cancers

MDPI

Review

Advances in Radiotherapy for Glioblastoma and IDH-Mutant High-Grade Astrocytoma: A Biological and Mechanistic Perspective

Fatemeh Fekrmandi * and Arnab Chakravarti

Department of Radiation Oncology, The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH 43210, USA
* Correspondence: fatemeh.fekrmandi@osumc.edu

Simple Summary

Glioblastoma and IDH-mutant high-grade astrocytomas are aggressive brain cancers that can recur despite surgery, radiation, and chemotherapy. This review examines how radiation damages tumor cells, why some cells resist treatment, and how normal-brain injury can affect cognition. These mechanisms inform newer approaches, including radiosensitizing drugs, immunotherapy combinations, electric-field therapy, proton beams, and adaptive treatment. Promising biological or dosimetric findings do not necessarily improve survival or long-term function. Future progress requires matching treatments to molecular features while protecting brain function, particularly in patients expected to survive for many years.

Abstract

Glioblastoma (GBM) and IDH-mutant high-grade astrocytoma remain therapeutically challenging. Historical GBM chemoradiation trials reported median overall survival of approximately 15–17 months; contemporary outcomes vary with molecular features, patient selection, and additional therapies. The 60 Gy in 30 fractions partial-brain regimen remains the reference standard for fit patients with newly diagnosed GBM. This narrative review examines radiotherapy based on its underlying biology, distinguishing GBM from IDH-mutant astrocytoma under the WHO molecular framework. It links DNA damage, cell-death programs, and radiation-induced immune signaling to the treatment response and DNA repair, stemness, hypoxia, and the microenvironment to resistance. These mechanisms motivate DNA-damage-response inhibitors, molecularly matched radiosensitizers, and immunotherapy combinations. Tumor treating fields are considered as an adjunctive non-ionizing modality. Proton therapy, FLASH, and MRI-guided adaptive radiotherapy are evaluated for their rationale and normal-tissue effects. Neurocognitive injury is discussed alongside the limitations of proposed hippocampal-sparing objectives. Personalization requires molecular selection and mechanism-matched treatment, with the clinical validation of benefits beyond dosimetry or imaging alone.

Keywords: glioblastoma; radiotherapy; radiation biology; radioresistance; glioblastoma stem cells; DNA damage response; radiosensitizers; tumor treating fields; radioimmunotherapy; neurocognitive preservation; FLASH radiotherapy

Check for updates

Academic Editor: Hans Christiansen

Received: 8 October 2026
Revised: 11 November 2026
Accepted: 16 November 2026
Published: 19 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

This review focuses on glioblastoma (GBM, WHO grade 4, IDH-wildtype) and IDH-mutant astrocytoma (WHO grades 3 and 4). GBM accounts for approximately half of

malignant primary brain tumors in adults, with median survival under two years in clinical-trial populations [1]. Population-based outcomes are generally poorer, whereas selected younger patients with MGMT-methylated tumors survive substantially longer [2]. The WHO 2021 framework uses molecular features including the IDH status, 1p/19q codeletion, and CDKN2A/B homozygous deletion to refine diagnosis and grading [3], with further refinements proposed by cIMPACT-NOW [4,5].

Postoperative radiotherapy improved survival in historical randomized malignant-glioma trials [6]. EORTC 26981-22981/NCIC CE.3 subsequently established concurrent and adjuvant temozolomide with focal radiotherapy (60 Gy in 30 fractions) for newly diagnosed GBM [7]. Persistent recurrence reflects diffuse infiltration, heterogeneous blood–brain barrier permeability, immunosuppression, and repair-competent stem-like cells. These barriers explain why improved delivery alone may be insufficient, without excluding contributions from the target definition and geometric uncertainty.

After summarizing current care, this review connects radiation response and resistance to radiosensitizers, immunotherapy combinations, adjunctive tumor treating fields, and normal-tissue sparing.

The clinical advances are evaluated against their mechanistic rationale: DNA repair inhibition to counter radioresistance, immunotherapy to exploit radiation-induced immune signaling, and delivery modifications to limit normal-tissue injury. Throughout, biological plausibility is distinguished from demonstrated clinical benefit.

This narrative review incorporates publications from 1980 to 2026, emphasizing contemporary clinical and mechanistic evidence alongside foundational trials, guidelines, trial registrations, and conference abstracts. During revision, targeted PubMed searches and primary-source checks were used to verify cited reports and trial attribution (updated 5 November 2026); this was not a systematic literature search.

2. Current Standard of Care: State of the Art

2.1. Newly Diagnosed Glioblastoma

The Stupp regimen remains standard for patients aged ≤70 years with a good performance status, improving the median overall survival from 12.1 to 14.6 months compared with radiotherapy alone in the pivotal 2005 trial (HR 0.63; $p < 0.001$); the benefit was more clearly demonstrated in MGMT promoter-methylated tumors, whereas its magnitude in unmethylated disease remains uncertain [7]. NCCN lists standard chemoradiation followed by adjuvant temozolomide with alternating electric field therapy as the preferred category 1 regimen. For younger patients with a good performance status, chemoradiation remains standard regardless of the MGMT status; radiotherapy alone is an option particularly for older or frail patients with unmethylated tumors or when chemotherapy is contraindicated [8]. The 2025 ASTRO guideline reinforces partial-brain fractionated radiotherapy [9]. The outcomes with radiotherapy alone in MGMT-unmethylated disease remain poor, motivating the radiosensitizer strategies in Section 3.9. See Table 1 for dose-fractionation regimens by clinical scenario.

Table 1. Dose-fractionation regimens by clinical scenario.

Scenario	Regimen	Systemic Therapy	Evidence and Clinical Status	Refs.
Newly diagnosed GBM, age ≤ 70 y, KPS ≥ 60	60 Gy/30 fx	TMZ 75 mg/m^2/d, then adjuvant	Standard of care; add TTFields during maintenance TMZ after chemoradiation (category 1)	[7,8,10]
Elderly, good performance status	40.05 Gy/15 fx	TMZ	Category 1 in age ≥ 65 y	[8,11]

Table 1. *Cont.*

Scenario	Regimen	Systemic Therapy	Evidence and Clinical Status	Refs.
Elderly, good performance status	34 Gy/10 fx	—	RT-alone regimen established; TMZ combination extrapolated	[8,12]
Older/frail, selected patients	25 Gy/5 fx	—	Abbreviated option when a longer course is unsuitable. RT alone; TMZ combination extrapolated	[8]
Poor performance status (KPS < 60)	Hypofx RT alone, TMZ alone, or supportive care	—	Individualized	[8]
IDH-mutant grade 3–4 astrocytoma	59.4–60 Gy/30–33 fx	Adjuvant TMZ ×12 cycles in grade 3; grade 4 individualized	Grade 3: CATNON-supported; concurrent TMZ did not demonstrate an OS benefit. Grade 4: extrapolated evidence	[13]
Reirradiation, selected recurrence	35 Gy/10 fx	Concurrent bevacizumab	RTOG 1205: PFS benefit versus bevacizumab alone; no demonstrated OS benefit	[14]
Reirradiation, macroscopic recurrence 1–6 cm	39 Gy/13 fx	—	Regimen used in the randomized GLIAA imaging-guidance trial; not a randomized comparison of reirradiation versus no reirradiation	[15]
Reirradiation, low-volume recurrence	16 Gy ×1, or 24–25 Gy/3–5 fx	± bevacizumab	ISRS-recommended for selected patients; predominantly non-randomized evidence; comparative toxicity advantage unproven	[16]
Recurrence + immunotherapy protocol	8 Gy ×3 (FSRT)	Anti-PD-1 ± GITR agonist	Investigational, neoadjuvant designs	[17]

Abbreviations: fx, fractions; Hypofx, hypofractionated; FSRT, fractionated stereotactic radiotherapy.

2.2. Elderly and Frail Patients

CE.6/EORTC 26062 established hypofractionated radiotherapy (40 Gy in 15 fractions) plus temozolomide over hypofractionated radiotherapy alone in patients aged ≥65 years (9.3 vs. 7.6 months; HR 0.67; $p < 0.001$), and the Nordic and NOA-08 trials made MGMT testing central to selection [11,12,18]. For selected older patients, 40.05 Gy/15 fractions with temozolomide has randomized evidence, whereas 34 Gy/10 fractions and 25 Gy/5 fractions are established RT-alone schedules; adding temozolomide to these shorter schedules is extrapolated [8,11,12]. Several ongoing trials relevant to older patients are attempting to close adjacent evidence gaps (Table 2).

2.3. IDH-Mutant High-Grade Astrocytoma

IDH-mutant astrocytomas (WHO grades 3 and 4) are biologically and clinically distinct from IDH-wildtype glioblastoma, with a younger age at onset, slower growth, and markedly longer survival, which shifts the therapeutic emphasis toward durable disease control with the minimization of late toxicity. Under the 2021 WHO classification, a CDKN2A/B homozygous deletion now defines grade 4 within IDH-mutant astrocytoma irrespective of histologic necrosis or microvascular proliferation, and this molecular grade carries independent prognostic weight relevant to radiotherapy decision-making [3].

Table 2. Selected ongoing and recently reported trials.

Identifier/Name	Phase	Population	Question	Ref.
NCT05781321 (SAGA)	2, randomized	Newly diagnosed adult GBM	Short-course versus standard-course RT with TMZ; 12-month OS non-inferiority; closed to accrual	CT.gov
NCT04752280 (GRIPS)	3	Newly diagnosed GBM	Proton versus photon RT; conventional or hypofractionated schedules; primary endpoint: grade ≥2 toxicity within 4 months	[19]
NCT04574856	2	Newly diagnosed GBM	Response-adaptive multiparametric MRI-guided dose intensification. Active, not recruiting	[20]
NCT05904119 (LEGATO)	3, randomized	First GBM progression	Lomustine with versus without reirradiation; OS endpoint; recruiting	CT.gov
NCT04555577	1	Newly diagnosed MGMT-unmethylated GBM	Peposertib + RT; window-of-opportunity expansion for intratumoral drug concentration	[21]

The final CATNON analysis, with a median follow-up of 10.9 years, confirmed that 12 cycles of adjuvant temozolomide significantly prolonged overall survival in 1p/19q non-codeleted, IDH-mutant anaplastic glioma (HR 0.54; $p < 0.0001$), with median overall survival of 12.5 years in the IDH-mutant subgroup receiving adjuvant temozolomide, whereas concurrent temozolomide did not demonstrate a statistically significant overall survival benefit (HR 0.81; $p = 0.09$ in IDH-mutant tumors) [13]. These findings establish radiotherapy followed by 12 cycles of adjuvant temozolomide as the postoperative standard for IDH-mutant grade 3 astrocytoma, without establishing a requirement for concurrent temozolomide in this population. The applicability to IDH-mutant grade 4 astrocytoma remains less certain: although CATNON included exploratory analyses of tumors with a CDKN2A homozygous deletion, now classified as grade 4, it was not designed to establish the optimal chemotherapy schedule across contemporary grade 4 disease. Treatment recommendations for this population therefore remain extrapolated from grade 3 astrocytoma and glioblastoma trials, and the role of concurrent temozolomide remains uncertain.

The dose and target principles for IDH-mutant grade 3–4 astrocytoma follow the high-grade template (59.4–60 Gy in 1.8–2.0 Gy fractions) [8]. For long-term survivors, late neurocognitive and neuroendocrine injury is an important consideration. However, the absence of prospective evidence demonstrating the inferiority of reduced-dose approaches does not establish their non-inferiority. Routine dose de-escalation remains investigational and requires prospective validation, with a separate evaluation of grade 3 and grade 4 disease and relevant molecular risk groups. In particular, favorable outcomes in selected grade 3 populations should not be extrapolated to grade 4 disease [3,8,22].

This rationale underlies the NCCN recommendation to consider proton therapy specifically for grade 3 IDH-mutant and 1p/19q codeleted tumors to spare the uninvolved brain. Prospective proton cohorts of IDH-mutant grade 2–3 glioma report preserved quality of life and stable-to-improved neurocognition at a long follow-up, but do not establish superiority over photon therapy [23,24]. Because grade 2 IDH-mutant astrocytoma and oligodendroglioma frequently transform to a higher grade, the timing of radiotherapy relative to chemotherapy and the cumulative brain dose budget across a patient's disease course are increasingly recognized as central management questions distinct from those in glioblastoma.

IDH-targeted therapy raises unresolved questions about the optimal sequencing and timing of radiotherapy, particularly in higher-grade disease. The biological rationale for combining or sequencing IDH inhibition with radiotherapy is not straightforward. Mutant IDH produces the oncometabolite 2-hydroxyglutarate, which remodels the epigenome and, in preclinical work, impairs homologous-recombination repair, suggesting that IDH-mutant tumors may be relatively radiosensitive and raising the concern that pharmacologic IDH inhibition could paradoxically restore repair capacity and blunt radiosensitivity if given concurrently [25]. Whether IDH inhibitors are best used to defer radiotherapy in lower-grade disease or integrated with it in higher-grade disease is therefore an unresolved sequencing question with direct radiobiological stakes.

2.4. Treatment Planning Principles

Planning uses post-contrast T1-weighted MRI to delineate the enhancing tumor and the resection cavity, with T2/FLAIR informing assessments of non-enhancing disease. In IDH-mutant grade 3 astrocytoma, tumor-related T2/FLAIR abnormalities are included in the GTV, excluding changes attributed to edema; in GBM, their incorporation depends on the delineation protocol. A protocol-specific GTV-to-CTV expansion (typically 1–2 cm) accounts for microscopic disease and respects anatomical barriers; a CTV-to-PTV margin (typically 3–5 mm) accounts for geometric uncertainty and depends on immobilization and image guidance [8,9]. The optic apparatus, brainstem, cochleae, hippocampi, pituitary, and lenses are contoured with constraints, per Table 3. The conventional 1.5–2 cm expansion is derived from historical pathologic and recurrence-pattern data, but it has been challenged by evidence that most recurrences arise within the high-dose region regardless of the margin width and by adaptive and reirradiation datasets suggesting that smaller margins do not obviously worsen local control while meaningfully reducing the irradiated normal brain [9,26,27].

Table 3. Organs at risk: dose constraints and proposed sparing objectives.

Structure	De Novo Constraint/Planning Objectives (Conventional Fractionation)	Reirradiation: Candidate Cumulative EQD2 ($\alpha/\beta = 2$ Gy)	Refs.
Optic nerves/chiasm	Dmax ≤ 54 Gy	75–80 Gy	[8,9,26]
Brainstem	Dmax ≤ 54–60 Gy	85–100 Gy	[8,9,26]
Normal brain	Minimize V60Gy; no universal volume threshold established	100–110 Gy possibly reasonable; large-volume constraints undefined	[26,27]
Any brain tissue (radionecrosis endpoint)	—	>120–130 Gy associated with necrosis (ISRS; $p = 0.003$)	[16]
Hippocampus (left)	Mean ≤ 30 Gy: proposed objective, not validated for adult high-grade glioma; prioritize tumor coverage	Not defined	[28,29]
Cochlea	Mean ≤ 35–45 Gy	Not defined	[9]
Lens	Dmax as low as achievable (<7 Gy)	Not defined	[9]
Pituitary	Mean as low as achievable	Not defined	[9]

Note: Hippocampal and normal-brain sparing objectives are not validated toxicity thresholds. Candidate reirradiation values represent the cumulative maximum or near-maximum EQD2 across both courses ($\alpha/\beta = 2$ Gy), without assumed tissue recovery. Source studies used heterogeneous point or small-volume dose metrics; these estimates are not interchangeable or validated tolerance limits [26].

3. Recent Advances

3.1. Molecular Mechanisms of Radiotherapy Treatment Effect

Ionizing radiation induces DNA double-strand breaks and oxidative damage, engaging apoptosis, mitotic catastrophe, necrosis/necroptosis, ferroptosis, pyroptosis, senescence, and autophagy-related responses according to the cellular context, oxygenation, dose, and fractionation [30,31]. Cytosolic DNA can activate cGAS–STING–TBK1–IRF3 signaling, type I interferon production, dendritic cell recruitment, antigen presentation, and T cell priming [32,33]. Calreticulin exposure, HMGB1 release, and extracellular ATP can promote an in situ vaccination effect, although clinical efficacy in GBM remains unproven [34]. In preclinical models, doses above approximately 12–15 Gy per fraction can induce TREX1, degrading cytosolic DNA and attenuating STING signaling. This model-dependent threshold has not been clinically validated and should not determine patient fractionation schedules [35]. These pathways motivate radioimmunotherapy while also engaging counter-regulatory immunosuppression.

3.2. Radiotherapy Treatment Resistance

Near-universal local recurrence reflects intrinsic and adaptive radioresistance, although target delineation and geometric uncertainties may also contribute. Glioblastoma stem-like cells (GSCs) are central: they exhibit constitutive DNA-damage-response activation driven by high replication stress, preferential checkpoint engagement through CHK1/CHK2 and ATM/ATR, and enhanced homologous-recombination repair via RAD51, allowing the efficient repair of radiation-induced breaks before division [36,37]. This enhanced repair capacity is a therapeutic vulnerability—combined ATR/PARP or ATM inhibition abrogates GSC radioresistance in preclinical models, providing direct rationale for the DNA-damage-response inhibitors in Section 3.9. Critically, stemness is not a fixed, cell-intrinsic property but is actively maintained by the tumor microenvironment: the hypoxic, particularly perinecrotic, niche stabilizes HIF-1α, sustains self-renewal, and reduces the oxygen-dependent fixation of radiation damage [38]; extracellular-matrix stiffness and integrin signaling reinforce a stem-like, radioresistant state; and bidirectional crosstalk with tumor-associated macrophages and microglia supplies pro-survival and immunosuppressive cues [39]. This niche-driven, plastic view of resistance implies that durably radiosensitizing GBM may require disruption of the microenvironment, as well as the repair machinery. Additional adaptive strategies include therapy-induced proneural-to-mesenchymal transition, tumor microtube-mediated intercellular networking, blood–brain barrier remodeling with efflux-transporter upregulation, and an immunosuppressive myeloid compartment [39].

3.3. Dose Escalation: Imaging-Guided Strategies

The randomized SPECTRO GLIO trial found no survival benefit from MRSI-guided escalation to 72 Gy (median OS 22.2 versus 22.6 months) [40]. Diffuse infiltration and heterogeneous resistance may limit focal intensification, but the negative trial does not exclude other imaging-guided strategies. Multiparametric MRI-defined hypercellular/hyperperfused boost volumes with mid-treatment adaptive replanning remain under evaluation (NCT04574856) [20,41].

3.4. Proton Beam Therapy

Protons reduce the integral dose to the uninvolved brain through the Bragg peak, although the entrance dose, range uncertainty, and secondary radiation remain relevant. Planning conventionally assumes an RBE of 1.1, rather than a fixed biological value [42,43]. In a secondary analysis of a randomized proton-versus-IMRT trial, grade ≥ 3 lymphopenia was less frequent with protons (14% versus 39%; $p = 0.024$) [44]; preclinical work also

supports immune-sparing effects [45]. However, preventing lymphopenia has not been shown to improve survival. A systematic review of eight studies (310 patients) reported stable or improved cognition after protons, but non-randomized designs and selection bias limit comparative inferences [46]. Prospective lower-grade and IDH-mutant cohorts likewise report stable cognitive and quality-of-life outcomes without establishing superiority over photons [23,24]. NCCN supports the consideration of protons in selected favorable-prognosis gliomas to spare the uninvolved brain [8].

A randomized phase 2 GBM trial found fewer adverse events and less fatigue with protons but no statistically significant difference in the time to cognitive failure or survival [43]. A single-arm study of older patients reported encouraging outcomes with short-course protons incorporating 18F-DOPA PET and MRI targeting, but historical comparisons cannot establish superiority [42]. Further studies include SAGA (NCT05781321; short-course versus standard-course RT), GRIPS (NCT04752280; protons versus photons) [19], and PRIDE (5-year functional survival in favorable-prognosis primary brain tumors) [47]. A systematic review reports acceptable toxicity and dosimetric advantages with charged particles, without establishing comparative survival benefit [48].

3.5. Tumor Treating Fields

EF-14 randomized patients with supratentorial GBM, KPS ≥ 70, and no progression after chemoradiation to maintenance TMZ with or without TTFields. Median overall survival from randomization was 20.9 versus 16.0 months (HR 0.63), supporting a benefit in this selected population [10]. Subgroup and pooled analyses support the consistency of the survival findings [49,50]. Although TTFields does not use ionizing radiation, it is included as an adjunct to the chemoradiation treatment pathway and for its potential mechanistic interactions with radiotherapy [51].

Proposed TTFields mechanisms include mitotic disruption, impaired DNA repair, altered motility and membrane permeability, and immune stimulation, motivating combination studies [51,52]. Greater device usage is associated with longer survival, but usage comparisons are observational. Daily wear (commonly targeted at ≥18 h), scalp toxicity, the cosmetic and psychosocial burden, and costs can limit uptake [51].

3.6. FLASH Radiotherapy

FLASH-RT delivers therapeutic doses at ultra-high average dose rates (commonly ≥40 Gy/s), but the normal-tissue-sparing FLASH effect also depends on the total dose, delivery time, and pulse structure—including the dose per pulse, pulse width, and repetition frequency—rather than the average dose rate alone [53–55]. For example, a preclinical electron-FLASH glioblastoma study used 1.8 µs pulses, delivering up to 14 Gy per pulse in one or two pulses, with a 100 Hz repetition frequency for two-pulse delivery; these are experimental settings, not established clinical requirements [53].

In orthotopic glioblastoma, hypofractionated FLASH was isoefficient with a conventional dose rate for growth delay, while sparing learning and memory, and cured immunocompetent animals developed durable antitumor immunity [53,54]. The proposed mechanisms, still unresolved, include transient radiolytic oxygen depletion, a reduced peroxyl-radical burden with NRF2-mediated antioxidant signaling, preserved mitochondrial integrity in non-malignant cells, reduced persistent DNA damage, and blunted inflammatory and immune-cell depletion [55].

A treatment-planning study found no net normal-tissue sparing for the evaluated GBM plans, suggesting that modeled FLASH benefits may be offset by the hypofractionated schedules examined. These findings depend on the planning assumptions and do not

establish a general limitation of intracranial FLASH [56]. Beam control, dosimetry, and clinical translation remain challenging; FLASH remains preclinical for glioma.

3.7. Reirradiation for Recurrent Disease

Reirradiation is considered for selected recurrent GBM patients after a multidisciplinary assessment of the performance status, tumor size and location, interval from prior RT, cumulative dose, and available alternatives [8,9]. ASTRO conditionally supports several reirradiation techniques and concurrent bevacizumab in selected settings; an interval of at least six months is commonly used [9].

NRG Oncology/RTOG 1205 randomized 170 eligible patients with recurrent GBM progressing ≥6 months after chemoradiation to reirradiation (35 Gy in 10 fractions) with concurrent bevacizumab versus bevacizumab alone [14]. There was no overall survival benefit (median 10.1 vs. 9.7 months; HR 0.98), but progression-free survival improved (7.1 vs. 3.8 months; HR 0.73; $p = 0.05$), with six-month PFS rising from 29.1% to 54.3% ($p = 0.001$). Acute grade ≥3 treatment-related events occurred in 5%, with no delayed high-grade events [14]. GLIAA/NOA-10 compared FET-PET- versus MRI-guided reirradiation using 39 Gy/13 fractions, without improved PFS (4.0 versus 4.9 months). The regimen showed manageable toxicity in selected patients: grade 3–4 radionecrosis occurred in 8% versus 7%, respectively, with no treatment-related deaths [15].

For low-volume recurrence, ISRS practice guidelines are derived from a PRISMA-compliant meta-analysis of 62 studies and 2640 patients, with recommendations based on Delphi methodology [16]. Single-fraction radiosurgery to a median 16 Gy was used in 75% and hypofractionated radiosurgery (2–5 fractions; median 25 Gy in 5) in 25%. Median overall survival from reirradiation was 10.2 months, and pooled neurological toxicity was 4% with hypofractionated versus 7% with single-fraction treatment ($p = 0.001$); this non-randomized comparison does not establish a causal toxicity reduction [16]. ISRS recommends 16 Gy in one fraction or 24–25 Gy in 3–5 fractions as safe and apparently effective, while cautioning that limited prospective data preclude definitive conclusions [16].

Cumulative tolerance remains uncertain. ReCOG reviewed 27 studies with heterogeneous constraints; no included study used tissue recovery factors, and no clear relationship between cumulative constraints and radionecrosis emerged [26]. The candidate cumulative maximum or near-maximum EQD2 limits ($\alpha/\beta = 2$ Gy) were 75–80 Gy for optic pathways and 85–100 Gy for the brainstem; 100–110 Gy for the normal brain was considered potentially practicable, with larger-volume constraints undefined [26]. ISRS identified an association between a cumulative EQD2 above 120–130 Gy and radionecrosis [16]. These estimates are derived from different endpoints and largely retrospective datasets and are not interchangeable. A secondary RTOG 0525 analysis associated salvage treatment with longer survival, but treatment selection limits a causal interpretation [57].

3.8. Immunotherapy–Radiotherapy Combinations

Radiation-induced immune signaling provides a rationale for checkpoint combinations [32,35], but GBM has a myeloid-dominant microenvironment, T cell dysfunction, heterogeneous blood–brain barrier permeability, and treatment-related lymphopenia that can limit the response [39,45]. A Cochrane review found no established clinical benefit from nivolumab-based strategies across the evaluated GBM settings [58]. A phase 2 multi-arm study evaluated retifanlimab (anti-PD-1) and INCAGN01876 (GITR agonist), with or without neoadjuvant stereotactic RT (8 Gy × 3). A small, exploratory, non-randomized comparison associated RT addition with longer PFS (11.7 versus 2.0 months) and OS (20.1 versus 9.4 months), requiring confirmation rather than establishing a benefit [17].

3.9. Radiosensitizers and Molecularly Targeted Agents

Given the uncertain magnitude of temozolomide benefits in MGMT-unmethylated glioblastoma and the role of DNA-damage-response pathways in GSC radioresistance (Section 3.2), DDR inhibitors are a biologically motivated investigational radiosensitizer class [39]. A phase 1 trial of the DNA-PK inhibitor peposertib with radiotherapy in newly diagnosed MGMT-unmethylated glioblastoma reported preliminary safety and survival findings in a conference abstract, including grade 3 radiation necrosis and scalp dermatitis. Survival estimates from this small, uncontrolled dose-escalation study do not establish the clinical benefit. Exploratory associations involving baseline and acquired DDR-gene mutations do not demonstrate on-target causality [21]. The PARADIGM phase 1 trial established the feasibility of concurrent olaparib with radiotherapy in older patients but was not designed to establish efficacy [59].

The NCT Neuro Master Match (N2M2) phase 1/2a umbrella trial (228 patients) met its prespecified efficacy endpoint only in the temsirolimus arm among patients with activated mTOR signaling (6-month PFS 39.1%, compared with 18.5% in the standard-of-care group; median overall survival in the temsirolimus arm was 15.4 months). The temsirolimus comparison was non-randomized and does not establish a survival benefit. Atezolizumab, asunercept, and palbociclib did not meet their efficacy endpoints; two arms never opened for a lack of matching patients, and idasanutlin closed early. No relevant adverse interaction with concurrent radiotherapy was identified [60]. Biomarker-matched RT trials face spatial and temporal heterogeneity, limited tissue, difficulty distinguishing predictive from prognostic markers, and fragmented accrual across small molecular subgroups [60].

Platinum-based agents, additional PARP inhibitors, and nanoparticle radiosensitizers engineered for blood–brain barrier penetration remain in preclinical and early clinical development [61]. The unifying theme is biomarker-matched radiosensitization, which now requires randomized confirmation.

3.10. Post-Radiotherapy Neurocognitive Effects

Cognitive impairment reflects tumor effects, progression, and treatment; radiation-related deficits vary in timing, severity, and reversibility and affect memory, attention, and processing speed [62,63]. The fraction size and survival horizon influence late-toxicity considerations [62,64]. Mechanisms include injury to hippocampal and subventricular neural progenitors, chronic microglial inflammation, oligodendrocyte-precursor loss and demyelination, and microvascular injury with blood–brain barrier disruption [62,64,65]. These mechanisms motivate sparing, but the clinical benefit requires validation.

Prospective data suggest hippocampal dose–response relationships but do not establish universal constraints for adult high-grade glioma. A mature prospective study of young patients with benign or low-grade brain tumors proposed a mean left-hippocampal dose $\leq$30 Gy to limit intelligence quotient decline [28]. A dosimetric analysis of a randomized GBM fractionation trial associated a higher mean left-hippocampal dose with a Mini-Mental State Examination decline ($p = 0.005$), with automated replanning reducing that dose by 43% without compromising coverage [29]; a prospective cohort showed that hippocampal and subventricular-zone sparing was feasible without progression in spared regions [66]. These findings support individualized sparing objectives rather than validated avoidance thresholds. Adequate tumor coverage must take priority, particularly when infiltrative disease involves these regions. Expected survival and molecular prognosis should inform the emphasis on late toxicity, with greater relevance for long-term survivors of IDH-mutant disease.

Dose-dependent cortical thinning also occurs in vulnerable regions, including entorhinal and inferior parietal cortices [67]. Cognitive preservation strategies include dose-sparing

delivery and supportive interventions; memantine evidence primarily comes from the brain-metastasis setting.

3.11. Adaptive Radiotherapy and Emerging AI Applications

AI applications include auto-segmentation and workflow support, for which NRG Oncology emphasizes clinical validation and quality assurance [68]. These applications are distinct from MRI-guided adaptation, which does not inherently require AI; evidence that AI itself improves glioma outcomes remains limited.

The single-arm phase 2 UNITED trial evaluated weekly MRI-guided adaptive radiotherapy using a 5 mm CTV margin, with marginal failure as its primary endpoint. It did not establish survival or neurocognitive superiority over conventional treatment [27].

MR-guided adaptation can reduce the normal-tissue dose and accommodate anatomical change, but improvements in clinical toxicity, long-term neurocognition, and survival remain unproven. Resource demands include longer treatment sessions, repeated contouring and replanning, and limited platform access. Response-adaptive dose intensification and anatomical replanning address different hypotheses; the AI integration of multimodal imaging remains a development goal rather than validated biological target selection [69].

3.12. Hypofractionation: Expanding Indications

A randomized high-grade glioma study of a moderately hypofractionated simultaneous integrated boost versus standard IMRT reported no significant PFS or OS advantage [70]. Direct comparisons of abbreviated versus six-week chemoradiation remain limited in patients older than 70 years [8]. The performance status, tumor volume, travel burden, and patient preference therefore remain important alongside comparative evidence; selected trials are summarized in Table 2.

4. Integrating Advances: Toward Personalized Radiotherapy

Personalization links molecular classification, resistance mechanisms, and normal-tissue injury. Each can inform the treatment design, but clinical validation determines whether a biologically attractive strategy should enter routine care.

The IDH status informs prognosis and systemic treatment, while proton selection also depends on expected survival, the location, comparative dosimetry, and access. A CDKN2A/B homozygous deletion refines IDH-mutant grading, and MGMT methylation informs expectations of TMZ benefits [3,13]. DDR inhibition is an investigational strategy for repair-mediated resistance, particularly in MGMT-unmethylated GBM; early peposertib and N2M2 signals require confirmation [21,39,60]. Radiation-induced immune signaling similarly supports combination studies without establishing efficacy or a clinically validated TREX1 fraction-size threshold [17,32,35].

The mechanisms of cognitive injury provide biological targets for normal-tissue sparing, but do not convert exploratory dose objectives into validated constraints [62].

Protons, adaptation, and AI-assisted planning can improve aspects of the dose distribution or workflow, but are supported by different evidence levels. Protons reduced lymphopenia in a trial-derived analysis [44]; long-term cognitive and survival advantages remain unproven. Long survival in CATNON's IDH-mutant subgroup receiving adjuvant TMZ underscores the importance of late toxicity, without itself validating a sparing technique [13]. TTFields has randomized survival evidence after chemoradiation, whereas the additional benefit from concurrent RT or immunotherapy combinations remains unresolved [10,50,52].

SPECTRO GLIO and GLIAA did not meet their primary endpoints, but their findings apply to the tested strategies and do not exclude other imaging-guided or adaptive

approaches [15,40]. Advanced imaging can supplement MRI for selected targeting and response questions without necessarily improving clinical outcomes [42].

Future studies should integrate molecular selection, mechanism-matched radiosensitization, and normal-tissue sparing, evaluating imaging and geometric refinements against clinical endpoints. Conventional 60 Gy/30-fraction RT remains the reference for fit patients with newly diagnosed GBM.

5. Conclusions

Radiotherapy remains indispensable in the multimodal management of malignant gliomas, and the past decade has produced substantial technical and biological advances. TTFields has expanded maintenance treatment options after chemoradiation but is an adjunctive non-ionizing modality rather than an advance in radiotherapy itself; its real-world impact remains tempered by the adherence demands, dermatologic toxicity, device burden, and contested cost-effectiveness. Evidence varies across approaches: randomized trials inform proton therapy and selected reirradiation regimens, whereas hippocampal-sparing and MR-guided adaptation rely mainly on single-arm studies and dosimetric or observational analyses. These data do not establish consistent survival or long-term cognitive advantages. The 2005 backbone of 60 Gy in 30 fractions to a partial-brain volume remains the reference against which every innovation is measured, and none has displaced it.

Diffuse infiltration, immunosuppression, heterogeneous drug access, and hypoxic or repair-competent stem-like populations remain barriers to durable control. Delivery improvements may help address some treatment limitations, but should not be assumed to overcome all biological resistance mechanisms.

Negative trials should refine future hypotheses rather than exclude entire technologies. Randomized confirmation, appropriate molecular stratification, and patient-centered endpoints are needed to determine which innovations improve outcomes.

Author Contributions: Conceptualization, F.F. and A.C.; writing—original draft preparation, F.F.; writing—review and editing, F.F. and A.C.; visualization, F.F.; supervision, A.C. All authors have read and agreed to the published version of the manuscript.

Funding: Research was supported by The Ohio State University Comprehensive Cancer Center in addition to the following funding sources R01CA108633 (A.C.), 1R01CA169368 (A.C.), 1RC2CA148190 (A.C.), National Cancer Institute grant number U10CA180850-01 (A.C.), The Brain Tumor Funders Collaborative Grant (A.C.), and in-kind grants by Varian.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Schaff, L.R.; Mellinghoff, I.K. Glioblastoma and Other Primary Brain Malignancies in Adults: A Review. *JAMA* **2023**, *329*, 574–587. [CrossRef] [PubMed]
2. Chen, J.; Boldig, C.M.; Wu, Q.; Cardenas, H.M.; Bernard, K.N.; Darko, K.; Grogan, P.T.; Sun, Y.; Macaulay, R.J.; Fonkem, E.; et al. Trends in Treatment and Survival Among Patients with Glioblastoma in the United States from 2000 to 2020. *Cancers* **2026**, *18*, 2780. [CrossRef] [PubMed]
3. Bent, M.J.V.D.; Geurts, M.; French, P.J.; Smits, M.; Capper, D.; Bromberg, J.E.C.; Chang, S.M. Primary brain tumours in adults. *Lancet* **2023**, *402*, 1564–1579. [CrossRef] [PubMed]
4. Wesseling, P.; Capper, D.; Reifenberger, G.; Sarkar, C.; Hawkins, C.; Perry, A.; Kleinschmidt-DeMasters, B.; Komori, T.; Paulus, W.; Santosh, V.; et al. CIMPACT—NOW update 11: Proposal on adaptation of diagnostic criteria for IDH—And H3 -wildtype diffuse high-grade gliomas and for posterior fossa ependymal tumors. *Brain Pathol.* **2025**, *36*, e70035. [CrossRef] [PubMed]

5. Brat, D.J.; Aldape, K.; French, P.J.; Louis, D.N.; Nasrallah, M.P.; Reifenberger, G.; E Reuss, D.; Touat, M.; Bent, M.J.V.D.; Wesseling, P.; et al. CIMPACT-NOW update 12: Refining Pathology-based Risk Stratification and Grading for IDH-mutant Gliomas. *Neuro-Oncology* **2026**, *28*, 2069–2089. [CrossRef] [PubMed]
6. Walker, M.D.; Green, S.B.; Byar, D.P.; Alexander, E.J.; Batzdorf, U.; Brooks, W.H.; Hunt, W.E.; MacCarty, C.S.; Mahaley, M.S.J.; Mealey, J.J.; et al. Randomized Comparisons of Radiotherapy and Nitrosoureas for the Treatment of Malignant Glioma after Surgery. *N. Engl. J. Med.* **1980**, *303*, 1323–1329. [CrossRef] [PubMed]
7. Stupp, R.; Mason, W.P.; van den Bent, M.J.; Weller, M.; Fisher, B.; Taphoorn, M.J.B.; Belanger, K.; Brandes, A.A.; Marosi, C.; Bogdahn, U.; et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *N. Engl. J. Med.* **2005**, *352*, 987–996. [CrossRef] [PubMed]
8. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers*; Report No.: Version 2.2026; National Comprehensive Cancer Network: Plymouth Meeting, PA, USA, 2026.
9. Yeboa, D.N.; Braunstein, S.E.; Cabrera, A.; Crago, K.; Galanis, E.; Hattab, E.M.; Heron, D.E.; Huang, J.; Kim, M.M.; Kirkpatrick, J.P.; et al. Radiation Therapy for WHO Grade 4 Adult-Type Diffuse Glioma: An ASTRO Clinical Practice Guideline. *Pract. Radiat. Oncol.* **2025**, *15*, 451–471. [CrossRef] [PubMed]
10. Stupp, R.; Taillibert, S.; Kanner, A.; Read, W.; Steinberg, D.; Lhermitte, B.; Toms, S.; Idbaih, A.; Ahluwalia, M.S.; Fink, K.; et al. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. *JAMA* **2017**, *318*, 2306–2316. Erratum in *JAMA* **2018**, *319*, 1824. https://doi.org/10.1001/jama.2018.3431. [CrossRef] [PubMed]
11. Perry, J.R.; Laperriere, N.; O'cAllaghan, C.J.; Brandes, A.A.; Menten, J.; Phillips, C.; Fay, M.; Nishikawa, R.; Cairncross, J.G.; Roa, W.; et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. *N. Engl. J. Med.* **2017**, *376*, 1027–1037. [CrossRef] [PubMed]
12. Malmström, A.; Grønberg, B.H.; Marosi, C.; Stupp, R.; Frappaz, D.; Schultz, H.; Abacioglu, U.; Tavelin, B.; Lhermitte, B.; E Hegi, M.; et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. *Lancet Oncol.* **2012**, *13*, 916–926. [CrossRef] [PubMed]
13. Bent, M.J.V.D.; A Ghisai, S.; Wick, W.; Sanson, M.; Brandes, A.A.; Clement, P.M.; Erridge, S.C.; A Vogelbaum, M.; Nowak, A.K.; Baurain, J.-F.; et al. Concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): Final and exploratory analyses of a randomised, open-label, phase 3 trial. *Lancet Oncol.* **2025**, *27*, 45–56. [CrossRef] [PubMed]
14. Tsien, C.I.; Pugh, S.L.; Dicker, A.P.; Raizer, J.J.; Matuszak, M.M.; Lallana, E.C.; Huang, J.; Algan, O.; Deb, N.; Portelance, L.; et al. NRG Oncology/RTOG1205: A Randomized Phase II Trial of Concurrent Bevacizumab and Reirradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma. *J. Clin. Oncol.* **2023**, *41*, 1285–1295. [CrossRef] [PubMed]
15. Grosu, A.-L.; A Weber, W.; Graf, E.; Mix, M.; Nestle, U.; Schimek-Jasch, T.; Wiehle, R.; Mader, I.; Würtemberger, U.; Langen, K.-J.; et al. O-(2-[18F]fluoroethyl)-L-tyrosine-PET-guided versus contrast-enhanced T1-weighted MRI-guided re-irradiation in patients with recurrent glioblastoma (GLIAA/NOA-10 ARO2013-01): A multicentre, open-label, randomised trial. *Lancet Oncol.* **2025**, *27*, 169–180. [CrossRef] [PubMed]
16. Pinzi, V.; Kotecha, R.; Sahgal, A.; Gorgulho, A.; Lim-Fat, M.J.; Levivier, M.; Ma, L.; Paddick, I.; Regis, J.; Sheehan, J.P.; et al. International Stereotactic Radiosurgery Society (ISRS) practice guidelines for radiosurgery in recurrent high-grade glioma. *Neuro-Oncology* **2025**, *28*, 353–370. [CrossRef] [PubMed]
17. Bagley, S.J.; Mathew, D.; Desai, A.S.; Chen, K.; Long, Q.; Shabason, J.E.; Lustig, R.A.; Kurtz, G.; Alonso-Basanta, M.; Maloney, E.; et al. PD1 inhibition and GITR agonism in combination with fractionated stereotactic radiotherapy for the treatment of recurrent glioblastoma: A phase 2, multi-arm study. *J. Clin. Oncol.* **2023**, *41*, 2004. [CrossRef]
18. Wick, W.; Platten, M.; Meisner, C.; Felsberg, J.; Tabatabai, G.; Simon, M.; Nikkhah, G.; Papsdorf, K.; Steinbach, J.P.; Sabel, M.; et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. *Lancet Oncol.* **2012**, *13*, 707–715. [CrossRef] [PubMed]
19. König, L.; Jäkel, C.; Doeberitz, N.V.K.; Kieser, M.; Eberle, F.; Münter, M.; Debus, J.; Herfarth, K. Glioblastoma radiotherapy using Intensity modulated Radiotherapy (IMRT) or proton Radiotherapy—GRIPS Trial (Glioblastoma Radiotherapy via IMRT or Proton BeamS): A study protocol for a multicenter, prospective, open-label, randomized, two-arm, phase III study. *Radiat. Oncol.* **2021**, *16*, 240. [CrossRef] [PubMed]
20. Kim, M.M.; Aryal, M.P.; Suresh, K.; Rosen, B.S.; Parmar, H.; You, D.; Leung, D.; Clarke, N.; Fortunato, J.; Al-Holou, W.; et al. A Phase 2 Study of Multiparametric Magnetic Resonance Imaging-Guided High-Dose Response-Adaptive Radiation Therapy With Concurrent Temozolomide in Patients With Newly Diagnosed Glioblastoma: Results From an Interim Analysis. *Int. J. Radiat. Oncol. Biol. Phys.* **2025**, *122*, 605–610. [CrossRef] [PubMed]
21. Majd, N.; Yeboa, D.; Wang, S.; Weathers, S.-P.S.; Yuan, Y.; Al Anssari, H.; Kamiya-Matsuoka, C.; O'BRien, B.J.; Aaroe, A.; Patel, C.B.; et al. Phase I clinical trial of peposertib plus radiation in adults with newly diagnosed MGMT-unmethylated glioblastoma. *J. Clin. Oncol.* **2024**, *42*, 2076. [CrossRef]

22. Kotecha, R.; Schiff, D.; Chakravarti, A.; Fleming, J.L.; Brown, P.D.; Puduvalli, V.K.; Vogelbaum, M.A.; Gondi, V.; Gallus, M.; Okada, H.; et al. Multidisciplinary Management of Isocitrate Dehydrogenase–Mutated Gliomas in a Contemporary Molecularly Defined Era. *J. Clin. Oncol.* **2024**, *42*, 2588–2598. [CrossRef] [PubMed]
23. Pelak, M.J.; Hummer, A.; Hug, E.; Töpfer, S.; Flechl, B.; Mozes, P.; Fossati, P.; Fussl, C.; Surböck, B.; Hainfellner, J.; et al. Patient-Reported Outcomes, Neurocognitive Functioning, and Oncologic Results of Pencil Beam Scanning Proton Beam Therapy for CNS WHO G2 and G3 IDH1-Mutant Diffuse Adult Glioma: A Single Institution Experience. *Int. J. Radiat. Oncol. Biol. Phys.* **2025**, *126*, 1085–1096. [CrossRef] [PubMed]
24. Slater, J.M.; Horick, N.K.; Nachtigall, L.B.; Parsons, M.W.; A Tritos, N.; Faje, A.T.; Dietrich, J.; Fullerton, B.; Sherman, J.C.; Curry, W.T.; et al. Cognitive function, quality of life, and survival outcomes in patients with lower grade gliomas treated with proton radiation therapy: A phase II study. *Neuro-Oncology* **2026**, *28*, 1266–1276. [CrossRef] [PubMed]
25. Sulkowski, P.L.; Oeck, S.; Dow, J.; Economos, N.G.; Mirfakhraie, L.; Liu, Y.; Noronha, K.; Bao, X.; Li, J.; Shuch, B.M.; et al. Oncometabolites suppress DNA repair by disrupting local chromatin signalling. *Nature* **2020**, *582*, 586–591. [CrossRef] [PubMed]
26. Slevin, F.; Chen, X.S.; Rosen, B.S.; Shen, C.J.; Mayo, C.; Zhang, L.; Butala, A.A.; Ajithkumar, T.; Kim, M.M.; Murray, L. Constraints, cumulative doses and toxicity outcomes in glioma reirradiation: A systematic review and radiobiological comparison from the Reirradiation Collaborative Group (ReCog). *Int. J. Radiat. Oncol. Biol. Phys.* **2026**, *126*, 64–86. [CrossRef] [PubMed]
27. Detsky, J.S.; Chan, A.W.; Moore-Palhares, D.; Safavi, A.H.; Perry, J.; Fat, M.J.L.; Atenafu, E.G.; Das, S.; Lipsman, N.; Heyn, C.; et al. MRI-guided adaptive radiotherapy for high grade glioma (UNITED): A single-centre, single-arm, non-inferiority, phase 2 trial. *Lancet Oncol.* **2026**, *27*, 729–737. [CrossRef] [PubMed]
28. Goda, J.S.; Dutta, D.; Krishna, U.; Goswami, S.; Kothavade, V.; Kannan, S.; Maitre, M.; Bano, N.; Gupta, T.; Jalali, R. Hippocampal radiotherapy dose constraints for predicting long-term neurocognitive outcomes: Mature data from a prospective trial in young patients with brain tumors. *Neuro-Oncology* **2020**, *22*, 1677–1685. [CrossRef] [PubMed]
29. Yang, F.; Dinakaran, D.; Heikal, A.A.; Tari, S.Y.; Ghosh, S.; Amanie, J.; Murtha, A.; Rowe, L.S.; Roa, W.H.; Patel, S. Dosimetric predictors of toxicity in a randomized study of short-course vs conventional radiotherapy for glioblastoma. *Radiother. Oncol.* **2022**, *177*, 152–157. [CrossRef] [PubMed]
30. Frey, B.; Rückert, M.; Deloch, L.; Rühle, P.F.; Derer, A.; Fietkau, R.; Gaipl, U.S. Immunomodulation by ionizing radiation—Impact for design of radio-immunotherapies and for treatment of inflammatory diseases. *Immunol. Rev.* **2017**, *280*, 231–248. [CrossRef] [PubMed]
31. Saini, S.; Gurung, P. A comprehensive review of sensors of radiation-induced damage, radiation-induced proximal events, and cell death. *Immunol. Rev.* **2024**, *329*, e13409. [CrossRef] [PubMed]
32. Demaria, S.; Golden, E.B.; Formenti, S.C. Role of Local Radiation Therapy in Cancer Immunotherapy. *JAMA Oncol.* **2015**, *1*, 1325–1332. [CrossRef] [PubMed]
33. Wilkins, A.C.; Patin, E.C.; Harrington, K.J.; Melcher, A.A. The immunological consequences of radiation-induced DNA damage. *J. Pathol.* **2019**, *247*, 606–614. [CrossRef] [PubMed]
34. Citrin, D.E. Recent Developments in Radiotherapy. *N. Engl. J. Med.* **2017**, *377*, 1065–1075. [CrossRef] [PubMed]
35. Lynch, C.; Pitroda, S.P.; Weichselbaum, R.R. Radiotherapy, immunity, and immune checkpoint inhibitors. *Lancet Oncol.* **2024**, *25*, e352–e362. [CrossRef] [PubMed]
36. Carruthers, R.D.; Ahmed, S.U.; Ramachandran, S.; Strathdee, K.; Kurian, K.M.; Hedley, A.; Gomez-Roman, N.; Kalna, G.; Neilson, M.P.; Gilmour, L.; et al. Replication Stress Drives Constitutive Activation of the DNA Damage Response and Radioresistance in Glioblastoma Stem-like Cells. *Cancer Res.* **2018**, *78*, 5060–5071. [CrossRef] [PubMed]
37. Ahmed, S.U.; Carruthers, R.; Gilmour, L.; Yildirim, S.; Watts, C.; Chalmers, A.J. Selective Inhibition of Parallel DNA Damage Response Pathways Optimizes Radiosensitization of Glioblastoma Stem-like Cells. *Cancer Res.* **2015**, *75*, 4416–4428. [CrossRef] [PubMed]
38. Shi, T.; Zhu, J.; Zhang, X.; Mao, X. The Role of Hypoxia and Cancer Stem Cells in Development of Glioblastoma. *Cancers* **2023**, *15*, 2613. [CrossRef] [PubMed]
39. Wisdom, A.J.; Temple, H.; Cui, Y.; Del Vecchio, C.T.; Kim, T.; White, F.M.; Floyd, S.R.; Spranger, S. Mechanisms, Microenvironments, and Models: Understanding Therapeutic Resistance in Glioblastoma. *Int. J. Radiat. Oncol. Biol. Phys.* **2026**, *125*, 1480–1491. [CrossRef] [PubMed]
40. Laprie, A.; Noel, G.; Chaltiel, L.; Truc, G.; Sunyach, M.-P.; Charissoux, M.; Magne, N.; Auberdiac, P.; Biau, J.; Ken, S.; et al. Randomized phase III trial of metabolic imaging-guided dose escalation of radio-chemotherapy in patients with newly diagnosed glioblastoma (SPECTRO GLIO trial). *Neuro-Oncology* **2023**, *26*, 153–163. [CrossRef] [PubMed]
41. Kim, M.M.; Sun, Y.; Aryal, M.P.; Parmar, H.A.; Piert, M.; Rosen, B.; Mayo, C.S.; Balter, J.M.; Schipper, M.; Gabel, N.; et al. A Phase 2 Study of Dose-intensified Chemoradiation Using Biologically Based Target Volume Definition in Patients With Newly Diagnosed Glioblastoma. *Int. J. Radiat. Oncol. Biol. Phys.* **2021**, *110*, 792–803. [CrossRef] [PubMed]

42. Vora, S.; Pafundi, D.; Voss, M.; Buras, M.; Ashman, J.; Bendok, B.R.; Breen, W.; Hu, L.; Kizilbash, S.; Laack, N.; et al. Short-course hypofractionated proton beam therapy, incorporating 18F-DOPA PET and contrast-enhanced MRI targeting, for patients aged 65 years and older with newly diagnosed glioblastoma: A single-arm phase 2 trial. *Lancet Oncol.* **2024**, *25*, 1625–1634. Erratum in *Lancet Oncol.* **2025**, *26*, e11. https://doi.org/10.1016/S1470-2045(24)00713-7. [CrossRef] [PubMed]
43. Brown, P.D.; Chung, C.; Liu, D.D.; McAvoy, S.; Grosshans, D.; Al Feghali, K.; Mahajan, A.; Li, J.; McGovern, S.L.; McAleer, M.-F.; et al. A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma. *Neuro-Oncology* **2021**, *23*, 1337–1347. [CrossRef] [PubMed]
44. Mohan, R.; Liu, A.Y.; Brown, P.D.; Mahajan, A.; Dinh, J.; Chung, C.; McAvoy, S.; McAleer, M.F.; Lin, S.H.; Li, J.; et al. Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: Phase II randomized study of protons vs photons. *Neuro-Oncology* **2020**, *23*, 284–294. [CrossRef] [PubMed]
45. Coupey, J.; Pham, T.N.; Toutain, J.; Ivanova, V.; Hue, E.S.; Helaine, C.; Ismail, A.; Saulnier, R.; Simonin, G.; Rousseau, M.; et al. Proton Radiotherapy Offers Immune-Sparing Benefits in Glioblastoma Treatment. *Int. J. Radiat. Oncol. Biol. Phys.* **2026**, *126*, 1061–1074. [CrossRef] [PubMed]
46. Scagliotti, E.; Capetti, B.; Conti, L.; Fiore, G.; Fanizzi, C.; Bertani, G.; Pravettoni, G.; Locatelli, M. Effects of proton therapy on cognition in adults with brain tumors: A systematic review. *J. Neuro-Oncol.* **2025**, *176*, 121. [CrossRef] [PubMed]
47. Dasgupta, A.; Ghosh, S.; Chatterjee, A.; Kannan, S.; Goswami, S.; Ranjith, C.P.; Punde, R.; Meena, L.; Shinde, P.; Konthoujam, M.; et al. Proton versus photon radiotherapy in adults with primary brain tumors evaluating functional survival: A phase 3 randomized controlled trial study protocol (PRIDE). *Radiat. Oncol.* **2026**, *21*, 38. [CrossRef] [PubMed]
48. Wang, Y.; Liu, R.; Zhang, Q.; Dong, M.; Wang, D.; Chen, J.; Ou, Y.; Luo, H.; Yang, K.; Wang, X. Charged particle therapy for high-grade gliomas in adults: A systematic review. *Radiat. Oncol.* **2023**, *18*, 29. [CrossRef] [PubMed]
49. Ram, Z.; Kim, C.-Y.; Hottinger, A.F.; Idbaih, A.; Nicholas, G.; Zhu, J.-J. Efficacy and Safety of Tumor Treating Fields (TTFields) in Elderly Patients with Newly Diagnosed Glioblastoma: Subgroup Analysis of the Phase 3 EF-14 Clinical Trial. *Front. Oncol.* **2021**, *11*, 671972. Erratum in *Front. Oncol.* **2022**, *12*, 902929. https://doi.org/10.3389/fonc.2022.902929. [CrossRef] [PubMed]
50. Ballo, M.T.; Conlon, P.; Lavy-Shahaf, G.; Kinzel, A.; Vymazal, J.; Rulseh, A.M. Association of Tumor Treating Fields (TTFields) therapy with survival in newly diagnosed glioblastoma: A systematic review and meta-analysis. *J. Neuro-Oncol.* **2023**, *164*, 1–9. [CrossRef] [PubMed]
51. Rominiyi, O.; Vanderlinden, A.; Clenton, S.J.; Bridgewater, C.; Al-Tamimi, Y.; Collis, S.J. Tumour treating fields therapy for glioblastoma: Current advances and future directions. *Br. J. Cancer* **2020**, *124*, 697–709. Erratum in *Br. J. Cancer* **2021**, *125*, 623. https://doi.org/10.1038/s41416-021-01451-5. [CrossRef] [PubMed]
52. Chen, D.; Le, S.B.; Ghiaseddin, A.P.; Manektalia, H.; Li, M.; O'dEll, A.; Rahman, M.; Tran, D.D. Efficacy and safety of adjuvant TTFields plus pembrolizumab and temozolomide in newly diagnosed glioblastoma: A phase 2 study. *Med* **2025**, *6*, 100708. [CrossRef] [PubMed]
53. Montay-Gruel, P.; Acharya, M.M.; Jorge, P.G.; Petit, B.; Petridis, I.G.; Fuchs, P.; Leavitt, R.; Petersson, K.; Gondré, M.; Ollivier, J.; et al. Hypofractionated FLASH-RT as an Effective Treatment against Glioblastoma that Reduces Neurocognitive Side Effects in Mice. *Clin. Cancer Res.* **2020**, *27*, 775–784. [CrossRef] [PubMed]
54. Liljedahl, E.; Konradsson, E.; Gustafsson, E.; Jonsson, K.F.; Olofsson, J.K.; Ceberg, C.; Redebrandt, H.N. Long-term anti-tumor effects following both conventional radiotherapy and FLASH in fully immunocompetent animals with glioblastoma. *Sci. Rep.* **2022**, *12*, 12285. [CrossRef] [PubMed]
55. Guo, Y.; Hao, S.; Huang, Q.; Di, C.; Gan, L.; Xie, Y.; Li, Q.; Si, J. Unraveling the dual nature of FLASH radiotherapy: From normal tissue sparing to tumor control. *Cancer Lett.* **2025**, *630*, 217895. [CrossRef] [PubMed]
56. Hörberger, F.; Petersson, K.; Ceberg, S.; Bäck, S.; Adrian, G.; Ceberg, C. Investigating the therapeutic potential of FLASH radiotherapy—A treatment planning study. *Radiother. Oncol.* **2025**, *209*, 110947. [CrossRef] [PubMed]
57. Shi, W.; Bryan, M.S.; Gilbert, M.R.; Mehta, M.P.; Blumenthal, D.T.; Brown, P.D.; Valeinis, E.; Hopkins, K.; Souhami, L.; Andrews, D.W.; et al. Investigating the Effect of Reirradiation or Systemic Therapy in Patients With Glioblastoma After Tumor Progression: A Secondary Analysis of NRG Oncology/Radiation Therapy Oncology Group Trial 0525. *Int. J. Radiat. Oncol. Biol. Phys.* **2018**, *100*, 38–44. [CrossRef] [PubMed]
58. de Melo, S.M.; da Silva, M.E.E.N.; Torloni, M.R.; Riera, R.; De Cicco, K.; Latorraca, C.O.; Pinto, A.C.P.N. Anti-PD-1 and anti-PD-L1 antibodies for glioma. *Cochrane Database Syst. Rev.* **2025**, *2025*, CD012532. [CrossRef] [PubMed]
59. Derby, S.; Jackson, M.R.; Williams, K.; Stobo, J.; Kelly, C.; Sweeting, L.; Shad, S.; Herbert, C.; Short, S.C.; Williamson, A.; et al. Concurrent Olaparib and Radiation Therapy in Older Patients With Newly Diagnosed Glioblastoma: The Phase 1 Dose-Escalation PARADIGM Trial. *Int. J. Radiat. Oncol. Biol. Phys.* **2024**, *118*, 1371–1378. [CrossRef] [PubMed]
60. Wick, W.; Lanz, L.-M.; Wick, A.; Harting, I.; Dettmer, S.; Suwala, A.K.; Ketter, R.; Tabatabai, G.; Seliger, C.; Glas, M.; et al. Molecularly matched targeted therapies plus radiotherapy in glioblastoma: The phase 1/2a N2M2 umbrella trial. *Nat. Med.* **2025**, *31*, 3534–3541. [CrossRef] [PubMed]

61. Elati, A.H.; Davies, E.W.; Mishra, M.V.; Winkles, J.A.; Woodworth, G.F.; Kim, A.J. Platinum-based therapeutics as emerging multi-modal radiosensitizers in glioblastoma treatment. *Adv. Drug Deliv. Rev.* **2026**, *232*, 115811. [CrossRef] [PubMed]
62. Greene-Schloesser, D.; Moore, E.; Robbins, M.E. Molecular Pathways: Radiation-Induced Cognitive Impairment. *Clin. Cancer Res.* **2013**, *19*, 2294–2300. [CrossRef] [PubMed]
63. Soussain, C.; Ricard, D.; Fike, J.R.; Mazeron, J.-J.; Psimaras, D.; Delattre, J.-Y. CNS complications of radiotherapy and chemotherapy. *Lancet* **2009**, *374*, 1639–1651. [CrossRef] [PubMed]
64. A Kirkman, M.; Day, J.; Gehring, K.; Zienius, K.; Grosshans, D.; Taphoorn, M.; Li, J.; Brown, P.D. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. *Cochrane Database Syst. Rev.* **2022**, *2022*, CD011335. [CrossRef] [PubMed]
65. Lumniczky, K.; Szatmári, T.; Sáfrány, G. Ionizing Radiation-Induced Immune and Inflammatory Reactions in the Brain. *Front. Immunol.* **2017**, *8*, 517. [CrossRef] [PubMed]
66. Gui, C.; Vannorsdall, T.D.; Kleinberg, L.R.; Assadi, R.; A Moore, J.; Hu, C.; Quiñones-Hinojosa, A.; Redmond, K.J. A Prospective Cohort Study of Neural Progenitor Cell-Sparing Radiation Therapy Plus Temozolomide for Newly Diagnosed Patients With Glioblastoma. *Neurosurgery* **2020**, *87*, E31–E40. [CrossRef] [PubMed]
67. Seibert, T.M.; Karunamuni, R.; Kaifi, S.; Burkeen, J.; Connor, M.; Krishnan, A.P.; White, N.S.; Farid, N.; Bartsch, H.; Murzin, V.; et al. Cerebral Cortex Regions Selectively Vulnerable to Radiation Dose-Dependent Atrophy. *Int. J. Radiat. Oncol. Biol. Phys.* **2017**, *97*, 910–918. [CrossRef] [PubMed]
68. Rong, Y.; Chen, Q.; Fu, Y.; Yang, X.; Al-Hallaq, H.A.; Wu, Q.J.; Yuan, L.; Xiao, Y.; Cai, B.; Latifi, K.; et al. NRG Oncology Assessment of Artificial Intelligence Deep Learning–Based Auto-segmentation for Radiation Therapy: Current Developments, Clinical Considerations, and Future Directions. *Int. J. Radiat. Oncol. Biol. Phys.* **2023**, *119*, 261–280. [CrossRef] [PubMed]
69. Srinivasan, S.; Njeh, C.F. Adaptive Radiotherapy in the Era of Image Guidance and Artificial Intelligence: A Critical Review. *Cancers* **2026**, *18*, 2281. [CrossRef] [PubMed]
70. Zhong, L.; Zhou, P.; Chen, L.; Chen, D.; Wen, L.; Diao, X.; Zhang, A.; Gao, Y.; Chen, G.; Li, X.; et al. Modified Target Delineation and Moderately Hypofractionated Radiotherapy for High-Grade Glioma. *JAMA Netw. Open* **2025**, *8*, e2523053. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.