Stereotactic laser ablation of high-grade gliomas

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Evolving research has demonstrated that surgical cytoreduction of a high-grade glial neoplasm is an important factor in improving the prognosis of these difficult tumors. Recent advances in intraoperative imaging have spurred the use of stereotactic laser ablation (laser interstitial thermal therapy [LITT]) for intracranial lesions. Among other targets, laser ablation has been used in the focal treatment of high-grade gliomas (HGGs). The revived application of laser ablation for gliomas parallels major advancements in intraoperative adjuvants and groundbreaking molecular advances in neuro-oncology. The authors review the research on stereotactic LITT for the treatment of HGGs and provide a potential management algorithm for HGGs that incorporates LITT in clinical practice.
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KEY WORDS • laser ablation • laser interstitial thermal therapy • glioma •
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GLIOMAS account for 28% of the nearly 70,000 primary brain tumors diagnosed in the US annually.^{14,18,53} Most gliomas are classified as high-grade gliomas (HGGs): anaplastic gliomas (WHO Grade III) and glioblastomas multiforme ([GBMs], WHO Grade IV). High-grade gliomas represent 80% of malignant primary brain tumors.^{14,18,53} In spite of intensive research over the past several decades, overall prognosis for HGGs remains poor.⁷² Although we have learned a great deal about the molecular and cellular biology of malignant glioma over the last decade, we have much work to do to translate our scientific understanding into improved therapeutic approaches.^{10,11,50,52,72,77} More aggressive resections have been shown to play a role in improving clinical outcomes.^{11,12,37,42,61} Although extent of resection is important, this is always counterbalanced against the potential for functional impairments associated with surgery, which can also reduce the overall prognosis.^{25,37,43} New technologies that enable an improved balance between tumor cytoreduction and the need to preserve relevant brain function are emerging. Specifically, MRI-guided laser interstitial thermal therapy (LITT) is becoming an

important surgical tool for treatment of HGGs in several clinical contexts. In this work we review the technology, clinical experience with, and general indications for LITT, along with emerging applications of this approach.

Stereotactic LITT

Stereotactic LITT is a minimally invasive treatment for intracranial lesions. This method stems from similar minimally invasive ablation techniques pioneered by general surgeons.^{19,35,40,68} Stereotactic laser ablation produces high temperatures that lead to tissue coagulation, necrosis, and cellular apoptosis.^{2-4,7,32,60,73} Research in animals has shown that ablation produces a histologically proven immediate disruption of the blood-brain barrier (BBB) and subsequent neovascularization, which can be observed as enhancement on MRI sequences.^{3,4,6,7,47,73} Stereotactic laser ablation techniques for intracranial lesions have historically been limited by the inability to monitor ablation progress or temperature intraoperatively. Online intraprocedural treatment monitoring is critical for stereotactic LITT to assess real-time tissue temperature and avoid treatment beyond the target zone. Fortunately, recent technological advances in intraoperative MRI now enable accurate intraoperative thermal monitoring. Intraprocedural repetitive measurements of T1-weighted 2D fast low-angle shot sequences or similar methodologies

Abbreviations used in this paper: BBB = blood-brain barrier; BCNU = carmustine; GBM = glioblastoma multiforme; GTR = gross-total resection; HGG = high-grade glioma; KPS = Karnofsky Performance Scale; LITT = laser interstitial thermal therapy.

provide the temporally sensitive thermometry measurements necessary to create controlled and conformal lesions (Fig. 1A).^{28,32–34}

Additionally, stereotactic laser ablation has been further streamlined by clinicians and industry innovators to make laser ablation an optimal and safe procedure.^{23,28,45,49} There are currently 2 frequently used stereotactic LITT technologies for intracranial ablations: Neuroblate (Monteris Medical) and Visualase. Although both technologies serve to provide the same ultimate results (i.e., target ablation), each has its own advantages. One version of Neuroblate has a side-firing probe that can be rotated, advanced, and retracted by an MRI-compatible driver for conformal treatments and a large radius of treatment, at the potential cost of treatment time (Fig. 1B). The standard Visualase system (Fig. 1C) and an alternative Neuroblate version use a diffuse-tip probe that generates a uniform ellipsoid ablation zone around the center of the probe. This method saves time at the expense of target conformality. Depending on whether it is a diffuse-tip probe or a side-firing probe, the effective treatment radius ranges from approximately 1 to 2 cm. Thus, because the probe can be moved back and forth along its implanted axis, the “treatment” column can be as large as 3 cm (or larger with the side-firing type). This impacts the size of lesions that can be treated. Tumors less than 3 cm in maximal diameter can be readily treated with single-trajectory LITT. As the tumor gets larger, or the anatomical dimensions become less globoid, treatment may require more than one trajectory. Also, as the size becomes greater than 3 cm, it is important to consider the mass effect of the tumor, which can occasionally be transiently exacerbated by LITT. To date, LITT has been used to treat both primary and meta-

static brain tumors, radiation necrosis, and epilepsy foci with varying degrees of success.⁵⁷ Here, we review the literature on the use of LITT for HGGs and discuss a possible role for this procedure in clinical settings for both newly diagnosed and recurrent HGGs.

Treatment of Newly Diagnosed HGGs

Anaplastic astrocytomas carry a 2-year survival rate of up to 50%²⁴ and have a strong tendency to progress to GBM in approximately 2 years.⁵¹ Glioblastoma multiforme accounts for the majority of adult brain tumors and, without treatment, the median overall survival in patients with GBM is reported to be 9 weeks.¹⁷ The current standard of care for newly diagnosed GBM with temozolomide and radiation therapy increases median survival to 14.6 months.⁷² The temozolomide and radiation combination therapy is well tolerated and increases 2-, 3-, and 5-year survival to 27.2%, 10.1%, and 9.8%, respectively.⁷² Cytorreduction by resection has also been shown to increase survival in patients with HGG compared with biopsy alone. Several retrospective studies have shown increased median survival with gross-total resection (GTR) of HGGs.^{12,37,42,61} This has been corroborated by a prospective study of 124 newly diagnosed patients with HGG, which demonstrated that GTR was associated with longer survival and better quality of life than biopsy alone.¹¹

Surgical adjuvants such as intraoperative MRI^{15,29,36,66} and 5-aminolevulinic acid^{46,70,71} are associated with greater extent of HGG resection and improved progression-free survival. Hence, the current standard treatment algorithm for newly diagnosed HGGs is GTR of the enhancing tumor, followed by temozolomide and radiation

Fig. 1. Stereotactic laser ablation of brain tumors. **A:** Example of intraoperative thermometry monitoring during LITT of an insular brain tumor. In the left and center panels, green lines indicate target periphery. Yellow, blue, and black lines indicate the edge of low-, medium-, and high-dose margins. The right panel shows an example of cumulative temperature measurements during LITT. Reproduced with permission from *Neurosurgery*. Hawasli AH et al: Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. *Neurosurgery* 73(6):1007–1017, 2013. **B:** Image of Neuroblate probe with side-emitting laser. **C:** Image of Visualase probe with uniform laser emission.

Laser ablation for gliomas

therapies.^{52,77} Although chemoradiation therapy is generally well tolerated, surgery is not always a viable option. In certain circumstances, the patient may be too ill to tolerate a craniotomy for tumor resection. In other situations, the tumor may be in a location involving eloquent cortex or deep-seated structures, in which case resection would lead to significant neurological deficits. For these patients, current treatment typically includes biopsy for diagnosis followed by chemoradiation.⁵² Therefore, novel technologies such as LITT aimed at maximal local cytoreductive therapy would potentially have a significant impact on overall outcomes for these patients. The main treatment indication for the use of LITT in newly diagnosed HGG has been for patients with inoperable brain tumors or those who are not candidates for open surgery due to advanced age and/or medical comorbidities. Common tumor locations that are ideal for up-front LITT include deep gray matter regions (e.g., thalamus and basal ganglia), the corpus callosum, and the insula (Fig. 2A and B)—providing cytoreductive therapy while minimizing the morbidity of the surgical approach.

Treatment of Recurrent HGGs

In spite of maximal surgical and chemoradiation therapy, tumor progression is inevitable in the vast majority of patients with HGG. Survival for patients with recurrent HGGs remains poor, at 3–9 months.^{5,21} There is little consensus on the optimal management strategy for recurrent HGGs. Several retrospective Level of Evidence III–IV studies⁷⁴ support repeat tumor resections, as long as the patient's performance status is not low and preoperative tumor volume is not excessive.^{1,5,16,26,30,55} A randomized, double-blind, placebo-controlled trial also supported the implantation of carmustine (BCNU) wafers in tumor cavities after repeat operation.¹⁰ Although salvage temozolomide had previously been used for recurrent GBM,^{9,56,80} recent Level II evidence clinical studies in patients with recurrent GBM have demonstrated that salvage chemotherapy combining bevacizumab, an anti-angiogenic agent, with cytotoxic drugs can extend progression-free survival and overall survival to 6.1 and 9.2 months, respectively.^{21,75,82} Finally, emerging agents that target tumorigenesis pathways, such as new angiogenesis inhibitors and other novel agents, show promise as therapeutic options.⁷⁶ In select patients, salvage chemotherapy for recurrent HGGs is optimally preceded by repeat resection.^{1,5,16,26,30,55,74,81} However, for a range of reasons, there are subsets of patients who are not ideal candidates for traditional open surgery, and many patients decline open surgery due to associated morbidity. For these patients, LITT has been considered a reasonable option for many reasons (Fig. 2C).

There are several advantages and arguments for the use of LITT in select patients with recurrent HGGs. First, recurrent lesions that are small, focal, and nodular are particularly amenable to a focal therapy. Given that recurrence is local in the majority of patients, LITT can target these areas focally. Second, reoperation in many patients with recurrent HGG can lead to more morbidity because of the patient's frailty and higher risk for wound heal-

Fig. 2. Radiographic results after stereotactic laser ablation of brain tumors. **A:** Preoperative (left) and postoperative (right, 3 months post-LITT) T1-weighted axial MRI of brain obtained with Gd contrast showing thalamic GBM treated de novo with LITT. Postoperative image shows stable ring enhancement at the edge of treatment zone. Reproduced with permission from *Neurosurgery*. Hawasli AH et al: Magnetic resonance imaging-guided focused laser interstitial thermal therapy for intracranial lesions: single-institution series. *Neurosurgery* 73(6):1007–1017, 2013. **B:** Preoperative (left) and postoperative (right, 5 months post-LITT) T1-weighted axial MRI of brain obtained with Gd contrast showing GBM in right corpus callosum treated with LITT. **C:** Preoperative (left) and postoperative (right, 3 months post-LITT) T1-weighted axial MRI of brain obtained with Gd contrast showing treatment of recurrent frontal lobe GBM.

ing complications after prior radiation and chemotherapy. Third, salvage chemotherapy may achieve better efficacy following maximal safe cytoreduction. Fourth, a cytoreductive approach provides the best option in tumors in which other therapies have been exhausted. Finally, LITT can be used repeatedly because there is no demonstrable dose toxicity (as with radiation) and the tumor does not develop resistance to LITT (as seen with chemotherapy).

The Radiographic Effects of LITT

Besides history taking and physical examination, neuroradiological imaging such as MRI is the primary method to assess responses to brain tumor therapies. Hence, during the past several decades, radiographic responses to LITT have been reported by numerous groups. Although radiographic responses to LITT for HGGs are described in detail below, it is important to understand the basic general observations after LITT for brain tumors. The first effect that is seen after LITT (within days of treatment) is central coagulation, which is observed as T1-weighted hyperintensity consistent with coagulated blood products in the center of the lesion (Fig. 3A and B). This often has a semiuniform “ground glass” appearance.

FIG. 3. Exemplar MRI studies showing immediate postoperative effects of LITT on brain tumors. **A:** Preoperative (*pre*) T1-weighted MRI study obtained with Gd (T1+) demonstrates an enhancing insular tumor. **B:** Postoperative (*post*) T1-weighted MRI study obtained without Gd (T1–) on the day after surgery shows isointensity within the tumor center representing coagulation products. **C:** Postoperative (*post*) diffusion-weighted imaging (DWI) MRI study shows diffusion restriction at the peripheral edge of the tumor. **D:** Postoperative (*post*) T1-weighted MRI study obtained with Gd (T1+) shows a new contrast-enhancing rim just outside the periphery of the tumor corresponding with the edge of the ablation zone. Reproduced with permission from Neurosurgery. Hawasli AH et al: Magnetic resonance imaging-guided focused laser interstitial thermal therapy for subinsular metastatic adenocarcinoma: technical case report. *Neurosurgery* 70 (2 Suppl Operative):332–338, 2012.

This may be observed on postoperative CT scans as central hyperdense blood products. Additionally, LITT often produces a rim of diffusion restriction at the edge of the treatment zone (Fig. 3C) and a peripheral rim of enhancement (Fig. 3D), which is thought to represent a degradation of the surrounding BBB.^{47,59,60,62} Subsequent effects vary depending on the tumor, the patient, and responses to LITT, which are described below.

Methods

A comprehensive search of the English literature was performed using PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) and Google Scholar (<http://scholar.google.com/>). Clinical research articles on stereotactic laser ablation for brain tumors were selected and evaluated for possible inclusion in the review. Inclusion criteria for study selection were as follows: 1) human study; 2) use of stereotactic laser ablation for brain tumors; and 3) at least a portion of the cohort reported had HGGs (WHO Grade III or IV gliomas). The study results also had to provide a Level IV or better level of evidence. This included randomized, controlled trials; prospective cohort studies; case-controlled studies; retrospective cohort studies; case series; and case reports. Expert opinions, reviews without presentation of clinical data, and reports without HGGs were excluded. Each article was thoroughly reviewed for details on treatments and outcomes.

Results

Article Selection

The preliminary search for the use of laser therapy for brain tumors yielded 145 abstracts. After exclusion of nonhuman studies, expert opinions, and review articles lacking direct clinical data, 28 articles were identified. Each article was reviewed in detail and 10 were excluded for absence of HGGs, yielding a total of 18 eligible human clinical research publications on the use of laser ablation to treat HGGs (Table 1). The studies published between 1990 and 2014 included a total of 230 patients and were case series and case reports without control cohorts. Although some patients were probably reported in more than one manuscript, duplication in data used between clinical studies was not easily ascertainable and could not be confirmed.

Treatment of HGGs With Stereotactic Laser Ablation

In the 18 eligible studies reviewed, 174 HGGs were reported to have been treated with LITT. The WHO grade was reported in 15 studies (Table 1). Glioblastomas (WHO Grade IV) and anaplastic gliomas/oligodendrogliomas (WHO Grade III) accounted for 106 (66%) and 55 (34%) patients, respectively. The number of patients with newly diagnosed versus recurrent tumors was available in 12 of 18 studies. Fifty-three patients (34%) were treated up front (*de novo*) for newly diagnosed HGGs, and 105 patients (66%) were treated with salvage therapy for recurrent HGGs. Twelve manuscripts reported tumor locations: 39 (38%), 16 (16%), and 15 (15%) of the 103

TABLE 1: Clinical studies of stereotactic laser ablation for HGGs*

Authors & Year	Study Design	Only HGG in Study?	Total Cohort	HGGs					Pre-Tx Tumor Size
				HGG Cohort	WHO Grade (IV/III)	Newly Diagnosed/Recurrent	HGG Tumor Locations (no. of lesions)		
Sugiyama et al., 1990	case series	unknown	3	3	NR	unknown	unknown	1.2–3 cm†	
Bettag et al., 1991	case series	yes	5	5	NR	NR	F (2), T (2), Th (1)	NR	
Sakai et al., 1992	case series	no	5	2	2/0	1/1	P (2)	NR	
Bettag et al., 1992	case series	NR	5	5	NR	unknown	unknown	2–3.5 cm†	
Kahn et al., 1994	case series	no	8	3	1/2	unknown	P (1), TP (1), CC (1)	1.8–2.7 cm†	
Schwabe et al., 1997	case series	no	18	4	3/1	unknown	F (2), TP (1), FP (1)	2–3.5 cm†	
Reimer et al., 1998	case series	yes	4	4	1/3	0/4	F (3), T (1)	1–3.5 cm†	
Leonardi et al., 2001	case series; technical note	no	24	21	9/12	0/21	NR	2.2 cm†	
Lumenta et al., 2001	case series	no	24	18	7/11	13/5	NR	2.8 cm†	
Leonardi & Lumenta, 2002	case series	no	24	17	6/11	nearly all recurrent	NR	2.1–2.6 cm†	
Schulze et al., 2004	case series	no	8	8	5/3	NR	NR	NR	
Schwarzmaier et al., 2005	case report	yes	2	2	2/0	0/2	T (1); PO (1)	20 cm³	
Schwarzmaier et al., 2006	case series	yes	16	16	16/0	0/16	F (4), P (2), O (1), T (2), PO (3), TP (2), CC (1), FT (1)	21.6 ± 18.6 cm³§	
Jethwa et al., 2012	case series	no	20	7	6/1	3/4	F (5), T (1), MB (1)	0.37–68.9 cm³	
Carpentier et al., 2012	case series	yes	4	4	4/0	0/4	F (1), T (2), F/CC† (1)	3.83–8.86 cm³	
Hawasli et al., 2013	case series	no	17	11	10/1	7/4	F (3), P (2), CC (1), Th (4), BG (1)	14.1 ± 10.7 cm³§	
Sloan et al., 2013	case series	yes	10	10	10/0	0/10	F (3), P (3), T (2), TO (1), TP (1)	2.6–19 cm³	
Mohammadi et al., 2014 ⁴⁴	case series	yes	34	34	24/10	16/19†	F (15), P (5), T (5), I (2), CC (1), Th (7)	0.7–49.9 cm³	

* BG = basal ganglia; CC = corpus callosum; F = frontal; FP = frontoparietal; FT = frontotemporal; I = insula; MB = midbrain; NR = not reported; O = occipital; P = parietal; PO = parietooccipital; T = temporal; Th = thalamic; TO = temporooccipital; TP = temporoparietal; Tx = treatment.

† Maximum diameter.

‡ Two lesions treated in 1 patient who underwent salvage therapy.

§ Values expressed as the mean ± SD.

HGGs in which location was reported were located in the frontal, temporal, and parietal lobes, respectively. Twenty-one (20%) of these 103 HGGs were located in difficult to access locations, including 12 in the thalamus (12%), 5 in the corpus callosum (5%), 2 in the insula (2%), 1 in the basal ganglia (1%), and 1 in the midbrain (1%). Pretreatment tumor size measurements were either reported as maximum diameters or volumes in 11 studies. Maximum diameters ranged from 1 to 3.5 cm and volumes ranged from 0.37 to 68.9 cm³. Treatment times were reported as either laser times or total operative times (Table 2). Laser times ranged from 1.5 to 40 minutes and operative times ranged from 2 to 16 hours. Early publications subjectively reported that ablation covered the entire enhancing portion of the tumors. Recent reports have provided quantitative coverage data. Although thermal distribution data varied, recent authors reported treatment of tumor periphery at 42°C–45°C. Although there is probably some patient duplication among studies and some variation in laser technologies, laser wattages, intraoperative temperature monitoring, and other therapies received during the studies, the cumulative data offered valuable information about the potential use of LITT for the management of HGGs.

Radiographic Outcomes After Treatment of HGGs With Stereotactic Laser Ablation

The radiographic outcomes after LITT for HGGs were reported in 16 of 18 studies (Tables 3 and 4). Not all reported patients who received LITT for HGG underwent follow-up imaging, and radiographic follow-up for each patient was difficult to assess. In 3 studies, only immediate radiographic outcomes were reported. Five studies reported the presence of central necrosis of the tumor after ablation in at least 53 patients, as demonstrated on T1- and T2-weighted MRI sequences. Gadolinium enhancement of the tumor periphery shortly after LITT was re-

ported in 4 studies and 47 patients with HGG. Ten articles reported decreases in HGG size after ablation in at least 51 patients. Reduced tumor size on neuroimaging was reported 0.5–10 months after LITT.^{7,13,62–65} Kahn et al. and Hawasli et al. reported 15%–87% and 67% decreases, respectively, in tumor size after LITT on follow-up imaging.^{27,32} At least 22 patients showed no recurrence during the study duration. Sakai et al. and Reimer et al. reported radiographic recurrences at 15, 8, and 6 months post-LITT.^{58,60} Hawasli et al. reported radiographic recurrences in 5 of 11 patients at a mean of 6.2 months post-LITT.²⁷ Mohammadi et al. reported radiographic progression in 23 patients with 5 central, 12 peripheral, and 6 distant recurrences.⁴⁴ Hence, immediate radiographic analyses generally showed initial treatment effects including central tumor necrosis and peripheral enhancement. Despite reporting variability, several studies showed a reduction in HGG size, ranging from within days of LITT to within 33 months. These radiographic findings suggested that laser ablation is a potential treatment option for patients with HGGs.

Clinical Outcomes After Treatment of All HGGs With Stereotactic Laser Ablation: Overall Analysis

Clinical outcomes after LITT for all HGGs (both newly diagnosed and recurrent HGGs) were reported in 12 of 18 studies reviewed. Some studies reported individual times until cancer progression, time until death, and time until neurological deterioration. Other articles provided overall median or mean values for their cohorts. Individual results were reported in 6 studies. In these, tumor progression for all HGGs was reported at 2.6–15 months after LITT. Times until death due to tumor progression were reported at 4.1–23 months after LITT (Table 3). The median or mean clinical outcome statistics were reported on LITT for HGG in 6 manuscripts. In patients with HGG treated with LITT, overall median

TABLE 2: Treatment data on stereotactic laser ablation for HGGs

Authors & Year	Tx Times	Tumor Tx Coverage	Thermal Distribution
Sugiyama et al., 1990	30–40 min*	complete enhancement	42.5–43.5°C at periphery
Sakai et al., 1992	NR	NR	63°C at center; 43–33°C at periphery
Kahn et al., 1994	10–30 min*	complete enhancement	43°C at periphery
Reimer et al., 1998	4–33 min*	complete enhancement	NR
Leonardi et al., 2001	2–27 min*	1.8- to 2.7-cm diameter	NR
Lumenta et al., 2001	2–27 min*	NR	NR
Schulze et al., 2004	10–16 min,* mean 224 min†	NR	NR
Jethwa et al., 2012	13.9 ± 10.7 min (1.83–35.9 min)*‡	0.95–9.63 cm ²	NR
Carpentier et al., 2012	93 sec (30–180 sec)*	3.76 cm ³ (1.8–8.9 cm ³)	43–50°C of all enhancing tumor
Hawasli et al., 2013	6 ± 2 hrs†‡	45°C: 19.7 cm ³ ; 52°C: 17.9 cm ³	92.6% at 45°C; 86.9% at 52°C
Sloan et al., 2013	17.1 ± 13.5 min*‡	78% (57–90%)	43°C at periphery for 2–60 min
Mohammadi et al., 2014 ⁴⁴	median 7.5 hrs (2–16 hrs)†	high-dose: 91% (28–100%), 0.66 cm ³ untreated; low-dose: 98% (34–100%), 0.19 cm ³ untreated	43°C at periphery for 2–10 min

* Laser time.

† Total operative time.

‡ Values expressed as the mean ± SD.

TABLE 3: Overall clinical data on stereotactic laser ablation for HGGs*

Authors & Year	HGG Cohort	Radiographic Outcomes	Clinical Outcomes	No. of Major Complications
Sugiyama et al., 1990	3	all tumors disappeared on follow-up	2 alive at 12 & 31 MO; 1 died at 23 MO	NR
Bettag et al., 1991	5	necrotic tumor center & transient edema	NR	NR
Sakai et al., 1992	2	Case 1, rec at 15 MO; Case 2, no rec at 12 MO	Case 1, progressed at 15 MO & died at 23 MO; Case 2, PFS at 12 MO	NR
Bettag et al., 1992	5	early central necrosis; reduced HGG size, 1 MO	NR	NR
Kahn et al., 1994	3	15–87% size reduction at 1 MO	NR	NR
Schwabe et al., 1997	4	immediate central necrosis & surrounding enhancement; long term, tumors reduced in size	NR	3 transient cerebral edema
Reimer et al., 1998	4	Case 1, reduced perfusion & size at 6 MO; Case 2, rec at 8 MO; Case 3, rec at 6 MO; Case 4, no rec at 12 MO	Case 1, seizures w/o progression at 6 MO; Case 2, progression at 8 MO; Case 3, progression at 6 MO; Case 4, PFS at 12 MO	1 transient aphasia
Leonardi et al., 2001	21	universal central tumor necrosis & peripheral enhancement	NR	2 neuro deficit
Lumenta et al., 2001	18	subtotal or partial ablations for most pts; immediate central tumor necrosis w/ peripheral enhancement	WHO III: med PFS 17 MO; WHO IV: med OS, PFS, & time to neuro deterioration were 7, 3, & 4 MO, respectively	1 transient neuro deficit, 1 apraxia & abscess, 2 infection, 1 seizure
Leonardi & Lumenta, 2002	17	NR	2 w/ neuro improvement: mean OS 30 MO (WHO III), 9 MO (WHO IV); mean PFS 10 MO (WHO III), 4 MO (WHO IV)	2 neuro deficit, 1 major infection
Schulze et al., 2004	8	reduced HGG size, 2 MO	1 pt reported as rec free & surviving at 2 MO	NR
Schwarzmater et al., 2005	2	reduced HGG size, 10 MO	Case 1, PFS 5 MO, OS 13 MO; Case 2, OS 15 MO	NR
Schwarzmater et al., 2006	16	reduction in tumor size	med OS 6.9 MO; Group 1: med OS 5.2 MO; Group 2: med OS 11.2 MO	1 transient paresis, 3 neutropenia, 1 thrombocytopenia, 1 transaminitis
Jethwa et al., 2012	7	NR	NR	1 cerebral edema
Carpentier et al., 2012	4	gross-total ablation in all cases w/ immediate peripheral enhancement; reduced lesion size observed at 1.5, 1, 2, & 0.5 MO in Cases 1–4, respectively	med PFS 1 MO, med OS 10 MO	1 transient aphasia, 1 CSF leak, 1 seizure
Hawasli et al., 2013	11	tumor reduced to $91.4 \pm 17.1\%$ & $67.4 \pm 8.4\%$ † of baseline at 5 & 10 MO; mean radiographic recs 6.2 MO	progression: 5/11, at 9.2, 8.4, 2.6, 7.6, & 3.2 MO; deaths: 3/11, at 0.1,† 4.1, & 1.7† MO	3 transient aphasia, 2 transient paresis, 2 hyponatremia, 1 DVT, 1 fatal infection
Sloan et al., 2013	10	mean percentage of tumor treated was 78% (range 57–90%)	med OS 10.4 MO, med OS for low-, medium-, & high-dose groups 7.4, 6.5, & 14.3 MO, respectively; stable, improved, & worsened KPS scores seen in 6, 3, & 1 pts, respectively	1 pseudoaneurysm, 1 hemiparesis, 1 transient hemianopia, 1 transient dysphasia
Mohammadi et al., 2014 ⁴⁴	34	radiographic progression seen in 23/34: 5 local/central, 12 periphery, & 6 distant recs	overall, 71% of cases (25/35 tumors) progressed during follow-up; med 1-yr survival estimated at $68 \pm 9\%$ † overall, 12/34 pts (35%) died during study & progression caused death in 10, & although overall med PFS was 5.1 MO, gross-total ablation increased PFS from 4.6 to 9.7 MO	5 transient neuro deficit, 2 permanent neuro deficit, 1 seizure, 1 hyponatremia, 1 DVT, 2 infection, 3 significant intracranial hemorrhage

* DVT = deep vein thrombosis; med = median; MO = months post-LITT; neuro = neurological; OS = overall survival after LITT; PFS = progression-free survival; pt = patient; rec = recurrence.

† Death due to systemic illness and not progression of HGG.

‡ Values expressed as the mean $\pm$ SD.

TABLE 4: Stereotactic laser ablation for recurrent HGGs: radiographic volumetric data

Authors & Year	Pre-Tx Tumor Size	Post-Tx Tumor Size	Change in Size	Time to Radiographic Response
Sugiyama et al., 1990	1.2–3 cm*	NR	NR	NR
Kahn et al., 1994	1.8–2.7 cm*	0.5–1.7 cm*	11–81% reduction	50–100 days
Reimer et al., 1998	1–3.5 cm* (4.2–110 cm ³)	NR	NR	1.5–3 mos
Leonardi et al., 2001	2.2 cm* (21.2 cm ³)	NR	NR	NR
Lumenta et al., 2001	2.8 cm* (21.2 cm ³)	16.3	23% decrease	7 wks
Leonardi & Lumenta, 2002	2.1–2.6 cm* (III, 2.1 cm ³ ; IV, 2.6 cm ³)	NR	NR	NR
Schulze et al., 2004	NR	NR	qualitative size reduction reported	2 wks
Schwarzmaier et al., 2005	12 & 2 cm* (mean 20 cm ³)	10 & 0.5 cm*	17% & 75% reduction	8 & 33 mos
Schwarzmaier et al., 2006	21.6 ± 18.6 cm ³ †	NR	NR	NR
Jethwa et al., 2012	9 cm ³ (0.37–68.9 cm ³)	NR	NR	NR
Carpentier et al., 2012	2 cm* (0.38–5.5 cm ³); 3.83–8.86 cm ³	0.1–3 cm ³	50–90% reduction	7–60 days
Hawasli et al., 2013	14.1 ± 10.7 cm ³ †	9.5 cm ³	33% reduction	7–10 mos
Sloan et al., 2013	6.8 cm* (2.6–19 cm ³); 2.6–19 cm ³	NR	NR	24–48 hrs
Mohammadi et al., 2014 ⁴⁴	0.7–49.9 cm ³	NR	NR	NR

* Maximum diameter.

† Values expressed as the mean ± SD.

or mean progression-free survival ranged from 1 to 17 months post-LITT. The median or mean overall survival post-LITT ranged from 6.9 to 30 months.^{13,27,38,41,44,64,65,67} Most recently, Mohammadi et al. reported a 1-year estimated survival after LITT for mixed recurrent and newly diagnosed HGGs at 68% and overall progression-free survival at 5.1 months post-LITT.⁴⁴ Several authors have noted similar factors that contribute to better response to LITT. Consistent with traditional surgery, Mohammadi et al. found that a greater extent of ablation (i.e., gross-total ablation) increased progression-free survival from 4.6 to 9.7 months post-LITT.⁴⁴ In addition to greater extent of ablation, higher-dose LITT may also be associated with improved radiographic responses and clinical outcomes.^{27,41,67}

Eleven studies reported a total of 52 complications, some more severe than others. For the most common complications in the overall cohort of 174 patients, there were 4 reports of cerebral edema (2%), which typically improved with time and steroid therapy; 30 reports (17%) of neurological deficits or injury (many transient); and 6 (3%) reports of infection. Karnofsky Performance Scale (KPS) data were reported in 9 studies (Table 5). Preoperative KPS scores ranged from 0 to 100 and, when reported, postoperative KPS scores ranged from 40 to 90.

The varying reporting measures, mixed patient cohorts, mix of newly diagnosed and recurrent tumors, often lower performance statuses, difficult tumor locations, and duplication undoubtedly make interpretation of these data difficult. These limitations are magnified by adjuvant therapies and their potential effects on outcomes and by varying times of total follow-up (Table 5). Nonetheless, outcome results from these heterogeneous studies with mixed recurrent and newly diagnosed WHO Grade IV HGGs highlight LITT as a potential treatment option for HGGs. Furthermore, when taken as a whole, the cumulative data

suggest that gross-total LITT may provide some benefit for patients with HGG who do not qualify for traditional surgical options. Therefore, the current combined data show suggestions of clinical benefit and provide equipoise for better-controlled clinical investigations.

Stereotactic Laser Ablation for WHO Grade III Versus Grade IV HGGs

The LITT data for HGGs often included both Grades III and IV tumors as mixed cohorts. One-third of the tumors treated were Grade III. Given the differences in pathology and outcomes between grades, this mixture makes interpretation of data somewhat difficult. Fortunately, several authors have reported separate outcome measures for the 2 grades or have only included WHO Grade IV tumors in their case series. Lumenta et al. and Leonardi and Lumenta reported that median progression-free survival for WHO III HGGs was 17 and 10 months post-LITT, respectively.^{38,41} Leonardi and Lumenta found that overall survival for WHO Grade III tumors was 20 months post-LITT.³⁸ Several authors reported WHO Grade IV–specific outcome data.^{13,38,41,64,65,67} Progression-free survival for WHO Grade IV HGGs ranged from 1 to 5 months post-LITT. Overall survival post-LITT ranged from 7 to 15 months.

Stereotactic Laser Ablation as a Salvage Therapy for Recurrent HGG: Subgroup Review

Repeat resection plus chemotherapy increases survival for patients with recurrent HGGs from 6 months to 9 months when compared with chemotherapy alone.⁵ Unfortunately, not all patients are candidates for open surgery. For these individuals, several groups have enrolled patients in clinical trials to evaluate whether adding minimally invasive LITT could improve outcomes when compared with chemotherapy alone. Twelve articles reported

Laser ablation for gliomas

TABLE 5: Stereotactic laser ablation for recurrent HGGs: performance and adjuvants*

Authors & Year	Pre-LITT KPS (range)	Post-LITT KPS	Follow-Up Time From LITT (range)	Adjuvant Tx w/ LITT (no. of pts)
Sugiyama et al., 1990	100, 0, & 80	NR	31, 23, & 9 MO	NR
Sakai et al., 1992	0 & 90	NR	23 & 12 MO	all received ACNU
Kahn et al., 1994	NR	NR	13, 9, & 6 MO	1 received XRT
Lumenta et al., 2001	NR	NR	3.5–4.2 MO	NR
Leonardi & Lumenta, 2002	III: mean 78; IV: mean 69	III: 50% deteriorated, 50% unchanged; IV: 100% deteriorated after 1–3 MO	NR	NR
Schwarzmaier et al., 2005	60 & 70	70 & 50	30 & 15 MO	TMZ
Schwarzmaier et al., 2006	70	NR	9.1 ± 6.3 MO	TMZ, DOX; DOX + ACNU; ACNU + TEN; THAL
Carpentier et al., 2012	70, 50, 90, & 90	NR	through death	Cases 1, 2, & 4: IR & BEV after rec; Case 3: BCNU & TMZ
Hawasli et al., 2013	74.1	40–90	5.8 MO (0.1–11.2 MO)	newly diagnosed: TMZ/XRT; salvage: BEV (3)
Sloan et al., 2013	80 (70–90)	low-dose LITT: no change; high-dose LITT: 10- to 20-point improvement at 2 wks	15 MO (3.6–39 MO)	NR
Mohammadi et al., 2014 ⁴⁴	80 (50–90)	NR	7.2 MO	newly diagnosed: TMZ/XRT; salvage: TMZ (6), Cytosan (3), BEV (2), CCNU (2), PCB (1)

* ACNU = nimustine; BEV = bevacizumab; CCNU = lomustine; DOX = liposomal doxorubicin; IR = irinotecan; PCB = procarbazine; TEN = teniposide; THAL = thalidomide; TMZ = temozolomide; XRT = radiotherapy.

the use of LITT for 106 patients with recurrent HGGs (Table 6). Eight articles reported outcomes for salvage-specific HGG treatments and 4 did not. In 6 articles, only patients with recurrent HGGs were reported. Among the largest cohorts, Leonardi and Lumenta reported results on recurrent HGGs and stratified by tumor grade. Leonardi and Lumenta report that the mean progression-free survival for recurrent Grade III and IV HGGs was 10 and 4 months, respectively.³⁸ The mean overall survival for recurrent Grade III and IV HGGs was 30 and 9 months, respectively.³⁸ Schwarzmaier et al. reported that the overall survival of 16 patients with recurrent HGG after LITT was 11.2 months.⁶⁵ Carpentier et al. reported that overall survival among 4 patients with HGGs was 10 months after LITT.¹³ Most recently, Sloan et al. reported that survival in patients treated with salvage high-dose LITT was 15.2 months.⁶⁷ Hence, subgroup analysis of recurrent HGGs found that treatment with LITT may lead to an overall survival of 9–15.2 months after treatment. Although adjuvant therapies are probably contributing to this promising outcome, it appears to be similar to previously published survival rates seen with traditional open surgery and chemotherapy. These data suggest that LITT may serve as a viable salvage treatment.

De Novo Stereotactic Laser Ablation for Newly Diagnosed HGGs: Subgroup Review

Retrospective data suggest that GTR of newly diagnosed HGGs increases median survival from 8 to 13 months.¹² This has been corroborated by prospective Level II evidence that greater extent of resection of HGGs

improves both quality of life and length of survival.¹¹ Unfortunately, not all patients with HGGs are candidates for a craniotomy for tumor resection. In 5 studies, authors reported treating a total of 40 patients with newly diagnosed HGGs (de novo therapy; i.e., first-time therapy). Although it was not consistently reported, most were treated with LITT rather than open traditional resection due to tumor location or patient factors preventing open resection. Reporting of de novo–specific therapy outcomes is even more sparse and difficult to interpret than for recurrent lesions. Sakai et al. treated a parietal newly diagnosed de novo tumor and reported no evidence of progression or recurrence at 12 months post-LITT (Table 3).⁶⁰ Hawasli et al. reported recurrence at 2.6 and 3.2 months in 2 of 7 patients with de novo lesions, but had a short study window for 3 of 7 patients.²⁷ One of 7 patients died at 4.1 months due to tumor progression. Despite the data available for all HGGs, outcome data on de novo–treated HGGs is very sparse. Therefore, without additional clinical experience, it is difficult to draw any specific conclusions about this subset of patients.

Discussion

Controversy Over Focal Therapy for HGGs

It is well established that HGG tumor cells often metastasize great distances from the enhancing portion of the tumor and sometimes even to the contralateral hemisphere.^{52,77} Despite retrospective studies supporting the use of stereotactic radiosurgery for HGGs, randomized

TABLE 6: Stereotactic laser ablation for recurrent HGGs: subgroup analysis

Authors & Year	Recurrent HGG Cohort	Outcomes After LITT for Recurrent HGGs
Sakai et al., 1992	1	rec at 15 MO, death at 23 MO
Reimer et al., 1998	4	Case 1—reduced perfusion & size at 6 MO; Case 2—rec at 8 MO; Case 3—rec at 6 MO; Case 4—no rec at 12 MO
Leonardi et al., 2001	21	initial radiographic central tumor necrosis & peripheral enhancement; clinical outcomes for salvage-specific therapy NR
Lumenta et al., 2001	5	initial radiographic central tumor necrosis & peripheral enhancement; clinical outcomes for salvage-specific therapy NR
Leonardi & Lumenta, 2002	17*	2 w/ neuro improvement; mean OS for WHO III & IV was 30 & 9 MO, respectively; mean PFS for WHO III & IV was 10 & 4 MO, respectively; KPS was maintained above 70 for 15 MO (WHO III) & 7.5 MO (WHO IV)
Schwarzmaier et al., 2005	2	Case 1: reduced tumor vol at 10 MO, OS 13 MO; Case 2: reduced tumor vol at 10 MO, OS 15 MO
Schwarzmaier et al., 2006	16	reduced tumor size; overall med OS 6.9 MO; med OS (early group) 5.2 MO; med OS (late group) 11.2 MO
Jethwa et al., 2012	4	NR
Carpentier et al., 2012	4	gross-total ablation in all cases w/ immediate peripheral enhancement; reduced tumor size observed in all pts (0.5–1.5 MO); med PFS & OS were 1 & 10 MO, respectively
Hawasli et al., 2013	4	radiographic tumor vol decreased (Case 1) or was stable (Cases 2–4) on follow-up imaging; 3 of 4 tumors recurred at 9.2, 8.4, & 7.6 mos, & 0 pts died during the study
Sloan et al., 2013	10	78% of tumor vol treated; low-dose OS 314, 265, & 96 days; medium-dose OS 334 & 62 days; & high-dose OS 485, 305, 319, 434, & 767 days
Mohammadi et al., 2014 ⁴⁴	19†	outcomes after salvage-specific therapy NR

* Reported as “nearly all” recurrent HGGs.

† 19 tumors in 18 patients.

prospective studies found no survival benefit for radiosurgery when added to conventional radiation.⁶⁹ This observation could be used to argue against a significant effect on outcome for a focal therapy such as LITT. However, modern radiosurgery does not produce an effect on tissue for several weeks to months;⁴⁸ LITT should more appropriately be compared with open resection, which is acutely cytoreductive and has been shown to have an impact on HGGs.^{1,5,11,12} The LITT procedure can produce an acute gross-total ablation that immediately coagulates the entire enhancing portion of the tissue or induce short-term necrosis and apoptosis.^{47,59,60,62} This has been observed radiographically as immediate central necrosis of the tumor. Furthermore, beyond the analogy of resection, preliminary animal studies in LITT have indeed shown that laser ablation acutely leads to breakdown of the BBB.^{3,4,6,7,73} The breakdown in the BBB in regions where metastatic cells may reside may potentiate adjuvant therapy and immune reactions postulated to occur after LITT. These properties of LITT have the potential to exert positive effects to a wider area than the ablated region. Furthermore, with advanced intraoperative imaging capabilities, LITT has the potential to achieve gross-total ablation without the morbidity of open surgery. These findings argue that LITT offers acute ablation of the tumor and should not necessarily be compared with historical results in radiosurgery trials.

Use of LITT for Select Patients With HGG: Incorporating a Laser Therapy Into a Standard Practice Algorithm

After GTR and temozolomide plus radiation com-

bination therapy, standard management algorithms for newly diagnosed HGGs may vary slightly from institution to institution depending on clinical trials. Treatment strategies for recurrent HGGs are probably even more disparate from hospital to hospital. Clinical trials vary from immunotherapies to targeted molecular therapies, and many require a significant amount of tumor sample for vaccine generation or correlative studies. However, for some patients open surgery is not an option due to deep location of the tumor or comorbid conditions. Review of the literature revealed that approximately 20% of HGGs with LITT treated thus far have been in deep locations, especially the thalamus and basal ganglia. For this group of patients, LITT offered a minimally invasive option with reduced operative times, less blood loss, and shorter hospital stays.^{27,67} Generally, LITT may serve as a cytoreductive option for some of these patients over biopsy alone or no surgery at all.

Because the data on LITT for HGGs consist of Level IV evidence, additional clinical experience is essential to evaluate the efficacy of LITT in both newly diagnosed and recurrent HGGs. To achieve additional experience and data, it would be beneficial to incorporate LITT into the treatment algorithms of patients with HGG (Fig. 4). If a patient with newly diagnosed HGG is a viable surgical candidate and is interested in traditional resection, we propose that they continue with standard of care traditional craniotomy for gross-total and maximally safe resection and tissue collection, followed by standard chemoradiation in or outside of a clinical trial (Fig. 4A, left column). However, if a patient presents with newly diagnosed HGG and is not a candidate for open resection (e.g., due to difficult to access

Fig. 4. Management algorithm for patients with HGG that includes LITT for the treatment of (A) newly diagnosed and (B) recurrent HGGs.

tumor in the thalamus) or declines traditional surgery, 2 surgical options can be offered: 1) standard of care biopsy alone (Fig. 4A, center column); or 2) needle biopsy and treatment with stereotactic LITT (Fig. 4A, right column). An open biopsy may be performed with craniotomy for the collection of adequate tumor volume needed for some immunotherapy and clinical trials; that is a clear advantage of this option (Fig. 4A, center column). For patients undergoing stereotactic needle biopsy (Fig. 4A, right column), the biopsy procedure could be immediately followed by gross-total LITT of the tumor. All treatments would be followed by chemoradiation.

The typical pathways available for recurrent tumors are more limited due to the lack of effective conventional therapies. Level II–III evidence supports repeat resection followed by salvage chemotherapy and clinical trial participation (Fig. 4B, left column). However, patients who are not candidates or who decline traditional resection can either immediately begin salvage chemotherapy within or outside of clinical trials (Fig. 4B, center column), or they may be offered salvage LITT followed by salvage chemotherapy (Fig. 4B, right column). Creating a streamlined and clinically reasonable management algorithm to enroll candidates for LITT will generate the

data necessary to evaluate treatment efficacy with case-control cohorts.

Emerging Application—Laser Therapy as a Potential Adjunct to Chemotherapy

Enhanced Delivery of Chemotherapy. To circumvent the BBB in local drug delivery to the brain, recent approaches have focused on bypassing it. One method is the use of Gliadel wafers, a polymer implant impregnated with BCNU, which are placed intraoperatively in the resection cavity to circumvent the BBB. This approach resulted in a statistically significant but modest improvement in survival in both newly diagnosed and recurrent GBM.^{10,78,79} The modest survival benefit of Gliadel could be due to the short duration of drug delivery, because most BCNU is released within 5 days.²⁰ However, the fact that 5 days of direct BCNU delivery can improve survival of patients with GBM to a degree approaching that achieved by 8 months of systemic chemotherapy is remarkable in itself, supporting the hypothesis that the BBB is a critical barrier to the cytotoxic chemotherapy effect. Unfortunately, Gliadel is not widely used due to its complication profile. Another approach to bypassing the BBB is the convection-enhanced delivery system, in which a catheter is surgically inserted into the tumor to deliver chemotherapy.⁸ This invasive procedure requires prolonged hospitalization and meticulous maintenance of the external catheter to prevent serious complications, and as a result remains investigational and is rarely used.

Disruption of Peritumoral BBB. The use of MRI-guided LITT to induce sustained disruption of the peritumoral BBB raises the intriguing possibility that laser ablation might not simply represent a tool for cytoreduction, but might also be a vehicle for enhancing drug delivery. During LITT, the maximal temperature in the core can reach greater than 70°C, resulting in coagulation necrosis. The temperature in the peritumoral region is lower but remains high enough (> 40°C) to disrupt the BBB. This has been histologically demonstrated by local extravasation of dyes, antibodies, and chemotherapy.^{47,59,60,62} Disruption of the BBB is radiographically evidenced by new peritumoral contrast enhancement extending several centimeters from the tumor edge (versus the original tumor enhancement that is lost due to the heat ablation). These observations suggest that an interesting byproduct of laser ablation is the disruption of the peritumoral BBB. These radiographic changes often persist for several weeks, providing a rare window of opportunity during which drug delivery can potentially be enhanced to eliminate infiltrative tumor cells in the tumor periphery, where most recurrences occur.

Although the procedure remains under investigation, current data show that LITT causes BBB disruption.^{22,47,54,59,60,62} Indeed, the role of hyperthermia in increasing BBB permeability has been previously described in several animal models of brain hyperthermia. In a rodent model of human glioma, the global heating of a mouse's head to 42°C for 30 minutes in a warm water bath significantly increased the maximal brain concentration of a thermosensitive liposome encapsulated with the

chemotherapeutic drug Adriamycin.²² To affect locoregional hyperthermia in the brain, retrograde infusion of a hyperthermic saline solution at 43°C into the rat left external carotid artery reversibly increased BBB permeability to Evans blue albumin in the left cerebral hemisphere.⁵⁴ In the most analogous method to LITT in humans, LITT in rodents resulted in locoregional disruption of the BBB as evidenced by increased locoregional passage of the Evans blue dye, serum proteins (e.g., fibrinogen and IgM), and the cytotoxic drug paclitaxel.⁵⁹ Based on these data, it is reasonable to hypothesize that hyperthermia-induced disruption of the peritumoral BBB by LITT represents a potential tool to enhance delivery of chemotherapy to this region and effectively target residual disease, in addition to primary cytoreduction. Indeed, clinical trials are underway to test this in patients with recurrent HGGs (<http://clinicaltrials.gov/show/NCT01851733>).

Conclusions

The clinical data and guidelines support traditional GTR as the standard of care for both newly diagnosed and, occasionally, for recurrent tumors. However, data presented in this review suggest that LITT may serve as a viable focal treatment option for HGG in patients who are not candidates for open resection. The literature currently available is Level IV evidence without case-matched controls. Therefore, although results are promising, conclusions remain limited. The mixed results for LITT for HGGs are probably due to many factors including mixed patient cohorts, a lack of control data, treatment factors, tumor grades, concurrent therapies, and a combination of recurrence and newly diagnosed tumors. When evaluated as a subgroup, recurrent tumors appeared to have a median survival time potentially better than historical controls, but case-controlled data are currently unavailable. To date, subgroup analysis of de novo treatment for newly diagnosed tumors is less conclusive. Going forward, LITT may be incorporated into a rigorous patient treatment algorithm used by multidisciplinary neuro-oncology groups to better refine and understand clinical efficacy and indications.

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