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BACKGROUND: Laser interstitial thermal therapy (LITT) for glioblastoma (GBM) has been reserved for poor surgical candidates and deep "inoperable" lesions. We present the first reported series of LITT for surgically accessible recurrent GBM (rGBM) that would otherwise be treated with surgical resection.

OBJECTIVE: To evaluate the use of LITT for unifocal, lobar, first-time rGBM compared with a similar surgical cohort.

METHODS: A retrospective institutional database was used to identify patients with unifocal, lobar, first-time rGBM who underwent LITT or resection between 2013 and 2020. Clinical and volumetric lesional characteristics were compared between cohorts. Subgroup analysis of patients with lesions ≤20 cm^3 was also completed. Primary outcomes were overall survival and progression-free survival.

RESULTS: Of the 744 patients with rGBM treated from 2013 to 2020, a LITT cohort of 17 patients were compared with 23 similar surgical patients. There were no differences in baseline characteristics, although lesions were larger in the surgical cohort (7.54 vs 4.37 cm^3, $P = .017$). Despite differences in lesion size, both cohorts had similar extents of ablation/resection (90.7% vs 95.1%, $P = .739$). Overall survival (14.1 vs 13.8 months, $P = .578$) and progression-free survival (3.7 vs 3.3 months, $P = 0.495$) were similar. LITT patients had significantly shorter hospital stays (2.2 vs 3.0 days, $P = .004$). Subgroup analysis of patients with lesions ≤20 cm^3 showed similar outcomes, with LITT allowing for significantly shorter hospital stays.

CONCLUSION: We found no difference in survival outcomes or morbidity between LITT and repeat surgery for surgically accessible rGBM while LITT resulted in shorter hospital stays and more efficient postoperative care.

KEY WORDS: Craniotomy, Glioblastoma, LITT, Recurrent

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Despite aggressive multimodal treatment, glioblastoma (GBM) is associated with an almost uniformly poor prognosis and inevitable recurrence. The management of recurrent GBM (rGBM) remains uncertain with additional chemoradiation and repeat surgery used with varying degrees of success.[1-4] Laser interstitial thermal therapy (LITT) is a novel, cytoreductive and less invasive treatment option for patients with rGBM.[5-7] LITT offers patients a less morbid and efficient means of achieving necessary cytoreduction for GBM recurrence while avoiding many surgery-related complications.[5,7,8] To date, the use of LITT for rGBM has largely been restricted to patients who are poor surgical candidates or have deep-seated "inoperable" lesions.

We describe the efficacy and safety of LITT to treat unifocal, lobar, first-time rGBM. By limiting the scope of the study to patients with unifocal, lobar, and first-time disease, we aim to

ABBREVIATIONS: HR, hazards ratio; **KPS,** Karnosfksy performance status; **LITT,** laser interstitial thermal therapy; **OS,** overall survival; **rGBM,** recurrent glioblastoma.

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report the use of LITT in patients who historically would likely have undergone repeat open surgery. We compare our LITT experience with a similar cohort of patients treated with surgical resection, allowing our survival outcomes to be contrasted by the results of maximal surgical management.

METHODS

Patient Selection

A retrospective single-institution database identified patients who underwent surgery or LITT for unifocal, lobar, first-time rGBM between 2013 and 2020. Institutional review board approval was obtained (Institutional Review Board #9176), and patient consent was waived as retrospective analysis did not affect treatment. Included patients had unifocal, lobar, first-time rGBM at the site of the initial tumor—multifocal or deep lesions (thalamus, basal ganglia, corpus callosum, or insula) were excluded (Figure 1). All patients tissue biopsy diagnosis of GBM and previously underwent any combination of resection, chemotherapy, and radiation. GBM recurrence was determined in accordance with Response Assessment in Neuro-Oncology (RANO) criteria.[9,10] All patients were evaluated by multidisciplinary tumor board before treatment recommendation.

Data Acquisition

Three-dimensional anatomic contouring with BrainLab Elements software (BrainLab) was used for volumetric analysis. Preoperative contrasted T1-weighted MRI was used to determine tumor volume (contrast enhancing and necrotic tissue). For surgical cases, residual tumor was defined as pathologic contrast enhancement seen within 24 hours of resection. For LITT cases, postoperative ablation volume was the area within the rim of enhancement showing the extent of permanently damaged tissue, as previously described.[11] Contrast enhancement extending beyond LITT ablation was deemed residual tumor, consistent with prior reports.[11] Extent of resection/ablation was calculated as $\left[\left(100 - \frac{\text{residual tumor volume}}{\text{preoperative tumor volume}}\right) \times 100\right]$.

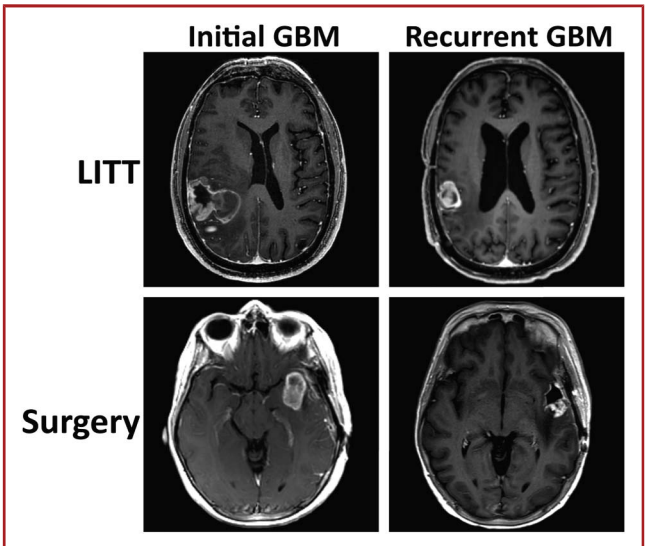

FIGURE 1. *Initial GBM and preoperative first-time recurrence; (top left figure) MRI of initial GBM diagnosis of patient who underwent LITT for recurrent GBM; (top right figure) preoperative MRI showing GBM recurrence of patient who underwent LITT; (bottom left figure) MRI of initial GBM diagnosis of patient who underwent surgery for recurrent GBM; (bottom right figure) preoperative MRI showing GBM recurrence of patient who underwent surgery. GBM, glioblastoma; LITT, laser interstitial thermal therapy.*

Surgical Technique

Standard craniotomies using/extending prior exposures were used. The following surgical adjuncts were used as needed: stereotactic guidance, intraoperative MRI, and fluorescence guidance using 5-aminolevulinic acid. All patients were admitted to the intensive care unit (ICU) for standard postoperative management.

LITT Procedure

LITT was performed in an integrated 1.5-T intraoperative MRI suite. The Neuroblate Laser Ablation System (Monteris Medical Corporation) or Visualase Thermal Therapy System (Medtronic Inc) was used per surgeon preference. Stereotactic laser placement was performed using the BrainLAB VarioGuide system (BrainLab) or the Robotic Surgical Assistant (ROSA) ONE Brain robot (MedTech). Ablation was completed according to a protocol previously described by our group and others.[6,8,11-17] All patients were admitted to a stepdown unit after ablation with the intent to discharge the following morning.

Postoperative Follow-up

Patients had serial appointments and imaging according to standardized institutional protocols. Preoperative Karnosfksy Performance Status (KPS) was documented at the time of neuro-oncology and/or tumor board evaluation within 2 weeks of operative recommendation. Postoperative KPS was documented during the first postoperative clinical appointment (4-6 weeks). If patients died before postoperative evaluation, they were assigned a KPS of 0. Tumor progression was determined by multidisciplinary tumor board review—for surgical cases, tumor progression was new pathologic contrast enhancement; for LITT cases, tumor progression was new contrast enhancement extending beyond the prior LITT ablation. Overall survival (OS) was the time between recurrent treatment and death; progression-free survival (PFS) was the time between recurrent treatment and radiological tumor progression (or death, whichever was earlier).

Statistical Analysis

Differences in characteristics were assessed with the Fisher exact tests for categorical variables, two-sample t tests for continuous variables, and Wilcoxon two-sample tests for ordinal variables. OS and PFS were calculated with Cox proportional hazards regression, reporting adjusted hazards ratios (HRs) that controlled clinically relevant prognostic factors. Survival was graphed with a Kaplan–Meier curve. Patients still alive (or without progression) at their last known contact were censored at that time. To address differences in lesion size between the cohorts, outcomes were further analyzed for patients with lesions ≤20 cm^3. Statistical significance was set at $P < .05$.

RESULTS

Between 2013 and 2020, 744 patients were treated with LITT or surgery for rGBM (Figure 2). After excluding patients with

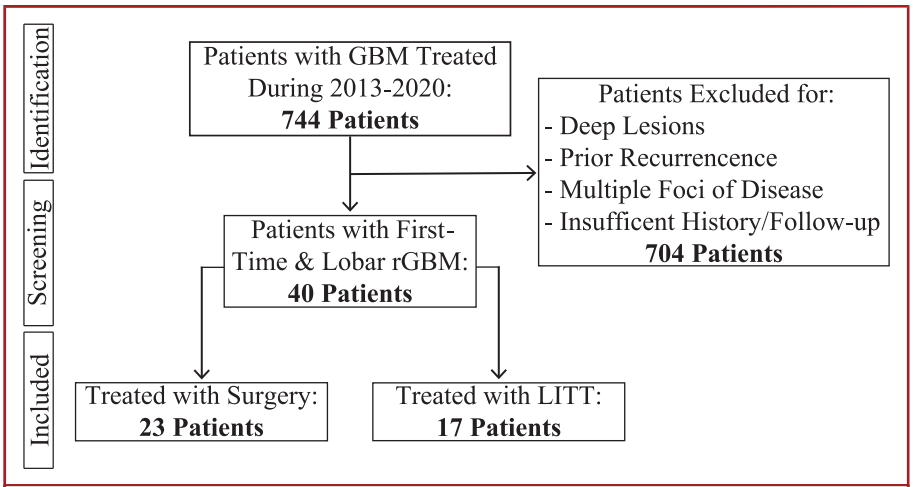

FIGURE 2. *Diagram describing the method of patient selection, exclusion, and ultimate inclusion. GBM, glioblastoma; LITT, laser interstitial thermal therapy; rGBM, recurrent GBM.*

multifocal disease, prior recurrences, and deep-seated lesions, 40 patients with unifocal, lobar, and first-time rGBM were identified. Of the 40 patients, 17 underwent LITT and 23 had surgery. Indications for LITT were a mix of patient preference, surgeon preference, and lesional characteristics. There were no baseline differences between the cohorts (Table 1). Information regarding tumor characteristics, treatment decisions, and postoperative management is available in **Supplementary Table 1**, https://links.lww.com/NEU/D252.

LITT and surgical outcomes and complications are detailed in Table 2.

Surgical Cohort

Surgical patients had a median tumor volume of 7.54 cm^3 (4.18, 21.4) and a 95.1% ± (SD = 8.9) mean extent of resection, with 16 patients (70%) achieving gross total resection. From a median preoperative KPS of 90, 5 patients (22%) had a decrease of 10 points, 3 (13%) of 20 points, and 1 (9%) of 60 points. Three patients (13%) developed pseudomeningoceles postoperatively, with 1 requiring shunting.

At a median follow-up of 13.8 months, 22 patients (96%) had disease progression or died. Five patients (21%) required repeat surgical resection, and 1 patient underwent LITT. Two patients (9%) underwent repeat surgical resection, followed by LITT for subsequent progression. No patients in the surgical cohort developed surgical site infections.

LITT Cohort

LITT patients had a median tumor volume of 4.4 cm^3 (1.77, 7.02) and a 90.7% ± (SD = 16.1) extent of ablation, with 10 patients (59%) achieving gross total ablation. 65% of LITT patients were offered surgery but chose LITT out of personal preference. No LITT patients required ICU treatment. From a median KPS of 90, 3 patients (18%) had a decrease of 10 points. Two patients (12%) developed surgical site infections, both resulting in osteomyelitis requiring debridement.

At a median follow-up of 12.8 months, 16 patients (94%) had disease progression or died. Five (29%) patients underwent surgery, and 1 patient underwent repeat LITT for subsequent disease progression.

Primary and Secondary Outcomes

The median OS for LITT was 14.1 months (95% CI = 4, 19.7) compared with 13.8 months (7.1, 18.1) for surgery. Kaplan–Meier analysis showed no difference in OS curves (Figure 3A). The median PFS for LITT was 3.7 months (2.3, 8.1) compared with 3.3 months (2.3, 5.1) for surgery. Kaplan–Meier analysis showed no difference in PFS curves (Figure 3B). After adjusting for tumor volume and age, adjusted Cox proportional hazards regression showed no difference in OS (HR = 1.44 (0.65, 3.2), $P = .37$) or PFS (HR = 1.3 (0.6, 2.81), $P = .509$; **Supplementary Table 2**, http://links.lww.com/NEU/D253).

LITT patients had significantly shorter hospital stays (2.2 ± 2.1 days vs 3.0 ± 1.1 days, $P = .004$), with 59% of patients discharged the morning after admission (Table 2). To eliminate size bias, subgroup analysis of patients with lesions ≤20 cm^3 was completed, including all 17 patients LITT patients comparted with 17 surgical patients. Again, there was no difference in OS (tumor volume and age adjusted HR = 1.71, $P = .223$) and PFS (tumor volume and age adjusted HR = 1.74, $P = .199$). Kaplan–Meier analysis showed no difference in OS and PFS curves (Figure 4). Patients undergoing LITT again had significantly shorter hospital stays ($P = .011$).

DISCUSSION

In our experience, LITT for unifocal and lobar rGBM showed no difference in survival outcomes or safety when comparted with repeat surgical resection while LITT resulted in significantly shorter hospital

TABLE 1. Patient Demographics and Clinical Characteristics

Variable	Response	LITT (N = 17)	Surgery (N = 23)	*P* value
Age at time of surgery (y)	Mean + SD	60.2 ± 11.5	59.7 ± 12.9	.908[a]
	Median (IQR)	59 (52, 67)	57 (49, 68)	
Female		7 (41%)	11 (48%)	.755[b]
Race	African American	3 (18%)	1 (4%)	.178[b]
	White	14 (82%)	17 (74%)	
	Hispanic	0 (0%)	2 (9%)	
	Asian	0 (0%)	3 (13%)	
BMI	Mean + SD	27.6 ± 4.6	28.7 ± 7.1	.557[a]
	Median (IQR)	28.5 (23.7, 29.2)	26.6 (23.8, 33.5)	
Preoperative history				
Seizures		6 (35%)	10 (43%)	.747[b]
Diabetes mellitus		3 (18%)	2 (9%)	.634[b]
Hypertension		14 (82%)	12 (52%)	.092[b]
Hyperlipidemia		5 (29%)	7 (30%)	>.99[b]
Coronary artery disease		3 (18%)	4 (17%)	>.99[b]
History of stroke		0 (0%)	1 (4%)	>.99[b]
Asthma/chronic obstructive pulmonary disease		1 (6%)	2 (9%)	>.99[b]
Chronic kidney disease		0 (0%)	1 (4%)	>.99[b]
Anxiety/depression		10 (59%)	8 (35%)	.200[b]
Deep venous thrombosis +/− pulmonary embolism		4 (24%)	2 (9%)	.373[b]
Tobacco	Never	12 (71%)	12 (52%)	.493[b]
	Current	1 (6%)	1 (4%)	
	Former	4 (24%)	10 (43%)	
Preoperative KPS	60	0 (0%)	2 (9%)	.4453
	70	1 (6%)	0 (0%)	
	80	3 (18%)	6 (26%)	
	90		10 (59%)	12 (52%)
	100	3 (18%)	3 (13%)	
	Median (IQR)	90 (90, 90)	90 (80, 90)	
Operative characteristics				
Location	Frontal	7 (41%)	4 (17%)	.317[b]
	Temporal	4 (24%)	10 (43%)	
	Parietal	3 (18%)	6 (26%)	
	Occipital	3 (18%)	3 (13%)	
Laterality	Left	10 (59%)	14 (61%)	>.99[b]
	Right	7 (41%)	9 (39%)	
Tumor volume (cm^3)	Mean + SD	4.7 ± 3.4	13.6 ± 13.9	.017[c]
	Median (IQR)	4.37 (1.77, 7.02)	7.54 (4.18, 21.4)	
Extent of resection (%)	Mean + SD	90.7 ± 16.1	95.1 ± 8.9	.739[c]
	Median (IQR)	100 (89, 100)	100 (93.9, 100)	
Disposition	Home	13 (76%)	20 (87%)	.815[b]
	SAR	1 (6%)	1 (4%)	
	Acute care	3 (18%)	2 (9%)	

BMI, body mass index; KPS, Karnosfksy performance status; LITT, laser interstitial thermal therapy.
[a]*P* value from 2-sample *t* test.
[b]*P* value from Fisher exact test.
[c]*P* value from Wilcoxon 2 sample test.

stays and more efficient postoperative care. By limiting the scope of the study to patients with unifocal, lobar, first-time disease, our study is the first reported series of LITT explicitly for patients with surgically accessible lesions that could otherwise be treated with a craniotomy as our standard of care. Given that LITT is historically reserved for nonsurgical patients with deep-seated lesions, our study is also the first to compare LITT with an equal surgical cohort of patients with rGBM, allowing our findings to have an element of clinical equipoise between the 2 treatment modalities.

There is a paucity of quality data regarding the use of LITT for rGBM, with most of the literature focusing on LITT for deep-seated "inoperable" lesions.[6-8,11] The largest such series by Kamath et al[5] described LITT for 41 patients with rGBM leading to an OS of 11.8 months and PFS of 7.3 months. However, all

TABLE 2. Comparing Postoperative Outcomes and Complications Between LITT and Surgery

Variable	Response	LITT (N = 17)	Surgery (N = 23)	*P* value[a]
ICU 96 h		0 (0%)	1 (4%)	>.99
Surgical site infection requiring treatment		2 (12%)	0 (0%)	.174
Urinary retention		0 (0%)	2 (9%)	.499
Wound dehiscence		1 (6%)	0 (0%)	.425
New neurological deficit		1 (6%)	5 (22%)	.216
Change in KPS between preoperative and postoperative	0	14 (82%)	13 (57%)	.064[b]
	10	3 (18%)	5 (22%)	
	20	0	3 (13%)	
	60	0	2 (9%)	
Length of stay	Mean + SD	2.2 ± 2.1	3.0 ± 1.1	.004[b]
	Median (IQR)	1 (1, 2)	3 (2, 4)	
Disposition	Home	13 (76%)	20 (87%)	.815
	Subacute rehab	1 (6%)	1 (4%)	
	Acute care	3 (18%)	2 (9%)	
Readmission 30 d		2 (12%)	3 (13%)	>.99
Readmission 90 d		3 (18%)	5 (22%)	>.99
Return to OR		2 (12%)	1 (4%)	.565
Death w/in 30 d		0 (0%)	1 (4%)	>.99

ICU, intensive care unit; OR, odd ratio; KPS, Karnosfksy Performance Status; LITT, laser interstitial thermal therapy.
[a]*P* values from Fisher exact test.
[b]*P* value from Wilcoxon 2-sample test.
No patients had complications of deep venous thrombosis, pulmonary embolism, urinary tract infection, myocardial infarction, ileus, surgical hematoma, or stroke.

included patients were considered poor surgical candidates, and the authors did not differentiate between lobar and deep-seated tumors, and the number of prior recurrences and lesions at the time of LITT were not clarified. Given that the clinical approach to rGBM depends heavily on tumor location, size, previous treatments, and the degree of disease burden, it is difficult to draw conclusions from such studies with poorly defined cohorts. The remainder of the literature is composed of small similarly heterogeneous cohorts treated with LITT as "salvage therapy" in patients unfit for surgery.[6,7,18-21] Hong et al[22] previously showed that LITT was as efficacious as a craniotomy for achieving local control of brain metastasis of varying pathologies, although primary brain tumors such as GBM were not the aim of the study. Our study is the first to exclusively focus on LITT for unifocal, lobar, first-time rGBM, with our findings augmented by tumor volumetric analysis. In addition, the majority of our LITT cohort electively chose to undergo laser ablation despite being offered surgery, thus potentially increasing the generalizability of our findings and avoiding the ill-defined heterogeneity of patients that has been a major limitation of the prior reported literature.

On subgroup analysis of patients with tumors ≤20 cm^3 (the maximum lesion volume generally considered amenable to LITT at our institution), we again found no differences in survival or safety while LITT patients again had shorter hospital stays. The similar outcomes observed despite differences in preoperative tumor size may be explained by prior reports showing that preoperative rGBM tumor volume does not carry significant prognostic value.[23,24] In addition, the importance of extent of resection/ablation cannot be understated—recent studies have shown that decreasing postoperative residual tumor volume is associated with improved OS and favorable clinical outcomes.[1,23,25-28] Our study's finding of similar outcomes between LITT and surgery are concordant with these previous reports in that, despite differing preoperative tumor size, both cohorts had similar extents of resection/ablation. Furthermore, the literature shows that the established survival benefit of increasing extent of resection may start at ≥80%,[25] a cutoff achieved by 88% of our LITT cohort and 87% of our surgical cohort. Finally, all patients included in our study had grade 0 to 1 lesions according to the National Institutes of Health rGBM Scale, which further exemplifies the similar tumor burden carried by both cohorts.[29] We believe that our cohorts sharing similar tumor characteristics, preoperative prognoses, and extents of resection/ablation explains the equivalent outcomes seen between LITT and surgery, independent of differences in preoperative lesion size.

In our experience, the benefits of LITT are augmented by efficient postoperative care—highlighted by shorter hospital stays, more expeditious chemoradiation, and earlier resumption of necessary medications such as anticoagulation. In our study, LITT patients had significantly shorter hospital stays, and all were admitted to stepdown units postprocedurally, with more than half discharged the following morning. Conversely, all surgical patients invariably required ICU care, and 65% required at least 3-day hospital stays. Moreover, as our LITT experience evolved, most patients in our institution treated with LITT for GBM will be cleared to undergo chemoradiation without delay and, if needed, anticoagulation can be restarted within days. This is contrasted by

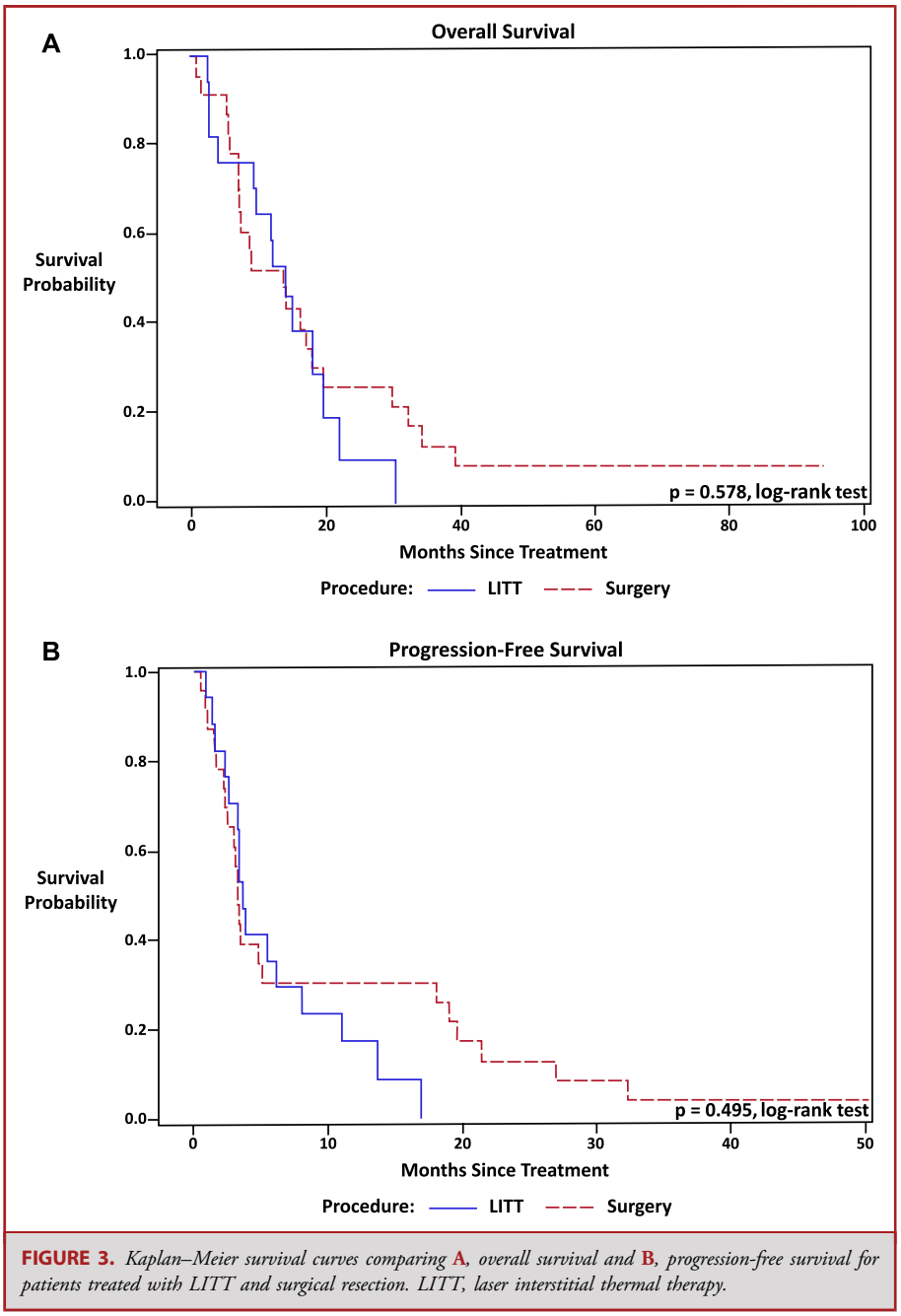

FIGURE 3. *Kaplan–Meier survival curves comparing* **A**, *overall survival and* **B**, *progression-free survival for patients treated with LITT and surgical resection. LITT, laser interstitial thermal therapy.*

our standard postcraniotomy paradigm where patients wait 3 to 4 weeks before chemoradiation to allow for wound healing and routinely wait 2 weeks before anticoagulation resumption.

It should be noted that although there were no statistical differences in morbidity between cohorts, surgical patients experienced unfavorable outcomes not seen in the LITT cohort. Despite both cohorts having an equal median preoperative KPS, nearly half of surgical patients experienced a postoperative drop in KPS, more than double the LITT cohort—this finding was not statistically significant ($P = .064$) likely secondary to small sample size. Furthermore, only surgical patients experienced >10-point drop in postoperative KPS or had surgery-related complications such as pseudomeningoceles requiring shunting. These findings are consistent with prior reports repeatedly showing that surgery for rGBM is associated with increased morbidity.[2,3,27] However, our LITT cohort also experienced notable procedural morbidity—namely, 2 patients developed osteomyelitis of the trajectory path requiring surgical debridement. In both cases, the

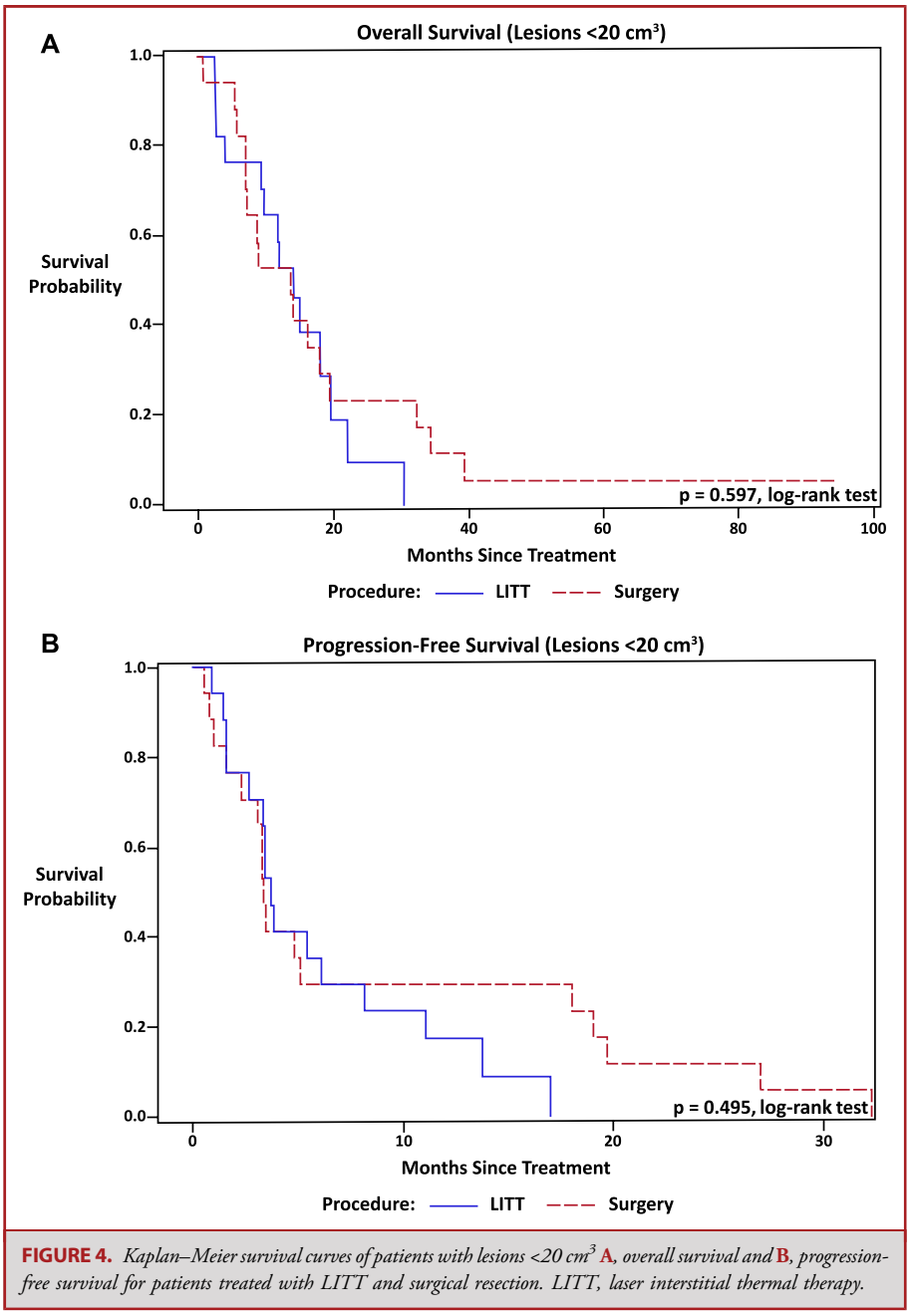

FIGURE 4. *Kaplan–Meier survival curves of patients with lesions <20 cm³* **A**, *overall survival and* **B**, *progression-free survival for patients treated with LITT and surgical resection. LITT, laser interstitial thermal therapy.*

trajectory of the laser fiber traversed through the devascularized bone flap which, together with a history of chemotherapy and radiation to the area, likely predisposed to wound-healing complications and infection. Our LITT practice has since evolved to avoid devascularized bone and prior incision sites when possible. In addition, we now favor avoiding undersizing the stab incisions needed to pass the laser fiber, which may predispose the adjacent previously radiated skin to thermal/mechanical injury during drilling despite use of a drill guide.

Although our study found LITT and surgery to have similar outcomes, the utility of surgery cannot be overstated. For patients requiring debulking to relieve mass effect, LITT is contraindicated, and such patients should proceed with surgical resection. Furthermore, only surgery offers surgeons the ability to achieve maximal resection of both the contrast-enhancing and non–contrast-enhancing tumor—this concept of "supramaximal" resection has been shown to improve survival and cannot usually be achieved with LITT.[30] The ability to achieve maximal or

"supramaximal" resection may explain why surgical patients in our study with favorable right frontal or nondominant parietal lesions that were completely resected had the longest survival (55-96.7 months). Finally, surgery continues to be a qualification requirement for patients in many clinical trials for rGBM, making LITT a potentially disqualifying choice of treatment. We hope that our study can show that LITT is safe, effective, and should not restrict patients from pursuing the clinical trials they so desperately need.

Limitations

Our study is limited by the small number of patients in each cohort limiting statistical power. Furthermore, our study has an element of calendar-time bias in that patients in the surgical cohort are over-represented in the earlier years of the study period while LITT patients were more prevalent in the later years because of the relative novelty of LITT. Our study may also be limited by a bias of indication given that patients treated with surgery may have been healthier or better able to tolerate a procedure than patients treated with relatively less invasive LITT. Although we have attempted to control for differences between the study's cohorts, further studies with larger patient cohorts that also control for lesion size, location, and number of recurrences would be beneficial.

CONCLUSION

LITT for the up-front management of unifocal and lobar rGBM compared with repeat surgical resection carries equivalent efficacy with an added benefit of shorter hospital stays. In patients who are amenable to either LITT or open surgery for GBM recurrence, LITT should be considered to avoid surgery-related morbidity and decrease hospital resource utilization without compromising survival outcomes. The potential for LITT to have a positive effect on quality-of-life measures compared with patients treated with a craniotomy is not known at this time but should be a topic of further investigation.

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The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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Supplementary Table 1. Expanded patient treatment and tumor characteristics.
Supplementary Table 2. Results of Cox proportional hazard regression analysis.

COMMENT

This work expands on the emerging evidence regarding the utility of LITT in recurrent GBM (rGBM) patients. The authors carefully reviewed their series of "operable" rGBM patients with "first recurrence" and identified closely matched cohorts of patients treated with LITT and open surgery. While this study was not powered or positioned to assess differences in survival, the authors did observe important differences in the length of stay and need for advanced post-operative care. Of note, they did not observe differences in procedural morbidity. The authors provide important considerations regarding the limitations of this study and of LITT in the setting of mass effect. Importantly, they note that LITT also opens the opportunity to pursue additional therapies (eg, radiotherapy) and restart medications (eg, anti-coagulation) sooner in the post-operative period, potentially improving outcomes for these patients. Additional studies looking at the impact of this set of potential benefits would be important and timely next steps in the development of LITT-based strategies.

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