

# Document ID: GBM-2024-009

## Title: Hypofractionated Radiotherapy Versus Standard Radiotherapy in Elderly Glioblastoma Patients: Quality of Life and Cognitive Outcomes

### Publication Type

Clinical Trial (Randomized Phase III)

### Year of Publication

2024

### Patient Demographics

- Age Group:** 65-82 years (median age: 73 years)
- Sample Size:** 211 patients (106 hypofractionated RT, 105 standard RT)
- Condition:** Newly diagnosed glioblastoma unsuitable for or declining extensive surgery (biopsy-only: 48.3%, subtotal resection: 51.7%)
- Gender Distribution:** 51% male, 49% female
- ECOG Performance Status:** 1-2 (ECOG 0 patients excluded to focus on frail elderly)
- \*\*Median Mini-Mental State Examination (MMSE):** 24 (range: 18-28)
- Comorbidity Index:** Median Charlson Comorbidity Index 6 (range: 4-11)

### Disease Focus

Glioblastoma multiforme in frail elderly population with emphasis on balancing survival benefit against quality of life and cognitive preservation

### Treatment Discussed

**Hypofractionated Radiotherapy Arm:** - Total dose: 40 Gy in 15 fractions over 3 weeks - Concurrent temozolomide: 75 mg/m<sup>2</sup> daily during radiotherapy - Maintenance temozolomide: 150-200 mg/m<sup>2</sup> days 1-5/28 for up to 6 cycles - Target volume: GTV + 1.5 cm margin (reduced compared to standard)

**Standard Radiotherapy Arm:** - Total dose: 60 Gy in 30 fractions over 6 weeks - Concurrent temozolomide: 75 mg/m<sup>2</sup> daily during radiotherapy - Maintenance temozolomide: 150-200 mg/m<sup>2</sup> days 1-5/28 for up to 6 cycles - Target volume: GTV + 2 cm margin (standard protocol)

Both arms used IMRT or VMAT techniques with image guidance.

### Study Outcome Summary

**Primary Endpoint (Overall Survival):** - Hypofractionated RT: median OS 10.1 months (95% CI: 8.7-11.8) - Standard RT: median OS 9.8 months (95% CI: 8.2-11.3) - Hazard ratio: 0.93 (95% CI: 0.69-1.25, p=0.65) - non-inferior (pre-specified non-inferiority margin HR 1.25)

**Secondary Survival Endpoints:** - Median progression-free survival: - Hypofractionated: 5.2 months (95% CI: 4.3-6.4) - Standard: 5.4 months (95% CI: 4.5-6.2) - HR: 1.04 (p=0.78)

- 12-month overall survival:

- Hypofractionated: 37.7%
- Standard: 34.3%

### **Quality of Life Assessment (Primary Patient-Reported Outcome):**

*EORTC QLQ-C30 Global Health Status:* - Baseline mean scores: Hypofractionated 56.3, Standard 55.8 - At 3 months: Hypofractionated 58.7 (maintained), Standard 52.1 (declined,  $p=0.032$ ) - At 6 months: Hypofractionated 54.2, Standard 49.8 ( $p=0.18$ ) - Time to 10-point deterioration: Hypofractionated 7.8 months vs Standard 5.9 months (HR 0.71,  $p=0.041$ )

*Fatigue Scores:* - Shorter treatment duration in hypofractionated arm associated with less cumulative fatigue during radiotherapy phase ( $p=0.003$ ) - By 3 months post-RT, fatigue scores equivalent between arms

### **Cognitive Function Assessment:**

*MMSE Serial Measurements:* - Baseline: Both arms 24 points (median) - At 3 months: - Hypofractionated: 23 points (1-point decline) - Standard: 21 points (3-point decline,  $p=0.019$ ) - Proportion maintaining MMSE  $\geq 20$  at 6 months: - Hypofractionated: 64.2% - Standard: 51.4% ( $p=0.042$ )

*Hopkins Verbal Learning Test (HVLT):* - Delayed recall at 3 months showed better preservation in hypofractionated arm (mean decline 2.1 vs 3.8 points,  $p=0.028$ )

*Trail Making Test B:* - Executive function decline less pronounced in hypofractionated arm at 3 months ( $p=0.035$ )

**Functional Independence:** - Karnofsky Performance Status maintained  $\geq 70$  at 3 months: - Hypofractionated: 68.9% - Standard: 57.1% ( $p=0.046$ ) - Activities of Daily Living (ADL) independence preserved longer in hypofractionated arm (median 8.2 vs 6.7 months,  $p=0.037$ )

**Treatment Completion:** - Completed planned radiotherapy: - Hypofractionated: 94.3% - Standard: 82.9% ( $p=0.007$ ) - Completed  $\geq 4$  cycles maintenance TMZ: - Hypofractionated: 61.3% - Standard: 54.3% ( $p=0.28$ )

**Safety/Toxicity:** - Grade 3/4 radiotherapy-related toxicity: - Hypofractionated: 8.5% - Standard: 12.4% ( $p=0.34$ ) - Hematologic toxicity similar between arms - Radiation necrosis: - Hypofractionated: 5.7% - Standard: 8.6% ( $p=0.42$ )

**Caregiver Burden:** - Caregiver Reaction Assessment scores favored hypofractionated arm due to fewer hospital visits - Transportation burden significantly reduced (3-week vs 6-week treatment course)

### **FDA Approval Status**

**Both Approaches Approved** - Radiotherapy (both standard fractionation and hypofractionated regimens) combined with temozolomide is part of FDA-approved standard of care for glioblastoma. The choice of fractionation schedule represents physician judgment based on patient factors rather than a distinct regulatory approval.

### **Key Findings**

Hypofractionated radiotherapy (40 Gy/15 fractions) demonstrated non-inferior overall survival compared to standard fractionation (60 Gy/30 fractions) in frail elderly glioblastoma patients, while offering significant advantages in quality of life, cognitive preservation, and treatment completion rates.

The shorter treatment course (3 weeks vs 6 weeks) provided meaningful benefits for elderly patients with limited life expectancy, reducing treatment burden, transportation challenges, and caregiver stress. Higher completion rates suggest improved tolerability.

Cognitive outcomes favored hypofractionated radiotherapy with better preservation of memory, executive function, and overall mental status at 3 months. This may reflect reduced cumulative radiation exposure to surrounding normal brain tissue and shorter duration of daily treatments.

Functional independence and activities of daily living were maintained longer with hypofractionated approach, translating to improved quality of remaining life for elderly patients. The ability to preserve independence represents a critical outcome for this population.

The study supports hypofractionated radiotherapy as the preferred approach for frail elderly glioblastoma patients, particularly those with limited performance status, significant comorbidities, or logistical barriers to prolonged daily treatment. The approach aligns with geriatric oncology principles prioritizing quality of life alongside survival.

For carefully selected elderly patients with excellent performance status and minimal comorbidities, standard fractionation may still be considered, though the current evidence suggests hypofractionation provides optimal benefit-burden balance for most elderly patients.

## Citations

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**Clinical Trial Registration:** EudraCT 2020-004567-21

**Institutional Review Board:** Multi-national ethics approval across 45 participating centers

**Quality of Life Committee:** Independent committee oversaw PRO data collection and analysis

**Neurocognitive Assessment:** Certified neuropsychologists administered standardized testing

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**Conflict of Interest:** All authors declare no conflicts; independent academic study without industry sponsorship.