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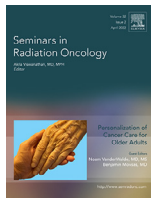

Hypofractionation in Older Adults With Glioblastoma

Drucilla Edmonston, MD,*,† Noam Vanderwalde, MD, MS,† and Matthew Ballo, MD†

Glioblastoma (GBM) is the most common primary brain malignancy, and its incidence and aggressiveness both increase with age.[1] The median age at diagnosis is 64 years with a peak incidence between 75 and 84 years.[2] GBM carries a poor prognosis which is worse in older adults. Young, robust patients are often treated with maximal safe resection followed by adjuvant chemotherapy and radiation (RT) based on the results of a phase 3 study performed in patients age 18-70 (median age 56),[3] while the optimal management of GBM in older, less functional patients is not as well-defined. Owing to concerns over toxicity and treatment tolerability, frequent medical comorbidities, and generally poorer functional status; older patients have historically been excluded from standard-setting GBM trials and are often not offered combined modality therapy. While it has been shown that RT does offer a survival benefit in patients over the age of 65, there exists a tedious balance between the hardship imposed by extensive therapy and the benefit of local disease control.[4,5]

Over the last several decades, multiple prospective studies have investigated the use of alternative treatment regimens in older adults (Table) in an effort to tilt this balance in favor of improving survival outcomes while preserving health-related quality of life. To that end, there has been a movement towards hypofractionated RT in this population, whereby a definitive course of RT is delivered over a more convenient course of 3 or fewer weeks. The first such investigation was performed by Roa et al. in a phase III trial which compared standard course RT to a dose of 60 Gy in 30 fractions vs a hypofractionated course of RT to a dose of 40 Gy in 15 fractions in 100 patients 60 years and older with a Karnofsky performance status (KPS) of 50 or greater.[6] Chemotherapy was not administered in either arm before or during RT but was permissible at the time of disease progression. The authors discovered no difference in overall survival between the 2 regimens (5.1 vs 5.6 months), and there was a decreased need for post-treatment corticosteroids in the hypofractionated arm.[6] The second such study was the phase III Nordic trial conducted by Malmström et al., which compared standard course radiotherapy to 60 Gy in 30 fractions vs Temozolomide (TMZ) alone vs hypofractionated RT to a dose of 34 Gy in 10 fractions in patients over the age of 60 with WHO performance status 0-2.[7] Again, no combination therapy was administered. The hypofractionated regimen was associated with improved ability to complete planned treatment compared to standard course RT (95% vs 72%). The intended 6 cycles of TMZ were completed in only 34% of the chemotherapy alone arm participants. The authors found that both TMZ and hypofractionated RT were associated with superior survival outcomes compared to conventional RT in patients over the age of 70, while there were no significant differences in patients between the age of 60 and 70. These 2 trials support the notion that hypofractionated RT alone is at least as effective as conventionally fractionated RT alone for older patients with GBM. Another study by Roa et al. explored the idea of further abbreviating radiation therapy for older adults and frail patients. Between 2010 and 2013, 98 patients who were classified as frail, elderly, or both (age $\geq$ 50 with KPS between 50 and 70, or age $\geq$ 65 with KPS 50-70 or 80-100) were randomized to receive short-course RT (25 Gy in 5 daily fractions) vs hypofractionated RT (40 Gy in 15 daily fractions).[2] No chemotherapy was permitted in either group. The results showed short course RT was non-inferior to hypofractionated RT with a median survival of 7.9 vs 6.4 months, respectively (P = 0.988). Median progression-free survival was 4.2 months in both arms (P = 0.716), and quality of life at 1 and 2 months post-RT was also similar.[2] However, the question regarding the tolerability and efficacy of multimodality therapy in older adults utilizing hypofractionated RT was still debatable.

More recently, the benefit of combined modality hypofractionated RT was addressed in a phase II trial by Minniti et al. which enrolled 71 patients aged 70 years or older with a favorable performance status (KPS $\geq$ 60) and a diagnosis of GBM.[8] Enrollees were treated with hypofractionated RT to 40 Gy in 15 fractions with concurrent and adjuvant TMZ for 1 year. Median survival was an impressive 12.4 months, with 1- and 2-year overall survival rates of 58% and 20%,

*Department of Radiation Oncology, University of Tennessee Health Science Center, Memphis, TN
†West Cancer Center and Research Institute, Memphis, TN
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Address reprint requests to Drucilla Edmonston, MD, Department of Radiation Oncology, 7945 Wolf River Blvd, Germantown, TN 38138 E-mail: DEdmonston@westclinic.com

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Table Phase II-III Prospective Trials of Hypofractionated Radiotherapy in Elderly Patients With Glioblastoma

Study	N	Key Eligibility Criteria	Adjuvant Intervention	Median Survival
Roa et al. (2004)	100	Age ≥ 60 years Histologically confirmed GBM KPS ≥ 50	Standard RT (60 Gy in 30 fractions) Vs Hypofractionated RT (40 Gy in 15 fractions)	Standard RT: 5.1 months Hypofractionated RT: 5.6 months
Malström et al. (2012)	291	Age ≥ 60 years Biopsy-proven GBM WHO PS ≤2 (3 if due to neurologic deficits)	TMZ alone vs Standard RT (60 Gy in 30 fractions) Vs Hypofractionated RT (34 Gy in 10 fractions)	TMZ: 8.3 months Standard RT: 6.0 months Hypofractionated RT: 7.5 months *Significant only for TMZ vs standard RT (p=.01) and for standard RT vs hypofractionated RT in pts > 70 (p= .02)
Minniti et al. (2011)	71	Age ≥ 70 Histologically confirmed GBM KPS ≥ 60	Hypofractionated RT (40 Gy in 15 fractions) + concurrent and adjuvant TMZ	12.4 months
Perry et al. (2017)	562	Age ≥ 65 Biopsy-proven GBM ECOG ≤2 Deemed unsuitable for standard fractionation	Short-course RT alone (40 Gy in 15 fractions) Vs Short-course RT with TMZ	RT alone: 7.6 months RT+TMZ: 9.3 months (P=<.001)
Roa et al. (2015)	98	Frail patients (age ≥ 50 with KPS 50-70%) Elderly and frail patients (age ≥ 65 with KPS 50-70%) Elderly patients (age ≥ 65 with KPS 80-100%) Histologically confirmed GBM	Short-course RT (25 Gy in 5 daily fractions) Vs Hypofractionated RT (40 Gy in 15 fractions)	Short-course RT: 7.9 months Hypofractionated RT: 6.4 months
Navarria et al. (2019)	30	Age ≥ 70 KPS ≥ 60 Histologically confirmed high-grade glioma Estimated survival ≥ 3 months	Hypofractionated RT (52.5 Gy in 15 fractions) + TMZ if feasible	8.0 months

ECOG, Eastern Cooperative Oncology Group; GBM, Glioblastoma multiforme; KPS: Karnofsky Performance Status; RT, Radiotherapy; TMZ, Temozolomide; WHO PS, World Health Organization Performance Status.

respectively. Median progression-free survival was 6 months and the rate of grade 3-4 toxicity was 22%. All patients completed the intended RT, while patients received a median of 6 of the 12 intended cycles of adjuvant TMZ. The authors concluded that hypofractionated RT plus concurrent and adjuvant TMZ is well tolerated in this population and could improve survival. Subsequently, Perry et al. published the results of their phase III trial in 2017.[9] In this study, 562 patients aged 65 and older with a favorable performance status but who were deemed by their physician to be ineligible for standard chemoRT (reasons for ineligibility were not collected or published) were randomized to receive hypofractionated RT alone (40.05 Gy in 15 fractions) vs the same RT with concurrent and adjuvant TMZ. The authors reported a median overall survival of 9.3 vs 7.6 months in favor of combined modality therapy (hazard ratio 0.67, 95% confidence interval, 0.65-0.80, $P < 0.001$). Median progression-free survival was also significantly better in the hypofractionated chemoRT group (5.3 months vs 3.9 months; hazard ratio 0.5; 95% confidence interval, 0.41 to 0.60; $P < 0.001$). Compliance with RT did not differ between the groups and, unsurprisingly, toxicity was slightly higher with multimodality therapy than with hypofractionated RT alone. Health-related quality of life was comparable between the 2 study arms. This trial provided the first phase III evidence to support the safety and efficacy of hypofractionated radiotherapy and concurrent chemotherapy in older adult glioblastoma patients.[9] With data supporting a median survival between approximately 5 and 9 months even with combined therapy in this population, Navarria et al sought to improve outcomes through dose escalation. They enrolled 30 patients aged 70 years and older with acceptable performance status to evaluate the safety and efficacy of adjuvant hypofractionated radiotherapy to a dose of 52.5 Gy in 15 fractions (BED 70.88 Gy) with TMZ in a small phase II trial.[10] Concurrent and adjuvant TMZ was able to be administered in 23% of patients, while 41% received only adjuvant TMZ. Authors reported a median patient age of 75 years, median OS of 8 months, 6-month OS 90%, and 12-month OS 30% (Navarria et al, 2019).

Interpreting the cumulative results of these studies and applying their findings to clinical practice remains a challenge given the differences in ages and performance statuses included in each trial. Additionally, even understanding what made patients eligible for combined modality therapy but not for standard dose RT is difficult given that Perry et al. did not define ineligibility for standard RT.[9] However, a few common prevailing themes emerge which can be used to inform clinical decision-making; (1) Hypofractionated RT is at least as effective as conventionally fractionated RT for treatment of GBM in patients over age 70 and or those with poor performance status, (2) Hypofractionated RT administered with concomitant TMZ is tolerable in most older more functional patients and can prolong survival as compared to hypofractionated RT alone, and (3) several hypofractionation regimens over the course of 1-3 weeks are safe and efficacious in this group and treatment may be tailored to the convenience and performance status of the individual patients. A Geriatric Assessment (described in earlier articles) could be used as a method of better defining functional/performance statuses to help inform treatment options and decisions. Older adults with an excellent functional status (robust) may be most appropriate for combined modality therapy with conventional RT and concurrent/adjuvant TMZ. Those patients who are older than 70 or have moderate functionality (pre-frail) may be better candidates for hypofractionated RT with concurrent and adjuvant TMZ. While, those with a poor performance status (frail) may be best suited by a short course of hypofractionated RT alone using a 1 week, 2-week, or 3-week course depending on the expected patient tolerance and convenience.

Yet, there are still several important questions left unanswered. To date, conventionally fractionated chemoRT has never been prospectively compared to hypofractionated chemoRT for the treatment of glioblastoma in patients of any age. Is hypofractionated chemoRT an appropriate treatment in older adult patients who would be eligible and could tolerate a conventional course of definitive therapy, but whose quality of life might be improved by a truncated course of therapy? Future prospective trials may seek to further elucidate a clear definition for the role of hypofractionated radiotherapy in combination with chemotherapy for older adult glioblastoma patients. Additionally, the role of tumor-treating fields (TTF) in an older adult population as part of a hypofractionated treatment course still needs to be defined. TTF (Figure) is a technology that utilizes alternating electric fields delivered via arrays worn on the patient's skin to disrupt microtubule spindle formation and ultimately lead to mitotic cell death.[11] The initial data published in 2012 by Stupp et al. demonstrated a trend toward improved median survival in patients with recurrent GBM vs chemotherapy alone (6.6 vs 6 months, $P = 0.27$).[12] Further, TTF was associated with lower toxicity and improved quality of life. A subsequent phase III trial was performed investigating the use of this technology in primary GBM, in which patients were randomized to standard of care (surgery followed by concurrent chemoRT and adjuvant TMZ alone) vs surgery followed by concurrent chemoRT and adjuvant TTF plus TMZ. The authors reported a median survival of 20.9 months vs 16.0 months in favor of the TTF arm.[13] Post hoc subgroup analyses demonstrated a progression-free survival and overall survival benefit with TTF regardless of gender, age, performance status, MGMT status, location, and extent of surgery. Given its noninvasive nature and low toxicity profile, TTF may represent a worthy consideration alone or in combination with other modalities in the treatment of GBM in older or less functional patients and may be worthy of investigation in this population.

In summary, there are now several RT alone and combined modality treatment regimens for older adults with GBM. Choosing between these regimens can be challenging given the difficulty in interpreting which patients were eligible for the phase 2 and 3 studies that support these regimens. Better assessments of our patients' true functional status, convenience, and personal preferences can best help clinicians and their patients make informed and appropriate treatment decisions.

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