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Expedited chemoradiation after laser interstitial thermal therapy (LITT) is feasible and safe in patients with newly diagnosed glioblastoma

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Abstract

Background. High-grade gliomas (HGG) are incurable primary brain tumors. Laser interstitial thermal therapy (LITT) has emerged as an alternative to surgery for select patients. Hyperthermia can improve the efficacy of radiation and chemotherapy. Shortening the time between LITT and chemoradiation may maximize their biological and clinical benefits. This trial evaluated the safety and feasibility of expediting chemoradiation after biopsy and LITT in patients with newly diagnosed HGG.

Methods. Patients with suspected HGG were enrolled. Those with pathologic confirmation of HGG and deemed appropriate candidates for LITT and chemoradiation were considered evaluable. Participants underwent 6 weeks of adjuvant chemoradiation initiated within 7 days of LITT. Endpoints were assessed until the completion of radiation and included the occurrence of wound dehiscence; new, treatment-refractory seizures; cerebral edema; and completion of planned radiotherapy.

Results. Thirteen patients with suspected HGG were enrolled, and ten were considered evaluable. All 10 patients were diagnosed with glioblastoma (GBM, IDHwt). Three patients were deemed unevaluable: 2 patients with other CNS tumors and one GBM patient who developed grade 4 postoperative edema. Of 10 evaluable patients, the median age was 60.2 years (IQR: 51.0, 69.4), and median preoperative KPS was 90 (IQR: 90, 80). The median time between LITT and the initiation of chemoradiation was 7 days. There were no occurrences of significant protocol-related adverse events.

Conclusions. Accelerated initiation of chemoradiation after biopsy and LITT is safe and feasible for patients with newly diagnosed GBM. A larger study is needed to assess potential synergy of hyperthermia and chemoradiation to improve survival.

Key Points

- Expedited chemoradiation after LITT is safe and feasible for patients with newly diagnosed GBM.
- High-quality hyperthermia is associated with improved outcomes. Larger studies are needed to assess potential synergy of hyperthermia and chemoradiation.

Importance of the Study

GBM is highly resistant to radiation and chemotherapy, in part due to tumor heterogeneity and poor drug delivery beyond the blood–brain-barrier. Hyperthermia can alter tumor cells and their microenvironment to modulate therapeutic response. The biological consequences of hyperthermia include sensitizing glioma stem cells to radiation and disrupting the blood–brain-barrier to improve chemotherapy penetration. Studies suggest that these benefits are greater when the time interval between hyperthermia and chemoradiation is short. This clinical trial investigated the safety and feasibility of shortening the time between LITT and the initiation of chemoradiation to take advantage of the biological benefits of hyperthermia. All patients underwent biopsy at the time of LITT to establish the diagnosis of HGG. Our findings demonstrate the safety and feasibility of accelerated chemoradiation within 1 week of biopsy and LITT. These findings may be extended to patients that receive biopsy alone and therefore may apply to a broader patient population.

High-grade gliomas (HGG), including glioblastoma (GBM), are aggressive primary brain cancers and unfortunately, they remain largely incurable.[1] Standard treatment for patients includes maximal safe resection followed by radiation, temozolomide, and tumor treating fields (TTF).[2,3] However, the prognosis for patients, especially those with GBM is dismal. Despite improved outcomes with gross total resection (GTR), many patients are poor candidates for traditional craniotomy with tumor resection due to co-morbidities, large tumor size, or deeplocation.[4–6] Laser interstitial thermal therapy (LITT) has emerged as a minimally invasive, alternative approach for select patients with HGG, particularly for those with deep-seated tumors.[7–14] Retrospective analyses have shown that patients who receive biopsy and LITT may have improved outcomes compared to those who receive biopsy alone, though further studies are needed to validate this finding.[7,8] Laser hyperthermia immediately coagulates the enhancing tumor and induces tumor necrosis and apoptosis, and these cellular changes are observable as central necrosis on radiographic imaging.[13,15–17] Performed under real-time 3-dimensional magnetic resonance thermometry, initial studies of LITT have indicated encouraging progression-free survival rates (PFS) of > 9 months with adequate thermometry.[7,9] As a result, this modality is gaining momentum across the country as a new therapeutic option.

The heterogeneity of tumor cells and the inability of drugs to pass through the blood–brain-barrier contribute to therapeutic resistance.[18–20] Glioma stem cells (GSCs) are particularly resistant to standard treatments and are key drivers of disease progression.[21,22] Targeting these cells is therefore needed to provide durable tumor control. Laser hyperthermia may be one means of doing so. Beyond the high-temperature ablative zone within the enhancing tumor is a region of invasive tumor cells that receive lower-temperature heating. This mild-temperature hyperthermia has been recognized as a potent sensitizer to radiotherapy and chemotherapy.[15,23] In preclinical models of GBM, hyperthermia sensitized GSCs to radiation, increased blood–brain- barrier permeability and subsequent penetration of chemotherapy.[23–27] Hyperthermia may also alter the immune microenvironment to improve response to immune therapies.[16,28] LITT, as a form of locally delivered hyperthermia, therefore, holds promise in the treatment paradigm for HGGs. We hypothesized that expediting standard chemoradiation after LITT may improve tumor control for multiple reasons: (1) reduction of time for tumor cell repopulation after ablation, (2) radiosensitization of the treatment-resistant GSC population, (3) blood–brain-barrier breakdown leading to improved temozolomide penetration into the tumor, and (4) augmenting the anti-tumor immune response.

Currently, in clinical practice, a delay of over 3 to 5 weeks separates surgery from subsequent initiation of chemoradiation.[29] This delay allows for postoperative healing, prescribing and delivering chemotherapy, and the development of a customized radiation plan. Because LITT is minimally invasive and delivered through a small burr hole, as opposed to the craniotomy used in typical surgical resection of HGGs, less time is needed for healing before chemoradiation can begin. Furthermore, reduced tissue distortion with a minimally invasive LITT procedure may allow for preplanning of radiotherapy. In this study, we sought to maximize the biological benefits of LITT when used with standard-of-care chemoradiation by reducing the time interval between treatments. We assessed the feasibility of expediting chemoradiation and its impact on adverse events.

Methods

Study Design

This prospective single-institution safety and feasibility trial (NCT02970448) was conducted with approval from the Cleveland Clinic Institutional Review Board and was conducted in accordance with recognized ethical guidelines (U.S. Common Rule, 45 CFR 46, 21 CFR 50, 21 CFR 56, 21 CFR 312, 21 CFR 812, and 45 CFR 164.508-514). Written informed consent was obtained from all study participants.

Patients were included in the study if they were suspected to have a HGG on MRI, were appropriate candidates for LITT followed by chemoradiation, had pre-operative KPS > 60, age ≥ 18 years, adequate CBC, renal function, hepatic function, ECG, and used adequate contraception if fertile. Patients were excluded if they had a history of prior malignancy (except non-melanoma skin cancer), significant post-surgery hematoma, prior radiation resulting

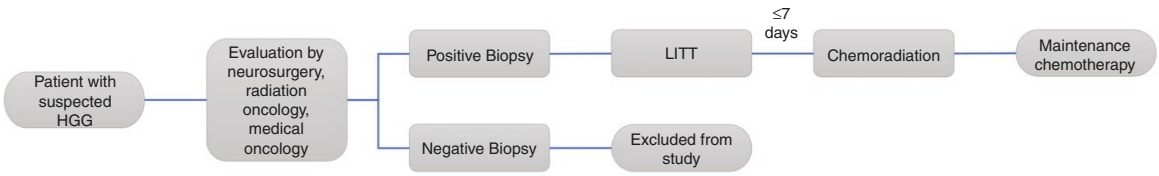

Figure 1. Clinical trial schema. Patients with suspected HGG were evaluated by the multi-disciplinary team and enrolled in the study if eligible. Biopsy was performed at the time of LITT. If the biopsy supported a diagnosis of HGG, patients received LITT. Upon confirmation of the diagnosis, patients went on to receive radiation and temozolomide within 7 days of LITT. Patients went on to receive maintenance temozolomide. If the biopsy did not support a diagnosis of HGG, patients came off study.

in overlapping radiation fields, severe co-morbidity that would confer excess risk of surgery, radiation or chemotherapy, or were pregnant or lactating. Patients were evaluated by a neuro-oncology team consisting of a neurosurgeon trained in LITT, radiation oncologist, and medical oncologist prior to surgery. All patients were considered appropriate candidates for LITT. Those patients that met inclusion and exclusion criteria were enrolled. Evaluable patients were those with a histologic diagnosis of HGG, completed LITT, and were candidates for radiation and temozolomide (TMZ) per Stupp protocol.[2] Subjects began their chemoradiation regimen within 7 days following LITT and went on to receive maintenance chemotherapy (Figure 1). Patients were permitted to receive tumor treating fields at the discretion of the treating physician.

Patient Data Collection

Demographic and clinical data, including age, tumor grade and location, tumor molecular profile including IDH mutation status, 1p/19q allelic loss, MGMT promoter hypermethylation, ATRX staining, EGFR amplification status, and Ki-67 index, treatment parameters including radiation dose, chemotherapy, thermal therapy parameters, date of surgery, start and end dates of radiation, and KPS at start of radiation were collected.

Delivery of LITT and Post-Operative Care

LITT was performed as reported in Mohammadi et al. (2014) using the NeuroBlate system.[9] The NeuroBlate System (Monteris Medical Corporation, Plymouth, MN) MRI-guided laser interstitial thermal therapy uses a gas-cooled side-firing (directional) laser and a variety of procedure-specific tools to thermally ablate target brain tissue in situ. M-Vision, a Monteris proprietary software, was used for planning and executing controlled LITT treatment with the NeuroBlate System. This software was used to calculate the extent of thermal ablation in real-time using an algorithm for heat kill of cells as a function time and temperature, and to determine the extent of thermal ablation in each patient. Each patient received a post-operative MRI within 48 h of surgery. To minimize the risk of wound dehiscence, stitches remained in place for up to 3–4 weeks. To reduce the risk of seizures, patients were placed on anti-epileptics before surgery and tapered off after 30 days if they were seizure-free. Patients received dexamethasone peri-operatively to reduce cerebral edema. A steroid taper was initiated at the discretion of the treating physicians.

Chemoradiation

Each patient was administered TMZ concurrent with radiotherapy at a daily oral dose of 75 mg/m^2. Patients received 60 Gy over 30 fractions of radiation by 3D-Conformal RT (3D-CRT) or intensity-modulated radiation therapy (IMRT). In the event of a delay in administering TMZ, radiation was permitted to begin without chemotherapy up to 5 fractions without being considered a protocol infraction.

Duration of Follow-up for Adverse Events

Subjects were followed for toxicity and adverse events during the observation window which extended from the completion of LITT to the end of radiation or discontinuation of treatment or until death. The clinical course of each event was followed until resolution or stabilization. Any serious adverse event that occurred after the study period and could have been possibly related to the study treatment or study participation was recorded and reported; however, no such reports were necessary in our study thus far. The total duration of follow-up for each patient for side effects of treatment was 10–12 weeks post-LITT. The primary endpoint for this study was defined as the binary occurrence of the following adverse events from the completion of LITT to the end of radiation therapy: CTCAE, v4.0, grade 3 wound dehiscence; grade 3 new, treatment-refractory seizures; grade 4 cerebral edema; and failure to complete planned radiation.

Treatment Outcomes and Characteristics

Disease progression was determined by brain MRI with perfusion and clinical status by the treating physician and consensus of the multidisciplinary tumor board. Progression-free survival (PFS) was defined as the date of LITT treatment to the date of documented progression on MRI or death from neurological causes, whichever came first. Overall survival (OS) was defined as the time between the date of LITT treatment and the date of death or last known follow-up, whichever was shorter.

Several treatment characteristics that have been shown or were hypothesized to be effect modifiers of response were also measured to better understand heterogeneity in outcomes within our small patient population. Specifically, the following variables were also collected: time from LITT surgery to radiation, duration of radiation therapy, incision to close time, total laser on time, length of stay, tumor volume, and % total ablation, which was defined by the volume of tumor left untreated by the yellow thermal dose threshold (TDT) line that corresponds to tissue heated to the equivalent of 43 °C for 2 min per the Monteris LITT ablation system.[30] The blue TDT line corresponds to tissue heated to the equivalent of 43 °C for 10 min. Both the yellow and blue TDT lines were captured and collected, but the yellow TDT line was used to calculate the "treated tumor area" and therefore quantify those with less than favorable ablation. "Favorable ablation" was defined using the same criteria as Mohammadi et al. (2014).[9] Briefly, the favorable ablation group was defined as < 0.05 cm^3 of tumor volume outside of the yellow TDT line, and < 1.5 cm^3 of tumor volume covered by the yellow TDT line but uncovered by the blue TDT line. "Unfavorable ablation" was defined as ≥ 0.05 cm^3 of tumor volume missed by the yellow TDT line, and ≥ 1.5 cm^3 of tumor volume covered by the yellow TDT line but uncovered by the blue TDT line. "Completeness of Ablation" was also measured and compared across subjects and was defined similar to de Groot et. al. as an ordinal variable with levels: subtotal (51–90%), near total (91–99%), or total (100%) ablation as defined by the yellow TDT line representing the outermost boundary of thermometry delivered during LITT.[7]

Statistical Methods

Median and interquartile ranges were used to summarize all continuous variables. Frequency counts and percentages were utilized to summarize categorical variables (eg, patient characteristics). OS and PFS were estimated by Kaplan–Meier method. Statistical analysis was carried out using SAS Studio 3.7 (SAS Institute, Cary, NC) and R version 4.4.1 (2024-06-14).

Results

Participants

Thirteen patients were enrolled in the study, of which 10 were considered evaluable. Two patients had tumors that were not HGG and were excluded from further analyses. These patients included one patient with primary CNS lymphoma and another with an IDH mutant grade 2 astrocytoma. One patient had GBM but developed grade 4 post-operative edema and was not considered appropriate for chemoradiation. These patients were deemed not evaluable per protocol. All patients were treated at the Cleveland Clinic between 2017 and 2024.

Demographic data for the ten evaluable patients are summarized in Table 1. Median follow-up was 14.8 months (IQR 6.2, 17.7). The median age at the time of LITT was 64 years (IQR 60, 70); 7 patients were male and 3 were female. The median KPS score was 90 (IQR 80, 90) preoperatively, 85 (IQR 80, 90) at the time of starting chemoradiation (50% of patients had KPS ≤ 80, and 50% of patients had KPS ≥ 90), and 80 (IQR: 80, 90) at the end of chemoradiation for those able to complete the LITT procedure with expedited chemoradiation (excluding one patient [subject 4] who did not complete treatment due to herpes encephalitis that was deemed unrelated to the treatment). All patients had tumors that were supratentorial, and 7 tumors were in the dominant lobe (Table 2). All tumors were IDH wild-type and 1p/19q intact, consistent with the diagnosis of GBM (Table 2). 3/10 patients had tumors with MGMT promoter hypermethylation, 9/10 had retention of ATRX staining on immunohistochemistry, and 3 patients had EGFR-amplified tumors. The median tumor volume was 9.8 cm^3 (IQR: 7.0, 16.4).

Treatment

The average percent total ablation from the LITT procedure was $94.2 \pm 3.8\%$. 9/10 (90%) patients achieved near total (91–99%) or total (100%) ablation. Only 2/10 (20%)

Table 1. Summary Table of Patient Demographics and Survival Outcomes

Characteristics	LITT (*N* = 10)
Sex (% male)	7/10 (70%)
Age (median, IQR)	60.2 years (51.0–69.4)
KPS preoperatively (median, IQR)	90 (80–90)
KPS at the start of radiation (median, IQR)	85 (80–90)
KPS at the end of radiation (median, IQR)	80 (80–90)
Time between LITT & radiation (median, IQR)	7 days (7–7)
Duration of radiation treatment (median, IQR)	41 days (38–43)
Radiation dose (median)	60 Gy
Living (N)	2/10 (20%)
Progression-free survival (Kaplan–Meier estimates, months, median & 95% CI)	5.4 (2.6—)
Overall survival (Kaplan–Meier estimates, months, median & 95% CI)	16.2 (5.1,—)

Table 2. Summary of Patient Tumor Characteristics and Associated Clinical and Survival Outcomes

Subject	1	2	3	4	5	6	7	8	9	10	All patients
Grade	4	4	4	4	4	4	4	4	4	4	**100% Grade 4**
Dominant Lobe? (Y/N)	Y	Y	N	Y	Y	N	Y	Y	N	Y	**70% Dominant**
Location (O = Occipital; F = Frontal; P = Parietal; T = Temporal; Th = Thalamic)	O	FP	T	PTO	F	Th	T	FP	T	T	
IDH Status	WT	WT	WT	WT	WT	WT	WT	WT	WT	WT	**100% WT**
1p/19q co-deletion (Y/N)	N	N	N	nr	N	nr	N	N	N	N	**(0/8) 0%**
MGMT promoter hyper-methylation (Y/N)	Y	N	N	Y	N	N	N	Y	N	N	**(3/10) 30%**
ATRX Present (Y/N)	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	**(9/10) 90%**
EGFR Amplified (Y/N)	Y	N	N	nr	N	N	N	Y	Y	N	**(3/9) 33%**
Ki-67 (%)	30%	5%	15-20%	nr	>70%	30%	>20%	>40%	15-20%	40%	
Tumor Volume (cm^3)	21.2	6.42	10.7	14	29.1	3.33	8.91	8.97	5.7	17.2	**9.8 (7,16.4)**
Tumor Treating Fields (TTF) Used (Y/N)	N	Y	N	N	N	N	N	N	Y	N	**2/10 (20%)**
Alive (Y/N)	N	N	N	N	N	N	N	Y	N	Y	**2/10 (20%)**
Progression (P), Death (D), or Censored (C)	P	P	P	D	P	P	P	P	P	C	
PFS (months)	15	2.3	4.3	2.2	21.2	2.6	3.6	6.6	7.6	15.4	**5.4 (2.6, -)**
OS (months)	30.5	14.1	9.7	2.2	29.4	3.7	5.1	26.3	18.4	15.4	**16.2 (5.1, -)**

*nr = not reported in the genetic testing for this patient, Y = yes, N = no.
**Patient #4 passed from herpes encephalitis unrelated to the LITT procedure or GBM progression.

patients treated with LITT achieved a "favorable ablation." Those with favorable ablation typically had smaller tumor volumes (7.67 cm^3 [IQR: 6.42, 8.91] vs. 12.4 cm^3 [IQR: 6.52, 20.2], respectively), shorter surgery (incision to close was 145 min [IQR: 129, 160] vs. 191 min [IQR: 163, 228], respectively) and laser on times (13 min [IQR: 11.6,14.4] vs. 16.6 min [IQR: 10.7,49.7], respectively), as expected (Table 3). Due to the small sample numbers of patients between groups, these descriptions are provided without statistical comparisons. Following LITT, the median time to begin chemoradiation was 7 days (IQR: 7, 7). The average duration of the chemoradiation treatment was 41 days (IQR: 38, 43). On post-operative MRI, we observed LITT-induced eggshell enhancement just beyond the T1-enhancing lesion that was ablated. This eggshell enhancement is thought to be related to treatment.[25] Two patients received TTF and no additional toxicities were noted in these patients. One patient used TTF for 3 months and another for 9 months.

Adverse Events and Survival Outcomes

Since LITT may increase post-operative edema, we recorded steroid use during radiation treatment. At the start of radiation, the median dose of dexamethasone was 4 mg per day. At the end of radiation, the median dexamethasone dose was 1 mg per day. Therefore, the dose of steroids used was not uncommon for GBM patients. Four patients were able to taper off steroids completely during radiation treatment, while 2 patients required increased dose of steroids. There was no correlation between increased steroid use during radiotherapy and treatment response. With the exception of the patient who developed herpes encephalitis, all patients were able to complete their planned 6-week course of chemoradiation. Five patients had evidence of pseudoprogression on MRI after completion of chemoradiation. They were managed conservatively with steroids.

Nine of the 10 subjects completed planned treatment without evidence of wound dehiscence, new treatment-refractory seizures, or significant cerebral edema (grade 4) (Table 4). One patient developed herpes encephalitis requiring hospitalization. Treatment for this patient was terminated prematurely, and he went on to hospice care. Patients developed fatigue, alopecia, headache, nausea, constipation, and radiation dermatitis, all grade 2 or less per CTCAE v4.0 (Table 4). These side effects were not unexpected for patients receiving chemoradiation. Five patients had radiographic evidence of pseudoprogression and were treated conservatively. Eight patients ultimately progressed. The median PFS of subjects following LITT with expedited chemoradiation was 5.4 months (95% CI: 2.6, --), while OS was 16.2 months (95% CI: 5.1, --) (Table 2). Only 2 patients had favorable ablation, and they had PFS of 3.6 and 21.2 months, and OS of 5.1 and 29.4 months, respectively. The patients with unfavorable ablation had a median PFS of 5.4 months (95% CI: 2.6,--) and median OS of 14.1 months (95% CI: 9.7, --) (Table 3). Similar results were found when comparing those with total ablation to those with near or subtotal ablation with higher estimates of PFS (5.6 months [95% CI:2.2,--] vs. 5.4 months [95% CI: 2.6,--] and OS (17.2 months [95% CI: 2.2,--] vs.14.1 months [95% CI: 9.7, --]), respectively (Table 3).

Feasibility of Expedited Chemoradiation

All patients were simulated for radiotherapy planning after surgery, even though pre-operative simulation was

Table 3. Comparison of Patients and their Associated Tumor and Ablation Characteristics

		Favorable/Unfavorable		Completeness of Ablation		
	Measure	**Favorable**	**Unfavorable**	**Subtotal**	**Near Total**	**Total**
	N	2	8	1	5	4
Progression-Free Survival (Months)	Kaplan Meier Estimates (95% CI)		5.4 (2.6,—)	5.4 (2.6,—)		5.6 (2.2,—)
Overall Survival (Months)	Kaplan Meier Estimates (95% CI)		16.2 (9.7,—)	22.3 (9.7—)		11.8 (2.2,—)
Tumor Volume (cm^3)	Median, IQR	7.67 (6.42,8.91)	12.4 (6.52,20.2)	14.5	10.7 (6.15,15.6)	7.67 (5.88,18.1)
Untreated Tumor Volume Yellow	Median, IQR	0 (0,0)	5.99 (0.65,13.2)	60.5	0.81 (0.34,19.7)	1.07 (0,7.91)
Untreated Tumor Volume Blue	Median, IQR	0.06 (0.02,0.1)	4.94 (1.7,13.5)	50.2	2.72 (0.9,15.4)	1.21 (0.04,5.94)
% Coverage Yellow TDT line	Median, IQR	100 (100,100)	97.6 (93.3,99)	3	97.3 (94.1,98.4)	100 (99.3,100)
% Coverage Blue TDT line	Median, IQR	99.3 (98.9,99.7)	89.5 (78.2,95.1)	214	89.6 (81.9,93.8)	99.3 (91.4,99.7)
Surgical Parameters-Incision to Close Time (min)	Median, IQR	145 (129,160)	191 (163,228)	214	190 (163,212)	160 (137,294)
Total Laser On Time (min)	Median, IQR	13 (11.6,14.4)	16.6 (10.7,49.7)	11.5	15.8 (12.3,22)	13 (3.52,79.8)

permitted. All patients started radiotherapy within the expedited 7-day window, demonstrating the feasibility of this approach. Nine patients started chemotherapy on the same day of radiotherapy, and one patient started within 2 fractions of radiotherapy. Overall, LITT with expedited chemoradiation was found to be both safe and feasible.

Discussion

This study suggests that expedited chemoradiation following biopsy and LITT is safe and feasible. No treatment-related serious adverse events were encountered when chemoradiation was initiated within 7 days of biopsy and LITT. This study also suggests that patients who receive biopsy alone may also be safely treated with chemoradiation within a week of biopsy.

Whether expediting chemoradiation after LITT confers a clinical benefit remains an open question. Our study is underpowered to address this question, and we continue to monitor patients for survival outcomes. The proportion of patients achieving favorable ablation (~20%) was consistent with previously published results.[9] These patients had smaller tumor volumes and shorter surgeries, also consistent with the literature.[7] In prior studies, near-total (91–99%) and total ablation (100%) can be achieved in roughly 86–90% of treatments.[7,9,31] Consistent with the literature, in our study, 90% of patients achieved either near-total or total ablation. Only 2 patients had "favorable ablation," which additionally considers the volume encompassed by the blue TDT line. More patients will need to be recruited to detect a difference in outcomes between those with and without favorable ablation. Future work should continue to emphasize high-quality heating or "favorable ablation" to optimize tumor control.

The timing of initiation of chemoradiation after gross total resection (GTR) and non-GTR of newly diagnosed GBM has not been assessed prospectively. Retrospective studies suggest either no significant difference or even worse outcomes for patients receiving resection followed by either early or delayed chemoradiation.[29,32–35] Nevertheless, some patients exhibit rapid early progression that is associated with poor clinical outcomes.[36] For these patients, early initiation of radiation and chemotherapy may be beneficial. In our study, we found that starting chemoradiation within 7 days of biopsy and LITT was well tolerated. Our study is underpowered to compare PFS and OS to that of historical controls.

While our study was performed at a single site to reduce logistical barriers to expediting chemoradiation after LITT, we did encounter multiple barriers. One contributing factor was the need for rapid pathologic diagnosis, which was required for further management decisions and insurance authorization of adjuvant treatments. With the updated WHO classification of gliomas, a formal diagnosis could not be issued until molecular analyses were performed and interpreted.[37] Some of these molecular studies were performed at outside institutions or companies, requiring shipping of tissues for testing, which delayed diagnosis. The most significant barriers that we encountered were related to insurance authorization for chemotherapy and

Table 4. Adverse Events Outcome Data

Primary Outcome: adverse event	Event rate (%)
Wound Dehiscence	0/10 (0)
Seizures	0/10 (0)
Cerebral edema	0/10 (0)
Failure to complete planned radiation	0/10 (0)
Secondary outcomes: adverse event	**Event rate (%)**
Fatigue (Grade)	
Grade 0	3/10 (30)
Grade 1	6/10 (60)
Grade 2	1/10 (10)
Alopecia (Grade)	
Grade 0	3/10 (30)
Grade 1	4/10 (40)
Grade 2	3/10 (30)
Constipation (Grade)	
Grade 0	4/10 (40)
Grade 1	5/10 (50)
Grade 2	1/10 (10)
Nausea (Grade)	
Grade 0	7/10 (70)
Grade 1	2/10 (20)
Grade 2	1/10 (10)
Headache (Grade)	
Grade 0	7/10 (70)
Grade 1	3/10 (30)
Radiation Dermatitis	
Grade 0	7/10 (70)
Grade 1	3/10 (30)

shipping of chemotherapy from specialty pharmacies to the patients. These delays led to one patient starting chemotherapy 2 days after the start of radiation therapy. We did not encounter delays with radiotherapy authorization, simulation, or planning. All radiotherapy simulations were performed after surgery in the outpatient setting. Contouring, planning, and quality checks were completed within 3 days of simulation.

Our study highlights that with appropriate coordination of team members from multiple departments, it is feasible to start chemoradiation within one week of surgery. We anticipate that expediting chemoradiation can be performed at other tertiary care institutions with cooperation from the multidisciplinary team. Extension of this paradigm may be more challenging in settings where team members are less integrated or do not offer LITT. Nevertheless, adoption of this paradigm can be performed under such situations. For example, some patients may receive biopsy alone by one neurosurgeon to establish a diagnosis of GBM and then undergo laser hyperthermia as a separate procedure by a different neurosurgeon who has expertise in LITT. Since a diagnosis will already have been made, then insurance authorization for radiation and chemotherapy can be requested while the patient is scheduled for LITT. Chemoradiation can then commence within a week of LITT. Our treatment paradigm of expediting chemoradiation can also be extended to patients who receive biopsy alone who are not candidates for LITT. In these patients, starting definitive radiation and chemotherapy may be more urgent.

Our study has several limitations. First, as our study was powered for our safety analysis, our survival analyses are underpowered and subject to censoring biases as 2 patients are still active in the study and undergoing follow-up. Second, all patients received a standard 6-week course of radiotherapy. Since hypofractionated radiation can be considered for elderly patients and patients with poor KPS, it is unclear whether these alternate radiotherapy regimens can also be safely expedited after biopsy and LITT.[38–40] We believe that it should be safe since patients who receive hypofractionated radiotherapy better tolerate shorter treatment courses and are less dependent on steroids.[40] Third, 2 of the 13 patients in our study whom we suspected had HGG based on imaging turned out to have either a low-grade glioma or primary CNS lymphoma. The unexpected diagnoses highlight the need to obtain a formal diagnosis prior to initiating treatment. To reduce the risk of patients dropping out of a trial due to diagnosis of a different cancer, development and refinement of non-invasive diagnostic technologies, such as radiomics, MR spectroscopy, PET imaging, or cell-free DNA or RNA approaches, are urgently needed to help establish the diagnosis.[41–45]

Our study establishes that expedited chemoradiation following LITT therapy is safe and feasible in patients with newly diagnosed GBM and sets the stage for a larger clinical trial comparing the clinical outcomes of expedited chemoradiation to standard chemoradiation timing. Such a trial would necessitate multi-institutional efforts in order to accrue patients in a timely manner. Our study also establishes a basis for the assessment of LITT with expedited chemoradiation for patients with recurrent GBM. For these patients, challenges such as the need for molecular diagnosis may be obviated and allow for more rapid initiation of chemoradiation. The design of these studies should also incorporate correlative studies to assess the biological and immunological consequences of LITT and chemoradiation. Understanding the mechanisms underlying this treatment paradigm may guide integration of adjuvant therapies, such as immune checkpoint inhibitors or targeted agents.

Keywords:

complications | expedited chemoradiation | laser interstitial thermal therapy | newly diagnosed glioblastoma | survival

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Authorship Statement

Experimental design: JSY, AMM; Data Collection: JSY, SMM, HD; Data Analysis: JSY, SMM, RZ, WW; Data Interpretation: JSY, SMM, RZ, WW, AMM; Manuscript Drafting: JSY, SMM, AMM; Manuscript Revisions: JSY, SMM, AMM, RZ, WW, HD, RP, ML, MG, GS, EM, JS, SC, GB, DP, MA.

Data Availability

The data presented in this manuscript are available per request to the corresponding author after publication.

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