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RE-IRRADIATION IN GLIOBLASTOMA MULTIFORME

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ABSTRACT

This review article addresses the role of re-irradiation in recurrent cases of previously treated Glioblastoma multiforme (GBM). The article particularly focuses on patient selection, imaging, dose fractionation regimens, radiation delivery techniques and follow up assesement, survival benefits and toxicities, when re-irradiation is used to treat local recurrences.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive and common primary malignant brain tumor in adults, characterized by rapid progression and poor prognosis. The standard initial treatment includes maximal safe surgical resection followed by concurrent chemoradio therapy with temozolamide and adjuvant chemotherapy. [1] Despite aggressive management, most patients experience recurrence, typically within 6 to 9 months after initial therapy.[2] The therapeutic options for recurrent GBM are limited and often palliative. Re-irradiation has emerged as a potential salvage therapy for selected patients.[3] However, concerns regarding cumulative radiation toxicity, particularly radiation necrosis, had limited its widespread application. With advances in radiation delivery techniques such as stereotactic radiosurgery (SRS), stereotactic radio therapy (SRT), and intensity-modulated radiotherapy (IMRT), reirradiation has regained interest as a viable treatment modality. Systematic reviews for endpoints like progression-free (PFS) or overall survival (OS) with the use of newer treatment modalities, have indicated a benefit with regards to PFS, but the benefit in terms of OS has still not been seen. [4-7]

MATERIALS AND METHODS

A literature search was conducted using PubMed, Scopus, and Google Scholar databases to identify peer-reviewed studies on re-irradiation in GBM from 2000 to 2024. Search terms included "re-irradiation," "glioblastoma," "recurrent glioma," "stereotactic radiotherapy," and "radiation necrosis." Inclusion criteria were studies reporting clinical outcomes, toxicity, and survival following re-irradiation in histologically confirmed recurrent GBM patients. Studies involving pediatric gliomas or those not differentiating GBM from other gliomas were excluded.

A total of 52 studies were reviewed, comprising retrospective analyses, prospective cohorts, and a few phase I/II trials. Key data extracted included patient selection criteria, radiation technique, total dose, fractionation schedule, time interval between initial and second irradiation, concurrent systemic therapies, survival outcomes, and toxicity profiles.

Patient Selection:

Careful patient selection is crucial for the success of re-irradiation. Factors influencing selection include age, Karnofsky Performance Status (KPS), tumor location and volume, interval since initial radiotherapy, repeat surgery and presence of symptoms. Typically, patients with KPS ≥ 60, and a progression-free interval of ≥ 6 months from initial treatment, independent of age and MGMT methylation status are considered suitable candidates [8,9]; with KPS being considered as a strongest predictor of OS, as it appears to be the single most common factor in multivariate analysis of prospective trials and in large retrospective cohorts. [4-

7, 10]

Imaging required to assess recurrence post primary treatment

Often, serial imaging (typically, MRI) and clinical evaluation form the basis for classifying treatment response and defining recurrence.

The Macdonald criteria, published in 1990, based on the product of maximal cross-sectional dimensions of enhancing foci, provided an objective methodology for tumor measurement and comparison over time. [5] These criteria standardized nomenclature for response assessment (i.e., complete response, partial response, stable disease, or progressive disease) according to changes in tumor size, while taking into account neurologic status and steroid use.

Over time, identification of limitations of the Macdonald criteria resulted in the development of the RANO criteria. [11] for treatment response assessment and definition of tumor recurrence, which took into account the non-enhancing disease, and addressed pseudoprogression and pseudoresponse. The RANO criteria defines recurrence as any of the following: at least 25% increase in sum of the products of perpendicular diameters (SPD) of well-defined and "measurable" enhancing lesions or significant increase in T2/FLAIR non-enhancing lesion while on stable or increasing corticosteroid doses, development of a new lesion, clear progression of "nonmeasurable" disease (i.e., unidimensional, ill-defined or <10 mm), or clinical deterioration not attributable to causes apart from tumor.

Pseudoprogression should be strongly considered if the enhancing lesion grows within 12 weeks of chemo-radiation.[8] The RANO criteria only consider such growth "progression" if the majority of new enhancement lies outside the high-dose region (i.e., 80% isodose line) or if there has been pathologic confirmation of disease.

Pseudoresponse should be considered in patients receiving anti-angiogenic therapy, which may cause rapid reductions in enhancement in tumors that subsequently demonstrate increased T2/FLAIR signal reflecting infiltrative tumor. [7]

Post contrast T1 weighted images are required to particularly assess in- field recurrences seen as 'contrast enhanced tumors' in GBM.[8,9] Additionally conventional T2 weighted/T2 FLAIR images can detect non enhanced tumor progression or edema seen as 'hyperintense signals'. To differentiate tumor recurrence from treatment induced changes such as radiation necrosis/ pseudoprogression, advanced imaging techniques (i.e., perfusion MRI, MR spectroscopy, AA-PET) are recommended as they can more accurately detect tumor-associated processes (neovascularisation, metabolic changes, cell proliferation). AA-PET imaging could be [11C]Methionine (MET) PET , [18F] fluoro-L-3,4-dihydroxyphenylalanine (FDOPA) PET, or [18F] fluoroethyltyrosine (FET) PET . The additional value of PET for target volume delineation needs to be revisited and cannot be unequivocally recommended at present. [12]

Re-imaging after an interval of four to eight weeks may elucidate the underlying pathology (stable/subsiding changes indicating pseudoprogression/radiation necrosis versus continued increase indicating recurrence).

In addition, the imaging finding should be correlated with the previously irradiated volume The prior radiation dose distribution and dosimetry can serve as a guidance in addition to imaging to decide for or against tumor progression.

Optimal target definition

Simulation CT (slice thickness 1–3 mm) should be performed using an individualised immobilisation thermoplastic mask and images should be acquired encompassing the entire cranium. MRI images for planning purposes similar to simulation CT (1 mm slice thickness, orthogonal plane) should be acquired and fused with the CT images. Target selection should include lesions not exceeding 5–6 cm in largest diameter, while larger lesions, multi-focal and leptomeningeal disease should be excluded from reirradiation.

Critical organs at risk should be contoured, especially the brain, brainstem, optic nerves, chiasm, and eyes. The data for Hippocampal sparing in reirrdiation of GBM is limited. Most GBMs are not near the hippocampal region, therefore sparing hippocampus can help preserve neuroocognitive functions. But GBM being diffusely infiltrative tumor, any attempt to spare hippocampus

may lead to hippocampal region harbor microscopic disease. Therefore, decision to spare hippocampus should be individualized based on tumor location, expected survival, prior cognitive function status and priority of local control rather than perseverance of neurocognitive function. Therefore hippocamal sparing can be attempted in select patients only, but not generally recommended.

GTV is typically defined as the visible lesion on MRI contrast- enhanced T1-weighted sequences as well as suspected new / progressing T2-weighted/T2-weighted FLAIR abnormalities or AA-PET avid regions [8].There is no consensus whether to include or not the perfusion suspect regions into the GTV. In the published literature there is no standard GTV to CTV margin; in the majority of studies the GTV corresponds to the CTV but others used margins ranging from 3 to 5 mm. A PTV margin should be created by a geometrical expansion of the CTV using a margin of up to 3 mm. [9]

Radiation Techniques:

Modern techniques have enabled precise targeting of recurrent lesions while sparing surrounding healthy brain tissue. Advanced IGRT techniques are recommended for reirradiation purposes. Common modalities include:

Stereotactic Radiosurgery (SRS):

Delivers a high radiation dose in a single fraction. Suitable for small lesions (< 3 cm).Median doses range from 15–20 Gy.

Stereotactic Radiotherapy (SRT):

Fractionated stereotactic radiation over 3–5 sessions (e.g., 25–35 Gy in 5 fractions). It offers a balance between efficacy and safety for larger lesions.

Hypofractionated IMRT/VMAT:

Used for larger or irregular lesions. Typical regimens include 30–40 Gy in 10–15 fractions.

Proton and Carbon Ion Therapy:

These modalities are under investigation and show promise due to their Bragg peak property and reduced exit dose.

On board CBCTs should be used prior to treatment delivery.

Radiation dose fractionation schedules

Data suggests improved PFS with doses above BED10 of 40 Gy for SRS and BED10 of 45 Gy for conventional fractionation.[13] The evidence for any additional gains of increasing the biologically effective dose much beyond 40–55 Gy appears rather weak.

ESTRO guidelines recommend to use a dose fractionation regimen that delivers a biological equieffective dose (corresponding to a EQD2Gy above 36 GY in 18 fractions to the target (using an a/b value of 3 Gy).[8] They also recommend to use few treatment fractions and the preferred use of radiosurgery (single fraction) for smaller tumors (< 3cm) The safe dose fractionation regimens followed for re irradiation are:

For tumor > 6 cm : Conventionally fractionated regimens to the dose of 40 Gy in 20 fractions are used.

For tumors > 3- 6 cm or tumors < 3cm but near critical organs like chiasm and brainstem: High-dose hypofractionation (27–30 Gy in 3–5 fractions) are preferred. Moderate Hypofractionation (35 Gy in 10 fractions of 3.5 Gy each) are used for larger and irregular lesions. Longer courses should be reserved for patients with longer expected OS.

For tumors < 3 cm: Single-fraction SRS (16 Gy -24 Gy) can be used.

Dose accumulation calculation:

PTV prescription for reirradiation should follow the primary goal of respecting safe or acceptable OAR dose limits . Thus, a PTV compromise is reasonable to keep OAR safe or acceptable and PTV prescription should only be adjusted if this is not achieved even with a significant PTV compromise. Tissue recovery is still a matter of debate and subject to investigation.[14] The minimum set of organs at risk (OAR) to be evaluated after biological dose acculmulation include brain, brainstem, optic nerves and chiasma,, cranial nerves in close proximity to PTV. Consistent recovery has been described for brain and spinal cord and thus should be considered when assessing cumulative doses to these organs. The dose recovery of optic nerves and tracts however is still uncertain, therefore careful asseseement is required before calculating dose accumulation. Two dose accumulation methods that can be employed: a)

Table 1: Shows the dose constraints for OAR to be used for reirradiation via conventional fractionation, SRT and SRS (per QUANTEC [15], AAPM TG-101 [16])

Organ at risk	Conventional fractionation (40 Gy in 20 fractions)	Stereotactic Radiotherapy (27-30 Gy in 5 fractions)	Steretactic Radiosurgery (16-24 Gy in 1 fraction)	Function preserved
Brainstem	Dmax < 20-25 Gy Cumulative dose < 100Gy EQD2	<31 Gy	< 12.5 Gy	To avoid necrosis
Optic nerves/chiasm	Dmax < 20-25 GY Cumulative dose < 100Gy EQD2	<25 Gy	< 8 10 Gy	To avoid neuropathy
lens	Dmax < 7 Gy Cumulative dose < 12 Gy EQD2	<10 Gy	<2-4 Gya	Cataract threshold
Cochlea	Dmean < 30 Gy	<30 Gy	<9 Gy	To prevent Hearing loss
Normal brain	V40 < 30-50 cc Avoid large V40	V25 Gy < 10 cc	V12 Gy < 5 10 cc	To avoid radionecrosis
Hippocampus (if sparing)	Dmean < 10 Gy			For neurocognitive sparing

Same OAR constraints are used for reirradiation as were for the first course with dose discount for first course. b) Cumulative OAR constraints are used.

Combined modality treatment

There is no need to change target definition, dose and fractionation when considering combined modality treatment. [8]

Most studies reporting on combined modality reirradiation use conventional (36 Gy in 18 fractions) and moderately hypo-fractionated (35 Gy in 10 fractions) treatment and show that the addition of either alkylating agents (Temoolamide) or bevacizumab (an anti-VEGF monoclonal antibody) is well tolerated reporting OS and PFS times of around 9–12 months and 4–7 months, respectively. [17,18] But no prospective trial has indicated that the combined modality is superior to reirradiation alone in terms of PFS or OS. There is also insufficient data to suggest specific role of maintenance systemic treatment post irradiation.

Follow up schedule post re-irradiation

Follow up for early acute toxicity should be done at 6 weeks, however follow up standard MRI is recommended every 3 months post reirradiation completion. In case of suspicion and to differentiate tumor progression from radiation necrosis/pseudoprogression, advanved MRI (perfusion and spectroscopy) or AA PET are re-commended. [8]

In case of further tumor progression and after exclusion of pseudoprogression/radiation necrosis, if there are no further reasonable treatments options, transition to best supportive care should be considered and further

imaging follow-up is not beneficial.

Efficacy:

Survival after re-irradiation varies across studies. Reported median overall survival (OS) from the time of reirradiation ranges from 6 to 12 months. Progression-free survival (PFS) typically ranges from 3 to 6 months.

Table 2 : Shows the Studies showing local control and survival benefits with Re-irradiation in GBM Tumors

Study	N	Technique	Dose/Fractionation	Median OS	Median PFS	Key Findings
Combs et al., 2011 [20]	172	FSRT	36 Gy / 2 Gy x18	8 months	5 months	Smaller volume and higher KPS better outcome
Minniti et al., 2012 [17]	86	SRT	30 Gy / 2.5 Gy x12	9 months	5.2 months	Favorable outcomes with limited toxicity
Navarria et al., 2011 [21]	53	FSRT + TMZ	36 Gy / 2 Gy x18	7.7 months	4.5 months	ReRT with TMZ safe, well tolerated
Gutin et al., 2009 [5]	25	SRT + Bev	30 Gy / 5 Gy x6	11 months	6 months	Bevacizumab may lower necrosis risk
Fogh et al., 2010 [22]	147	SRS	15 –24 Gy single fraction	8.6 months	NR	Good for small lesions (<3 cm)
Fogh et al., 2012 [22]	71	Hypo - IMRT	35 Gy / 5 Gy x7	10.3 months	5.6 months	Safe and effective with IMRT
Kazmi et al., 2019 [19]	2095	Mixed	Median 35 Gy	9.3 months	4.6 months	Larger tumor, short interval worse
Niyazi et al., 2014 [7]	198	FSRT	36 Gy / 2 Gy x18	7.5 months	4 months	Scoring system developed
Tsien et al., 2012 [10]	47	IMRT + Bev	35 Gy / 5 Gy x7	9.9 months	4.4 months	Bev may enhance reRT effect
Navarria et al., 2014 [21]	42	SRT	25 –35 Gy / 5 –7 Gy x5	11.1 months	6.3 months	Excellent local control

Toxicity:

Re-irradiation carries risks of both acute and late toxicities. [17,18] Acute side effects include fatigue, headache, and worsening of neurological symptoms, usually transient. The most feared late toxicity is radiation necrosis, occurring in up to 20% of cases. The risk is influenced by cumulative dose, interval between treatments, and volume irradiated. Strategies to minimize toxicity include conformal planning, fractionation, and judicious dose constraints to organs at risk.

Prognostic Factors:

Favorable prognostic indicators for survival post re-irradiation include: Younger age (< 60 years), High KPS, Smaller tumor volume, Longer interval (> 12 months) since initial radiotherapy, MGMT promoter methylation, IDH1 mutation.[12-16] Some prognostic scoring systems, such as the Heidelberg and Combs scoring systems, have been proposed to guide clinicians in selecting patients and estimating outcomes.

Emerging Strategies:

Novel approaches including re-irradiation with immune checkpoint inhibitors, tumor-treating fields, and personalized dosing based on genomic profiles are under investigation. Integration of radionomics and artificial intelligence in predicting response and toxicity is also gaining traction.

CONCLUSION

Re-irradiation is a feasible and moderately effective salvage option for selected patients with recurrent GBM, especially with advances in radiation delivery techniques. While it offers symptomatic relief and a modest survival benefit, the risk of toxicity, particularly radiation necrosis, mandates careful patient selection and planning. Prospective randomized trials are needed to define optimal dosing strategies, fractionation schedules, and combinations with systemic therapies. With an individualized approach, re-irradiation can play a meaningful role in the multidisciplinary management of recurrent GBM.

DISCUSSION

Radiobiological aspect of re-irradiation in recurrent GBM Recurrence within 6 to 9 months following standard radiation doses of 60 Gy in 30 fractions over 6 weeks in GBM tumors, indicates the high proliferative capacity, hypoxia and dominance of radioresistant clones in the recurrent disease. Considering the concept of 4 Rs of radiobiology in re irradiation of recurrent GBM tumors, we can see that normal brain tissue has some capacity to repair sublethal damage over time, however late responding tissues (white matter, brainstem) are vulnerable due to slower repair kinetics. Accelerated repopulation in GBM starts 3 – 4 weeks into radiotherapy. Re-irradiation aims to counter the fast tumor regrowth, along with sparing of normal tissue.

But the recurrent GBM tumors tend to be hypoxic and have tumor cells in radioresistant phases (S- Phase). So unlike radiosensitive rapidly proliferative cells in primary GBM which has high α/β ratio (~10 Gy) , the recurrent GBM tumor has low α/β ratio (~2 Gy), similar to the normal brain tissue. So the tumor is sensitive to change in dose per fraction. Therefore hypofractionated stereotactic radiotherapy regimens tend to offer better tumor control rates, along with sparing of normal brain tissue.

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