Novel Radiation Approaches

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KEYWORDS

• Radiation therapy • Radiotherapy • Glioblastoma • GBM • Trials • Protons • Carbon ions

KEY POINTS

- The standard dose/fractionation schedule for newly diagnosed glioblastoma is 60 Gy/30 fractions; alternative hypofractionated schedules (5–15 fractions) can be considered in select patients.
- The addition of multiparametric MRI, metabolic, and functional imaging to target volume delineation in radiotherapy is an active area of current investigation.
- Advances in particle therapy (protons, carbon ions, and boron neutron capture therapy) are currently being evaluated for patients with newly diagnosed and recurrent glioblastoma.
- Several re-irradiation strategies exist for recurrent patients, including stereotactic radiosurgery, fractionated stereotactic radiation therapy, hypofractionated radiotherapy, pulsed-reduced dose-rate radiotherapy, and particle therapy.

INTRODUCTION

The aggressive nature of glioblastoma necessitates a multimodal treatment regimen consisting of maximum safe resection and adjuvant chemoradiotherapy. Despite improvements in surgical techniques, advances in molecular diagnostics, and introduction of novel chemotherapeutic agents, biologically targeted treatments, and immunotherapy innovations, the locally progressive pattern of disease spread has only solidified the role of radiation therapy (RT) in the management of this disease. This article systematically addresses the key elements of RT, with an assessment of the key studies regarding dose and fractionation schedules, principles of target volume delineation, and role of particle therapy techniques to improve the therapeutic ratio of treatment. Finally, the role of RT at the time of relapse remains an evolving area, and emerging evidence of its value is reviewed in brief.

DOSE AND FRACTIONATION

The optimal dose, volume, and fractionation schedule was the subject of several legacy randomized clinical trials (**Table 1**).[1] Walker and colleagues[2] published a pooled analysis of 3 Brain Tumor Study Group trials that demonstrated that 60 Gy was associated with improved overall survival (OS) compared with 55 Gy, 50 Gy, or $\leq$45 Gy. Multiple studies subsequently assessed different RT dose-escalation strategies. One such approach is hyperfractionation, whereby RT is delivered using multiple smaller fractions delivered each day to a higher total dose. However, hyperfractionated RT delivered at 1.2 to 1.6 Gy per fraction twice daily up to 70.4 to 72 Gy

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Table 1
Clinical trials assessing different dose and fractionation schedules for newly diagnosed glioblastoma

Study	Key Population Criteria	Total Dose (Gy)	Number of Fractions	Dose per Fraction (Gy)	Interfraction Interval	Results
Ali et al,[3] 2018	694 patients with grade III (29%) or IV (71%) glioma	72 (with BCNU) 60 (with BCNU)	60 30	1.2 2	4–8 1 d	Hyperfractionated RT did not improve median OS (11.3 vs 13.1 mo, $P = .20$).
Andersen et al,[74] 1978	108 adults with grade IV astrocytoma (glioblastoma)	No RT 45	N/A 25 (5–6 fractions/wk)	N/A 1.8	N/A 1 d	RT improved OS at 6 mo ($P<.005$).
Bleehen et al,[75] 1991	474 patients with grade III (33%), III/IV (6%), or IV (61%) glioma	45 60	20 30	2.25 2	1 d 1 d	60 Gy improved median OS (12 vs 9 mo, $P = .007$).
Glinkski et al,[76] 1993	108 patients with grade III (59%) or IV (41%) astrocytoma	50 (WBRT) → 10 (tumor boost) 20 (WBRT) → 20 (WBRT) → 10 (tumor boost)	30 5 → 5 → 5	2 4 → 4 → 2	1 d 1 d; each course separated by 1 mo interval	Among grade IV, hypofractionated RT regimen improved 2 y OS (23% vs 10%, $P<.05$).
Keime-Guibert et al,[77] 2007	81 patients with glioblastoma, age ≥70, KPS ≥70	No RT (supportive care) 50	N/A 25	N/A 1.8	N/A 1 d	RT improved median OS (29.1 vs 16.9 wk, $P = .002$).
Kristiansen et al,[78] 1981	118 patients with grade III or IV astrocytoma	No RT (no CHT) 45 Gy (WBRT) 45 Gy (WBRT with bleomycin)	N/A 25 25	N/A 1.8 1.8	N/A 1 d 1 d	RT (but not bleomycin) improved median OS (10.8 vs 5.2 mo).
Malmström et al,[11] 2012	291 patients with glioblastoma, age ≥60	No RT (TMZ alone) 34 60	N/A 10 30	N/A 3.4 2	N/A 1 d 1 d	60 Gy worsened median OS (6 vs 8.3 [TMZ, $P = .01$] vs 7.5 [34 Gy, $P = .24$] mo).
Phillips et al,[79] 2003	68 patients with grade III (10%) or IV (90%) astrocytoma	35 60	10 30	3.5 2	1 d 1 d	Short course RT had similar median OS (8.7 vs 10.3 mo, $P = .37$).
Prados et al,[4] 2001	231 patients with glioblastoma	70.4 70.4 (with DMFO) 59.4 59.4 (with DMFO)	44 44 33 33	1.6 1.6 1.8 1.8	6–8 h (BID) 6–8 h (BID) 1 d 1 d	Hyperfractionated RT did not improve median OS (42 vs 41 wk, $P = .75$). No difference in OS with DMFO.

Roa et al,[10] 2004	100 patients with glioblastoma, age ≥60	40 60	15 30	2.67 2	1 d 1 d	Hypofractionated RT had similar median OS (5.6 vs 5.1 mo, $P = .57$).
Roa et al,[12] 2015	98 patients with glioblastoma, all elderly and/or frail	25 40	5 15	5 2.67	1 d 1 d	Short course RT (25 Gy) had noninferior median OS (7.9 vs 6.4 mo, $P = .988$).
Shin et al,[80] 1987	124 patients with grade III (71%) or IV (29%) astrocytoma	61.41 61.41 (with misonidazole) 58	69 (TID) 69 (TID) 30	0.89 0.89 1.93	3–4 h (TID) 3–4 h (TID) 1 d	Hyperfractionated RT improved median OS (39–49 vs 27 wk, $P<.001$). No difference in OS with misonidazole.
Walker et al,[16] 1978	303 patients with grade III (10%) or IV (90%) astrocytoma	Supportive care alone BCNU alone 50–60 (WBRT) 50–60 (WBRT with BCNU)	N/A N/A 25–35 25–35	N/A N/A 1.71–2 1.71–2	N/A N/A 1 d 1 d	RT improved median OS (34.5–37.5 vs 18.5 [BCNU] vs 14 [supportive care] weeks], $P = .001$).
Walker et al,[2] 1979	Pooled analysis of 621 patients with malignant gliomas enrolled on BTSG studies	≤45 50 55 60	25–35 25–35 25–35 25–35	1.71–2 1.71–2 1.71–2 1.71–2	1 d 1 d 1 d 1 d	60 Gy associated with improved survival over 55 Gy, 50 Gy, and ≤45 (42 vs 36 vs 28 vs 13.5 wk, respectively).

Abbreviations: BCNU, carmustine; BID, twice daily; BTSG, brain tumor study group; CHT, chemotherapy; DMFO, difluoromethylornithine; Gy, Gray; KPS, Karnofsky performance status; N/A, not applicable; OS, overall survival; RT, radiotherapy; TID, 3 times daily; TMZ, temozolomide; WBRT, whole brain RT.

provided no survival benefit compared with conventional RT.[3,4] The Radiation Therapy Oncology Group (RTOG) also evaluated a stereotactic radiosurgery (SRS) boost of 15 to 24 Gy before conventionally fractionated 60 Gy with BCNU (carmustine), but there was similarly no survival benefit.[5] Furthermore, trials assessing the addition of a brachytherapy boost using radioactive implants have also been negative.[6] As such, a conventionally fractionated dose of 60 Gy remains the standard of care for nonelderly patients with good performance status.[7] Recent studies have demonstrated the feasibility of doses of more than 60 Gy,[8,9] which provided the basis for the ongoing NRG BN001 phase II study (NCT02179086) assessing dose escalation using photons or protons with a simultaneous integrated boost technique to 75 Gy in 30 fractions.

Because glioblastoma is associated with an exceptionally poor prognosis in elderly and frail patients (5- to 9-month OS), several hypofractionated RT courses have been evaluated. Dose/fractionation schedules using 40 Gy/15 fractions,[10] 34 Gy/10 fractions,[11] and 25 Gy/5 fractions[12] have yielded similar survival outcomes in select patients. More recent data also established the safety and benefit of concurrent temozolomide with 40 Gy in 15 fractions among patients $\geq$65 years of age.[13]

PRINCIPLES OF TARGET VOLUME DELINEATION

RT target volumes for glioblastoma have evolved, but significant heterogeneity still exists across cooperative group guidelines.[7,14,15] Although early studies treated the whole brain to full dose, 3-dimensional imaging allowed treatment volumes to include only the partial brain at highest risk of recurrence, typically consisting of the resection cavity and contrast-enhancing (CE) residual tumor plus a 5-mm to 30-mm margin to account for microscopic disease.[7,14–16] Whereas the Adult Brain Tumor Consortium (ABTC), North Central Cancer Treatment Group (NCCTG)/Alliance, and Radiation Therapy Oncology Group (RTOG)/NRG include an initial T2/fluid-attenuated inversion recovery (FLAIR) target with a subsequent cone-down to the cavity and CE residual tumor, the European Organisation for Research and Treatment of Cancer (EORTC) uses a 1-phase approach based on the CE residual tumor and resection cavity alone, without intentionally targeting T2/FLAIR hyperintensity.[7,14] A detailed description of target volume variations is presented in **Table 2**, with corresponding examples of each in **Fig. 1**. Other key principles of target volume delineation include limiting target expansions to anatomic barriers of tumor spread (eg, falx cerebri, tentorium cerebelli), while ensuring coverage of areas at risk of contiguous tumor spread despite crossing midline (eg, anterior and posterior commissures).[15]

Currently, there are at least 3 different advanced imaging strategies seeking to redefine target delineation for glioblastoma: multiparametric magnetic resonance (MR), MR spectroscopy, and functional imaging. Dynamic CE MRI analyzes relative cerebral blood volume,[17,18] cerebral blood flow, and vascular permeability.[19] Together with diffusion-weighted MRI, a surrogate for tumor cellularity,[20] these images can be integrated into a multiparametric imaging signature that has been associated with patterns-of-failure outcomes in glioblastoma.[21] A multi-institutional phase II trial (NCT02805179) is currently under way using this multiparametric advanced imaging approach to guide dose-intensified radiotherapy (75 Gy/30 fractions) and aims to evaluate the OS of patients treated with this paradigm. An initial report from the first 12 patients in this study demonstrated that the advanced imaging target volumes were approximately 2 times smaller than the T1 enhancement volumes and 10 times smaller than the FLAIR volumes, yet identified disparate high-risk areas, with only a 57% overlap with the enhancement region on MRI alone.[22] A different approach uses spectroscopic MRI (sMRI) to evaluate the regions of the brain with elevated choline-to-N-acetylaspartate ratios[23] and guide dose escalation to these areas of elevated tumor-related metabolic activity, which also correspond to the areas at risk for disease relapse.[24] Integration of a dose-escalation (75 Gy/30 fractions) approach to sMRI-defined high-risk regions has been successfully tested across multiple institutions using a cloud platform.[25] A phase II multi-institutional pilot study using sMRI-defined target volumes (NCT03137888) is also under way with co-primary endpoints of feasibility and incidence of adverse events; data from the first 18 patients have been promising.[25] Finally, functional imaging with novel amino acid PET radiotracers, in particular, [^{11}C]-Methionine (MET) PET has been correlated with areas at risk of disease progression to guide treatment planning[26] and studies have even developed radiobiological models to determine the dose needed to these areas to reduce the risk of relapse.[27] Similarly, [^{18}F]-Fluoroethyltyrosine (FET)-based target volume delineation has been used in clinical studies to augment volumes defined with anatomic MRI alone, with no documented marginal or distant failures.[28] Dose-

Table 2
Glioblastoma radiotherapy target volume delineation among cooperative groups

	ABTC	EORTC	NCCTG/Alliance	RTOG/NRG
One or 2 phase	Two-phase: 46 Gy → 14 Gy	One-phase 60 Gy	Two-phase: 50 Gy → 10 Gy	Two-phase: 46 Gy →14 Gy
Initial CTV	T2, T1-CE, cavity + 5 mm	T1-CE, cavity + 2–3 cm	T2, T1-CE, cavity + 2 cm to block edge	T2, T1-CE, cavity + 2 cm
Boost CTV	T1-CE, cavity + 5 mm	N/A	T1-CE, cavity + 2 cm to block edge	T1-CE, cavity + 2 cm
PTV	Generally 3–5 mm	Generally 5–7 mm	N/A	3–5 mm

Abbreviations: ABTC, adult brain tumor consortium; CE, contrast enhancement; CTV, clinical target volume; EORTC, European Organisation for Research and Treatment of Cancer; Gy, Gray; NCCTG, North Central Cancer Treatment Group; PTV, planning target volume; RTOG, Radiation Therapy Oncology Group.

escalation studies (72 Gy/30 fractions) to FET-PET–based regions demonstrated that all local relapses occurred within the 60-Gy isodose volume[29]; therefore, trials are currently under way to compare FET-PET with MRI alone in randomized settings (NCT01252459).[30] Each of the aforementioned approaches has merits and limitations; however, the future is clearly transitioning from anatomically delineated to biologically defined target volumes.

PARTICLE THERAPY ADVANCES

The radiobiological properties of particle therapy (such as protons, carbon ions, and boron neutron capture therapy [BNCT]) hold the promise to overcome the radioresistant nature of glioblastoma via activation of several unique molecular pathways.[31] The dosimetric profile of particle therapy allows for most of the dose to be accumulated into the tumor with little dose deposition beyond the distal edge

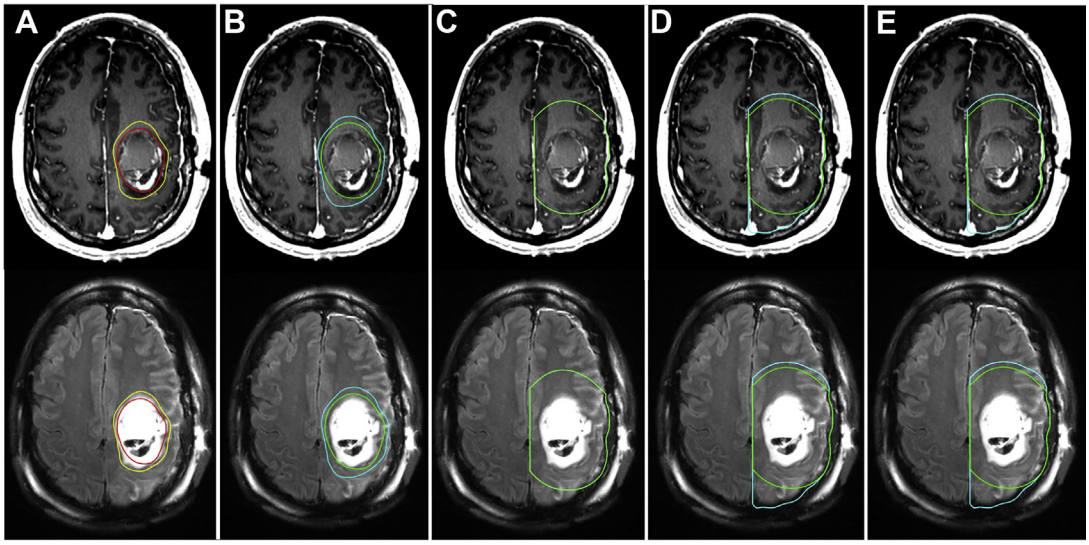

Fig. 1. Glioblastoma RT target volume delineation among different cooperative groups. Postoperative MRI T1 contrast-enhanced (*above*) and FLAIR (*below*) sequences. The gross tumor volume (GTV) initial is in yellow (97.73 cc) and GTV boost is in red (44.12 cc) (*A*). The ABTC volumes for clinical target volume (CTV) initial in cyan (46 Gy, 166.26 cc) and CTV boost in green (60 Gy, 81.83 cc) (*B*). The EORTC volume for the single phase CTV in green (60 Gy, 237.07 cc) (*C*). The NCCTG/Alliance volumes for CTV initial in cyan (50 Gy, 367.87 cc) and CTV boost in green (60 Gy, 237.07 cc) (*D*). The RTOG/NRG volumes for CTV initial in cyan (46 Gy, 367.87 cc) and CTV boost in green (60 Gy, 237.07 cc) (*E*).

of the treatment volume, resulting in superior dose conformality and reduced total integral dose to the brain.[32,33] As many of the central nervous system (CNS) organs-at-risk (OARs) have known dose-volume toxicity thresholds, particle therapy may allow for safer high-risk zone dose escalation, for example, in the hypoxic core.[34] Even reduction in integral dose to the brain alone with particle therapy (without any other benefits), and therefore the circulating blood pool, may reduce the treatment-induced lymphopenia observed with concurrent chemoradiotherapy, potentially translating into cost-effectiveness and improved survival.[35–37] Although limited data are currently available, several clinical trials have been recently completed or are under way, which may shed light on the use of particle therapy (**Table 3**).

Retrospective studies of proton therapy demonstrated the favorable safety, neurocognitive, and quality-of-life outcomes, and progression-free (PFS) and OS compared with photon series.[38–40] A phase II trial of 23 patients treated to a 90 Gy (with 57.6 Gy delivered with protons) resulted in a promising median OS of 20 months; most recurrences remained in-field and 30% developed symptomatic radiation necrosis.[41] Alternative approaches, such as hyper-fractionated concomitant boost techniques (50.4 Gy with photon therapy and 23.4 Gy cone-down) have resulted in reduced toxicities with similar OS (22 months).[38,42] The aforementioned NRG BN001 trial (NCT02179086) is currently randomizing patients with newly diagnosed glioblastoma to hypofractionated dose-escalated RT (75 Gy/30 fractions with photon therapy or proton therapy) or conventionally fractionated RT (60 Gy in 30 fractions with photon therapy) and will provide prospective assessment and comparable data with valuable information on OS, PFS, and treatment-related toxicities (including adverse events, neurocognitive function, and treatment-induced lymphopenia) (**Fig. 2**).

Carbon ion therapy has been evaluated in multiple phase I/II trials as a primary treatment modality or as a boost following photon therapy. In one study, 48 patients with high-grade gliomas (32 with glioblastoma) received 50 Gy/25 fractions with photon therapy along with nimustine hydrochloride followed by an 8 fraction boost with carbon ions in dose increments from 16.8 to 24.8 Gy. There was a stepwise increase in OS from 7 to 19 to 26 months, in the low-, middle-, and high-dose cohorts, respectively.[43] These promising results were evaluated in the recently completed CLEOPATRA trial (NCT01165671) in which patients were treated with photon therapy (50 Gy) and randomized to a proton therapy boost (10 Gy/5 fractions) or a carbon ion boost (dose-escalation paradigm to 18 Gy/6 fractions)[44]; results are pending.

BNCT is a type of particle therapy that uses a 2-step approach to selectively target malignant cells. A boron-10 (^{10}B)-labeled compound is first delivered and selectively localizes in tumor cells in high concentrations that are subsequently irradiated with low-energy thermal neutrons.[45] The resulting reaction yields high linear-energy-transfer α-particles and ^{7}Li-particles traveling within a single cell's diameter, thus selectively damaging tumor cells while preserving normal cells. Historically, the availability of these epithermal neutrons has been restricted to reactor-based facilities, but novel accelerator-based approaches have led to a resurgence of this approach in hospital-based facilities. To date, only small trials using BNCT for newly diagnosed glioblastoma have been published, each using the ^{10}B compounds sodium borocaptate (BSH) and/or boronophenylalanine (BPA) with heterogeneous treatment delivery techniques, such as intraoperative BNCT or with the addition of conventional photon therapy.[46–51] A recently completed phase II multicenter study of BNCT using BSH and BPA with concurrent TMZ has preliminarily reported a promising median OS of 21.2 months (NCT00974987).[45,52]

RE-IRRADIATION STRATEGIES

Several re-irradiation strategies have been evaluated in patients with progressive or recurrent disease, including SRS, fractionated stereotactic RT (FSRT), intraoperative RT, hypofractionated RT, conventionally fractionated re-irradiation with pulsed-reduced dose-rate techniques (PRDR), and particle therapy. Given the heterogeneous disease cohorts included in each of these series, comparative analysis across studies cannot be performed and instead a re-treatment paradigm with consideration of patient-related, disease-related, and treatment-related factors with comprehensive evaluation in a multidisciplinary setting is recommended to tailor recommendations for each patient (**Fig. 3**).

Stereotactic Radiosurgery/Fractionated Stereotactic Radiotherapy

SRS/FSRT represents an attractive re-irradiation technique for glioblastoma to both limit re-irradiation volume and expedite treatment among a group of patients with short survival. Several phase I-II studies have reported various dosing strategies with or without systemic therapy, resulting in median survival of 6 to 12.5 months and crude radiation necrosis rates of 0% to 13%. An

Table 3
Current and ongoing clinical trials of particle therapy for newly diagnosed and recurrent glioblastoma

NCT Number	Study Name	Study Type	Phase	Initial vs Recurrent Disease	N	Particle Therapy Technique	Total Dose (Gy/fx)	Study Start Date	Estimated Completion Date	Primary Outcome
NCT02179086	NRG BN001	Randomized	II	Initial	606	Proton	75 Gy/30 fx	10/2021	05/2021	OS
NCT02824731	ProtoChoice-Hirn	Nonrandomized	II	Initial (supratentorial) Recurrent (>40 Gy in treatment area)	346	Proton	Initial: 54–60 Gy/30 fx Recurrent: 30 Gy/6 fx or 36 Gy/13 fx	07/2016	07/2026	Late toxicity (AE, QOL, or decreased brain function)
NCT01854554	NA	Randomized	II	Initial	90	Proton	60 Gy/30 fx	05/2013	05/2020	Time to cognitive failure
NCT04536649	NA	Randomized	III	Initial	369	Proton, Carbon ion	60 Gy/30 fx (proton) $\pm$ 15 Gy/3 fx carbon ion boost	10/2020	09/2025	OS
NCT01165671	CLEOPATRA	Randomized	II	Initial	100	Proton boost, Carbon ion boost	10 Gy/5 fx (protons) 18 Gy/6 fx (carbon ion)	07/2010	01/2015	OS
NCT00974987	NA	Nonrandomized	II	Initial	32	Boron neutron capture therapy	24 Gy/2 fx	09/2009	02/2016	OS
NCT01166308	CINDERELLA	Nonrandomized and randomized	I/II	Recurrent	56	Carbon ion	30–42 Gy/ 10–16 fx	12/2010	04/2016	1-y OS

Abbreviations: AE, adverse events; fx, fraction; N, number; NA, not available; OS, overall survival; PFS, progression-free survival; QOL, quality of life.

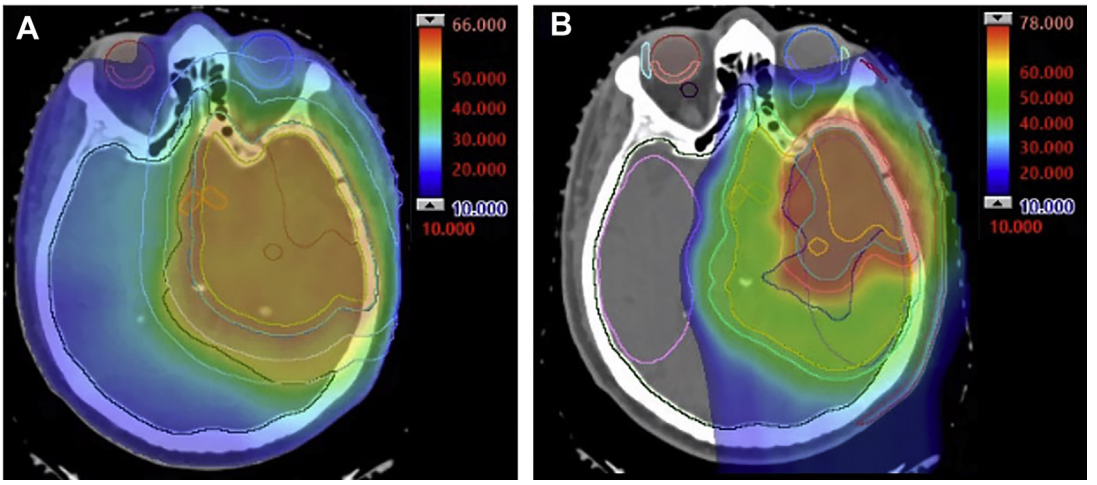

Fig. 2. Axial CT scans and corresponding isodose distributions for a patient enrolled onto the ongoing NRG BN001 clinical trial randomizing between (*A*) conventionally fractionated photon therapy (46 Gy in 23 fractions with a sequential boost to 60 Gy in 30 fractions) and (*B*) a dose-intensified schedule (75 Gy in 30 fractions with a simultaneous integrated boost of 51 Gy in 30 fractions, here depicted with proton therapy).

early dose-escalation study identified a maximum tolerated dose of 36 Gy/3 fractions.[53] The role of bevacizumab with SRS/FSRT re-irradiation (16 Gy in 1 fraction) was evaluated in a case control study that demonstrated a substantial reduction in the rate of radiation necrosis (43% vs 9%).[54] A 25-patient phase II study administered 30 Gy in 5 fractions with bevacizumab resulting in a median OS of 12.5 months and no radiation necrosis,[55] whereas another phase I study identified 33 Gy in 3 fractions as the maximum tolerated dose with bevacizumab.[56] Furthermore, a retrospective analysis of 297 patients with recurrent or residual glioblastoma treated with SRS found that bevacizumab was associated with improved OS, PFS, and reduced radiation necrosis.[57] Although the ideal dose/fractionation regimen has yet to be established, this approach should generally be limited to select patients with smaller target volumes (<5 cm).

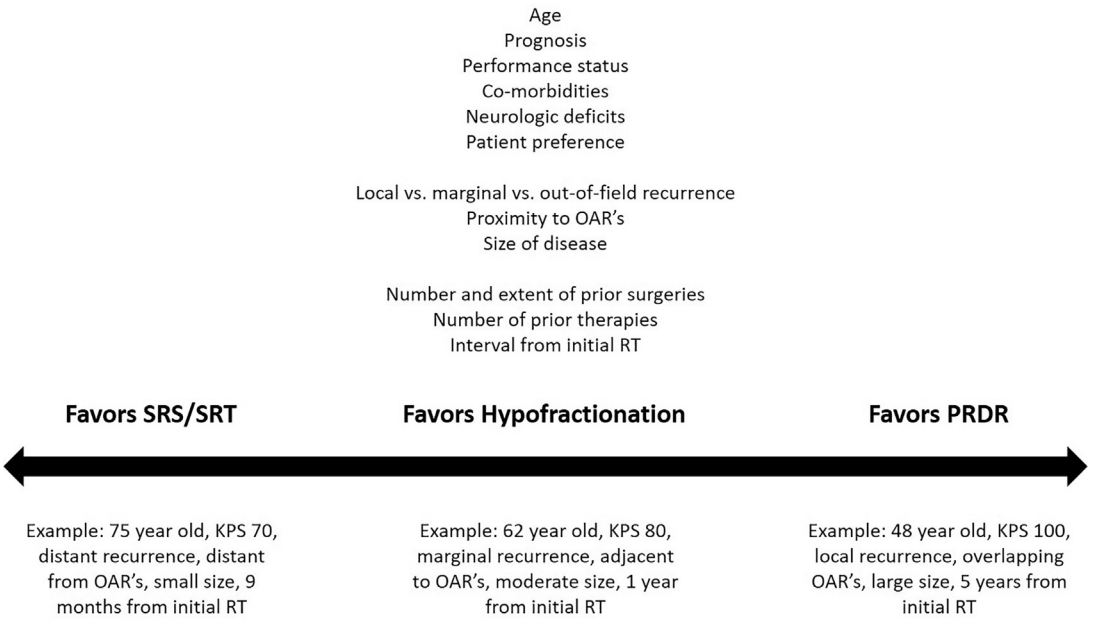

Fig. 3. Factors to consider for re-irradiation. KPS, Karnofsky performance status; SRT, stereotactic radiotherapy.

Hypofractionated Radiotherapy

Hypofractionated RT for re-irradiation may allow for expedited treatment compared with conventionally fractionated RT, while overcoming the toxicity associated with higher dose per fraction SRS/FSRT. However, early studies using hypofractionated RT doses of 20 to 50 Gy in 4 to 10 fractions (5 Gy per fraction) demonstrated high rates of radiation necrosis (23%–36%).[58,59] Subsequently, a lower dose per fraction regimen of 30 to 35 Gy in 10 fractions was found to have no grade 3 toxicity, but improved response rates compared with 24 Gy in 8 fractions.[60] Additional retrospective data from 147 patients supported a 35 Gy in 10 fractions regimen,[61] and led to the development of RTOG 1205, a multi-institutional phase II study of bevacizumab with or without hypofractionated RT (NCT01730950). Results were presented at the 2019 American Society of Radiation Oncology conference, demonstrating no difference in OS, but improved 6-month PFS with the addition of RT (54% vs 29%, $P = .001$).[62]

Pulsed-Reduced Dose-Rate

PRDR is a specialized technique that involves dividing the standard treatment delivery rate (4–6 Gy/min) into subfractions of approximately 0.2 Gy each, delivered at an effective dose-rate of 0.07 Gy/min.[63] Multiple series have demonstrated the safety of this approach with full-dose re-irradiation to large CNS target volumes, even with overlap of serial OARs.[64] Recently, the outcomes of a retrospective study of 80 patients with recurrent high-grade glioma (47 of whom received bevacizumab monotherapy and 33 were treated with PRDR and bevacizumab) reported improved PFS (4 vs 12 months) and OS (9 vs 16 months)[65] supporting this approach; additional results from a multicohort prospective study are forthcoming (NCT01743950).

Particle Therapy

Use of particle therapy approaches in the re-irradiation setting are limited to case series at present. In one study, patients were re-treated with a median dose of 33 Gy with proton therapy (following an initial median dose of 55 Gy and a median re-treatment interval of 16 months), resulting in a reported OS of 19.4 months.[66] The Proton Collaborative Group also reported a multi-institutional experience of re-irradiation in 45 patients to a median dose of 46.2 Gy with proton therapy (following an initial median dose of 60 Gy and a median re-treatment interval of 20 months), resulting in a reported OS of 14.2 months.[67] Prospective trials are under way to further evaluate these techniques, including the ongoing CINDERELLA trial in which patients with recurrent gliomas are randomized to carbon ion re-irradiation (dose escalation to 48 Gy in 16 fractions) or stereotactic photon RT (36 Gy in 18 fractions).[68] Several small studies have evaluated BNCT re-irradiation for recurrent malignant gliomas. A phase 1 study of 22 patients reported a median OS of 7 months following BNCT re-irradiation, whereas a more recent pilot study using BNCT re-irradiation followed by bevacizumab in 7 patients reported a median OS of 15.1 months.[69,70]

FUTURE DIRECTIONS

Although the median survival for patients with glioblastoma has remained disappointingly stagnant over the past 5 years, a number of prospective studies and clinical trials in radiation oncology have better defined key aspects of dose and fractionation, target volume delineation, particle therapies, and role of re-irradiation at the time of relapse. In addition, several innovative concepts related to radiotherapy technique and technology are currently in development. The introduction of MR linear accelerators in radiotherapy practice has allowed for frequent intrafraction imaging during chemoradiotherapy with observation of interfraction dynamic tumor morphologic changes; this may provide an avenue for on-line adaptive radiotherapy, especially in patients receiving hypofractionated treatments.[71] FLASH RT (delivered >40 Gy/s) has recently been demonstrated to provide tumor control without cognitive deficits in learning or memory in a glioblastoma mouse model; clinical systems are being outfitted with the necessary components to initiate clinical trials.[72] An in-beam PET scanner has been installed at the Italian National Center of Oncologic Hadrontherapy, which will allow for near real-time tracking and imaging of charged particles with millimetric accuracy.[73] These represent just a few of the exciting areas of RT research and development to support our overall mission to improve glioblastoma outcomes.

CLINICS CARE POINTS

- Conventionally fractionated radiotherapy to 60 Gy in 30 fractions is the standard dose for younger patients with glioblastoma with good performance status.
- Hypofractionated radiotherapy regimens are appropriate for elderly or poor performing patients who have a worse prognosis.

- Radiotherapy target volumes guidelines vary by cooperative groups.
- Several re-irradiation strategies are available, which should be chosen based on the unique clinical scenario, and are often administered in conjunction with bevacizumab.
- Owing to the poor prognosis of glioblastoma, patients should be enrolled on clinical trials when eligible.
- Numerous clinical trials assessing novel radiotherapy approaches are ongoing.

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