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Reframing Radical Chemoradiation for High-Grade Glioma: The Iatrogenic Immunosuppression Bottleneck and the Case for a Lymphocyte-Sparing, Molecularly Stratified Backbone

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Abstract

Newly diagnosed high grade glioma has been treated with radical radiotherapy with concomitant and adjuvant temozolomide (the Stupp regimen) since 2005, but median overall survival has only had a marginal improvement over the last 20 years, and recurrence is close to universal [1, 3]. Meanwhile, immune checkpoint blockade has now revolutionized treatment in melanoma and lung cancer, but has not had any positive effect in any large randomized trials in glioblastoma [15,16,17]. The two facts are typically broken down as two distinct points. We believe that they are related. We propose that the standard chemoradiation backbone itself is a powerful and durable immunosuppressive intervention, and that the treatment-related lymphopenia is an iatrogenic immunosuppression bottleneck – once the effector lymphocytes that any immunotherapy requires to mobilize are depleted, it may undermine the efficacy of both itself and any agents added to it. The principal causes of lymphopenia (radiation doses to circulating blood and to lymphocyte-rich structures, size of the target volume, temozolomide alkylation, and corticosteroids) can all be modified and therefore lymphopenia should not be considered as an inevitable side effect, but rather a quantifiable, partially avoidable side effect associated with the treatment of the organ-at-risk. We combine the 2021 WHO molecular reclassification of grade 4 gliomas [4] and the radiobiology of treatment-related lymphopenia to establish a backbone of lymphocyte-sparing molecularly stratified chemoradiation, and to define a biomarker-stratified randomized trial with preserved absolute lymphocyte count as a co-primary endpoint with survival. If it's accurate, the framework is a 20-year-old standard that's no longer a platform on which drugs are simply dropped on, but one that can be adjusted so that the drugs can perform better.

Keywords: *High-Grade Glioma; Glioblastoma; Radiotherapy; Temozolomide; Treatment-Related Lymphopenia; Immunotherapy; MGMT; WHO CNS5*

Introduction

The high-grade gliomas, mainly glioblastoma (now known as an IDH-wildtype, CNS WHO grade 4 astrocytic tumor) and the closely related Grade 3/4 astrocytomas, continue to be some of the deadliest forms of human cancer [4]. Therapy has been pretty consistent. The standard therapy is fractionated focal radiation therapy with the maximum safe dose of 60 Gy in 30 daily 2 Gy doses for 6 weeks, with concomitant temozolomide (TMZ) given at 75 mg/m2 daily and adjuvant TMZ at 150-200 mg/m2 5 days a week for 6 cycles every 28 days [1]. This therapy has been the reference standard since 2005 and is the most widely used first-line therapy globally, due to the high cost and limited availability of the other treatment modality that has shown survival benefit (tumor-treating fields) worldwide [21].

This regimen was set by the pivotal EORTC 26981/22981 to NCIC CE.3 trial. The addition of TMZ to radiotherapy increased median OS from 12.1 to 14.6 months and the difference was most evident in the tail of the survival curve: two years' survival was increased from 10.4 to 26.5%, and five years' survival from 1.9% to 9.8% [1,3]. That finding changed the perspective on glioblastoma from an illness with at least a possibility of long-term survival, and it clearly marked the regimen as a building block to create new combinations that work better. After 20 years, the platform has proven to be hard to better. This review offers one hypothesis which is specific and testable for part of that stasis and one possible path for moving forward.

The rest of this paper is organized as follows. The hypothesis is supported by a review of the evidence base in Section 2 and the molecular and immunological literature in Section 3. The methodology of the narrative synthesis is described in Section 3. The synthesized results are then presented across efficacy, molecular stratification and treatment-related lymphopenia in section 4. The central hypothesis and the proposed lymphocyte-sparing framework and falsifiable trial design is developed in section 5. Section 6 outlines some limitations and caveats and Section 7 concludes.

Literature Review

The survival benefit is real but molecularly concentrated

The benefit in terms of survival from the use of TMZ is not uniform across patients. In a companion study of the pivotal trial, the base methylation of the DNA repair enzyme O6-methylguanine-DNA methyltransferase (O6-MGMT), which renders the repair enzyme inactive, and thus makes tumor cells sensitive to alkylation, proved to be the most important predictor of benefit [2]. Patients with methylated tumors saw significant improvement, but not those with an unmethylated MGMT promoter. The survival benefit of the TMZ treatment was significant in the methylated disease (13.5 vs 7.7 months) but not in the unmethylated disease (10.0 vs 7.9 months) [5]. Two implications follow. First, the status of MGMT is predictive and not just prognostic of the efficacy of TMZ. Second, in the large unmethylated subgroup, a considerable portion of the toxicity of concurrent TMZ might be given for a modest return of anti-neoplastic activity, which is the heart of the immunologic argument that follows.

Intensification has mostly disappointed; one combination did not

Tactics to increase the backbone have not been highly successful, except of one encouraging example. The addition of lomustine to TMZ in the molecularly favorable disease (the CeTeG/NOA-09 trial) improved median overall survival from 31.4 m to 48.1 m (HR 0.60, p 0.0492) in a small trial which authors encouraged caution over, and with added myelotoxicity [8]. The overarching lesson is still the same: benefits ensue when tumor biology allows; benefits from increased cytotoxicity, when there is no matched biological rationale, tend to be toxicity.

Age and frailty: less radiation, similar relative benefit

For older, frailer patients, hypofractionated radiotherapy (40 Gy in 15 fractions), combined with TMZ, preserves much of the benefit of the standard six-week course of TMZ, but reduces the treatment time [5]; earlier trials further confirmed the feasibility of TMZ alone in elderly patients with MGMT-methylated tumors. In addition to their practical benefit, these data have a little known underlying mechanistic message: shorter radiotherapy courses lead to fewer fractions of the circulating blood pool, and the potential immunologic consequences are discussed in Section 4.

The 2021 reclassification changes who we are treating

The population to which the Stupp regimen is applicable has changed completely with the new WHO classification of CNS tumors (CNS5) in 2021 [4]. IDH-mutant grade 4 astrocytic tumours

have now been separated from glioblastoma and are now known as astrocytoma, IDH-mutant, CNS WHO grade 4, which are a biologically and prognostically distinct entity. What is important is that IDH-wildtype diffuse astrocytic gliomas can now be diagnosed as glioblastoma without any signs of necrosis or microvascular proliferation, if they have TERT promoter mutation, EGFR amplification, or both (7q gain and 10p loss) [4]. Important parts of the historical evidence base, such as the landmark chemoradiation trials, were created in cohorts of patients that were largely grouped by older, partially histologic diagnostic criteria, in which we would now distinguish different entities. Any molecular stratification should then be done from the beginning in any modern framework for the backbone; and survival rates and even the size of TMZ benefit should be interpreted as "from a heterogeneous population."

Immune checkpoint blockade has failed consistently

Immune checkpoint blockade has been a disappoint in glioblastoma: nivolumab showed no effect on survival in recurrent disease (CheckMate-143) [15]; nivolumab did not add to survival in newly diagnosed MGMT-unmethylated disease (CheckMate-498) [16]; and nivolumab did not add to survival in MGMT-methylated disease (CheckMate-548) [17]. The intrinsic cold tumor microenvironment, low mutational burden, and the blood-brain barrier are commonly believed to be causes of these failures. The concurrent backbone has been underemphasized in the literature, and this review aims to develop a complementary, partly iatrogenic explanation: the concurrent backbone may exhaust the very effector lymphocytes that the checkpoint inhibitors need.

Methodology

Study design: This work represents a hypothesis generating review, conceptual synthesis. There is no original patient level data reported. The goal was to combine three distinct bodies of evidence: efficacy literature for the chemoradiation backbone, the 2021 WHO molecular reclassification, and radiobiology of treatment-related lymphopenia - into a single falsifiable framework.

Sources of evidence & evidence selection. The following peer-reviewed publications in the field of neuro-oncology and radiation-oncology literature were identified as primary randomized controlled trials, pivotal cohort studies, dosimetric modelling studies and the systematic review of the literature. Landmark Phase III trials defining the standard of care (Stupp/EORTC-NCIC, Perry, EF-14, CeTeG/NOA-09), the 3 major trials of "checkpoint-blockade" (CheckMate-143, -498, -548), and mechanistic and dosimetric studies quantifying radiation dose to circulating lymphocytes and the clinical predictors of acute severe lymphopenia were prioritized.

Synthesis approach: The evidence was appraised critically instead of quantitatively because they were not homogenous (across the 2021 reclassification boundary) and so formal meta-analysis is not possible. Results of the trials were summarized to reveal the molecular concentration of benefit and consistency of failure of immunotherapy. The actionable levers of the factors that modulate lymphopenia were identified from dosimetric and clinical-predictor studies. This synthesis led to a single mechanistic hypothesis, which then led to a design of a trial to test this hypothesis that was falsifiable and biomarker-stratified.

Reporting of figures: All figures referred to in this paper are based on information reported in the primary sources cited, not on simulations or re-analyses of the information, as per the transparency statement.

Results and Analysis

The landmark survival evidence

The pictures presented by the synthesis of landmark randomized trials are consistent (Table 1). The combination of TMZ with radiotherapy yielded a small absolute median survival benefit with a significant long-term survival "tail. Further additions to the backbone resulted in survival gains

only when tumour biology was favorable, notably the combination of lomustine and MGMT-methylation. Tumor-treating fields were used and resulted in survival benefit with significant access and adherence barriers.

Table 1. Landmark randomized trials of the high-grade glioma backbone and its augmentations. RT, radiotherapy; TMZ, temozolomide; TTFields, tumor-treating fields; GBM, glioblastoma; OS, overall survival.

Trial (year)	Population	Comparison	Median OS	Effect
Stupp / EORTC-NCIC (2005)	Newly dx GBM, ≤70 y	RT vs RT + TMZ	12.1 → 14.6 mo	2-y 10.4%→26.5%; 5-y 1.9%→9.8% [1,3]
Perry (2017)	Newly dx GBM, ≥65 y	Short-course RT ± TMZ	7.6 → 9.3 mo	HR 0.67; benefit largest if MGMT-meth [5]
EF-14 (2017)	Newly dx GBM, post-CRT	TMZ ± TTFields	16.0 → 20.9 mo	HR 0.63; device worn ≥18 h/day [21]
CeTeG/NOA-09 (2019)	Newly dx GBM, MGMT-meth	TMZ ± lomustine	31.4 → 48.1 mo	HR 0.60; small trial, caution [8]

The Benefit is Molecularly Concentrated

Analysis across trials shows that the amount of TMZ benefit is correlated with the level of MGMT promoter methylation. The absolute difference in survival between TMZ and the other arms was much greater in the methylated disease (13.5 months vs 7.7 months) than in the unmethylated disease (10.0 months vs 7.9 months) [5]. This gradient allows the use of MGMT status as a predictive factor, and suggests that the immunologic price of concomitant TMZ is ill worth the anticipated tumor benefit in the unmethylated group.

The Backbone Systematically Depletes Circulating Lymphocytes

One of the most radiosensitive cells in the body are lymphocytes, and a dose of the magnitude of 0.5 Gy is lethal for a significant number of lymphocytes [18]. Even if the tumour is targeted, the blood pool is continually being radiated, and modelling of dose to circulating lymphocytes has demonstrated that a conventionally fractionated, six week course of treatment will provide immunologically significant dose to a significant proportion of the radiated blood pool, and that this is enhanced as the number of fractions and the volume of blood irradiated is increased [10]. Temozolomide has a known lymphopenic and myelosuppressive effect [27] while the corticosteroids create a third immunosuppressive effect [9]. A fourth mechanism recently described is that of circulating myeloid-derived suppressor cells (MDSC), which actively contribute to lymphopenia, not only in a parallel manner, but as a direct mechanism of their own [13]. Changes in the lymphopoeia of the empirical footprint are consistent: CD4 T cells and B cells are targeted, and the process may take place in approximately 40% of patients within 2 months, but neutrophils or platelets are not targeted and can last a year or longer [9,24].

The Depletion is Prognostically Adverse, and the Drivers Are Modifiable

Lymphopenia is not an unremarkable laboratory parameter. In a study of multiple series and a systematic review, severe lymphopenia is a predictor of shorter overall survival in malignant

glioma and solid tumors overall [14,23,25]. In one large patient cohort with glioblastoma, acute severe lymphopenia was correlated with the median overall survival of 18.2 months compared to 22.0 months [12]. The most important and accessible point is that the magnitudes of the drivers correlate with parameters that the treatment team can control: larger planning target volumes (PTVs) correlate with severe lymphopenia, and intensity-modulated radiotherapy (IMRT) reduces the incidence of lymphopenia compared with 3D-conformal radiotherapy (20% vs 37% in propensity matched analysis) [12]; higher mean and minimum doses to the whole brain and higher maximum doses to the hypothalamus predict lymphopenia, as does the volume of normal brain receiving approximately 25 Gy [18,19]. The circulating compartment is explicitly modelled for emerging proton and ultra-high-dose-rate (FLASH) approaches, which are able to spare the circulating compartment [20].

Table 2. Modifiable drivers of treatment-related lymphopenia. Each is a lever already within the treating team's control. ASL, acute severe lymphopenia; WB, whole brain; HT, hypothalamus.

Modifiable driver	Direction of effect	Representative evidence
Planning target volume	Larger PTV → more lymphopenia	PTV independently predicts acute severe lymphopenia [12]
RT technique	IMRT < 3D-CRT	ASL 20% (IMRT) vs 37% (3D-CRT), matched [12]
Whole-brain dose	Higher Dmean/Dmin → more	WB Dmean ≥34 Gy, Dmin ≥2 Gy predict lymphopenia [18]
Hypothalamus dose	Higher Dmax → more	HT Dmax ≥56 Gy predicts lymphopenia [18]
Fractionation / dose rate	Fewer fractions, FLASH → less	Short-course RT and FLASH reduce blood dose [5,20]
Temozolomide	Alkylation → lymphopenia	Limited benefit if MGMT-unmethylated [2,27]
Corticosteroids	Higher exposure → more	Independent lymphodepleting effect [9]

The Immunotherapy Failures, Re-Examined

Placing the checkpoint-blockade results side by side exposes a strikingly uniform pattern of failure across recurrent and newly diagnosed settings and across MGMT strata (Table 3). This consistency is compatible with the hypothesis that a shared upstream factor, the immunosuppressive backbone delivered concurrently, constrains the efficacy of agents that depend on an intact effector lymphocyte pool.

Table 3. Major randomized immune checkpoint blockade trials in glioblastoma. The pattern of failure is consistent across settings and MGMT strata. OS, overall survival; PFS, progression-free survival.

Trial	Setting	Experimental arm	Outcome
CheckMate-143	Recurrent GBM	Nivolumab vs bevacizumab	No OS improvement [15]
CheckMate-498	Newly dx, MGMT-unmethylated	RT + nivolumab vs RT + TMZ	Did not meet OS endpoint [16]

Trial	Setting	Experimental arm	Outcome
CheckMate-548	Newly dx, MGMT-methylated	Chemoradiation + nivolumab	Did not meet PFS/OS endpoints [17]

Discussion

The Central Hypothesis: An Iatrogenic Immunosuppression Bottleneck

The overall evidence presented is synthesized to build a new thesis. The backbone is not immunologically neutral. It is a long-term, comprehensive suppression of the immune system and its lymphopenia is marked, chronic, an ominous and most significantly, clearly modifiable. We refer to this convergence as the iatrogenic immunosuppressive bottleneck: four modifiable factors (radiation dose to circulating blood, size of the target volume, alkylation of DNA by temozolomide and corticosteroid use) converge on treatment-induced lymphopenia, which is associated with poorer survival and may inhibit the effect of immunotherapies.

Why this Explains the Immunotherapy Failures

In this place, the two static stories meet. Checkpoint inhibitors remove the brakes on T cells but are ineffective against T cells which the concurrent backbone has already destroyed or put in prolonged deficit. Any checkpoint blockade treatment given during or immediately after a treatment that causes chronic CD4 lymphopenia is a pharmacodynamic mismatch, similar to applying the accelerator with the backboard keeping the engine from accelerating. Rather than a better immunotherapy, the most critical factor that could influence the success of future immunotherapies for glioblastoma may be a less immunosuppressive backbone that's administered in a more optimal sequence.

The Proposed Framework: Lymphocyte-Sparing, Molecularly Stratified Chemoradiation

Axis 1 — Treat the circulating immune compartment as an organ at risk. Axis 1 — Consider the circulating immune compartment an organ at risk. Use the smallest oncologically defensible target margins; default to highly conformal delivery (IMRT/VMAT, or proton therapy if available); include planning constraints for mean and minimum dose to the whole brain, maximum dose to the hypothalamus, and volume of normal brain receiving approximately 25 Gy; and use models of dose to circulating blood as a plan evaluation metric, rather than an afterthought [10,12,18,19]. When validated the hypofractionation and ultra-high-dose-rate delivery are levers to reduce cumulative blood dose [5,20].

Axis 2 — Match systemic cytotoxicity to tumor biology (CNS5-aware). Confirm IDH status and molecular glioblastoma markers first; explore concomitant and adjuvant TMZ if it is predictive (e.g. MGMT-methylated disease); and consider de-intensified or alternative systemic approaches in MGMT-unmethylated disease, which may be immunosuppressive, but have limited expected benefit [2,4,5]. Don't forget that IDH-mutant grade 4 astrocytoma is a unique disease and should not be treated on glioblastoma protocols [4].

Sequencing principle — protect, then provoke. Where immunotherapy is used in combination, consider scheduling immune stimulations when the immune system is not completely depleted (e.g. neoadjuvant, early windows) rather than adding immune stimulants to the point of maximum lymphopenia. Treatment options include reducing corticosteroid exposure and a longitudinal monitoring of absolute lymphocyte count as an important immune function parameter.

A Falsifiable Test of the Framework

If a framework is worth proposing, it's worth trying to refute. We describe a practical, biomarker stratified randomized study. Patients should be newly diagnosed, molecularly confirmed IDH-wildtype glioblastoma (CNS5 criteria), with good performance status, after maximal safe resection, and be stratified by MGMT methylation and extent of resection (EOR). Standard backbone (60 Gy/30 fractions, conventional margins, standard TMZ) versus a lymphocyte-sparing backbone (reduced margins with highly conformal or proton delivery, explicit circulating-blood dose constraints and whole-brain/hypothalamus dose constraints, protocolized corticosteroid minimization), and TMZ is delivered identically in both arms, so that the radiation/immune variable is isolated.

Primary Endpoints: overall survival, preservation of absolute lymphocyte count (no more than 3/4 grades of lymphopenia after 3 months). If there is a modest survival signal, a mechanistic endpoint can be paired with to either confirm or refute the mechanism. Key correlatives included serial immunophenotyping (CD4 and CD8 counts and subsets of B-cells, myeloid-derived suppressor cells), dosimetric reconstruction of dose to circulating blood, neurocognitive outcomes, and a pre-specified interaction between lymphocyte preservation and MGMT status. **Decision Logic:** confirmation would take the form of improvement (or at least non-worsening) in survival in the context of maintaining lymphocytes; a dissociation (worsening of survival from preservation of lymphocytes) would falsify the strong causal version of the hypothesis without compromising its utility in immunotherapy combinations. The power to shed is the characteristic of a good hypothesis.

Limitations and Honest Caveats

There are a number of caveats to temper this proposal. First, the association between treatment-related lymphopenia and survival is consistent and adjusted; however, association is not causation, as is the possibility that reverse causation (more aggressive, higher-volume disease results in larger fields and poorer survival) is plausible, and is exactly why the randomized test of radiation/immune is needed [14]. Second, reducing target margins should never jeopardize the coverage of the tumour; the framework is based on the premise that the size of the target margins will be reduced within the oncologically validated range and will be accompanied by high-quality imaging. Third, many basic survival data are prior to the 2021 reclassification, and they contain mixed entities, so effect sizes are carried over from prior trials, and should be interpreted with caution [4]. Fourthly, technologies that spare lymphocytes, like proton and FLASH delivery, are unevenly distributed and, for FLASH, still largely in the early stages of research [20]. Lastly, this article does not provide original patient information, but rather a hypothesis and a synthesis and its conclusions must be tested with prospective data.

Conclusion

The treatment of radical radiotherapy with temozolomide has been considered as a platform on which new agents should be attached for the past 20 years. We have suggested otherwise: It is an active immunological intervention, whose collateral, longterm lymphocytopenia, is severe, prognostically bad, presumably self-limited, and potentially controllable by choices currently within the treating team's control. This iatrogenic immunosuppression bottleneck provides a coherent explanation that is partially testable, of why immunotherapy has so far failed in a disease that, in principle, it may have a chance. The positive side of the corollary is that the biggest potential advancement in the near term for high-grade glioma could be a redesign of a familiar treatment that doesn't destroy the immune system it will require later.

References

Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352:987–996.

Hegi ME, Diserens A-C, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005;352:997–1003.

Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma (5-year analysis of the EORTC-NCIC trial). Lancet Oncol. 2009;10:459–466.

Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncology. 2021;23:1231–1251.

Perry JR, Laperriere N, O'Callaghan CJ, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med. 2017;376:1027–1037.

Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma (Nordic trial). Lancet Oncol. 2012;13:916–926.

Wick W, Platten M, Meisner C, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly (NOA-08). Lancet Oncol. 2012;13:707–715.

Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet. 2019;393:678–688.

Grossman SA, Ye X, Lesser G, et al. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. Clin Cancer Res. 2011;17:5473–5480.

Yovino S, Kleinberg L, Grossman SA, Narayanan M, Ford E. The etiology of treatment-related lymphopenia in patients with malignant gliomas: modeling radiation dose to circulating lymphocytes. Cancer Invest. 2013;31:140–144.

Huang J, DeWees TA, Badiyan SN, et al. Clinical and dosimetric predictors of acute severe lymphopenia during radiation therapy and concurrent temozolomide for high-grade glioma. Int J Radiat Oncol Biol Phys. 2015;92:1000–1007.

Rahman R, et al. Clinical predictors of radiation-induced lymphopenia in patients receiving chemoradiation for glioblastoma: clinical usefulness of intensity-modulated radiotherapy in the immuno-oncology era. Radiat Oncol. 2019;14:51.

Liu KX, et al. Radiation-induced circulating myeloid-derived suppressor cells induce systemic lymphopenia after chemoradiotherapy in patients with glioblastoma. Sci Transl Med. 2023;15:eabn6758.

Venkatesulu BP, Mallick S, Lin SH, Krishnan S. A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. Crit Rev Oncol Hematol. 2018;123:42–51.

Reardon DA, Brandes AA, Omuro A, et al. Effect of nivolumab vs bevacizumab in patients with recurrent glioblastoma: the CheckMate 143 phase 3 randomized clinical trial. JAMA Oncol. 2020;6:1003–1010.

Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter (CheckMate 498). Neuro-Oncology. 2023;25:123–134.

Lim M, Weller M, Idbaïh A, et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter (CheckMate 548). Neuro-Oncology. 2022;24:1935–1949.

Cao Y, et al. Dosimetry of the brain and hypothalamus predicting acute lymphopenia and the survival of glioma patients with postoperative radiotherapy. Cancer Med. 2019;8:6072–6082.

Onishi M, et al. The need for radiotherapy optimization for glioblastomas considering immune responses. Jpn J Radiol. 2023;41:1062–1071.

Galts A, et al. FLASH radiotherapy sparing effect on the circulating lymphocytes in pencil beam scanning proton therapy: impact of hypofractionation and dose rate. Phys Med Biol. 2024;69:025006.

Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma (EF-14): a randomized clinical trial. JAMA. 2017;318:2306–2316.

Schatz J, et al. Radiation immunodynamics in patients with glioblastoma receiving chemoradiation. Front Immunol. 2024;15:1438044.

Wang X, et al. Association between treatment-related lymphopenia and survival in glioblastoma patients following postoperative chemoradiotherapy. Strahlenther Onkol. 2022;198:172–181.

Campian JL, Piotrowski AF, Ye X, et al. Serial changes in lymphocyte subsets in patients with newly diagnosed high-grade astrocytomas treated with standard radiation and temozolomide. J Neurooncol. 2017;135:343–351.

Grossman SA, Ellsworth S, Campian J, et al. Survival in patients with severe lymphopenia following treatment with radiation and chemotherapy for newly diagnosed solid tumors. J Natl Compr Canc Netw. 2015;13:1225–1231.

Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and EANO consensus review on current management and future directions. Neuro-Oncology. 2020;22:1073–1113.

Sengupta S, Marrinan J, Frishman C, Sampath P. Impact of temozolomide on immune response during malignant glioma chemotherapy. Clin Dev Immunol. 2012;2012:831090.