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Point/Counterpoint: The role of reirradiation in recurrent glioblastoma

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The management of recurrent glioblastoma remains a clinical challenge with a dearth of effective treatment options and a dismal prognosis.[1] While surgery, radiation therapy, alkylating agent chemotherapy, and tumor treating fields have demonstrated benefits for newly diagnosed glioblastoma, patients inevitably recur and face limited options at the time of recurrence. Lomustine is considered a standard of care option, as evidenced by its choice as a control arm in randomized clinical trials such as REGAL (NCT00777153),[2] EORTC 26101 (NCT01290939),[3] and GBM AGILE (NCT03970447),[4] particularly in patients with tumors harboring O6 methylguanine DNA methyltransferase gene (*MGMT*) promoter methylation. Lomustine is, however, associated with modest or marginal benefit.[5] Other chemotherapies have generally failed to demonstrate meaningful efficacy, and regorafenib represents the latest example of a promising therapy[6] for recurrent glioblastoma that failed to improve outcomes in further testing.[7]

With a paucity of good treatment options and failure to develop more effective systemic therapies for recurrent gliomas, reinitiation of initial standard therapies has been of interest in the field. Radiation therapy has long served as the most effective therapy available for glioblastoma, and the role of reirradiation has been of interest in the context of a long history of preclinical investigations and clinical practice supporting its use for CNS tumors.[8,9] While data continues to emerge, evidence has been accumulating to better inform clinical decision-making with respect to the role of reirradiation in the management of recurrent glioblastoma. Herein we delineate the pros and cons of reirradiation for recurrent glioblastoma whilst taking into account the limitations of the existing data.

Point: The Case in Favor of Reirradiation

Modern radiation techniques can deliver a conformal dose to the target while limiting the dose to surrounding normal brain tissues,[10] and several clinical series have suggested that reirradiation is a feasible option in appropriately selected recurrent glioblastoma patients.[9] Nevertheless, while safety data have generally been reassuring, the evidence of the efficacy of reirradiation for glioblastoma remains controversial, as most studies are retrospective, and the few prospective clinical studies completed have not demonstrated an overall survival benefit.

A growing number of studies provide a strong foundation to establish the safety and feasibility of reirradiation. Median survival times of 8 to 13 months have been reported using conventional (36 Gy in 18 fractions) and moderately hypofractionated (35 Gy in 10 fractions) reirradiation schedules given alone or in combination with systemic therapy, with a risk of radiation-induced brain necrosis of less than 10%.[11–16] A similar median survival time of 7 to 12.5 months has been observed for patients receiving 25–35 Gy in 5–7 Gy per fraction or 15–18 Gy given as single-fraction in 2 recent systematic reviews of reirradiation for recurrent glioblastoma.[17,18] The risk of radionecrosis remains generally low for patients with relatively small recurrent tumors (<10 mL or 3–3.5 cm in size), and studies generally report limited toxicity in this setting.[17,18]

In addition to establishing the safety of reirradiation, the combination of reirradiation with systemic therapy over reirradiation alone has been investigated in several studies. Retrospective series have shown that combinations of radiation, given either conventionally or as hypofractionated schedules, with alkylating agents are associated with longer overall and progression-free survival times compared to reirradiation alone, but this benefit may be limited to MGMT promoter methylated tumors.[19–22] The incorporation of bevacizumab with reirradiation has also been examined, given the potential for increased edema and symptomatology with reirradiation. Similar survival times have been reported following bevacizumab plus stereotactic radiosurgery compared to reirradiation alone.[23–25] Nonetheless, the use of bevacizumab with reirradiation has been associated with a

Table 1. Clinical Factors for Consideration in Favor of and Against Reirradiation

In favor of reirradiation	Against reirradiation
Prolonged interval since the initial course of radiation therapy	Compelling alternative treatment option (eg, clinical trial)
Small, focal recurrence	Short interval to progression after the initial course of radiation therapy
Good tolerance of the initial course of radiation therapy	Poor tolerance of the initial course of radiation therapy
Recurrence away from critical organs at risk (eg, brainstem, optic apparatus, and hippocampus)	Multifocal or disseminated disease
Good performance status	Poor performance status/frail
Motivated patient	The patient desires to prioritize supportive care or avoid further local therapy

reduction in treatment toxicity such as radionecrosis and symptomatic edema relative to reirradiation alone in retrospective studies,[25–27] which suggests a possible benefit of using this combination. Beyond bevacizumab, other series have failed to show significant survival benefits with the addition of other systemic agents to reirradiation.[14,28–30] In a secondary analysis of the NRG Oncology/RTOG-0525 trial evaluating dose-dense versus standard-dose temozolomide in newly diagnosed glioblastoma, Shi et al. investigated the impact on the outcome of reirradiation and/or systemic treatments (mainly bevacizumab) at recurrence and found no significant survival difference with any specific treatment strategy.[31] Currently, no clear recommendation about combining reirradiation with systemic therapy, including alkylating agents or bevacizumab, can be made. Moreover, safety data on immediate, mid-term, and long-term toxicity are scarce.

One important question is whether the addition of reirradiation to systemic treatment provides benefits over systemic treatment alone. NRG Oncology/RTOG 1205 (NCT01730950) was a phase II randomized trial of 182 patients with recurrent glioblastoma who received hypofractionated reirradiation (35 Gy in 10 fractions) plus bevacizumab versus bevacizumab alone.[12] Tsien et al. observed no significant improvement in overall survival (median 10.1 vs. 9.7 months); however, the 6-month progression-free survival was improved with reirradiation (54% vs 29%, $P < .001$). The treatment was well tolerated with few (5%) acute and no delayed grade 3 or greater toxicity. Even though reirradiation did not improve survival in a relatively heterogeneous clinical trial population, given the absence of alternative treatment options with a clear survival benefit, the meaningful improvement in progression-free survival with combined treatment should be considered an important clinical outcome. Given that disease progression can lead to a decline in quality of life, neurocognition, and/or functional status, NRG/RTOG1205 results suggest a meaningful benefit though further evaluation of neurocognitive and quality of life outcomes is necessary to confirm this. Currently, a prospective randomized EORTC phase III trial (European Union-funded LEGATO project, NCT05904119) is being undertaken to evaluate the potential superiority of combining a second course of radiation with lomustine, the standard systemic treatment for recurrent glioblastoma, over lomustine alone (https://legato-horizon.eu).[32] While the LEGATO trial evaluates reirradiation at the time of first recurrence, the optimal timing of reirradiation is not known, and reirradiation can be saved for later in a disease course for suitable patients if preferable alternatives such as clinical trial enrollment are possible at the time of first recurrence. Since reirradiation can be implemented at different time points in recurrent GBM, further caution is warranted in interpreting reirradiation studies as they do not restrict the use of radiation therapy as a subsequent salvage treatment.

While we await further data, reirradiation has emerged as a safe treatment option for selected patients with recurrent glioblastoma and may be associated with clinical benefit. Given the established safety record of reirradiation, appropriately selected patients may benefit from this treatment. Important factors for clinicians to consider in offering reirradiation include the interval since initial radiation, patient age, performance status, required treatment volume, location of organs at risk relative to the treatment target (eg, visual apparatus, brainstem, and hippocampus), neurologic status and deficits, and expectations for overall prognosis (Table 1). Generally, younger, good-performance patients with a prolonged interval since initial radiation and with small, focal recurrences may be better candidates for reirradiation than patients not fulfilling these criteria. A representative case where reirradiation was recommended and excluded is presented in Figure 1.

An improved understanding of the molecular features that may underpin greater radiosensitivity (eg, molecular signatures, DNA damage repair defects, metabolic pathway disruptions, markers of hypoxia, and autophagy) may allow for the identification of patients most likely to benefit from treatment in the future. A few retrospective studies have suggested possible molecular signatures such as the radiosensitivity index (RSI) and genomic-adjusted radiation dose may serve as predictive biomarkers of tumor sensitivity to radiation therapy,[33,34] but further research will be necessary to prospectively validate predictive biomarkers. Important opportunities to enhance the benefit of reirradiation include combining different radiotherapy schedules with systemic agents, novel dose fractionation schemes, and optimizing treatment volume delineation.

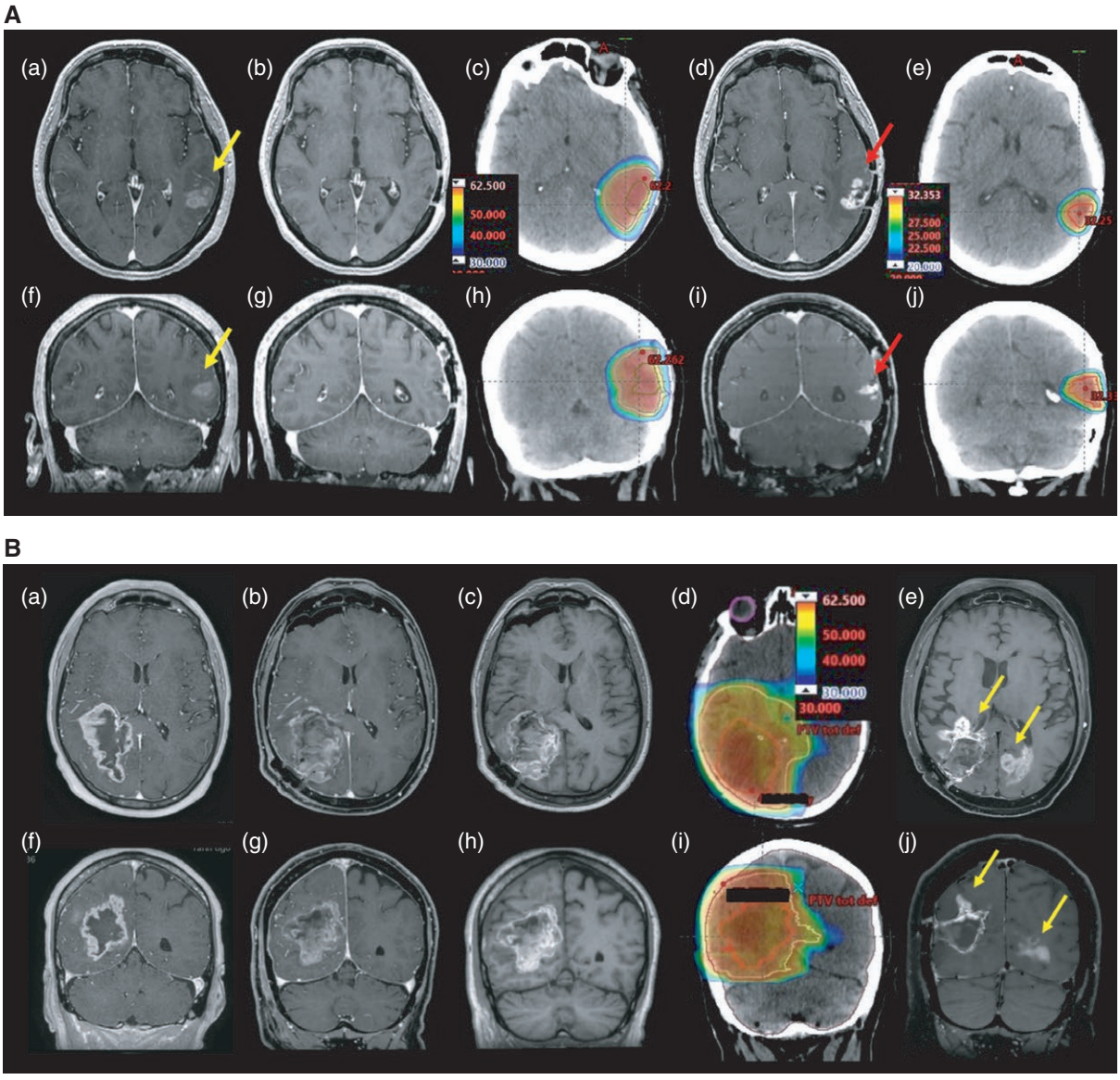

Figure 1. (A) A representative case suitable for reirradiation. A 48-year-old woman with an unremarkable past medical history was admitted to the hospital with a clinical presentation of seizures. Gadolinium-enhanced MRI showed a left temporal tumor measuring 3 cm in size (a, f). The patient underwent macroscopic total resection of the tumor (b, g), and histopathology was consistent with glioblastoma with MGMT promoter methylated. The patient received standard radiotherapy (c, h) with concurrent and adjuvant temozolomide (12 cycles). Two years after the end of chemotherapy the patient presented with dysphasia and an MRI revealed a locally recurrent tumor (d, i). The case was discussed in a multidisciplinary manner, and a second course of radiation was recommended. The patient received (stereotactic radiosurgery [5.5 Gy × 5 fractions]) (e, j) followed by lomustine. Factors in favor of a second course of radiation were: good KPS, location of recurrent tumor (risk of worsening speech), long interval after the first course of RT, and well-defined moderate-sized target. (B) A representative case unsuitable for reirradiation. A 64-year-old male patient presented with headache and visual field defects. Brain MRI showed a heterogeneously enhanced right occipito-parietal lesion on T1-weighted images after gadolinium injection (a, f). The patient underwent subtotal resection, which was determined by T1-weighted MRI sequences with (b, g) and without contrast (c, h). Pathological examination of the tumor identified it as MGMT promoter unmethylated glioblastoma. The patient then received standard radiochemotherapy 60 Gy in 30 fractions with concurrent and adjuvant temozolomide (d, i). One month after the sixth cycle of adjuvant chemotherapy, the patient complained of rapid neurological deterioration (unstable gait, left-sided weakness, confusion) with some recovery with dexamethasone initiation (8 mg per day). Gadolinium-enhanced MRI revealed diffuse periventricular and nodular enhancement around the posterior ventricular horns (e, j). Due to the widespread pattern of tumor progression (multiple lesions) and the short interval since the first course of radiation, a second course of radiotherapy was not recommended, and the patient was started on lomustine.

Counterpoint: The Case Against Reirradiation

While reirradiation is widely applied for the management of recurrent glioblastoma, an overall survival benefit for this approach has not been demonstrated. In the 2 available randomized trials, neither of them with a phase III design and both with limited patient numbers, reirradiation did not prolong survival. The NRG /RTOG1205 randomized phase II trial showed a similar median survival time following hypofractionated reirradiation (35 Gy/10 fractions) plus bevacizumab or bevacizumab alone.[12] Bergmann et al. found in their small phase II trial (35 high-grade gliomas including 29 glioblastomas) a median survival of 4.8 months with systemic pharmacotherapy (bevacizumab plus irinotecan, etoposide, temozolomide, or carboplatin) alone and 7.2 months with fractionated stereotactic radiosurgery plus bevacizumab-based pharmacotherapy without a statistically significant OS difference between the 2 arms.[35]

A recent meta-analysis compiling available data from randomized and non-randomized studies showed median overall survival times ranging from 4.3 to 9.5 months for reirradiation alone and from 4.8 to 17.9 months for reirradiation in combination with systemic pharmacotherapy.[36] Although the meta-analysis found that combined therapy with reirradiation and pharmacotherapy may have been associated with overall survival across studies with a hazard ratio of 0.73 (95% CI: 0.56–0.95), the evidence level reached only "low certainty" according to the Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[37] The results of the primary overall survival endpoint of LEGATO, the only randomized phase III trial comparing systemic chemotherapy (lomustine) to reirradiation added to lomustine, will be available in several years and will likely demonstrate conclusively whether or not reirradiation on an alkylating agent backbone improves survival.[32] Until these data become available, the indication for reirradiation in patients with recurrent glioblastoma needs to be carefully and critically reviewed for each patient, as class I evidence supporting such a recommendation is currently lacking.

So far, 2 randomized trials reported improved progression-free survival with reirradiation for recurrent glioblastoma. The NRG/RTOG1205 showed a better 6-month progression-free survival rate of 54% with combined reirradiation plus bevacizumab compared to bevacizumab alone (29%).[12] Bergman et al. demonstrated a median progression-free survival of 1.8 months with bevacizumab-based systemic pharmacotherapy and 5.1 months with reirradiation plus bevacizumab-based systemic pharmacotherapy.[35] With regards to overall survival, a meta-analysis found low-level evidence that combined radiotherapy and pharmacotherapy therapy improves progression-free survival over pharmacotherapy alone (HR 0.57 [95% CI: 0.41–0.79]).[36] The interpretation of the available data must account for the limited patient numbers, diverse pharmacotherapies and irradiation schemes used, and the inaccuracy of MRI-based response evaluation in recurrent glioblastoma, especially when treated with bevacizumab-containing regimens. Prospective data on safety and tolerability are limited, and there can be the risk of increased use of steroids, which may be associated with inferior survival.[38]

Another important limitation of currently available studies is the lack of neurocognitive testing and patient-reported outcomes. While initial studies have not shown reirradiation to negatively impact health-related quality of life or neurocognition,[39,40] the effects of reirradiation on these parameters remain poorly characterized and may be underestimated. An emphasis on neurocognitive and quality-of-life outcomes should be prioritized in future trial designs evaluating reirradiation. Given the unclear survival benefit of reirradiation, it is important to balance potential therapeutic benefits with the adverse effects on patient quality of life. The burden of reirradiation on patients involving multiple outpatient visits, in addition to hospital resources and associated system costs, should be considered when weighing the pros and cons of reirradiation in relation to alternatives such as bevacizumab and lomustine therapy. The ongoing LEGATO trial includes secondary endpoints evaluating neurocognitive outcomes, health-related quality of life, and health economic parameters, which will provide invaluable prospective data on these important outcome measures.[32]

Outlook

To place the role of reirradiation in perspective, it is probably fair to reconfirm that no single treatment has ever shown superiority over another treatment in an adequately powered trial for patients with recurrent glioblastoma.[1,41] While we do not challenge the consensus of considering lomustine as the best standard of care in the context of clinical trials, it is nevertheless true that, while no other treatment has been shown to be superior to lomustine, lomustine has also not been shown to be superior to placebo, and this is unlikely to be ever demonstrated.[5] Accordingly, we have in general not been successful in establishing solid evidence for the major pillars of salvage treatment for patients with glioblastoma, surgery, radiotherapy or pharmacotherapy. The LEGATO trial, an ongoing pragmatic phase III trial, may serve to further inform the role of reirradiation in this context.[32]

Reirradiation remains a treatment option for a selected patient population given the constraints in target volume and the low likelihood of benefit for patients progressing in the radiation field within a few months after initial treatment. For those considered eligible for reirradiation—such as the patients enrolled in the NRG/RTOG1205 or LEGATO—if a progression-free survival advantage, but no change in overall survival, can be achieved, there will need to be clarification on how we measure and value gains in local control and progression-free survival versus possible risks of therapy or possible costs in terms of cognition and quality of life. Future clinical trials in this field should ideally agree on the relevant, meaningful endpoints that need to be captured so that it can be possible to cross-reference them to clinical trial datasets that are already available or become available at a later time. In general, inclusion in a clinical trial should remain the first treatment option whenever feasible at first recurrence of a glioblastoma.

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Design and implementation: R.R., P.Y.W., and M.W.. Writing of the manuscript, revision, approval of the final version: all authors.

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