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Abstract

Laser interstitial thermal therapy (LITT) has been used for brain metastasis, epilepsy, and necrosis, as well as gliomas as a minimally invasive treatment for many years. With the improvement of the thermal monitoring and ablation precision, especially the application of magnetic resonance (MR) thermography in the procedure and the available of two commercial laser systems nowadays, LITT is gradually accepted by more neurosurgical centers. Recently, some new concepts, for example the adjuvant chemotherapy or radiation following LITT, the combination of immunotherapy and LITT regarding the glioma treatment are proposed and currently being investigated. The aim of this study is to summarize the evolution of LITT especially for brain gliomas and a possible outlook of the future.

Laser interstitial thermal therapy in gliomas

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Abstract

Laser interstitial thermal therapy (LITT) has been used for brain metastasis, epilepsy, and necrosis, as well as gliomas as a minimally invasive treatment for many years. With the improvement of the thermal monitoring and ablation precision, especially the application of magnetic resonance (MR) thermography in the procedure and the available two commercial laser systems nowadays, LITT is gradually accepted by more neurosurgical centers. Recently, some new concepts, for example the adjuvant chemotherapy or radiation following LITT, the combination of immunotherapy and LITT regarding the glioma treatment are proposed and currently being investigated. The aim of this study is to summarize the evolution of LITT especially for brain gliomas and a possible outlook of the future.

Keywords

Laser interstitial thermal therapy, blood brain barrier, immunotherapy, gliomas

1. Origins of laser thermotherapy

The term is an acronym for Light Amplification by Stimulated Emission of Radiation, which first appeared as a term in 1959. Laser thermal therapy was clinically used for tissue ablation in 1966, based on the theory that the energy produced by laser light could achieve a high peak power through a ruby tip and could be absorbed by the surrounding tissue as heat [1]. However, using lasers for destroying neoplasms was still problematic because of the lack of a mechanism to monitor and control the energy [1]. In 1983, as crystal-based neodymium-doped yttrium aluminum garnet (Nd:YAG) laser was introduced for tissue ablation, and some studies followed of laser ablation for brain tumors [2-5]. A critical technological milestone, magnetic resonance (MR) thermography, was introduced in 1994 – this could monitor the extent of ablation and tissue damage [6]. Until 2006, the use of the Nd:YAG laser has been mainly reported by neurosurgical centers from Germany, France and Japan [7-11]. Subsequently, the use of laser interstitial thermal therapy (LITT) entered into the commercial era beginning in 2007 and has been used primarily in Northern America. Until now, two types of laser system, Visualase (Medtronic, Fridley, Minnesota, USA) and NeuroBlate (Monteris Medical, Plymouth, Minnesota, USA) are commercially available [12, 13]. Figure 1 shows the principal aspects of LITT in a glioma case example.

2. Scientific evolution of pre-commercial clinical laser therapy in the brain

Before the Visualase system was approved in 2007, more than 20 studies had been reported to use Nd:YAG lasers for cerebral gliomas [2]. During that scientific period, the laser treatment was commonly called LITT, but also named interstitial thermo-therapy (ITT) or hyperthermia (HT) in some publications [4, 14]. Sugiyama et al. firstly reported a clinical series of 3 glioma cases mixed with 2 metastatic lesions treated by laser in 1990, in which thermocouples were used for temperature control [3], which meant additional intracerebral catheters. Based on some experimental

studies, Kahn et al. [6] further explored and confirmed the feasibility and effectiveness of MRI with multiplanar reconstruction for monitoring the LITT ablation in 6 gliomas and 2 other types of tumor. This method made the additional invasive thermocouples obsolete. The introduction of MR thermography made a major contribution to the widespread use of LITT for brain tumors. Subsequently, researchers used the technique in both primary and recurrent gliomas. Leonardi and Lumenta published one large case series of 24 patients with 30 laser procedures including both high and low grade primary cases in 2002. They reported the mean survival times and mean time to progression post-LITT of gliomas of different grades, and suggested LITT could be an alternative technique for selected glioma patients [15]. Clinical studies regarding the use of the Nd:YAG laser for glioma treatment were no longer reported in the pre-commercial era after Schwarzmaier and colleagues publishing their experience of 16 patients with recurrent high grade glioma in 2006, except one case report in 2012 [11, 16].

3. Commercial era of LITT

Currently, two commercial laser systems are clinically available. One is the Visualase Thermal Therapy System with diode lasers that transmit energy at a wavelength of 980 nm, which was approved by the United States Food and Drug Administration (FDA) in 2007. It was also approved in Europe by the CE (Conformité Européenne) in 2018. The other system is the NeuroBlate method with the Nd:YAG laser at a wavelength of 1064 , which gained approval from FDA in 2009. Several studies have detailed these two systems for various intracerebral lesions [12, 13, 17]. Regarding glioma treatment, Carpentier et al. first reported a case series of 4 patients with recurrent glioblastoma treated by Visualase in 2012, in which they deliberated whether recurrence was an optimal indication for using LITT [18]. In 2013, the results of the first-in-human Phase I study were published [19]. It evaluated the safety and efficacy of NeuroBlate in recurrent glioblastoma on three proposed thermal dosage levels, and suggested LITT is feasible and safe for this kind of intracranial tumor, especially in some patients with lesions impractical for conventional surgery. The

largest series was reported by Sharma and colleagues in 2016 [20]. They retrospectively analyzed the results of 62 gliomas mixed with other 18 cases treated by LITT to summarize their experience on prediction of postoperative motor deficit and they reported a high rate of morbidity when attacking the border of motor tracts.

4. LITT in Gliomas

Theoretically, glioma may not be an optimal indication for LITT treatment because of often irregular shape of the target and the invasive character of the pathology, even if the precise ablation and real-time monitoring are achievable. Figure 2 shows one case with irregular shape that could not be completely ablated. However, it is reasonable as a minimally invasive choice in the following circumstances: patients too sick for a craniotomy, some gliomas that are deeply seated or involving eloquent regions that make the risk of conventional surgery unacceptably high, in cases where patients are symptomatic with either recurrence versus radiation treatment effect (RTE) or where it can serve as a palliative therapy for some recurrent glioblastoma cases. Table 1 listed all studies using laser interstitial thermal therapy for gliomas.

Table 1. Laser interstitial thermal therapy in Gliomas

Author & year	No. of glioma cases (total cases)	Location of glioma (Case No.)	Chemotherapy (Case No.)	Complications (Case No.)	Follow-up
Sugiyama et al., 1990 [3]	3 (5)	NR	NR	NR	NR
Ascher et al., 1990 [21]	1 (2)	Thalamic	NR	NR	NR
Bettag et al., 1991 [4]	5	Frontal (2), thalamic (1), temporal (2)	NR	Edema	NR
Roux et al., 1992 [5]	4	third ventricle (2), thalamic (3)	NR	NR	NR
Kahn et al., 1994 [6]	6 (8)	Frontal (3), parietal (2), corpus callosum (1)	NR	NR	1 week to 13 months
Yaroslavsky et al., 1996 [7]	1	NR	NR	NR	NR
Kahn et al., 1997 [22]	2	Frontal (2)	NR	NR	12 months, 14 months

Schwabe et al., 1997 [23]	16 (18),	Frontal (3), parietal (1), temporal (1), temporoparietal (1), frontoprecentral (9), frontoopercular (1)	NR	NR	4 years (maximum)
Hata et al., 1998 [24]	1	Frontal	NR	NR	NR
Kahn et al., 1998 [25]	1	Frontoprecentral	NR	NR	4 months
Reimer et al., 1998 [8]	4	Frontal (3), temporal (1)	NR	NR	12 months
Schwarzmaier et al., 1998 [26]	3	Frontoprecentral (3)	NR	NR	NR
Lumenta et al., 2001 [9]	24	NR	NR	Neurological deterioration (4), infection (2), abscess (1), seizure (1)	82 months (maximum)
Leonardi et al., 2001 [27]	24	Frontal (7), parietal (5), temporal (1), frontotemporal (2), frontoparietal (2), parietooccipital (6), thalamic (1)	Chemotherapy pre-LITT (2)	Neurological deficit (4), superficial wound infection (2), seizure (1)	15 months
Leonardi and Lumenta, 2002 [15]	24	Frontal (7), parietal (5), temporal (1), thalamic (1), frontotemporal (2), frontoparietal (2), parietooccipital (6)	Chemotherapy pre-LITT (2)	Neurological deficit (4), superficial wound infection (2), seizure (1)	15 months
Von Tempelhoff et al., 2002 [28]	4	Corpus callosum (1), parietooccipital (1), frontal (1), temporal (1)	TMZ (2)	NR	NR
Vitzthum et al., 2004 [29]	8 (15)	NR	NR	None	NR
Schulze et al., 2004 [10]	8	NR	NR	NR	NR
Schwarzmaier et al., 2005 [30]	2	Temporooccipital parietooccipital	TMZ within 24h post-LITT	NR	13 months, 20 months
Schwarzmaier et al., 2006[11]	16	Frontal (3), parietal (2), occipital (1), temporal (1), parietooccipital (3), temporoparietal (2), corpus callosum (1), frontotemporal (1),	Chemotherapy (6)	Transient paresis (1), neutropenia (3), thrombocytopenia (1), transaminitis (1)	9.1 ± 6.3 months

		frontoparietal (1), parasagittal (1)			
Carpentier et al., 2012 [18]	4	Frontal (1), temporal (2), frontal and corpus callosum (1)	Chemotherapy (3)	Transient aphasia (1), seizure (1), CSF leak (1)	7 months (maximum)
Galldiks et al., 2012 [16]	1	parietal and temporal lobe	Pre-LITT	NR	8 months
Jethwa et al., 2012 [31]	10 (20)	Frontal (3), frontoparietal (2), temporal (1), corpus callosum (1), third ventricle (2), midbrain (1)	NR	Refractory edema (1), acute pituitary injury (1), inaccurate laser placement (1), arterial injury (1)	NR
Patel et al., 2013 [32]	9 (16)	NR	NR	NR	4 to 11 weeks
Sloan et al., 2013 [19]	10	Temporal (2), parietal (3), frontal (3), temporoparietal (1), tmeporooccipital (1)	Chemotherapy pre-LITT (10)	Edema at 48h (9), dysphasia (1) and hemiparesis (2) at 14d, Hemiparesis (1) and pseudoaneurysm (1) at 28d	4 to 12 weeks
Hawasli et al., 2013 [33]	11 (17)	Frontal (2), parietal (2), corpus callosum (1), thalamic (4), basal ganglia (1), insula (1)	Chemotherapy pre-LITT (4)	NR	0.1-11.2 months
Mohammadi et al., 2014 [34]	34	frontal (15), parietal (5), temporal (5), insula (2), corpus callosum (1), thalamic (7)	TMZ in all newly diagnosed cases. For recurrences: TMZ (6), BEV (2), cytoxan (3), lumostine (2), procarbazine (1)	Neurological deficit (7), seizure (1), DVT (1), hyponatremia (1), Infection (2)	7.2 months
Tiwari et al., 2014 [35]	6 (10)	NR	NR	NR	24 hours to 11 months
Sun et al., 2015 [36]	13 (28)	Frontal (3), temporal (3), parietal (5), cerebellum (1), occipital (1)	NR	NR	NR
Brandmeir et al., 2016 [37]	1 (5)	NR	NR	None	NR
Dadey et al., 2016 [38]	2	Third ventricle (2)	NR	None	4 and 9 months
Leuthardt et al.,	14 (20)	Temporal (3), frontal (6),	Early DOX	NR	16 weeks

2016 [39]		thalamic (1), parietal (3), parietooccipital (1)	post-LITT (4), later DOX post-LITT (9)		
Pisipati et al., 2016 [40]	5	Thalamic (3), frontal/corpus callosum (1), frontotemporalcorona radiate (1)	TMZ post-LITT (3)	Seizure (1)	2 months
Sharma et al., 2016 [20]	62 (80)	NR	NR	NR	7.0 ± 9.5 months
Thomas et al., 2016 [41]	21	Thalamic (1), insular (4), "butterfly" (5), motor (3), speech (3), temporal (1), splenium (2), cingulate (2)	CCNU post-LITT (2)	Functional decline (1), status seizure (1)	6 months (at least)
Tovar-Spinoza and Choi, 2016 [42]	9 (11)	Thalamic (3), intraventricular (2), tentorium (1), hypothalamic (1), peduncle (1), vermis (1)	Chemotherapy pre-LITT (2)	NR	12 to 35 months
Tovar-Spinoza and Choi, 2016 [12]	1	Temporal	NR	None	13mo
Wright et al., 2016[43]	8 (10)	Frontal (3), butterfly (2), thalamic (1), frontoparietal (2)	Chemotherapy post-LITT (7)	Transient shoulder weakness (1)	46 - 501 days
Miller et al., 2017 [44]	3 (17)	NR	NR	None	196 - 393 days
Ali et al., 2018 [45]	3	Frontotemporal (2), parietal (1)	BEV post-LITT (3)	None	26 weeks (range, 13-51 weeks)
Beaumont et al., 2018 [46]	15	Callosal (15)	CTX pre-LITT (6)	Hemiparesis (3), weakness (1), hydrocephalus (1), herniation (1), ventriculitis (1)	NR
Borghei-Razavi et al., 2018 [47]	3 (8)	NR	NR	Wound infection (1)	14.8 months (range, 0.4 - 37.5)
Laurent et al., 2018 [48]	9 (10)	Frontal (3), parietal (1), temporoparietal (1), frontotemporal (1), frontal and temporal (1), thalamic (1), parietooccipital (1), splenium (1)	NR	None	NR
Maraka et al., 2018 [49]	7 (8)	Temporal (2), parietal (1), frontal (1), thalamic (3)	BEV post-LITT (2)	NR	NR
Munier et al.	36 (96)	NR	NR	NR	NR

2018 [50]					
Zervos et al., 2018 [51]	1	Cingulate gyrus	NR	None	2 years
Elder et al., 2019 [52]	1	Temporal	None	NR	4 years
Hafez et al., 2019 [53]	1	Insular	Chemotherapy post-LITT	NR	2 years
Shah et al., 2019 [54]	6	Splenium (1), orbitofrontal (1), parietooccipital (1), cingulate (1), precuneus (1), genu (1)	TMZ (6)	None	19.7 months
Krivosheya et al., 2019 [55]	2	Cingulum (1), parahippocampal (1)	Chemotherapy post-LITT (2)	NR	2.5 and 6 years

Abbreviations: BEV: bevacizumab, CCNU: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, CSF: cerebrospinal fluid, CTX: cyclophosphamide, DOX: Doxorubicin, DVT: deep vein thrombosis, NR: not reported, TMZ: temozolomide

An interesting possible indication could be taking advantage of breakdown of the blood brain barrier (BBB) following LITT to make adjuvant chemotherapy more effective. The effect of BBB disruption after LITT has been reported to be indicated radiographically by peripheral contrast enhancement [6, 13, 23]. Recently, Leuthardt et al. reported that LITT-induced peritumoral BBB disruption peaked at around 3 weeks and lasted for about 4-6 weeks by detecting serum levels of specific enolase [39]. Although no direct evidence (such as a case control study) supports the LITT-induced BBB disruption leading to better outcome, in their work, Carpentier et al. speculated that BBB opening instead of local control by LITT improved survival for patients with recurrent glioblastoma [18].

LITT has been reported to be used as an alternative therapy in patients with difficult to access tumors, for example, gliomas in thalamus, corpus callosum and insula [34, 43, 46, 53, 54]. The extent of ablation (EOA) can be predicted from thermal-damage-threshold (TDT) lines or time-temperature history data in these commercial systems [56]. Just like the extent of resection in traditional glioma surgery, Mohammadi et al. reported that EOA was positively associated with the overall prognosis [34]. Missios et al. also reported similar results when the EOA

increased [57]. Munier et al. reported that a second ablation with higher power was helpful in cases where the initial thermal dose was insufficient [50]. However, the greater the EOA means the higher the risk of functional impairment caused by the technique itself, which is always counter consideration to be weighed against the benefit of LITT, or any invasive treatment. Sharma and colleagues in 2016 reported that even a minimal overlap between the TDT lines and cortical-spinal tracts can cause a postoperative motor deficit after LITT [20]. In addition to EOA, the dose of LITT may also be related to the prognosis [9]. A phase I study using escalating doses of LITT for assessing the safety and efficacy of NeuroBlate in 10 patients showed that two cases in the highest dose level suffered severe neurological deficits but no procedure-related mortality [19].

The perifocal edema in glioma cases has been reported to be increased transiently by LITT, which can lead to further symptoms and adverse events [12, 23, 47, 51, 52]. Pisipati et al. suggested resection of ablated glioma is an option to reduce LITT-related edema for decreasing the incidence of neurological deficits by reducing the inflammatory response [40]. Markaka et al. suggested using steroids or bevacizumab in order to control the post-surgical edema, even though this treatment period may be prolonged [49]. Using LITT for radionecrosis after stereotactic radiosurgery is of great importance and plays a significant role in brain metastatic diseases [58]. Another publication of this journal issue is discussing this topic as well.

Some further technical innovations have been reported to improve LITT procedures, including a 3D printed frame system to improve the speed and accuracy of workflow, staged LITT for left hemisphere-dominant insular lesion, and delivery of LITT in conscious patients to make ablations safer [37, 48, 53]. This concept parallels the increased use of traditional awake surgery in gliomas.

5. Outlook for LITT

Prospective randomized or case-control trials demonstrating a statistically significant effect of LITT in gliomas remain lacking. However, there is solid rationale for believing that targeted treatment in focal lesions or in combination with immunotherapy could lead to positive results [18]. Several studies are ongoing and registered. Some have been closed but remain unpublished to date. Those ongoing and promising focus on shortening the treatment time by replacing open surgery with LITT and thus making it possible to start radiation earlier. This could lead to an overall treatment time including both surgery and radiation of 7 weeks (versus 9-10 weeks currently) and possibly add valuable time to the patient's remaining life span (NCT02970448). Another group from Baltimore, USA is also focusing on the time delay after open surgery to radiation treatment and investigating a possible positive effect of LITT on shortening this waiting time (NCT04181684).

Most interesting are 3 new clinical trials with LITT including new adjuvant treatment. One group at the MD Anderson Cancer Center in Houston is investigating the combination of Lomustine and LITT in the treatment of recurrent malignant glioma. The hypothesis is that Lomustine works better after ablation and that this may be seen in overall survival and progression free survival. However, the estimated group size of 34 participants is rather small and detecting a significant effect might be difficult (NCT03022578). Two other new trials from New York and Cleveland are focusing on the combination of immunotherapy and LITT. The phase I/II study from the Cleveland group administers the checkpoint inhibitor pembrolizumab in 3 different groups combined with a LITT procedure. The phase 1 study group receives pembrolizumab 7 days prior to the LITT intervention. The phase II patient group receives the drug 14 days after LITT. The third group of patients receives pembrolizumab 35 days after the ablation, which, in theory, is outside the expected time window of BBB disruption. The monoclonal antibody pembrolizumab (Keytruda) is a human PD-1 (programmed death receptor-1)-blocking checkpoint inhibitor, which is not FDA approved for gliomas, however for many other tumor entities such as melanoma of non-small-cell lung carcinoma (NSCLC). This study

started in 2017 and is currently ongoing (NCT03277638). Lastly, the New York group conducts a phase I study using the checkpoint inhibitor avelumab, which is directed against the ligand of PD-1 (PD-L1), in the treatment of first recurrent glioblastoma. Since it is an early stage study, the tolerability and safety of this treatment is its focus. However, the study group is divided in 2 groups and one gets only avelumab, whereas the other group receives avelumab and a LITT procedure. This could help to answer whether ablation and BBB disruption aids in immunotherapy (NCT03341806). There is certainly much more room for further ablation and immunotherapy studies in the future and current results encourage such investigations.

Very diffuse or multifocal gliomas are not targets for LITT alone as they are not focal lesions and classically are candidates for systemic treatment. Yet, some sets of growing gliomas, for example in neurofibromatosis patients, could be a very interesting target as systemic and radiation treatment are weak options and sometimes even contraindicated [59]. Another neglected group in the past is the butterfly glioblastoma, and recent findings advocate focal treatment (surgery) for clinically well patients (higher Karnofsky performance status) [60]. Since these cases usually just get a stereotactic biopsy, this trajectory could be used for a laser catheter. Adding one from the other side would not enhance the surgical complexity but both could ablate most of the tumor and the patient would be mobilized and ready for adjuvant treatment almost immediately (i.e. there would be no delay as in just biopsy cases). If immunotherapy shows a significant difference in ablated cases, then this combination of primary biopsy, LITT and immediate immunotherapy after disruption of the BBB could become a new standard for butterfly gliomas. The new European LITT user community is considering this concept for a randomized trial.

6. Future Directions

There is still much we do not know about the interaction between catheter-delivered fiberoptic laser therapy and gliomas. Better understanding of the effect of the laser

on glioma tissue and the surrounding brain may allow for alterations in the timing and intensity of treatment. It is possible that the effect of heat could be used to provoke an immunological response in gliomas or improve the penetration of chemotherapy, as discussed above, or even increase the sensitivity to radiation. Gliomas are often irregular, very widely in size, and can be located anywhere in the brain. From a technical standpoint, desirable future innovations include the possibility of catheters whose laser energy can penetrate farther out into surrounding tissue, steer in nonlinear trajectories, achieve greater directionality than current systems, and whose tips can be tracked actively at the time of placement. Improved predictive algorithms, perhaps derived from artificial intelligence applied to databases of a great many cases performed on systems at many sites, could both better predict the effectiveness of ablation treatments and subsequently offer guidance to future users in optimizing settings of power and duration. Faster refresh times for MRI thermography and finer temperature resolution could help with improve ablation, particularly near highly eloquent structures. These innovations are likely to come through a combination of efforts driven by industry and individual investigators seeking to give glioma patients greater benefits from this technology.

Conclusion

LITT is currently used as a treatment for some focal recurrent glioma lesions on a personalized basis. Only well-designed randomized trials could lift this ablation treatment to a higher standard. The concepts of superior efficacy of immunotherapy through disruption of the BBB has been proposed, but still lacks proof as well. Overall, a significant benefit of LITT for gliomas might well rely on advances in immunotherapy and other systemic therapies that benefit from BBB disruption might have on the prognosis for gliomas in general.

Conflict of interest statement

The authors declare no conflict of interest.

Figure Legends

Fig 1. Procedure of LITT in a 65-year-old female patient with newly diagnosed glioblastoma (unpublished data). (A) Pre-surgical gadolinium-enhanced T1 MRI showing a hyperintensity (1.7×1.7×1.3 cm) in the right parietal lobe, (B) Intra-surgical T1 MRI showing the position of the catheter after biopsy, (C) the catheter pulled slightly out for further ablation of the lateral part of the lesion. After ablation, the necrosis in the center is demonstrated with slight contrast enhancement on the ablation border (D).

Fig 2. LITT treatment in one 66-year-old female patient with recurrent glioblastoma in the right thalamus and temporal lobe with an irregular border (unpublished data). (A) Intraoperative T1 MRI showing glioma infiltrated into peripheral brain tissue (white arrow) and the trajectory of the LITT catheter , (B) post-surgical T1 MRI showing the border of the ablation (red dashed circle) and residual contrast enhancement (most likely glioma infiltration) which was not reached with ablation (white arrow).

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Table 1. Laser interstitial thermal therapy in Gliomas

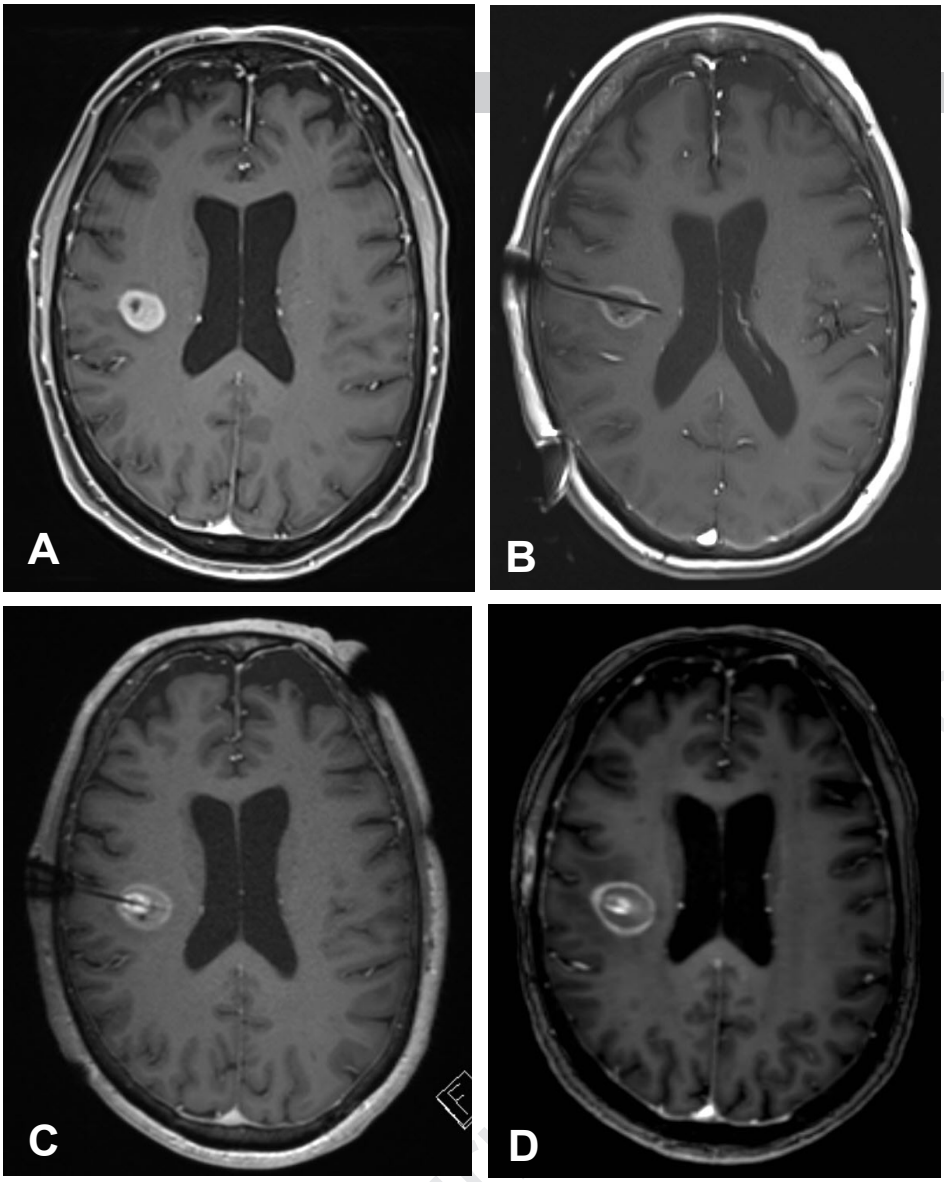
Author & year	No. of glioma cases (total cases)	Location of glioma (Case No.)	Chemotherapy (Case No.)	Complications (Case No.)	Follow-up
Sugiyama et al., 1990 [3]	3 (5)	NR	NR	NR	NR
Ascher et al., 1990 [21]	1 (2)	Thalamic	NR	NR	NR
Bettag et al., 1991 [4]	5	Frontal (2), thalamic (1), temporal (2)	NR	Edema	NR
Roux et al., 1992 [5]	4	third ventricle (2), thalamic (3)	NR	NR	NR
Kahn et al., 1994 [6]	6 (8)	Frontal (3), parietal (2), corpus callosum (1)	NR	NR	1 week to 13 months
Yaroslavsky et al., 1996 [7]	1	NR	NR	NR	NR
Kahn et al., 1997 [22]	2	Frontal (2)	NR	NR	12 months, 14 months
Schwabe et al., 1997 [23]	16 (18),	Frontal (3), parietal (1), temporal (1), temporoparietal (1), frontoprecentral (9), frontoopercular (1)	NR	NR	4 years (maximum)
Hata et al., 1998 [24]	1	Frontal	NR	NR	NR
Kahn et al., 1998 [25]	1	Frontoprecentral	NR	NR	4 months
Reimer et al., 1998 [8]	4	Frontal (3), temporal (1)	NR	NR	12 months
Schwarzmaier et al., 1998 [26]	3	Frontoprecentral (3)	NR	NR	NR
Lumenta et al., 2001 [9]	24	NR	NR	Neurological deterioration (4), infection (2), abscess (1), seizure (1)	82 months (maximum)
Leonardi et al., 2001 [27]	24	Frontal (7), parietal (5), temporal (1), frontotemporal (2), frontoparietal (2), parietooccipital (6), thalamic (1)	Chemotherapy pre-LITT (2)	Neurological deficit (4), superficial wound infection (2), seizure (1)	15 months
Leonardi and Lumenta, 2002 [15]	24	Frontal (7), parietal (5), temporal (1), thalamic (1), frontotemporal (2),	Chemotherapy pre-LITT (2)	Neurological deficit (4), superficial wound infection (2),	15 months

		frontoparietal (2), parietooccipital (6)		seizure (1)	
Von Tempelhoff et al., 2002 [28]	4	Corpus callosum (1), parietooccipital (1), frontal (1), temporal (1)	TMZ (2)	NR	NR
Vitzthum et al., 2004 [29]	8 (15)	NR	NR	None	NR
Schulze et al., 2004 [10]	8	NR	NR	NR	NR
Schwarzmaier et al., 2005 [30]	2	Temporooccipital parietooccipital	TMZ within 24h post-LITT	NR	13 months, 20 months
Schwarzmaier et al., 2006[11]	16	Frontal (3), parietal (2), occipital (1), temporal (1), parietooccipital (3), temporoparietal (2), corpus callosum (1), frontotemporal (1), frontoparietal (1), parasagittal (1)	Chemotherapy (6)	Transient paresis (1), neutropenia (3), thrombocytopenia (1), transaminitis (1)	9.1 ± 6.3 months
Carpentier et al., 2012 [18]	4	Frontal (1), temporal (2), frontal and corpus callosum (1)	Chemotherapy (3)	Transient aphasia (1), seizure (1), CSF leak (1)	7 months (maximum)
Galldiks et al., 2012 [16]	1	parietal and temporal lobe	Pre-LITT	NR	8 months
Jethwa et al., 2012 [31]	10 (20)	Frontal (3), frontoparietal (2), temporal (1), corpus callosum (1), third ventricle (2), midbrain (1)	NR	Refractory edema (1), acute pituitary injury (1), inaccurate laser placement (1), arterial injury (1)	NR
Patel et al., 2013 [32]	9 (16)	NR	NR	NR	4 to 11 weeks
Sloan et al., 2013 [19]	10	Temporal (2), parietal (3), frontal (3), temporoparietal (1), tmeporooccipital (1)	Chemotherapy pre-LITT (10)	Edema at 48h (9), dysphasia (1) and hemiparesis (2) at 14d, Hemiparesis (1) and pseudoaneurysm (1) at 28d	4 to 12 weeks
Hawasli et al., 2013 [33]	11 (17)	Frontal (2), parietal (2), corpus callosum (1), thalamic (4), basal ganglia (1), insula (1)	Chemotherapy pre-LITT (4)	NR	0.1-11.2 months

Mohammadi et al., 2014 [34]	34	frontal (15), parietal (5), temporal (5), insula (2), corpus callosum (1), thalamic (7)	TMZ in all newly diagnosed cases. For recurrences: TMZ (6), BEV (2), cytoxan (3), lumostine (2), procarbazine (1)	Neurological deficit (7), seizure (1), DVT (1), hyponatremia (1), Infection (2)	7.2 months
Tiwari et al., 2014 [35]	6 (10)	NR	NR	NR	24 hours to 11 months
Sun et al., 2015 [36]	13 (28)	Frontal (3), temporal (3), parietal (5), cerebellum (1), occipital (1)	NR	NR	NR
Brandmeir et al., 2016 [37]	1 (5)	NR	NR	None	NR
Dadey et al., 2016 [38]	2	Third ventricle (2)	NR	None	4 and 9 months
Leuthardt et al., 2016 [39]	14 (20)	Temporal (3), frontal (6), thalamic (1), parietal (3), parietooccipital (1)	Early DOX post-LITT (4), later DOX post-LITT (9)	NR	16 weeks
Pisipati et al., 2016 [40]	5	Thalamic (3), frontal/corpus callosum (1), frontotemporalcorona radiate (1)	TMZ post-LITT (3)	Seizure (1)	2 months
Sharma et al., 2016 [20]	62 (80)	NR	NR	NR	7.0 ± 9.5 months
Thomas et al., 2016 [41]	21	Thalamic (1), insular (4), “butterfly” (5), motor (3), speech (3), temporal (1), splenium (2), cingulate (2)	CCNU post-LITT (2)	Functional decline (1), status seizure (1)	6 months (at least)
Tovar-Spinoza and Choi, 2016 [42]	9 (11)	Thalamic (3), intraventricular (2), tentorium (1), hypothalamic (1), peduncle (1), vermis (1)	Chemotherapy pre-LITT (2)	NR	12 to 35 months
Tovar-Spinoza and Choi, 2016 [12]	1	Temporal	NR	None	13mo
Wright et al., 2016[43]	8 (10)	Frontal (3), butterfly (2), thalamic (1), frontoparietal (2)	Chemotherapy post-LITT (7)	Transient shoulder weakness (1)	46 - 501 days
Miller et al., 2017 [44]	3 (17)	NR	NR	None	196 - 393 days
Ali et al., 2018 [45]	3	Frontotemporal (2), parietal (1)	BEV post-LITT (3)	None	26 weeks (range, 13-51 weeks)

Beaumont et al., 2018 [46]	15	Callosal (15)	CTX pre-LITT (6)	Hemiparesis (3), weakness (1), hydrocephalus (1), herniation (1), ventriculitis (1)	NR
Borghei-Razavi et al., 2018 [47]	3 (8)	NR	NR	Wound infection (1)	14.8 months (range, 0.4 - 37.5)
Laurent et al., 2018 [48]	9 (10)	Frontal (3), parietal (1), temporoparietal (1), frontotemporal (1), frontal and temporal (1), thalamic (1), parietooccipital (1), splenium (1)	NR	None	NR
Maraka et al., 2018 [49]	7 (8)	Temporal (2), parietal (1), frontal (1), thalamic (3)	BEV post-LITT (2)	NR	NR
Munier et al. 2018 [50]	36 (96)	NR	NR	NR	NR
Zervos et al., 2018 [51]	1	Cingulate gyrus	NR	None	2 years
Elder et al., 2019 [52]	1	Temporal	None	NR	4 years
Hafez et al., 2019 [53]	1	Insular	Chemotherapy post-LITT	NR	2 years
Shah et al., 2019 [54]	6	Splenium (1), orbitofrontal (1), parietooccipital (1), cingulate (1), precuneus (1), genu (1)	TMZ (6)	None	19.7 months
Krivosheya et al., 2019 [55]	2	Cingulum (1), parahippocampal (1)	Chemotherapy post-LITT (2)	NR	2.5 and 6 years

Abbreviations: BEV: bevacizumab, CCNU: 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, CSF: cerebrospinal fluid, CTX: cyclophosphamide, DOX: Doxorubicin, DVT: deep vein thrombosis, NR: not reported, TMZ: temozolomide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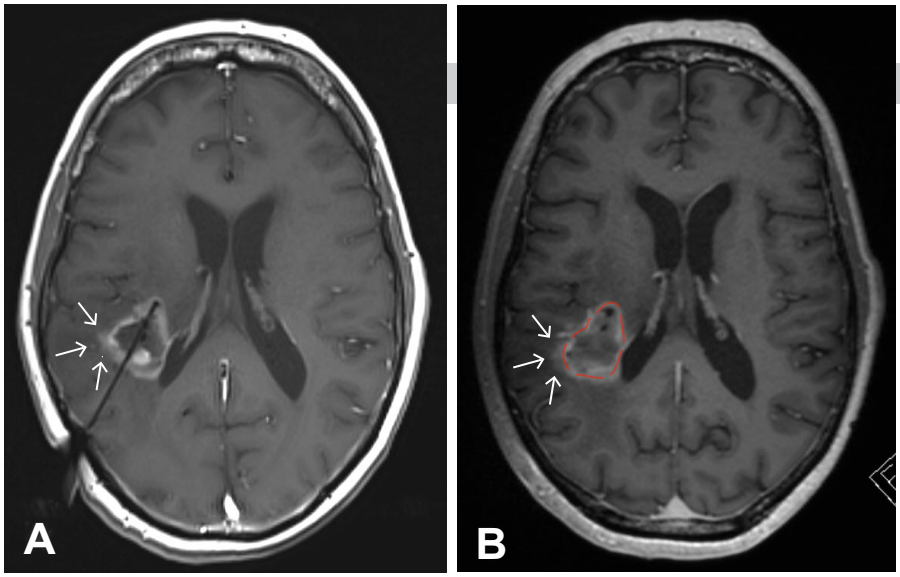

Highlights

- Laser interstitial thermal therapy as a minimally invasive treatment for glioma
- Breakdown of the blood brain barrier following LITT -- adjuvant chemotherapy or radiotherapy
- Combination of LITT and immediate immunotherapy for butterfly gliomas

Conflict of interest statement

The authors declare no conflict of interest.