# Reirradiation for Recurrent Glioblastoma: What We Know and What We Do Not

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*The Oncology Grand Rounds series is designed to place original reports published in the* Journal *into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series is to help readers better understand how to apply the results of key studies, including those published in* Journal of Clinical Oncology*, to patients seen in their own clinical practice.*

## CLINICAL CASES

### Case 1

Mr P is a 34-year-old right-handed man diagnosed 6 years ago with a right frontal isocitrate dehydrogenase wild-type (IDHwt) glioblastoma (GBM) with methylguanine methyl transferase (MGMT) promoter hypermethylation after a generalized seizure. A gross total surgical resection was followed by 60 Gy radiation in 30 fractions along with concurrent temozolomide, 75/mg/m$^2$/day, once daily for 42 days, followed by postradiation adjuvant temozolomide, 200 mg/m$^2$/day once daily × 5 days every 28 days for 12 months. He has had a normal family and work life over the past 5 years with no apparent sequelae from his tumor and now presents with a new magnetic resonance imaging (MRI)–documented asymptomatic 1-cm enhancing mass along the anterior margin of the previous right frontal lobe resection cavity (Fig 1A). Physical and neurologic examinations are normal, and the Karnofsky performance score (KPS) is 100.

### Case 2

Ms S is a 77-year-old right-handed woman who was diagnosed 5 months ago with an IDHwt GBM, MGMT promoter unmethylated in her right frontal lobe with extension across the corpus callosum, after 2 months of progressive confusion, expressive aphasia, and right-sided weakness. After a stereotactic biopsy, she was treated with 40 Gy radiation delivered in 15 fractions along with concurrent temozolomide 75/mg/m$^2$/day, once daily for 42 days and then received one cycle of adjuvant temozolomide 200 mg/m$^2$/day, once daily × 5 days, which caused severe and prolonged myelosuppression. Postradiation, the patient remained confused with worsening expressive aphasia and fatigue until an MRI scan 2 months after completing radiation showed significant progression of disease across the corpus callosum into the left frontal and parietal lobe and with anterior and inferior extension into the right temporal lobe (Fig 1B). On examination, she was a disoriented, ill-appearing patient in a wheelchair, with severe expressive and partial receptive aphasia and a worsening right-sided hemiparesis.

## CLINICAL CHALLENGES IN EVALUATION AND TREATMENT

Gliomas are a genetically, biologically, and clinically heterogenous group of primary brain tumors of neural/glial progenitor cell derivation that affect patients of all ages.[1] The clinical behavior of various types of gliomas runs the spectrum of tumors whose growth, if any, is measured in decades (juvenile pilocytic astrocytomas) to those that proliferate rapidly and whose invasiveness may lead to patient death in less than a year from diagnosis. The most common and most lethal of these tumors are GBMs, a tumor with an increasing incidence with age. Gliomas kill patients through profound locoregional tissue infiltration, causing cerebral edema, parenchymal destruction, and increased intracerebral pressure and eventually leading to death. The characteristic diffuse brain invasion makes a true complete surgical resection impossible without causing unacceptable permanent neurologic morbidity by removing large parts of the normal brain. Similarly, this diffuse infiltration of glioma cells into normal brain limits the doses of radiation that can be given safely for fear of permanent radiation damage to the brain. Despite significant advances in our understanding of the genetic and molecular biology of these tumors, the overall prognosis of patients remains suboptimal with a median survival of less than 2 years.[2]

As in most other solid tumors, a combination approach of surgical resection, radiation therapy, and chemotherapy remains the standard of treatment. Relative to most other tumors, however, the number of active drugs is small. Over four decades ago, a series of randomized clinical trials demonstrated that fractionated external radiation increased the median survival of patients with GBM from about 4 to 12 months, with a slight improvement in survival after the addition of adjuvant nitrosoureas.[3,4] Nearly 20 years later, a randomized trial demonstrated that temozolomide could increase the

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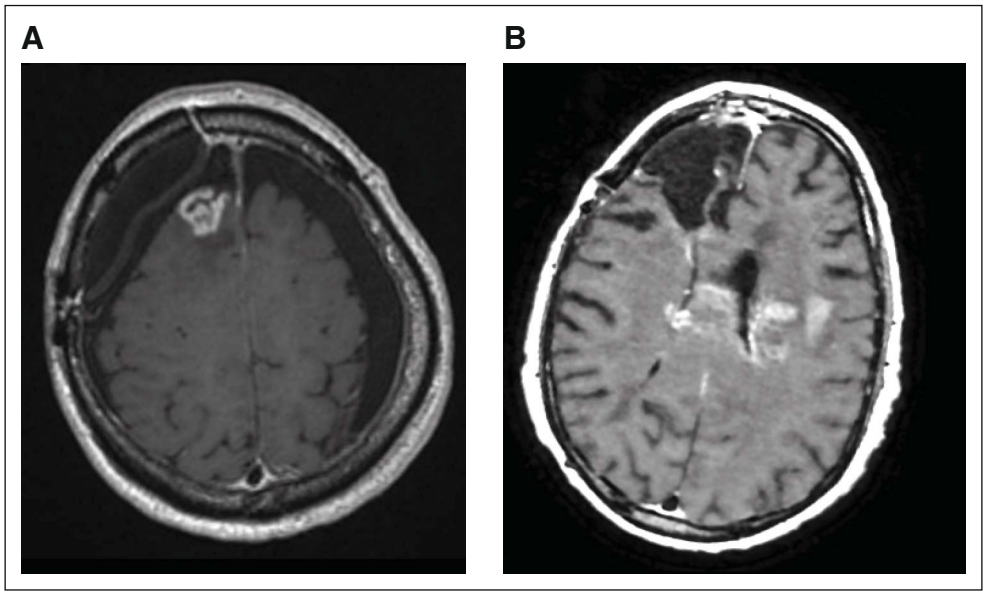


**FIG 1.** T1 Axial plus gadolinium contrast MRI scan. (A) Case 1. (B) Case 2. MRI, magnetic resonance imaging.

overall survival from 12 to 15 months when used concurrently and in the postradiation setting.[5] Recently, a randomized trial also suggested that sustained use of alternating electromagnetic fields (Optune, New York, NY) could increase survival.[6] Although bevacizumab has been shown to prolong progression-free survival (PFS) when used in either the upfront or recurrent setting, there has been no drug other than temozolomide that has demonstrated the ability to prolong overall survival in the upfront or recurrent setting.[7-9]

Given the paucity of consistently effective drugs at the time of GBM recurrence, there has long been an interest in reusing treatment strategies that have some proven utility in the initial treatment setting, specifically, surgery, radiation, and temozolomide.

Recommendations for repeat surgery in patients with recurrent GBMs are tempered by logistical, biologic, and neuroanatomic constraints. Some patients are too clinically or neurologically debilitated for surgery at the time of recurrence. Furthermore, the inherently infiltrative nature of GBMs often makes it impractical to resect a majority of the tumor. Finally, the neuroanatomic recurrence location affects the neurologic risks of surgery and often precludes re-resection. Such considerations are further tempered by numerous retrospective (but no prospective randomized) data that suggest that a majority (probably > 95%-100%) of the contrast-enhancing tumor seen on MRI scans needs to be resected (defined as a "gross total resection" or GTR) to offer potential prolongation of survival.[10] The validity of conclusions from such studies that patients who have GTRs live longer than those who do not is confounded by the inherent patient selection bias found in such analyses. Whether re-resection can improve survival in selected patients, inevitably patients succumb to their tumors, usually within a year of their recurrence.

The successful use of repeat temozolomide administration at recurrence is fraught with difficulty in that almost every patient has been previously treated with the drug. Promoter methylation of the MGMT gene is a biomarker for temozolomide (and nitrosoureas) sensitivity and is found in essentially half of all newly diagnosed IDHwt GBMs.[11] When tumors initially sensitive to temozolomide recur, however, they usually do so with un- or hypomethylated MGMT promoters, suggesting selection for a temozolomide-resistant phenotype. Having said that, there is a belief that if the patient has enjoyed long-term survival before recurrence (case 1, above), there may be a role for repeat temozolomide although that contention has never been prospectively studied.

The only drug approved for recurrent GBM in the past two decades has been bevacizumab on the basis of profound and prompt radiographic improvement in the recurrent setting in roughly half of treated patients. The profound initial radiographic responses seen with bevacizumab, however, are largely a function of their antivascular endothelial growth factor activity, thereby inhibiting the tumor-elicited vascular endothelial growth factor–mediated vascular/blood-brain barrier permeability seen in GBMs.[12] Thus, in effect, bevacizumab elicits a radiographic pseudoresponse by way of its vascular stabilizing properties, and the radiographic responses do not lead to improved overall survival of patients with GBM either when used with radiation and temozolomide in the newly diagnosed setting or when used alone or in combination with various other agents (including nitrosoureas) in the recurrent setting.[7-9] Nevertheless, blood-brain barrier stabilization can benefit patients by minimizing the amount of tumor-mediated cerebral edema and permit dexamethasone dose reductions to lessen the long-term side effects of steroids—an

 

effect that may be important for its use with reirradiation, as will be discussed below.[12]

There has been a renewed interest in exploring the safety and efficacy of repeat radiation given its place as the most effective overall treatment we have for treatment of newly diagnosed GBM.[13,14] The major issues revolve around both its effectiveness and safety in the recurrent setting. There are increasing data to suggest that recurrent GBMs undergo genetic (or more likely epigenetic) perturbations and molecular evolution that may increase their radiation resistance at recurrence.[15] Thus, it is thought that substantial doses of radiation would need to be used to have a realistic chance of inhibiting tumor growth for a long enough period of time to be clinically meaningful. Given that GBM recurrence is almost always local to the original site, the diffuse invasiveness of these recurrent tumors into the same surrounding normal brain parenchyma means that previously irradiated normal brain would again need to be irradiated—worrisome for inducing radiation neurotoxicity (eg, radiation necrosis). Ironically, when such radiation necrosis does occur, bevacizumab can radiographically and clinically alleviate much of the associated cerebral edema although it does not mitigate against normal tissue injury/destruction.

Despite these concerns, there are numerous single-site studies using a large array of dose administration schemas and treatment volumes, suggesting the feasibility of this approach relative to both safety and effectiveness.[13,14] Most of these were small trials that treated heterogeneous and selected groups of patients, making comparisons with more general historical controls difficult. Since reirradiation often exacerbates cerebral edema, several recent studies have used bevacizumab concurrently with the radiation, perhaps less for any true tumor radiation-sensitizing effect—through normalization of tumor vasculature and improved tumor oxygenation—and more for prophylaxis against radiation side effects.

With this as background, the study by Tsien et al[16] is the first randomized, multi-institutional trial of reirradiation in GBM. A heterogeneous group of patients and gliomas (neither the tumors' isocitrate dehydrogenase (IDH) nor MGMT promoter methylation status were known) were treated either with bevacizumab alone or together with radiation (35 Gy in 10 fractions). Patients in the reirradiated arm had a longer PFS than did those in the bevacizumab-alone arm; however, there was no difference in overall survival between the treatment groups. Given that bevacizumab has been shown to not increase survival in GBM, one is left to conclude that reirradiation also does not dramatically increase survival.

Consider these caveats: First, the authors of the study suggest that the radiation was well tolerated and the increased PFS translated to improved quality of life (QOL) and delayed symptom occurrence such that reirradiation may be beneficial to patients. Although there are certainly reasons to believe that this may be true, there were no QOL or detailed studies of neurocognitive function performed to know for certain whether the treatment did result in improved or possibly worse neurologic or functional outcome. A second caveat is that the patient and GBMs treated in this study were very heterogeneous relative to size, treatment planning (eg, only 60% of patients met the minimal protocol-determined quality standard for radiation planning), size of tumor, and tumor biology (eg, IDH and MGMT promoter methylation status, as well as other genetics), such that it is still possible that a subgroup of patients may very well have had prolonged survival had the trial been powered sufficiently to study these subpopulations.

In considering the effect of any therapeutic intervention in GBM, it is vitally important to understand that there are patient- and tumor-specific variables that can have as profound an effect on patient outcomes as a moderately effective intervention.[17] Thus, for any investigational treatments for which survival is the important end point, everything possible needs to be done to consider, control for, and stratify for such variables. Within the context of patient care, clinicians will also need to consider a similar set of factors when evaluating the potential benefits of any given treatment such as reirradiation in recurrent GBM.

The list of such variables is quite long, but we have already discussed several of them including the IDH status of the tumor. IDH-mutant and wild-type tumors have clearly different biology and very possibly different responses to interventions such as irradiation and reirradiation.[17] Other tumor genetics including those demonstrating mutations in genes such as NF1, ATM/ATR, DNA mismatch repair, and BRCA1 genes might be predicted to have greater radiation sensitivity although that is yet to be clinically validated. In addition, variables predicting potential toxicity of reirradiation need to be considered such as the proposed fractionation/dose plan, the required treatment volume, and the potential radiation sensitivity of the neuroanatomic structures within the treatment field (eg, visual apparatus, medial temporal lobes, and brain stem).

Also, the overall prognosis of the patient needs to be considered for the median survival of recurrent GBM is between 4 and 8 months and there are factors that can strongly suggest patients whose survival will be on the lower side of that median. Thus, negative prognostic factors such as older age, worse performance status, substantial neurologic/neurocognitive deficits, greater number of prior therapies for recurrence, and extent of disease recurrence should all be factored into any clinical trial design or for making a clinical recommendation for one's patient.

Finally, there are several additional important factors, not addressed by Tsien et al,[16] or well addressed in any other trial, that need to be considered when thinking about reirradiating a patient with a recurrent GBM. These factors include the following: (1) the optimal schema for dose

fractionation and target volume definition; (2) the value of temozolomide given concurrently with the reirradiation as a radiation sensitizer even if one suspects that the tumor is temozolomide-resistant, (3) does the calculus of the pros/cons of using reirradiation change in the postoperative (GTR) setting for recurrence?[18] (4) Is it always necessary to use concurrent bevacizumab with reirradiation?

## OUR MANAGEMENT APPROACH

As described above, to date, there is a suboptimal amount of level 1 prospectively acquired clinical trial data available to make general recommendations regarding how best to manage patients with recurrent GBMs. This is a function of both the paucity of proven effective drugs and treatments in the recurrent setting, and the dramatically heterogenous nature of both the patient population and tumor genetics makes such recommendations difficult. Despite lacking such level 1 data that objectively address the quantitative impact of these prognostic factors in recurrent GBM, clinicians faced with such patients will still need to seriously consider these issues when deciding how best to proceed.

To that end, our overall gestalt of the data that do exist, biased by our own cumulative clinical experience of over 60 years of caring for patients with glioma, is that reirradiation probably does benefit some patients with recurrent GBM, but we are currently not able to know for certain who those patients are. By contrast, we think that it is much easier to identify patients who should not be irradiated (Table 1). Those are patients who have any of, or at least some combination of, the poor prognostic factors for tumor control, radiation-induced neurotoxicity, and/or overall survival. These include short PFS from initial radiation, advanced age (although this remains controversial), widely disseminated recurrence requiring large treatment volumes (there is almost never a rationale for performing partial tumor radiation), poor KPS, poor neurologic status, and recurrence in eloquent areas of brain previously irradiated.[19,20] Furthermore, given the lack of impact on overall survival and its potential for significant toxicity, it is not at all clear to us that every patient who is offered reirradiation should also be treated expectantly with bevacizumab (eg, it can always be added later if required).

The above two cases represent the extremes of the types of patients where we think the role for reirradiation is clear on the basis of the factors described above. Case 1 represents a patient with uncommon GBM who has an extraordinary response to standard radiation and temozolomide with an extended PFS measured in years and with a small recurrence in a relatively noneloquent area of the brain. Given the effectiveness of the initial treatment, it is reasonable to assume that the recurrent tumor may be similarly sensitive to the same treatment regimen, including surgical resection. In addition, although not risk-free, reirradiation should be much safer in such a patient given the relatively localized recurrence, thereby allowing for a more limited radiation treatment field, and the long period of time since prior radiation, potentially allowing more time for repair of radiation-induced damage from the initial treatment.

**TABLE 1.** Reirradiation of Recurrent Glioblastoma: Factors to be Considered[a]

| Factor | In Support of Reirradiation | Against Reirradiation |
|---|---|---|
| Age | Younger (eg, < 70 years, but no absolute cutoff) | Elderly (eg, > 70 years, but no absolute cutoff) |
| KPS | Higher (eg, > 60 years, but no absolute cutoff) | Lower (eg, < 60 years) |
| Mental status/neurocognitive status | Good | Severely impaired |
| Other available reasonable therapeutic options | No | Yes |
| PFS from initial radiation to first recurrence | > 12 months (the longer the better) | < 12 months (the shorter the worse) |
| Site of recurrence relative to initial tumor | Distant, outside the prior radiation field | Within the prior radiation field |
| Neuroanatomic site of recurrence | Less radiation-sensitive areas of brain (unilateral cerebral cortex) | Eloquent and radiation sensitive areas of brain (eg, brainstem, visual apparatus, medial temporal lobes, and bilateral frontal lobes) |
| Radiographic pattern of recurrence | Localized, small (contrast enhancement and FLAIR) | Diffuse contrast and flare abnormality, large multifocality, and diffuse leptomeningeal involvement |
| Rapidity of radiographic and/or clinical progression | Relatively slowly | Rapid |
| Glucocorticoid requirement for control of symptomatic cerebral edema | Low (eg,< 4 mg/day once daily dexamethasone) | High (eg, > 8 mg/day once daily dexamethasone) |

Abbreviations: KPS, Karnofsky performance score; PFS, progression-free survival.

[a]These factors and the values listed therein are merely generalizations and do not represent definitive decision points unto themselves. Rather, individual clinical decisions should be based on a qualitative cumulative assessment of these factors, individualized for each patient, and within the context of discussions with the patient and family regarding realistic expectations and goals of care.

 

Indeed, in our experience, this is the patient with an unusual type of GBM who can still have a relatively extended survival after retreatment, and thus, we tend to use a more fractionated treatment regimen to minimize the chance of delayed radiation-induced neurocognitive damage. We would also consider treating the patient with both concurrent and adjuvant temozolomide if the patient's tumor (recurrent tumor if a re-resection was performed or initial tumor if not) showed MGMT promoter methylation.

Case 2 represents the opposite side of the clinical spectrum of patients with recurrent GBM. This is a patient whose tumor recurred relatively soon after the initial radiation, thereby declaring the relative radiation resistance of the tumor. Reirradiation is unlikely to reverse the patient's decline in neurologic function or KPS, mooting the point of reirradiation, and the diffuse and widespread tumor recurrence would require large volume radiation, thereby dramatically increasing the chance of acute/subacute neurotoxicity that might decrease quality of life or survival.

We chose to present these two cases because they represent clinical management decisions relative to reirradiation that we believe are relatively straightforward. Unfortunately, most patients with recurrent GBM fall somewhere between these two extremes and the current clinical trial data do not definitively tell us what to recommend to our patients. Given the paucity of effective treatments in this disease and the at most marginal clinical benefit of repeat surgical resection and reirradiation, we feel strongly that all appropriate patients should be offered and encouraged to enroll on good clinical trials, so we can develop and identify better treatments for these and future patients. If/when such clinical trial options are no longer available to any given patient, we believe that it is reasonable to consider a reirradiation approach for those patients with relatively good KPS and neurologic function and for whom it is judged that repeat radiation is unlikely to cause additional neurologic harm. Such a decision, however, must involve the patient and their family with frank discussions regarding the pros and cons, the unknowable outcome, and the clearly modest overall benefit that such a treatment can afford (and if the patient is unable to cognitively participate in such discussions and decisions for themselves, then they should not be considered for repeat radiation in our opinion). Importantly, we believe that it is also most appropriate to include the options of palliative and hospice care among the treatment options discussed with the patient and family.

Tsien et al[16] in NRG have done the field a great service by conducting this difficult-to-perform, first-of-its-kind multi-institutional randomized trial of reirradiation in recurrent GBM and demonstrating the improved PFS but lack of impact on overall survival. Future studies should more clearly define the role of bevacizumab and temozolomide in reirradiated patients and should validate the presumed improved QOL associated with improved PFS in reirradiated patients. Such future studies will hopefully better define specific subpopulations of patients who might truly experience improved survival from reirradiation of recurrent GBM.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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