyses

A recent meta-analysis comparing LITT with bevacizumab found that both treatments were equally effective in posttreatment symptomatic improvement, successful steroid taper, rate of recurrence, complete response, and progression.[36] Rates of partial response were higher for bevacizumab (79.6% vs 29.5%, $P = .001$) and of stable disease for LITT (6.6% vs 49.2%, $P = .002$). In addition, although there was no difference in the overall survival rates until 12 months, survival was significantly better at 18 months for LITT as compared with bevacizumab (46.4% vs 25%, $P = .038$).

A meta-analysis published in 2021 evaluated the effect of LITT for tumor recurrence and/or RN following stereotactic radiosurgery for brain metastases.[37] It reported a local control rate of 87.4% after 6 months (for the RN subgroup) and 76.3% after 12 months. These results were superior for RN compared with recurrent metastases (67.9% at 6 months, $P = .009$, 59.9% at 12 months, $P = .041$). However, overall survival was statistically not significantly different from the results for recurrent metastases (83.1% vs 69.2% at 6 months, $P = .104$, 66.8% vs 66.5% at 12 months, $P = .978$).

Current Studies

The authors found one registered recruiting study on this subject on clinicaltrials.gov. This randomized open-label study entitled "REMASTer: Recurrent Brain Metastases After SRS Trial" aims to compare LITT with steroids versus steroids alone for RN, as well as LITT alone versus LITT with hypofractionated radiotherapy for recurrent metastases. The study started in May 2022 and is expected to be completed by July 2026.

DISCUSSION

Brief Summary of the Results

Since the first report of LITT in a patient with RN, multiple studies have evaluated the procedure in infra- and supratentorial lesions of various origins. Its safety and effectiveness have been demonstrated (mostly retrospectively) for RN following radiotherapy for metastases, gliomas, and even arteriovenous malformations (see **Table 1**). Recent retrospective studies have shown that LITT is more successful than medical treatment at reducing steroid need, in slowing down progression, and increasing survival. In addition, a meta-analysis reported a superior overall survival at 18 months for LITT as compared with bevacizumab.[33,34,36]

Surgical Treatment of Radionecrosis

Although LITT is well tolerated in most patients, some patients may show a transient deterioration of neurological symptoms due to an initial increase in lesion size and surrounding edema. **Figs. 1** and **2** show the typical preoperative and postoperative course of LITT for RN with an initial increase of edema/lesion size with eventual shrinkage. Fortunately, this can very often be managed with short-term steroids, and in the medium-/long-term postoperative period, lesions and edema

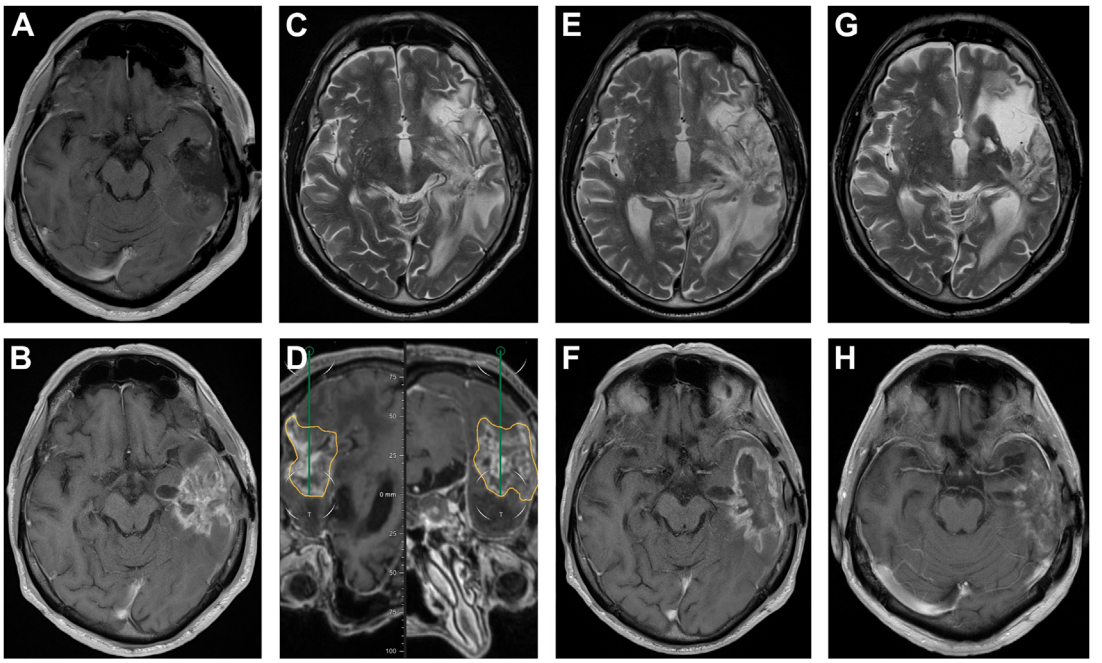

Fig. 1. Preoperative and postoperative course of LITT for radionecrosis (melanoma metastasis) (*A*). T1 postcontrast imaging after tumor resection showing no tumor remnant (*B*). T1 postcontrast imaging showing suspicion of radionecrosis (*C*). Increased T2-FLAIR signal around the lesion (edema) (*D*). Inline view of the planned LITT trajectory (*E*). Slight change of T2-FLAIR signal 1 month after LITT (*F*). T1 postcontrast imaging 1 month after LITT showing decrease of size of the lesion (*G*). Marked decrease of T2-FLAIR signal 3 months after LITT (the signal hyperintensity anterior of the lesion corresponds to cerebrospinal fluid in an old parenchymal defect and not to edema) (*H*). T1 postcontrast imaging 3 months after LITT showing significant shrinkage of the lesion.

tend to shrink, which has a net positive effect on steroid consumption.[14,16,24,35] However, this may be an important limitation in patients who present with acute neurological deficits, as rapid reduction of mass effect is of major importance and any increase in lesion volume may have dramatic consequences. In such cases, craniotomy with mass reduction may be superior to LITT.[32] As an alternative and potential future solution to this problem, there are some reports of LITT followed by minimal invasive resection.[30,31]

Indication for Laser Interstitial Thermal Therapy

RN is still not well understood, and its diagnosis and management is not well established. Therefore, arguments favoring LITT include the need for a biopsy, localization of the lesion well suited for LITT (and/or unfavorable for open resection), and resistance to steroids or taper failure.[35] Single (few) lesions and good systemic control may also be seen as essential parameters.[16,24,35] Neurological status is an important factor but there is no consensus as yet on its interpretation. Although progressing symptoms were seen as a prerequisite to use LITT by some investigators, others advocated the use of LITT in asymptomatic patients with growing lesions, as it has been shown to be more useful when used before neurological decline/steroid dependence.[24,35,38] Because of the complexity and relativity of some of these aspects, the authors firmly believe that the decision to use LITT in such patients should be discussed in multidisciplinary tumor conferences.

Outlook and Limitations

As highlighted by multiple reports on the discrepancy between imaging and biopsy results and even discrepant biopsy results from the same lesion, diagnosing RN remains a significant challenge. Tumor recurrence and radionecrosis may be present in a single lesion, which further complicates diagnosis. Furthermore, multiple reports in the neurosurgical literature do not distinguish between the 2 entities (see **Table 1**). However, this distinction is critical, as clinical outcomes may be very different for both pathologies, and LITT has been shown to be more successful in RN than in tumor recurrence. This indiscriminate reporting is thought to introduce significant heterogeneity in the literature.[37] As an additional limitation, most reports are retrospective and

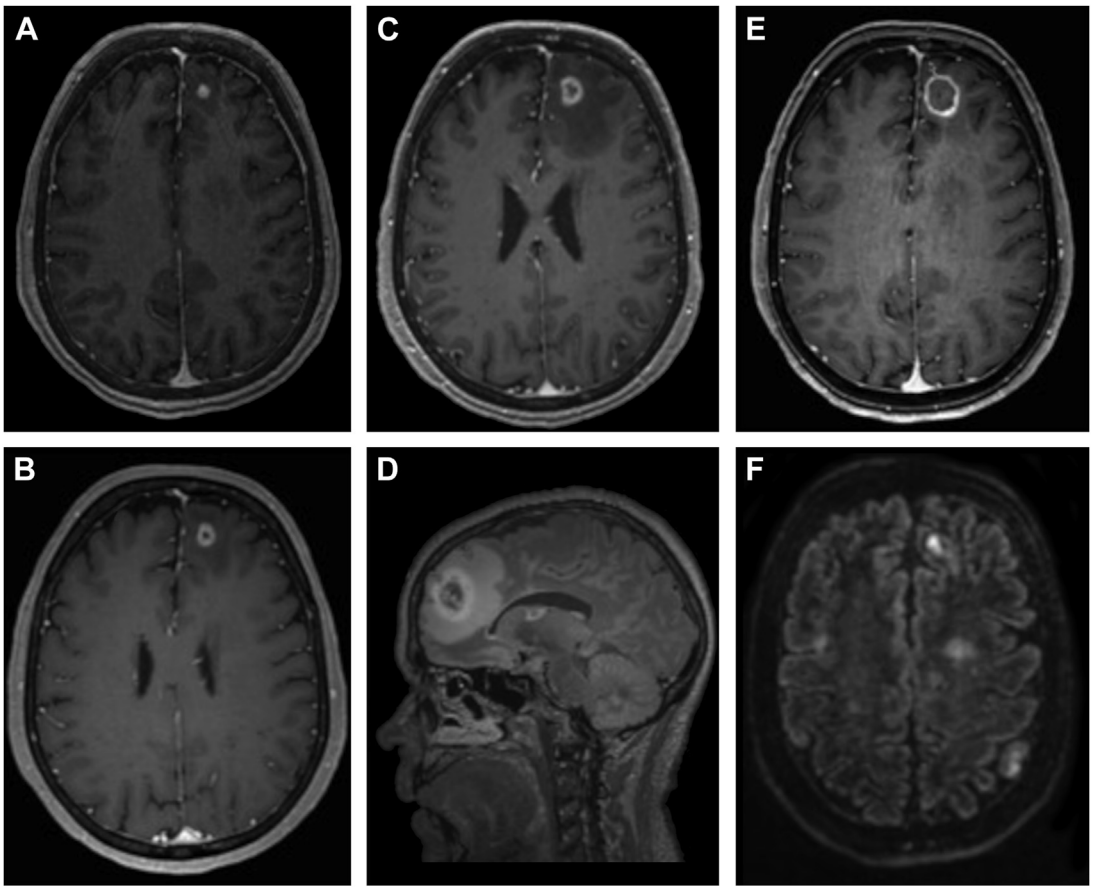

Fig. 2. Preoperative and postoperative course of LITT for radionecrosis (pulmonary carcinoma metastasis). (*A*). T1 postcontrast imaging showing the metastasis before radiation (*B*). T1 postcontrast imaging showing suspicion of radionecrosis (2 months before LITT) (*C*). T1 postcontrast imaging showing progression of the lesion (immediately before LITT) (*D*). Increased T2-FLAIR signal around the lesion (edema) during LITT (*E*). T1 postcontrast imaging showing the ablated lesion (intended to be larger than the contrast enhancing lesion) with decreased edema 1 month following LITT (*F*). Marked decrease of tumor size and of T2-FLAIR signal 3 months following LITT.

constitute small case series originating from very few institutions as shown in **Table 1**. These are severe drawbacks for evidence-based decision-making, and all efforts should be made to enroll patients in prospective registries/trials and provide as much detail about the underlying pathology as possible.

SUMMARY

In well-selected patient subgroups with lesions suspicious for RN, LITT may constitute an effective and safe treatment option and help hinder progression, lengthen survival, reduce neurological symptoms, and allow for successful steroid taper. Yet, the scientific literature on this subject is still scarce, mostly retrospective, and limited by a strong discrepancy in the classification of lesions and reported outcome measures. LITT for RN has become an additional tool for neurosurgeons to benefit patient prognosis and quality of life, which randomized controlled studies will need to prove.

DISCLOSURE

The authors report no competing interests.

CLINICS CARE POINTS

- LITT helps to wean off steroids in RN
- RN is difficult to differentiate from tumor recurrence/progress
- LITT often resulsts in initial increase in edema
- Large ablation volumes are recommended
- For RN, LITT may improve survival more effectively than medical therapy

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