Recurrent high-grade glioma treatment

- Profiling Glioma Stem Cell Dynamics via 3D-Based Cell Cycle Reporter Assays
- Modeling Glioma Stem Cell-Mediated Tumorigenesis Using Zebrafish Patient-Derived Xenograft Systems
- An In Vivo Model of Recurrent Glioblastoma
- Machine learning-driven SLC prognostic signature for glioma: predicting survival and immunotherapy response
- Development and validation of a deep learning algorithm for discriminating glioma recurrence from radiation necrosis on MRI
- Delivery of LOXL1-AS1-siRNAs using targeting peptide-engineered extracellular vesicles with focused ultrasound to suppress medulloblastoma metastasis
- Unlocking glioblastoma: breakthroughs in molecular mechanisms and next-generation therapies
- Independent histological validation of MR-derived radio-pathomic maps of tumor cell density using image-guided biopsies in human brain tumors

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see Recurrent Glioblastoma treatment.

Recurrent high-grade glioma, especially glioblastoma, remains one of the greatest challenges in neuro-oncology due to inevitable recurrence and limited therapeutic options.

General Principles

- Treatment must be individualized based on:
  - Age and functional status (KPS)
  - Time to recurrence (>6 months = better prognosis)
  - Tumor location and volume
  - Molecular markers (MGMT methylation, IDH status, etc.)

Treatment Options

1. Surgical Re-resection

- Recommended in patients with good KPS and accessible lesions
- Goals: reduce mass effect, obtain updated histology/molecular profile
- May improve overall survival in selected patients

2. Re-irradiation (re-RT)

- Techniques: hypofractionated RT, SRS, pulsed RT, proton therapy

- Indicated when recurrence occurs >6 months after initial RT and is focal
- Risk of radiation necrosis; may be reduced by adding bevacizumab

3. Systemic Therapy

Bevacizumab (BEV)

- Anti-VEGF monoclonal antibody
- Palliative effect: reduces edema and steroid need
- No proven OS benefit; improves PFS and symptoms

Chemotherapy

- Temozolomide rechallenge (if MGMT-methylated, long interval)
- Lomustine (CCNU) — modest benefit
- Combinations: BEV + lomustine (better PFS)
- Others: PCV, irinotecan, regorafenib (REGOMA trial)

Targeted Therapy

- Applicable in specific mutations (EGFR, BRAF, etc.)

4. Clinical Trials / Experimental Therapies

- Tumor Treating Fields (TTFields)
- Immunotherapy (PD-1 inhibitors – limited efficacy)
- Oncolytic viruses, CAR-T cells, vaccines
- Always consider clinical trial enrollment when available

Expected Outcomes

Treatment	Median OS (recurrence)	Comments
Surgery	9–12 months	Only for selected, high-functioning patients
Re-irradiation	6–10 months	Best if >6 months since initial RT
Bevacizumab alone	4–6 months	Improves symptoms, not OS
Lomustine	6–8 months	Modest benefit
BEV + lomustine	~9 months	↑PFS, unclear OS benefit
Clinical trial	Variable	Best option in qualified centers

Simplified Algorithm

1. **KPS ≥70, accessible lesion** → consider **surgical re-resection**

2. **Focal recurrence, >6 months from RT** → consider **re-RT ± BEV**
3. **Symptomatic edema or rapid progression** → consider **BEV ± chemo**
4. **Actionable mutations** → consider trials or targeted therapy
5. **Poor KPS, multiple recurrences** → palliative care, steroids

Systematic review and meta-analysis

In a systematic review and meta-analysis published in Therapeutic advances in neurological disorders of non-randomized, two-arm clinical trials comparing re-irradiation + bevacizumab versus bevacizumab alone in patients with recurrent high-grade gliomas (rHGG), aiming to demonstrate superiority in survival outcomes. Hammed et al. claim that the combination therapy improves overall survival (OS) and progression-free survival (PFS) without increasing grade ≥3 toxicity, and propose it as a potentially standard salvage approach [1].

 Critical Appraisal

1. Low-Level Evidence in Disguise

This is a meta-analysis based entirely on retrospective, non-randomized studies, with all the biases and heterogeneity that come with them. The use of ROBINS-I and II to “evaluate” these studies does not mitigate the inherent confounding by indication, selection bias, and lack of treatment standardization. The authors repeatedly conflate association with causation, ignoring the fact that hazard ratios in observational cohorts are not treatment effects.

2. Pooling Apples and Oranges

The methodology pools data across studies with wildly heterogeneous re-irradiation protocols (doses, volumes, pulsed vs. non-pulsed), variable use of BEV (dose, schedule), and differing baseline characteristics. Combining such studies and then reporting pooled HRs is statistical theater with no clinical applicability. Worse yet, subgroup analysis by age, gender, and performance status in this context becomes data dredging, not hypothesis testing.

3. Toxicity Reporting = Wishful Thinking

The authors claim no increase in grade 3 toxicity — without acknowledging that toxicity data are the weakest part of retrospective trials, often underreported and inconsistently graded. The meta-analysis fails to stratify by radiation volume or cumulative dose, which are critical in assessing toxicity in re-irradiation contexts.

4. Clinical Relevance? Minimal at Best

While the paper reports a statistically significant HR for OS (0.69), the absolute median survival gains are not reported. No mention is made of quality of life, neurocognitive outcomes, or steroid dependence, which are central in rHGG salvage treatment. Improving OS by a few weeks while ignoring the trade-offs is misleading at best and harmful at worst.

5. Prospective Trials? Good Luck

The authors end by calling for prospective trials — a noble gesture, but an empty one given that they

have already drawn definitive therapeutic conclusions. This dual messaging — “Here is the answer, but someone else should prove it” — is the hallmark of pseudo-precision medicine built on methodological sand.

 Final Verdict

This study offers an illusion of progress in recurrent high-grade glioma treatment. It recycles weak retrospective data through the statistical blender of meta-analysis and pours out hazard ratios that look impressive but mean very little. It is a classic case of overconfident conclusions from underpowered, heterogenous data.

Until proper randomized evidence emerges, clinicians should resist the temptation to treat these results as practice-changing. The paper is more editorial decoration than solid evidence.

References

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Hammed A, Al-Qiami A, Hasan A, Richter G, Zakria Alnajjar A, Rosenbauer J, Kostev K, Ismail O, Braun V, Tanislav C. Efficacy and safety of combining re-irradiation with bevacizumab compared to bevacizumab alone in the management of recurrent high-grade gliomas: a meta-analysis and systematic review. Ther Adv Neurol Disord. 2025 Jun 14;18:17562864251343574. doi: 10.1177/17562864251343574. PMID: 40529988; PMCID: PMC12171250.