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Reirradiation in recurrent glioblastoma

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Abstract

Reirradiation has emerged as a potentially valuable treatment strategy for recurrent glioblastoma, a disease characterized by inevitable local progression despite aggressive multimodal first-line therapy. Recent advances in radiotherapy techniques, improved patient selection, and evolving systemic treatment combinations have renewed clinical interest in this approach. This is reflected by recent publication of the first international consensus

guidelines (ESTRO/EANO) and the initiation of an European phase III randomized trial on reirradiation of patients with recurrent glioblastoma.

Retrospective and early-phase prospective studies have demonstrated that reirradiation is feasible and well tolerated in selected patients, with median overall survival ranging from 7 to 13 months. The ESTRO/EANO guidelines on reirradiation of glioma provide standardized recommendations for patient selection, dose constraints, and target volume delineation. Meta-analyses suggest improved outcomes when reirradiation is combined with systemic therapies, such as bevacizumab or lomustine. The phase III EORTC-2227-BTG (LEGATO) trial will provide definitive data on survival benefit.

Reirradiation is gaining acceptance as a palliative yet potentially impactful treatment for recurrent glioblastoma. While current evidence supports its use in selected cases, results from ongoing phase III LEGATO trial will determine its future role in standard care and inform evidence-based clinical decision-making.

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INTRODUCTION

Glioblastoma, isocitrate dehydrogenase (IDH) wild-type (GBM), representing the most common and the most aggressive glioma in adults, is a highly malignant brain tumor characterized by an almost inevitable recurrence following standard treatment, which includes maximal safe resection, radiotherapy with a total dose of 60 Gy delivered in 30 daily fractions, and concomitant and adjuvant temozolomide [1]. Although recent advances in the treatment of newly diagnosed glioblastoma including tumor treating fields, combination immunotherapy, oncolytic viruses, chimeric antigen receptor (CAR) T-cell therapy, therapeutic vaccines, and novel drug delivery strategies designed to enhance blood–brain barrier permeability have shown some promise, GBM remains an incurable disease with an almost inevitable progression [2–4]. Recurrences are typically local, occurring within the previously irradiated high-dose area.

The optimal management strategy at the time of progression, aligned with the principles of palliative care, remains

controversial, and no standardized fit-for-all recommendations currently exist [5]. As with any therapeutic approach for incurable oncologic disease, treatment decisions in this setting must be strictly individualized. This is particularly relevant for local treatment modalities, such as repeat surgery or reirradiation, which remain the cornerstone of GBM management. These interventions should be tailored to reflect the patient's preferences, the expectations of family and caregivers, and guided by a careful balance between treatment intensity, the risk of adverse effects, and the goal of achieving local disease control. This paradigm applies to all local therapies not only in the context of progressive GBM.

KEY POINTS

- Reirradiation in glioblastoma represents a rational approach to local tumor control, especially given that over 85% of recurrences occur within the high-dose area of prior irradiation.
- Modern radiotherapy techniques and careful patient selection have enabled reirradiation to be performed safely, even at high cumulative doses, with acceptable toxicity.
- The first international ESTRO/EANO consensus guidelines provide a comprehensive framework for clinical decision-making and technical planning of glioblastoma reirradiation.
- The ongoing LEGATO phase III trial will provide definitive evidence on the survival benefit of reirradiation combined with lomustine for first recurrence of IDH-wildtype glioblastoma.

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GLIOBLASTOMA REIRRADIATION AND THE AIM OF THIS NARRATIVE REVIEW

Reirradiation represents a potential approach for achieving local tumor control, which remains critical in GBM management. Although GBM has long been recognized as a disease affecting the entire brain, the majority of recurrences continue to manifest locally [6]. Notably, 87% of recurrences are in-field [7]. This is particularly relevant in patients for whom upfront gross total resection is not feasible.

Nevertheless, the concept of reirradiation has traditionally raised concerns regarding potential toxicity to previously irradiated healthy brain tissue. However, advancements in modern radiotherapy techniques, such as stereotactic radiotherapy and the integration of some stereotactic principles into normofractionated regimens, alongside improved patient selection, have led to a resurgence of interest in GBM reirradiation. Several recent reviews listed below have explored this topic, demonstrating that this approach can be performed with a reasonable safety profile.

The tolerance of critical brain structures to reirradiation has thus far been evaluated primarily through retrospective analyses. A systematic review focusing on reirradiation of diffuse brainstem gliomas, encompassing seven studies with a total of 90 patients, demonstrated clinical improvement and radiological response after a second course of radiotherapy, delivered at doses of 20–24 Gy in 2 Gy fractions, without significant toxicity [8]. Another study reporting 58 patients with malignant gliomas who underwent reirradiation found no relevant late toxicities, even at cumulative equivalent dose in 2 Gy fractions (EQD2) doses of 80.3 Gy to the optic chiasm, 79.4 Gy to the optic nerves, and 95.2 Gy to the brainstem (using an α / β ratio of 2 Gy for these structures) [9].

When evaluating potential radiation-related adverse effects, spatial relationships between the recurrent tumor and prior irradiation volumes must be considered [10▪]. According to the European Society for Radiotherapy and Oncology (ESTRO) and the European Organisation for Research and Treatment of Cancer (EORTC) consensus on reirradiation, two types are defined: type I reirradiation, where there is geometrical overlap

with previously irradiated volumes, and type II reirradiation, which involves concerns of cumulative dose toxicity without actual volume overlap [11].

Patterns of failure analysis not only informs the feasibility of reirradiation but may also provide insights into glioblastoma's invasiveness and radiosensitivity, possibly influencing target volume delineation [12]. This is especially pertinent in cases of vaguely enhancing, patchy, multicentric recurrences. where decisions regarding the addition of clinical target volume (CTV) margins remain debatable. These considerations are also reflected in ongoing studies, such as the LEGATO trial, which is discussed further in the following.

The objective of this narrative review is not to reiterate the prerequisites for reirradiation, as these have been comprehensively addressed in the current ESTRO/European Association of Neuro-Oncology(EANO) consensus recommendations [13▪▪]. Instead, we aim to highlight two pivotal publications on GBM reirradiation from the past year and guide readers towards key review articles essential for clinical decision-making. The definitive impact of reirradiation on overall survival will be elucidated by the LEGATO trial [14▪]. Both the latest guidelines and the LEGATO study are discussed in detail later in this review. Additionally, we provide an overview of published reviews to aid clinicians considering reirradiation for their current patients. Given the palliative nature of this indication, treatment decisions are largely left to physician discretion, as evidenced by the multitude of retrospective studies and cohort analyses. The pragmatic LEGATO trial will help determine whether reirradiation should become part of the standardized approach for patients with a recurrent GBM after failure of standard chemoradiation.

Current research focuses primarily on combining reirradiation with systemic therapies or exploring unconventional applications of reirradiation. A critical evaluation of radiotherapy in GBM over the past five decades reveals that, as the seminal Brain Tumor Study Group (BTSG) randomized trial established 60 Gy in 30 fractions as the standard of care, most advancements have pertained to improving treatment safety rather than efficacy [15]. This justifies ongoing efforts to enhance outcomes through combination therapies, such as reirradiation with

bevacizumab or lomustine.

A meta-analysis of 31 studies involving over 2000 patients evaluated combined chemoradiation versus systemic treatment alone or reirradiation for recurrent high-grade gliomas. Combination therapy demonstrated superior progression-free survival (PFS) and overall survival (OS): median PFS ranged from 5.1 to 12 months, and median OS from 7.2 to 16 months, compared to systemic therapy alone (median PFS 1.8–4.8 months, OS 4.8–9.7 months). Combination therapy significantly improved PFS (hazard ratio 0.57) and OS (hazard ratio 0.73) without increasing the incidence of grade ≥3 adverse events. Similarly, combination therapy again showed improved PFS and OS when compared to reirradiation alone [median PFS 2–6.7 months (hazard ratio 0.52) and OS 4–14.3 months (hazard ratio 0.69) [5]. These results suggest that combining reirradiation with systemic therapy may enhance survival outcomes while maintaining acceptable toxicity profiles.

Examples of unconventional radiotherapy applications include FLASH radiotherapy [16▪], spatially fractionated grid radiotherapy for recurrent tumors, and neoadjuvant radiotherapy approaches [2,17–20].

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RATIONALE FOR THE INCREASED INTEREST IN GLIOBLASTOMA REIRRADIATION

In recent years, numerous reviews focusing on GBM reirradiation have been published, including the first consensus recommendations clarifying indications, treatment strategies, and expected outcomes of GBM reirradiation (ESTRO-EANO recommendations for glioblastoma reirradiation, see the following) [13▪▪]. The number of patients eligible for reirradiation is expected to increase due to several factors: improved supportive care options (notably management of cerebral edema, also with Boswellia serrata [21▪] or vitamin E [22]), better organization of patient care through clinical pathways [23,24], and a trend towards smaller treatment margins in upfront radiotherapy. The latter is driven by the recent ESTRO-EANO guidelines, which recommend a 1.5 cm margin to cover microscopic disease in GBM radiotherapy [25]. A similar approach is being adopted for grade II and III

astrocytomas [26▪▪], which may also become candidates for reirradiation, regardless of whether the recurrence meets grade IV criteria.

The most significant prospective study to date is the phase II randomized trial NRG Oncology/RTOG 1205, comparing reirradiation plus bevacizumab versus bevacizumab alone in recurrent GBM [27]. This trial confirmed the safety of reirradiation (35 Gy in 10 fractions) and demonstrated a prolongation of progression-free survival (PFS): median PFS was 7.1 months in the combination arm compared to 3.8 months with bevacizumab monotherapy (hazard ratio 0.73; P = 0.05) [27].

Across various studies where bevacizumab was used as a control arm, PFS consistently ranged between 3.5 and 4.2 months [27–29], with its primary clinical benefit being symptom control and quality of life improvement rather than a significant extension of survival. Considering the phenomenon of pseudoresponse associated with bevacizumab, it is likely that 'true' progression occurs even earlier, emphasizing the persistent unmet clinical need for effective treatment of recurrent GBM. On the other hand, bevacizumab's positive effects – being a monoclonal antibody that inhibits vascular endothelial growth factor A and thus slows angiogenesis – are sometimes leveraged in individualized palliative care during brain irradiation, depending on drug availability. Nonetheless, some radiation oncologists consider it merely an expensive corticosteroid. Importantly, bevacizumab is also being investigated as a means to enable isotoxic dose escalation, as explored in the ongoing NOA-28/PRIDE trial [30].

While phase II studies primarily provide a 'suggestion of efficacy', current evidence supports that reirradiation with an accelerated regimen of 35 Gy in 10 fractions is well tolerated and effective. Definitive 'proof of efficacy', as the objective of phase III randomized clinical trials, will be evaluated in the ongoing LEGATO trial. Of note, both trials used a total dose of 35 Gy delivered in 10 daily fractions, while several retrospective studies employed different hypofractionation schedules.

A range of dose and fractionation schedules have been employed in glioblastoma reirradiation. Hypofractionated regimens such as 30–35 Gy in 10 fractions are most commonly used,

offering a balance between efficacy and safety in patients with limited volume recurrence and good performance status. Alternatively, normofractionated schedules (e.g. 40–45 Gy in 20–25 fractions) may be preferred for larger or critically located lesions, where lower dose per fraction could reduce toxicity. As noted by Minniti *et al.* [31], regimen selection is influenced by tumor size, location, prior dose, and time interval since the initial radiotherapy.

A broader prerequisite for the more widespread use of reirradiation, not limited to brain tumors, is greater accessibility to proton therapy. Proton therapy offers the promise of reduced dose burden to healthy brain tissue during upfront radiotherapy, thereby potentially expanding the indications for safe reirradiation of recurrences [32]. Although the dosimetric advantages of proton therapy are well documented, it remains unclear whether these translate into improved clinical outcomes, such as extended survival or better neurological function in glioma patients. Some centers have already adopted proton therapy for newly diagnosed lower grade gliomas on a case-by-case basis; however, current evidence does not support its designation as standard of care. Reirradiation of recurrent glioblastoma can prolong disease control in carefully selected patients. The literature reports median OS ranging from 7 to 13 months following reirradiation, typically achieved through stereotactic techniques [33].

This growing interest in reirradiation is further reflected in the recent Special Issue titled 'Reirradiation: Pushing Boundaries in Radiation Oncology'. This unique initiative, the first-ever joint effort across the four journals of the European Society for Radiotherapy and Oncology, provides a comprehensive overview of the current reirradiation landscape, highlighting recent advances, clinical evidence, ongoing challenges, and innovations as the boundaries of radiation oncology are being pushed. In the following sections, we will discuss the current and first-ever consensual recommendations for glioblastoma reirradiation.

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EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY/EANO RECOMMENDATION ON REIRRADIATION OF GLIOBLASTOMA

In 2025, the first international consensus recommendations for glioblastoma reirradiation were published, jointly issued by the ESTRO and EANO. These guidelines provide a comprehensive framework for the safe and effective application of reirradiation in patients with recurrent glioblastoma [13▪▪] .

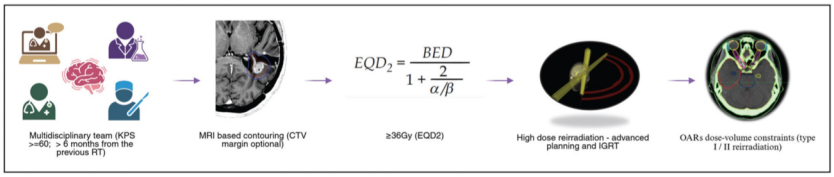
The multidisciplinary ESTRO/EANO consensus-based guideline was developed to offer practical guidance on the safe implementation of CNS reirradiation in glioblastoma, focusing on technical feasibility and treatment quality. Key topics include patient selection with defined clinical and diagnostic criteria for recurrence, target volume delineation, dose and fractionation regimens, tre

atment planning and delivery, combination therapies, and follow-up strategies. The guideline presents a total of 18 recommendations and 9 consensus statements [13▪▪] .

These recommendations are based on a systematic literature search identifying eligible publications on GBM reirradiation, published in peer-reviewed journals in English between 1 January 2005 and 31 March 2023. The search strategy in PubMed, Embase, and the Cochrane Library included the following terms: re-irradiation OR re irradiation OR reirradiation OR ((retreatment OR repeat) AND (radiotherapy OR irradiation)) AND (glioma OR glioblastoma). The results, comprising 18 prospective and 109 retrospective studies, are detailed in the supplementary materials of the guidelines [13▪▪] .

For patients with recurrent GBM, reirradiation may be considered in those with a Karnofsky Performance Status (KPS) at least 60 and a minimum interval of more than 6 months since prior radiotherapy, regardless of patient age or O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status (Fig. 1). The following treatment parameters are recommended: gross tumor volume (GTV) delineation should be based on contrast-enhanced T1-weighted MRI sequences, with a GTV-to-clinical target volume (CTV) margin being optional. A planning target volume (PTV) margin of up to 3 mm is advised, depending on the individual immobilization system and image-guided radiotherapy (IGRT) protocols. A reirradiation delivering a biologically equivalent dose above 36 Gy in 18 fractions (corresponding to a EQD2 of 36 Gy) is

recommended [13▪▪] . This is achieved by majority of regimens usually used in clinical practice including 35 Gy in 10 fractions (EQD2 = 39.4 Gy), 25 Gy in 5 fractions (EQD2 = 31.25 Gy), 30 Gy in 5 fractions (EQD2 = 40 Gy), and 30 Gy in 6 fractions (EQD2 = 37.5 Gy), all calculated using an α / β ratio of 10.



Summary of the main recommendations in the ESTRO/EANO consensus guideline. Data from [13▪▪]. Main recommendation for glioblastoma reirradiation includes the multidisciplinarytumor board indication for treatment. Target volumes for at least 36 Gy (EQD2) are based on MRI, and the dose is delivered employing advanced planning respecting dose-volume constraints for organs at risk.

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EORTC-2227-BTG (LEGATO, NCT05904119)

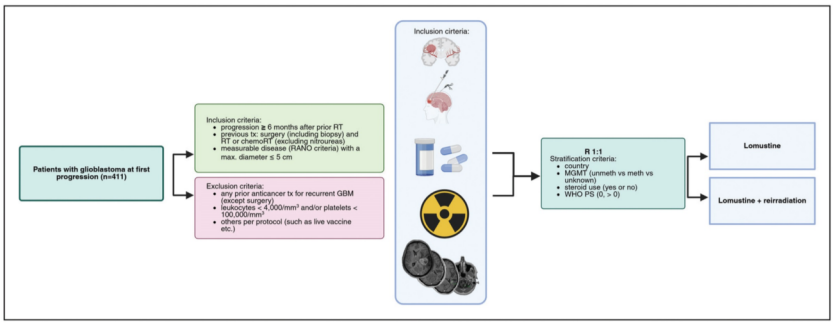
The only ongoing phase III prospective clinical trial – and the first ever initiated to assess the efficacy and benefit of reirradiation in glioblastoma – is the publicly funded EORTC-2227-BTG trial, activated in March 2024 with an expected completion in 2028. The LEGATO trial (Lomustine with or without reirradiation for first progression of glioblastoma: a randomized phase III study) is supported by the European Union's Horizon Europe Research Programme (Project number: 101103655, 2227@eortc.org). It evaluates the addition of reirradiation (35 Gy in 10 fractions) to lomustine chemotherapy (110 mg/m 2 every 6 weeks) in patients experiencing first progression of glioblastoma after prior chemoradiotherapy. Patients in the control arm receive lomustine monotherapy at the same dosage [14▪] .

This trial addresses a highly relevant clinical question frequently debated by multidisciplinary tumor boards worldwide when managing high-grade glioma recurrences, regardless of surgical

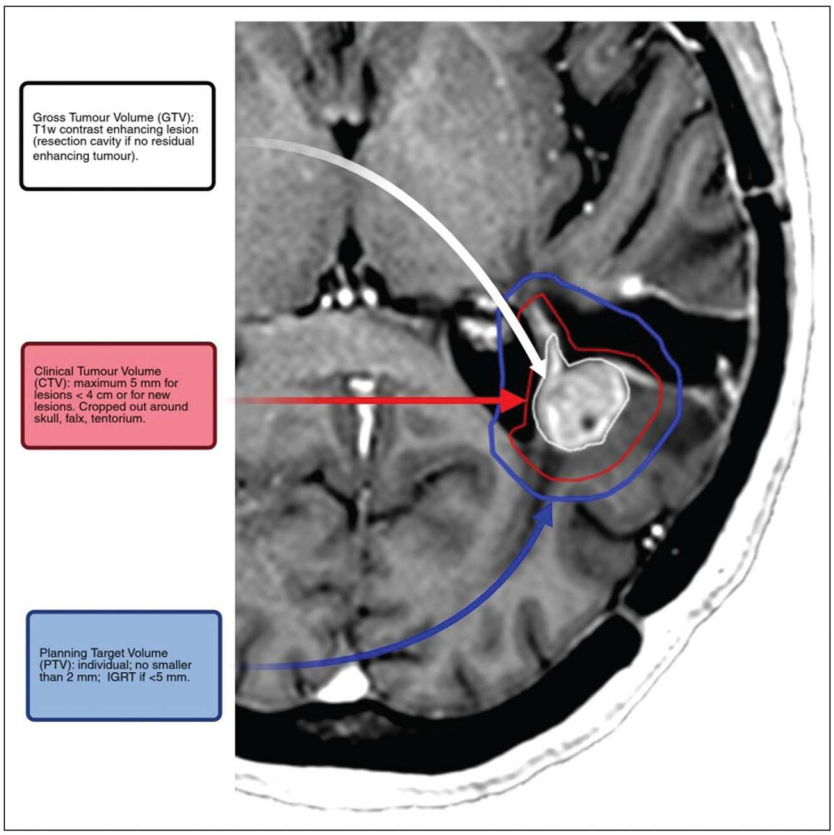
resectability. The results of the LEGATO trial are expected to provide robust recommendations for daily practice in radiation oncology and neuro-oncology, guiding optimal management of first glioblastoma progression. Specifically, the trial will determine whether lomustine alone or in combination with reirradiation offers superior overall survival, while also evaluating health-related quality of life and health economic outcomes.

At the time of publication of this review, patient enrollment is ongoing. Active participation of both patients and clinical centers is strongly encouraged, as enrolling patients into clinical trials remains a key recommendation in the NCCN guidelines for nearly all tumor types, emphasizing that the best available care is often within the context of a clinical trial.

A total of 411 adult patients with histologically confirmed IDH wild-type glioblastoma will be enrolled, regardless of MGMT promoter methylation status (which serves as a stratification factor). Eligible patients must have received standard first-line treatment (surgery followed by chemoradiotherapy with temozolomide) and present with first disease progression according to RANO criteria, occurring no earlier than 6 months after completion of prior radiotherapy. Additional inclusion criteria are the presence of a radiologically measurable lesion per RANO criteria with a maximum diameter of 5 cm and an ECOG performance status of 0–2 (Figs. 2 and 3).



Main characteristics of the EORTC-2227-BTG (LEGATO) trial [14•]. Summary of study design of LEGATO trial. Main inclusion, exclusion, and stratification criteria are listed. Patients are randomized to lomustine alone and lomustine + reirradiation arm.



Target definitions for reirradiation. Gross tumor volume, clinical target volume, and planning target volume for glioblastoma reirradiation as per EORTC-2227-BTG (LEGATO) trial. Data from [14▪].

Exclusion criteria include early progression (<6 months from prior radiotherapy), poor performance status (>2), or other significant contraindications to reirradiation or chemotherapy. Notably, patients who have undergone gross total resection of the recurrent lesion are also eligible. LEGATO is designed as a pragmatic clinical trial, aimed at addressing the question 'Does this treatment work in the real world?' as opposed to exploratory trials, which typically assess whether a treatment has the potential to work under ideal conditions [34] .

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SUMMARY OF LATEST REVIEWS

Given the increasing interest in glioblastoma reirradiation – reflected by the seminal publication of the first international consensus guidelines and the ongoing phase III LEGATO trial – numerous reviews have recently been published addressing this topic. In Table 1, we present a summary of the most relevant and influential reviews, serving as a curated selection for readers seeking further insight into glioblastoma reirradiation.

Table 1

Summary of current reviews focused on glioblastom reirradiation

All listed review articles are peer-reviewed, written in English, and focus on reirradiation in glioblastoma or high-grade gliomas. The selection includes publications indexed in PubMed between May 2024 and May 2025.

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CONCLUSION

Reirradiation has become an increasingly relevant option in the multidisciplinary management of recurrent glioblastoma, supported by improved radiotherapy techniques, refined patient selection, and emerging data on combination strategies. The recent publication of international ESTRO/EANO consensus guidelines and the launch of the EORTC-2227-BTG (LEGATO) phase III trial mark a turning point toward standardizing its use. Future research should focus on identifying predictive biomarkers for treatment response, optimizing integration with systemic agents, and evaluating novel approaches such as proton therapy or spatially fractionated regimens. As the field evolves, prospective trials and real-world data will be crucial to establish the clinical benefit of reirradiation in routine practice.

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Conflicts of interest

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Keywords:

glioblastoma; high-grade gliomas; LEGATO trial; reirradiation