Radiotherapy for elderly patients with glioblastoma: an assessment of hypofractionation and modern treatment techniques

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Abstract: Glioblastoma (GBM) is a disease with a poor prognosis. For decades, radiotherapy has played a critical role in the management of GBM. The standard of care radiation prescription is 60 Gy in 30 fractions, but landmark trials have historically excluded patients older than 70 years. Currently, there is considerable variation in the management of elderly patients with GBM. Shortened radiation treatment (hypofractionated) regimens have been explored since conventional treatment schedules are lengthy and many elderly patients have functional, cognitive, and social limitations. Clinical trials have demonstrated the effectiveness of hypofractionated radiotherapy (40 Gy in 15 fractions) to treat elderly or frail patients with GBM. Although previous studies have suggested these unique hypofractionation prescriptions effectively treat these patients, there are many avenues for improvement in this patient population. Herein, we describe the unique tumor biology of glioblastoma, key hypofractionated radiotherapy studies, and health-related quality of life (HRQOL) studies for elderly patients with GBM. Hypofractionated radiation has emerged as a shortened alternative and retrospective studies have suggested survival outcomes are similar for elderly patients with GBM. Prospective studies comparing hypofractionation with conventional treatment regiments are warranted. In addition to evaluating survival outcomes, HRQOL endpoints should be incorporated into future studies.

Keywords: Elderly; glioblastoma; radiation; hypofractionation

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults and has a median survival rate of 12–15 months (1). The incidence of GBM increases significantly with age (1), with a median age of diagnosis of 65 years (2). Age is an important prognostic factor in GBM; elderly patients with GBM frequently have comorbidities, unfavorable tumor biology, an increased risk of treatment

toxicity, and may receive less aggressive treatment (3). Currently, there is a lack of consensus regarding optimal treatment management in the elderly population, and elderly patients with GBM have historically been excluded from landmark clinical trials (4,5). Randomized trials that included elderly patients have demonstrated the survival benefit of radiation therapy (RT) over supportive care (6). Hypofractionated RT has emerged as a common alternative, and some studies have shown short-course regimens may result in similar or improved outcomes for elderly patients with GBM (7,8). Herein, we discuss the current standard of care for GBM, differences in tumor biology within the elderly patient population, studies evaluating the role of hypofractionation in elderly patients with GBM, and how hypofractionation impacts health-related quality of life (HRQOL).

Glioblastoma management

Surgery

Maximal safe resection is generally recommended for GBM patients (9). Randomized trials have reported subtotal or gross total resection (GTR) versus biopsy alone increases overall survival (OS) (10). GTR also improves survival outcomes in the elderly patient population (11). A randomized trial including elderly patients compared surgical resection to biopsy alone and found surgical resection resulted in improved OS (171 *vs.* 85 days) (12). When surgical resection is not possible, stereotactic or open biopsy can obtain a histologic diagnosis to assist with molecular testing. With recurrent GBM, salvage surgery is sometimes considered in patients with good performance status if >6 months has passed since initial surgical resection (13).

Radiation therapy

RT plays a key role in the management of GBM to improve local control and OS. Multiple phase III trials have demonstrated the benefit of adjuvant RT for patients with GBM (7,14-16). A prior Brain Tumor Study Group study showed a significant dose-response relationship that revealed an increase in OS when incrementally increasing the radiation dose from 45 to 60 Gy (15). Currently, the treatment standard of 60 Gy in 30 fractions over six weeks is based on a phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada

Clinical Trials Group (NCIC CTG) (2). In 2010, Chen *et al.* conducted a phase I trial determining the maximal tolerated RT dose intensification with temozolomide (TMZ) in patients with newly diagnosed GBM (17). This study reported 60 Gy in 6 Gy fractions within 2 weeks with concomitant and adjuvant TMZ had acceptable tolerance in patients with a T1-weighted enhancing tumor less than 6 cm. Multiple studies evaluating dose-escalation have not shown a survival advantage, although a recent meta-analysis suggests a potential benefit in certain populations (18-20).

Although studies have shown elderly patients have improved survival with RT versus supportive care alone without reducing QOL or cognition (6), shorter-course radiation alternatives were explored in hopes of decreasing treatment burden while still preserving survival outcomes. In a randomized study of patients ≥60 years, there was no significant difference in OS or QOL in the standard arm (60 Gy in 30 fractions) versus the hypofractionated arm (40 Gy in 15 fractions) (8). Subsequently, Roa *et al.* compared two RT regimens (short-courses 25 Gy in 5 fractions *vs.* 40 Gy in 15 fractions) (21). The authors found there was no significant difference in OS, progression free survival (PFS), and QOL between the two schedules, suggesting the shortened 1-week regimen may be an appropriate option for selected elderly patients with GBM.

Systemic therapy

TMZ is an alkylating agent that has ushered in a new standard of care for patients with newly diagnosed GBM. In 2005, a phase III study by the EORTC and the National Cancer Institute of Canada Clinical Trials Group (NCIC) found the addition of TMZ to RT (60 Gy in 30 fractions) resulted in a significantly improved median OS compared to RT alone (14.6 *vs.* 12.1 months) (2). The survival advantage was sustained throughout five years of follow-up, and patients with MGMT promoter methylation were more likely to benefit from the chemotherapy (22). These findings changed the standard of care, and modern hypofractionation studies also include TMZ (23).

The Nordic trial explored a different hypofractionated schedule of 34 Gy in 10 fractions (7). In their study, there were three treatment arms: standard RT (60 Gy in 30 fractions), hypofractionated radiation of 34 Gy in 10 fractions, or TMZ alone (administered days 1 to 5 every 28 days for up to six cycles). For patients older than 70 years, survival was better with hypofractionated RT compared to standard RT. Notably, patients who

received the protracted radiotherapy regimen of 60 Gy in 30 fractions in both the Roa and Nordic studies had a high rate of radiation discontinuation prior to completing the full radiation prescription (7,21). More recently, Perry *et al.* conducted a phase III trial evaluating the addition of TMZ to short-course RT regimens (23). In this study, TMZ added a survival benefit compared to RT alone (9.3 *vs.* 7.6 months). A more detailed discussion of hypofractionation in the elderly population will be outlined in later sections. Wick *et al.* published results from NOA-08 suggesting patients >65 years with specific biomarkers may have favorable long-term outcomes with TMZ monotherapy (24,25). In the study, receptor tyrosine kinase I (RTK I) and mesenchymal subgroups were not strong prognostic factors, but patients with the IDH-WT RTK II methylation subclass demonstrated the largest benefit by multivariate analysis.

A phase II trial evaluated the addition of bevacizumab, a monoclonal antibody to VEGF (vascular endothelial growth factor), to hypofractionated RT and TMZ to reduce radionecrosis and improve disease control (26). Although the median OS was 16.3 months, bevacizumab failed to decrease the high rate of radiation necrosis. Another phase II study of patients with recurrent GBM treated with RT (30 Gy in 5 fractions) plus bevacizumab reported no radionecrosis with a median survival of 12.5 months (27). Youland *et al.* conducted a retrospective analysis of patients with recurrent high-grade gliomas treated with reirradiation; in their study, the authors noted radionecrosis occurred in four patients, but no radionecrosis was observed in patients receiving concurrent bevacizumab (0% *vs.* 19%, P=0.03) (28). RTOG 0825 sought to determine if the addition of bevacizumab to the standard of care improved OS or PFS in newly diagnosed GBM (29). The authors determined bevacizumab did not improve OS and did improve PFS, but did not reach significance. Bevacizumab has also been used concurrently with hypofractionated reirradiation in the NRG/RTOG 1205 phase II trial (30). Although the study confirmed the safety of reirradiation, bevacizumab plus hypofractionated RT did not demonstrate improved median OS. The phase II ARTE trial randomized patients ≥65 years to hypofractionated RT (40 Gy in 15 fractions) with or without bevacizumab (31). Although the study results did not suggest bevacizumab improves survival outcomes, molecular biomarkers may be a useful tool for identifying patients that may benefit from

Investigators are now interested in combining hypofractionated RT with agents that may potentially led to

radiosensitization or anti-tumor effects (32). A phase I study evaluated gefitinib, a tyrosine kinase inhibitor, in patients with recurrent GBM (33). Fractionated SRS (36 Gy in three fractions) with gefitinib (daily dose of 250 mg) was well tolerated.

Tumor-treating fields (TTFields)

TTFields is a non-invasive treatment approach involving alternating electrical fields (34). Researchers propose TTFields are able to inhibit cancer cell proliferation by interfering with microtubule polymerization (35). Stupp *et al.* demonstrated the addition of tumor-treating fields to RT and TMZ resulted in a statistically significant improvement in PFS and OS (36). In their final analysis, the authors reported median OS was 20.9 months in the radiation, TMZ, and tumor-treating field group and 16.0 months in the radiation and TMZ-alone group. In the subgroup analysis, patients ≥65 years maintained the survival benefit with the addition of tumor-treating fields (17.4 *vs.* 13.7 months).

Pulsed radiotherapy

Pulsed RT is a novel low-dose rate therapy strategy that divides 2 Gy fractions into ten 0.2 Gy pulses. This treatment modality has demonstrated efficacy in GBM preclinical studies (37,38) and may result in superior normal-tissue sparing compared to stereotactic RT. In 2021, the first prospective trial results investigating pulsed RT in patients with newly diagnosed GBM found median OS was longer (20.9 months) compared to historical controls with no decline in QOL or neurocognitive function (39).

Tumor biology differences in elderly patients

Research suggests elderly patients with GBM may have less favorable molecular signatures compared with younger patients (40). Bozdag *et al.* (41) analyzed patients from The Cancer Genome Atlas and found elderly patients (≥70 years) with GBM exhibited pro-angiogenic phenotypes compared to younger patients (≤40 years) using computational analyses of high-throughput genomic data. Furthermore, another study suggested that certain genetic markers have variable effects on survival based on age; in one study, genetic alterations in TP53 and CDKN2A/p16 were prognostically unfavorable in older patients, but favorable in younger patients (42). A study by Nghiemphu *et al.* found older patients with GBM (≥55 years) had a 1.4-fold higher

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expression of vascular endothelial growth factor (VEGF)-A than younger patients (43). One phase II trial has found the addition of bevacizumab to TMZ in a cohort of elderly patients ≥70 years had an acceptable tolerance level (44). Methylation status of MGMT has also been found to be an important prognostic factor. The Nordic trial reported patients ≥60 years treated with TMZ with MGMT promoter methylation had significantly longer survival than those without methylation (9.7 vs. 6.8 months), similar to what was reported in other trials (7). As researchers uncover additional molecular factors unique to elderly patients with GBM, there is the hope that additional targeted treatments will be developed and implemented.

Modern day hypofractionation

The history of radiation fractionation has evolved significantly over nearly a century. As early as the 1930s, pioneers in the field reported splitting the total radiation dose into smaller fractions resulted in favorable clinical outcomes compared to a single dose (45). For decades, a fraction size of 2 Gy was considered to be the standard while increases in fraction size (≥3 Gy) were coined "hypofractionation" (46). In recent decades, technological advances (e.g., three-dimensional treatment planning, intensity modulated radiation therapy, stereotactic radiotherapy) have led to a paradigm shift, allowing providers to deliver high-doses to the tumor/target volume while sparing normal tissue (47).

Hypofractionated radiotherapy in the elderly population

There is significant variation in the elderly GBM management and a pressing need to find an optimal treatment approach for the elderly population (48). Critical trials that were used to establish the standard of care for patients with newly diagnosed GBM set the upper age limit to 70 years (2,22). This age cut-off was controversial considering the median age of newly diagnosed GBM is 65 years according to data from various countries (49-51). Furthermore, studies found patient outcomes decline with age (52), suggesting the established treatment regimen may not be suitable for the elderly population. Elderly patients frequently have various functional, cognitive, and social limitations (53); tools have been developed to group elderly cancer patients based on functional status, comorbidities, cognition, nutritional status, psychological

state, and social support [e.g., comprehensive geriatric assessment (CGA)] (54). Varying hypofractionation schemes have been reported in the literature that range from "moderate" (3 Gy) to "extreme" (5–8 Gy) for the elderly or frail patient population with poor prognosis (55-60). Researchers have surmised hypofractionated RT may limit tumor repopulation (61), increase cell kill (62), and improve local control in certain radioresistant tumors (63) while decreasing overall treatment time.

Over the past decade, numerous disease sites (e.g., breast, prostate, rectum) have transitioned to hypofractionated regimens; a paradigm shift that was, in part, a result of technological advances in RT that have allowed the use of high dose-per-fraction (64). Many trials have determined short-course RT outcomes are non-inferior (65-68) and some studies have found short-course schedules were associated with decreased treatment failure (69). The current standard of care for GBM is 60 Gy in 30 fractions for patients <70 years and a hypofractionated regimen (e.g., 40 Gy in 15 fractions) as an acceptable, more convenient alternative for elderly or frail patients (8). To date, there have not been large phase III clinical trials comparing the standard of care radiation (60 Gy in 30 fractions) to hypofractionated RT (40 Gy in 15 fractions). Nonetheless, studies involving elderly patients with GBM have been conducted, and key studies are highlighted below.

In 2004, the EORTC/NCIC phase III trial by Stupp et al. demonstrated improved median and 2-year survival for patients with GBM treated with RT plus TMZ (2). A 5-year analysis found the benefits of TMZ with RT were sustained throughout follow-up and MGMT status was the strongest prognostic factor (22). Additionally, the updated analysis demonstrated all prognostic subgroups had improved OS with the addition of TMZ. Notably, a survival benefit was reported in patients 60–70 years (22).

Given the poor survival outcomes of elderly patients with GBM, investigators were uncertain if the treatment burden associated with 6 weeks of RT provided significant benefit compared to shorter-course regimens. Roa et al. conducted a prospective study comparing standard RT (60 Gy in 30 fractions, n=51) and a shorter-course (40 Gy in 15 fractions, n=49) in patients ≥60 years with GBM (8). OS were similar between the two groups (5.1 months for standard vs. 5.6 months for hypofractionated). However, this trial was designed as a superiority trial and was not powered to determine non-inferiority of the hypofractionated arm. Of note, a larger proportion of patients (26% in the standard arm vs. 10% in the short course arm) did not complete

radiation treatment.

In 2012, Malmström *et al.* published results from the Nordic phase III trial comparing TMZ (n=93), hypofractionated RT (34 Gy in 10 fractions over 2 weeks, n=98), and standard RT (60 Gy in 30 fractions over 6 weeks, n=100) for patients ≥60 years (7). Median OS was significantly longer with TMZ compared to standard RT (8.3 *vs.* 6.0 months), but OS was similar for patients who received TMZ or hypofractionated RT (8.4 *vs.* 7.4 months). For patients older than 70 years, TMZ and hypofractionated RT resulted in improved survival compared to standard RT. The authors also reported patients with MGMT promoter methylation had significantly longer survival (9.7 *vs.* 6.8 months). Again, a greater proportion of patients receiving standard treatment did not finish their prescribed radiation course (28% *vs.* 5% in the hypofractionated arm).

In a phase III study, Roa *et al.* explored alternative RT regimens for elderly and/or frail patients: either a shorter-course (25 Gy in 5 fractions, n=48) or the common hypofractionated regimen (40 Gy in 15 fractions, n=50) (21). The authors reported the short-course was non-inferior; median OS was greater in the short-course arm (7.9 *vs.* 6.4 months) and median PFS rates were equivalent in both arms (4.2 months). However, 56% of the patients on this study had Karnofsky Performance Status (KPS) <70%, so it may be more applicable for selected frail and elderly patients.

In 2017, Perry *et al.* conducted a randomized trial evaluating the benefit of adding TMZ to shorter course RT (40 Gy in 15 fractions) (23). The trial included patients ≥65 years who were randomized to RT alone or RT plus concomitant and adjuvant TMZ. The addition of TMZ resulted in longer median OS (9.3 *vs.* 7.6 months) and median PFS (5.3 *vs.* 3.9 months). Subgroup analysis revealed patients with methylated MGMT status had a greater TMZ benefit (13.5 *vs.* 7.7 months, P<0.001), but patients with unmethylated MGMT status also experienced a survival benefit that approached but did not reach significance (10.0 *vs.* 7.9 months, P=0.06).

Today, a standard RT prescription for elderly patients with GBM is 40 Gy in 15 fractions. However, the BED for 40 Gy in 15 fractions is lower than the BED for 60 Gy in 30 fractions. Previous studies have shown dose escalation from 45 to 60 Gy has significant survival improvement at each interval, suggesting that elderly patients receiving 40 Gy in 15 fractions may be underdosed (15). An analysis by Perlow *et al.* evaluated outcomes of elderly GBM patients (≥65 years) that received either 52.5 Gy in 15 fractions or 40 Gy in 15 fractions (70). The authors found OS was greater in the 52.5 Gy group compared to the 40 Gy group (14.1 *vs.* 7.9 months); there were no significant differences between treatment groups. Furthermore, there was not a significant difference in toxicity between the two treatment groups and no grade IV or V toxicities. These findings suggest RT de-escalation in the elderly or frail population may negatively impact survival outcomes.

A subsequent study by Perlow *et al.* pooled elderly and/or frail patients with GBM from 3 phase I/II studies and a prospective registry study (71). Patients ≥65 years or with a KPS <70 treated with accelerated hypofractionated RT (52.5 Gy in 15 fractions) were included in the analysis. The median age for this study was 73 years and patients had a median OS and PFS or 10.3 and 6.9 months, respectively. Grade III toxicity was only observed in 2 patients (3.2%) and there were no grade IV or V toxicity. Compared to prior studies (7,21,23,72), this hypofractionated isoeffective RT regimen had superior OS (10.3 *vs.* 6.4–9.3 months) without a notable increase in toxicity.

There have been other hypofractionated accelerated RT treatment schedules (60 Gy in 20 fractions) that have demonstrated comparable survival outcomes to conventional RT, but excluded elderly patients (73,74). Elderly patients with good KPS scores may be appropriate candidates for this treatment regimen, but retrospective and prospective evaluation is needed.

HRQOL

HRQOL is increasingly being recognized as an important end point, particularly for patients with aggressive cancers (75,76). GBM treatment and disease-related side-effects may include cognitive dysfunction, fatigue, and personality changes that can affect the social interactions and the ability to perform activities of daily living (77). As hypofractionation survival outcomes are being assessed in elderly patients with GBM, monitoring the effects to HRQOL is of equal importance.

Several studies have found a hypofractionated regimen does not lead to a significant decline in HRQOL within the elderly patient population. Minniti *et al.* reported elderly patients that received 40 Gy in 15 fractions had stable or improved HRQOL (78). Reddy *et al.* similarly found hypofractionation (60 Gy in 10 fractions) was associated with stable HRQOL as well as an improvement in insomnia, future uncertainty, motor dysfunction, and drowsiness (79).

Radiation necrosis is a potential side effect of hypofractionated RT (80), and symptomatic radiation

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necrosis frequently leads to a decline in HRQOL (81). Bevacizumab has been explored as a potential agent for reducing rates of symptomatic necrosis and brain edema via decreasing vascular permeability (27). In a phase II trial for newly diagnosed GBM, Omuro *et al.* demonstrated an aggressive RT schedule (36 Gy in 6 fractions) with concomitant and adjuvant bevacizumab was safe and convenient for patients (82). A subsequent phase I/II trial by Pollom *et al.* assessed longitudinal HRQOL in patients treated with dose escalated five-fraction SRS (25–40 Gy in 5 fractions) and found no significant changes in HRQOL compared to historical controls (83). In this trial, patients who experienced symptomatic adverse radiation effects were treated with bevacizumab. Although 27% of patients experienced adverse radiation-related effects with dose-escalation, there was not a significant decline in HRQOL. These findings suggest dose escalation may be clinically favorable.

Perspective

Defining "elderly"

Currently, the literature lacks a clear definition of what is defined as "elderly", where some studies consider patients that are 60 years (8) while others choose ≥65 years (23) as the cut-off age. A propensity score matched analysis found outcomes were similar in patients aged 65–69 compared to older patients ≥70 years (84). This finding suggests hypofractionated regimens should also be considered in this group of younger elderly patients with GBM.

The need for prospective studies

Numerous studies have evaluated hypofractionated RT in elderly patients with GBM, but many of these studies are retrospective. Furthermore, there is significant heterogeneity in the hypofractionation schemes (e.g., number of fractions, total dose), making it difficult to interpret available data. To date, there is a lack of prospective trials comparing hypofractionation with conventional RT in the elderly population. Hypofractionation appears to be a safe, well-tolerated alternative for elderly or frail patients with GBM, and there is a need for adequately powered prospective studies comparing hypofractionation and conventional fractionated RT survival outcomes. A phase III trial (NCT05439278, not yet recruiting) is planning to compare outcomes of patients ≥70 years receiving either conventional RT (60 Gy in 6 weeks) or hypofractionated RT (40 Gy in 3 weeks). Lastly, there is a need for effective treatment options following GBM recurrence. One such study is NCT05393258 (recruiting) that is evaluating temporally modulated pulsed RT delivered in multiple small doses.

Conclusions

Glioblastoma is one of the most aggressive cancer types and is associated with a poor prognosis, particularly in the elderly population. Currently, there is an ongoing debate regarding optimal treatment management in this specific patient population. Less aggressive interventions may be employed since elderly patients commonly have functional, cognitive, and social limitations. Historically, RT has played a critical role in the management of GBM, but conventional treatment schedules are typically lengthy and may lead to early treatment discontinuation (7,21). Hypofractionated RT has emerged as a shortened alternative and retrospective studies have suggested survival outcomes are similar for elderly patients with GBM. Prospective studies comparing hypofractionation with conventional treatment regimens are warranted. In addition to evaluating survival outcomes, HRQOL end points should be incorporated into future studies.

Footnote

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