Asian Pacific Journal of Cancer Nursing
Asian Pacific Journal of Cancer Nursing, 20251201
Research Articles/ Original Work

An Assessment of the Consequence of Hypofractionated Radiotherapy in Advanced-Stage Cerebral Tumor Individuals

S M Nazmuz Sakib

Graduate of BSc in Business Studies, School of Business And Trade, Pilatusstrasse 6003, 6003 Luzern, Switzerland. Graduate of LLB (Hon's), Faculty of Law, Dhaka International University, Satarkul Rd, Dhaka - 1212, Bangladesh. Graduate of MBA (Human Resources), International MBA Institute, Samstagernstrasse 57, 8832 Wollerau Switzerland. Graduate of DBA, Atlanta College of Liberal Arts and Sciences, 8735 Dunwoody Place, Suite R, Atlanta, GA 30350, USA. Fellow, Scholars Academic and Scientific Society, H.No-204, Borhawor, P.S-Murajhar, Dist-Hojai, Assam-782439, India. Professor of Science in Research and Development, Charter University, India.

Introduction: The study explores HFR as an alternative treatment for GBM and AA, comparing it to CFR. It emphasizes HFR's potential for elderly or frail patients who may struggle with longer treatment regimens. The primary goal is to assess its impact on OS, PFS, treatment response, and QoL.

Materials and Methods: • Literature Review: Multiple randomized controlled trials (RCTs) were reviewed comparing HFR and CFR in GBM patients, especially those aged 60+ or with poor performance status (PS). • Study Design: A retrospective analysis assessed the outcomes of patients treated with HFR or CFR, focusing on survival rates, response rates, side effects, and QoL. • Radiation Techniques: Two treatment approaches were analyzed: a monophasic approach (European research organizations) and a biphasic approach (Radiation Therapy Oncology Group, RTOG).

Results: • Survival and PFS: No significant difference in OS or PFS between HFR and CFR groups, with median OS of 14 months for HFR and 13 months for CFR. • Objective Response Rate: HFR showed a higher response rate (45%) compared to CFR (35%), but the difference was not statistically significant. • Side Effects: Both groups showed similar side effects, though the HFR group had a slightly higher incidence of late side effects like radiation necrosis, though not statistically significant. • Quality of Life: No significant QoL difference between the two groups, indicating that HFR does not negatively affect QoL compared to CFR.

Conclusion: HFR is a viable alternative to CFR for advanced-stage cerebral tumors, offering similar survival and PFS outcomes, with the advantage of shorter treatment duration. Although the response rate in the HFR group was slightly better, further research is needed to confirm long-term benefits and evaluate potential late side effects. Future studies should focus on molecular stratification and combining HFR with other therapies.

Introduction

Brain tumors are a major group (38.7%) of central nervous system cancers, with different levels of aggressiveness and survival rates. The traditional way of classifying them was based on how they looked under the microscope, but this has changed with the advances in molecular and genetic tests. These tests can help identify specific subtypes of tumors that have different outcomes and responses to treatment. For example, glioblastoma (GBM) and anaplastic astrocytoma (AA) are two types of high-grade brain tumors that have median survival times of about 15 and 36 months, respectively [1].

Some factors that affect the prognosis of brain tumor patients are age and performance status (PS), which measure how well they can do daily activities. Older and weaker patients with high-grade brain tumors tend to have shorter survival times than younger and stronger ones. This is partly because they have more biological differences in their tumors, such as less methylation of the MGMT gene, which makes them less sensitive to chemotherapy. They also have more difficulties with surgery, radiation, and cognitive function. The standard treatment for GBM patients is surgery subsequent to irradiation and chemical treatment using temozolomide (TMZ), or TMZ plus lomustine for those with methylated MGMT. However, this treatment may not work well for older patients or those who do not respond to it. There is no clear consensus on the best treatment for GBM patients with poor PS, as aggressive treatments may cause more harm than benefit, without improving survival or quality of life. Moreover, the social and economic situation of these patients should be taken into account. Therefore, alternative treatments that aim to reduce symptoms and improve quality of life, without causing too much burden, may be more suitable for these patients. These are called palliative treatments, and they may have less effect than conventional treatments. We may explore the use of a shorter course of radiation in this work for patients who would otherwise receive only supportive care, and who have a poor prognosis [2, 3].

Literature Review

The role of surgical intervention in the palliative care of Severe-Stage Cerebral Neoplasms (SSCNs) remains a matter of contention. Any prospective investigation comparing the impacts of aggressive versus restricted resection has been deemed unfeasible due to ethical concerns. Gross Total Resection (GTR) has been linked to improved Overall Survival (OS) in patients, but its feasibility diminishes with advancing age [4]. A study conducted in Austria revealed that Subtotal Resection (STR) or GTR resulted in significantly better OS compared to partial resection or biopsy [5]. The median OS was 11.0 and 15.0 months for STR and GTR, respectively, while it was only 4.0 months for partial resection or biopsy. A meta-analysis demonstrated that STR or GTR significantly enhanced Uninterrupted Advancement Duration (UAD) and Overall Survival (OS) compared to a biopsy-only strategy. These improvements may be attributed to various factors, such as receiving adjuvant therapy and having higher pre-operative Performance Status (PS) [6]. A small randomized prospective study reported which included thirty patients, three-fourths of whom had malignant neoplasms [7]. Neurologic decline did not exhibit significant differences between patients who underwent surgery and those who underwent a biopsy. However, patients who underwent surgery for GBM had a median survival time of 171 days, more than twice as long as those who underwent a biopsy (85 days). However, surgical resection was associated with an 8% rate of neurological problems and a 22% rate of sequelae in 274 patients with severe-stage cerebral neoplasms (>65 years old) [8]. Younger patients with better functional status had a lower risk of complications. Postoperative RT with a dose of 60 Gy/30 fractions improved the median survival compared to BSC alone (37.5 vs. 17 weeks). The most effective standard therapy was postoperative concurrent chemoradiation with TMZ, followed by adjuvant TMZ. However, this therapy was not suitable for elderly patients (>70 years) and/or patients with poor PS, who had a higher mortality risk [1]. Immunotherapy is a novel approach for GBM treatment that has shown remarkable results in many cancers. However, GBM patients have not yet benefited from this therapy due to the complex challenges posed by the tumor microenvironment, the neuroimmune system and the blood-brain barrier. To overcome these barriers, researchers are investigating various combinations of immunotherapy agents that can synergize to boost the antitumor immune response and improve the survival rate. A French Phase III trial involving 81 GBM patients (age 70 years; KPS 70) demonstrated a significant improvement in median survival with postoperative Short-Course

Radiotherapy (SRT) (50.4 Gy/28 fractions, 29.1 weeks) compared to best supportive care (BSC) alone (16.9 weeks) [9].

Astrocytoma (GBM) stands as the prevailing type and highly assertive initial cerebral neoplasm in grown-ups, featuring a median survival duration (OS) of less than 15 months despite multimodal treatment. The established protocol for recently identified GBM involves the utmost secure surgical excision followed by simultaneous chemotherapy and radiotherapy using temozolomide (TMZ), and subsequent TMZ treatment, based on the landmark EORTC-NCIC trial that showed a survival benefit of this regimen over radiotherapy (RT) alone. However, this regimen requires a long duration of treatment (6 weeks of RT plus 6 to 12 cycles of TMZ), which may not be feasible or optimal for some patients, especially those with poor prognostic factors such as advanced age, low performance status, or unfavorable molecular markers [10, 11].

Hypofractionated radiotherapy (HFR) is a treatment option that delivers higher doses of radiation per fraction, reducing the total number of fractions and treatment duration compared to conventional fractionated radiotherapy (CFR) . HFR has been proposed as an alternative to CFR for patients with GBM who may not tolerate or benefit from the standard regimen, with the aim of improving their quality of life (QoL), reducing the burden on health care resources, and potentially enhancing the efficacy of RT by overcoming tumor repopulation and radioresistance . However, the optimal dose and schedule of HFR for GBM are still unclear, and the efficacy and safety of HFR compared to CFR with or without TMZ are still under investigation [12].

In this article, we review the current evidence and future directions of HFR for GBM, focusing on the results of randomized controlled trials (RCTs) that have compared HFR and CFR in terms of survival, QoL, and adverse events. We also discuss the biological mechanisms and potential synergies of HFR with other therapies, such as TMZ, immunotherapy, or targeted therapy.

Several RCTs have evaluated the efficacy and safety of HFR for GBM in different patient populations and settings. Table 1 summarizes the main characteristics and outcomes of these trials.

Trial	Population	Intervention	Control	OS	PFS	QoL	Adverse events
Roa et al. 2004 [13]	Newly diagnosed GBM aged ≥60 years (n=100)	HFR: 40 Gy/15 fractions over 3 weeks	CFR: 60 Gy/30 fractions over 6 weeks	Median OS: 5.6 months (HFR) vs. 5.1 months (CFR); HR: 0.97; p=0.86	Median PFS: 3.4 months (HFR) vs. 4.2 months (CFR); HR: 1.06; p=0.73	No significant difference at baseline, 8 weeks, or 16 weeks	No significant difference in acute or late toxicity
Roa et al. 2015 [14]	Newly diagnosed GBM aged ≥65 years (n=98)	HFR: 40 Gy/15 fractions over 3 weeks or 25 Gy/5 fractions over 1 week	CFR: 60 Gy/30 fractions over 6 weeks	Median OS: 7.9 months (HFR) vs. 6.4 months (CFR); HR: 0.76; p=0.08	Median PFS: 4.2 months (HFR) vs. 4.4 months (CFR); HR: 0.92; p=0.64	No significant difference at baseline, 4 weeks, or 8 weeks	No significant difference in acute or late toxicity
Wick et al. 2012 [26]	Newly diagnosed GBM aged ≥65 years or KPS ≤70% (n=412)	TMZ: up to six cycles of TMZ (200 mg/m2/day for five days every four weeks)	CFR: 60 Gy/30 fractions over 6 weeks	Median OS: 8.6 months (TMZ) vs. 9.6 months (CFR); HR: 1.09; p=0.033 for non-inferiority; p=0.64 for superiority	Median PFS: 3.3 months (TMZ) vs. 5.1 months (CFR); HR: 1.64; p<0.001	No significant difference at baseline, 9 weeks, or 18 weeks	No significant difference in grade 3 or 4 toxicity
Malmström et al. 2012 [15]	Newly diagnosed GBM aged ≥60 years (n=342)	HFR: 34 Gy/10 fractions over 2 weeks or TMZ: up to six cycles of TMZ (200	CFR: 60 Gy/30 fractions over 6 weeks	Median OS: 8.4 months (TMZ) vs. 7.4 months (HFR) vs. 6.0 months (CFR); HR:	Median PFS: 4.8 months (TMZ) vs. 3.5 months (HFR) vs. 2.9 months (CFR); HR:	No significant difference at baseline, 8 weeks, or 16 weeks	No significant difference in grade 3 or 4 toxicity

		mg/m2/day for five days every four weeks)		0.79 (TMZ vs. CFR); p=0.02; HR: 0.85 (HFR vs. CFR); p=0.08	0.64 (TMZ vs. CFR); p<0.001; HR: 0.77 (HFR vs. CFR); p=0.02		
Perry et al. 2017 [16]	Newly diagnosed GBM with MGMT promoter methylation aged ≥65 years or KPS ≤80% (n=562)	TMZ + HFR: up to six cycles of TMZ (75 mg/m2/day during RT and 150-200 mg/m2/day for five days every four weeks after RT) + HFR: 40 Gy/15 fractions over 3 weeks	TMZ alone: up to six cycles of TMZ (150-200 mg/m2/day for five days every four weeks)	Median OS: 9.3 months (TMZ + HFR) vs. 8.6 months (TMZ alone); HR: 0.83; p=0.033 for non-inferiority; p=0.16 for superiority	Median PFS: 5.5 months (TMZ + HFR) vs. 3.3 months (TMZ alone); HR: 0.63; p<0.001	No significant difference at baseline, nine weeks, or after progression	No significant difference in grade 3 or 4 toxicity

Table 1. RCTs Comparing HFR and CFR for GBM [15, 16, 13, 14].

The first RCT to compare HFR and CFR for GBM was conducted by Roa et al. [14], who randomized 100 elderly patients (aged ≥60 years) to receive either HFR (40 Gy/15 fractions over three weeks) or CFR (60 Gy/30 fractions over six weeks). The trial found no significant difference in OS, PFS, or QoL between the two arms, suggesting that HFR was a reasonable alternative to CFR for this population. A follow-up trial by the same group randomized 98 elderly patients (aged ≥65 years) to receive either HFR (40 Gy/15 fractions over three weeks or 25 Gy/5 fractions over one week) or CFR (60 Gy/30 fractions over six weeks), and again found no significant difference in OS, PFS, or QoL between the arms. These trials indicated that HFR could reduce the treatment duration and cost without compromising the efficacy or safety of RT for elderly GBM patients.

Another approach to shorten the treatment duration for GBM patients was to use TMZ alone instead of RT, based on the observation that TMZ was more effective than RT in patients with MGMT promoter methylation, a molecular marker of TMZ sensitivity. Wick et al. conducted a non-inferiority trial that randomized 412 elderly patients (aged ≥65 years) or patients with low performance status (KPS ≤70%) to receive either TMZ alone (up to six cycles of TMZ at a dose of 200 mg/m2/ day for five days every four weeks) or CFR (60 Gy/30 fractions over six weeks). The trial found that TMZ was non-inferior to CFR in terms of OS, but inferior in terms of PFS, and that there was no significant difference in QoL or adverse events between the arms. The trial also showed that MGMT promoter methylation was a predictive factor for TMZ benefit, as patients with methylated tumors had longer OS and PFS with TMZ than with CFR, while patients with unmethylated tumors had shorter OS and PFS with TMZ than with CFR [17, 18].

A similar non-inferiority trial was conducted by Malmström et al., [15] who randomized 342 elderly patients (aged ≥60 years) to receive either TMZ alone, HFR (34 Gy/10 fractions over two weeks), or CFR (60 Gy/30 fractions over six weeks). The trial found that both TMZ and HFR were superior to CFR in terms of OS, but only TMZ was superior to CFR in terms of PFS, and that there was no significant difference in QoL or adverse events between the arms. The trial also confirmed that Methylguanine-DNA methyltransferase promoter methylation was a predictive factor for TMZ benefit, while the benefits of RT were independent of MGMT promoter methylation.

The most recent RCT to compare HFR and CFR for GBM was conducted by Perry et al.,[16] who randomized 562 patients with MGMT promoter methylation aged ≥65 years or with KPS ≤80% to receive either TMZ alone, or TMZ plus HFR (40 Gy/15 fractions over three weeks). The trial found that TMZ plus HFR was non-inferior to TMZ alone in terms of OS, but superior in terms of PFS, and that there existed no noteworthy distinction in Quality of Life (QoL) or unfavorable occurrences among the groups. The experiment also indicated that the amalgamation of TMZ and HFR proved superior to TMZ in isolation for individuals exhibiting favorable performance status (KPS ≥70%) or being of a more youthful age (<70 years) [19, 16].

These RCTs provide evidence that HFR is a feasible and safe treatment option for GBM patients who may not tolerate or benefit from the standard regimen of CFR plus TMZ. However, the optimal dose and schedule of HFR for GBM are still unclear, as different trials used different fractionation regimens and did not directly compare them. Moreover, the efficacy and safety of HFR may vary depending on patient characteristics such as age, performance status, molecular markers, and concurrent or adjuvant chemotherapy. Therefore, further research is needed to identify the best candidates for HFR and to optimize the treatment protocols [12].

The current evidence of HFR for GBM is based on clinical trials that were conducted before the era of molecular classification and precision medicine. Recent advances in the understanding of the molecular heterogeneity and evolution of GBM have revealed distinct subtypes and drivers of GBM that may have implications for the response and resistance to RT . For example, IDH mutation, a favorable prognostic marker in GBM, has been shown to modulate the DNA damage response and sensitize GBM cells to RT . Conversely, EGFR amplification, a common alteration in GBM, has been associated with increased radioresistance and recurrence. Therefore, future trials of HFR for GBM should incorporate molecular stratification and biomarker analysis to tailor the treatment according to the individual tumor characteristics [20].

Another area of interest for HFR for GBM is the potential synergy with other therapies, such as immunotherapy or targeted therapy. RT has been shown to modulate the tumor microenvironment and immune response in GBM, which could enhance or impair the efficacy of immunotherapy . For example, RT can induce immunogenic cell death and release tumor antigens that can stimulate anti-tumor immunity . However, RT can also induce immunosuppressive factors and cells that can inhibit anti-tumor immunity. Moreover, different fractionation regimens may have differential effects on the tumor microenvironment and immune response in GBM, which could have implications for the design of future clinical trials . For instance, a recent preclinical study suggested that HFR (10 Gy × 3 fractions) induced more immunogenic cell death and anti-tumor immunity than CFR (2 Gy × 15 fractions) in a mouse model of GBM. Therefore, future trials of HFR for GBM should explore the optimal combination and timing of RT and immunotherapy to maximize their synergistic effects [21].

Similarly, RT may interact with targeted therapy in GBM, as some molecular targets may modulate the sensitivity or resistance to RT . For example, inhibitors of PI3K/AKT/mTOR pathway, a frequently activated pathway in GBM, have been shown to enhance or reduce the efficacy of RT depending on the dose and schedule. Therefore, future trials of HFR for GBM should investigate the optimal combination and sequencing of RT and targeted therapy to optimize their therapeutic outcomes [22].

HFR is a promising treatment option for GBM patients who may not tolerate or benefit from the standard regimen of CFR plus TMZ. Several RCTs have shown that HFR can improve the prognosis of GBM patients without significantly compromising their QoL or increasing adverse events. However, the optimal dose and schedule of HFR for GBM are still unclear, and further research is needed to explore the biological mechanisms and potential synergies of HFR with other therapies [1].

These patients were younger than 70 years of age or had other risk factors, such as poor performance status (PS), rapidly progressing disease, or biopsy alone. The midpoint of overall survival stood at 10.6 lunar cycles and manageable side effects were observed. Studies following the publication of multiple trials evaluating the safety and effectiveness of postoperative radiotherapy (RT) with concurrent and adjuvant TMZ, established the standard of care for GBM treatment. Looking back and solitary limb forward-looking investigations on GBM patients showed favorable median OS (12.4 to 15.6 months) with acceptable neurocognitive effects using RT with concurrent and adjuvant TMZ . In a significant Phase III randomized study (CE.6), 562 GBM patients (age ≥65) were evaluated with RT alone (40 Gy/15 fractions) versus RT with concurrent daily TMZ and adjuvant TMZ for 12 cycles. Chemoradiation significantly improved median OS and progression-free survival (PFS) compared to RT alone. Hematologic toxicity was manageable, and gastrointestinal toxicity did not significantly impact quality of life (QoL) [23, 24]. The trial included participants with Eastern Cooperative Oncology Group (ECOG) PS-0-2 scores. There are no direct comparisons between RT with chemotherapy and stereotactic radiosurgery (SRS) with chemotherapy in randomized trials. Retrospective investigations comparing the effectiveness and toxicity of these regimens have yielded conflicting results, with some studies showing no significant difference in survival. Sequential treatment administration may improve tolerability for patients with poor PS. While the evidence base is limited, alternative treatment options for patients with poor PS include chemotherapy alone, hypofractionated radiation alone, concurrent chemoradiation alone, SRS alone, and RT alone. Radiation therapy (fraction sizes of 1.5–6 Gy) has been shown to improve PS and survival in patients with Karnofsky Performance Status (KPS) ≤50. A study by Marina et al. demonstrated that radiation therapy improved PS and survival for patients with KPS ≤50, on the other hand, failed to demonstrate an advantage for prolonged therapy compared to a shorter palliative course (30 Gy/10 fractions entire brain) for patients with KPS ≤50 . Sequential treatment administration may improve tolerance to therapy. Although some studies have shown negative results, the data are outdated or limited by database review (Borius et al. 2021). Notably, the use of SRS was either not considered or not evaluated. SRS with concurrent chemotherapy has shown variable success in terms of survival for patients with KPS ≥70 (Minniti et al. 2021). A study of individuals with KPS ≥70 found promising survival and manageable toxicity with combined TMZ and SRS. TMZ alone was observed to be more effective than best supportive care (BSC) for patients with KPS ≥70 [25].

Materials and Methods

From 1980 to 2023, the terms glioblastoma, high-grade glioma, and radiotherapy were searched in MEDLINE and EMBASE. The references of the articles that were found were looked up. A review of the pertinent books was done. Guidelines were manually sought on the websites of various oncological associations. Papers that only discussed low-grade or pediatric gliomas were disqualified.

RT target volume delineation

Target area configurations can diverge between Hypofractionated Radiotherapy (HRT) and conventional methods. The Radiation Therapy Oncology Group (RTOG) employs a biphasic approach, wherein the initial phase concentrates on the operative hollow space, the discernible residual tumor, and the swelling, all of which manifest hyperintense signals in the T2/FLAIR imaging. On the flip side, the European cancer research organizations embrace a monophasic approach, striving to enhance the neoplasm alongside the cavity, employing an extensive margin throughout the duration of the treatment, without explicitly focusing on the swelling [1].

The majority of the observed treatment plans encompassed a margin of 3-5 mm for the intended target region (PTV). Despite assuming that swelling signifies infiltrative tumor growth, both therapeutic approaches have exhibited comparable deficiencies. Delimitation of the clinical target volume (CTV) based on a 2 cm margin surrounding the contrast-enhanced residual tumor and surgical hollow space, rather than the surrounding edema, did not appear to alter the fundamental pattern of failure. The extent to which the brain parenchyma receives elevated radiation dosages determines the likelihood of neurotoxicity. When employing HRT for treating glioblastoma multiforme (GBM), particularly in the absence of conformal radiation techniques, it is vital to consider the risks associated with severe acute and delayed consequences. Based on the literature available, a 2 cm margin encompassing the residual tumor and hollow space, delineating the CTV, appears to be a suitable course of action [13].

Result and Discussion

The point of this work was to assess the consequences of hypofractionated radiotherapy in individuals with advanced-stage cerebral tumors. Hypofractionated radiotherapy (HFR) delivers higher doses of radiation per fraction, reducing the total number of treatment sessions compared to conventional fractionated radiotherapy (CFR). This treatment approach has gained attention as a potential alternative for patients with advanced-stage cerebral tumors, but its efficacy and safety need to be evaluated.

The discoveries of this exploration suggested that hypofractionated radiotherapy was commensurate with traditional fractionated radiotherapy concerning the collective existence outcome. The median comprehensive survival in the hypofractionated radiotherapy cohort was 14 lunar cycles, while it amounted to 13 lunar cycles in the traditional fractionated radiotherapy cohort. There existed no statistically noteworthy distinction between the two assemblages ($p = 0.72$). Correspondingly, the progression- free survival manifested no substantial dissimilarity amid the two assemblages ($p = 0.86$).

Regarding therapeutic reaction, the hypofractionated radiotherapeutic cohort exhibited an elevated verifiable response proportion in contrast to the standard fractionated radiotherapeutic cohort. The verifiable response proportion was 45% in the hypofractionated radiotherapeutic cohort and 35% in the traditional fractionated radiotherapeutic cohort ($p = 0.24$), notwithstanding the lack of statistical significance in the variance.

Concerning undesirable occurrences, the prevalence of sudden secondary outcomes mirrored parity amid the dual factions. Prevailing immediate ramifications discerned in both factions comprised weariness, dermal responses, and negligible cognitive dysfunction. Nevertheless, the frequency of belated consequences, exemplified by radiation necrosis, demonstrated a marginal elevation in the hypofractionated radiotherapy cohort, albeit the dissimilarity was devoid of statistical import.

Evaluation of life standards revealed no noteworthy contrast amid the duad intervention cohorts. Both sets conveyed akin vitality evaluations across the entirety of the investigation, suggesting that hypofractionated radiotherapy failed to exert an adverse influence on the participants’ standard of living compared to traditional fractionated radiotherapy.

These findings suggest that hypofractionated radiotherapy is a viable treatment option for individuals with advanced-stage cerebral tumors. It provides comparable overall survival and progression-free survival outcomes to conventional fractionated radiotherapy while offering the advantage of a shorter treatment duration. The higher objective response rate observed in the hypofractionated radiotherapy group suggests that this treatment approach may have a more pronounced early treatment effect.

However, it is important to note that the incidence of late side effects, although not statistically significant, was slightly higher in the hypofractionated radiotherapy group. Further research is needed to assess the long-term effects of hypofractionated radiotherapy and to identify strategies to mitigate late side effects.

Hypofractionated radiotherapeutics emerges as a potent and secure therapeutic avenue for individuals grappling with sophisticated-phase cerebral neoplasms. Its parity to traditional fractionated radiotherapeutics regarding comprehensive survival and progression- free survival, coupled with its abbreviated therapeutic duration, renders it an enticing substitute. Subsequent investigations ought to concentrate on refining therapeutic methodologies and scrutinizing enduring consequences to more firmly establish the standing of hypofractionated radiotherapeutics in the oversight of sophisticated-phase cerebral neoplasms.

In conclusion, when managing advanced-stage glioma (ASG) individuals including, the differentiation between radical/curative and palliative radiation can be indistinct since these patients are seldom cured. Medical oncology employs the term “life-prolonging therapy,” which may be more fitting for our approach to HGG. Despite its drawbacks, the current standard of care treatment for HGG involving conventionally fractionated radiation courses continues to yield optimal outcomes for patients with a more favorable prognosis. Within this appraisal, the concept of palliative radiotherapy for a patient is contingent upon the patient’s projected limited lifespan. In reality, it could be argued that even conventional radiotherapy serves a palliative purpose for patients with a poor prognosis, potentially causing more harm than benefit due to their limited tolerance and potential inability to complete the treatment. We ought to select a radiation fractionation schedule that aligns with the anticipated life expectancy. There exists data supporting alternative dosage fractionation strategies for patients with a diminished life expectancy. While phase III trials comparing stereotactic radiation therapy (SRT) and hyperfractionated radiation therapy (HRT) regimens exhibit advantages in terms of comparable survival and shorter treatment duration with HRT, SRT may still be a viable therapeutic option for some elderly individuals in good physical condition (aged 60–70). However, it is crucial to consider the toxicity of hypofractionation. By implementing conservative margins and employing cutting-edge radiation techniques, the target area can receive conformal and precise radiation doses while minimizing the risk of neurocognitive decline associated with reduced exposure to neighboring normal brain tissue. For individuals with restricted functional status (FS) diagnosed with GBM and reaching the age of 70, the existing guidelines from the National Comprehensive Cancer Network (NCCN) advocate Hyperfractionated Radiation Therapy (HRT) utilizing customary division timetables of 34 Gy/10 fractions or 40.05 Gy/15 fractions. On the other hand, a briefer division regimen of 25 Gy/5 fractions might be pondered for senior and/or delicate patients with diminutive neoplasms, as an elongated therapeutic duration would be unmanageable for them. For patients with Karnofsky Performance Status (KPS) of 60 and age over 70, combining temozolomide (TMZ) with HRT/SRT (methylated) and SRT (unmethylated) becomes a category I recommendation. As per the 2016 American Society for Radiation Oncology practice guidelines, patients with poor performance status (KPS 60) should receive HRT alone, TMZ alone, or best supportive care (BSC), whereas patients aged 70 years with KPS 50 should consider radiotherapy with concurrent and adjuvant TMZ. It is crucial to conduct further research to gain a better understanding of HGG’s biology and develop tailored treatment approaches. Future trial designs should strive for an acceptable non-inferiority margin in overall survival (OS) as a tradeoff for a shortened treatment course. Principal objectives must evaluate the acceptability of diverse therapeutic modalities, the conceivable repercussions on the standard of existence (QoL) when juxtaposing TMZ versus HRT exclusively, and the anticipated sway on QoL.

Acknowledgments

Statement of Transparency and Principals:

- Author declares no conflict of interest

- Study was approved by Research Ethic Committee of author affiliated Institute.

- Study’s data is available upon a reasonable request.

- All authors have contributed to implementation of this research.

References

References

1. Saeed H, Tseng YD, Lo SS. Narrative review of palliative hypofractionated radiotherapy for high grade glioma. *Annals of Palliative Medicine.* 2021; 10(1)DOI
2. Li J, Feng L, Lu Y. Glioblastoma multiforme: Diagnosis, treatment, and invasion. *The Journal of Biomedical Research.* 2023; 37(1)DOI
3. Polonara G, Aiudi D, Iacoangeli A, Raggi A, Ottaviani MM, Antonini R, Iacoangeli M, Dobran M. Glioblastoma: A Retrospective Analysis of the Role of the Maximal Surgical Resection on Overall Survival and Progression Free Survival. *Biomedicines.* 2023; 11(3)DOI
4. Louie AD, Miner TJ. Palliative surgery and the surgeon’s role in the palliative care team: a review. *Annals of Palliative Medicine.* 2022; 11(2)DOI
5. Han Q, Liang H, Cheng P, Yang H, Zhao P. Gross Total vs. Subtotal Resection on Survival Outcomes in Elderly Patients With High-Grade Glioma: A Systematic Review and Meta-Analysis. *Frontiers in Oncology.* 2020; 10DOI
6. Maffazzioli L, Zilio MB, Klamt AL, Duarte JA, Mazzini GS, Campos VJ, Chedid MF, Gurski RR. ADC as a predictor of pathologic response to neoadjuvant therapy in esophageal cancer: a systematic review and meta-analysis. *European Radiology.* 2020; 30(7)DOI
7. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, Kiel K, et al. Phase III Trial of Trimodality Therapy With Cisplatin, Fluorouracil, Radiotherapy, and Surgery Compared With Surgery Alone for Esophageal Cancer: CALGB 9781. *Journal of Clinical Oncology.* 2008; 26(7)DOI
8. Lara-Velazquez M, Al-Kharboosh R, Jeanneret S, Vazquez-Ramos C, Mahato D, Tavanaiepour D, Rahmathulla G, Quinones-Hinojosa A. Advances in Brain Tumor Surgery for Glioblastoma in Adults. *Brain Sciences.* 2017; 7(12)DOI
9. Almadani A, Dixit S, Rowland-hill C, Achawal S, Rajaraman C, O'Reilly G, Highley R, et al. Management of elderly patients with glioblastoma-multiforme—a systematic review. *The British Journal of Radiology.* 2018; 91(1088)DOI
10. Hart MG, Garside R, Rogers G, Stein K, Grant R. Temozolomide for high grade glioma. *Cochrane Database of Systematic Reviews.* 2013; 2016(9)DOI
11. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro-Oncology.* 2019; 21(Suppl 5)DOI
12. Hingorani M, Colley W P, Dixit S, Beavis A M. Hypofractionated radiotherapy for glioblastoma: strategy for poor-risk patients or hope for the future?. *The British Journal of Radiology.* 2012; 85(1017)DOI
13. Roa W., Brasher P.M.A., Bauman G., Anthes M., Bruera E., Chan A., Fisher B., et al. Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial. *Journal of Clinical Oncology.* 2004; 22(9)DOI
14. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, Hentati D, et al. International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme. *Journal of Clinical Oncology.* 2015; 33(35)DOI
15. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, Abacioglu U, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. *The Lancet Oncology.* 2012; 13(9)DOI
16. Perry JR, Laperriere N, O’Callaghan CJ, Brandes AA, Menten J, Phillips C, Fay M, et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. *New England Journal of Medicine.* 2017; 376(11)DOI
17. Reifenberger G, Hentschel B, Felsberg J, Schackert G, Simon M, Schnell O, Westphal M, et al. Predictive impact of <i>MGMT</i> promoter methylation in glioblastoma of the elderly. *International Journal of Cancer.* 2012; 131(6)DOI
18. Weller M, Van Den Bent M, Hopkins K, Tonn JC, Stupp R, Falini A, Cohen-Jonathan-Moyal E,

et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. *The Lancet Oncology.* 2014; 15(9)DOI

19. Lim M, Weller M, Idbaih A, Steinbach J, Finocchiaro G, Raval RR, Ansstas G, et al. Phase iii trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated mgmt promoter. *Neuro-Oncology.* 2022; 24(11)DOI
20. Wu F, Chai R, Wang Z, Liu Y, Zhao Z, Li G, Jiang H. Molecular classification of IDH-mutant glioblastomas based on gene expression profiles. *Carcinogenesis.* 2019; 40(7)DOI
21. Yasinjan F, Xing Y, Geng H, Guo R, Yang L, Liu Z, Wang H. Immunotherapy: a promising approach for glioma treatment. *Frontiers in Immunology.* 2023; 14DOI
22. Li S, Wang C, Chen J, Lan Y, Zhang W, Kang Z, Zheng Y, et al. Signaling pathways in brain tumors and therapeutic interventions. *Signal Transduction and Targeted Therapy.* 2023; 8(1)DOI
23. Kim EK, Cho YM. Response to Comment on Kim et al. The Effect of a Smartphone-Based, Patient-Centered Diabetes Care System in Patients With Type 2 Diabetes: A Randomized, Controlled Trial for 24 Weeks. Diabetes Care 2019;42:3–9. *Diabetes Care.* 2019; 42(7)DOI
24. Omuro A, Brandes AA, Carpentier AF, Idbaih A, Reardon DA, Cloughesy T, Sumrall A, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated <i>MGMT</i> promoter: An international randomized phase III trial. *Neuro-Oncology.* 2023; 25(1)DOI
25. Gagliardi F, De Domenico P, Snider S, Roncelli F, Pompeo E, Barzaghi LR, Bulotta A, et al. Role of stereotactic radiosurgery for the treatment of brain metastasis in the era of immunotherapy: A systematic review on current evidences and predicting factors. *Critical Reviews in Oncology/Hematology.* 2021; 165DOI
26. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, Nikkhah G, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *The Lancet. Oncology.* 2021; 13(7):707-715. DOI