Laser Interstitial Thermal Therapy: Lighting the Way to a New Treatment Option in Neurosurgery

Advancements in the tools used by neurosurgeons, such as the operative microscope and image-guided stereotaxis, have redefined over time the surgical management of lesions of the brain and spinal cord. Over the past 4 decades, techniques to disrupt neural pathways for treatment of movement disorders and pain conditions or to ablate tumors have been developed that involve the stereotactic placement of a radiofrequency probe as a heat generator. More recently, heat generation within the brain parenchyma and spine has been achieved in an image-guided fashion using small-diameter catheter-based lasers (laser interstitial therapy [LITT]). LITT has been applied for the treatment of gliomas, metastasis, radiation necrosis, epileptogenic foci, and epidural spinal metastasis. In the following paragraphs, we aim to describe the antecedents that led to the development of LITT technology, describe its current use, and lay the foundation for future clinical application.

The deposition of thermal energy in the brain as a way of producing coagulative necrosis for tissue destruction has been well described. Heating of tissue above 43°C results in tissue necrosis with surrounding edema, which subsequently undergoes granulation, cystic changes, and gliosis. Although early use of radiofrequency ablation by stereotactic placement of brain lesions demonstrated the ability to heat specific locations within the brain and to follow the tissue response to heating using magnetic resonance imaging (MRI), the lack of direct feedback control of the radiofrequency ablation created an unsafe margin of error in which the extent of tissue ablated and establishment of safety margins could not be achieved. In addition, it was found that the ablation volume did not correlate with the radiofrequency dose administered, which meant that a predictable extent of ablation could not be achieved. An initial attempt at laser thermal delivery in an experimental tumor model was reported by Bown et al in 1983 utilizing neodymium-doped yttrium aluminum (Nd:YAG) laser; however, this delivery system also lacked feedback control. Because of these limitations, the interest in intracranial thermal ablation waned. The reemergence of stereotactic thermal ablation has been driven by 2 important technological developments. First, efficient catheter-based lasers emitting in the near-infrared range have been developed that are capable of producing brain tissue heating at a distance and in a predictable manner. Second, MRI acquisition sequences for the determination of tissue temperature changes have been developed that allow accurate and rapid determination of tissue temperature changes.

Commercially available LITT systems are designed in such a way that a protective delivery sheath can be stereotactically placed to allow the passage of a fiber-optic laser emitter into the body of the targeted lesion. The sheath tip is fabricated from optically transparent material and is adapted to a gaseous CO₂ or water-cooling mechanism. Two types of lasers are currently available: a 980-nm diode laser (Visualase, Medtronic Inc, Dublin, Ireland) and a 1064-nm Nd:YAG laser (NeuroBlate, Monteris Medical, Inc, Plymouth, Minnesota). The diode laser allows for faster heating because of higher absorption by tissue water molecules, but it has shorter tissue penetration than the Nd:YAG laser.

MRI thermometry has enabled the rapid feedback control on tissue heating required to enhance safety of stereotactic ablation in the brain. Temperature changes can be monitored with short temporal resolution of 1 second and a spatial resolution of 2 mm. The ability to spatially monitor temperature change allows the delineation of a target volume to receive thermal energy and the use of safety cutoff markers to avoid injury of eloquent tissue. By monitoring heating as the laser is powered on and off, predictive algorithms for tissue injury can be used to give an estimate of the injured tissue.

**ABBREVIATIONS:** LITT, laser interstitial therapy; Nd:YAG, neodymium-doped yttrium aluminum
during the procedure. This allows for further assessment of the completeness of ablation of a target lesion. Measurement of the rate of increase in damaged tissue during heating has been used to demonstrate that the lesion characteristics can influence heat distribution and time to complete ablation. Recurrent metastasis/radiation necrosis and epilepsy foci show faster ablation dynamics than glioblastoma. Immediate postablation imaging allows quick determination of the ablated volume. The MRI changes associated with acute and chronic thermal brain tissue injury have been well described. Three concentric layers of tissue change occur: a central region of coagulative necrosis, an area of vasogenic and cytotoxic edema, and an area of enhanced vascular permeability.

APPLICATION OF LITT IN NEURO-ONCOLOGY

LITT offers several advantages over traditional therapies for the management of intracranial tumors.

1. Avoiding a craniotomy may permit lesion ablation in medically fragile patients who would not tolerate blood loss or fluid shifts or in whom wound healing is impaired.

2. There is no risk of ionizing radiation damage, which can generate radiation necrosis or risk of secondary malignancy. Importantly, LITT provides a salvage option in the setting of previously radiated recurrent metastasis or radiation necrosis. Given the increased use of immunotherapy for metastatic disease and the need to avoid prolonged and high doses of steroids, LITT treatment of recurrent metastasis or radiation necrosis will likely play an important role in local control of metastatic disease to the brain. Several groups are accumulating data on the use of LITT for these diagnoses. In the first pilot study reported, 8 of 9 tumors with complete ablation showed no local recurrence, with a median follow-up of 14.2 months.

3. Shortening the procedure time to achieve complete tumor ablation is expected to reduce anesthetic time. The mean total procedure time reported recently for LITT in primary brain tumors is 2.9 hours. This total surgical time is shorter than most open craniotomies for recurrent primary brain tumor in practice; however, no standardized direct comparison has been made so far. It has been our experience that there is variability in the LITT procedure time depending on the location of tumor, size of lesion, type of system used, and type of registration method. As more experience is developed, these variables should be investigated for their effect on LITT operative time. Furthermore, a single-center experience is unlikely to give true estimates of the efficiency of LITT procedure because of differences in resources and level of experience.

4. The catheter-based insertion of the laser source in LITT permits treatment of tumors that would not have been considered operable in the past and offers the opportunity for repeated treatments in multiple orientations. For example, high-grade gliomas in the corpus callosum, insula, and thalamus can be ablated. In these lesions, LITT allows for cytoceduction, which would not otherwise be possible, with the potential to contribute to prolonged progression-free survival. Furthermore, in recurrent glioblastoma in which open surgery is complicated by risk of wound dehiscence, infection, and neurological deficit, LITT can be used to achieve cytoceduction of enhancing focal tumor nodules with low morbidity if important cortical and subcortical structures are protected from thermal injury. When LITT has been used as a salvage therapy for recurrent glioblastoma, the median overall survival after ablation has been reported to be 10 months.

5. Because the procedure involves only a 4-mm stab incision at the scalp, patients can be quickly transitioned to receive adjuvant radiation or chemotherapy without the need to wait for tissue healing required after a craniotomy. A recent study looking at doxorubicin-laden liposome biodistribution in areas of thermal ablation in a breast cancer model suggests that these areas show enhanced chemotherapy absorption and retention. The tandem use of chemotherapy agents with laser ablation may be considered, although this has not yet been reported in humans. In glioblastoma patients treated with LITT, blood-brain barrier opening is observed in the peritumoral tissue, as evidenced by increased vascular transfer constant (Ktrans) and serum brain specific enolase. The increased permeability was highest in the first few days after the procedure and remained above baseline for 4 weeks. The current practice at the University of Miami is to allow the start of bevacizumab 1 week after laser ablation of recurrent glioblastoma. We have treated 5 patients with this protocol to date with no wound complications.

The indications and overall efficacy and safety of LITT for brain tumors are currently undergoing active investigation. Early studies show a complication rate similar to that of open surgery in patients with recurrent glioma (16.7% vs 11% major complication, respectively). The current indications for treatment include locally recurrent metastasis after radiosurgery, deep-seated malignant gliomas, follicular recurrent gliomas, and radiation necrosis. In addition, at the University of Miami, we have treated a number of recurrent meningiomas that were deemed inoperable. Typically, the size of treated lesions should not exceed 2 cm in maximum diameter when measured perpendicular to the long axis of the tumor. The size limitation for a single catheter trajectory is due to decreasing heat transfer with increasing distance from the catheter. Larger lesions can be treated by using multiple catheters; however, lesions causing significant mass effect are not considered candidates for this procedure because of the edema surrounding ablated tissue and increase in lesion volume after ablation.

EPILEPSY SURGERY WITH LITT

Surgical excision of epileptogenic foci such as mesial temporal sclerosis and malformations of cortical development have yielded significant improvement in the control of seizures in patients affected by intractable focal epilepsies. Because disruption of
neurons can be achieved with coagulative necrosis, the use of LITT has been pioneered for the management of intractable focal epilepsy. In patients with mesial temporal sclerosis, the laser catheter is placed occipitally along the long axis of the hippocampus and amygdala. The effects of stereotactic laser amygdalohippocampectomy on preservation of temporal lobe neocortical function has been studied in 19 patients. In this select group, object recognition and naming outcomes in dominant temporal lobe procedures and famous face recognition in nondominant temporal lobe procedures was preserved with laser amygdalohippocampectomy compared with a decline seen in a majority of patients undergoing standard surgical procedures to treat temporal lobe epilepsy. Long-term outcome studies and neurocognitive assessments done in a randomized fashion in anterior temporal lobectomy vs stereotactic laser amygdalohippocampectomy are needed. Other emerging uses of LITT in lesional epilepsy are its use in the ablation of symptomatic cavernous malformations, focal cortical dysplasia, and hypothalamic hamartomas. In the largest pediatric series, with 11 patients having the diagnosis of focal cortical dysplasia, Engel I outcome was achieved in 45%, with a mean follow-up of 22 months. Although multiple cases have been described for the treatment of other epileptogenic foci such as periventricular nodular heterotopia, cortical tubers, and nonlesional insular focus, it is not possible to assess the effectiveness of these therapies because of the small number of cases and short follow-up. The use of LITT in nonlesional epilepsy is also in development; the first case of posterior extension of an incomplete corpus callosotomy into the splenium has recently been reported.

APPLICATION OF LITT IN SPINAL TUMORS

Autopsy studies have shown that as many as 30% to 70% of patients who have cancer develop spinal metastases, with up to 50% requiring some form of treatment. With continued advances in high-dose radiation delivery techniques, the emphasis in the surgical management of metastatic spinal tumors has become separation surgery and spinal stabilization. The focus with separation surgery is sufficient epidural tumor resection to facilitate neurological recovery and to allow a safe margin for delivery of high-dose radiation therapy, while minimizing the length of surgery, extent of spinal column disruption, and blood loss. The group at Memorial Sloan-Kettering Cancer Center published a large series of patients treated with separation surgery and stereotactic radiosurgery who demonstrated a less than 10% rate of local progression at 1 year, irrespective of tumor histology or radiosensitivity.

LITT holds great potential as a technique to achieve the goals of separation surgery in a minimally invasive fashion. This carries special significance for neurologically intact cancer patients who are poor surgical candidates because of medical comorbidities and who do not have spinal instability, but have epidural metastatic tumor progression with encroachment on the dura that would preclude the possibility of stereotactic radiosurgery. With the use of real-time neuronavigation, a Jamshidi needle is advanced into the epidural space at the level of interest via a transpedicular approach by breaching the medial wall of the pedicle at the posterior border of the vertebral body. A Kirschner wire is then passed through the needle to maintain the trajectory, and a plastic, MRI-compatible cannula is then passed to maintain access. With real-time MRI thermal feedback, the lesion is then ablated. Tatsui et al published a series of 11 patients with radio-resistant epidural tumor compression treated with this technique followed by stereotactic radiosurgery. At 2 months follow-up, the group demonstrated improvement in preoperative visual analog scale pain scores and a significant reduction in mean thickness of epidural tumor volume. LITT demonstrates potential as an adjunct in the multimodal treatment of metastatic spine tumors; however, the data available are limited and preliminary. Further work to establish indications, limitations, and expected efficacy is required.

FUTURE DIRECTIONS

The future development of LITT will require overcoming several important limitations. Current treatment-planning software is based on normal brain heating parameters and heat transfer equation. Given the heterogeneity of brain tumors and local cerebral perfusion, which may affect heat transfer, it is unlikely that a damage estimate based on tissue heating equations will be sufficient for exact lesional ablation. In fact, even in the same grade of glioma, thermal response is variable. Achieving the maximal extent of tumor ablation for each lesion has been shown to improve effectiveness of LITT and is the overall goal of treatment. Although potential injury to adjacent structures is tolerable to a certain extent in noneloquent areas where ablation can extend beyond the desired target volume, the use of LITT adjacent to highly functional areas will require more refined damage analysis and built-in safety margins. The overlay of preoperative functional MRI data and diffusion tensor tractography for ablation planning is also envisioned to enhance safety in the treatment of juxtacortical and deep lesions, respectively. Overlay of functional MRI is currently available on the NeuroBlate system. The use of multimodality imaging and 3-dimensional planning of thermal tissue injury will ultimately result in safer application of this technology. One potential method of enhancing tissue damage estimation and maximizing lesional cell death is to use temperature-sensitive MRI probes, which would highlight areas that have achieved sufficient threshold temperature for irreversible cell damage. Future application of LITT for the temperature-sensitive activation of drug delivery or photodynamic therapy of tumors is also envisioned.

Laser interstitial thermal ablation for the management of surgical lesions of the brain and spine is expected to continue to be applied in larger patient populations and studied in a prospective manner for defined indications. The clinical application of this technology requires defined patient selection criteria and detailed reporting of outcomes and complications. The technology must be compared with standard alternatives such as conformal radiation, radiosurgery for tumors, and open surgery in the setting of brain
and spine tumors. LITT does offer an opportunity for ablation of previously inoperable brain lesions, which is probably the greatest advantage of this technology over alternatives. It remains to be determined whether intervention in disease-specific groups will improve tumor control, survival, and quality of life. It is important to balance the defined advantages of this new tool with the hype generated by cultural references to laser treatment. As clinicians and scientists, it is our duty to identify how this new tool can be used most effectively and continue to understand how thermal ablation in all its various delivery modalities can be used for neurosurgical purposes.

Disclosures

Drs Hanft, Ivan, Jagid, and Komotar are paid consultants of Medtronic. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in the article.

REFERENCES


40. Santino A, Dantu W, Mainini F, Delli Castelli D, Aime S, Terreno E. Polymeric vesicles loaded with gadoteridol as reversible and concentration-


COMMENT

Diaz et al present a succinct albeit basic introduction to the development of, current indications for and future applications of laser interstitial thermal therapy. While each of these individual topics has been reviewed in greater detail in prior manuscripts, this informal review will serve as a nice introduction for those unfamiliar with the field. It should not be mistaken, however, for a systematic review with any attempt to rigidly survey the literature and collate the results.

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