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Laser Interstitial Thermal Therapy for Recurrent Glioblastoma: Pooled Analyses of Available Literature

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Abstract

OBJECTIVE/BACKGROUND: The efficacy of laser interstitial thermal therapy (LITT) in recurrent glioblastoma (rGBM) is unknown. The goal of this study was to conduct a systematic review and pooled analysis of the literature for outcomes on patients with rGBM undergoing LITT.

METHODS: A literature search was performed to retrieve all studies investigating overall survival, postprocedure survival, and progression-free survival outcomes of patients with rGBM undergoing LITT. Statistics were pooled together by meta-analysis of mean using a weighted random-effects or fixed-effect model.

RESULTS: Eleven studies were included in the final cohort, representing a total of 134 patients with rGBM. The pooled mean age of the cohort at the time of recurrence was 56.7 ± 4.56 years; 41% of the cohort were female. For delivery of LITT, 2 studies used neodymium-yttrium aluminum-garnet laser (Nd:YAG laser), 3 studies used the Visualase system, 5 studies used the NeuroBlate system, and 1 study used both the NeuroBlate and the Visualase system. A total of 8 studies with 107 patients had available data for overall median survival. The pooled overall survival was found to be 18.6 months (95% confidence interval [CI] 16.2—21.1). A total of 6 studies with 93 patients had available data for post-LITT survival. The pooled post-LITT survival was found to be 10.1 months (95% CI 8.8—11.6). A total of 8 studies with 119 patients had available data for progression-free survival. Pooled progression free survival was found to be 6 months (95% CI 5.3—6.7).

CONCLUSIONS: LITT is a novel minimally invasive procedure which, when used with optimal adjuvant therapy, may confer survival benefit for patients with rGBM.

Keywords

Glioblastoma; Laser interstitial therapy; Literature review; Pooled analysis; Recurrent glioblastoma; Survival outcomes; Thermal ablation

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Glioblastoma (GBM) is the most aggressive primary intracranial tumor and constitutes 15%—20% of all primary intracranial tumors.[1,2] Despite advances in therapies, the median survival ranges from 14 to 16 months and 2-year survival rate of ~30%, even with maximal therapy.[3,4] The poor prognosis is largely due to tumor recurrence, with studies suggesting an inevitable outcome of recurrence after 32—36 weeks from initial multimodal treatment,[5,6] and 6-month progression-free survival rate ranging from 5% to 15%.[7,8] Median survival after recurrent GBM (rGBM) is approximately 30 weeks.[9] In the context of rGBM, there is no standard of care, and current treatment options have limited efficacy.[10] Only approximately 25% of recurrent glioblastomas are considered eligible for repeated surgery, and tumors in eloquent areas are often not eligible. In addition, the survival benefit of repeat surgery resection has been under revision. A retrospective cohort study failed to demonstrate survival benefit of second tumor resection and another study showed that repeated surgery provided only a 3-month benefit of survival. Upon second resection, the increased risk of neurologic deficits and wound-healing complications warrants a more thorough risk-benefit assessment.[11] Other treatment options include lomustine,[12] temozolomide rechallenge,[12] bevacizumab with or without Irinotecan,[13-15] intermediate-frequency electrical fields, or tumor treatment fields.[15] Laser interstitial thermal therapy (LITT) is a minimally invasive cytoreductive option that is increasingly employed.

LITT is a novel treatment modality that has been used for a variety of intracranial lesions. The treatment typically features a stereotactically guided laser probe that is used to deliver controlled heat to surrounding tissues while using magnetic resonance thermography to monitor and conform the energy in real time.[16] Potential advantages of LITT over repeat surgery include a decreased risk of wound-healing complications and cerebrospinal fistulae, decreased recovery time, as well as the ability to safely treat deep-seated lesions that may otherwise not be amenable to surgical resection.[17]

In the current manuscript, we conducted a systematic review of the available literature with quantitative pooling of overall survival and progression-free survival data to summarize outcomes of patients with rGBM undergoing LITT.

METHODS

Search Strategy

The current study was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[18] The search strategy was designed around the question: “What are the outcomes of patients with rGBM undergoing LITT as assessed by overall median survival, post-LITT survival and progression free survival?” An expert librarian first performed a comprehensive electronic search in PubMed, Embase, Scopus, evidence-based medicine, and Web of Science for studies published until April 13, 2020. We have attached the actual search strategy as a supplemental file (Supplementary Methods). Two investigators (A.M.-C. and M.A.A.) independently reviewed the identified articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart for search methodology and subsequent exclusions is provided in Figure 1. Institutional review board approval was neither sought nor required, as we only used published data for the study.

Selection Criteria

We included studies if they matched the following criteria: 1) documented recurrence of GBM after initial therapy; and 2) provided quantitative data on overall survival, post-treatment survival, or progression-free survival after LITT. When studies included patients with multiple tumor pathologies, only patients with rGBM were included. Studies with pooled data without distinction of rGBM cases were excluded. Survival metrics were calculated from studies that reported individual data for patients with rGBM but not overall median or progression-free survival.

Data Extraction

The following data were extracted from the included studies: 1) first author and year of publication, 2) sample size of overall patients and those with rGBM, 3) time to progression/recurrence, 4) type of LITT system used, 5) adjuvant treatments, 6) complications, 7) overall survival 8) post-LITT survival, and 9) progression-free survival post-LITT. All data points were abstracted directly from article manuscripts, tables, and figures by 3 investigators (M.R., A.M.-C., and M.A.A.).

Statistical Analysis

The primary outcomes of the study were 1) median overall survival 2) median post-LITT survival, and 3) progression-free survival. All statistics were pooled together by a meta-analysis of means using weighted random-effects or fixed-effect model depending on heterogeneity.[19] When a study did not report any variance metric (95% confidence interval [CI], standard error, or standard deviation) for continuous outcomes of interest, we imputed these using established methods.[20] Heterogeneity was assessed using the I^2 statistics, with values >50% denoting significant heterogeneity.[21] We also performed sensitivity analyses, by excluding from each analysis studies that used older LITT systems (other than the Visualase or the NeuroBlate system).

Quality Assessment of Included Studies

We assessed the quality of each study using the modified Newcastle—Ottawa Scale for noncomparable studies.[22] Since none of the outcomes had more than 10 studies available, we did not generate funnel plots to observe publication bias (Table 1).[33]

RESULTS

Search Strategy and Study Characteristics

The initial comprehensive search identified 739 articles, describing 627 unique studies. After screening the abstracts and applying the exclusion criteria, we identified 25 eligible studies that underwent full-text screening. Eleven studies met all inclusion and exclusion criteria and were used for data extraction. These studies described a total of 134 patients with rGBM.[17,23-32] Most studies were published during the last decade, between 2012 and 2019,[17,23-31] with the exception of Reimer et al. (1998)[17,23-31] and Schwarzmaier et al. (2006).[17,23-31]

Demographics and Clinical Characteristics of the Cohort

The pooled mean age and variance of the cohort at the time of recurrent diagnosis was 56.7 ± 4.56 years of age. Based on 10 studies, 41% (50/121) of the pooled cohort was female. The most commonly involved region was the frontal lobe (42.5%), followed by the parietal lobe (29%), the temporal lobe (26.1%), corpus callosum (20.9%), and thalamus (14.2%). For delivery of LITT, the 2 older studies[28,29] both used neodymiumdoped yttrium aluminum garnet (Nd:YAG laser; Domier, Friedrichshafen, Germany), 3 studies[17,23-31] used the Visualase Thermal Therapy System (Visualase, Inc., Houston, Texas, USA), 5 studies[17,23-31] used the NeuroBlate system (Monteris Medical Corporation, Plymouth, Minnesota, USA), whereas 1 study[17,23-32] used both the Visualase and the NeuroBlate systems (Table 2).

Overall Median Survival

A total of 8 studies with 107 patients had available data for overall median survival. The pooled overall survival was 18.6 months (95% CI 16.2—21.1) with an overall I^2 of 98.7% (Table 3).

We also performed a sensitivity analysis to include only those studies that used either the NeuroBlate or the Visualase, thereby excluding the 2 older studies with Nd:YAG laser. This analysis revealed the pooled overall survival to be 20.2 months (95% 17.4e23.1).

Post-LITT Survival

A total of 6 studies with 93 patients had available data for post-LITT survival. The pooled post-LITT survival was 10.2 months (95% CI 8.8—11.6). The overall I^2 of the analysis was 91% (Table 4).

We again performed a sensitivity analysis to include only those studies that used either the NeuroBlate or the Visualase, thereby excluding the sole study that used a Nd:YAG laser. This analysis revealed the pooled post-LITT survival to be 10.9 months (95% 9.1—12.6).

Progression-Free Survival

A total of 8 studies with 119 patients had available data for progression-free survival. The pooled progression-free survival was 6.2 months (95% CI 5.37—6.95). The overall I^2 of the analysis was 80.3% (Table 5).

We also performed a sensitivity analysis to include only those studies that used either the NeuroBlate or the Visualase, thereby excluding one study that used Nd:YAG laser. This analysis revealed a pooled progression-free survival of 6 months (95% CI 5.2—6.7).

DISCUSSION

Laser interstitial therapy has emerged as a minimally invasive alternative to surgery for recurrent glioblastoma. LITT results in heat-induced protein denaturation propagated through an ablation radius of 20 mm. Visualase and NeuroBlate are the 2 systems approved by the Food and Drug Administration that are available in the United States and appear equivalent to each other with regard to efficacy as determined by laser wavelength and

exposure time. The incorporation of a CO_2—saline cooling system permits power up to 15 W with maximum temperature threshold of 90°C and 50°C at the ablation and periphery zones, respectively.[34] The addition of visible helium to the invisible CO_2 laser increased efficiency, precision, and applicability in neurosurgical procedures. LITT developed after the use of Nd:YAG laser in an experimental brain model by Bown in 1983.[35] Through LITT, tumor necrosis occurs with temperatures between 50°C and 80°C. The incorporation of magnetic resonance imaging software for the Arhenius thermal dose model allows appropriate feedback-control for increased preservation of surrounding tissue but also increased predictability of tissue necrosis.[36] Real-time extent of thermal ablation can be calculated through a software incorporated within the NeuroBlate System capable of predicting tissue damage based on temperature and exposure time, which determines the thermal damage threshold (TDT).[32] Mohammadi et al.[27] demonstrated that the extent of tumor coverage by TDT lines has an impact on overall survival on patients with high-grade glioma. The authors suggest that the concept of tumor coverage by TDT lines may be analogous to “extent of resection,” which is discussed in open surgical resection literature.

LITT has surged as a viable option to radiotherapy or repeated surgery for recurrent GBM. In our study, to address possible selection bias introduced by different LITT modalities, we performed a sensitivity analysis comparing outcomes from studies using modern LITT modalities such as NeuroBlate versus Visualase,[17,23-32] and the Nd:YAG laser.[28,29] We observed that difference in survival time was around 1 month. This confirms previous results of no superiority between LITT modalities.[37] In a recent retrospective review, preoperative Karnofsky Performance Score (KPS; ≤70) before LITT was associated with increased number of motor deficit and overall survival.[38] However, data regarding LITT improving quality of life in recurrent GBM have yet to be discussed.[39]

Heterogeneity in LITT timing during different disease stages poses a challenge in terms of evaluating the role of this treatment modality on patients with recurrent disease. Throughout the study, we provide a framework that seeks to increase decision-making capacity on the management of recurrent GBM. Patients with recurrent tumors might be more frequently eligible for this procedure as an alternative to avoid a second open surgery. A recent systematic review reported an overall survival of 22 months in patients undergoing a second surgery with chemotherapy at recurrence.[40] Our analysis indicates an overall survival of 18.6 months from diagnosis. Following recurrence, a second surgery and chemotherapy was associated with an extended survival of 9.6 months, whereas our analysis reports a post-LITT survival of 10.9 months. In addition, we found a post-LITT PFS of 6 months, which is slightly superior to the 4.8 months following repeated surgery and chemotherapy in this retrospective study.[40] According to these data, one of the advantages associated to the LITT option is possible chemotherapy avoidance at recurrence. Furthermore, for inoperable cases such as deep-seated or near-to-eloquent-areas gliomas, where biopsy might be the only option, LITT is associated with an additional survival of 7 months.[41] Continued improvement in the technology and reduction in the steepness of the learning curve over time have also been thought to contribute to improved survival.[27,29,38,41] However, the study by Schwarzmaier et al.[29] showed that not only the learning curve but also longer interval between recurrence and LITT, lower KPS, and larger tumor volume might have influenced the poorer outcomes of the early years. Appropriate patient selection is an important factor

in safety and efficacy, with more favorable outcomes among patients with lesions <3 cm diameter, in those with a predicted achievable ablation ≥80%, and in those with KPS ≥70.[27,29,38,41]

Complications do occur and inversely correlate with overall survival.[41] Among the most common reported serious complications are brain edema,[23] hydrocephalus,[23,25,26] transient and permanent neurologic deficit,[23,25] seizure,[17] as well as possibility of leptomeningeal spread and seeding.[32] Patients with larger and newly diagnosed lesions have a greater risk of complications than those with recurrent, smaller tumors.[23] Compared with open surgery, LITT is associated with significantly reduced postoperative hospital stay and overall cost.[41] From this study, we can conclude that LITT is a safe and effective method in this population that could be used as an alternative to surgery in selected cases. The numbers of catheters used during the LITT procedure is a determinant factor when assessing both safety and cost and making accurate comparisons with surgery from an overall effectiveness point of view. However, given limited data available for these variables, further research is required to make a closer effectiveness comparison with surgery.

The current study is not a pooled analysis, as the absence of hazard ratios pre-cluded a true meta-analysis. The study is limited by the risk of selection bias due to lack of stratification for known survival prognostic factors in glioblastoma such as isocitrate dehydrogenase mutation status,[42] or Ki67 index,[43] subventricular zone location,[44] presentation at younger than 50 years of age,[45] or O^6-methylguanine-DNA methyl-transferase methylation status.[46] Future studies will be necessary to better define the risks and efficacy of LITT in specific biomolecular tumor contexts.[29] The study is also limited by the small cohort, with only 10 studies meeting eligibility criteria for inclusion in our analysis. In one of the studies, deaths among nearly one-half of the patients were due to non—tumor-related causes, and 4 patients did not complete follow-up by the time the study ended (follow-up less than 85%).[29] Specific information regarding patients with rGBM in relation to progression-free survival, survival after LITT, and overall median survival could not be extrapolated from 3[24,29,32] and 4[25,27,28,30] studies, respectively. Another limitation accounts for nonaccoutrements of outcomes defined in relation to optimal thermal ablation technique defined per the TDT lines coverage. In addition, this analysis includes patients who may have not be eligible for surgical resection and therefore underwent LITT; this could have introduced a selection bias to our study that should be acknowledged. Similarly, these findings could as well emphasize how LITT is a safe alternative to surgery when surgery resection of recurrent GBM is not feasible. We would like to acknowledge the intrinsic limitation when interpreting survival analysis, given a lack of specific distinction between treatment-related pseudoprogression and actual disease progression. Although our data are based on best-available literature, any of the herein included studies specifically address characterization of real recurrence versus pseudoprogression. For example, we previously observed that 16% of patients treated for presumed tumor progression were indeed cases of pseudoprogression due to treatment-related radiographic changes. This observation might serve as a call for improving accuracy of outcomes reported on rGBM-related research.

CONCLUSIONS

Results in our study show that LITT provides a survival at least comparable with that of open surgery for patients with rGBM. LITT is a safe and effective treatment comparable with the current standard of care for recurrent GBM that can be used as an alternative to surgery. While no clear benefit over open surgery in terms of survival can be established yet, additional advantages such as decreased morbidity and hospital costs make LITT an attractive alternative in this population of patients. In patients where surgery is not amenable, LITT is associated with extended benefit on survival. Safety and effectiveness in LITT rely on appropriate patient selection and center experience.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

CI	Confidence interval
GBM	Glioblastoma
KPS	Karnofsky Performance Score
LITT	Laser interstitial thermal therapy
Nd:YAG laser	Neodymium-doped yttrium aluminum garnet
rGBM	recurrent glioblastoma
TDT	Thermal damage threshold

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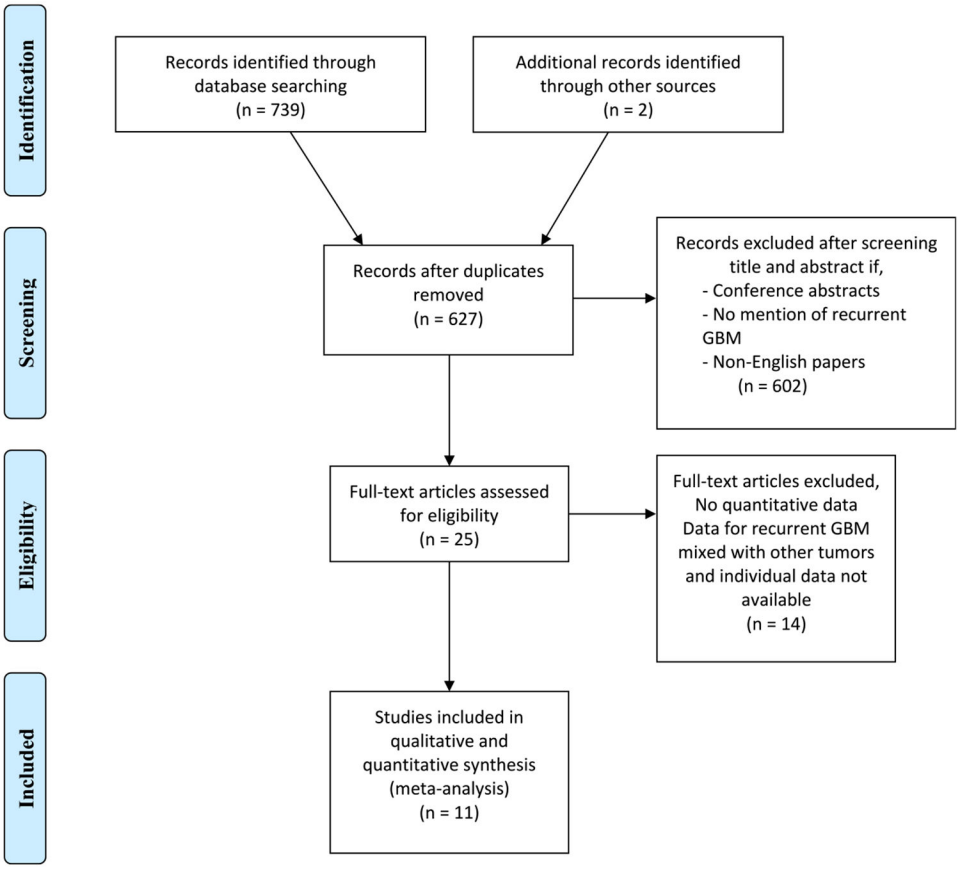

Figure 1.

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) study selection flowchart.

Table 1.

Assessment of the Quality of Included Studies According to the Modified Newcastle—Ottawa Quality Assessment Scale

	Quality Assessment Criteria						
Study	**Representativeness of Exposed Cohort**	**Representativeness of Nonexposed Cohort**	**Ascertainment of Exposure**	**Outcome of Interest**	**Assessment of Outcome**	**Adequate Duration of Follow-up**	**Adequate Follow-up of Cohorts**
Beaumont et al., 2018[23]	***	—	***	***	**	***	***
Carpentier et al., 2012[24]	**	—	***	**	**	**	***
Hawasli et al., 2013[25]	***	—	***	*	***	***	***
Kamath et al., 2019[26]	***	—	***	***	**	***	***
Mohammadi et al., 2014[27]	***	—	***	*	**	*	*
Reimer et al., 1998[28]	**	—	***	*	**	***	***
Schwarzmaier et al., 2006[29]	***	—	***	**	**	*	*
Shah et al., 2020[30]	***	—	***	**	**	***	***
Ali et al., 2018[31]	**	—	***	***	**	***	***
Sloan et al., 2013[32]	***	—	***	**	***	***	***
Thomas et al., 2016[17]	***	—	***	***	***	***	***

Representativeness of exposed cohort: very representative, retrospective institutional cohort (***); somewhat representative, selected patients (**); not representative (*).

Representativeness of nonexposed cohort: not available.

Ascertainment of exposure: all patients in cohort received treatment (***).

Outcome of interest: study reports all of the outcomes evaluated in this analysis (***); study reports most of the outcomes evaluated in this analysis (**); study reports some of the outcomes evaluated in this analysis (*).

Adequate duration of follow-up: study reports complete lifespan of all patients with GBM (***); study reports complete follow-up for most patients with GBM (**); study reports complete follow-up for some patients with GBM (*).

GBM, glioblastoma.

Table 2.

Demographic and Clinical Characteristics of Patients in Each Study

Study	N	Patients with rGBM	Age at Recurrence Diagnosis, Mean ± SD	Female	Intracranial Region of Recurrence*	Median KPS	Outcomes Assessed	LITT System
Beaumont et al., 2018[23]	15	6	52.16 ± 10.9	66.70%	Corpus callosum (15)	80	OS, post-LITT survival, PFS	NeuroBlate
Carpentier et al., 2012[24]	4	4	50.25 ± 7.8	25%	Temporal (2), frontal (2)	N/A	OS, post-LITT survival	Visualase
Hawasli et al., 2013[25]	11	4	71 ± 4.7	25%	Thalamus (4), frontal (1), corpus callosum (1), insular (1). basal ganglia (1), parietal (2)	N/A	PFS	NeuroBlate
Kamath et al., 2019[26]	54	41	58.8 ± 10.8	31.50%	Frontal (14), temporal (8), parietal (9), occipital (1), parieto-occipital (4), temporo-parietal (4), corpus callosum (8), insular (2), thalamic (8)	N/A	OS, post-LITT survival, PFS	NeuroBlate
Mohammadi et al., 2014[27]	34	19	56 ± 4.56	38%	Frontal (15 lesions), thalamic (7), parietal (5), temporal (5), insular (2), corpus callosum (1)	N/A	PFS	NeuroBlate
Reimer et al., 1998[28]	4	4	59 ± 4.24	50%	Temporal (1), frontal (3)	N/A	PFS	Nd:YAG laser
Schwarzmaier et al., 2006[29]	16	16	62 ± 4.56	37.50%	Frontoparietal (1) Frontal (3) parieto-occipital (3) temporo-parietal (3) occipital (1) parietal (1) temporal (1) corpus callosum (1) frontotemporal (1) parasagittal (1)	70	OS, post-LITT survival	Nd:YAG laser
Shah et al., 2020[30]	91	14	54 ± 4.56	50%	Frontal (4), frontoparietal (2), parietal (1), temporal (6), occipital (1),	91	OS, PFS	Visualase
Ali et al., 2018[31]	3	3	52 ± 12.6	66.70%	Frontotemporal (2), parietal (1),		Post-LITT survival, PFS	Visualase
Sloan et al., 2013[32]	10	10	55 ± 4.56	20%	Frontal (3), temporal (2), parietal (3), temporoparietal (1), temporo-occipital (1),	80	OS, post-LITT survival	NeuroBlate
Thomas et al., 2016[17]	13	13	48.9 ± 4.56	N/A	Frontal (6), temporal (1), corpus callosum (2), cingulate (2), insular (2)	80	OS, post-LITT survival, PFS	Visualase and NeuroBlate

rGBM, recurrent glioblastoma; SD, standard deviation; KPS, Karnofsky Performance Score; LITT, laser interstitial thermal therapy; OS, overall survival; N/A, not available; PFS, progression-free survival.

Table 3.

Overall Survival for Recurrent GBM

Study	Sample Size	Overall Survival (95% CI)
Beaumont et al., 2018[25]	6	27.78 months (16.35—39.22)
Kamath et al., 2019[28]	41	22.30 months (17.19—27.41)
Ali et al., 2018[24]	3	15.00 months (9—21)
Sloan et al., 2013[31]	10	20.56 months (10.64—30.48)
Shah et al., 2020[30]	14	23.00 months (17.89—28.11)
Thomas et al., 2016[17]	13	23.00 months (17.89—28.1)
Carpentier et al., 2012[26]	4	27.25 months (24.21—30.29)
Schwarzmaier et al., 2006[32]	16	9.40 (8.57—10.23)
Overall (pooled)	107	18.62 months (16.18—21.06)

GBM, glioblastoma; CI, confidence interval.

Table 4.

Overall Survival Post-LITT for Recurrent GBM

Study	Sample Size	Survival Post-LITT (95 %CI)
Beaumont et al., 2018[23]	6	27.78 months (16.35—39.22)
Kamath et al., 2019[26]	41	11.80 months (9.29—14.31)
Ali et al., 2018[31]	3	9 months (2.8—15.22)
Sloan et al., 2013[32]	10	10.53 months (6.89—14.17)
Thomas et al., 2016[17]	13	7.00 months (4.01—9.99)
Carpentier et al., 2012[24]	4	10.75 months (7.71—13.79)
Schwarzmaier et al., 2006[29]	16	6.9 months (6.07—7.73)
Overall (pooled)	93	10.19 months (8.76—11.62)

LITT, laser interstitial thermal therapy; GBM, glioblastoma; CI, confidence interval.

Table 5.

Progression-Free Survival Post-LITT for Recurrent GBM

Study	Sample Size	Progression-Free Survival (95% CI)
Beaumont et al., 2018[23]	6	4.50 months (2.40—6.60)
Kamath et al., 2019[26]	41	7.30 months (5.46—9.14)
Ali et al., 2018[31]	3	4.25 months (1.70—6.80)
Shah et al., 2020[30]	14	5.60 months (4.34—6.86)
Mohammadi et al., 2014[27]	34	5.10 months (4.29—5.91)
Thomas et al., 2016[17]	13	5.00 months (3.70—6.30)
Hawasli et al., 2013[25]	4	8.26 months (7.28—9.24)
Reimer et al., 1998[28]	4	7.00 months (5.63—8.37)
Overall (pooled)	119	6.16 months (5.37—6.95)

LITT, laser interstitial thermal therapy; GBM, glioblastoma; CI, confidence interval.