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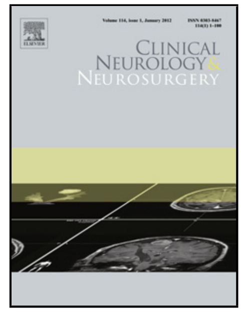

Survival outcomes in patients with recurrent glioblastoma treated with Laser Interstitial Thermal Therapy (LITT): A systematic review

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Title:

Survival outcomes in patients with recurrent glioblastoma treated with Laser Interstitial Thermal Therapy (LITT): A systematic review.

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Highlights

- LITT is an emerging minimally invasive procedure increasingly utilized for treatment of deep and recurrent GBMs.
- Laser interstitial thermal therapy (LITT) provides an effective treatment with low morbidity for selected patients harboring recurrent glioblastoma.
- LITT should be included in the armamentarium of neurosurgical oncologist for treatment of recurrent glioblastomas.

Abstract

Objective: To study the role of laser interstitial thermal therapy in recurrent glioblastoma and to assess its effect in the overall survival and in progression-free survival.

Methods: A MEDLINE and Pubmed search was performed for the key words "laser interstitial thermal therapy", "LITT" and "glioblastoma". Studies investigating overall survival and progression-free survival of recurrent glioblastoma after laser interstitial thermal therapy were selected.

Results: A total of 17 studies met the selection criteria, accounting for 203 patients with recurrent glioblastoma who underwent 219 laser interstitial thermal therapy treatments. The median age was 57.4 years and there was male predominance (65.8% male Vs 34.2% female). The most common location resulted frontal lobe (29%), followed by temporal (23.9%), parietal (21.4%) and occipital lobes (2.6%). Additional locations included thalamus, corpus callosum and cerebellum (23.1%). Pre-treatment median tumor size was 8.9 cm^3. Morbidity was 6.4 % with a median hospital stay of 3.5 days. The most common complications were seizures (2%), motor deficits (1.5%), wound infection (1.5%), transient hemiparesis (1%) and hemorrhage (0.5%). No deaths were reported due to LITT procedure. The median progression-free survival and the median overall survival after laser interstitial thermal therapy resulted 5.6 months and 10.2 months, respectively. The median overall survival from diagnosis was 14.7 months. All patients underwent adjuvant chemotherapy after treatment.

Conclusion: Laser interstitial thermal therapy provides an effective treatment with low morbidity for selected patients harboring recurrent glioblastoma. Laser interstitial thermal therapy should be included in the armamentarium of neurosurgical oncologist for treatment of recurrent glioblastomas.

Keywords:

Brain tumor; Glioblastoma; Laser; LITT; Overall Survival.

1. Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. Despite intense research over the past 40 years and new innovative surgical tools, the overall survival (OS) of patients with GBM continues to be poor. With the current standard of care consisting of gross total resection (GTR) followed by radiotherapy and temozolamide and second surgery in case of recurrent GBM, the OS from diagnosis results about 18.5 months [1,2]. In the last years, due to its minimal invasiveness, laser interstitial thermal therapy (LITT) became a new treatment option for a variety of applications in neurosurgery, including primary or secondary brain tumors [3]. LITT is a thermocoagulative therapy for cancer treatment which allows the delivery of laser energy directly into the tumor tissue via percutaneous insertion of an optical fiber, which causes tissue damage and necrosis in the tumor. The near real–time feedback of the thermal dose delivery enables the surgeon to precisely control the damage inflicted on the tumor, maximizing its safety and effectiveness, resulting in heating the treated tissue, causing enzyme induction, protein denaturation, melting of membrane lipids, vessel sclerosis and coagulation necrosis [4,5]. Two of the most common commercially available LITT systems that have been used in neurosurgery include the NeuroBlate System (Monteris Medical, Inc.) and the Visualase Thermal Therapy System (Medtronic Inc.). In patients with GBM, surgery is usually indicated as the first stage of treatment, along with chemotherapy and radiation therapy. However, due to the aggressive nature of this tumor, recurrence is unavoidable. At the moment, there is no standard treatment for recurrent GBM, although several clinical studies described a survival benefit after reoperation. The objective of this review is to study the role of LITT in patients with recurrent GBM and to assess its role in survival outcomes.

2. Materials and methods

A Pubmed and MEDLINE search were performed to identify articles from the period 2000 to present relevant to LITT for recurrent GBM. PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were followed [6]. The key words “laser interstitial thermal therapy”, “LITT” and “glioblastoma multiforme” were used in both “AND” and “OR” combinations. The inclusion criteria were the following: (1) case series reporting patients with recurrent GBM treated with LITT. Exclusion criteria were the following: (1) review articles, (2) single case report, (3) case series reporting only other intracranial lesions or only newly diagnosed GBM treated with LITT, (4) cases series where it was not feasible to extract data of recurrent GBM patients, (5) case series on the same dataset; (6) studies with insufficient data. The flow chart for inclusion and exclusion criteria is presented in Fig. 1.

3. Results

The database search yielded 71 articles. After the removal of duplicates, 39 articles were eligible for screening. A total of 17 articles met the selection criteria, accounting for 203 patients with recurrent GBM who underwent 219 LITT treatments [4,7-22]. It was reported a median age of 57.4 years and a male predominance (65.8% male Vs 34.2% female). The most common location was frontal lobe (29%), followed by temporal (23.9%), parietal (21.4%) and occipital lobes (2.6%). In 23.1% of patients, recurrent GBM was located in the midline (thalamus, corpus callosum and cerebellum). Pre-treatment median recurrent tumor size resulted 8.9 cm^3. Detailed data are presented in Table 1. Morbidity was 6.4 % with a median total hospital stay of 3.5 days. The most common complications were seizures (4 patients), motor deficits (3 cases), wound infection (3 cases), transient hemiparesis (2 patients) and hemorrhage (1 case). No deaths were reported due to LITT procedure. OS and progression-free survival (PFS) after LITT were obtained in 11 studies (including 149 patients) and 13 studies (including 177 patients), respectively. The median OS and the median PFS resulted 10.2 months and 5.6 months, respectively. The OS (114 patients, 10 studies) from diagnosis was 14.7 months (Table 2). All patients underwent adjuvant chemotherapy after treatment.

4. Discussion

LITT is an emerging minimally invasive procedure increasingly utilized for treatment of deep and recurrent GBMs. It offers a targeted thermal ablation of selected lesions with minimal damage to off-target healthy tissue. Pooling the results of 19 studies, our review provides representative data on the survival outcomes and complications after LITT in patients with recurrent GBM.

4.1. Survival outcomes after LITT for recurrent GBM

Several clinical studies support the value of aggressive interventions for recurrent GBMs [23-26]. GTR at repeat craniotomy is associated with longer OS and should be offered to patients in good performance status at the time of recurrence [23,24]. A recent systematic review reported that OS after second surgery is 18.5 months [2]. Improved survival after second surgery appears to be related to reduced tumor burden that prolongs recurrence and allows improved efficacy of radio- and chemotherapy. Recent clinical series described the results of LITT as an upfront treatment in patients with deep seated newly diagnosed GBM and in patients with recurrent GBM that are not candidate for a second surgery [19].

In our review, we analyzed the survival outcomes of 219 patients treated with LITT after glioblastoma recurrence. The median OS after diagnosis resulted 14.7 months, ranging from 7.3 (Shah et al.) [17] to 26 months (Carpentier et al.) [9], whereas the median OS after LITT resulted 10.2 months, ranging from 6.1 (Ali et al.) [7] to 14 months (Schwarzmaier et al.) [19]. These data suggest a slightly worse OS since diagnosis, but a similar OS after second treatment to several series reporting patients with recurrent GBM who underwent second surgery [27-30]. Lu et al. [27] in their meta-analysis including eight observational studies reporting patients with recurrent glioblastoma treated with repeat surgery, found an OS from diagnosis and recurrence ranging from 18.86 to 29 months and 6.8 to 11.4 months, respectively. Another review on 28 studies and 2279 patients who underwent second surgery, reported that median OS from diagnosis and second surgery were 18.5 months and 9.7 months, respectively [2]. In our study on patients treated with LITT at recurrence median PFS after first surgery was slightly lower compared to the current literature on repeat surgery for recurrent GBMs. This can be probably due to the fact that up to 23.1% of patients treated with LITT harbored lesions located in deep structures such as thalamus, basal ganglia and midbrain. In these locations, GTR is not generally achieved during first surgery, resulting in a lower median PFS and OS from diagnosis, compared to series reporting repeat surgery for lobar GBMs [28-30]. The effect of GTR on OS and PFS at first surgery and repeat surgery has been extensively reported [23,24,31]. Recently, Perrini at al. [23] showed that median OS in selected patients with cortical/subcortical GBMs who had GTR at recurrence after initial GTR increased was significantly increased compared with survival of patients who had subtotal resection at recurrence after initial GTR (47 months vs 14 months, p=0,009). The effective role of multiple surgical interventions for recurrent GBM remains under discussion. Chaichana et al.[28] reported that repeated resections can improve OS from 15.5 months after second surgery to 22.4 and 26.6 months after 3 and 4 surgical resections, respectively. Schwarzmaier et al.[16] reported an OS from diagnosis of 18 months (range 16-20 months) and an OS after LITT of 6.9 months in 16 patients with recurrent GBM, with only one transient hemiparesis and no mortality. In 2013, Sloan and colleagues[4] reported their series of 10 patients with recurrent GBM. The OS from diagnosis and PFS were 10.5 months and 8 months respectively with a post-treatment morbidity of 30%. In 2019, Sharma et al.[18] and Kamath et al.[11] reported the larger series to date, with respectively 53 and 37 patients with recurrent GBM treated with LITT. In these series, the OS after LITT was 11 month and 11.8 months, respectively.

In this scenario, LITT seems to be a promising treatment for selected recurrent high-grade gliomas [32]. Potential advantages of LITT includes its minimal invasiveness, the possibility of treating deep lesions, being used multiple times and the benefit of not stopping chemotherapy [9]. For selected patients with recurrent GBM, LITT can be considered a minimally invasive alternative approach for cytoreductive intervention. The three major factors to consider preoperatively when planning LITT are lesion location, size and shape [33]. Lesions unfavorable for LITT include hypervascular lesions, diffuse neoplasms involving bilateral or multiple lobes or very large tumors in which treatment would be subtotal [11]. Lesions in constricted locations (basal ganglia, posterior fossa), which are difficult to approach surgically, are also a complex target for LITT, although this was not a contraindication to treatment in recent series[11]. Size represents the most important criterion in the decisional process for LITT procedure and in term of OS. Authors suggest that with a single laser catheter the maximum target diameter should not be more than 3 cm, because malignant edema can occur in larger lesions [7, 34]. In our review we found that the pre-treatment median volume resulted 8.9 cm^3. Patients with tumor volume ranging from 23 to 40,2 cm3 [16] had a shorter OS than patients with tumor volume between 0.9 and 25.9 cm3 [11] and between 0.3 and 12 cm3 [8], which resulted 9.4, 22.3 and 20.4 months, respectively.

4.2. Treatment-related complications

In 1983 Bown[35] showed the therapeutic effects of LITT, previously called SLITT (stereotactic guided laser-induced interstitial thermotherapy)[12], due to tissue hyperthermia. Although this treatment was used for different brain pathologies, in the 20th century it was not widely accepted as a treatment for glioma due to its potential complications related to the extent of thermal damage. Advances in technology in the last few years led to a reduction of new neurological deficits and other postoperative complications and to an increase in the number of LITT procedures in patients with GBM. Among all 17 studies analyzed in our review including 203 patients, the overall morbidity resulted 6.4%, and seizures and wound infection were the most common complications. In contrast with our analysis, the morbidity reported by Lee et al.[3] in their review investigating patients with recurrent high-grade gliomas treated with LITT until 2016, was 15%. The lower rate of complications in our study can be the result of the improvement of technological features of LITT, namely the development of real-time magnetic resonance (MRI) thermometry and the development of LITT systems that successfully integrate MRI thermometry data and enhanced control over laser energy delivery into a standard workflow. Lee et al. [3] did not report data about median OS and median PFS of all studies included in the review, probably a higher morbidity affected median OS and PFS. As changes in tissue temperature affect the water proton resonance frequency signal in a linear relationship, a heat damage map can be updated throughout the procedure and used to guide the boundaries of laser ablation [36]. Furthermore, novel miniframes, novel MRI coil and functional neurosurgical navigation, that permit increased trajectory angles, have been used in last recent years, resulting in lower morbidity. Whereas Sloan et al.[4] reported the higher rate of complication (30%) in 2013, recent studies [7,8,11,13,17,18] (published in 2018 and 2019) reported an overall morbidity of 2.7%. Comparing the two most common commercially available LITT systems, morbidity was 6.9% and 10.7% by using Visualase Thermal Therapy System and NeuroBlate System, respectively. There are very few data in the literature regarding the role of the extent of tumor coverage by the LITT-induced hyperthermic field on outcome for recurrent GBM. Mohammadi et al.[14] reported the important role of extent of thermal damage threshold (TDT), as a larger percentage of the tumor covered by LITT correlates with an improvement of PFS. Based on statistical analysis, Mohammadi et al. [14] reported that higher median tumor coverage improves PFS ($P = 0.02$). The prognostic role of the extent of TDT of tumor volume should be considered analogous to the concept of "extent of resection" in surgical treatment of GBM [14]. Due to constant technological advances and the growing experience in selecting and treating patients with LITT, it is plausible that the efficacy in tumor ablation in term of OS will increase in the next few years [36], minimizing neurological morbidities and tissue-healing issues that sometimes occur with a repeat craniotomy and tumor resection.

4.3. Adjuvant treatment for recurrent GBM

Adjuvant chemotherapy was performed after LITT in all patients included in our study. Some authors suggest that LITT procedure leads to a breakdown of the blood–brain barrier (BBB) due to tissue damage and improves chemotherapy drugs diffusion into the tumor [19]. Recently, Carpentier and colleagues[9] reported that LITT do not increase BBB permeation and its effect on adjuvant chemotherapy in term of survival was minimal.

For patients with recurrent GBM a wider variety of chemotherapeutic drugs were proposed and used including second-line temozolomide (TMZ), bevacizumab alone or in combination, lomustine (CCNU), irinotecan and doxorubicin often in combination with nimustine (ACNU) or TMZ. Bevacizumab showed some efficacy in the treatment of recurrent GBM and was subsequently used in combination with other chemotherapy agents of which irinotecan appears to have the best response [37,38]. Alkylating chemotherapeutic agents remains the standard of care for patients with recurrent GBM [39].

4.4. Strength and limitations

Our review has several limitations. The included series are often small, retrospective and single-institution experience. For this reason, comparison between different studies may not provide a comprehensive representation of survival outcomes after LITT. Secondly, some studies [14,16,18] reported more than one LITT treatment on the same patients. In addition, technological improvements of this minimally invasive technique occurred over the last years leading to better survival and lower morbidity.

5. Conclusion

LITT is a safe and effective treatment for recurrent GBM and may offer an effective alternative to repeat surgery in properly selected patients. Although our study supports the efficacy and safety of LITT, prospective multicentric studies are needed to confirm the role of this minimally invasive procedure in patients with recurrent GBM.

Conflict of interest

None.

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FIGURE LEGENDS

Fig. 1 PRISMA flow-diagram of studies selection.

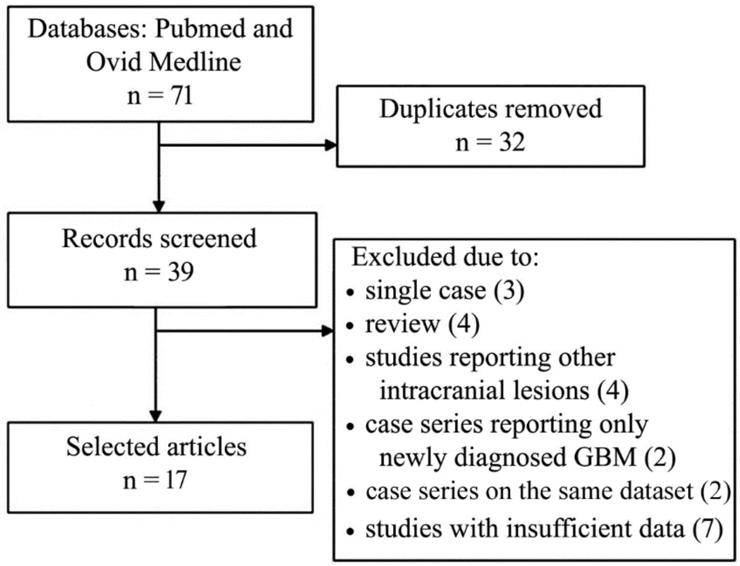

Table 1 – Baseline characteristics of patients and location of lesions treated with LITT

Author	Year	Patients with rGBM	Mean age (range)	Sex	Tumor location (No.)	No. of LITT treatments	Pretreatment tumor volume (cm^3)	LITT surgical technology
Leonardi & Lumenta[13]	2002	6	60	-	-	-	-	-
Schwarzmaier et al.[21]	2005	2	57 (47-67)	2/0	temporoccipital (1), parietoccipital (1)	2	2	Signa SP/i
Schwarzmaier et al.[18]	2006	16	62 (44-69)	10/6	frontal (5), temporal (3), parietal (5), occipital (1), midline (2)	26	21.6 ± 18.6	Signa SP/i
Carpentier et al.[9]	2012	4	50.3	3/1	frontal (2), parietal (2)	5	2 (1.3-2.5)	Visualase Th.
Sloan et al.[4]	2013	10	55 (34–69)	8/2	frontal (3), temporal (4), parietal (3)	10	6.8 (2.6–19)	NeuroBlate
Hawasli et al.[10]	2013	4	71 (64-73)	3/1	frontal (1), parietal (2), insula (1)	4	10.9 (2.4-22.2)	NeuroBlate
Mohammadi & Schroeder[17]	2014	10	-	-	-	10	-	NeuroBlate
Mohammadi et al.[16]	2014	18	-	-	-	19	10	NeuroBlate
Sun et al.[22]	2015	6	57.3 (23-70)	5/1	frontal (1), parietal (2), temporal (1), occipital (1), cerebellum (1)	6	3.2 ± 1.9	Visualase Th.
Wright et al.[24]	2016	1	51	1/0	frontal (1)	-	13.2	NeuroBlate
Thomas et al.[23]	2016	13	48.9	-	frontal (3), temporal (4), splenium (2), cingulate (2), insular (2)	13	14.6	-

Beaumont et al.[8]	2018	4	57.8 (48-65)	1/3	parietal (2), callosal (2)	4	6.1 (0.3-12)	NeuroBlate
Maraka et al.[15]	2018	2	-	-	temporal (1), frontal (1)	2	21.6 (11.03-32.12)	Visualase Th.
Ali et al.[7]	2018	3	52 (39-69)	1/2	frontotemporal (2), parietal (1)	3	5.6 (1.8-12)	Visualase Th.
Sharma et al.[20]	2018	53	58 (19-82)	36/17	-	-	3.80	-
Shah et al.[19]	2019	14	54 (29-73)	7/7	frontal (4), frontoparietal (2), parietal (1), temporal (6), occipital (1)	14	3.8 (0.5-15.8)	Visualase Th.
Kamath et al.[11]	2019	37	58.8 (35-78)	-	frontal (10), temporale (6), parietal (7), occipital (1), corpus callosum (6), insular (1), thalamic (6)	41	12.5±13.4	NeuroBlate

NeuroBalte, NeuroBlate System (Monteris Medical Inc.); rGBM, recurrent glioblastoma multiforme; Signa SP/i, Signa SP/i (General Electric); Visualase Th., Visualase Thermal Therapy System (Medtronic Inc.).

Table 2 – Clinical outcome after treatment with LITT

Authors	Year	Complications (No.)	Mortality (%)	Mean hospital stay (day)	Pre-op KPS (range)	Post-op KPS (range)	OS from diagnosis (months) (range)	OS after LITT (months) (range)	PFS (months) (range)
Leonardi & Lumenta[13]	2002	0	0	-	-	-	17	9	4
Schwarzmaier et al.[21]	2005	0	0	6 (2-10)	80 (70-90)	70	18 (16-20)	14 (13-15)	-
Schwarzmaier et al.[18]	2006	transient hemiparesis (1)	0	12.0 ± 4.2	70	70	9.4 ± 1.3	6.9 ± 1.7	-
Carpentier et al.[9]	2012	seizures (1)	0	1	70 (50-90)	70 (50-90)	26	11	10
Sloan et al.[4]	2013	wound infection (1), motor deficit (1), hemorrhage (1)	0	3	80 (70–90)	80 (60-100)	10.5 (2-25.6)	10.5	8
Hawasli et al.[10]	2013	transient hemiparesis (1)	0	1.7 (1-3)	50	50	-	-	8.4
Mohammadi & Schroeder[17]	2014	motor deficit (2)	0	-	-	-	-	-	2.8
Mohammadi et al.[16]	2014	0	0	3	80 (50-90)	-	8	-	6
Sun et al.[22]	2015	-	-	1	-	-	-	-	-
Wright et al.[24]	2016	wound infection (1)	0	-	-	-	-	9,3	3.1

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Thomas et al.[23]	2016	seizures (1)	0	-	80	-	-	8	5
Beaumont et al.[8]	2018	0	0	1	80	80	20.4 (8-34.9)	6.8 (2.4-12.5)	3.5 (2.2-4.9)
Maraka et al.[15]	2018	0	0	-	-	-	-	-	-
Ali et al.[7]	2018	0	0	1	-	-	7.4 (2.8-11.9)	6.1 (3-11.9)	4 (2.8-5.1)
Sharma et al.[20]	2018	0	0	-	80 (50-100)	-	-	11	4.4
Shah et al.[19]	2019	wound infection (1)	0	1	90	90	7.3 (5.6-13.5)	-	5.6
Kamath et al.[11]	2019	seizures (2)	0	3.2 ± 4.6	-	-	22.3	11.8	7.3

KPS, Karnofsky Performance Score; OS, overall survival; PFS, progression-free survival.