Renaissance of laser interstitial thermal ablation

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Laser interstitial thermal therapy (LITT) is a minimally invasive technique for treating intracranial tumors, originally introduced in 1983. Its use in neurosurgical procedures was historically limited by early technical difficulties related to the monitoring and control of the extent of thermal damage. The development of magnetic resonance thermography and its application to LITT have allowed for real-time thermal imaging and feedback control during laser energy delivery, allowing for precise and accurate provision of tissue hyperthermia. Improvements in laser probe design, surgical stereotactic targeting hardware, and computer monitoring software have accelerated acceptance and clinical utilization of LITT as a neurosurgical treatment alternative. Current commercially available LITT systems have been used for the treatment of neurosurgical soft-tissue lesions, including difficult to access brain tumors, malignant gliomas, and radiosurgery-resistant metastases, as well as for the ablation of such lesions as epileptogenic foci and radiation necrosis. In this review, the authors aim to critically analyze the literature to describe the advent of LITT as a neurosurgical, laser excision tool, including its development, use, indications, and efficacy as it relates to neurosurgical applications.

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LASER interstitial thermal therapy (LITT) is a minimally invasive technique for treating intracranial tumors percutaneously. The concept has existed since the late 1970s, and in 1983 Bown and colleagues⁶ used a neodymium-doped yttrium aluminum garnet (Nd:YAG) laser and achieved focal tissue coagulation in an experimental brain tumor model without tissue vaporization. Several experimental animal models were developed and further demonstrated the brain tissue changes in response to hyperthermia.^{11,12,17,53,54} However, the lack of accurate control and the inability to monitor the laser-induced thermal effects limited the widespread application of this therapy. The development of magnetic resonance (MR) thermography,¹⁴ based on the temperature dependence of the proton resonance frequency, allowed real-time image guidance of laser thermal energy delivery and rendered the treatment of deep, otherwise inaccessible lesions feasible.

Current commercially available LITT systems have been used for the treatment of neurosurgical lesions, including difficult-to-access malignant gliomas^{45,46} and radiosurgery-resistant metastases,^{9,20} as well as the ablation of lesions

such as epileptogenic foci⁵⁵ and radiation necrosis.^{23,39} In this review, we aim to critically analyze the literature to describe the advent of LITT as a neurosurgical, laser excision tool, including its development, use, indications, and efficacy as it relates to neurosurgical applications.

Biological Effects of Laser Therapy

Laser electromagnetic radiation (EMR) has been the most frequently used source of illumination in the treatment of cancer. In tumors it relies on the principle of using high-intensity EMR to treat tumors and incorporates a number of variables such as wavelength, power density, duration of exposure, and method of exposure, such as surface versus interstitial irradiation.¹⁷ Initially, the application of laser therapy was confined to surface regions, such as the skin or the digestive tract lumen, due to sole reliance on visual control for monitoring.²⁶ Interstitial laser irradiation allows the delivery of laser energy directly into the tumor tissue, maximizing its penetration and effectiveness, while minimizing its destructive effects on surrounding normal tissues.¹⁷ It had been known that the

ABBREVIATIONS EMR = electromagnetic radiation; GBM = glioblastoma multiforme; LITT = laser interstitial thermal therapy; Nd:YAG = neodymium-doped yttrium aluminum garnet; OS = overall survival; PFS = progression-free survival; PRF = proton resonance frequency; TDT = thermal-damage-threshold.

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thermal effects of EMR were confined to the region where the optical energy was absorbed,⁵⁰ but the lack of an effective, real-time monitoring system limited the application of laser therapy, especially in deep locations.

The major biological effect of laser interstitial irradiation is thermal damage.⁴⁷ At the interface of laser radiation and biological tissue, laser light photons are absorbed by surrounding tissue molecules, causing excitation and release of thermal energy. After EMR energy is converted to heat, redistribution of heat takes place through convection and conduction via blood flow. Heat redistribution is not a uniform process and relies on the applied laser power and the properties of the surrounding tissues.²⁶ Laser EMR with wavelength in the near-infrared part of the spectrum has the greatest degree of tissue penetration, on the order of 2–10 mm.³³ The properties that characterize the distribution of laser light in tissues are absorption, scattering, and bending. Absorption is mainly determined by water and hemoglobin content.³³

LITT results in heating the treated tissue and causing enzyme induction, protein denaturation, melting of membrane lipids, vessel sclerosis, and coagulation necrosis. Heat-induced tissue necrosis results from a temperature increase above 43°C, with the time until cell death depending exponentially on temperature.³³ Rapid increases in temperature can cause tissue carbonization, which subsequently changes the tissue optical properties and limits laser penetration.³⁷ Overheating can also lead to tissue vaporization, which if not released, could lead to an increase in intracranial pressure.³⁸

The optical properties of the target tissue also affect laser thermal delivery. Yaroslavsky and colleagues⁵⁶ analyzed the optical properties of selected native and coagulated human brain structures in the spectral range between 360 and 1100 nm. The absorption coefficients, the scattering coefficients, and the anisotropy factors of the samples were determined, and analysis revealed that thermal coagulation reduced the optical penetration depth substantially. The highest penetration depths for all tissues investigated were found in the wavelength range between 1000 and 1100 nm, in the near-infrared part of the spectrum. Svaasand and Ellingsen⁵¹ reported measurements of the optical properties of human brain tissue and demonstrated heterogeneity and age-dependent differences in optical penetration depth. The following year, Svaasand⁴⁹ published an analytical dosimetry model for laser-induced hyperthermia used for an *in vivo* murine mammary adenocarcinoma strain. The author concluded that the depth of thermal necrosis was a function of optical wavelength, power density, exposure time, and cooling conditions. Eggert and Blazek¹⁶ evaluated the optical properties of meninges, normal human brain tissue, and brain tumors at the spectral range between 200 and 900 nm. Within the visible and near-infrared spectral range, white matter showed the lowest level of absorption and the shortest penetration depth, low-grade gliomas revealed optical properties similar to those of gray matter, and meningiomas and glioblastomas showed significantly higher levels of absorption. The goal of LITT is to achieve selective thermal injury of pathological tissue while maintaining a sharp thermal border between the normal and tumor tissues.

Types of Lasers Used for LITT

The two main types of lasers used for LITT are the continuous-wave Nd:YAG, with a wavelength of 1064 nm and diode lasers with wavelengths between 800 and 980 nm that operate at a wide range of powers.^{37,38,45} Nd:YAG lasers achieve the highest degree of tissue penetration at wavelengths between 1000 and 1100 nm, within the near-infrared spectrum where scattering of light is greater than its absorption, thus resulting in greater tissue penetration.^{37,47} They are indicated for use in soft tissues with high blood perfusion,³⁷ such as brain tissue that is highly vascularized and perfused. Diode lasers have a higher water absorption coefficient than does the Nd:YAG laser and are thus capable of producing lesions in less time. The combination of rapid energy deposition and high optical absorption allows for sharp thermal gradients at the boundary of the ablation zone.⁹

LITT Probes

Laser thermal ablation is introduced into the tumor via an optical fiber, typically of a 600- μ m diameter of which the terminal approximately 1 cm is exposed.³⁷ Such fibers can be damaged if they absorb part of the laser energy they conduct and thus are made of heat-resistant, flexible material that typically do not absorb light between 200 and 2000 nm. Quartz or sapphire optical fibers have been used and allow the transmission of laser energy with practically no loss. Initial LITT treatments used a bare tip probe design that resulted in overheating, tissue carbonization, and subsequent diminished thermal penetration and often times optical fiber damage.⁴⁷ Subsequent developments in probe design introduced enclosure of the optical fiber in a diffusion sheath, which allowed for the power density to be reduced across the tip and for a higher laser power to be used; it also offered a nonstick surface lining the exposed optical fiber.^{7,37}

One of the most important advances in LITT probe design was the introduction of a cooling mechanism that takes the form of a sheath-like device that cools the optical fiber with a constant stream of fluid (water or saline) or cooled gas (liquid CO₂). The cooling mechanism removes heat from the probe-tissue interface and minimizes carbonization or vaporization and allows for creation of larger treated volumes.^{1,38} The cooled probe surface further minimizes probe adherence to treated tissues and decreases the incidence of probe failure.

The pattern of thermal energy deposition at the probe tip typically resembles a uniform ellipsoid lesion along the axis of the fiber. Advances in probe design led to the development of side-firing laser probes, allowing for asymmetrical tissue penetration. Cooling of the laser probe tip further accentuates the directionality of such side-firing probes. This control of the directionality of thermal energy deposition allows for “sculpting” of the laser thermal effect and conformal laser thermal coagulation of asymmetrical tumors.

Histological Changes Induced by LITT

Heat creates tissue necrosis via both acute and chronic

effects that include edema, neuronal swelling, and cell membrane disruption.⁴³ Heat-induced tissue necrosis results from temperature increase above 43°C.³³ The combination of tissue necrosis and edema may result in an increase in the volume of the treated lesion.⁴⁵ The edema is resorbed and after approximately 1 week posttreatment, granulation tissue forms, which may be followed by development of cystic changes and a gliotic margin surrounding unresorbed necrotic tissue.³⁷

Norred and Johnson³⁷ have described 3 tissue regions surrounding the laser probe after interstitial thermal therapy that can be seen on MRI and correspond to distinct histological appearances and findings. The first zone is closest to the laser probe tip and represents the area of greatest energy absorption and tissue destruction. At temperatures of 50°C–100°C, the tissues surrounding the probe tip undergo coagulation necrosis. Carbonization and vaporization occur typically at temperatures greater than 100°C, and the resulting carbonized tissues exhibit increased energy absorption, which limits the penetration of the thermal delivery. The second zone is an intermediate region with necrotic tissue and increased interstitial fluid, and the third zone is a marginal zone comprising injured but viable cells. Tissue necrosis occurs at the zone closest to the probe tip and the intermediate zone.

MR Thermometry

Several investigators examined the thermal effects of interstitial laser thermal effects by measuring changes in temperatures in vivo by several techniques, including infrared detectors,⁴ thermometers,^{12,25} thermistors placed over the skin¹⁵ or interstitial thermistor probes,¹⁷ subcutaneous thermocouple probes,²² and thermographic cameras.³¹ Real-time image guidance was explored as a means of monitoring treatment delivery and ensuring safety, and MRI was investigated as a potential imaging modality because of its soft-tissue contrast, sensitivity to temperature, and ability to visualize thermal lesions.¹¹ The goal remained to develop an MRI sequence that would allow the visualization and quantification of the deposition of heat energy in the treated and surrounding tissue while providing adequate spatial and temporal resolution.

Standard T2-weighted MRI sequences accurately demonstrate thermal lesions after treatment but cannot be used for real-time monitoring because of a time delay of more than 15 minutes before the lesion appears.¹⁰ Magnetic resonance thermography based on the temperature-dependent water proton resonance frequency (PRF) was investigated for temperature monitoring of interstitial thermal therapy. De Poorter¹⁴ reported on the excellent linearity and temperature dependence of the PRF and its ability to detect temperatures well without being hindered by the different tissue types. Since then, PRF-based phase mapping methods have formed the basis of MR thermometry and have been the preferred noninvasive temperature monitoring sequence for many in vivo applications.⁴¹ The concept of PRF-based phase mapping relies on the fact that hydrogen nuclei (protons) are screened more efficiently from the magnetic field when in a free H₂O molecule than in an H₂O molecule that is hydrogen-bonded to another. As

temperature increases, the number of hydrogen bonds decreases and thus the susceptibility of the medium changes, leading to a lower magnetic field and lower PRF.⁴¹

The ability to accurately visualize temperature changes using MR thermometry allowed the development of MR thermometry-based feedback control of LITT using a computer workstation and appropriate software. McNichols and colleagues³² reported on the use of such an integrated feedback-controlled system used on an animal model, including brain lesioning. Their lesions were correlated with histological findings, and they reported accurate MR thermometry estimation of thermal necrosis and no carbonization, vaporization, or applicator damage under feedback control.

Radiographic Appearance of LITT-Treated Lesions

Magnetic resonance imaging within the first 3 months after LITT reveals a distinct pattern of 3 zones that correspond to the histological zones of tissue injury. The probe tract can be seen, especially on T2-weighted images, and a decrease in the contrast enhancement of the lesion is typically seen on T1-weighted images.³⁸ A central zone is seen surrounding the probe tract, hypointense on T1-weighted images and hyperintense on T2-weighted images. Surrounding the central zone, a peripheral zone is seen that is surrounded by a contrast-enhancing margin, which confers a distinct “eggshell”-like appearance to the lesion. Beyond the peripheral zone, a margin dose of edema is seen, hypointense on T1-weighted and hyperintense on T2-weighted images. The lesion typically enlarges to approximately 1.5 times its original size and can remain enlarged for up to 40 days due to the edema that ensues following thermal damage.^{38,44,53,54} Resorption of the necrotic center continues over the next few months after treatment (for at least 6 months^{38,44}), and during that time the edema decreases and the lesion can decrease to half its original size (Fig. 1).

Commercially Available LITT Systems Used in Neurosurgery

Two of the most common commercially available LITT systems that have been used in neurosurgery include the NeuroBlate System (Monteris Medical, Inc.) and the Visualase Thermal Therapy System (Medtronic Inc.).

The Visualase system is an integrated, MRI-guided, minimally invasive laser ablation system. It consists of a 15-W, 980-nm diode laser generator that supplies energy to a disposable 1.65-mm-diameter outer cooling catheter that contains a 1-cm-long fiberoptic applicator with a light-diffusing tip.^{9,27} The cooling catheter is connected to a peristaltic roller pump that circulates sterile saline to cool the probe tip and surrounding tissues.⁹ The probe allows for thermal delivery in an ellipsoid-cylindrical distribution. The system is connected to a computer workstation that is subsequently connected to an MRI unit, which allows the display of real-time thermographic data at the treatment site. Extracted thermal data produce color-coded “thermal” and “damage” images based on an Arrhenius rate

FIG. 1. Postcontrast T1-weighted MR images in a representative case of a left mesial parietal GBM treated using LITT. The 24-hour postoperative image demonstrates the central tract of the laser probe, blood products, and decreased tumor enhancement. At 3 months, a peripheral rim of enhancement (eggshell pattern) is seen surrounded by residual edema. Contrast enhancement gradually decreased until 3 years posttreatment.

process model.^{32,52} A feedback control mechanism exists, and temperature limits can be designated as safety points on the pretreatment MR image. If during treatment an increase in temperature above the designated limit is detected at those points, the laser is automatically deactivated.

The NeuroBlate system uses a CO₂ gas-cooled laser probe and thermocouple that deliver controlled laser en-

ergy to the intended target.³⁶ The system uses an Nd:YAG laser optical fiber, with a laser output of 12 W, and both side-firing and diffuse-tip probes are available. The probes are available with diameters of 3.2 mm and 2.1 mm and are inserted using stereotactic guidance using one of several patient-probe interfaces including the AXiiiS device, which serves as a miniature stereotactic guidance frame, aligns to the target, and provides the appropriate trajectory for probe insertion and cranial bolts in addition to some other devices (Fig. 2). The system is connected to a computer workstation that connects to the MRI system, which provides real-time thermographic data. The software displays the extent of thermal energy delivery as thermal-damage-threshold (TDT) lines. A yellow line surrounds the target volume that has been heated to 43°C for at least 2 minutes, a blue line surrounds the target volume that has been exposed to 43°C for at least 10 minutes, and a white line corresponds to tissue exposed to 43°C for 60 minutes. The tissue outside the yellow TDT line is considered to have no permanent damage, the tissue inside the blue line is considered to have severe damage, and the tissue within the white line has undergone coagulation necrosis³⁶ (Fig. 3).

Clinical Applications of LITT

There have been several investigations into potential clinical applications for LITT in neurosurgery. LITT is a minimally invasive alternative to open surgical interventions, harnessing the powers of stereotaxy and thermal ablation. Focally contained, surgically inaccessible lesions are primary targets of this method although it is being more frequently used in cases of surgically accessible lesions as well. LITT can also serve as an alternative in the management of radioresistant tumors or in cases in which the threshold for radiation therapy has been exceeded. Recently, LITT has also been explored as a means for high-precision ablation of focal epileptogenic foci in adults⁵⁵ and children.¹³ Most publications on LITT consist of feasibility and small series,^{2,5,7-9,19,27-29,35,39,42,43,45,46,48,52} and to date, there have been no randomized trials comparing the

FIG. 2. Intraoperative photograph showing the laser probe placement through a skull bolt.

FIG. 3. Screen shot of the M-Vision LITT treatment software, showing the 3 treatment slices that are displayed for treatment and the sagittal and coronal views that demonstrate the cumulative laser thermal treatment. The *orange circles* are temperature reference points. The tumor contour is displayed in *light blue* as well as the direction of laser firing for treatment. The *deep blue line* demonstrates the TDT line that is equivalent to exposure to 43°C for at least 10 minutes. The *green circle* represents the limits of temperature detection via MR thermometry.

effectiveness of this technique with standard treatments (Tables 1–4).

Advantages of LITT over craniotomy include shorter hospital stay, reduced blood loss and postoperative pain, and the ability to perform adjuvant therapies such as chemotherapy or radiation therapy shortly after the procedure given the small incision and reduced healing time. Limitations of LITT include the inability to treat large and irregular lesions or lesions adjacent to major blood vessels or highly vascular lesions. Transient lesion volume increases in the immediate perioperative period may lead to neurological deficits and need for pharmacological or surgical intervention. Lastly, the inability to achieve optimal probe placement in some cases can potentially limit the technique. LITT has been studied in the following clinical applications.

Gliomas

Numerous authors^{2,5,7,24,27–29,33,42,43,45,46,48} have investigated the use of LITT in the treatment of malignant gliomas. Schwarzmaier and colleagues⁴⁵ reported their results of performing LITT in 16 patients with recurrent glioblastoma multiforme (GBM) using a continuous Nd:YAG laser source. The reported post-LITT median survival was 6.9 months and was better than the historical survival of < 5 months for recurrent GBM patients at that time. No permanent neurological deficits or deaths related to the procedure were reported in that series. Hawasli and colleagues²⁴

also reported on using LITT to treat 11 gliomas (4 recurrent) and 5 brain metastases, assessing the efficacy and safety of the procedure. Jethwa and colleagues²⁷ described their experience with Visualase system–based LITT for 20 patients with a various lesions including GBM, meningioma, ependymoma, and hemangioblastoma and demonstrated feasibility and safety of the procedure.

The largest series has been reported by Mohammadi and colleagues.³⁵ They described the results of a multicenter study of 34 patients who harbored high-grade gliomas (24 glioblastoma and 10 anaplastic lesions) and who underwent NeuroBlate-based LITT as an upfront or salvage therapy. The median progression-free survival (PFS) was 5.1 months and the 1-year overall survival (OS) estimate was $68\% \pm 9\%$. Greater tumor coverage by the TDT lines correlated with longer PFS. Missios and colleagues³⁴ used the NeuroBlate system to perform LITT in 11 patients with glioblastoma and similarly demonstrated significantly increased PFS and a trend toward increased OS in patients with a wider extent of thermal coverage (> 98% blue TDT line coverage or < 0.05 cm³ not covered by the yellow TDT line). Sloan and colleagues⁴⁶ reported the results of the first human study of the NeuroBlate system in a Phase I investigational device exemption–managed study to evaluate dose escalation tolerance and safety of the system in 10 patients with recurrent GBM. Median OS was 10.5 months after LITT and the procedure-related mortality rate was 0%.

Few other small case series and case reports exist de-

TABLE 1. Studies using LITT to treat primary and recurrent gliomas

Authors & Year	Tumor Type	No. of Patients	Location of Tumors (no.)	Range of Lesion Diameter or Vol	Monitoring Imaging Modality	Complications (no.)
Bettag et al., 1991	Grade II/III gliomas	5	Frontal (2); thalamic (1); temporal (2)	1–3.5 cm	CT, MRI	Local cerebral edema
Sugiyama et al., 1990	Gliomas, metastases	3	NR	1–2.5 cm	CCTS	NR
Ascher et al., 1991	Grade II gliomas	8	NR	NR	NR	NR
Roux et al., 1992	Grade II gliomas	4	3rd ventricle (2); basal ganglia (3)	2.5–3.7 cm	CCTS	NR
Kahn et al., 1994	Grade II/III/IV gliomas	6	Frontal (3); parietal (2); corpus callosum (1)	1.8–3.4 cm	MRI	NR
Leonardi et al., 2001	Grade II/III/IV gliomas	24	Frontal (7); frontotemporal (2); frontoparietal (2); temporal (1); parietal (5); parietooccipital (6); thalamic (1)	NR	0.2-T MRI	Neurological deficit (4; 2 temporary); superficial wound infection (2); seizure (1)
Schulze et al., 2004	Grade III/IV gliomas	8	NR	NR	0.5-T MRI	None
Schwarzmaier et al., 2006	Recurrent GBM	2	Temporal (1); parietooccipital (1)	NR	0.5-T MRI	NR
Carpentier et al., 2012	Recurrent GBM	4	Temporal (2); corpus callosum (1); frontal (1)	0.38–8.86 cm ³	1.5-T MRI	Neurological deficit (1); seizures (1)
Jethwa et al., 2012	Grade III/IV gliomas; hemangioblastoma; chordomas; metastasis; ependymomas	20	Frontal (6); frontoparietal (2); temporal (1); parietal (2); corpus callosum (2); thalamus (1); 3rd ventricle (2); midbrain (1); cerebellum (3)	0.95–9.63 cm ³	1.5-T MRI	Vascular injury (1); cerebral edema/hemicraniectomy (1); inaccurate placement/hemicraniectomy (1); pituitary injury (1)
Sloan et al., 2013	Recurrent GBM	10	Temporal (2); frontal (3); parietal (3); temporooccipital (1)	2.6–19 cm ³	1.5-T MRI	Vascular injury (1); neurological deficit (3; 2 transient)
Hawasli et al., 2013	Grade III/IV gliomas	11	Frontal/parietal (4); insula (1); thalamus (4); basal ganglia (1); corpus callosum (1)	2–21.2 cm ³	1.5-T MRI	Neurological deficit (5; all transient); DVT (1); hyponatremia (1); fatal meningitis (1)
Mohammadi et al., 2014 ³⁵	Grade III/IV gliomas	35	Frontal (15); temporal (5); parietal (5); insula (2); thalamus (7); corpus callosum (1)	0.7–49.9 cm ³	1.5-T MRI	Neurological deficit (7; 5 permanent); DVT (1); hyponatremia (1); wound infection (2)

CCTS = computer-controlled temperature system; DVT = deep vein thrombosis; NR = not reported.

scribing the use of LITT with smaller radiation doses (typically < 6 W) and less sophisticated delivery and monitoring systems, sometimes without MR thermography, for a small number of patients (< 10 each).^{2,5,28,40,48} Across the studies in the LITT literature on gliomas, there is significant variability in the monitoring imaging modalities that are used, likely as a result of the long time span over which these studies were completed. Most of the earlier studies were limited to a small number of patients^{2,48} and lacked detailed reports on tumor characteristics, outcomes, and adverse effect reporting. However, the most recent series^{7,24,27,34,46} have followed a significantly improved methodology to investigate the feasibility of this technique.

The lesion location has varied, with most tumors located in deep parts of the brain. A wide range of tumor sizes have been treated. Some studies^{28,29,42,43,45,48} have reported short-term follow-up, demonstrating decreased perilesional edema and tumor size. Longer-term follow-up and the existence of a control population would be useful to establish the efficacy of LITT.

Complications have been reported with the use of LITT, most of which are related to the location of the primary lesion. Complications include wound infection,²⁹ neurological deficits,^{7,24,27,29,34,46} vascular injuries,^{27,46} and cerebral edema.^{5,27} Although pooled results from these studies^{5,7,24,27,29,34,46} should be interpreted with caution, given the

TABLE 2. Studies using LITT to treat cerebral metastases

Authors & Year	Tumor Type	No. of Patients	Location of Tumors (no.)	Range of Lesion Diameter or Vol	Monitoring Imaging Modality	Complications
Sugiyama et al., 1990	Metastases	2	NR	2.6–5.0 cm	CCTS	NR
Roux et al., 1992	Pituitary adenoma; metastatic melanoma	2	Pituitary (1); thalamic (1)	1.5–2.1 cm	CCTS	NR
Kahn et al., 1994	Lymphoma; adenocarcinoma	2	Thalamic (1); parietal (1)	NR	MRI	NR
Schulze et al., 2004	Metastases	8	NR	2–2.8 cm	0.5-T MRI	None
Carpentier et al., 2008	Metastatic breast & lung adenocarcinoma	6	Occipital (1); frontal (2); temporal (1); parietal (2)	0.9–2.5 cm	1.5-T MRI	None
Carpentier et al., 2011	Metastatic breast & lung adenocarcinoma	7	NR	1–3 cm	1.5-T MRI	None
Hawasli et al., 2013	Metastases (colon, fallopian tube, melanoma, & NSCLC)	5	Insula (1); frontoparietal (1); parietal (1); frontal (2)	5.2–9.9 cm ³	1.5-T MRI	None

NSCLC = non-small cell lung cancer.

widely varied methodologies, the overall rate of complications, which themselves range from mild to severe, was 28.6% (range 20%–50% per study). Transient or permanent neurological complications were observed in 11.1% of all patients.^{5,7,27,29,46} A potentially severe complication is the vascular injury, which was severe enough to necessitate intervention in 3.2% of the patients from all studies reporting complications.^{5,7,27,29,46} Refractory cerebral edema, resulting in a hemicraniectomy, was also reported in one study.²⁷

Cerebral Metastases

Deep-seated cerebral metastases resistant to radiation therapy are another potential target for LITT. Most studies on this topic, however, are small, demonstrate great variability, and interpretation of the results is limited given the varied pathology of the metastatic lesions treated. In a Phase I trial, Carpentier and colleagues⁹ investigated the safety and feasibility of Visualase system-based LITT in 4 patients with 6 total metastases and reported similar complications to those observed in the glioma literature. The same author with other coauthors 3 years later reported on a larger series of 7 patients with 15 metastatic tumors and noted no tumor recurrence within the thermal ablation zone and a median OS of 19.8 months.⁸ Hawasli and colleagues²⁴ reported on their experience with NeuroBlate LITT in 5 patients with metastatic foci and described shorter PFS and OS durations of 8 and 5.8 months, respectively, after laser treatment.

In general authors have demonstrated an initial transient increase in tumor volume^{8,9} followed by shrinkage

of the lesion. Fabiano and Qiu²⁰ published a report on 2 patients with cerebral metastases in whom LITT failed. Both patients initially experienced a response to treatment but the lesions recurred 6 and 11 months after LITT, and examination of the resected tumors demonstrated active tumor without radiation necrosis in both patients. Further investigation is needed to demonstrate the utility of LITT in this patient population.

Radiation Necrosis

Radiation necrosis is a common late complication of radiation therapy occurring in approximately 5% of patients and developing several months or as late as 2–3 years after treatment.^{21,39} The use of LITT for management of this pathology remains restricted to individual case reports and a small patient series. Rahmathulla and colleagues³⁹ presented the first report on the use of LITT for medically refractory radiation necrosis, noting resolution of the lesion 7 weeks after treatment and a weaning of the patient from steroids. Similarly, Fabiano and Alberico¹⁹ reported on a persistently enhancing lesion and refractory cerebral edema treated 14 weeks after radiosurgery, with subsequent improvement of symptoms. Torres-Reveron et al.⁵² reported on 6 patients with radiation necrosis in whom the lesions exhibited a good volumetric response 4.5–6 months after LITT.

Epilepsy

Surgical interventions for epilepsy have evolved from standard lobectomies to individually tailored approaches

TABLE 3. Studies using LITT to treat radiation necrosis

Authors & Year	Tumor Type	No. of Patients	Location of Tumors (no.)	Lesion Diameter	Monitoring Imaging Modality	Complications
Rahmathulla et al., 2012	Radiation necrosis after metastasis treatment	1	Motor cortex	2 cm	1.5-T MRI	None
Torres-Reveron et al., 2013	Radiation necrosis after metastasis treatment	6	Frontal (3); cerebellar (2); parietooccipital (1)	0.68–3.03 cm	1.5-T MRI	NR

TABLE 4. Studies using LITT to treat epileptogenic lesions

Authors & Year	No. of Patients	Location of Lesions (no.)	Monitoring Imaging Modality	Complications
Curry et al., 2012	5	Cingulate tuber (1); mesial temporal sclerosis (1); hypothalamic hamartoma (2); frontal cortical dysplasia (2)	1.5-T MRI	None
Wellmer et al., 2014	2	Frontal (2)	3-T MRI	Transient mouth paresis (1)
Gonzalez-Martinez et al., 2014	1	Frontal (1)	1.5-T MRI	None
Esquenazi et al., 2014	2	Periventricular nodular heterotopia (2)	3-T MRI	Transient visual deficit (1)

and resections,⁵⁵ and focal destruction of the epileptogenic focus could potentially have the same outcome as resection. Because LITT is a minimally invasive technique that can deliver high-precision focal thermal ablation, and it has been explored as a new approach to epilepsy surgery. Wellmer and colleagues⁵⁵ reported on the use of stereotactic radiofrequency thermocoagulation for the ablation of focal cortical dysplasia in 2 patients with pharmacoresistant epilepsy. Both patients were seizure free at 12 and 5 months, and no deficits were encountered. While the technique does not rely on laser thermal ablation, it shares similarities with LITT, including the stereotactic placement of a probe and thermal ablation. Esquenazi and colleagues¹⁸ described the safety and feasibility of LITT for the ablation of periventricular nodular heterotopia in 2 patients with pharmacoresistant epilepsy and the authors reported mixed outcomes. Curry and colleagues¹³ reported on 5 pediatric patients who underwent LITT for ablation of focal epileptogenic lesions. No complications were described and all patients were seizure free in a follow-up period of 2–13 months. In a publication of their surgical technique, Gonzalez-Martinez and colleagues²³ reported on the combined use of a Visualase LITT system with a ROSA robot (Medtech Surgical Inc.) and intraoperative MRI to place LITT probes safely and efficiently for the treatment of an epileptogenic lesion.

Future Directions

Further development of LITT for neurosurgical applications will rely both on technological advances and refinement of the hardware and software, as well as larger clinical trials, including randomized prospective trials, demonstrating the efficacy of the modality for different pathologies, especially in the glioma population. There are anecdotal reports on the use of LITT to ablate cavernous malformations, as yet unpublished. Improvements in the probe design and technology may allow greater tumor thermal coverage, decreased need for multiple entries, and greater tissue penetration. Selective tumor thermal delivery, with sparing of the normal brain tissue, may be achievable with the use of nanoparticles to induce tissue-specific hyperthermia. Studies have demonstrated a selective uptake by tumor cells of gold nanoshells coated with polyethylene glycol,^{3,30} which can enhance the ablative effect of LITT and improve tissue selectivity.

Conclusions

LITT has emerged as a promising modality in neuro-

surgery for the treatment of lesions that are surgically inaccessible or have failed to be resolved by standard treatment modalities. The initial technical difficulties that limited its initial use have been largely overcome, and several studies have demonstrated the safety profile of this technique. Larger prospective series and standardized indications and protocols are required to demonstrate the efficacy of this technique for these challenging pathologies.

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