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Commentary: Laser Interstitial Thermal Therapy for First-Line Treatment of Surgically Accessible Recurrent Glioblastoma: Outcomes Compared With a Surgical Cohort

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LITT is an increasingly used minimally invasive surgery in neuro-oncology. Current literature has demonstrated its safety and efficacy in treating primary brain tumors, brain metastases, and radiation necrosis, particularly in the context of those poorly suited for open resection. The paper entitled "Laser Interstitial Thermal Therapy for First-Line Treatment of Surgically Accessible Recurrent Glioblastoma: Outcomes Compared With a Surgical Cohort" is a retrospective analysis of patients who underwent either open resection or LITT for treatment of operable recurrent glioblastoma (rGBM) tumors.[1] Often, LITT is used in settings in which the therapeutic window for open resection is narrowed, such as for deep-seated focal lesions or in the context of radiographic progression after prior radiotherapy (which could represent recurrent tumor or radiation necrosis). This study was the first to directly compare LITT with open resection for the first-time recurrence of GBM in comparable operative circumstances (unifocal and lobar lesions) and provides insight into the implications of LITT as an alternative to open resection for first-line management of rGBM lesions.

Critically, the authors note that most patients were offered both therapies and underwent shared decision-making in consideration of several factors including patient and surgeon preferences. In this study, the patients who elected to undergo LITT experienced similar overall survival (OS) and progression-free survival (PFS) as compared with the open resection cohort. In addition, patients in the LITT cohort had significantly shorter hospital stays, were able to resume other treatments earlier, and had fewer declines in Karnofsky Performance Status scores at 4 to 6 weeks postoperatively. Conversely, the authors likewise highlighted unique benefits of open resection, namely the ability to achieve maximal resection and directly reduce mass effect and the ability to retain eligibility for enrollment in clinical trials (more difficult after LITT for rGBM).

This study, although limited by its retrospective nature and the small subset of patients with rGBM, offers helpful perspective for physicians and patients confronting GBM recurrence and treatment options. In managing patients with rGBM, consideration of the "oncofunctional" balance is critical, as the sequalae of tumor progression must be weighed along with the neurocognitive and individual risks of each potential treatment. Both open resection and LITT ablation pose risk of further neurological impairment, especially in cases where the tumor is located adjacent to or within sensitive areas.[2] LITT has been associated with preservation of neurocognitive performance in prior studies,[3] although potential adverse effects include seizures, hemorrhage, and worsening edema.[4] With OS and PFS for rGBM seemingly similar across both LITT and open resection, LITT may be the favored option when lesions are appropriately sized and located, when a less invasive operation and/or shorter hospital stay is desired, and when earlier access to subsequent therapy is perhaps more important than offering clinical trial options. Ultimately, a patient's individual needs are best served by an informed conversation between patient and caregiver, with the above considerations offered.

The authors' study presents a valuable addition to the existing literature on LITT and its role in the neuro-oncology treatment arsenal. Brief discussion of the current landscape for management of rGBM is useful in providing a larger context for these findings. The National Comprehensive Cancer Network (NCCN) currently recommends resection only in the context of local recurrence or for reducing the symptomatic burden of large legions, which may sometimes accompany consideration of clinical trials for which the patient may be eligible. After resection, or in cases of unresectable tumors or diffuse or multiple lesions, recommendations include

TABLE. Summary of Ongoing Phase 2, 3, and 4 Clinical Trials Investigating the Treatment of rGBM as Registered With the US National Library of Medicine at ClinicalTrials.gov Starting Since 2020

Start year	Study name	Eligibility	Intervention
2020	A study testing the effect of immunotherapy (ipilimumab and nivolumab) in patients with rGBM with elevated mutational burden	First or second recurrence of GBM with recent biopsy within 28 days of starting study and no laser ablation of tumor within 4 months of the study and no prior bevacizumab or immune checkpoint inhibitors	Combination PD-1 inhibitor antibody (nivolumab) with a CTLA-4 inhibitor antibody (ipilimumab)
2020	VB-111 in surgically accessible recurrent/ progressive GBM	First or second rGBM in patients who have not undergone SRS to recurrent lesion with no past use of VEGF inhibitors	Adenovirus encoding PPE-1, an endothelial growth stimulator, (VB 111) administered before and after surgery. After surgery, VB111 administered with or without angiogenesis inhibitor (bevacizumab)
2020	Exablate blood-brain barrier disruption for the treatment of rGBM in subjects undergoing carboplatin monotherapy	rGBM after first line therapy planning to use carboplatin monotherapy	Disruption of the BBB with exablate technology followed by administration of alkylating chemotherapy (carboplatin) on the day of exablate treatment
2020	Niraparib/TTFields in GBM	Recurrence of GBM after radiotherapy	Combination therapy of wearable electric field stimulating treatment (TTfield) with PARP inhibitor (niraparib), plus or minus surgical resection after initiation of TTfield if eligible
2020	Sacituzumab govitecan in rGBM	Recurrence after radiotherapy (and temozolomide if DNA methylated)	TROP-2–directed antibody combined with a topoisomerase inhibitor (sacituzumab govitecan)
2020	Open-label study investigating of OKN-007 combined with temozolomide in patients with rGBM	rGBM after radiotherapy and progression after induction and maintenance temozolomide in patients who have not received bevacizumab treatment	Combination treatment of alkylating chemotherapy (temozolomide) with small molecule inhibitor of cell proliferation and angiogenesis (OKN-007)
2020	rGBM treated with neurosurgical resection and IORT using the xoft axxent eBx system and bevacizumab (IORT)	First or second recurrence of GBM. Tumors must be resectable and have undergone previous radiation	Single-fraction radiation therapy at the time of surgical resection, IORT followed by treatment with angiogenesis inhibitor (bevacizumab)
2020	Ultrasound-based blood-brain barrier opening and albumin-bound paclitaxel for rGBM (SC9/ABX)	rGBM after 1-2 treatment failures with maximum tumor region diameter 70 mm	Sequential administration of DNA synthesis inhibiting chemotherapy (carboplatin), followed by sonication using SC9 to open the blood-brain barrier followed administration of albumin-bound microtubule-inhibitor chemotherapy (ABX)
2020	A study of selinexor in combination with standard-of-care therapy for newly diagnosed or rGBM	Newly diagnosed and rGBM with prior radiation and 1-2 trials of systemic therapy	Comparison between combination of selective inhibitor of nuclear transport (selinexor) with either stereotactic radiosurgery, alkylating chemotherapy agent (temozolomide), a nitrosourea (lomustine), and angiogenesis inhibitor (bevacizumab), or Ttfield therapy
2020	Verteporfin for the treatment of recurrent high-grade egfr-mutated glioblastoma	rGBM tumors with EGFR mutation or amplification who have received prior radiation and temozolomide treatment	Photodynamic therapy (verteporfin)
2020	Study of NUV-422 in adults with recurrent or refractory high-grade gliomas and solid tumors	High-grade gliomas, HR+HER2− breast cancer, metastatic castration-resistant prostate cancer, or rGBM− for patients with rGBM must have had prior radiation and temozolomide therapy and never received bevacizumab therapy	For rGBM administration of CDK 2, 4, and 6 inhibitor (NUV-422) either before and after surgical resection or after surgical resection
2021	Testing the addition of the immune therapy drugs, tocilizumab and atezolizumab, to radiation therapy for rGBM	rGBM first recurrence after radiation therapy with ring enhancing FRST-targetable lesion and candidate for repeat surgery. Patients who have undergone prior ICI, bevacizumab, or other immunostimulatory treatment are ineligible.	Combination use of an IL-6 inhibitor (tocilizumab) with fractionated stereotactic radiosurgery and a selective PD-L1 inhibitor (azetolizumab) with or without open surgical resection

TABLE. Continued.

Start year	Study name	Eligibility	Intervention
2021	A study to evaluate safety and efficacy of ACT001 and anti–PD-1 in patients with surgically accessible rGBM multiforme	First or second recurrence of GBM in patients older than 18 years who are eligible for surgery	Comparison of plasminogen activating inhibitor-1 inhibitor (ACT001) alone or in combination with a PD-1 inhibitor (pembrolizumab)
2021	A study of berubicin in adult subjects with rGBM multiforme	rGBM after first-line therapy failure who have not received subsequent chemotherapy treatment and who have never received lomustine nor bevacizumab therapy	Comparison of cytotoxic anthracycline topoisomerase II inhibitor (berubicin) with standard-of-care nitrosourea (lomustine)
2021	Ph I/II study of NMS-03305293 + TMZ in adult patients with rGBM	IDH wild-type rGBM in patients who have received 1-6 rounds of TMZ and have not received prior treatment with bevacizumab, PARP inhibitors, procarbazine, lomustine, vincristine, or carmustine wafer implants	Combination of novel PARP inhibitor (NMS-03305293) with temozolomide compared with nitrosourea standard (lomustine)
2021	Trial of anti–PD-1 immunotherapy and stereotactic radiation in patients with rGBM	rGBM with diameter <6 cm and planned surgical intervention and reirradiation and no prior treatment with anti–PD-1, anti–PD-L1, or anti–PD-L2 therapy	Combination of anti–PD-1 antibody (pembrolizumab) with stereotactic radiosurgery and surgical resection
2022	PARP inhibition for gliomas (PI-4G or π4g)	rGBM in patients who have never received treatment with a PARP inhibitor	PARP inhibitor (niraparib) monotherapy
2022	CYNK-001 IV and IC in combination with IL2 in surgical eligible rGBM with IDH-1 wild type (CYNK001GBM02)	rGBM patients with IDH wild-type tumors who have had 2 or fewer recurrences and are eligible for surgical resection	Combination treatment with natural killer cell therapy (CYNK-001), administered both intravenously and intracavitary, and IV recombinant human IL2

ABX, albumin-bound paclitaxel; BBB, blood-brain barrier; CDK, cyclin-dependent kinase; CTLA, cytotoxic T-lymphocyte-associated antigen; EGFR, epidermal growth factor receptor; FRST, fractionated stereotactic radiation therapy; GBM, glioblastoma; ICI, immune checkpoint inhibitor; IDH, isocitrate dehydrogenase; IORT, intraoperative radiation therapy; PARP, poly-ADP ribose polymerase; PD-1, programmed cell death protein 1; rGBM, recurrent glioblastoma; SRS, stereotactic radiosurgery; TMZ, temozolomide; VEGF, vascular endothelial growth factor.

systemic therapy, alternating electric field therapy, reirradiation, and clinical trials. Palliative or supportive care is recommended for patients with poor performance status.[5] These broad recommendations highlight the heterogeneity of treatment options, which complicates collection of OS data and also heralds the need for breakthrough therapies.

rGBM prognosis following standard treatment options was explored in a 2017 multicenter study in the Netherlands that stratified patients into supportive care, systemic treatment, open resection, and reirradiation. The authors reported an all-patient OS of 6.5 months with 3.1, 7.3, 11.0, and 9.2 months for the respective treatment cohorts.[6] Systemic therapies for rGBM, including bevacizumab, nitrosoureas, chemotherapies, and immune checkpoint inhibitors, have been reported to enhance OS and PFS beyond baseline or to reduce tumor burden. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF) that was U.S. Food and Drug Administration–approved for rGBM in 2009, continues to be used alone or in combination with other agents to address tumor-related symptoms and edema, although it did not prove to be effective in significantly prolonging OS in phase III trials.[7] Temozolomide, a mainstay of initial GBM therapy per the Stupp protocol, has been shown to have specifically increased efficacy in tumors with methylated O^6 methylguanine-DNA-methyltransferase (MGMT) promotors.[8] Nitrosoureas, alkylating agents that readily cross the blood-brain barrier, have been used in the recurrent setting alone or in conjunction with bevacizumab, and the combination therapy has been shown to enhance OS at the 9-month benchmark compared with either bevacizumab or a nitrosourea (lomustine) alone.[9] Immune checkpoint inhibitors, such as pembrolizumab and nivolumab, have also been investigated in rGBM and demonstrated some efficacy, especially in patients with high programmed death-ligand 1 (PD-L1) expression levels compared with those with low PD-L1 expression levels.[10] These systemic therapies are promising in prolonging life and reducing symptoms; however, none have been found to be curative or universally effective in managing rGBM.

Ongoing research and clinical trials exploring novel strategies for rGBM provide patients with additional treatment opportunities after exhaustion of traditional therapies. New directions in rGBM treatment use targeted therapies based on tumor gene sequencing, DNA repair, and tumor metabolism.[11] chimeric antigen receptor (CAR)-T cells have been used in trials to target GBM-specific or associated antigens, but subsequent studies have shown sporadic responses with concern that the hypoxic tumor environment and antigen heterogeneity and escape pose challenges to prolonged response.[12,13] Oncolytic viruses, which have been used in clinical trials for

several decades, continue to show variable success, with many studies showing promising outlier patients who respond to therapy well beyond the typical median survival.[14,15] Other trials have attempted to improve outcomes with strategies intended to enhance the delivery of therapeutic agents across the blood-brain barrier, modifying treatments that have shown success in non-central nervous system cancers. Such processes are being explored with bromodomain and extraterminal protein (BET) inhibitors,[16] Poly-ADP ribose polymerase (PARP) inhibitors,[17] and natural killer (NK) cell therapy.[18] Table provides a brief outline of the 18 currently recruiting phase 2, 3, and 4 clinical trials for rGBM in the United States initiated since 2020. Worldwide, 53 such registered trials are ongoing.

The heterogeneity of rGBM necessitates a treatment algorithm with numerous strategies to control tumor growth and mitigate symptom burden. Without a clear path forward, the treatment of rGBM remains an experimental and variable course that must be personalized to the individual patient's tumor biology, prior treatment, and risk tolerance for both outcomes and adverse events. The present study provides valuable data on the role that LITT can play in this clinical context. Further research is necessary to better understand the nuances in neurocognitive changes, response to subsequent treatments, and OS outcomes following these procedures to identify patients most likely to benefit from the technology.

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