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Original Research

Neoadjuvant PD1 blockade with laser interstitial thermal therapy for recurrent high-grade glioma

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ABSTRACT

Background: While immune checkpoint inhibitors (ICI) induce potent responses against several systemic malignancies, clinical efficacy against high-grade glioma has been limited by immunosuppression, low mutational burden and limited lymphocyte infiltration into tumors. Laser interstitial thermal therapy (LITT) induces coagulative necrosis and disrupts the peritumoral blood–brain barrier (BBB), creating a potentially antigenic milieu. We hypothesized that neoadjuvant and adjuvant ICI would synergize with LITT to potentiate antitumor immune responses and enhance survival.

Methods: This retrospective study is an exploratory case series that includes 9 adult patients with recurrent IDH wild-type glioblastoma (GBM, n = 6), IDH mutant high-grade astrocytoma (n = 2) and H3K27M mutant diffuse midline glioma (n = 1). All patients received neoadjuvant anti-PD1 ICI prior to LITT and most received adjuvant ICI (8/9). Disease burden was followed through radiographic volume segmentation of gadolinium-enhancing disease. Patients were followed for progression-free (PFS) and overall survival (OS).

Results: Patients (age 29–64 years; 7 male, 2 female) had pre-operative mean tumor volumes of 11.15 cm^3 (range 2.93–26.09 cm^3). Mean ablation volume was 12.08 cm^3 (range 5.14–18.60 cm^3). There were no perioperative complications. All patients showed an initial increase in gadolinium-enhancing volume after LITT. Seven of 9 (78 %) patients demonstrated subsequent regression in total gadolinium-enhancing volume. Three non-contiguous satellite lesions naïve to laser ablation exhibited complete or near-complete regression in 2 patients. Median PFS was 5.90 months (range 1.00–41.23), and median OS was 9.97 months (range 1.20–41.23).

Conclusions: Combination therapy with neoadjuvant and adjuvant pembrolizumab and LITT is feasible and safe in recurrent high-grade glioma. Responses may be more robust in certain molecular subtypes of glioma. Further studies are needed to investigate this potential synergy.

Abbreviations: IDH, isocitrate dehydrogenase; GBM, glioblastoma; H3K27M, histone 3 K27M; BBB, blood brain barrier; LITT, laser interstitial thermal therapy; MPRAGE, magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo; PFS, progression-free survival; OS, overall survival; GTR, gross total resection; GKRS, gamma knife radiosurgery; STR, subtotal resection; CMV, cytomegalovirus, ICI, immune checkpoint inhibition.

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1. Introduction

Adult high-grade gliomas encompass malignant brain tumors classified on the basis of driver mutations and include isocitrate dehydrogenase (IDH) wild-type glioblastoma (GBM), IDH mutant high-grade astrocytoma and oligodendroglioma, and histone 3 K27M (H3K27M) altered diffuse midline glioma [1]. Although these tumors are conventionally treated with maximal safe resection and chemoradiotherapy, they inevitably recur and demonstrate rapid progression [2]. Recent studies have shown that novel immuno-oncologic therapies evaluated in newly-diagnosed and recurrent high-grade glioma fail to recapitulate clinical successes seen against aggressive and treatment-resistant extracranial malignancies [3–7]. Reasons for failure include low mutational burden [8], poor intratumoral T cell infiltration behind the blood brain barrier (BBB), and an immunosuppressive tumor microenvironment populated by M2-polarized macrophages [9], $CD4^+$ $CD25^+$ $FoxP3^+$ regulatory T cells [10], and functionally exhausted $CD8^+$ and $CD4^+$ T cells [11–13]. T cell dysfunction is, in part, regulated by the programmed death ligand 1 and receptor (PD-L1/PD1) axis [14], which has been selectively targeted in high-grade glioma as adjuvant therapy with disappointing results [15–17]. Recent studies, however, suggest that anti-PD1 ICI may enhance local and systemic antitumor immunity to offer survival advantage when delivered as a neoadjuvant in some patients with recurrent or newly diagnosed disease [18–20].

MRI-guided laser interstitial thermal therapy (LITT) is a well-described surgical technique that achieves cytoreduction of intracranial tumors via laser-induced hyperthermia and cell death in lieu of conventional surgery through open craniotomy [21–24]. Importantly, LITT induces irreversible tumor cell death through coagulative necrosis [25–28], rather than through apoptotic mechanisms, thereby coupling a necrotic and potentially antigen-inducing event with the production of pro-inflammatory mediators [29,30]. The end result is a milieu which may induce the activation, maturation, and migration of antigen-presenting cells from the tumor microenvironment to local draining lymph nodes, facilitating the cross-priming of endogenous $CD8^+$ T cells against tumor antigens [31–33]. Local hyperthermia has also been shown to disrupt the peritumoral blood–brain barrier for up to 6 weeks, which may potentiate both the egress of tumor antigens into peripheral blood and lymph nodes to engender immune responses, and the influx of circulating effector T cells towards dead tumor cells [34,35]. The potential synergy between thermal ablation and immune modulation is not new and several studies have demonstrated early promise in other malignancies [36,37]. In this study, we present a cohort of patients with recurrent high-grade glioma treated with neoadjuvant anti-PD1 ICI, LITT, and adjuvant anti-PD1 ICI.

2. Methods

2.1. Patient demographics

This single-institution, retrospective analysis of exploratory nature included a case series of nine patients treated by a single neurosurgeon (D.G.P.) between 2019–2024. This retrospective study was approved by the institutional review board at our institution.

Clinical variables including age at time of LITT, histopathological diagnosis, site of primary disease treatment, and molecular profile were obtained from medical records, Table 1. Tumor specimens were obtained at the time of LITT in 7 of 9 patients. In case 4, specimen was obtained at time of biopsy 5 weeks prior to LITT. In case 5, specimen was obtained at the time of surgical resection 3 weeks prior to LITT.

2.2. Surgical management

Procedures were performed under general endotracheal anesthesia. Seven of 9 patients (78 %) underwent stereotactic needle biopsy followed by laser ablation. Cases 4 and 5 underwent laser ablation alone given their recent surgical biopsy or resection. Patients were registered using the BrainLab neuro-navigation system. A trajectory was designed for placement of the biopsy needle and laser probe, and the VarioGuide System of the BrainLab system was utilized for frameless image-guided stereotactic alignment with the trajectory. After adequate biopsy specimen was obtained, the needle was withdrawn and a cranial bolt from the NeuroBlate System (Monteris Medical) was applied in alignment with the pre-planned trajectory. A sterile cap was used to cover the bolt, and the patient was transferred to the intraoperative MRI (3 T Siemens) suite. Under sterile conditions, a diffuse tip laser probe was advanced to the desired depth and connected to the Monteris robotic device. After MRI sequences confirmed satisfactory probe placement, laser ablation was initiated with MRI thermography confirming target temperature and extent of ablation. At the end of the procedure, the laser probe was removed, the cranial bolt was capped, and the patient was transferred to the operating room for cranial bolt removal and wound closure. We purposely limited the amount of post-operative corticosteroid therapy in the majority of patients to avoid counteracting the immunomodulatory effects of ICI therapy. There were no neurological sequelae in patients who did not receive post-operative corticosteroids.

Table 1
Patient demographics and tumor characteristics. Age is reported at time of index operation (LITT ± stereotactic biopsy). Immunohistochemistry (IDH1 R132H, TP53, and ATRX), PCR (1p19q), and pyrosequencing (MGMT) were performed from prior specimens during primary biopsy or resection (n = 8), or at the time of LITT (n = 1, Case 7). Cases 4–6 and 9 were treated with LITT at first recurrence, remaining cases were treated at 2nd recurrence or beyond.

Case	Age	Sex	Diagnosis	Target Location	WHO Grade	IDH	MGMT	ATRX	TP53	DNA methylation class/ subclass
1	35	M	IDH mutant astrocytoma	Right Frontal	4	IDH1 R132C	Methylated	Mutant	Overexpressed	Not performed
2	34	M	IDH mutant astrocytoma	Left Frontal	4	IDH1 R132H	Methylated	Mutant	Overexpressed	IDH glioma, subclass high grade astrocytoma
3	49	F	IDH wild-type glioblastoma	Left Temporal	4	Wild type	Unmethylated	Wildtype	Overexpressed	Not performed
4	57	M	IDH wild-type glioblastoma	Left Temporoparietal	4	Wild type	Unmethylated	Wildtype	Rare expression	Glioblastoma, IDH wildtype, subclass midline
5	53	M	IDH wild-type glioblastoma	Corpus Callosum	4	Wild type	Unmethylated	Wildtype	Rare expression	Glioblastoma, IDH wildtype, subclass mesenchymal
6	64	M	IDH wild-type glioblastoma	Right Splenium	4	Wild type	Unmethylated	Unknown	Overexpressed	Glioblastoma, IDH wildtype, subclass mesenchymal
7	64	F	IDH wild-type glioblastoma	Left frontal and cingulate	4	Wild type	Unmethylated	Wildtype	Rare expression	Glioblastoma, IDH-wildtype, subclass mesenchymal
8	29	M	H3K27M mutant DMG	Corpus Callosum	4	Unknown	Unmethylated	Unknown	Rare expression	Diffuse midline glioma H3 K27M-altered
9	58	M	IDH wild-type glioblastoma	Left Periatrial	4	Wild type	Methylated	Wildtype	Absent expression	Glioblastoma, IDH wildtype, subclass mesenchymal

2.3. Tumor volume segmentation

Pre-operative, intraoperative and post-operative MR studies were reviewed. Tumor volume segmentation was performed on post-contrast T1-weighted MPRAGE (magnetization-prepared 180 degrees radio-frequency pulses and rapid gradient-echo) sequence using BrainLab Elements Software. The same approach was used for estimation of ablation volumes. All available MRIs for each patient were analyzed to follow tumor volumes over time. MRIs were independently reviewed at select timepoints by board-certified neuroradiologists. Following segmentation, lesion volumes were generated and recorded for every lesion and summed to generate total tumor volume for each patient.

2.4. Follow-up

Disease progression was determined by either clear radiographic evidence or by institutional tumor board consensus favoring imaging findings to represent true progression rather than treatment effect. Patients were followed for progression-free survival (PFS) and overall survival (OS).

2.5. Data availability

The data generated in this study are available upon request from the corresponding author.

3. Results

3.1. Case series

The 9 patients are described in Supplementary Information, Supplementary Fig. 1 and Supplementary Table 1. Details regarding neoadjuvant and adjuvant ICI dosing and timing, steroid exposure, and bevacizumab use can be found in Supplementary Table 1.

3.2. Patient demographics, tumor characteristics and treatment summary

Nine patients aged 29–64 years (7 male, 2 female) with biopsy-confirmed IDH wild-type GBM (n = 6), IDH-mutant high-grade astrocytoma (n = 2), and H3 K27M diffuse midline glioma (n = 1) were included in this study. Patients were deemed candidates for LITT with neoadjuvant anti-PD1 ICI after radiographic and/or clinical progression of disease and if surgical resection was considered the less favorable intervention. Of the 9 patients, 4 were treated at first recurrence, and 5 at second recurrence or beyond. Patient demographics, diagnosis, primary site of disease and molecular characteristics are summarized in Table 1. Representative histopathology is shown in Fig. 1. Because postoperative corticosteroid therapy can reduce ICI efficacy, we limited dexamethasone dosing in most patients. The final dose of neoadjuvant anti-PD1 ICI was administered a mean of 16.56 ± 5.41 days (range 3–45 days) prior to LITT (Supplementary Table 1).

Of the 9 cases, one patient (Case 3) suffered rapid clinical decline from disease progression and expired 36 days after laser ablation. Of the remaining 8 patients, 7 of 8 received both neoadjuvant and adjuvant anti-PD1 antibody (pembrolizumab in 7 patients and nivolumab in 1) (Fig. 2). One patient (Case 4) received dual checkpoint inhibition on trial (NCT03367715) at initial diagnosis with ipilimumab/nivolumab and did not continue adjuvant immunotherapy following LITT. The mean follow-up duration was 487 ± 147 days (range 36–1237 days), with the endpoint defined as the time used to calculate OS and PFS.

3.3. Safety

There were no complications arising from the LITT procedure or its combined use with ICI.

3.4. Radiographic correlates of neoadjuvant anti-PD1 ICI and LITT procedure

Tumor burden was inferred from volumetric analysis of enhancing tissue in post-contrast T1 weighted MPRAGE sequences. Ablation volumes were measured on post-operative day 1 gadolinium-enhanced

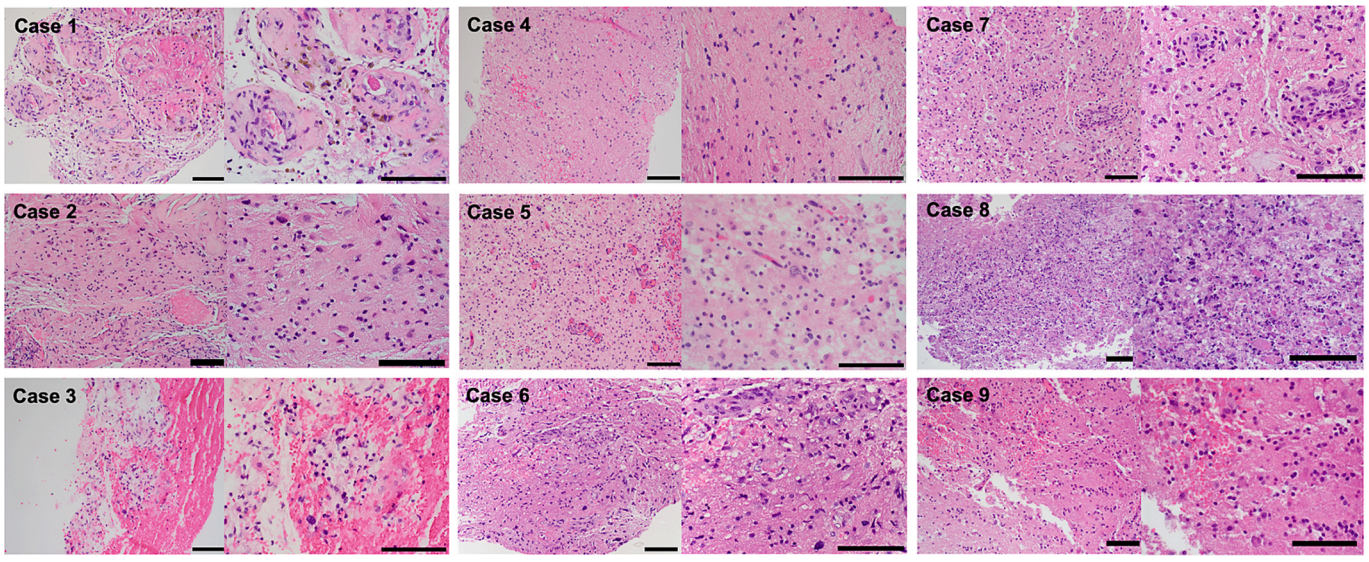

Fig. 1. Representative histopathology. Low power (20×, left panel) and high power (40×, right panel) H&E images are shown for each patient. Scale bar = 100 μm. Case 1: IDH-mutant astrocytoma; necrotic debris with vascular hyperplasia and atypical cells. Case 2: IDH-mutant astrocytoma with gemistocytic morphology. Case 3: GBM; large, atypical cells. Case 4: GBM; hypercellular brain tissue with scattered, infiltrating atypical cells with elongated nuclei. Case 5: GBM; infiltrating glioma with large, atypical cells. Case 6: GBM; marked nuclear pleomorphism and microvascular proliferation. Case 7: GBM; marked nuclear pleomorphism, microvascular proliferation, hyalinized vasculature. Case 8: H3K27M-mutant diffuse midline glioma; necrotic tissue with scattered clusters of atypical cells and predominantly perivascular, lymphohistiocytic inflammation. Case 9: GBM; mildly-to-moderately infiltrative glioma with angulated, atypical nuclei and foci of necrosis. Specimens were obtained concurrently at time of LITT for all cases, except Cases 4–5, in which specimen was obtained <5 weeks prior to LITT.

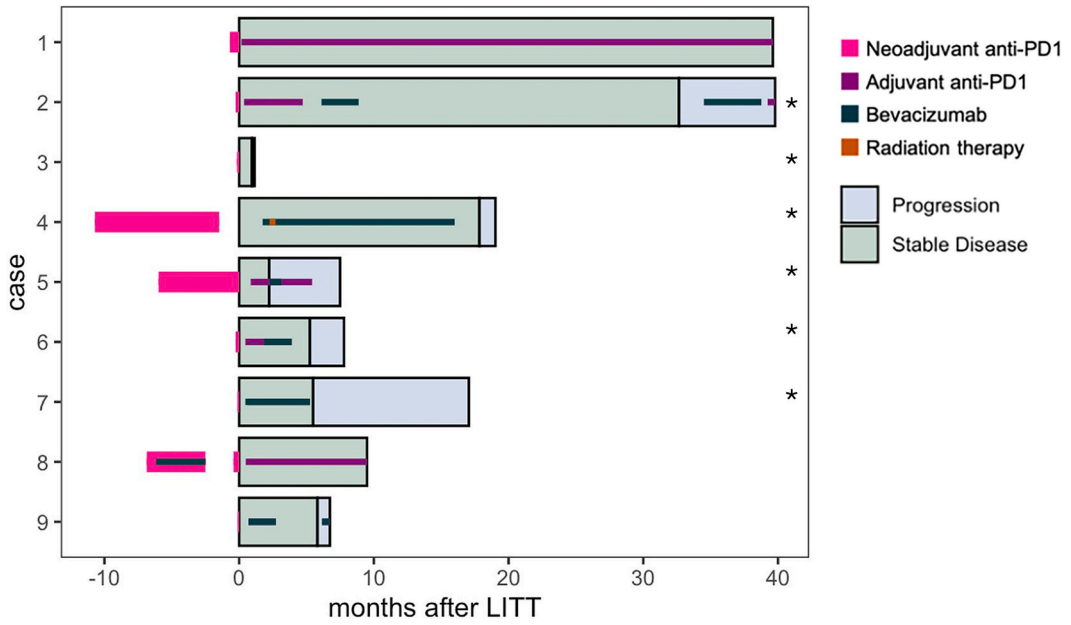

Fig. 2. Treatment and outcomes timeline. Swimmer plot of individual patients depicting start/stop times for neoadjuvant and adjuvant anti-PD1 immunotherapy, bevacizumab, and radiotherapy relative to index procedure (LITT). * Indicates hospice or death.

MPRAGE sequences. Pre-operative mean enhancing total tumor volume was 11.15 ± 2.99 cm^3 (range 2.93–26.09 cm^3). The mean ablation volume was 12.08 ± 1.71 cm^3 (range 5.14–18.60 cm^3) (Fig. 3). Enhancing tumor volumes were measured serially for short and long-term follow-up (Fig. 4A). Only one patient (Case 3) suffered rapid disease progression and expired within 36 days of LITT, precluding extended radiographic surveillance. Of the eight remaining patients, all showed an initial increase in total gadolinium enhancement after LITT, prior to subsequent tumor regression. The first radiographic evidence of regression of gadolinium enhancement occurred between 2–4 months after LITT in 7 of 8 (88 %) patients (Cases 1, 4–9) and at 7 months in one patient (Case 2). Although some regressions coincided with bevacizumab use, two patients had regressions without antiangiogenic therapy (Cases 1 and 8). Responses were durable in two patients; Cases 1 and 2 (IDH1 mutant astrocytomas) showed sustained radiographic responses through 33 and 34 months of surveillance, respectively. Progressive disease occurred anywhere between 4–9 months for the remaining patients. It should be noted that for case 5, although there was marked reduction in total tumor burden, the patient was determined to have disease progression at the 2-month mark when a lesion in the contralateral centrum semiovale was identified (**Supplementary Fig. 1**).

In individual cases, disease progression was determined by either consensus at a multidisciplinary tumor board or by clear radiographic

	Ablation Volume
Case 1	18.6 cm^3
Case 2	13.8 cm^3
Case 3	18.4 cm^3
Case 4	17.4 cm^3
Case 5	10.9 cm^3
Case 6	7.57 cm^3
Case 7	9.04 cm^3
Case 8	5.14 cm^3
Case 9	7.89 cm^3

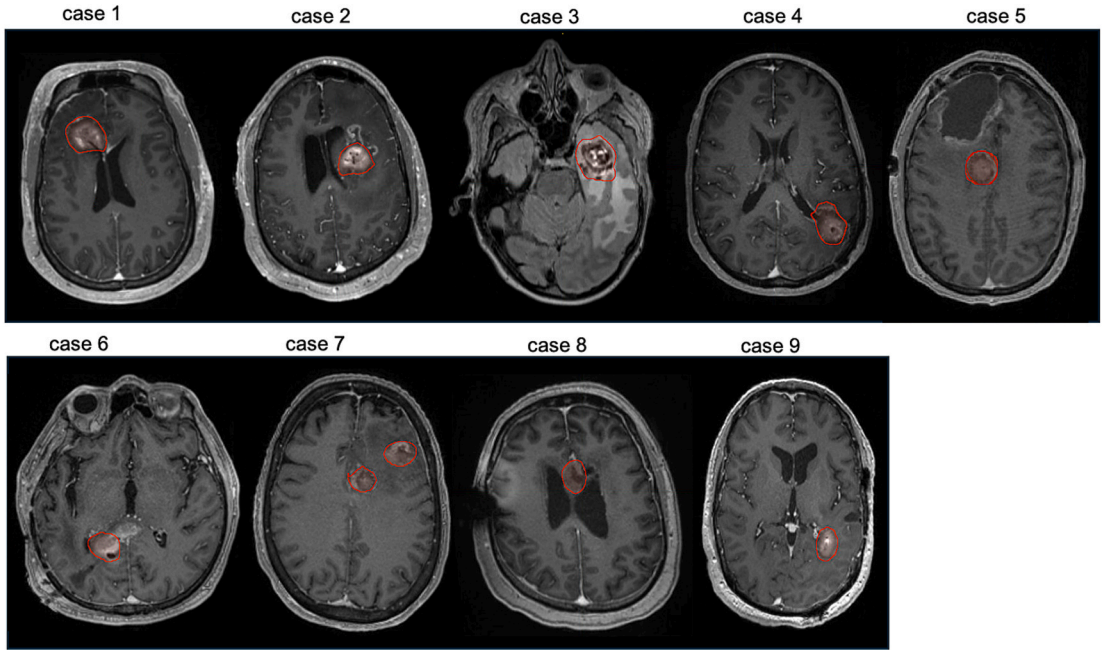

Fig. 3. Laser ablation volumes. Representative MRI images (axial post-contrast T1-weighted MPRAGE sequences) with superimposed contour lines demonstrating the outline of the ablation volume. The table indicates the estimated thermal ablation volume for each case.

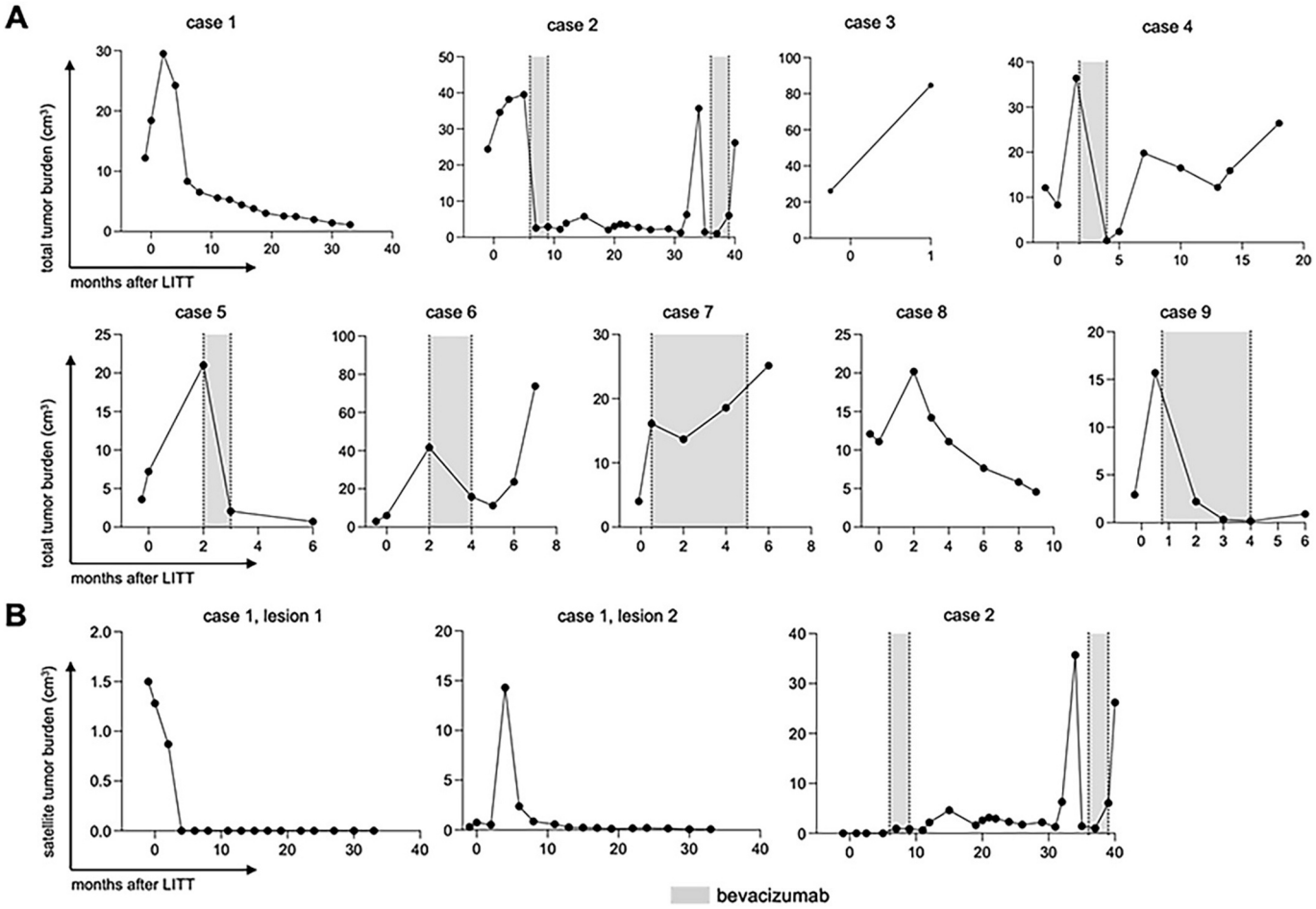

Fig. 4. Longitudinal assessment of total gadolinium enhancement (A) and satellite lesion enhancement (B). Free-form segmentation was performed using BrainLab Elements software on all available post-contrast T1-weighted MPRAGE sequences to generate volumetric estimates of gadolinium enhancement and tumor burden. (A) Total tumor volumes were measured at baseline prior to index surgery (LITT ± stereotactic biopsy) and serially over time. Index surgery was defined as time zero. Each time point represents an MRI. Shaded areas represent periods of bevacizumab therapy. (B) Of 9 patients, cases 1 and 2 had discrete, non-contiguous lesions measured independently. Tumor volumes of these lesions were measured at baseline prior to index surgery (LITT ± stereotactic biopsy) and serially over time. Index surgery was defined as time zero. Shaded areas represent periods of bevacizumab therapy.

changes in combination with clinical deterioration. Response Assessment in Neuro-Oncology (RANO) principles were considered where applicable; however, strict RANO criteria were not applied broadly for this analysis.

We analyzed the enhancing tumor volume of non-contiguous, satellite lesions distal to the site of LITT to determine if neoadjuvant anti-PD1 ICI could synergize with LITT to promote distant anti-tumor immune responses. Cases 1 and 2, both IDH1 mutant astrocytomas, showed evidence of satellite lesions on baseline MRI. Of the two satellite lesions identified in Case 1, both showed complete or near complete regression without the use of anti-angiogenic therapy (Fig. 4B). Case 2 showed the development of a satellite lesion at 7-month follow-up with subsequent regression (Fig. 4B). All volumetric analyses are shown in **Supplementary Fig. 1**.

3.5. Survival

Mean PFS was 13.69 months and median PFS was 5.90 months (range 1.00–41.23 months) (Fig. 5A). Mean OS was 16.23 months and median OS was 9.97 months (range 1.20–41.23 months) (Fig. 5B). For patients with IDH wild-type GBM (Cases 3–7, 9), mean PFS was 6.36 months and median PFS was 5.45 months (range 1.00–18.10 months) (Fig. 5C). Mean OS was 8.97 months and median OS was 7.89 months (range 1.20–19.3 months) (Fig. 5D). Cases 1 and 2, who harbored IDH1 mutations and case 8, who harbored the H3K27M mutation, exhibited the best responses. Case 1 remains disease-free at 41 months, case 2 did not progress until 33 months, and case 8 remained disease-free nearly 11 months after LITT at the time of this writing.

4. Discussion

In this study, we report a case series of 9 patients with recurrent high-grade glioma treated with neoadjuvant anti-PD1 immune checkpoint inhibition (ICI), followed by LITT and adjuvant ICI. Our data indicate both the safety and feasibility of this approach. The clinical rationale for combining these strategies was based on prior work evaluating both the beneficial anti-tumoral and pro-inflammatory effects and shortcomings of either therapy in isolation. A recent phase II trial in recurrent GBM evaluated neoadjuvant anti-PD1 ICI prior to re-resection and immune monitoring data showed the functional activation of tumor-infiltrating, interferon gamma-secreting, and clonally expanding T lymphocytes in some patients [18,19]. The randomized study hinted that these anti-tumor responses conferred an improved survival benefit in patients receiving anti-PD1 ICI in the neoadjuvant setting, although a follow-up single cohort study showed a less dramatic impact on survival in all-comers and suggested neoadjuvant therapy may improve survival in a more narrow, yet undefined, molecular subset of GBM [19]. These data insinuate that timing of ICI relative to local therapy plays a crucial role

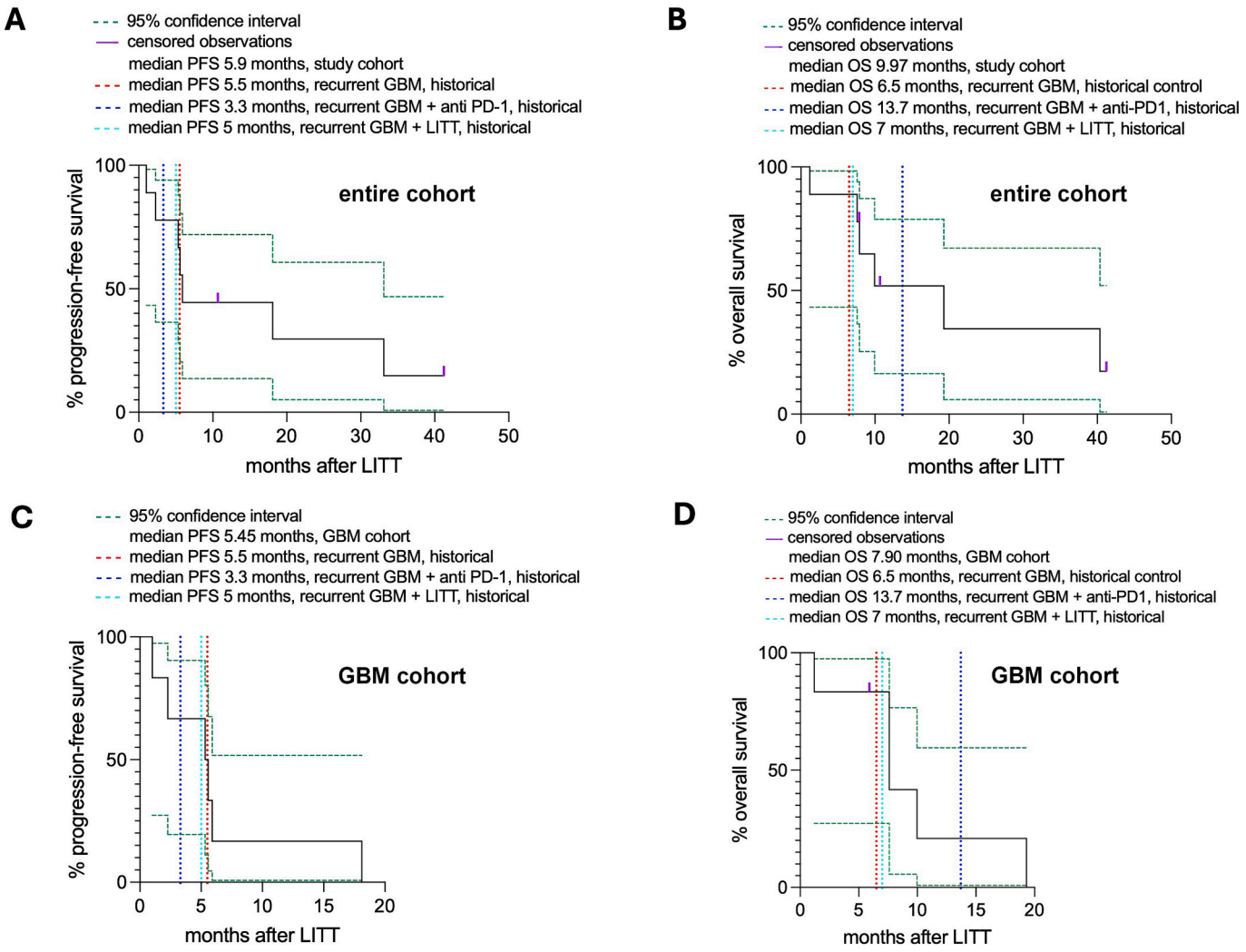

Fig. 5. Progression-free and overall survival in all study patients (A, B) and in GBM patients (C, D). In the overall study cohort, Kaplan-Meier plot depicts PFS (A) and OS (B) of all patients versus GBM historical controls. In the IDH wild-type GBM portion of the study cohort, Kaplan-Meier plot depicts PFS (C) and OS (D) of the GBM patients versus GBM historical controls [18,40,41].

in the induction of a functional antitumor immune response and in altering clinical outcomes. Indeed, a preceding phase III trial evaluated nivolumab monotherapy without subsequent surgery in recurrent GBM and showed no significant difference in median OS when compared to single agent bevacizumab [17]. Another phase II randomized trial found no improvement in median OS and 6-month PFS with adjuvant pembrolizumab and bevacizumab or pembrolizumab alone in patients with recurrent GBM compared to historical benchmarks [38]. More recently, a case report showed that neoadjuvant triple ICI therapy against PD1, CTLA4 and LAG3 in a patient with newly diagnosed treatment-naïve GBM, followed by surgical resection, resulted in prolonged disease remission [38]. Taken together, these results support a potential for synergy between neoadjuvant ICI in combination with cytoreductive surgery, at least in a subset of patients.

LITT offers a minimally invasive alternative to open surgery for deep-seated tumors or treatment-refractory recurrent disease. A recent *meta*-analysis also indicates that LITT may be associated with reduced post-operative and permanent neurologic deficits in recurrent disease (0.02 %) when compared to newly diagnosed disease (4.15 %), despite similar OS and PFS [39]. Our cohort was exclusively recurrent cases, underscoring the importance of careful patient selection for LITT therapy. We hypothesized thermal ablation could induce antitumor responses in the setting of a pro-inflammatory microenvironment precipitated by the local coagulative necrosis produced by LITT and potentiated by neoadjuvant ICI. In this study, 7 of 9 patients showed transient increase followed by radiographic regression below the pre-treatment baseline of total gadolinium enhancement, which nominally reflects tumor burden. In addition, three satellite lesions naïve to thermal ablation regressed following treatment. This latter observation raises the possibility of an abscopal effect, though interpretations are limited by the small sample size and confounding factors related to patient-specific events. For example, case 2 suffered a cranial wound infection prior to initiation of ICI and LITT and the consequence of these inflammatory states on antitumor immunity cannot be accounted for. Similarly, case 4 participated in a clinical trial (NCT03367715) and received both nivolumab and ipilimumab prior to LITT.

In this study, our cohort demonstrated a median PFS of 5.90 months and median OS of 9.97 months. Pooled outcomes in our cohort appear encouraging when viewed in the context of historical benchmarks for recurrent high-grade glioma, where mean OS and PFS are 10.0 and 4.9 months, respectively. Among patients with IDH wild-type GBM (6 patients), median PFS and OS were 5.45 and 7.89 months. These outcomes could be potentially promising when considered alongside historical controls of recurrent GBM after first-line treatment (5.5 and 6.5 months) [40], recurrent GBM treated with neoadjuvant and adjuvant anti-PD1 ICI (3.3 and 13.7 months) [18], and recurrent GBM treated with LITT (5 and >7 months) [41]. While these findings offer an interesting insight into the potential for future therapeutic strategies, survival outcomes in

this case series should be interpreted with caution and cannot be directly compared with results from controlled clinical trials or population-level studies.

Of particular interest are the two patients with IDH-mutant astrocytomas (Cases 1 and 2). These two patients showed the greatest clinical benefit from the combination of LITT and ICI, in terms of PFS and OS, as well as possible abscopal effects. One of them has been maintained on ICI for over 3 years with no evidence of progression. Previous literature has shown that median PFS in recurrent IDH mutant high-grade astrocytoma is in the order of 7–15 months [42,42,43], suggesting the combination of LITT and anti-PD1 ICI may be superior to historical controls, though a direct comparison cannot be made. Although these observations are essentially anecdotal given the small size of the cohort, they merit further study and may suggest a unique vulnerability of IDH-mutant tumors to ICI in combination with thermal ablation.

Collectively, our findings suggest that pairing neoadjuvant anti-PD1 ICI with LITT in the setting of recurrent high-grade glioma is safe and feasible. However, given the biological heterogeneity of the tumor types included in this study (IDH wild-type GBM; IDH mutant astrocytoma; H3K27M diffuse midline glioma), aggregated results should be considered descriptive and exploratory rather than conclusive. Additional prospective studies will be needed to determine efficacy in larger patient cohorts stratified by IDH mutational status.

5. Limitations

Limitations of this study include the small size and retrospective analysis of the cohort; the inclusion of three different subtypes of high-grade glioma (IDH wild-type GBM; IDH mutant astrocytoma; H3K27M diffuse midline glioma); the variability in therapy before and after the index treatment; and the use of bevacizumab, which, by blunting gadolinium enhancement, may artificially prolong radiographic estimates of PFS. An additional caveat of the study lies in the lack of baseline PD-L1 and PD1 expression data and the absence of other immune correlates, which limits a comprehensive interpretation of treatment responses. Moreover, the limited availability of tumor tissue obtained through needle biopsies restricts a detailed evaluation of immune infiltration following neoadjuvant anti-PD1 ICI. Future studies should aim to characterize PD-L1 and PD1 expression in addition to lymphocytic infiltration prior to and after initiation of therapy.

An additional limitation lies in the use of gadolinium enhancement as a measure of tumor burden, as it may also represent inflammatory or reactive changes associated with LITT or ICI therapy. Distinguishing pseudoprogression from true progression is further complicated by the well-recognized phenomenon of post-LITT increase in vascular permeability and edema, which can transiently worsen both clinical presentation and apparent radiographic “tumor burden,” particularly in the first 1–3 months post-LITT period. This represents an important imaging limitation and a caveat to interpretation of radiographic response in this study. Conversely, a strength of our study is the use of volumetric estimation of gadolinium enhancement, which provides a longitudinally quantifiable indirect measure of tumor burden.

6. Conclusion

To our knowledge, this is the first report of neoadjuvant ICI and LITT in recurrent high-grade glioma and builds on previous data evaluating ICI in the adjuvant setting [43]. Our data demonstrate the safety of the approach and merit consideration for future prospective studies further assessing safety, and also efficacy. Future studies should also aim to characterize the T-cell repertoire and functionality in both the intratumoral and systemic compartments to identify immune mechanisms that correlate with outcome, as well as stratify efficacy as a function of the presence or absence of the IDH and H3K27M mutations.

CRediT authorship contribution statement

Carter M. Suryadevara: Writing – review & editing, Writing – original draft, Formal analysis. **Hayley Donaldson:** Writing – original draft, Formal analysis. **Hammad A. Khan:** Writing – review & editing, Formal analysis. **Karenna J. Groff:** Writing – original draft, Formal analysis. **Claire D. Kim:** Formal analysis, Investigation, Writing – review & editing. **Siddhant Dogra:** Writing – review & editing, Formal analysis. **Jose Gautreaux:** Writing – review & editing, Methodology. **Leah Geiser Roberts:** Writing – review & editing, Conceptualization. **Matthew G. Young:** Writing – review & editing, Formal analysis. **Matija Snuderl:** Writing – review & editing, Formal analysis. **David Zagzag:** Writing – review & editing, Formal analysis. **Christopher M. William:** Writing – review & editing, Formal analysis. **J. Ricardo McFaline-Figueroa:** Writing – review & editing, Methodology. **Maria del Pilar Guillermo Prieto Eibl:** Writing – review & editing, Formal analysis. **Christine A. Cordova:** Writing – review & editing, Methodology. **Sylvia Kurz:** Writing – review & editing, Methodology. **Marissa Barbaro:** Writing – review & editing, Methodology. **Dimitris G. Placantonakis:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: D. G.P. has received consultant fees from Tocagen, Synaptive Medical, Monteris, Robeaute, Advantis, and Servier Pharmaceuticals in the past.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2025.111823.

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