Laser Ablation of Recurrent Malignant Gliomas: Current Status and Future Perspective

Recurrent malignant glioma continues to be a clinical challenge, and repeat surgery is an option in only select patients. Stereotactic laser ablation, a new minimally invasive technique, can be used as an alternative to surgery. We review the current literature on laser ablation for recurrent malignant gliomas as well as discuss practical and theoretical advantages and disadvantages of this emerging technique in comparison with repeat surgery or radiation. We also discuss the potential for laser ablation to augment adjuvant therapies, namely, chemotherapy, radiation, and immunotherapy.

KEY WORDS: Glioblastoma, Laser thermal therapy, Recurrent malignant glioma, Stereotactic laser ablation

Surgical resection, followed by adjuvant chemotherapy and radiation therapy, continues to be the mainstay of therapy for newly diagnosed high-grade gliomas (HGGs). The standard of care has remained unchanged for nearly a decade despite many efforts to develop therapeutic innovations. If a tumor is surgically accessible, surgery remains the initial treatment for most patients. Almost all patients with an HGG will have a recurrence, but only a select group of patients qualify for repeat surgery or repeat irradiation. Stereotactic laser ablation or laser interstitial thermotherapy (LITT) is an emerging minimally invasive technique that leads to cell death via the administration of heat. Laser ablation of primary and recurrent HGGs that would formerly have undergone biopsies is increasingly performed by neurological oncologists. We review the benefits and limitations of laser thermotherapy as a potential new treatment for recurrent gliomas and discuss future therapeutic advancements.

BENEFIT OF CYTOREDUCTION

Surgery provides cytoreduction of the tumor and remains the preferred initial therapy for newly diagnosed HGGs. Two randomized, controlled trials were conducted that demonstrate surgical resection to be beneficial for patients with newly diagnosed malignant gliomas. Many observational studies demonstrate a correlation between the extent of surgical resection and both progression-free survival and overall survival in newly diagnosed gliomas. Analysis of multiple prospective cohorts demonstrated that repeat surgery for recurrent HGGs does not correlate with survival. However, there is a correlation between the extent of resection and survival in patients undergoing repeat surgery for recurrent HGGs. For example, in 1 case series, the extent of resection >80% for recurrent HGGs correlated with an improvement in overall survival. Given the current data, it is imperative to determine which patients may benefit from repeat surgery for recurrent HGGs. Clinical scales can be used to predict patient survival. Preoperative criteria such as performance status, age, volume, and involvement in eloquent brain areas can be used to stratify malignant gliomas into 3 survival groups (poor, intermediate, and good). Tumors in an eloquent location, low functional status, and large tumor volume are factors that significantly correlate with a poor prognosis. A practical clinical scale that considers performance score and the presence of ependymal enhancement can also provide a practical assessment of whether repeat surgery would be beneficial. These scales can provide guidance to clinicians to determine which patients would benefit from surgical resection.

Stereotactic laser ablation reliably results in tumor cytoreduction (Figure). Stereotactic laser
Ablation has been used as a salvage therapy for recurrent gliomas. Multiple case series provide preliminary data to indicate that laser ablation can be safe and effective for recurrent gliomas. To date, the largest case series consists of 21 patients with recurrent gliomas. This study did not include some clinical outcome measures such as functional performance and survival but was rather a technical feasibility investigation. More modern series, within the past 10 years, demonstrated safety and an overall survival that spanned 10 to 15 months after treatment. However, no prospective clinical trial has been conducted to compare laser ablation and surgical resection. In a multi-institutional study including patients with both recurrent and newly diagnosed HGGs, greater extent of tumor coverage by laser thermal treatment correlated with improved progression-free survival. Favorable tumor coverage was related to size. Tumors of $<10$ mL of volume were able to be more completely ablated by laser treatment, which in turn correlated with better survival. Similar to traditional open surgery, the extent of laser thermal tumor ablation, similar to the extent of surgical resection, appears to correlate with survival.

One of the main advantages of LITT compared with conventional surgery is the ability to treat tumors in locations such as the insula, corpus callosum, and thalamus that might require traversing eloquent tissue or vascular territories for conventional resection. Some neurosurgeons routinely use tractography in their surgical planning, but no data have yet been published in which planning with tractography is compared with planning without tractography. LITT is also minimally invasive and therefore significantly reduces the incision size used compared with traditional therapy. With regard to patients with recurrent gliomas who often have a previous healed incision or have undergone radiation and/or bevacizumab (BVZ) use, smaller incisions can decrease the risk of complications such as wound breakdown and infection. Another benefit is the visualization of treatment volume with real-time magnetic resonance imaging (MRI) thermometry (Table)—a benefit that LITT shares with resection using intraoperative MRI. In open surgery, the borders of HGG masses are hard to differentiate from normal brain parenchyma, given the infiltrating nature of the tumor. Historically, the amount of contrast-enhancing tumor that is surgically resected is used to determine the extent of resection. The supplementation of conventional surgery with intraoperative MRI, intraoperative fluorescence guidance, or awake monitoring can improve a surgeon’s ability to achieve maximal safe

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**TABLE. Advantages and Disadvantages of Laser Thermotherapy Compared With Open Surgery**

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<tr>
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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Surgery</td>
<td>Provides more specimen; sampling error less likely</td>
<td>Difficult to determine tumor border</td>
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<td></td>
<td>Can reduce both tumor bulk and surrounding edema</td>
<td>Not able to safely access all locations</td>
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<tr>
<td>Laser thermotherapy</td>
<td>Minimally invasive</td>
<td>Size limitation</td>
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<td></td>
<td>Real-time magnetic resonance imaging to identify region of ablation</td>
<td>Increased edema after ablation in some cases</td>
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<td></td>
<td>Can be used for difficult-to-access lesions</td>
<td>May require multiple trajectories</td>
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<td></td>
<td>May enhance antitumor immune response</td>
<td>Potential for thermal injury to large blood vessels</td>
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FIGURE. Magnetic resonance imaging of a 70-year-old man who presented with aphasia, visual field deficit, and sensory loss with an enhancing lesion in the left parietal region (left). The patient underwent laser ablation with the laser placed along the long-axis trajectory (middle). The patient had symptomatic improvement immediately, and postoperative imaging showed central necrosis of the tumor with a decrease in tumor bulk (right).
During LITT, MRI thermometry is used to identify the areas of energy absorption and tissue destruction. Therefore, neurosurgeons can visualize the area of tumor undergoing cell death/necrosis. After LITT, there is a continuous reduction in metabolically active tumor volume as evaluated by $^{11}$C-methionine positron emission tomography.

Tumor size is a limitation for LITT. For neurosurgical applications, the Nd:YAG laser is used to provide the highest level of tissue penetration. Typically, lesions 2 to 3 cm in diameter can be treated with 1 trajectory. Larger tumors require more trajectories, and the prolonged operating time may make this option less attractive if the lesion is amenable to open surgery. Also after LITT, there may be an increase in cerebral edema surrounding the necrotic core of the tumor. In some patients, this increased edema in the acute period can lead to worsening neurological symptoms and can require aggressive medical management. On the other hand, the ability of LITT to eliminate small vessels that no longer have an intact blood-brain barrier (BBB) has the potential to reduce cerebral edema and associated symptoms. At our institution, we maintain patients on high-dose steroids for 24 hours after ablation followed by a 3- to 5-day taper depending on the amount of preoperative edema. Aggressive medical management of edema via hyperosmolar therapy and admission to the intensive care unit are reserved for patients who have symptoms of edema refractory to high-dose steroids. However, to date, at our institution, patients requiring aggressive medical management have been patients with metastatic lesions rather than HGGs.

Typically, laser ablation of intracranial lesions leads to expected hemorrhagic necrosis, but there are instances of moderate to severe hemorrhage after ablation. In 1 series of LITT for glioma, 3 of 34 patients had significant hemorrhage. More than half of the patients had noticeable hemorrhage on MRI in the ablation region after treatment, but this was an expected outcome and did not cause symptoms. All of the 3 patients with significant hemorrhage were patients with newly diagnosed HGGs in locations that were too deep for surgical evacuation. From our experience, we caution laser ablation close to large blood vessels. We have had a morbid postoperative hemorrhage that was recognized immediately during the postprocedure MRI in the left temporal lobe near the middle cerebral artery. The patient did have aphasia and hemiparesis, which improved over time with rehabilitation. We have had no further morbid hemorrhages after this case because we changed our practice and avoid ablation near the middle cerebral artery. However, the mechanisms of these postoperative hemorrhages are still unknown. A pseudoaneurysm that caused a delayed hemorrhage 6 weeks after ablation also required treatment in another patient who underwent LITT for a recurrent glioma, perhaps providing a clue to the underlying pathophysiology of unexpected significant hemorrhage.

More studies are needed to establish the potential role that LITT may play in recurrent glioma. Currently, there are no studies to compare outcomes of conventional surgery vs outcomes with LITT. Combined with stereotactic brain biopsy, LITT distinguishes between tumor recurrence and radiation necrosis. In cases of radiation necrosis, it has the potential to reverse and stop the progression of the causal radiation vasculopathy in cases of pseudoprogression rather than recurrence. Furthermore, LITT provides reliable cytoreduction for even the most radiation-resistant recurrent malignant gliomas. In our experience, we find LITT to be ideal for patients with radiographic evidence of recurrent HGGs who are not candidates for open resection but are in need of cytoreduction for symptomatic relief. However, there are many potential ways that LITT can be used to augment current or emerging therapies for recurrent HGGs.

**POTENTIAL TO IMPROVE ADJUVANT THERAPY**

Current adjuvant therapy for newly diagnosed HGGs includes chemotherapy and radiation. Stupp et al. demonstrated that the addition of temozolomide (TMZ) to standard radiation improves survival in HGG patients, and TMZ remains a standard of care. TMZ has been approved for use in recurrent HGGs as well and provides improvement in quality of life in these patients. In patients with recurrent HGGs, O$_6$-methylguanine methyltransferase promoter methylation remains a prognostic marker for improved outcome after TMZ treatment. TMZ in combination with other therapeutic agents has not been shown to have improved efficacy compared with single-agent TMZ therapy. In addition to TMZ, there have been trials of multiple chemotherapeutic agents in the treatment of recurrent HGGs. Multiple trials have evaluated niososurées as single-agent therapy. The anti-vascular endothelial growth factor antibody BVZ is approved by the US Food and Drug Administration for the treatment of recurrent HGGs. For newly diagnosed HGGs, BVZ provides a benefit in progression-free survival but not overall survival. For recurrent HGGs, several studies indicate a benefit in progression-free survival with BVZ treatment compared with historical controls. A recent trial comparing lomustine alone or in combination with BVZ indicated a benefit in progression-free survival, but not overall survival, with combination lomustine and BVZ in patients with recurrent HGGs. Higher functional status and concurrent therapy with irinotecan are positive prognostic factors in recurrent HGG patients receiving BVZ therapy. In summary, alkylating chemotherapeutic agents and BVZ remain the standard of care for patients with recurrent HGGs.

Due to the BBB, many chemotherapeutic agents do not reach the tumor, and, therefore, local delivery is a method to circumvent this obstacle. After laser ablation, there is a perilesional zone of BBB breakdown that persists. LITT may be able to enhance local drug delivery in the perioperative period given these properties. In 14 patients with recurrent HGGs, disruption of the peritumoral BBB persisted for weeks after laser ablation. The peak of permeability was within 1 to 2 weeks. The ability to break down the BBB after LITT may be potentially exploited and allow for the administration of therapeutic agents in the weeks after laser ablation.
External beam radiation is also a standard adjuvant therapy for HGGs. For recurrent HGGs, no prospective studies exist to determine the benefits of repeat irradiation. A repeat irradiation dose of 40 Gy is widely accepted as a treatment threshold in order to prevent significant radiation toxicity. Repeat irradiation is an accepted salvage therapy for recurrent gliomas.\textsuperscript{45} Stereotactic radiosurgery has been accepted as a possible salvage therapy for recurrent HGGs.\textsuperscript{46-48} Improved overall survival in patients with recurrent HGGs undergoing salvage stereotactic radiosurgery was associated with young age, Karnofsky Performance Scale score $>70$, absence of neurological deficits, and previous external beam radiation after surgical resection.\textsuperscript{55} Stereotactic radiosurgery does not provide an additional survival advantage to patients with HGGs, suggesting that some tumor cells and, perhaps more importantly, tumor stem cells are resistant to even very high radiation doses including those cells in hypoxic regions.\textsuperscript{50,51} Tumor cells, including those in the hypoxic areas and tumor stem cells, are, however, all uniformly sensitive to heat energy delivery, a function of both temperature and time, achievable with LITT.

Hyperthermia can enhance the sensitivity of cancer cells to radiation-induced cell death.\textsuperscript{52} In 1 study, the use of simultaneous hyperthermia and radiation therapy improved survival of HGG patients after radiotherapy.\textsuperscript{53} The effects of hyperthermia timing on radiation sensitivity of recurrent HGGs remain to be fully elucidated. Multimodal therapy appears to be beneficial for patients with recurrent HGGs compared with chemotherapy alone.\textsuperscript{54} Neurosurgical oncologists are best suited to determine how best to integrate laser thermal ablation with current chemotherapy and radiation treatments.

**IMMUNOTHERAPY**

Hyperthermia induces protein denaturation and destruction of the cell membrane, causing irreversible cell damage and resulting in necrosis.\textsuperscript{55}\textsuperscript{55} Hyperthermia has been found to improve the antitumor adaptive immune response via several mechanisms such as increasing tumor antigen presentation, releasing chemokines to attract leukocytes, inducing heat shock protein expression, and activating antigen-presenting cells in the tumor microenvironment.\textsuperscript{56} Dendritic cells are master antigen-presenting cells, and dendritic cell cancer vaccines have shown great promise. The release of heat shock proteins from cancer cells can aid in the activation and maturation of dendritic cells. Heat shock proteins can also chaperone immunogenic peptides that are ultimately presented to T cells. These proteins in the microenvironment can induce tumor-specific immunity.\textsuperscript{3} Dendritic cell vaccinations have shown promise in brain tumor immunotherapeutic strategies and have been used clinically for patients with recurrent HGGs since 2003.\textsuperscript{57} Hyperthermia can enhance anticancer adaptive immune responses, and this can be a potential area of future investigation. In laser ablation of newly diagnosed and recurrent HGGs, the treated tumor undergoes necrosis, leaving a depot of denatured protein, promotion of heat shock protein release, and the potential for the production of tumor-specific antigen. Understanding and exploiting these pathways have the potential to lead to enhanced antitumor immune response and to the development of more effective immunotherapeutic interventions.

**CONCLUSION**

Laser ablation continues to evolve in neurosurgical practice. The most frequent current use of laser ablation by neurosurgical oncologists in the treatment of patients with malignant gliomas is as a salvage therapy in recurrent disease. For recurrent disease, laser ablation can reliably ablate tumor bulk resistant to nonsurgical treatment modalities. Laser ablation has the potential to augment adjuvant and immune therapy. Clinical and translational studies are needed to further understand the mechanisms of and to quantify the benefits of laser ablation in order to optimally exploit the potential of this burgeoning technology.

**Disclosures**

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**REFERENCES**

LASER ABLATION OF RECURRENT MALIGNANT GLIOMAS


