Magnetic Resonance Imaging-Guided Laser Interstitial Thermal Therapy for Glioblastoma of the Corpus Callosum

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BACKGROUND: Glioblastoma of the corpus callosum is particularly difficult to treat, as the morbidity of surgical resection generally outweighs the potential survival benefit. Laser interstitial thermal therapy (LITT) is a safe and effective treatment option for difficult to access malignant gliomas of the thalamus and insula.

OBJECTIVE: To assess the safety and efficacy of LITT for the treatment of glioblastoma of the corpus callosum.

METHODS: We performed a multicenter retrospective analysis of prospectively collected data. The primary endpoint was the safety and efficacy of LITT as a treatment for glioblastoma of the corpus callosum. Secondary endpoints included tumor coverage at thermal damage thresholds, median survival, and change in Karnofsky Performance Scale score 1 mo after treatment.

RESULTS: The study included patients with de novo or recurrent glioblastoma of the corpus callosum (n = 15). Mean patient age was 54.7 yr. Mean pretreatment Karnofsky Performance Scale score was 80.7 and there was no significant difference between subgroups. Mean tumor volume was 18.7 cm³. Hemiparesis occurred in 26.6% of patients. Complications were more frequent in patients with tumors >15 cm³ (RR 6.1, P = .009) and were associated with a 32% decrease in survival postLITT. Median progression-free survival, survival postLITT, and overall survival were 3.4, 7.2, and 18.2 mo, respectively.

CONCLUSION: LITT is a safe and effective treatment for glioblastoma of the corpus callosum and provides survival benefit comparable to subtotal surgical resection with adjuvant chemoradiation. LITT-associated complications are related to tumor volume and can be nearly eliminated by limiting the procedure to tumors of 15 cm³ or less.

KEY WORDS: Corpus callosum, Glioblastoma, Glioma, Laser, LITT, Monstros

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Glioblastoma (GBM) is the most common primary malignant brain tumor in adulthood.¹ Median survival for patients with newly diagnosed GBM remains less than 24 mo despite extensive research efforts.^{2,3} Factors influencing prognosis include age,

functional status of the patient at the time of diagnosis, genetic profile of the tumor, and extent of resection.^{4,5} Cytoreductive therapy by means of surgical resection has been shown to improve prognosis in patients with high-grade gliomas^{6–8} and is thus, the primary modality of treatment, along with adjuvant chemotherapy and radiation.⁹ For tumors in deep-seated brain regions, gross-total or near-total resection cannot be achieved without significant morbidity and is therefore not commonly attempted. High-grade gliomas of the corpus callosum represent a particularly aggressive and difficult to treat subgroup.^{10,11} While maximal cytoreduction provides a clear survival benefit for patients with GBM, for tumors of the corpus callosum,

ABBREVIATIONS: DTI, diffusion tensor imaging; FLAIR, fluid attenuation inversion recovery; GBM, glioblastoma; GTR, gross-total resection; LITT, laser interstitial thermal therapy; NICU, neurointensive care unit; OS, overall survival; PFS, progression-free survival; SPL, survival postLITT; SWI, susceptibility-weighted imaging; TDT, thermal damage threshold

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the morbidity of aggressive resection generally outweighs the potential benefit. There is, however, a potential role for maximal safe subtotal resection, although the precise extent and cytoreductive modality remains to be determined.

The use of magnetic resonance imaging (MRI)-guided laser interstitial thermal therapy (LITT) has shown promise as a safe and effective treatment for deep-seated brain tumors.^{12,13} The technique employs the stereotactic placement of a laser probe into the tumor with real-time monitoring of the extent of thermal ablation by magnetic resonance thermometry, allowing targeted thermal injury to the lesion. Depending on the degree of heating, the treatment results in either apoptosis or coagulative necrosis of target tissue. In this report, we describe the use of LITT for the treatment of GBM specifically involving the corpus callosum and

demonstrate that LITT is a safe and effective treatment modality for lesions 15 cm³ or less. As the present study is an interim analysis focused on safety and proof of concept, a randomized controlled trial will be required to formally establish the efficacy of this surgical strategy. Nevertheless, LITT should be considered as a treatment option for high-grade gliomas of the corpus callosum.

METHODS

Patient Selection

We performed a multicenter retrospective analysis of prospectively collected data, to evaluate the safety and efficacy of LITT (NeuroBlate, Monteris Medical, Minneapolis, Minnesota) for GBM of the corpus

FIGURE 1. Axial postcontrast T1 MRI images demonstrating representative patients that underwent LITT for GBM of the corpus callosum. Included in the study were patients with *de novo* or recurrent tumors within the corpus callosum or deep frontal lesions with significant callosal involvement. Upper row: cases 9, 15, and 5; lower row: 6, 7, and 13 (left to right).

callosum. Patients were accrued from August 2011 to August 2015 and their data maintained in an institutional database. The study was performed with the approval of the Institutional Review Board and in accordance with the Health Insurance Portability and Accountability Act. Informed consent was waived. Patients were prospectively recruited by the senior authors at both institutions (ECL and AMM). Each case was evaluated by a multidisciplinary team including neurosurgeons, medical oncologists, and radiation oncologists before enrolment. Patients with high-grade tumors of the corpus callosum or deep-seated frontal tumors extending into the corpus callosum that were not amenable to gross-total resection (GTR) were included. The cohort included patients with recurrent GBM as well as newly diagnosed patients with GBM treated de novo (Figure 1). If the patient had no prior histological diagnosis, a stereotactic biopsy was performed at the time of the LITT procedure. Demographics, clinical data, radiological findings, treatment-related data including volumetric coverage at 2 thermal damage thresholds, laser-on time, and number of trajectories, as well as histological and molecular pathology data were reviewed. The primary endpoint was the safety and efficacy of LITT as a treatment for high-grade tumors of the corpus callosum. Secondary endpoints included the extent of tumor coverage, progression-free survival (PFS), survival postLITT (SPL), overall survival (OS), change in Karnofsky Performance Status 1 mo post-treatment (Δ KPS), and the frequency of major and minor complications. Molecular pathology was not included as an endpoint due to the lack of available data for several patients referred from outside institutions.

LITT Procedure

The Neuroblate System (Monteris Medical) was used to perform LITT on tumors involving the corpus callosum as previously described.¹² All procedures were performed in an operating suite with intraoperative MRI. Prior to surgery, patients underwent stereotactic T1 MRI brain with and without contrast as well as diffusion tensor imaging (DTI) tractography and resting state functional connectivity MRI to identify corticospinal tracts and language, motor cortex, respectively. The LITT procedure was performed under general anesthesia and prophylactic antibiotics, anti-seizure medication and steroids (dexamethasone 10 mg) were administered at induction. The patient's head was secured in an MRI-compatible Mayfield head holder and STEALTH neuronavigation (Medtronic, Dublin, Ireland) was registered to preoperative imaging. The probe entry point was determined and the operative site was prepped and draped. A 3.5 mm twist drill hole was made using a power drill, and the laser probe was then inserted based on the predetermined trajectory and depth as defined by stereotactic navigation. The probe entry site was typically positioned several centimeters above the superior temporal line to allow for the trajectory to be roughly parallel with the corpus callosum. This varied depending on whether the lesion in the corpus callosum was unilateral or bilateral. If the lesion was predominantly unilateral, the angle of approach was further above the superior temporal line (Figure 2A). If the lesion was bilateral, the trajectory was lowered to stay within the thickness of the corpus callosum, but within its natural bend to allow for bilateral access (Figure 2B). Once inserted, the laser was then activated and its thermal effect on the tissue was monitored with continuous MRI thermometry using proton resonance frequency shift-based phase data from gradient-echo pulse sequences. Neuroblate software (Monteris Medical) provides real-time thermal isodose data, defined by thermal damage threshold (TDT) lines, which are used to calculate treatment effect. LITT results in enzyme activation, protein denaturation, membrane breakdown, vessel sclerosis, and coagulative

necrosis.¹⁴ Apoptosis of target tissue occurs at 43°C, while necrosis occurs with heating above 43°C where time to cell death is related exponentially to temperature. The software records thermal injury by delineating 3 dose regions during the procedure: the white region corresponds to tissue exposed to thermal equivalent of 43°C for 60 min; the blue region corresponds to tissue exposed to the thermal equivalent of 43°C for 10 min; the yellow region indicates tissue exposed to thermal equivalent of 43°C for 2 min. After laser treatment, the probe is removed and the soft tissue closed with a single absorbable suture. At the conclusion of the procedure, the patients were extubated and admitted to the neurosurgical intensive care unit for postoperative observation.

Data Analysis

All study participants were assessed by the treating neurosurgeon at outpatient follow-up and underwent neurological examination and serial neuroimaging to assess evolving characteristics of the tumor postLITT and to evaluate for recurrence or progression. Neuroimaging

TABLE 1. Demographic and Clinical Data for Patients With Callosal GBM Undergoing LITT

Case #	Age (yr)	Sex	Tumor type	Side	Location	Tumor volume (cm ³)	Initial pathology	Prior treatment	Preop KPS
1	40	F	De novo	R	Frontal, callosal	29.23	GBM		90
2	54	F	De novo	R	Frontal, callosal	8.28	GBM		60
3	62	M	De novo	R	Frontal, callosal	12.19	GBM		90
4	66	M	De novo	L	Frontal, callosal	18.25	GBM		80
5	56	M	De novo	L	Frontal, callosal	20.38	GBM		80
6	46	M	Recurrent	R	Frontal, callosal	21.21	LGG	Craniotomy, XRT, CTX	70
7	36	F	Recurrent	L	Frontal, callosal	12.29	LGG	Biopsy, XRT, craniotomy, CTX	80
8	62	M	Recurrent	R	Parietal, callosal	8.81	GBM	Craniotomy, XRT, CTX	90
9	65	F	Recurrent	BL	Callosal	8.04	GBM	XRT, CTX	100
10	69	M	De novo	BL	Callosal	47.10	GBM		80
11	49	M	De novo	R	Callosal	10.40	GBM		90
12	56	F	Recurrent	R	Parietal, callosal	0.30	GBM	Craniotomy, XRT, CTX	70
13	50	M	De novo	R	Callosal	19.72	GBM		90
14	48	F	Recurrent	L	Callosal	1.10	GBM	Craniotomy, XRT, CTX	80
15	62	M	De novo	BL	Callosal	62.77	GBM		60

was obtained within 48 h postoperatively and subsequently at 3-mo intervals. Median PFS, SPL, and OS were calculated. All study participants were queried in the National Death Index database to assess survival status. Statistical analysis was performed using the IBM SPSS v21 (IBM Inc, Armonk, New York). For continuous variables, Levene's test for equality of variances was performed followed by the Student *t*-test. Values of *P* < .05 were considered statistically significant. Categorical variables were explored with the Chi-squared and Fischer exact tests. Two-tailed significance values were reported unless specifically stated otherwise. Bivariate correlations were assessed with the Pearson correlation. Survival analysis was performed using the Kaplan–Meier method with the Mantel–Cox log-rank statistics. Median values were reported for all survival measures. Power analysis using a normal distribution with an effect size of 25% (increased PFS) and the observed variance indicated 32 participants per group were required to achieve 80% power. Interim data were reported due to the identification of a statistically significant safety threshold.

RESULTS

Patient Characteristics

The study included 15 patients with either de novo or recurrent GBM originating in or significantly involving the corpus callosum (Table 1). The mean patient age at the time of LITT treatment was 54.7 ± 9.8 yr (range 36–69 yr) and 60% of patients were male. The mean pretreatment KPS was 80.7 ± 11.6 and there was no significant difference between the de novo and recurrent subgroups (80.0 ± 12.3 vs 81.7 ± 11.7 , *P* = .797, 2-tailed). The mean tumor volume at the time of LITT was 18.7 ± 16.9 cm³, and ranged widely from 0.3 to 62.8 cm³. Four patients had undergone previous treatment for GBM, including craniotomy with biopsy or GTR, followed by concurrent chemoradiation or radiotherapy alone. These patients subsequently presented with recurrent enhancing tumor and were treated with LITT. Two additional patients were

initially diagnosed with low-grade glioma, underwent treatment and experienced recurrent enhancing tumor for which they underwent craniotomy with GTR. Histological diagnosis at that time was GBM and both patients experienced a second recurrence for which LITT was performed. Nine additional patients underwent de novo treatment with LITT after initial radiological diagnosis of GBM of the corpus callosum. In addition to the classic “butterfly” gliomas of the corpus callosum, the study also included tumors with significant extension into the frontal lobe as well as recurrent frontal and parietal tumors extending into the corpus callosum. All cases for which molecular pathology was available were isocitrate dehydrogenase 1 (IDH1) wild-type (ie, nonmutant) and 42% demonstrated O6-methylguanine-DNA methyltransferase (MGMT) methylation (Table, Supplemental Digital Content).

Treatment Data

LITT data including volumetric thermometry and procedure-related variables are presented in Table 2. Mean target tumor volume was 18.7 ± 16.9 cm³ and ranged widely, as described above. Tumor volume corresponding to 43°C for 2 min (yellow TDT line), which is associated with apoptosis, and to 43°C for 10 min (blue TDT line), which is associated with necrosis,¹⁵ were $95.4 \pm 7.7\%$ and $91.2 \pm 11.5\%$, respectively. The majority of patients required 1 (*n* = 6) or 2 (*n* = 6) probe trajectories. Three patients underwent 3 probe trajectories, 2 of which were large tumors of the anterior callosum with significant frontal extension, while the third was a large bilateral tumor of the splenium. The number of probe trajectories was positively correlated with tumor volume (*P* = .027, 2-tailed). Mean operative time was 7.7 ± 4.5 h and was not correlated with tumor volume (*P* = .817, 2-tailed). However, mean operative time was significantly different between the 2 institutions where LITT was performed

TABLE 2. Treatment Data for Patients With Callosal GBM Undergoing LITT

Case no.	Target volume (cm ³)	% coverage yellow isodose	% coverage blue isodose	No. trajectories	Operative time (h)	Complications	ICU stay (days)	Hospital stay (days)
1	29.23	98.6	96.8	3	10.0	Edema, herniation	9	11
2	8.28	99.0	96.0	1	6.0	Hemiparesis	1	2
3	12.19	96.0	84.0	2	5.0		1	1
4	18.25	98.9	94.0	2	15.0	Hemiparesis	4	6
5	20.38	100.0	99.9	3	11.0		1	2
6	21.21	75.0	65.2	2	14.0	Ventriculitis	1	2
7	12.29	99.6	98.2	2	10.0		1	3
8	8.81	100.0	100.0	1	3.5		1	2
9	8.04	100.0	98.0	2	15.0		1	4
10	47.10	81.0	69.0	3	6.0	Weakness	1	2
11	10.40	98.8	95.8	1	3.8		1	3
12	0.30	100.0	100.0	1	2.5		1	1
13	19.72	95.2	92.0	1	4.7	Hydrocephalus	7	7
14	1.10	100.0	100.0	1	3.2		1	1
15	62.77	89.1	79.0	2	5.1	Hemiparesis, visual field defect	1, 1	1, 4
mean	18.7	95.4	91.2	1.8	7.7		2.1	3.3
sd	16.9	7.7	11.5	0.8	4.4		2.5	2.7

(9.6 ± 4.3 vs 3.9 ± 1.1 , $P = .013$, 2-tailed). A similar difference was seen for “laser on time” (3.7 ± 2.2 vs 0.6 ± 0.4 , $P = .001$, 2-tailed). Postoperatively, patients typically spent 1 night in the neurointensive care unit (NICU) for observation followed by an additional day in hospital for imaging, coordination of oncology care, and discharge planning. When complications were encountered the mean ICU and hospital stay were increased, 3.4 and 4.6 d, respectively.

Clinical Outcome after LITT

Median PFS and SPL were 3.4 ± 0.5 and 7.2 ± 2.8 mo, respectively. OS was significantly longer, 18.2 ± 6.9 mo, with 2 patients living more than 40 mo (Figure 3; Table 3), both of which were secondary GBMs. Given the potential for bias, survival analysis was also performed excluding the 2 secondary GBMs. While median PFS and SPL were not significantly different (3.1 ± 0.3 and 7.0 ± 1.3 mo, respectively), OS was significantly reduced, 8.5 ± 6.9 mo. Both complete tumor coverage at the yellow TDT (43°C for 2 min) or $>90\%$ coverage at the blue TDT (43°C for 10 min) provided a 29% increase in PFS (4.0 ± 0.8 vs 3.1 ± 1.4 mo, $P = .107$), although this difference did not achieve statistical significance (Figure 4). Median OS was significantly longer for recurrent tumors compared to those treated de novo (20.0 ± 9.9 vs 7.0 ± 2.9 mo, $P = .022$); however, neither PFS nor SPL were significantly different (3.6 vs 3.1 mo and 7.2 vs 7.0 mo, respectively; Figure 5). TDT coverage, however, was not significantly different between tumor subtype (de novo vs recurrent: $90\% \pm 10\%$ vs $94\% \pm 14\%$ and $95\% \pm 6\%$ vs $96\% \pm 10\%$, blue and yellow TDTs, respectively). Notably, increased laser on time was negatively correlated with both PFS and SPL ($P = .060$, 2-tailed). All except 3 patients underwent adjuvant chemotherapy after LITT. Eight patients received concurrent temozolomide

and radiotherapy after LITT prior to radiographic progression, 2 patients received lomustine only, and 2 additional patients received multiagent therapy with temozolomide and doxorubicin. A single patient also received a dendritic cell vaccine. Mean KPS and ΔKPS following LITT was 71.4 ± 17.9 and -8.6 ± 12.3 . Five patients underwent salvage chemotherapy following radiographic progression with agents including avastin, lomustine, cyclophosphamide, disulfiram, etoposide, and rindopepimut. At the time of manuscript preparation, all patients had demonstrated radiographic progression on surveillance imaging and all had died.

Complications

Ten patients (67%) had an overnight stay in the NICU and were discharged on or before postoperative day 3 (Table 2). Hemiparesis occurred as an anticipated complication in 3 patients and due to procedure-related intracranial hemorrhage in a single patient. Two such patients had mild weakness that returned to baseline at follow-up, while 2 others had significant weakness and remained nonambulatory. Inferior quadrantanopia occurred in a single patient. Three additional patients experienced major complications. One patient developed postoperative hydrocephalus and required placement of an external ventricular drain that was subsequently weaned with difficulty. Another patient was discharged home on postoperative day 2 but was readmitted on day 17 due to ventriculitis. The patient underwent treatment with intravenous antibiotics and had SPL of 34.3 mo, significantly longer than the cohort mean of 7.2 mo. The third patient underwent a prolonged LITT procedure lasting more than 10 h, developed malignant peritumoral edema with subfalcine herniation, and required decompressive craniectomy. The patient had a prolonged NICU course and failed to recover

TABLE 3. Outcome Data for Patients With Callosal GBM Undergoing LITT

Case no.	KPS 1 mo postop	Δ KPS	Progression	Progression-free survival (mo)	Adjuvant therapy postLITT	Survival post LITT (mo)	Overall survival (mo)	Death
1	n/a	n/a	n/a	n/a		0.4	0.4	Y
2	50	−10	Y	3.1	Tmz, RTX	17.9	18.2	Y
3	70	−20	Y	3.1	Tmz, RTX	7.0	7.0	Y
4	40	−40	Y	0.4		2.7	2.7	Y
5	70	−10	Y	4.1	Tmz, RTX	5.0	5.0	Y
6	60	−10	Y	3.6	Lomustine	34.3	43.3	Y
7	80	0	Y	9.5	Tmz, RTX	23.5	41.8	Y
8	90	0	Y	2.8	Tmz, RTX	7.2	34.9	Y
9	90	−10	Y	4.0	Lomustine	5.0	8.0	Y
10	60	−20	Y	0.6		2.2	2.9	Y
11	100	10	Y	4.5	Tmz, RTX	21.5	22.5	Y
12	70	0	Y	2.2	Tmz, Dox, DcVax	2.4	20.0	Y
13	90	0	Y	9.1	Tmz, RTX	23.8	23.8	Y
14	80	0	Y	4.9	Tmz, Dox	12.5	18.7	Y
15	50	−10	Y	3.4	Tmz, RTX	8.5	8.5	Y

postoperatively. No patient experienced postoperative dysphasia, abulia, or akinetic mutism following LITT.

Patients experiencing complications had significantly larger mean tumor volume (29.5 vs 9.2 cm^3 , $P = .030$). Complications were more frequent in patients with tumors >15 cm^3 (RR 6.1 , $P = .009$) and were associated with a 31% decrease in SPL, although this difference did not achieve statistical significance (5.0 ± 3.0 vs 7.2 ± 3.9 mo, $P = .522$; Figures 6A and 6B). Tumors treated de novo had 4-fold more complications, but also had significantly greater mean volume at the time of treatment (25.4 ± 18.3 vs 8.6 ± 7.7 cm^3 , $P = .028$, 1-tailed), confounding this finding. The extent of tumor coverage by a given TDT, laser-on time, number of probe trajectories, and overall operative time were not significantly associated with complication frequency. There was no significant difference in PFS or SPL based on tumor type (de novo vs recurrent: 3.1 ± 0.2 vs 3.6 ± 0.7 and 7.0 ± 2.9 vs 7.2 ± 4.6 mo, respectively) at the time of LITT, as described above.

Surveillance Imaging PostLITT

All patients had postoperative imaging performed within 48 h of the LITT procedure. Consistent with previous reports, MRI typically demonstrated 5 zones of tissue damage following LITT: probe track; central zone; peripheral zone; a thin rim at the outer border of the peripheral zone; and peritumoral edema.^{12,16} In all cases, the central zone exhibited areas of hemorrhage on susceptibility-weighted imaging (SWI) or T2 Star, with a surrounding rim of contrast enhancement at the outer border of the peripheral zone (Figure 7). Fluid attenuation inversion recovery (FLAIR) hyperintensity representing edema was apparent immediately postoperatively. The ring of enhancement slowly faded but remained persistent, consistent with previous studies demonstrating persistent enhancement

for up to 4 yr.¹⁶ Although the peritumoral edema significantly improved by 12 mo, there was a surrounding rim of T1 hyperintensity, mild contrast enhancement, and residual SWI artifact present throughout the duration of the study (Figure 7).

DISCUSSION

LITT is a safe and effective treatment option for difficult to access primary and recurrent malignant gliomas including lesions of the thalamus and insula, as well as supratentorial metastatic carcinomas.^{12,15,17,18} In the present study, we extend this treatment paradigm to GBM of the corpus callosum, a location with particularly poor survival due to the inability to achieve GTR. In the present study, PFS and SPL were 3.4 and 7.2 mo, respectively, with OS of 18.2 mo. This compares to recent data from a matched pair analysis of patients with callosal GBM demonstrating that patients who underwent maximal safe surgical resection ($\sim 65\%$ volume reduction) followed by adjuvant chemoradiation had significantly improved median survival compared to those receiving biopsy only along with chemoradiation (7.0 vs 3.5 mo).¹⁹ The comparable survival achieved with LITT or surgical resection demonstrates the well-defined role of cytoreduction in maximizing survival after glioma surgery and suggests that cytoablation with LITT is clinically comparable to the cytoreduction achieved with open surgery.

Hemiparesis was the most common postoperative complication and was encountered in one-quarter of patients (26.6%). Although this subgroup had a statistically significant decrease in PFS (0.6 ± 1.3 vs 4.0 ± 0.4 mo, $P = .014$) and ΔKPS (-20 ± 14.1 vs -4.0 ± 8.4 , $P = .021$), these data are confounded by the fact that patients experiencing hemiparesis also had greater mean tumor volume (34.1 ± 25.2 vs 11.4 ± 7.4 cm^3 , $P = .170$) and all were treated de novo. Patients with tumors >15 cm^3 were

6 times more likely to experience a complication, and this was associated with a 31% decrease in SPL. These patients also had a statistically significant reduction of thermal isodose coverage below the optimal level (100% yellow, 90% blue) and greater than 2-fold increase in laser-on time, suggesting a maximal volume

FIGURE 5. Kaplan-Meier survival curves for de novo and recurrent GBM treated with LITT. **A**, Median OS for patients with recurrent GBM treated with LITT was significantly longer than those treated de novo (20.0 ± 9.9 vs 7.0 ± 2.9 mo, $P = .022$, Mantel-Cox log-rank). **B**, Median PFS (3.6 ± 0.7 vs 3.1 ± 0.2 mo, $P = .457$) and SPL (data not shown) were not significantly different.

threshold may be necessary to maximize the efficacy and safety of LITT for callosal and other deep-seated tumors. Efforts are currently underway to standardize the LITT procedure between the contributing institutions of the present study. Nevertheless, additional studies with increased sample size will be necessary to identify factors independently associated with improved survival

FIGURE 6. Complication frequency was positively correlated with tumor volume. **A**, Patients experiencing complications had significantly greater tumor volume (29.5 vs 9.2 cm³, $P = .030$, 2-tailed) and a reduction of thermal isodose coverage below optimal TDT levels (91% yellow, 85% blue). Complications were significantly more frequent in patients with tumor volume >15 cm³ (RR 6.1, $P = .009$; hashed line) and **B**, were associated with a 31% decrease in SPL (5.0 ± 3.0 vs 7.2 ± 3.9 mo, $P = .486$), although this difference did not achieve statistical significance.

and the occurrence of complications. Until these data become available, the 15 cm³ volume threshold (~3 cm spheroid) should be considered when performing LITT for deep-seated gliomas.

The absence of postoperative language deficits following LITT underscores the minimally invasive nature of the procedure. Two recent studies aimed at the safe surgical resection of callosal GBMs reported postoperative language deficits including abulia and akinetic mutism ranging from 4% to 44% in the early postoperative period.^{19,20} In the latter study, 28% of patients that underwent open surgical resection remained abulic at 6-wk follow-up. Interestingly, this complication was prevented in a second cohort by using task-based awake techniques to identify and preserve the cingulate gyrus. With LITT, there is minimal to no disruption of medial frontal structures and the TDTs are precisely controlled during ablation using continuous MRI thermometry. Nevertheless, the present study did not include detailed speech and neuropsychological testing; thus, subtle deficits of language and cognitive performance may not have been identified.

While there was no significant difference in the post-treatment survival between de novo and recurrent subgroups, complications were significantly more frequent in the former, occurring in the majority (67%) of patients. As described above, de novo lesions

also had significantly greater tumor volume, with no significant difference in thermal isodose coverage. Thus, it remains unclear whether the safety of LITT is related to tumor type (de novo vs recurrent) for callosal GBM. Nevertheless, it is tantalizing to speculate that recurrent gliomas may have less extensive neovascularization due to radiation effect and decreased tumor proliferation that in turn, confers a decreased probability of clinically significant treatment-related interstitial edema.

The present data suggest that 100% coverage at the yellow TDT and at least 90% coverage at the blue TDT maximizes the survival benefit of LITT for GBM of the corpus callosum. A recent multicenter study of LITT for high-grade gliomas reported a statistically significant difference in PFS between “favorable” and “unfavorable” treatment groups (9.7 vs 4.6 mo, $P = .020$).¹³ Interestingly, although these groups were defined based on untreated tumor volume at both the yellow and blue TDT lines, all patients in the “favorable” treatment group had at least 90% coverage at the blue TDT, consistent with the findings of the present study. The ability to safely target LITT with a goal of 90% coverage at the blue TDT line not only maximizes PFS but also surpasses the extent of resection necessary to achieve a statistically significant increase in PFS for callosal and newly diagnosed GBMs (65% and 78%, respectively).^{19,21} Nevertheless, as subgroup analysis was beyond the scope of the present study, a sufficiently powered prospective study will be necessary to define the extent of thermal isodose coverage that optimizes survival and safety.

CONCLUSION

LITT represents a safe and effective treatment option for GBM of the corpus callosum and provides survival that is comparable to safe surgical resection with adjuvant chemoradiation. Thermal isodose coverage should be greater than 90% at the blue TDT line to maximize survival. LITT-associated complications are related to tumor volume and can be nearly eliminated by limiting the procedure to tumors of 15cm³ or less. LITT is a promising minimally invasive technique to treat deep-seated intraparenchymal lesions that are not amenable to craniotomy and open surgical resection.

Disclosures

Dr Leuthardt has a nonpaid consulting relationship with Monteris Medical. Dr Barnett is a paid consultant for Monteris Medical and holds stock options. The other authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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COMMENT

The authors present a retrospective analysis of 15 patients treated at 2 centers using laser interstitial thermal therapy (LITT) for the treatment of glioblastomas of the corpus callosum. They report

outcomes using LITT alone that are comparable to previous studies demonstrating progression-free and overall survival benefits for patients treated with subtotal resection along with standard adjuvant chemo- and radiotherapy. Whereas their data is consistent with this, the limited sample size limits a definitive comparison of outcomes between these 2 approaches. The authors present a novel approach for the treatment of these difficult to access lesions with the hypothesis that increased survival stems from the cytoreduction accomplished by both LITT and subtotal resection with LITT showing particular promise for tumors <15 cubic cm.

Previous studies have suggested that subtotal resection of >65% of tumor volumes provides an overall survival benefit in patients with glioblastoma of the corpus callosum.¹ In theory, stand-alone LITT therapy presents an attractive alternative to open resection by achieving cytoreduction of viable tumor cells with a less invasive approach. As the authors suggest this approach may be more useful for small tumors with volumes less than 15 cubic cm. While subtotal cytoreduction may provide some survival benefit, ablation alone does not address tumor mass effect and may in fact exacerbate mass effect in the perioperative period as seen in the current study. Furthermore, mean operative time in the current study is greater than that of a standard craniotomy with comparable complication rates. Approaches combining LITT and transsulcal resection of necrotic tumor may provide solution to this challenge of mass effect reduction and it is possible that further experience with the surgical technique may decrease operative time.²

The management of these tumors may also benefit from reclassification of their “unresectable” status. Several groups are using combinations of diffusion tensor imaging (DTI) guided navigation, tubular transsulcal approaches, and awake mapping to increase extent of resection.³ Our group has begun using a mix of these techniques with encouraging early results. Though no strong data currently exists for increasing survival benefit with increased extent of resection in this particular tumor location, it would be reasonable to hypothesize that such a benefit would be comparable to that seen with gross-total resection of gliomas elsewhere in the brain. Depending on the pathology, inter-hemispheric approaches might also be useful for some cases. Ultimately a combination of techniques to achieve maximal cytoreduction along with decreased mass effect with preservation of critical white matter pathways may provide for the best possible outcomes in these difficult to access lesions.

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