7 Laser Interstitial Thermal Therapy for Brain Metastasis

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Case Vignettes

Case 1

A 75-year-old male smoker was diagnosed with stage IIIB squamous carcinoma of the lung. He underwent carboplatin/docetaxel chemotherapy. Six months later, the patient started to have clumsiness with his right hand and problems with fine motor movements; subsequently, he started to drag his right leg. MRI revealed two intracranial lesions (left frontal and left cerebellar) consistent with metastases due to existing lung cancer. Both lesions were treated with Gamma Knife radiosurgery (GKRS) The left frontal 16-mm diameter metastasis was treated with 24 Gy at 68% isodose, and the left frontal 25.3-mm diameter metastasis received staged treatment with 18 Gy and then with 12 Gy at 57% isodose. Both frontal and cerebellar lesions disappeared over the course of 2 years. At the end of the second year, the cerebellar lesion started to regrow with new dysmetria and inability to perform rapid alternating movements on the left side. MRI studies showed increased cerebral blood volume (CBV) on a perfusion study, and our tumor board recommended Laser Interstitial Thermal Therapy (LITT) for this recurrent lesion. One trajectory was used for treatment (Fig. 7.1). The patient was followed up for over 2 years with disappearance of the cerebellar lesions as shown in Fig. 7.2. His neurological complaints diminished gradually. Unfortunately, the patient died 3 years after LITT due to progression of his primary disease.

Case 2

A 44-year-old woman was diagnosed with triple negative breast carcinoma with metastases to regional lymph nodes. She underwent modified radical mastectomy followed by chemotherapy at an outside medical center. She was diagnosed with two intracranial metastatic lesions 8 months after initial diagnosis and received staged GKRS (18 + 12 Gy at 50% isodose). The smaller lesion showed a good response to treatment, but the large right thalamic tumor persisted. Four months after GKRS this lesion started to grow, and the patient was subsequently referred to our clinic. We performed perfusion MRI imaging, which revealed an elevated CBV, suggesting that this lesion was most likely to be regrowing metastasis

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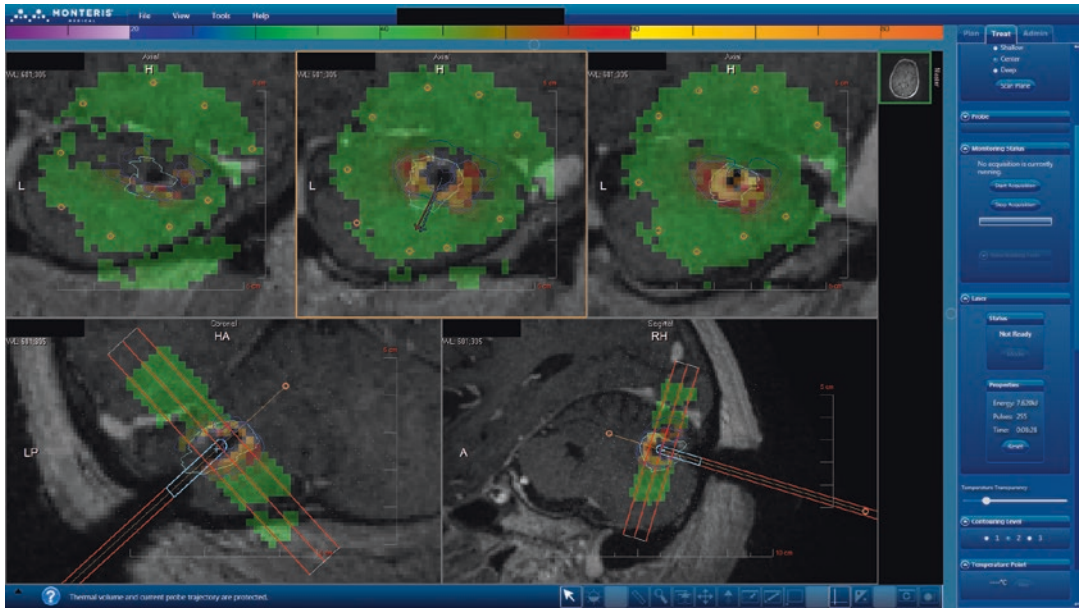

Fig. 7.1 Screenshot during the LITT procedure for a cerebellar metastatic lesion. Blue line: coagulation necrosis, turquoise line: tumor borders, green zone: MR thermometry zone, yellow circles in green zone: MR thermometry readings, blue arrow: planned direction, red arrow: actual location (red will move to blue subsequently). Yellow straight line depicts the probe tract, and yellow circle at the end demonstrates the maximum length the probe can reach

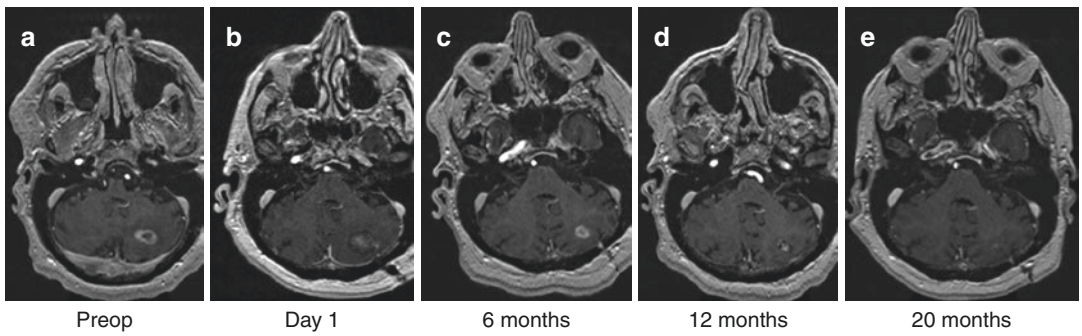

Fig. 7.2 Magnetic resonance imaging (MRI) showing recurrent cerebellar metastasis from squamous cell carcinoma of the lung. (**a**) T1-weighted MRI with gadolinium showing preoperative lesion. (**b**) Post-op day 1, (**c**) post-op month 6, (**d**) post-op month 12, (**e**) post-op month 20

and not radiation injury. At the time of presentation, patient had no neurological deficit. Her past medical history did not include any other pathology than her breast cancer.

She underwent stereotactic biopsy that confirmed recurrent cancer followed by LITT with three trajectories from the same burr hole (Fig. 7.3) during the same procedure. The tumor diameter at the time of diagnosis was 41 mm, and the entire tumor was ablated. Her postoperative course was uneventful, and she was discharged 2 days after the surgery without any complications. On subsequent follow-up, the edema around the tumor diminished significantly and almost disappeared at 6 months (Fig. 7.4). There was also a volumetric response to LITT, and tumor shrunk from 18.9 to 14.7 cm^3 in 6 months (Fig. 7.5). Despite a significant decrease in

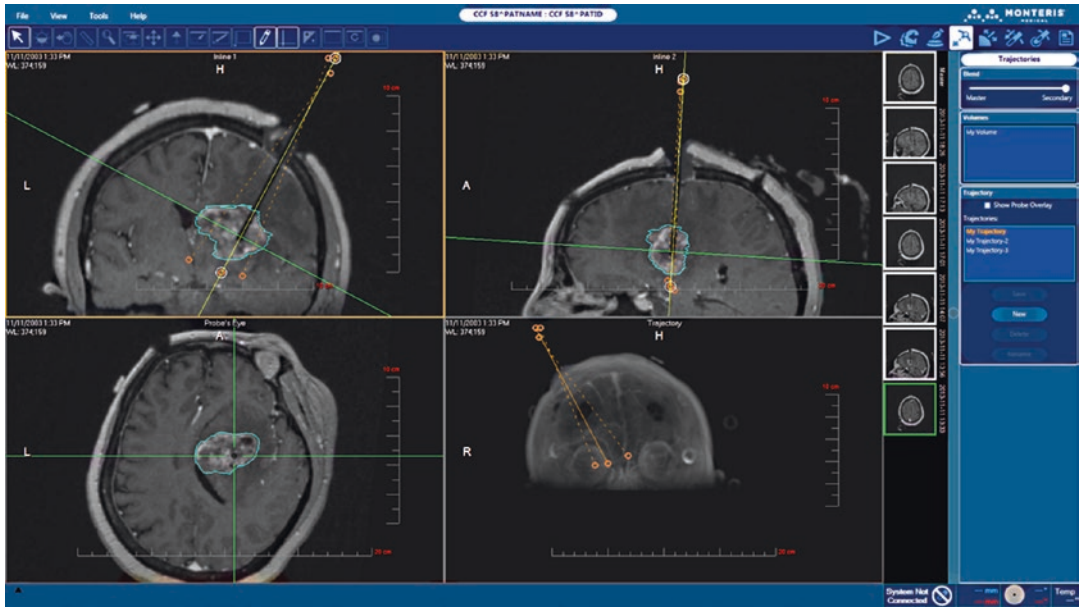

Fig. 7.3 Intraoperative screenshot of LITT with four inline windows. Three straight lines show the trajectories for each treatment

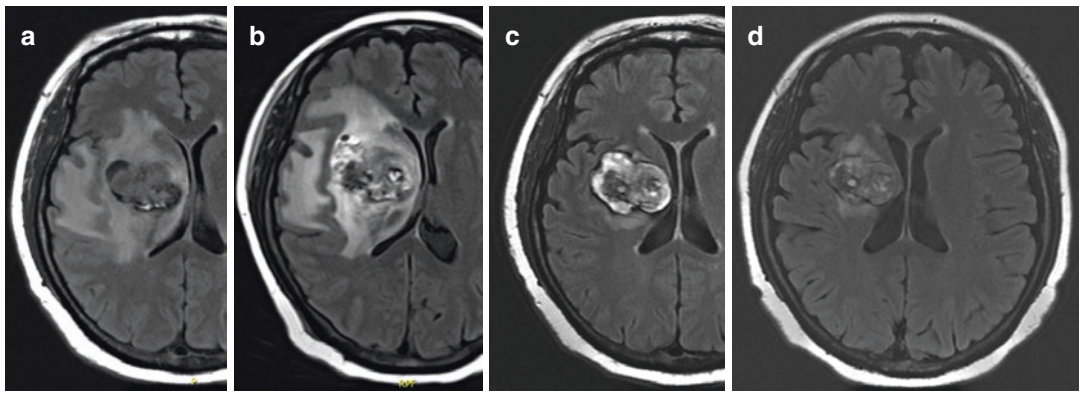

Fig. 7.4 Magnetic resonance imaging (MRI) showing thalamic metastasis from squamous cell carcinoma of the lung. (**a**) T2 Flair MRI showing preoperative recurrent lesion. (**b**) Post-op day 1, (**c**) post-op month 3, (**d**) post-op month 6

edema, new contrast enhancing areas appeared on the posterior border of the tumor, which were positive for recurrence (Fig. 7.5d).

Introduction

Advances in cancer diagnosis and the advent of newer treatment modalities have increased the prevalence of brain metastasis. The last two decades have seen a paradigm shift in the treatment of these lesions. Although previously patients with brain metastasis are commonly considered incurable, more and more patients now are being treated, and the average treated lesion size is getting smaller. This can largely be attributed to the evolution and development of newer treatment approaches, with increasing recent emphasis on focal therapies whenever possible. MRI-guided laser interstitial thermal therapy (LITT) is one of

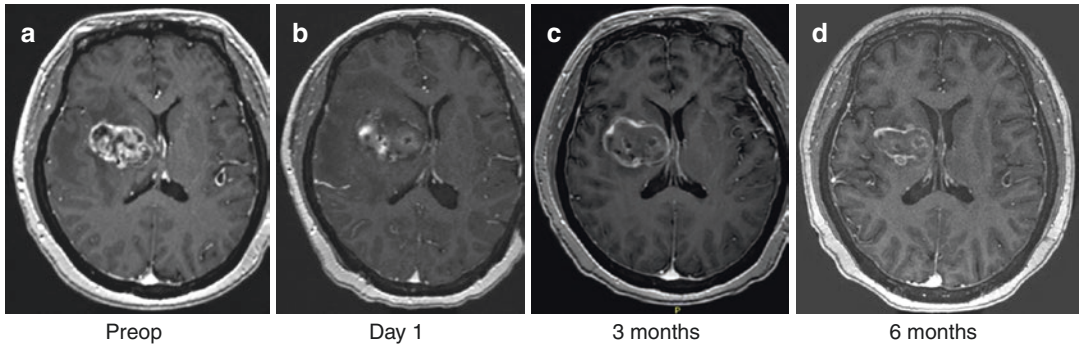

Fig. 7.5 Magnetic resonance imaging (MRI) showing recurrent thalamic metastasis from squamous cell carcinoma of the lung. (**a**) T1 weighted MRI with gadolinium showing preoperative lesion. (**b**) Post-op day 1, (**c**) post-op month 6, (**d**) post-op month 12, (**e**) post-op month 20

the newest tools in the neurosurgical armamentarium and can be used for minimally invasive treatment of a variety of intracranial tumors.

A laser (light amplification by stimulated emission of radiation) probe is directed to the desired area for thermal coagulation of the surrounding structures [1]. The mechanism of laser ablation relies on thermal energy (bioheat) transferral to the tissue surrounding the laser probe [2]. The overall effect is coagulation necrosis and blood vessel sclerosis by photocoagulation [3]. Similarly, microwave or ultrasound waves can be used as a heat-producing source for targeted lesioning purposes in the human body [4]. Two out of these three methods are currently being used in neurosurgery. Ultrasound ablation is mainly used for ablation purposes for neurodegenerative diseases such as essential tremor [5]. LITT was first employed in surgery by Bown et al. [6] and then in neurosurgery by Kahn et al. [7] for various intracranial tumors with the help of real-time MR imaging. The method is frequently used as an alternative treatment model for tumors that are not good candidates for surgery [8]. The inherent minimally invasive nature of the procedure promotes shorter hospital stay and decreased morbidity compared to conventional surgical procedures [9].

Unwanted side effects of LITT are carbonization and vaporization both of which happen as tissue reaches 100 °C temperature. Monitoring the temperature inside the thermal lesion as it is generated is a key step in the procedure and is accomplished by using MR thermometry.

Different types of lasers differ importantly in the depth of tissue penetration. For example, it is 4 mm for neodymium-doped yttrium aluminum garnet (Nd-YAG) lasers but 0.4 mm for argon laser. One of the most frequently used lasers is the CO_2 laser, and its tissue penetration is 30 μm. The best tissue penetration is with the Nd-YAG laser because it has a longer wavelength. Shorter wavelength lasers produce more heat, but less tissue penetration, and therefore carry a greater risk of thermal tissue necrosis.

Historically, Q-switched ruby lasers were first used in medicine to remove tattoos in the 1960s [10]. A ruby laser has a short wavelength (694 nm) that has been effectively used in dermatological procedures since its first application. Bown et al. used CO_2 lasers for the treatment of tumors in the early 1980s and reported that although long-wavelength laser can penetrate deeper distances and can be used for larger lesions, this type of laser reaches maximum temperature very quickly (in seconds), and it can cut and vaporize tissue instead of creating coagulation necrosis, and therefore, it is not practical to use in deep tissues [6].

Currently, lasers in the near-infrared (in Nd-YAG laser range) are used for LITT. Due to their long wavelength, they can be safely used for deeply located tumors and can stay in one position during the procedure for an extended period of time because they only slowly reach the maximum temperature [6]. Currently, both the technologies used in neurosurgery – Neuroblate (Monteris Co, Plymouth, MN, USA) and

Visualase (Medtronic, Minneapolis, MN, USA) use solid-state lasers in the near-infrared range (1064 nm at 12 W), but the cooling systems they use differ. The Neuroblate system uses a CO_2 gas-cooled laser probe, whereas the Visualase system uses a saline-based system that circulates around the probe and cools it [11].

Laser use in neurosurgery dates back to 1990 when Sugiyama et al. demonstrated the safe use of an Nd-YAG laser in intracranial tumors [12]. This long-wavelength laser was utilized with tomography with successful lesioning. Even though this long-wavelength and low-power lasers were utilized in the 90s, unsophisticated laser probes and a lack of intraoperative real-time monitoring posed difficulties for LITT use in neurosurgery. The Nd-YAG laser is, however, very suitable to use in well-perfused soft tissues such as brain white matter [13].

The groundbreaking factor for utilization of LITT is the development of MRI thermography. Before this technology, lasers were used in 1980s with a surge in interest but subsided in a decade due to difficulty of monitoring or predicting the degree of thermal damage. The publication rate on LITT shows us that after introduction of MR thermography (1994), the number of publications on LITT has exponentially increased (Fig. 7.6). MR thermography provides real-time monitoring of thermal damage inside the tissue, thereby maximizing lesion ablation while minimizing damage to nearby healthy structures [14]. Laser energy increases the temperature in the targeted area and breaks hydrogen bonds inside the cell, while at the same time increases the number of free water molecules. MR thermography can measure temperature in this tissue using a method called Proton Resonance Frequency Shift (PRFS) [15]. MR thermography is not restricted to LITT; it can also be used with intracranial ultrasound [16] and radiofrequency ablation in other parts of the body [17].

Tissue optical properties depend on multiple factors such as the level of parenchymal hyaluronic acid that is present. It has been shown that the penetration of laser energy in gray matter is much higher than in white matter [18]. Also, laser penetration/absorbance in abnormal tissue differs from that achieved in healthy parenchyma. Low-grade gliomas absorb less laser energy than high-grade gliomas, but it has been shown that low-grade glial tumors exhibit much more absorption than normal gray matter [18].

There are three zones of thermal effect inside the target area. The first zone around the probe absorbs maximum energy and creates true coagulation necrosis, along with carbonization and/or

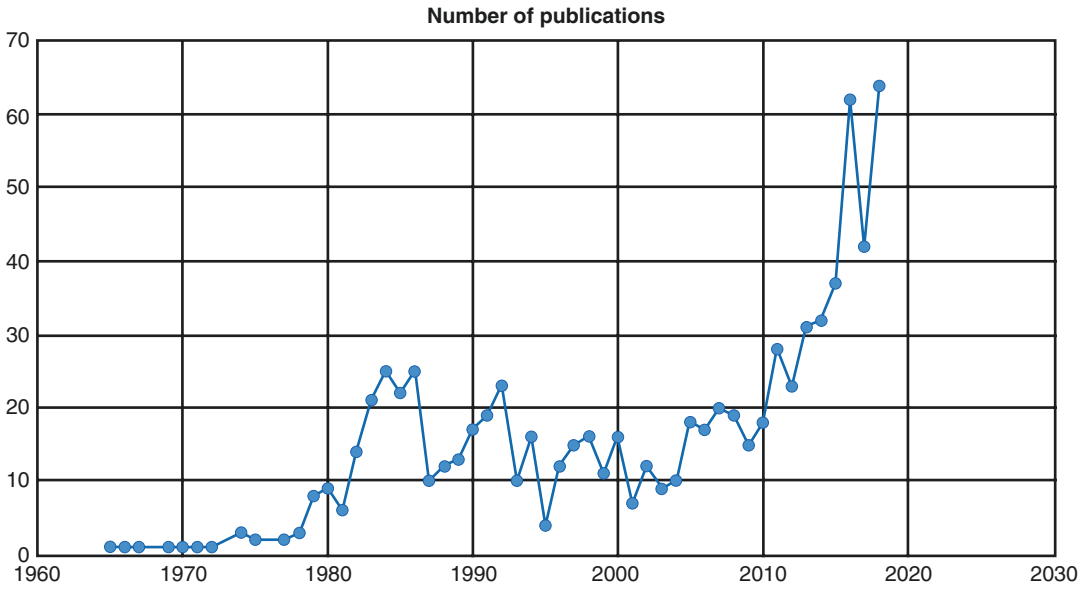

Fig. 7.6 Number of publications that are listed on PubMed about laser ablation of brain tumors since 1965

vaporization, depending on the degree of temperature that LITT achieved. Coagulation necrosis occurs when tissue temperature goes above 50 °C. Carbonization and vaporization occur when tissue temperatures pass 100 °C. The second zone also undergoes coagulation necrosis, and the third zone may receive a certain degree of thermal damage, but cells in this zone would be theoretically viable [19].

In this chapter, we discuss the current indications and review the literature in an effort to shed light on the current role of LITT in the treatment of brain metastases.

Operative Technique

At our institution, the LITT procedure is performed with the NeuroBlate System which uses a solid-state diode laser in the Nd-YAG range (1064 nm at 12 W). This laser energy is transferred to the target tissue via a CO_2 gas-cooled side-firing (directional) laser probe. The trajectory planning and insertion of the laser probe into the tumor are completed through the use of surgical navigation devices and a variety of tools specific to the NeuroBlate System. The location of the laser probe within the tumor is confirmed by intraoperative MRI. The lasing portion of the treatment is planned and controlled via the NeuroBlate System computer workstation utilizing proprietary M°Vision™ (Monteris Medical Corporation, Plymouth, MN) software under real-time MR-thermography guidance. The real-time extent of thermal ablation is calculated by the company's proprietary M°Vision software, which is based on the algorithm of heat-kill of cells (a relationship between time and temperature) and demonstrated as thermal damage threshold (TDT) lines which include distinct yellow, blue, and white TDT lines. The yellow TDT line represents the area of tissue that has been heated to the equivalent of 43 °C for at least 2 minutes; the blue TDT line represents heating to the equivalent of 43 °C for at least 10 minutes; and the white TDT line represents the equivalent of 43 °C for 60 minutes or heated to a higher temperature for a shorter interval. These TDT lines are true indicators of treatment effect on tumor tissue (Fig. 7.4) [20].

Diagnosis and Management

Metastatic brain tumors derive from a variety of different systemic cancers, most commonly of lung origin, regardless of gender, followed by breast and gastrointestinal in females and gastrointestinal and melanoma origins in males [21]. An intracranial lesion can be considered a brain metastasis without doing a biopsy if it has radiological features suggestive of metastasis in a patient with a primary cancer which has a predilection to spread to the brain. In case of ambiguity, due to atypical radiological features of absence of a known primary, stereotactic biopsy of the brain lesion is to be considered.

Recent clinical trials demonstrated that stereotactic radiosurgery (SRS) is comparable with or superior to whole brain radiotherapy (WBRT) in the management of brain metastasis. It can be used for multiple metastatic lesions, can be combined with WBRT or can be applied to a surgical-resection cavity. It is often considered a first-line treatment for patients with 1–3 brain metastases identified at the time of their diagnosis [22]. Radiation necrosis is a common posttreatment effect of SRS that can be very difficult to diagnose and treat. Advanced imaging modalities like perfusion MRI or fluorodeoxyglucose positron emission tomography (FDG-PET) can help differentiate radiation necrosis from tumor recurrence or progression [23, 24].

Surgery for brain metastases should be considered when there is diagnostic uncertainty or if the tumor is growing rapidly and causing neurological symptoms despite steroids [25]. LITT can be a good alternative for recalcitrant metastatic tumors, which have not been controlled by other therapeutic modalities, and it is often considered a last resort treatment modality for brain metastasis. Ahluwalia et al. showed that LITT can demonstrate complete response in 75% of the patients when total tumor ablation was achieved although 62.5% of the tumors progressed when ablation was subtotal [26]. Ali et al. reported that the use of hypo-fractionated stereotactic radiosurgery after LITT for recurrent metastatic tumors resulted in a lesion control rate as high as 100% compared to 57% for LITT alone [27].

Evidence

The first application of lasers to intracranial metastatic lesions goes back to 1986 when Tobler et al. reported a successful treatment of midbrain metastasis with laser ablation [28]. At that time, LITT was still in its infancy and was not coupled with MRI thermography. Since then, multiple new treatment methods for metastatic diseases have emerged, especially the use of stereotactic radiosurgery (SRS). Despite the substantial success rate of SRS, ~15% of the brain metastases are resistant to radiation [29], and LITT can be a good alternative to conventional surgery for these cases. The type of the primary source of the metastatic lesion can be an important predictor of SRS failure. Renal cell carcinoma [30], colorectal adenocarcinoma [31], BRAF wild-type melanoma [32], and triple negative breast carcinoma [33] have all been identified as SRS-resistant histologies [34]. LITT may be a good alternative or post-SRS salvage treatment for these patients.

Reports of successful utilization of LITT on metastatic lesions are sparse. An early noteworthy study by Carpentier et al. included patients who failed previous treatments such as chemotherapy, radiosurgery, radiotherapy, or immunotherapy. These studies excluded radiation necrosis from the study and worked on only recurrent metastatic lesions. Hawasli et al. reported on the use of LITT on a number of different pathologies prospectively. Among these, five metastatic tumors that were in surgically unresectable areas showed robust responses to laser ablation [35–37].

Areas of Uncertainty in LITT for Treatment of Brain Metastasis

Stereotactic radiosurgery (SRS) is widely considered the initial treatment of choice for many patients with intracranial metastases [38]. However, the treatment of lesions which recur after initial SRS can be challenging. These lesions are either recurrent metastatic disease, radiation necrosis, or a combination of the two. There are no clear imaging characteristics to differentiate between these two entities, and re-irradiation may exacerbate injury from the first treatment that is masquerading as progressive tumor. Various treatment options have been utilized for cerebral radiation necrosis including observation, hyperbaric oxygen, pentoxifylline, Vitamin E, steroids, and bevacizumab, but none of them have shown a clear benefit over the other. Surgical resection is often undertaken to confirm diagnosis and reduce mass effect. In patients refractory to drug therapy with steroids, VEGF inhibitors like bevacizumab have shown some promise [39]. However, it is not FDA approved for treatment of post-radiosurgical enhancing lesions.

LITT has gained much interest in the recent years for treatment of post-SRS enhancing lesions. It has the distinct advantage of being both diagnostic and therapeutic, and at the same time, it is minimally invasive and can help prevent major cranial surgeries in patients who already have other systemic comorbidities [40, 41]. Patient selection is key to successful treatment with LITT. It is well suited for deep-seated and difficult to access lesions. However, it can also be used for patients who have superficial lesions, but are otherwise too ill for craniotomy, have a thin scalp due to prior radiation or multiple surgeries, or who prefer a minimally invasive approach.

Another concern in the treatment of a post-SRS enhancing lesion is delayed recurrence of the enhancing lesion *after* treatment with LITT. One possible reason for delayed failure after LITT may be that lesion was really a recurrent tumor, rather than radiation necrosis. Most of the previously published literature does not clearly describe the pathological findings in their series of treated cases [42, 43]. In cases of radiation necrosis, transient resolution of cerebral edema and suspension of the cytokine cascade promoting tissue injury may be sufficient for long-term control. In contrast, LITT used for treatment of recurrent tumor may require a more extensive ablation to prevent recurrence and the addition of post-LITT fractionated SRS [44].

Complications in LITT

Previous publications regarding the use of LITT have suggested that it is safe and well-tolerated modality of treatment for a variety of intracranial lesions, including malignant tumors and metasta-

sis. However, the complication and technical malfunctions of LITT have been less frequently discussed. Review of literature on LITT treatment, including 25 clinical reports and treatment of 243 patients, reported a 20% rate of complication [45] including four (1.6%) catheter malpositions, which resulted in subdural hematoma [46], hemorrhage from arterial injury [47] and sub arachnoid hemorrhage [48], and one instance of tumor seeding along the track [49]. However, recent improvements in localization technologies, especially the skull anchoring devices, provide high degree of accuracy in catheter placement. Hemorrhage risks can be further reduced by using CT angiogram fused with the MRI while planning, especially in cases requiring long trajectories. Various complications related to tissue hyperthermia have also been described previously, which include new or worsening neurological deficits (like dysphasia [36, 37], homonymous hemianopia [50], seizure [51]), infection (cerebral abscess [52]), malignant cerebral edema [47], and CSF leak [51]. These can be minimized using smaller diffuser tips when possible [45] and by using tractography for planning and treatment of lesions close to eloquent structures [53].

Key Points

- There is currently insufficient evidence to recommend LITT as first-line therapy for brain metastases.
- It can be a very useful *adjunct* to SRS, especially in metastatic lesions which prove refractory to SRS or when radiation necrosis develops after SRS.
- It may also be considered an alternate to surgical resection in patients with deep seated and difficult to access lesions which are otherwise unsuitable for SRS.
- Further prospective trials studying SRS versus LITT are needed to assess its full safety and efficacy profile, particularly as a first-line therapy.

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