Review

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Posted Date: 9 July 2025

doi: 10.20944/preprints202507.0848.v1

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 doi:10.20944/preprints202507.0848.v1

Review

Radiotherapy in Glioblastoma Multiforme: Evolution, Limitations, and Molecularly Guided Future

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Abstract

Glioblastoma multiforme (GBM), the most aggressive primary brain tumor in adults, has a poor prognosis due to rapid recurrence and treatment resistance. This review examines the evolution of radiotherapy (RT) for GBM management, from whole-brain RT to modern techniques like intensity-modulated RT (IMRT) and volumetric modulated arc therapy (VMAT), guided by 2023 European Society for Radiotherapy and Oncology (ESTRO)-European Association of Neuro-Oncology (EANO) and 2025 American Society for Radiation Oncology (ASTRO) recommendations. The standard Stupp protocol (60 Gy/30 fractions with temozolomide [TMZ]) improves overall survival (OS) to 14.6 months, with greater benefits in O6-methylguanine-DNA methyltransferase (MGMT)-methylated tumors (21.7 months). Tumor Treating Fields (TTFields) extend OS to 31.6 months in selected cases. However, 80–90% of recurrences occur within 2 cm of the irradiated field due to tumor infiltration and radiorresistencia driven by epidermal growth factor receptor (EGFR) amplification, phosphatase and tensin homolog (PTEN) mutations, cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) deletions, tumor hypoxia, and tumor stem cells. Pseudoprogression, distinguished using Response Assessment in Neuro-Oncology (RANO) criteria and positron emission tomography (PET), complicates response evaluation. Targeted therapies (e.g., bevacizumab, PARP inhibitors) and immunotherapies (e.g., pembrolizumab, oncolytic viruses), alongside advanced imaging (multiparametric magnetic resonance imaging [MRI], amino acid PET), support personalized RT. Future strategies, including reirradiation, hypofractionation, stereotactic radiosurgery, neoadjuvant therapies, proton therapy (PT) and boron neutron capture therapy (BNCT), aim to enhance efficacy for GBM IDH-wildtype, but phase III trials are needed to improve survival and quality of life.

Keywords: glioblastoma multiforme; radiotherapy; temozolomide; MGMT methylation; proton therapy; tumor treating fields; targeted therapies; immunotherapies; personalized medicine; advanced imaging

 doi:10.20944/preprints202507.0848.v1

1. Introduction

Glioblastoma multiforme (GBM), the most common malignant primary brain tumor in adults, has an incidence of 3–5 cases per-100,000 people annually, with a male predominance (1.6:1) and peak incidence at 50–60 years [1–4]. According to the 2021 World Health Organization (WHO) classification, GBM is defined as an isocitrate dehydrogenase (IDH)-Wild-Type (IDH-wt), grade 4 astrocytoma, diagnosed by histological features (necrosis, microvascular proliferation) or molecular markers, including telomerase reverse transcriptase (TERT) promoter mutation, epidermal growth factor receptor (EGFR) amplification, or +7/−10 chromosomal alterations [5]. Most GBMs arise de novo, though a small percentage develop from lower-grade gliomas; risk factors include prior cranial radiotherapy (RT) or hereditary syndromes such as Cowden, Turcot, Lynch, Li-Fraumeni, or neurofibromatosis type I [2]. Characterized by rapid progression and treatment resistance, GBM has a poor prognosis, with a median overall survival (mOS) of 12–15 months and a 5-year survival rate below 10%, varying by prognostic factors such as age, functional status, O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, tumor location, and involvement of deep structures or functional areas [6–9]. Multidisciplinary treatment combines maximal safe resection, RT, and chemotherapy (CTx), with no defined second-line therapy, necessitating personalized approaches. Despite recent advances, limited progress in improving outcomes underscores the urgent need for innovative strategies to improve oncologic outcomes and quality of life. This review explores the evolution, limitations, and molecularly guided advances in RT for GBM management.

2. Evolution of Radiotherapy in GBM: Foundations, Standards, and International Guidelines

The first-line treatment for GBM involves maximal safe resection, followed by adjuvant RT and CTx to target residual microscopic disease due to the tumor's infiltrative nature [10,11]. Preoperative neuronavigation magnetic resonance imaging (MRI) and early postoperative contrast-enhanced MRI (within 48–72 hours) are recommended, with intraoperative biopsy for diagnosis confirmation if resection is not feasible [2,10]. RT should begin 3–6 weeks post-surgery to minimize recurrence risk [10,11].The standard protocol, established by the European Organisation for Research and Treatment of Cancer (EORTC) 26981/22981 trial, combines normofractionated RT (60 Gy in 30 fractions) with concomitant temozolomide (TMZ, 75 mg/m²/day), followed by 6 cycles of adjuvant TMZ (150–200 mg/m²/day, 5/28 days), improving overall survival (OS) from 12.1 to 14.6 months, particularly in patients with MGMT promoter methylation (Table 1) [12]. This regimen is recommended for patients ≤70 years with good functional status (Karnofsky Performance Status [KPS] ≥60) [13,14]. Extending TMZ beyond 6 cycles lacks evidence [15]. Tumor Treating Fields (TTFields), which disrupt cell division with alternating electric fields, further improve OS to 31.6 months in MGMT-methylated tumors (EF-14 trial) with minimal toxicity (mainly skin irritation) and are endorsed by National Comprehensive Cancer Network (NCCN) and American Society for Radiation Oncology (ASTRO) 2025 guidelines for supratentorial GBM (Table 1) [12,16,17]. Other therapeutic innovations and systemic treatment options are discussed in the therapeutic innovations section.

Table 1. Survival Patterns in Glioblastoma Multiforme by MGMT Methylation Status and Therapy.

Intervention	Median Survival – Unmethylated	Median Survival – Methylated	Conclusion
Surgery + RT	11.8 months	15.3 months	RT alone improves OS in methylated tumors, but the benefit is limited.
Surgery + RT + TMZ	12.7 months	21.7 months	The addition of TMZ significantly increases

 doi:10.20944/preprints202507.0848.v1

			OS in methylated tumors (p = 0.007).
Surgery + RT + TMZ + TTFields	16.9 months	31.6 months	The combination of TTFields with RT and TMZ offers the greatest OS benefit, especially in methylated tumors.

Legend: RT: Radiotherapy; TMZ: Temozolomide; TTFields: Tumor Treating Fields; OS: Overall Survival. Adapted from Roubil JG et al. [17], with data from Stupp et al. [12,16].

Hypofractionated RT (40.05 Gy/15 fractions with TMZ, 34 Gy/10 fractions, or 25 Gy/5 fractions without TMZ) is effective and better tolerated in elderly (≥70 years) or frail patients (KPS 50–70), offering comparable OS with reduced toxicity, as supported by clinical trials and meta-analyses (Table 2) [18–24]. ASTRO 2025 and European Society for Radiotherapy and Oncology (ESTRO)-European Association of Neuro-Oncology (EANO) 2023 guidelines conditionally recommend these regimens for elderly or frail patients, while those with poor KPS (≤40) or extreme frailty may receive hypofractionated RT alone, TMZ alone (if MGMT-methylated), or palliative care to prioritize quality of life [10,11,13,14,25].

Table 2. Summary of studies on hypofractionation in patients with GBM.

Study	Patients	Treatment	Results	Conclusion
Roa et al. (2004) [19]	N=100 ≥60 y.o. KPS ≥50.	RT (60 Gy/6 weeks) vs. RT (40 Gy/3 weeks).	-OS comparable (5.1 vs. 5.6 months). - Better tolerance - Lower use of post-treatment steroids in short RT.	Short RT is effective and more comfortable
Perry et al. (2017) [18]	N= 562 ≥65 y.o.	RT (40 Gy/15fr) ± concomitant and adjuvant TMZ.	- Better OS with combination (9.3 mo vs. 7.6 m), especially in MGMTmet - More hematological adverse effects with TMZ	Short RT + TMZ improves OS. Standard in eligible patients
Malmström et al. Nordic Trial (2012) [22]	N=342 ≥60 y.o. WHO 0-2	TMZ vs RT 60 Gy/6 weeks vs RT 34 Gy/2 weeks.	-OS: TMZ 8.3 m / RT 6.0 mo / hypofractionated RT 7.5 mo - greater benefit in >70 years - MGMTmet: predictive marker of response to TMZ (OS 9.7mo vs 8.2 in RT)	- TMZ and hypofractionated RT > standard RT - TMZ vs. hypofractionated RT in patients >70 years old, depending on MGMTmet. Individualized management

 doi:10.20944/preprints202507.0848.v1

Roa et al. IAEA Trial (2015) [20]	N=98 ≥65 y.o. and/or fragile	RT (25 Gy/5fr) vs. RT (40.05 Gy/15fr).	Similar OS (7.9 vs. 6.4 mo).	Hypofractionated RT is feasible and effective in frail patients
Minniti et al. (2009) [21]	N=43 ≥70 y.o. KPS ≥60	RT 30Gy/6fr vs adj. TMZ	-OS 9.3 mo -PFS 6.3 mo -Best in KPS>70 -Acceptable toxicity	Combination is effective and safe in selected patients with limited prognosis

Legend: RT: Radiotherapy; TMZ: Temozolomide; KPS: Karnofsky Performance Status; WHO: World Health Organization scale; OS: Overall Survival; PFS: Progression-Free Survival; MGMTmet: MGMT Methylation; mo: Months; fr: Fractions.

RT techniques have evolved from whole-brain RT (WBRT) in the 1970s to three-dimensional conformal RT (3D-CRT) in the 1990s, and now to intensity-modulated RT (IMRT) and volumetric modulated arc therapy (VMAT), which optimize dose delivery and spare healthy tissues. Treatment planning integrates thin-slice CT and MRI (T1 with gadolinium, T2/FLAIR) performed ≤14 days before RT for precise tumor and organ-at-risk delineation. ASTRO 2025 and ESTRO-EANO 2023 guidelines prioritize IMRT/VMAT over 3D-CRT to reduce neurological toxicity. ESTRO-EANO 2023 recommends a single-phase approach (gross tumor volume [GTV]: surgical cavity + T1 enhancement, clinical target volume [CTV]: GTV + 15 mm, edema optional only for non-hyperintense T1 tumors), while ASTRO 2025 allows a single phase (edema optional) or two phases (initial phase with T2/FLAIR, boost without edema), with CTV of 10–20 mm and planning target volume (PTV) of 2–5 mm with image-guided RT (IGRT) (Table 3) [11,12,14,25–29]. A randomized trial with 245 patients with grade 3–4 gliomas compared the RTOG/NRG approach (including edema with a boost) and the EORTC approach (including edema in the initial phase), finding no significant differences in grade 3–4 toxicity (36.1% vs. 32.3%) or recurrence patterns (predominantly central), though neurocognitive outcomes were not assessed [30,31]. The MD Anderson Cancer Center (MDACC) protocol, excluding edema, improved OS (17 vs. 12 months) and quality of life without increasing toxicity, suggesting smaller volumes may be beneficial (Table 3) [27].

Table 3. Summary of Radiotherapy Volumes for GBM.

Guideline/Study	GTV	CTV	PTV	Edema Inclusion
EORTC (Stupp) [12]	Tumor + cavity	CTV1: GTV + edema + 20mm CTV2: GTV + 25mm	PTV = CTV + 3-5mm	Yes, included in initial phase
RTOG/NRG (2019) [14]	Phase 1: tumor + edema; Phase 2: tumor + cavity	CTV1: GTV1 + 20mm CTV2: GTV2 + 20mm	PTV = CTV + 3-5mm	Yes, included in initial phase
ESTRO-EANO 2023 [25]	Surgical cavity + post-surgical T1 enhancement	GTV + 15 mm (adjusted to anatomy)	CTV + individual margin (usually ≤3 mm with IGRT)	Not systematically included
ESTRO-ACROP 2016 [26]	Cavity + residual tumor	GTV + 15–20 mm, adjusted to anatomical barriers	CTV + 3–5 mm	Not systematically included
Minniti et al. (2010) [28]	Surgical cavity + post-surgical T1 enhancement	CTV1: GTV + 2 cm CTV2: GTV + 1 cm	CTV + 3mm	Not included

 doi:10.20944/preprints202507.0848.v1

Chang et al. (2007) [29]	Cavity + T1 tumor	CTV1: GTV + 20mm CTV2: GTV + 5mm	CTV + 5mm	Not included
ASTRO 2025 (1-phase) [11]	Surgical cavity + post-surgical T1 enhancement	GTV + 10–20 mm (adjusted to anatomy, including edema is optional)	PTV = CTV + 3-5 mm	Optional.
ASTRO 2025 (2-phase) [11]	Phase 1: cavity + T1 + T2/FLAIR enhancement Phase 2: cavity + T1 enhancement	CTV1: GTV1 + 10–20 mm CTV2: GTV2 + 10–20 mm (adjusted to anatomy)	PTV = CTV + 3-5 mm	Yes, included in initial phase; not in phase 2
MDACC Kumar et al. (2020) [27]	Cavity + T1 enhancement	Initial GTV + 2 cm, boost GTV + 5 mm	CTV +5mm	Not included

Legend: GTV: Gross Tumor Volume; CTV: Clinical Target Volume; PTV: Planning Target Volume; IGRT: Image-Guided Radiotherapy; MDACC: MD Anderson Cancer Center.

Post-treatment follow-up includes MRI at 4 weeks, then every 2–4 months, per Response Assessment in Neuro-Oncology (RANO) criteria. Pseudoprogression, challenging to distinguish from true progression, may require advanced imaging (diffusion MRI, spectroscopy MRI, or amino acid positron emission tomography (PET)/CT), correlating findings with conventional MRI. In case of progression, a personalized approach is recommended, considering tumor characteristics (size, location, molecular profile), initial treatment response, age, KPS, symptoms, needs, and patient preferences, with multidisciplinary evaluation of options (reoperation, reirradiation, or systemic therapy) [11,25]. These advances underscore the need for tailored RT strategies to optimize GBM treatment outcomes.

3. Limitations of Radiotherapy in GBM

RT combined with TMZ is a cornerstone of GBM treatment but faces technical, biological, and clinical limitations that reduce efficacy and lead to high recurrence and resistance rates. These barriers, summarized in Table 4, underscore the need for innovative strategies discussed later.

Table 4. Limiting Factors of Radiotherapy in the Treatment of GBM.

Category	Limitation	Description/Evidence
Technical	Local recurrence	80-90% of recurrences occur within 2 cm of the irradiated field due to diffuse infiltration, even with IMRT, VMAT, or proton therapy [32]
	Dosimetric constraints	Limits such as <54 Gy to the brainstem and optic chiasm restrict dose escalation; proton therapy minimizes irradiated volumes [25].
	Acute and late toxicity	Fatigue, radiation necrosis, and cognitive deficits; brain volumes (V20Gy, V40Gy) increase neurotoxicity, reducible with IMRT, VMAT, and proton therapy [25].

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	Delay in RT initiation	Delays >6 weeks worsen OS and PFS; moderate delays (~6 weeks) may benefit patients with residual disease [33,34].
	Cost and adherence of new technologies	Tumor-Treating Fields (TTFields) extend PFS by 2.7 months (6.7 vs. 4.0 months), limited by cost and adherence (≥18 hours/day) [35].
Biological	Tumor infiltration	The diffuse nature of GBM allows tumor cells to escape the radiation field [32].
	Tumor hypoxia	Tumor hypoxia, by activating HIF-1α, reduces RT efficacy by promoting cell survival [37].
	Cellular radioresistance	Tumor stem cells and pathways like MGMT, EGFR/PTEN, and CDKN2A/B drive resistance; PARP inhibitors (e.g., veliparib) and other radiosensitizers show promise by inhibiting DNA repair. [36,37].
	EGFR amplification	In 40-60%, activates PI3K/Akt and RAS/RAF/MAPK, conferring resistance; PTEN mutations (~40%) enhance this pathway; inhibitors like erlotinib have limited benefits [37,38].
	SVZ as a reservoir	The SVZ, with mutated stem cells (TERT, PTEN, TP53, EGFR), drives regrowth; irradiating the SVZ with doses ≥56 Gy (ipsilateral) or ≥50 Gy (contralateral) does not improve PFS or OS [39,40].
	RT-induced lymphopenia	Extensive irradiation causes grade 3+ lymphopenia (14% with protons vs. 39% with photons), limiting immunotherapy efficacy [41].
Clinical	Pseudoprogression	Affects 30-40% of patients with methylated MGMT after TMZ, complicating radiological assessment up to 12 weeks [42,43].
	Lack of clinical impact of biomarkers and advanced imaging	Multimodal imaging (multiparametric MRI, amino acid PET) enables RT personalization, achieving a median OS of 23 months in a phase I trial [44]. Biomarkers (EGFR, PTEN, TERT) allow patient stratification but, except for MGMT methylation, do not improve OS in phase III trials [45].
	Lack of consistent benefits from combined therapies	Targeted therapies and immunotherapies do not improve OS, though they extend PFS in nGBM [46].

Legend: PFS: Progression-Free Survival; OS: Overall Survival; IMRT: Intensity-Modulated Radiotherapy; VMAT: Volumetric Modulated Arc Therapy; PT: Proton Therapy; MGMT: O6-Methylguanine-DNA Methyltransferase; EGFR: Epidermal Growth Factor Receptor; PTEN: Phosphatase and Tensin Homolog; TERT: Telomerase Reverse

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Transcriptase; TP53: Tumor Protein p53; SVZ: Subventricular Zone; HIF-1α: Hypoxia-Inducible Factor 1-Alpha; nGBM: Newly Diagnosed Glioblastoma Multiforme; rGBM: Recurrent Glioblastoma Multiforme; RT: Radiotherapy; TMZ: Temozolomide; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography.

Technically, 90% of GBMs recur within 2 cm of the irradiated field due to diffuse infiltration [32], despite advanced techniques like IMRT, VMAT, or proton therapy (PT). High doses cause fatigue, radiation necrosis, and cognitive deficits, linked to irradiated brain volumes receiving 20 Gy (V20Gy) and 40 Gy (V40Gy) , though IMRT, VMAT, and PT reduce neurotoxicity [25]. Dosimetric constraints (<54 Gy to brainstem and optic chiasm) limit dose escalation [25]. Delays >6 weeks from surgery to RT worsen OS and PFS, though moderate delays (~6 weeks) may benefit patients with residual disease [33,34]. TTFields extend PFS by 2.7 months (6.7 vs. 4.0 months) but are limited by cost and adherence (≥18 hours/day) [35]. Biologically, GBM radioresistance is driven by genetic heterogeneity, including EGFR amplification (40–60%), phosphatase and tensin homolog (PTEN) mutations, or or cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) deletions, and tumor stem cells [36,37]. Poly (ADP-ribose) polymerase (PARP) inhibitors such as veliparib and other radiosensitizers show promise in early-phase trials by inhibiting DNA repair, awaiting phase III confirmation [36,37]. EGFR amplification activates the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) pathway, conferring RT resistance, with limited benefits from inhibitors like erlotinib [38]. Tumor hypoxia, mediated by hypoxia-inducible factor 1-alpha (HIF-1α), promotes resistance [37]. The subventricular zone (SVZ), a reservoir of tumor stem cells with genetic alterations, drives recurrence; irradiating the SVZ with doses ≥56 Gy (ipsilateral) or ≥50 Gy (contralateral) does not significantly improve PFS or OS [39,40]. RT-induced lymphopenia (14% with PT vs. 39% with photons) limits immunotherapy efficacy [41]. Clinically, pseudoprogression (30–40% with methylated MGMT) complicates assessment up to 12 weeks [42,43]. Multimodal imaging, including multiparametric MRI and amino acid PET enables RT personalization, achieving a median overall survival (mOS) of 23 months in a phase I trial without significant toxicity [44]. Biomarkers (EGFR, PTEN, TERT, MGMT) enable stratification; only MGMT methylation improves OS in phase III trials [45]. A recent meta-analysis showed that combined targeted therapies improve PFS in newly diagnosed GBM (nGBM) but not OS in nGBM or recurrent GBM (rGBM), reflecting tumor heterogeneity and molecular resistance [46].

4. Molecular Determinants in Glioblastoma Multiforme

Most GBMs, classified as IDH-wt, exhibit aggressive biology and radioresistance due to genetic and epigenetic alterations that enhance DNA repair and cell survival [45]. MGMT methylation (~45%) increases sensitivity to chemoradiation (CRT), while EGFR, PTEN, and TERT contribute to resistance [12,45]. Patients with MGMT methylation show significantly higher OS (21.7 vs. 15.3 months) and better response to reirradiation in relapse compared to unmethylated cases [12,47,48] (Table 5).

Table 5. Molecular Biomarkers in RT for GBM.

Biomarker	Frequency (IDH-wt)	Impact on RT	Therapeutic Status
Methylated MGMT	~45 %	Greater sensitivity to RT + TMZ	Standard treatment with TMZ. ESCAT I [12,47,48]
IDH1/2 Mutation	~10 %	Greater radiosensitivity and better prognosis	Favorable stratification. ESCAT I [53]
Amplified EGFR	40–60 %	Activates PI3K/AKT; resistance to RT	Inhibitors without relevant clinical efficacy. ESCAT IIIA [50]

 doi:10.20944/preprints202507.0848.v1

PTEN mutation/loss	~40 %	PI3K/AKT pathway; promotes resistance to RT	No approved effective therapies [49,52]
PIK3CA mutation	~10 %	Stimulates cellular survival signals	No approved effective therapies. [49,52]
Amplified CDK4/6	~15 %	Stimulates cell cycle progression	Inhibitors under clinical study. [49,52]
CDKN2A/B deletion	~50 %	Loss of cell cycle control; poor prognosis	No effective targeted therapies. [45,51]
TERT mutation	>80 %	Uncertain impact; possible role in immune evasion	Under investigation as an immunotherapeutic target. [3,54]

Legend: IDH: Isocitrate Dehydrogenase; wt: Wild-Type; MGMT: O6-Methylguanine-DNA Methyltransferase; RT: Radiotherapy; TMZ: Temozolomide; ESCAT: ESMO Scale for Clinical Actionability of Molecular Targets; EGFR: Epidermal Growth Factor Receptor; PTEN: Phosphatase and Tensin Homolog; PI3K/AKT: Phosphatidylinositol 3-Kinase/Protein Kinase B; CDK4/6: Cyclin-Dependent Kinases 4 and 6; TERT: Telomerase Reverse Transcriptase; CDKN2A/B: Cyclin-Dependent Kinase Inhibitor 2A/B.

A key radioresistance mechanism in IDH-wt GBMs is activation of the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway, driven by EGFR amplification and PTEN loss, which promotes proliferation, inhibits apoptosis, and enhances DNA repair post-RT [49]. Inhibitors like erlotinib yield modest results (ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT) IIIA) [50]. Other alterations, including phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations and cyclin-dependent kinases 4 and 6 (CDK4/6) amplification, enhance cell cycle progression, while CDKN2A/B homozygous deletion, causing loss of cyclin-dependent kinase inhibitor 2A (p16^INK4a^) and alternate reading frame protein p14 (p14^ARF^), is linked to poor prognosis [45,51]. These biomarkers lack effective targeted therapies due to signaling redundancy and pharmacokinetic limitations in the central nervous system [52]. In contrast, IDH1/2 mutations (~10%) confer greater radiosensitivity and better prognosis (ESCAT I) [53]. TERT promoter mutations, present in >80% of IDH-wt GBMs, activate telomerase and may promote immune evasion, though their role as predictive markers or therapeutic targets remains unclear [3,54]. Ongoing clinical trials are exploring TERT as a potential immunotherapeutic target, particularly in combination with immune checkpoint inhibitors, to enhance RT efficacy in immunosuppressive tumor microenvironments [3]. Given the limited clinical impact of standard RT in unfavorable molecular subgroups, radiosensitization strategies are being explored to enhance its therapeutic effect [55]. Among the most promising are poly (ADP-ribose) polymerase (PARP) inhibitors, which interfere with single-strand DNA break repair, exacerbating radiation-induced damage [56]. These inhibitors are particularly relevant for MGMT-unmethylated tumors, where TMZ resistance limits therapeutic options [12]. Although preclinical evidence shows synergy between PARP inhibitors and RT, their clinical efficacy is still under evaluation [45]. A recent phase II trial demonstrated that the PARP inhibitor veliparib, combined with TMZ and RT, improved PFS in MGMT-unmethylated patients, pending phase III confirmation (see Section 4 for details) [36]. RT-induced lymphopenia restricts synergy with immunotherapy, but MGMT methylation identifies patients with favorable immune microenvironments, and PT may reduce lymphopenia to enhance combined therapies [41]. Genomic profiling is a promising approach to personalize RT and its combination with targeted therapies or immunotherapy, with EANO 2025 guidelines recommending systematic profiling to optimize diagnosis and identify candidates for personalized trials [55,57].

 doi:10.20944/preprints202507.0848.v1

5. Advances in the Treatment of Glioblastoma Multiforme

GBM is an aggressive brain tumor with a high recurrence rate. In non-elderly patients with good functional status (KPS ≥70), the Stupp protocol has been the standard of care for nearly two decades [12]. However, tumor resistance has limited progress over the past decade [37]. Novel approaches, including advanced radiotherapies, immunotherapies, targeted therapies, advanced imaging, and nuclear medicine, aim to improve tumor control and quality of life while reducing toxicity.

5.1. Technological Advances in Therapies

Technological advancements have enhanced the precision of treatment, minimizing damage to healthy tissues [58]. PT is increasingly relevant, particularly in reirradiation and selected cases [58]. It leverages the Bragg peak, depositing maximum energy at the end of its range with a sharp fall-off, to target the tumor, with a relative biological effectiveness (RBE) of 1.1 [58]. A phase II trial (NCT01854554) demonstrated that PT (60 Gy/30 fractions) significantly reduced grade ≥3 lymphopenia (14% vs. 39%), minimized irradiated brain volumes (V5–V40), and preserved immune function, potentially enhancing immunotherapy efficacy [6,41]. Although it did not delay cognitive decline compared to IMRT, it reduced fatigue and grade ≥2 toxicity, lowering doses to critical structures, suggesting potential for cognitive preservation in low-grade gliomas [6,59]. The NRG-BN001 trial is evaluating PT dose escalation versus photons, with results pending [60,61]. Carbon ion radiotherapy (CIRT) achieves a median mOS of 18 months in nGBM, surpassing 14 months with photons plus TMZ [62]. Boron neutron capture therapy (BNCT) reports an mOS of 25.7 months in nGBM with TMZ and 18.9 months in rGBM [63,64]. Magnetic resonance-guided radiotherapy (MRgRT) achieves an mOS of 18.5 months and a PFS of 11.6 months in nGBM (UNITED, non-randomized phase II), with UNITED2 ongoing [65,66]. TTFields, a standard in NCCN (category 1) and American Society of Clinical Oncology (ASCO) guidelines but not endorsed by the National Institute for Health and Care Excellence (NICE) due to cost-effectiveness, low adherence, and biases in EF-14 (unblinded, selected patients), achieve an mOS of 20.9 months (PFS 6.7 months) in nGBM (phase III EF-14) and an mOS of 10.3 months in rGBM (EF-11). These biases include lack of blinding and selection of healthier patients, potentially inflating efficacy estimates. Trials include phase II 2-THE-TOP (NCT03405792), reporting an mOS of 24.8 months and PFS of 12.0 months with pembrolizumab plus TMZ in nGBM [14], and ongoing phase III trials (TRIDENT with RT/TMZ, EF-41 with TMZ plus pembrolizumab in nGBM) [67–69]. Modulated electrohyperthermia (mEHT), laser interstitial thermal therapy (LITT), and magnetic hyperthermia (MHT) have limited evidence in rGBM, supported by non-randomized phase I/II trials [70–73]. These techniques, detailed in Table 6, face challenges related to cost and accessibility.

Table 6. Technological Advances in Therapies against GBM.

Technique	Description	mOS/PFS	Evidence	Results Pending	Limitations
PT	Focused dose delivery (Bragg peak, spread-out Bragg peak [SOBP], intensity-modulated proton therapy [IMPT], RBE 1.1)	nGBM: mOS 21-24 months; PFS 6.6-8.9 months	Phase II (NCT01854554, n=67; PT vs. XRT); reduces grade ≥3 lymphopenia (14% vs. 39%, p=0.024), fatigue (24% vs. 58%, p=0.05), toxicity grade ≥2 (0.35 vs. 1.15, p=0.02), V5-V40[41,59–61]	NRG-BN001 (NCT02179086): Phase III randomized, dose escalation PT vs. photons in nGBM[60,61]	Cost, accessibility

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CIRT	High energy transfer, RBE 2.5-5	nGBM: mOS 18 months; rGBM: mOS 8 months	nGBM: CIRT boost (18 GyE/6 fx) or with TMZ (retrospective randomized phase II); rGBM: 45 GyE/15 fx (non-randomized comparative)[62]	CINDERELLA (NCT01166308): Phase I/II, CIRT vs. FSRT in rGBM; CLEOPATRA (NCT01165671): Phase II randomized, CIRT vs. proton boost in nGBM[62]	Cost, limited centers
BNCT	Selective damage with boron-10 (L-BPA, BSH); planning with 18F-BPA PET	nGBM: mOS 25.7 months (with surgery+TMZ); rGBM: mOS 18.9 months	nGBM: Surgery, BNCT (~40 Gy-Eq) and TMZ, without conventional RT; rGBM: Non-randomized Phase II (JG002), minimum 39.8 Gy-Eq [63,64]	under investigation, non-randomized [63,64]	Toxicity (cerebral edema, hyperamylasemia, alopecia); infrastructure
MRgRT	Daily adaptation with T1/T2 MRI	nGBM: mOS 18.5 months, PFS 11.6 months (long course); marginal failure 4.1%	Non-randomized Phase II UNITED (NCT04726397, n=98; CTV 5 mm, 60 Gy/30 fx)[65,66]	UNITED2 (NCT05565521): Phase II non-randomized, 40 Gy/15 fx + boost 52.5 Gy/15 fx, PFS at 6 months [65]	Cost, evidence in development
TTFields	Alternating electric fields (200 kHz, 1-3 V/cm); with TMZ+RT	nGBM: mOS 20.9 months, PFS 6.7 months (EF-14) rGBM: mOS 10.3 months (EF-11) nGBM: mOS 24.8 months, PFS 12.0 months, 1-year survival 82.61% (2-THE-TOP)	Phase III EF-14 (NCT00916409, n=695; TTFields+TMZ in nGBM, HR 0.63, p<0.001); phase III EF-11 (NCT00379470, TTFields in rGBM); phase II 2-THE-TOP (NCT03405792, TTFields+TMZ+pembrolizumab in nGBM) [67–69]	Phase III TRIDENT (NCT04471844): RT/TMZ in nGBM; EF-41 (NCT06556363): TMZ+pembrolizumab+TTFields in nGBM[67–69]	Cost, adherence, dermatitis; NICE does not endorse it due to cost-effectiveness, EF-14 biases (unblinded, selected patients)
mEHT	Thermal radiosensitization (13.56 MHz, 40-43°C);	nGBM: 1-year survival 73.33%; rGBM:	Observational studies 2006–2018 (n=450); 1 nGBM study, 6 rGBM studies (with ddTMZ);	In research, non-randomized [70–72]	Weak evidence, not in guidelines, few centers

 doi:10.20944/preprints202507.0848.v1

	immunogenic potential	mOS 7.7 months, 1-year survival 37.33%	phase I for safety; no RCTs [70–72]		
LITT	MRI-guided laser thermal ablation	rGBM: mOS ~8-12 months	Phase I/II in rGBM; comparable to re-surgery in unifocal lobar rGBM; no RCTs [73]	In research, non-randomized [73]	Small focal lesions, no RCTs, post-procedural edema
MHT	AMF-guided hyperthermia with magnetic nanoparticles (40–45°C)	rGBM: mOS not reported	Phase I/II in rGBM with RT; Proven safety and feasibility; no RCTs.[73]	In research, non-randomized [73]	No RCTs, technical challenges (MNP, thermometry), few centers

Legend: AMF: Alternating magnetic field; BSH: Sodium borocaptate; CIRT: Carbon ion radiotherapy; ddTMZ: Dense dose temozolomide; FSRT: Fractionated stereotactic radiotherapy; GyE: Gray equivalent; HR: Hazard ratio; IMPT: Intensity-modulated proton therapy; L-BPA: L-4-boronophenylalanine; LITT: Laser interstitial thermal therapy; mEHT: Modulated electrohyperthermia; MHT: Magnetic hyperthermia; MNP: Magnetic nanoparticles; MRgRT: Magnetic resonance-guided radiotherapy; RBE: Relative biological effectiveness; RCTs: Randomized clinical trials; SOBP: Spread-out Bragg peak; V5–V40: Volume of tissue receiving 5 to 40 Gy of radiation; XRT: Photon radiotherapy.

5.2. Modified Fractionation Schedules

Modified fractionation schedules optimize RT by counteracting tumor repopulation and reducing treatment duration [37,74]. Hypofractionation, standard in elderly patients with poor functional status (40 Gy/15 fractions), shows promise in younger patients (50–60 Gy/20 fractions with TMZ). The randomized phase II HART-GBM trial achieved an mOS of 26.5 months compared to 22.4 months with standard fractionation [74]. An institutional study reported an mOS of 19.8 months [75], and a meta-analysis showed a 12-month OS of 71.3% across various ages [76]. Hyperfractionation shows no clear benefit, with similar survival outcomes and moderate toxicity compared to standard fractionation [37,77]. Dose escalation (75 Gy/30 fractions) improves PFS but not mOS (NRG-BN001, randomized phase II, mOS 18.7 months, PT arm ongoing) [60]. Dose escalation with a CIRT boost (16.8–24.8 GyE) achieves an mOS of 18 months [62]. Toxicities include radionecrosis (6.7–14.2%) and cognitive decline [75,78,79]. Tumor heterogeneity and hypoxia necessitate phase III trials, as detailed in Table 7.

Table 7. Modified Fractionation Schedules.

Schedule/ Description/ Indications.	mOS/PFS	Evidence	Ongoing Trials	Limitations
Hypofractionation: 50–60 Gy/20 fractions with TMZ, primarily in younger patients (≤65 years, KPS ≥70)	mOS: 26.5 months, PFS: 13.2 months [74]; mOS: 19.8 months, PFS: 7.7 months [75]; 12-month OS: 71.3%, 12-month PFS:	HART-GBM trial (phase II, 60 Gy/20 fx vs. 60 Gy/30 fx, n=83, with TMZ, patients aged 16–65 years) [74]; Institutional study (50 Gy/20 fx vs. 60 Gy/30 fx, n=41, with TMZ,	SAGA (NCT05781321, randomized phase II, 5–10 fx photons guided by [18F]-FDOPA PET, evaluating survival, cost-	Grade ≥3 radionecrosis (6.7% HFRT, 7.7% CFRT), tumor heterogeneity [75,78]

 doi:10.20944/preprints202507.0848.v1

	40.8% (various ages) [76]	patients <65 years) [75]; Meta-analysis (n=484, phase I/II and retrospective, various ages) [76]; Meta-analysis (n not specified, phase II/III, HFRT vs. CFRT, various ages) [78]	effectiveness, and failure patterns, patients ≥18 years, ClinicalTrials.gov)	
Hyperfractionation: 37 × 1.6 Gy or 30 × 1.8 Gy bid with TMZ, experimental	No clear benefit (mOS 14.9 vs. 16.9 months, p=0.26) [77]	Retrospective analysis (HFRT vs. NFRT, n=484, with TMZ) [77]; Review (variable dose, with TMZ) [37]		Lack of efficacy; moderate toxicity [37,77]
Dose escalation: 75 Gy/30 fx (IMRT/PT) with TMZ or 16.8–24.8 GyE boost (CIRT), selected patients (KPS ≥70)	mOS: 18.7 months (photons), improved PFS (60); mOS: 18 months (CIRT boost) [62]	NRG-BN001 trial (randomized phase II, 75 Gy/30 fx vs. 60 Gy/30 fx, n=299, with TMZ, photons) [60]; CIRT retrospective study (16.8–24.8 GyE/8 fx after 50 Gy photons, n=32) [62]	NRG-BN001 (PT arm, randomized phase II) [60]; CLEOPATRA (CIRT boost, randomized phase II) [62]	Grade ≥3 radionecrosis (up to 29%), tumor heterogeneity, no mOS improvement [60,79]

Legend: bid: Twice daily; CIRT: Carbon ion radiotherapy; ddTMZ: Dense dose temozolomide; FSRT: Fractionated stereotactic radiotherapy; GyE: Gray equivalent; HR: Hazard ratio.

5.3. Reirradiation

Reirradiation is a viable option for rGBM in patients with recurrence more than 6 months after initial RT, following multidisciplinary discussion. The 2025 ESTRO/EANO guidelines (KPS >60, tumor volume <35 cm^3) and ASTRO 2025 guidelines (KPS ≥70, tumor volume ≤6 cm^3) endorse its selective use [11,80]. Post-contrast T1 MRI delineates the GTV, complemented by [18F]-FET or [18F]-FDOPA PET to detect recurrence [80,81]. Regimens such as hypofractionated RT (35 Gy/10 fractions) with bevacizumab (BEV) achieve an mOS of 10.1 months and PFS of 3–6 months, with approximately 5% radionecrosis [80]. NRG Oncology/RTOG 1205 demonstrated improved PFS with hypofractionated RT plus BEV [80]. The LEGATO trial evaluates lomustine with or without reirradiation [82]. Hypofractionated stereotactic RT (25 Gy/5 fractions) showed outcomes similar to 35 Gy/5 fractions, with lower toxicity but higher radionecrosis in larger volumes [83]. CIRT (45 Gy RBE/15 fractions) improves mOS (8.0 months) compared to photons [62]. PT achieves an mOS of 7.8–19.4 months in reirradiation [61]. While not detailed here, brachytherapy, pulsed low-dose-rate radiotherapy (pLDR), and flash radiotherapy are promising for recurrent GBM [11,37] See Table 8.

Table 8. Reirradiation.

Modality	Description	Indications	MOS/ PFS	Evidence	Trials	Limitations
HFRT/. **CFRT**	35 Gy/10 fx or 36 Gy/18 fx ± BEV (CTV: GTV + ≤5 mm,	KPS >60, recurrence >6 months, volume <35 cm^3	mOS 7–12 months, PFS 3–6	NRG Oncology/RTOG 1205 (phase II, HFRT + BEV,	LEGATO (phase III, lomustine ± HFRT)	Radionecrosis (~5%), lack of phase III trials [80]

 doi:10.20944/preprints202507.0848.v1

	adjusted to anatomical barriers; PTV: CTV + ≤3 mm) [80]	(ESTRO/EANO); KPS ≥70, volume ≤6 cm³ (ASTRO), multidisciplinary discussion [11,80]	months [80]	mOS 10.1 months) [80]	[82]	
SRS/ HSRT	SRS: 12–15 Gy/1 fx (CTV: GTV, usually without margin; PTV: CTV + 0–1 mm); HSRT: 25 Gy/5 fx (CTV: GTV, without margin; PTV: CTV + 3 mm) [80,81,83]	SRS: volume <10 cm³; HSRT: volume ≤150 cm³ (median 55 cm³) [80,81,83]	mOS 9–11 months, PFS 5–6 months [80,81,83]	Retrospective trials (SRS, volume <12.5 cm³) [80]; Phase II, HSRT 25 Gy/5 fx, mOS 9.2 months, PFS 4.9 months; 35 Gy/5 fx shows no improvement in PFS (4.9 vs. 5.2 months) or OS (9.2 vs. 10 months) [83]		Radionecrosis (<3.5% if volume <12.5 cm³ [80]; ~25% in HSRT [83]), phase II escalation from 25 Gy/5 fx to 35 Gy/5 fx does not improve PFS (4.9 vs. 5.2 months) or OS (9.2 vs. 10 months) [83]
CIRT/PT	CIRT: 45 Gy RBE/15 fx; PT: 33–46.2 Gy variable (CTV: GTV + ≤3 mm, adjusted to anatomical barriers; PTV: CTV + ≤3 mm) [61,62,81]	Selected patients [61,62,81]	mOS 7.8–19.4 months, PFS 5.5–13.9 months [61,62,81]	Retrospective studies (CIRT, PT) [81]; CIRT 45 Gy RBE/15 fx, mOS 8.0 months vs. photons [62]; PT 33–46.2 Gy, mOS 7.8–19.4 months, low toxicity [61]	CINDERELLA (phase I/II, CIRT vs. FSRT) (61)	Cost, accessibility, limited prospective data, toxicity not reported

Legend: BEV: Bevacizumab; CIRT: Carbon ion radiotherapy; fx: Fraction; HSRT: Hypofractionated stereotactic radiotherapy; PT: Proton therapy; RBE: Relative biological effectiveness; SRS: Stereotactic radiosurgery.

5.4. Neoadjuvant Therapy

Neoadjuvant therapy (NAT) reduces tumor volume to facilitate resection or enhance CRT, though it faces challenges such as the need for invasive stereotactic biopsy to confirm diagnosis [84]. In preoperative NAT, BEV in patients with low KPS improves resection (>95%), with an mOS of 15.7 months [85]. POBIG (phase I) evaluates stereotactic RT (6–14 Gy/1 fraction) [86], and PARADIGMA (phase II, NCT03480867) explores RT plus TMZ [84]. In postoperative NAT for unresectable GBM, TMZ plus BEV, the most promising regimen, achieves an mOS of 12.5 months and PFS of 7.4–8.6 months, but BEV increases intracranial hemorrhages [84,87,88]. In resectable GBM, MAGMA (phase III) evaluates neoadjuvant TMZ (75 mg/m² daily) and extended adjuvant TMZ (150–200 mg/m² until progression) before CRT (60 Gy/20 fractions), achieving an mOS of 23 months in MGMT-methylated cases [89]. Neoadjuvant immunotherapies, such as pembrolizumab in resectable rGBM and triple immunotherapy (nivolumab plus ipilimumab plus relatlimab) in nGBM, show potential in selected subgroups [90,91]. Preliminary data from a single nGBM case in the GIANT trial (NCT06816927) suggest no recurrence at 17 months, pending further validation [91]. Future trials should combine

 doi:10.20944/preprints202507.0848.v1

immune checkpoint inhibitors (ICIs) with intratumoral oncolytic viruses to enhance immune responses, with strict patient selection due to variable toxicity [84]. ICI immunotherapy combined with oncolytic viruses may benefit selected subgroups [84] (Table 9)

Table 9. Neoadjuvant Therapy Studies in GBM.

Preoperative Neoadjuvant Therapy for GBM				
Modality	**Description**	**mOS/PFS**	**Trial/ Evidence**	**Limitations**
Preoperative RT	SRS (6–14 Gy/1 fx)	Not reported	POBIG (phase I) [86]	No phase III trials
RT + Preoperative TMZ	RT + Preoperative TMZ	Not reported	PARADIGMA (phase II, NCT03480867) [84]	Pending results
BEV	BEV (10 mg/kg) preoperative	mOS: 15.7 months, PFS: 10.1 months	Miyake et al. (phase II, n=12) [85]	Small sample size; limited data on toxicity
Pembrolizumab	Pembrolizumab (ICI, 200 mg every 3 weeks) pre-surgery	mOS: 13.7 months	(phase II, rGBM) [90]	Small sample size, immunological toxicity, dose heterogeneity, potential influence of steroids and bevacizumab
Triple Immunotherapy	Nivolumab + ipilimumab + relatlimab pre-surgery	No recurrence at 17 months (n=1)	GIANT (phase I, nGBM, NCT06816927) [91]	Single case; preliminary data
Postoperative Neoadjuvant Systemic Therapy Prior to Standard Chemoradiotherapy for Unresectable or Inoperable GBM				
Modality	**Description**	**mOS/PFS**	**Trial /Evidence**	**Limitations**
TMZ + BEV	TMZ (75 mg/m²) + BEV (10 mg/kg) pre-RT	mOS: 12.5 months, PFS: 7.4–8.6 months	Bihan et al. (retrospective, n=8)(87) Balana et al. (phase II, n=102) [88]	Intracranial hemorrhages*; increased toxicity
Postoperative Neoadjuvant Systemic Therapy Prior to Chemoradiotherapy for Resectable GBM				
Modality	Description	mOS/PFS	Trial/Evidence	Limitations
TMZ	TMZ (75 mg/m² daily) <7 days post-surgery and extended adjuvant (150–200	mOS: 23 months, PFS: 11.5 months	Jiang et al. (retrospective, n=375);	Hematological toxicity, MAGMA pending

 doi:10.20944/preprints202507.0848.v1

mg/m² until progression), before CRT (60 Gy/20 fx in MAGMA)		MAGMA (phase III) [89]**

Legend: BEV: Bevacizumab; fx: Fraction; ICIs: Immune checkpoint inhibitors; SRS: Stereotactic radiosurgery. *Note: Intracranial hemorrhages primarily associated with BEV (4.2% in Balana et al.) [88]. **Note: Greater benefit in MGMT-methylated cases (HR 0.60, Jiang et al.) [89].

5.5. Immunotherapy, Targeted Therapies, and Chemotherapy

Chemotherapies, targeted therapies, and immunotherapies are evaluated for nGBM and rGBM (Table 10).

Table 10. Immunotherapy, Targeted Therapies, and Chemotherapy.

Category	Modality	mOS/PFS	Evidence	Notes
Chemotherapy (nGBM)	Standard TMZ	mOS 14.6 months, mPFS 6.9 months	EORTC/NCIC CE.3 [12]	Standard treatment
	Intensive TMZ	No improvement in mOS or PFS	RTOG 0525 [92]	Not recommended
	Lomustine + TMZ	mOS 48.1 months	CeTeG/NOA-09 [96]	Methylated MGMT
Chemotherapy (rGBM)	Metronomic TMZ	PFS-6 24% (1st recurrence); PFS-6 4.4% (post-BEV)	Phase II, [93]	Limited efficacy, especially after bevacizumab
	Lomustine	mPFS 1.5 months	EORTC 26101 [94,95]	Limited efficacy; alone or with bevacizumab
Targeted Therapies (nGBM)	BVZ	mOS 16.8 months, mPFS 10.6 months	AVAglio, RTOG 0825 [95,97,98]	Not recommended as initial treatment; see Table 9 for neoadjuvant use
	Cilengitide + TMZ	No improvement SG/PFS	CENTRIC, CORE [95,99]	Not recommended
	PARP inhibitors (e.g., veliparib)	6-month PFS 46% (95% CI: 36%–57%) vs. 31% (95% CI: 18%–46%) in nGBM with unmethylated MGMT; no mOS benefit (12.7 vs. 12.8 months)	Phase II VERTU, preclinical synergy with RT/TMZ 36	Promising for 6-month PFS in nGBM with unmethylated MGMT, requires phase III confirmation, limited by tumor heterogeneity
Targeted Therapies (rGBM)	BVZ	mOS 9.2 months, mPFS 4.2 months	BRAIN, EORTC 26101, BELOB [94,95,98]	Recommended in symptomatic relapse;

 doi:10.20944/preprints202507.0848.v1

				see Table 9 for neoadjuvant use.
	Regorafenib	mOS 7.4 months, mPFS 2.0 months	REGOMA [95]	Limited efficacy in rGBM
	BRAF/MEK inhibitors	Partial answers	Basket trials [95]	Compassionate use or use in clinical trials
	IDH inhibitors (vorasidenib)	No data in GBM	Phase I [95]	In research for IDH-mutant gliomas
	Erlotinib, Everolimus	Ineffective	Phase II [38,95]	Not recommended
IT (rGBM)	ICI: Nivolumab	mOS 9.8 months	CheckMate 143 [3,90]	No advantage over BEV
	ICI: Pembrolizumab	mOS 13.8 months, mPFS 3.3 months, PFS-6 19.5%	Phase II (NCT02852655) [90,102]	Phase II, neoadjuvant to surgery; benefit in subgroups; see Table 9.
	ACT: CAR-T, TILs, LAK	mOS 20.5 months, 1 RC	Phase I [90]	Phase I, preliminary data
	Vaccines: DCVax-L	mOS 13.2 months	Phase III [90]	Phase III, without RT; benefit in mOS, non-standard
	OV: DNX-2401, G47Δ, PVSRIPO	mOS 12.5-20.2 months	Phase I/II [90,101]	Preliminary results from CAPTIVE (DNX-2401 + pembrolizumab, ongoing)
	Cytokines: L19TNF + lomustine	mPFS 43.3 weeks	[90]	Phase I, preliminary data.
IT (nGBM)	ICI: Nivolumab + RT	mOS 13.4 months	CheckMate 498 [100]	No advantage over TMZ + RT; MGMT not methylated
	ICI: Nivolumab + TMZ + RT	mOS 28.9 months	CheckMate 548 [100]	No advantage over TMZ + RT; methylated MGMT
	Vaccines: DCVax-L	mOS 19.3 months	Phase III [90]	Phase III, with RT + TMZ; benefit in mOS, non-standard
	Vaccines: Rindopepimut + TMZ	mOS 20.0 months	ACT IV [90,103]	Phase III, no improvement in OS; not recommended for EGFRvIII+
	Cytokines: IFN-α + TMZ	mOS 26.7 months	Phase III [90]	Phase III, adjuvant after RT; benefit in mOS, non-standard

 doi:10.20944/preprints202507.0848.v1

	Triple IT	No recurrence at 17 months	GIANT, ongoing [91]	Neoadjuvant to surgery; single case; ongoing trials

Legend: ACT: Adoptive cellular therapies; BEV: Bevacizumab; CR: Complete response; ICI: Immune checkpoint inhibitors; IT: Immunotherapy; OV: Oncolytic viruses; PFS-6: 6-month progression-free survival.

Standard TMZ chemotherapy, established by the EORTC/NCIC CE.3 trial, is the reference treatment in nGBM, improving survival compared to RT alone [12], though intensive TMZ offers no benefit (RTOG 0525) [92]. In rGBM, metronomic TMZ shows limited activity, particularly after BEV (RESCUE), and lomustine offers modest results (EORTC 26101) [93-95]. Lomustine plus TMZ achieves an mOS of 48.1 months in nGBM with MGMT methylation (CeTeG/NOA-09) [96]. Chemotherapy- and RT-induced lymphopenia, as discussed in Section 4, may limit subsequent immunotherapy efficacy. Targeted therapies, such as BEV, do not extend OS in nGBM (AVAglio, RTOG 0825; mOS 16.8 months, mPFS 10.6 months) but improve disease control in rGBM (BRAIN, EORTC 26101, BELOB; mOS 9.2 months, mPFS 4.2 months) [94,95,97,98] (see Table 9 for its neoadjuvant role). PARP inhibitors, such as veliparib, tested in the VERTU trial, are a promising targeted therapy in nGBM with unmethylated MGMT by enhancing radiation-induced damage, one of the few strategies with clinical evidence in specific subgroups [36].Cilengitide is ineffective in nGBM (CENTRIC, CORE) [95,99], as are erlotinib and everolimus, both inhibitors of tumor signaling pathways [38,95]. Regorafenib has limited efficacy in rGBM (REGOMA), outperforming erlotinib or everolimus but with modest benefits [95]. BRAF/MEK inhibitors show promising responses in BRAF V600E-mutated cases [95]. IDH inhibitors, such as vorasidenib, are under investigation for IDH-mutant gliomas, with no data in GBM [95]. In immunotherapy, nivolumab does not outperform BEV in rGBM (CheckMate 143) or TMZ with RT in nGBM with unmethylated (CheckMate 498) or methylated MGMT (CheckMate 548), where treatment-induced lymphopenia may reduce efficacy [3,90,100]. Adoptive cellular therapies and oncolytic viruses, such as G47Δ (modified herpes simplex virus) or DNX-2401 (adenovirus), are promising in rGBM. DNX-2401, in monotherapy (20% 3-year survival) or combined with pembrolizumab in the CAPTIVE trial (mOS 12.5 months, ongoing), shows preliminary efficacy, though immunosuppression from dexamethasone and RT may limit its effectiveness [90,101]. Neoadjuvant pembrolizumab before surgery in rGBM improves survival with an mOS of 13.8 months in specific subgroups [90,102] (see Table 9 for neoadjuvant use). The DCVax-L vaccine benefits nGBM (mOS 19.3 months) and rGBM (mOS 13.2 months) but is not standard; rindopepimut does not improve survival in EGFRvIII-positive nGBM (ACT IV) [90,103]. Other vaccines are in development for GBM [90]. Cytokines like interferon-alpha (IFN-α) enhance TMZ in nGBM (mOS 26.7 months, phase III), though not standard, and neoadjuvant triple immunotherapy before surgery prevents recurrences in isolated nGBM cases (GIANT, ongoing) [3,91]. The blood–brain barrier (BBB) and treatment-induced immunosuppression limit the combination of immunotherapy with RT [90] (Table 10).

5.6. Advanced Imaging and Theranostics

Multiparametric MRI, including T1/T2-FLAIR, dynamic susceptibility contrast perfusion (DSC), diffusion-weighted imaging (DWI), and magnetic resonance spectroscopy (MRS), detects gliomas with high sensitivity, evaluates recurrence per RANO 2.0 criteria, including non-enhancing disease in IDH-mutant gliomas, and distinguishes pseudoprogression from true progression using DSC, DWI, and MRS (Table 11) [43,104,105]. Challenges include high costs and the need for specialized expertise in interpreting multiparametric MRI [104,105]. PET with amino acid tracers ([18F]-FET, [11C]-MET, [18F]-FDOPA, [18F]-FACBC) and [68Ga]-PSMA-11 differentiates recurrence from pseudoprogression with high specificity [106–109]. These techniques optimize RT planning by improving tumor delineation and enabling dose escalation in high-risk regions. A phase I trial using multiparametric MRI and [18F]-FDOPA PET achieved an mOS of 23 months without significant toxicity, though phase III trials have not confirmed OS benefits [44].Theranostics with [131I]-IPA

 doi:10.20944/preprints202507.0848.v1

achieves an mOS of 16 months in rGBM, limited by BBB penetration [107] (Table 11). Ongoing trials are evaluating novel theranostic agents [107,109].

Table 11. Advanced Imaging and Theranostics.

Modality	Application	Performance	Limitations
Multiparametric MRI	Diagnosis, recurrence, pseudoprogression	High sensitivity, RANO 2.0; DSC (90% sensitivity, 88% specificity), DWI (ADC >1200 × 10^{-6} mm^2/s), MRS (low Cho/Cr and Cho/NAA) for pseudoprogression [43,104,105]	Cost, need for specialized interpretation
PET 18F-FET	Theranostics (general)	High specificity (~80-90%), PET RANO 1.0 [106,107]	Cost, accessibility
PET [11C]-MET	Diagnosis, recurrence/ pseudoprogression	~95% sensitivity/specificity for grading; high accuracy for recurrence [107,108]	Short half-life, accessibility
PET [18F]F-DOPA	Diagnosis, recurrence/ pseudoprogression	92% sensitivity, 75% specificity for recurrence [106]	Cost, need for additional studies
PET [18F]FACBC	Diagnosis, recurrence/ pseudoprogression	90% sensitivity, 83% specificity for recurrence [107]	Need for further studies, accessibility
PET [68Ga]-PSMA-11	Diagnosis, recurrence/ pseudoprogression	High uptake in high-grade gliomas [109]	Need for further studies
Multiparametric MRI/PET-guided RT	Personalized RT with dose escalation	mOS 23 months in a phase I trial using multiparametric MRI and [18F]-FDOPA PET; no OS benefit in phase III trials [44]	Cost, accessibility, need for phase III validation
Theranostics [131I]-IPA	Treatment, evaluation	mOS 16 months in rGBM [107,109]	Limited BBB penetration, need for validation
Theranostics (general)	Treatment, evaluation	Ongoing trials (e.g., [177Lu]-PSMA, [177Lu]-6A10, [177Lu]-NeoB) [108,109]	Limited BBB penetration, need for validation

 doi:10.20944/preprints202507.0848.v1

Legend: ADC: Apparent diffusion coefficient; BBB: Blood–brain barrier; Cho: Choline; Cr: Creatine; DSC: Dynamic susceptibility contrast perfusion; DWI: Diffusion-weighted imaging; MRS: Magnetic resonance spectroscopy; NAA: N-acetyl aspartate; RANO 2.0: 2023 criteria for glioma evaluation; PET RANO 1.0: Criteria for amino acid PET.

6. Conclusions and Future Directions

Despite significant advancements in GBM management, RT continues to face inherent limitations, primarily due to diffuse tumor infiltration and intrinsic radioresistance, often driven by specific molecular alterations. While advanced RT techniques, including IMRT, adaptive RT, PT, and TTFields, have refined dose precision, their direct translation into substantial clinical benefits remains limited.

However, promising strategies are emerging. Neoadjuvant approaches, modified fractionation (such as hypofractionated RT), and reirradiation for recurrent GBM show therapeutic potential. The integration of various systemic therapies, including immunotherapies, chemotherapies, and targeted agents, is crucial for enhancing tumor control. Furthermore, radiotheranostics are expanding treatment possibilities.

The future of GBM RT lies in leveraging molecular biomarkers (e.g., MGMT methylation, IDH mutations) and advanced imaging to enable truly tailored treatment planning. The paramount challenge will be to effectively integrate complex tumor biology, cutting-edge technological tools, and comprehensive clinical data, ideally through AI-driven predictive models, to achieve precise and adaptive RT planning. Only through this integrated and individualized approach can we anticipate significant improvements in oncological outcomes for GBM patients.

Author Contributions: Conceptualization, C.F.; methodology, C.F.; literature review, C.F., R.C., A.D., and I.G.; writing—original draft preparation, C.F., R.C., A.D., and I.G.; writing—review and editing, C.F., R.C., A.D., and I.G.; data curation, R.C.; supervision, C.F. and F.C.; resources, F.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article as all data discussed are derived from publicly available sources cited in the references.

Acknowledgments: None.

Conflicts of Interest: F. C. declares the following conflicts of interest: sponsored research support from Janssen; consulting or advisory roles with Janssen and AstraZeneca; honoraria for lectures or educational activities from Janssen, Roche Farma, AstraZeneca, Astellas, Recordati, and Ipsen; and travel, accommodation, or expense support from AstraZeneca, Astellas, Janssen, and Roche Farma. The remaining authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

3D-CRT: Three-Dimensional Conformal Radiotherapy
ADC: Apparent Diffusion Coefficient
AMF: Alternating Magnetic Field
ASCO: American Society of Clinical Oncology
ASTRO: American Society for Radiation Oncology
BBB: Blood-Brain Barrier
BEV: Bevacizumab
BNCT: Boron Neutron Capture Therapy
BSH: Sodium Borocaptate
CDK4/6: Cyclin-Dependent Kinases 4 and 6

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CDKN2A/B: Cyclin-Dependent Kinase Inhibitor 2A/B
CFRT: Conventional Fractionated Radiotherapy
Cho: Choline
CIRT: Carbon Ion Radiotherapy
Cr: Creatine
CRT: Chemoradiation
CT: Chemotherapy
CTV: Clinical Target Volume
ddTMZ: Dense Dose Temozolomide
DSC: Dynamic Susceptibility Contrast Perfusion
DWI: Diffusion-Weighted Imaging
EGFR: Epidermal Growth Factor Receptor
EORTC: European Organisation for Research and Treatment of Cancer
ESCAT: ESMO Scale for Clinical Actionability of Molecular Targets
ESTRO: European Society for Radiotherapy and Oncology
EANO: European Association of Neuro-Oncology
FSRT: Fractionated Stereotactic Radiotherapy
GBM: Glioblastoma Multiforme
GTV: Gross Tumor Volume
GyE: Gray Equivalent
HFRT: Hypofractionated Radiotherapy
HIF-1α: Hypoxia-Inducible Factor 1-Alpha
HR: Hazard Ratio
HSRT: Hypofractionated Stereotactic Radiotherapy
ICI: Immune Checkpoint Inhibitor
IDH: Isocitrate Dehydrogenase
IGRT: Image-Guided Radiotherapy
IMPT: Intensity-Modulated Proton Therapy
IMRT: Intensity-Modulated Radiotherapy
KPS: Karnofsky Performance Status
L-BPA: L-4-Boronophenylalanine
LITT: Laser Interstitial Thermal Therapy
MDACC: MD Anderson Cancer Center
mEHT: Modulated Electrohyperthermia
MHT: Magnetic Hyperthermia
MNP: Magnetic Nanoparticles
mOS: Median Overall Survival
MRI: Magnetic Resonance Imaging
MRS: Magnetic Resonance Spectroscopy
MRgRT: Magnetic Resonance-Guided Radiotherapy
NAA: N-Acetyl Aspartate
NAT: Neoadjuvant Therapy
NCCN: National Comprehensive Cancer Network
NICE: National Institute for Health and Care Excellence
nGBM: Newly Diagnosed Glioblastoma Multiforme
OS: Overall Survival
PARP: Poly (ADP-Ribose) Polymerase
PET: Positron Emission Tomography
PFS: Progression-Free Survival
PI3K/AKT: Phosphatidylinositol 3-Kinase/Protein Kinase B
PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PT: Proton Therapy
PTEN: Phosphatase and Tensin Homolog
PTV: Planning Target Volume
RANO: Response Assessment in Neuro-Oncology
RBE: Relative Biological Effectiveness
rGBM: Recurrent Glioblastoma Multiforme
RT: Radiotherapy
SRS: Stereotactic Radiosurgery

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SVZ: Subventricular Zone
TERT: Telomerase Reverse Transcriptase
TMZ: Temozolomide
TP53: Tumor Protein p53
TTFields: Tumor Treating Fields
V20Gy: Volume Receiving 20 Gray
V40Gy: Volume Receiving 40 Gray
VMAT: Volumetric Modulated Arc Therapy
WBRT: Whole-Brain Radiotherapy
WHO: World Health Organization
wt: Wild-Type

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