Chapter 9

Laser Interstitial Thermal Therapy in Glioblastoma

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Additional information is available at the end of the chapter

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Abstract

Laser interstitial thermal therapy is a minimally invasive ablative technique that continues to gain popularity in treatment of a variety of intracranial and spinal disorders. In the field of neuro-oncology it continues to be used for treatment of a variety of intracranial neoplasms, including glioblastoma—the most common malignant primary brain tumor. Maximizing the extent of resection in patients with glioblastoma was shown to prolong patient survival. Many patients present, however, with tumors that are nonresectable due to proximity to eloquent cortical or subcortical areas, or involvement of deep brain structures. LITT procedure, on the other hand, is minimally invasive and involves placing a laser catheter under stereotactic guidance and monitoring the size of the lesion produced as a result of laser ablation using MR thermography in real time. Therefore, a number of studies explored the potential of laser ablation to accomplish significant cytoreduction and thus potentially improve patient's outcomes and prolong survival. The following chapter will review the principles of laser ablation and its current role in treatment of glioblastoma.

Keywords: laser interstitial thermal therapy, laser ablation, glioma, minimally invasive

1. Introduction

Laser interstitial thermal therapy (LITT) is a minimally invasive ablative technique that continues to gain popularity in a variety of domains of neurosurgery including neuro-oncology, epilepsy surgery, spine oncology and degenerative spine surgery, as well as chronic pain syndromes. In neuro-oncology, laser ablation is used for treatment of a variety of intracranial neoplasms but used most frequently for treatment of recurrent brain metastases and radiation necrosis, as well as treatment of recurrent and newly diagnosed, difficult to access gliomas and other deep-seated tumors. The procedure involves placing a laser catheter

under stereotactic guidance, and the size of the lesion produced as a result of laser ablation is monitored using MR thermography in real time. The minimal invasiveness of the procedure makes it a good choice in patients that cannot tolerate a large operation due to either burden of disease or poor performance status.

Glioblastoma is a diffuse primary brain neoplasm with poor prognosis. The invasive nature and malignant potential of this tumor make its treatment a challenge. The current standard of care management paradigm consists of a multidisciplinary approach by combining maximal safe tumor resection with subsequent chemotherapy and radiation [1]. Despite maximal treatment, survival rates of glioblastoma remain poor with median survival of 14–16 months. Recent evidence indicates, however, that the extent of resection of high-grade gliomas correlates with patient survival [2–6]. In a similar sense, laser ablation can provide effective tumor cytoreduction to maximize the effectiveness of adjuvant treatments. Furthermore, there is promising evidence that hyperthermia may have additional synergistic effects with radiation, as well as disrupt blood-brain barrier (BBB) and thus facilitate chemotherapy delivery to target tissues [7, 8].

The following chapter will focus on describing the principles of laser ablation and the equipment used to deliver laser energy to brain tumors, as well as discussing current evidence for the use of laser thermal therapy in management of high-grade gliomas.

2. Background

2.1. The use of hyperthermia

The concept of using heat to destroy cancerous tissue has been attempted multiple times in the past. It was, however, difficult to develop a mechanism of heat delivery to the affected tissues that would allow controlled ablation of tissues in question. One of the earliest references to the efficacy of mild hyperthermia in cancer destruction is found in 1891 in the report by Dr. Coley, an orthopedic surgeon, who made an observation of complete resolution of an inoperable sarcoma in a patient after *Streptococcus pyogenes* infection [9]. He suggested that the high fevers that accompany the illness injured cancer cells sufficiently to destroy them. He followed up that work by describing a series of 10 patients that were successfully treated with "bacterial toxin therapy" [9]. Unfortunately, his results were not reproduced by others.

In the years to come, radiation therapy and chemotherapy have established themselves as mainstream treatments for cancer. It was not until 1967 when Cavaliere et al. demonstrated selective sensitivity to heat of cancer cells, thus suggesting the use of hyperthermia as part of cancer therapy [10]. Follow-up work in animal models corroborated that notion. It was demonstrated that hyperthermia preferentially affects glioma cells compared to surrounding brain tissue. Local hypoxia and more acidic microenvironment within tumor contributes to this selective sensitivity to heat of glioblastoma [11]. Furthermore, hyperthermia potentiates the effects of radiation and chemotherapy observed in vitro [12–14].

Other factors, however, influence the effectiveness of hyperthermia. In vitro experiments showed that only 50% of sarcomas were responsive to hyperthermia resulting in tumor

remission, whereas the other 50% had no response to elevated temperatures [15]. The threshold temperature at which irreversible damage occurs is different across species. While cell cycle arrest and increased cell death in rodent cell lines occurs at 43°C, in human cell lines that threshold is at 41°C [16].

The mechanism by which mild hyperthermia induces damage to cancer cells may involve activation of apoptosis pathways in a temperature dependent fashion, resulting in changes of expression of heat shock proteins such as HSP 27 and 72. The latter display antitumor properties by initiating immunologic response resulting in activation of natural killer cells directed against tumor cells [17].

2.2. Principles of laser thermal therapy

Laser interstitial therapy is an ablative technique that results in tissue destruction as a result of heating. Photons produced by the laser light are absorbed by the surrounding tissues causing excitation and release of excess energy as heat [18]. Once the critical thermal threshold is reached, protein denaturation and irreversible tissue coagulation ensues resulting in permanent tissue damage.

The first lasers that were attempted for tissue ablation were ruby-based [19]. The amount of energy and thus tissue damage produced by these lasers was difficult to control. In 1983, Bown et al. first described the use of the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser for tissue ablation [20]. At present, two commercially available FDA-approved systems are available for use in neurosurgery in the United States: The NeuroBlate System (Monteris Medical, Plymouth, MN) and the Visualase Thermal Therapy System (Medtronic Inc., Minneapolis, MN). Laser ablation uses laser energy in the near-infrared range where the main tissue interactions are heating and coagulation (as opposed to cutting for the CO_2 laser). Both commercial laser ablation systems use diode lasers—one at the Nd:YAG wavelength (1064 nm) and the other at 980 nm. Although there have been claims that one is superior to the other, these are not founded in fact [21]. Lasers in this near-infrared range only penetrate a few millimeters into brain tissue. This heat is then propagated by conduction to allow for ablation radii that may extend up to 15–20 mm.

The wavelength of the laser light is what determines the efficiency of energy transfer to the tissues and, as a result, the volume of the lesion produced. Furthermore, the duration of tissue exposure to the laser light affects the amount of energy transferred and thus the amount of heating produced, with longer duration of exposure resulting in higher temperatures achieved in exposed tissues [22–24]. The design of the optical fiber and the laser catheter further affects the properties of the laser. Initially, lasers had to be used at very low power (1–5 W) to avoid excessive heating that results in tissue charring. Improvement in laser catheter design with the development of cooling mechanisms allowed use of higher power while still protecting nearby tissues. This also provides a non-stick catheter surface that allows the laser probe to glide easily through tissues. Current cooling systems employed in laser probe design use either cooled gas system with CO_2, or a continuous flow of saline through a sheath surrounding the optic fiber.

The laser probe tip is made of either sapphire or quartz to avoid altering the optical properties of the laser light. This design results in a spherical light distribution at the tip of the probe, and as a result, thermal energy is delivered in a symmetrical ellipsoid shape that is centered along the probe axis. The NeuroBlate System, in addition to the spherical probe design, also offers a side-firing probe which allows the surgeon to robotically control the direction of maximal heat distribution and may have an advantage in treating irregularly shaped lesions, or lesions near eloquent areas.

The Visualase system uses a 15 W 980 nm diode laser that is cooled with circulating sterile saline solution [25]. The diameter of the catheter is 1.65 mm. The laser probe tip comes with a light diffusing tip that results in spherical light distribution producing an ellipsoid area of tissue damage. This non-pulsed system produces faster lesions but the application of heat is limited to several minutes. The system is connected to a workstation that displays real-time thermography data as "thermal" and "damage" images [26, 27]. A number of safe points can be set on the pre-treatment MRI, and when the set temperature is reached at that point, the laser is deactivated.

The NeuroBlate System uses a 12 W solid-state Dornier diode laser that operates at Nd:YAG wavelength of 1064 nm [28]. The laser catheter is cooled with CO_2 gas [29]. The probes come in two diameters: 3.2 and 2.2 mm. The light diffusing tip comes in two configurations: spherical, used to produce elliptical lesions along the probe axis, and side-firing probes, that enable treatment of complex and irregularly shaped lesions. The computer interface displays thermal damage as thermal-damage-threshold (TDT) lines. The yellow line represents tissue volume that is exposed to the equivalent of 43°C for 2 min, the blue line is equivalent to exposure to 43°C for 10 min, and the white line surround the volume that received the equivalent of thermal energy of 43°C for 60 min. Based on the Arrhenius equation, the higher the temperature, the less time it takes to generate each TDT-line.

2.3. MR thermography

The use of laser ablation for treatment of tumors was first described by Bown in 1983 [20]. The first report of intracranial use for brain lesion laser ablation came out in 1990 [22]. Despite that, laser interstitial thermal therapy did not gain wide-spread use due to lack of the ability to monitor the extent of ablation and tissue damage. A variety of methods were attempted to measure thermal energy delivered to tissues and included skin thermometers, subcutaneous and interstitial probes, infrared detectors, and thermographic cameras, none of which were accurate enough to predict the size of the resulting thermal lesion [30–32]. Introduction of MR thermography revolutionized the application of laser thermal therapy since for the first time it allowed monitoring of the extent of tissue damage in real time [27]. The principle of MR thermography relies on detecting differential temperature-specific proton resonance frequency in the water molecules. At a given temperature, a proportion of water molecules are interconnected in space via hydrogen bonds between molecules. As the temperature of tissues increase during laser ablation, more water molecules are freed up from the hydrogen bonds between H_2O molecules. During application of the magnetic field, proton nuclei within free water molecules are mobilized more effectively resulting in a different proton resonance

frequency, and this difference is used to interpolate local temperature using well defined relationship [18, 33]. MR thermography does not measure the actual temperature of tissue, rather the change in temperature over time, therefore an accurate core temperature is required at the start of each ablation. The Arrhenius model is then applied to estimate the degree of tissue damage that is produced based on the temperature and the amount of time that the tissues are exposed to a given temperature. Subsequently, computer software is used to visualize the temperature damage produced in real time with accurate temporal and special resolution.

2.4. Biological effect of LITT

Heating tissue results in different types of tissue damage. Several different zones of tissue damage have been described. Heating tissues to up to 40°C typically does not disrupt cellular homeostasis. Once the temperature increases in the range of 42–45°C, the cells display marked susceptibility to cellular damage [34]. This range is typically explored in hyperthermia experiments. Further increase in temperature from 46 to 60°C results in significant cytotoxicity and consequent rapid cell death [35]. At temperatures exceeding 60°C, the damage sustained by mitochondrial enzymes, as well as cellular nucleic acids and proteins is so severe that coagulative necrosis takes place [36]. Finally, heating tissues to near boiling temperatures results in charring, tissue evaporation and carbonization, that may result in life-threatening intracranial pressure increases if not immediately relieved. In addition to temperature thresholds, the length of time that the tissue exposed to a particular temperature determines the extent of tissue damage with longer exposures resulting in equivalent damage that is observed at higher temperatures [18]. For instance, heating tissues to 43°C for 2 min will result in reversible tissue damage. Whereas heating tissues to this temperature for 10 min will result in permanent injury, and for 60 min will result in coagulative necrosis.

As tissue heating occurs, concentric zones of damage can be identified [18, 37–39]. In the area around the fiber, the temperatures can reach high numbers in excess of 60°C resulting in central core area of coagulative necrosis. If the temperature in the area adjacent to the fiber inadvertently reaches 100°C, tissue vaporization occurs and a pseudocavity is formed. Immediately outside the core area lies the intermediate zone of permanently damaged tissue with increased interstitial fluid content. The outermost zone of damage that represents marginal zone consists of edematous but viable brain tissue. Histologically, the marginal zone is defined by lack of evidence of apoptosis and vessel thrombosis, and containing axonal swelling, shrinking neurons, and hypertrophied endothelial cells—markers of reversible tissue injury. Following a laser ablation procedure, tissues typically exhibit an increase in size due to the presence of necrotic tissue and perilesional edema. Over time, however, the necrotic core of the lesion is replaced by granulation tissue resulting in lesion shrinkage and scar formation.

2.5. Radiographic appearance

The typical appearance of high grade glioma is an irregular and heterogeneously enhancing lesion on T1-weighted images. After treatment, there are typical changes that are observed on subsequent imaging studies [40–42]. Immediately after procedure one can appreciate an area of hyperintensity within the lesion on T1-weighted MRI images. This finding corresponds to

coagulated blood products within the ablated area. On the corresponding CT scans this would appear as a hyperdense area typical in appearance of blood products. With administration of contrast, there is typically an area of peripheral rim enhancement. This is thought to represent an area of sublethal tissue damage with disrupted blood-brain barrier and leaky capillaries [7].

3. Application of laser therapy for treatment of intracranial disease

3.1. Laser in glioma treatment

Since the first implementation of laser therapy for intracranial tissue ablation, treatment of a variety of intracranial lesions was attempted, including metastases, radiation necrosis, meningiomas, ependymomas, as well as gliomas. High grade gliomas constitute 14.9% of primary tumors brain tumors and 47.1% of all malignant primary brain and other CNS tumors. Despite maximal therapy, survival remains poor. Survival without any treatment is 9 weeks [43]. With maximal treatment according to the latest guidelines, the survival is prolonged to 14.6 months [1]. The combined use of radiation and temozolomide protocols increase survival rates to 27% at 2 years [1]. Recently, several retrospective studies have demonstrated that increasing the extent of resection of glioblastoma, improves patient survival [2–5]. Furthermore, intraoperative use of surgical adjuncts such as intraoperative MRI or 5-ALA that allow visualization of the partially resected tumor and thus allow for a better extent of resection correlate with prolonged progression free survival [44, 45].

Many newly diagnosed glioblastomas involve deep or eloquent cortical or subcortical areas thus rendering these lesions difficult to resect or unresectable from an open surgery perspective. In these situations, the use of destructive, minimally invasive techniques such as LITT is very attractive as a means to cytoreduce the tumor. At other times patients may be too sick to undergo a lengthy open craniotomy for tumor resection. Finally, treatment of recurrent glioblastoma is challenging as very few effective options exist at present, thus the possibility of using laser ablation for treatment of recurrent tumor ads another tool to the neurosurgeon's armamentarium.

In 2013, the first human phase I study was published that used escalating dose of laser therapy to assess safety of the procedure and its efficacy in controlling tumor growth in patients with recurrent high-grade gliomas [41]. The study recruited 11 patients from two institutions and was completed using the NeuroBlate System. Three thermal damage threshold lines were assessed: yellow line (equivalent to heating of tissues to 43°C for 2 min), blue (43°C for 10 min), and white (43°C for 60 min). Ultimately, ten patients underwent LITT treatments and were followed for a minimum of 6 months or until death. Initially three patients were treated to the yellow TDT line and followed for 14 days to assess for signs of toxicity. If two out of three patients developed signs of toxicity, no further dose escalation was performed. If no toxicity was observed, the dose of treatment was escalated to first the blue line, and then the white line. The mean size of treated tumors was 6.8 cm^3, and an average of 78% of total tumor volume was covered. Median overall survival was 10.5 months after LITT which was increased compared to historic controls of 3–9 months [46, 47]. The median PFS at 6 months

and median overall survival in the study was >30%. One patient had a new permanent postoperative neurological deficit, and one patient had a vascular injury resulting in a pseudoaneurysm. Both patients were in the white TDT line subgroup. This study demonstrated that LITT is a feasible and safe treatment modality for recurrent high-grade gliomas, and that the blue line should be used as the margin of treated area.

The first multicenter study to investigate whether cytoreduction achieved with the use of laser for difficult to access high-grade gliomas could have a similar survival benefit compared to surgery was a retrospective study that looked at outcomes in 34 patients with high grade gliomas that were treated with LITT, 19 of them treated upfront, and 16 patients as salvage therapy [48]. The median overall survival was not reached in the study. One year estimated overall survival was 68%, and median progression free survival was 5.1 months. They also demonstrated that increased coverage by the thermal damage threshold lines correlated with better progression free survival of 9.7 vs. 4.6 months. The latter also relates to tumor volume with smaller tumors being easier to achieve complete coverage with TDT lines. When looking at failure patterns, 5 tumors recurred within the treatment field, 12 patients recurred at the periphery of the treated volume, 5 tumors recurred within 2 cm of the original area of enhancement, and one case had a remote recurrence. Overall, the authors concluded that LITT is an effective treatment modality for newly diagnosed and recurrent high-grade gliomas with improved outcomes correlating with extent of tumor coverage by analogy with extent of resection in surgical series.

Recently, a meta-analysis of the efficacy of LITT treatment of newly diagnosed and recurrent high-grade gliomas was published [49]. Ivan et al. extracted information and analyzed the data pertaining to treatment and outcomes of newly diagnosed high-grade gliomas treated with LITT. They identified four articles that reported treatment of 25 patients with newly identified gliomas. Tumor volume was available for 22 patients and the mean was 16.5 cm^3, whereas the extent of volume treated with laser was available for 9 patients with an average of 82.9% tumor coverage. Complications data was available for 13 patients, and there were no intraoperative mortality or complications. Serious postoperative complications occurred in two patients, one succumbing to postoperative central nervous system infection, and another one requiring hemicraniectomy for malignant post treatment cerebral edema. No permanent new postoperative neurological complications were noticed among these patients. Outcome analysis revealed a mean follow up of 7.6 months, with 12 patients still followed or lost to follow-up. Median overall survival was 14.2 months and the average PFS was 5.1 months. These results are similar to results reported in the literature that vary from 8.5 to 14.5 months [50, 51]. Thus, this systematic review demonstrates that LITT is a safe and effective procedure for newly diagnosed high-grade gliomas achieving outcomes similar to cases with open surgical resection.

Even with the full complement of modern treatments, the survival of glioblastoma patients remains poor in the range of 14–16 months after surgery, chemotherapy and radiation. Recurrence is the rule rather than the exception, at which point the prognosis is quite poor with the 6-month progression free survival rates of 5–15% [52, 53]. Reoperation in the recurrent setting was shown to be of benefit [54]. The risk of complications needs to be weighed against potential survival benefit, which is where the role for the use of LITT in recurrent

high-grade gliomas could be exploited the most. A recent systematic review summarized the outcomes of laser-mediated cytoreduction in high-grade gliomas [55]. Six articles were identified that included outcome analysis for treatment of 64 lesions in 63 patients. The range of pre-treatment tumor volumes was from 0.37 cm^3 to 68.9 cm^3. Postoperatively, serious complications included a permanent neurological deficit in 7 patients (12%), vascular injuries in 3 patients (3%), and wound infection in 1 patient (2%). The authors did not comment on outcome measures due to differences in outcome metrics used in the studies. Thus, they concluded that currently there is insufficient evidence to recommend LITT for treatment of recurrent high-grade gliomas. It is a technique that allows safe and accurate ablation of tumor tissue, though the complication rate associated with this procedure remains around 15% that is similar to open craniotomy procedures [56, 57].

3.2. Laser ablation near eloquent areas

The most common complication reported after laser ablation is a temporary or permanent neurological deficit, such as hemiparesis or aphasia. The reported complication rates range from 0 to 29.4% for transient and 0–10% for permanent postoperative neurological deficits. In many instances it is the damage to subcortical tracts that results in a new deficit. Recently, diffusion weighted imaging (DTI) with fiber-tracking algorithms started to be increasingly used in tumor resection surgery to avoid injury to eloquent white matter tracts. A recent study investigated the role of integration of DTI fiber tracts in laser thermal therapy. Using the NeuroBlate System, Sharma et al. looked that the extent of the overlap of the thermal damage threshold lines with the cortical fibers that would result in a postoperative motor deficit [58]. Retrospective analysis of 80 patients who underwent LITT for tumor near a critical area was performed. Fourteen patients (17.5%) had developed a new postoperative deficit that was temporary in 3 patients and permanent in 11. When looking at the average volume or surface overlap between treated area and the corticospinal fibers, there was a significant difference between the group that developed a postoperative deficit and the group that did not. Therefore, even a minimal overlap between the treated area enclosed within thermal damage treatment lines and the descending motor fibers can cause a postoperative neurological deficit after laser ablation. Addition of DTI tractography to treatment plans of lesions located in proximity to eloquent areas can help avoid fiber damage and thus preserve neurological functioning of the patient and is routinely used in our ablations near critical subcortical fiber tracts.

3.3. Advantages of LITT

There are a number of characteristics of LITT that lead to its recent popularity and investigation for multiple applications in neurosurgery. The main one is the ability to produce a lesion in a location that is difficult to access with open surgery. It is a minimally invasive technique that requires a very small incision and subsequently a very short period of healing. Given the minimally invasive nature of the procedure, the operation can be done under local anesthesia in a cooperative patient. This allows treatment of lesions in patients that cannot otherwise tolerate a large craniotomy.

Furthermore, LITT is a thermal ablating technique, which means that at the time of tumor recurrence the procedure can be repeated. That is not always the case with ionizing radiation, for example, since there is cumulative accumulation of radiation dose that limits the number of treatments that can be safely offered. The procedure also offers the advantage of obtaining a tissue specimen, when combined with needle biopsy, for updated pathology and biomarkers to follow tumor evolution and response to therapy. Finally, the minimally invasive nature of the procedure allows continued use of adjuvant treatments around the time of the surgery, or very shortly thereafter, obviating the need of waiting at least 2–3 weeks for the tissues to heal before restarting chemotherapy of radiation. In fact, there is evidence that LITT may open up the blood-brain barrier in the vicinity of treatment area, thus enhancing delivery of chemotherapeutics in that time range [7].

3.4. LITT and blood-brain barrier

The blood-brain barrier (BBB) is one of the main challenges for chemotherapy delivery to brain tumors. Various methods have been attempted to bypass or disrupt the blood-brain barrier, including convection-enhanced delivery of implanted catheters into the tumor, intra-arterial mannitol injections, or focused ultrasound to temporally disrupt the blood-brain barrier. Recently, laser interstitial thermal therapy was implicated in disrupting the integrity of tumor endothelial cells post-treatment. The core of the lesion that is produced after laser ablation is coagulum that consists of a permanently damaged tissue, whereas at the periphery where the temperature reaches 40°C and is insufficient to result in cell death, however it does lead to physiological temporary disruption in cellular function resulting in transient disruption of the BBB. Imaging of the lesion after laser ablation therapy displays an area of peripheral contrast enhancement that was speculated to represent disruption of the blood-brain barrier. This was demonstrated in a rodent model where there was extravasation of Evans blue dye that was injected intravenously at the periphery of the lesion post ablation [59].

Recently, advanced MRI imaging was used to demonstrate the presence of blood-brain barrier disruption [7]. Dynamic contrast-enhanced MRI was used in 14 patients to determine transfer coefficients (Ktrans) as a measure of permeability at the periphery of the lesion produced by laser ablation. In all patients, Ktrans coefficient peaked after the procedure, and then declined gradually over the next 4 weeks. The authors also used brain specific enolase (BSE) serum levels as a marker of BBB breakdown, and those levels peaked at about 3 weeks, followed by gradual decline and normalization at 6 weeks. This data suggests that there is some breakdown of the blood-brain barrier in the first few weeks following laser ablation of primary brain tumors, and that this may facilitate chemotherapy delivery to residual infiltrated tumor in the immediate post-procedure period.

3.5. Sensitization to radiation

Radiation is one of the non-surgical modalities that has significant impact on survival in glioblastoma patients, yet the control rates remain poor despite maximal therapy. Several studies have demonstrated the synergistic effect of hyperthermia in sensitizing tumor tissues to radiation and improved tumor control [60–62]. A recent study investigated the mechanism by which

thermotherapy affects tumor cells that results in enhanced sensitivity to radiation [8]. Glioma stem cell (GSC) cultures and mice bearing glioma xenographs were first exposed to 42°C for 1 h followed by radiation. When compared to radiation or hyperthermia alone, glioma stem cells are most significantly affected when both modalities are used in combination. Exposure of GSC to heat and radiation reduced stem cell survival, proliferation, and DNA repair, as well as promoted cell death. On the molecular level, there was significantly less AKT phosphorylation in cells exposed to hyperthermia and radiation, and rescuing AKT phosphorylation levels reversed negative effects of heat and radiation maintaining viability of tumor stem cells. Furthermore, exposing the mice bearing glioma xenographs to hyperthermia and radiation consistently reduced tumor size in these animals, and significantly increased their survival compared to animals exposed to either hyperthermia or radiation alone. These results add further evidence that the addition of hyperthermia to the standard radiation treatment may have a significant additive effect with respect to tumor control that is mediated by altering phosphorylation levels of PI3K-AKT pathway. Thus, early radiation therapy after laser ablation procedure may have additive effect on controlling tumor growth and affecting glioma cell viability. Further studies are needed to explore the clinical potential of this combined treatment.

4. Representative cases

4.1. Patient 1

The first patient is a 48-year-old right handed gentleman who presented to hospital after sustaining a fall. A CT head was performed that revealed a 1.9 × 2.0 cm ring-enhancing lesion in the left cingulum with significant amount of surrounding edema (**Figure 1**). On initial evaluation, patient had 4/5 right hand weakness and right-sided pronator drift that improved with initiation of steroids. The lesion was located immediately below the paracentral lobule, and given its proximity to this eloquent area, a needle biopsy with subsequent laser ablation was offered to the patient, who agreed to proceed. The lesion was treated using two trajectories using a side-firing laser (Monteris) to ensure the full tumor volume was included within blue thermal threshold treatment lines. Postoperatively, his neurological exam remained stable with the exception of the transient neglect of right lower extremity. Pathology of the tumor was consistent with glioblastoma. Molecular analysis demonstrated negative staining for IDH-1 and p53, intact 1p/19q, and non-amplified EGFR. Proliferative index was moderate with Ki-67 about 9–10%. The patient underwent subsequent concurrent chemotherapy and radiation according to the Stupp protocol followed by twenty-two cycles of temozolomide. Following that, he was followed with regular MRI brain scans that demonstrated a significant decrease in the size of the lesion over the first 12 months. It remains stable without evidence of recurrence or progression 6 years after the initial procedure (**Figure 1**).

4.2. Patient 2

The second patient is a 66-year-old right handed woman who was evaluated for spells of dizziness and visual disturbance. Brain imaging demonstrated a homogenously enhancing right parahippocampal lesion measuring 1.2 × 0.9 cm with surrounding edema (**Figure 2**). Patient

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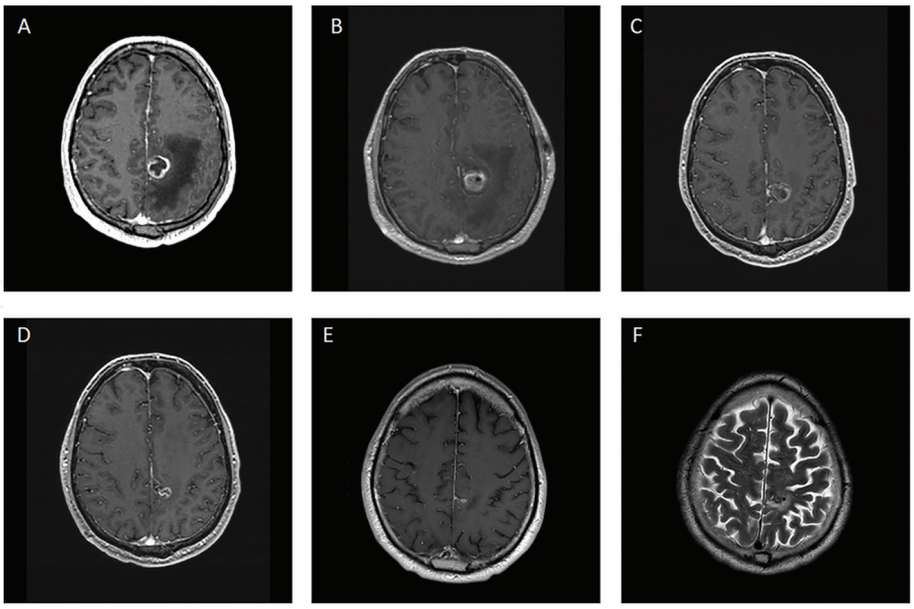

Figure 1. Representative axial T1-weighted MRI images obtained post gadolinium contrast administration. (A) Preoperative; (B) at 24 h post laser ablation; (C) at 3 months; (D) at 1 year; and (E) at 6 years post laser ablation; (F) a corresponding T2 weighted axial slice demonstrating very limited amount of edema surrounding the lesion.

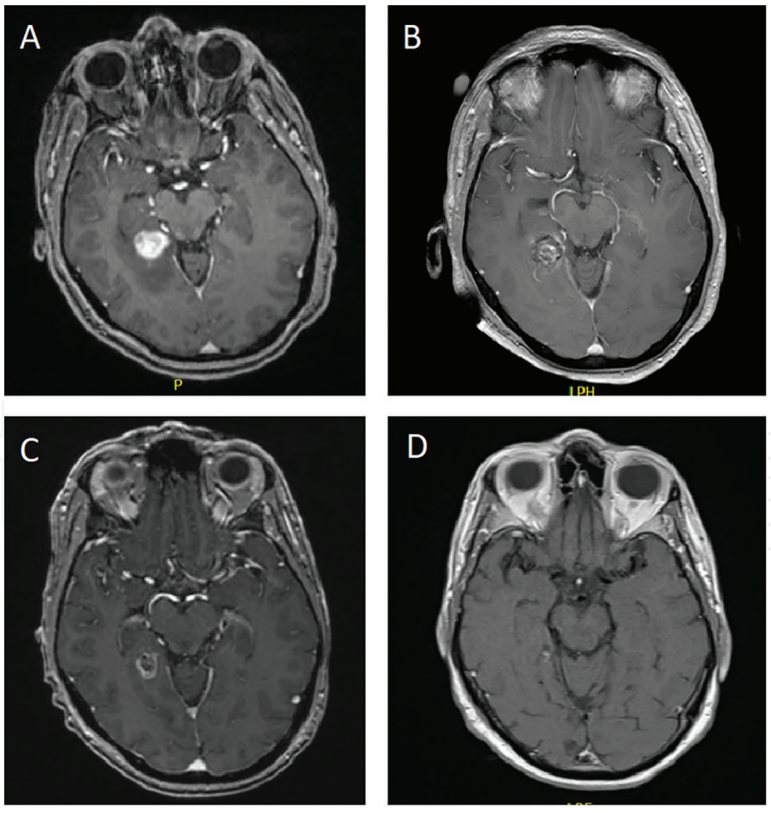

Figure 2. Representative MRI images of the right temporal lesion of patient 2. Axial T1-weighted MR images following contrast administration. The patient originally presented with a right mesial homogenously enhancing lesion (A). Immediately following laser ablation the characteristics of the lesion changed with markedly less contrast uptake (B). In the subsequent months, the lesion has continued to involute and significantly decreased in size at 3 months (C), and almost disappeared completely at 2.5 years (D).

was started on Keppra. Laser ablation of the lesion with a concurrent biopsy was recommended given the deep-seated location of the tumor. A single trajectory was used employing a side firing laser (Monteris). Complete tumor coverage was achieved as indicated by inclusion of the entire tumor volume within the blue thermal damage threshold lines. She had an uneventful postoperative course. No new postoperative deficits were associated with the procedure. Pathology showed a hypercellular glial tumor with marked nuclear atypia, frequent mitoses, and vascular proliferative changes, consistent with the diagnosis of glioblastoma. A Ki-67 labeling index in excess of 30% was focally noted. Greater than 80% of tumor cells stained positively with antibody to p53. 1p/19q chromosomes were intact, and EGFR was non-amplified. Following laser treatment, the patient received chemotherapy and radiation according to Stupp protocol, followed by adjuvant temozolomide for eight cycles that was stopped due to persistent myelosuppression. She was followed with regular MRI scans of brain with great local control with nearly complete resolution of the treated lesion. Unfortunately, at 2.5 years after procedure she developed disease progression at a remote site.

5. Conclusion

Laser thermal therapy is an effective treatment modality for newly diagnosed and recurrent gliomas. It may act in conjunction with radiation thus potentiating the effects of radiation. In addition, it may result in transient disruption of blood-brain barrier in the area of treatment and thus facilitate chemotherapy delivery postoperatively. Further studies examining the outcomes of new and recurrent glioma treatment would help to define the role that laser ablation play in management of this devastating brain tumor.

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