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Original Article

Accelerated hypofractionated radiation for elderly or frail patients with a newly diagnosed glioblastoma: A pooled analysis of patient-level data from 4 prospective trials

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BACKGROUND: The standard of care for elderly or frail patients with glioblastoma (GBM) is 40 Gy in 15 fractions of radiotherapy. However, this regimen has a lower biological effective dose (BED) compared with the Stupp regimen of 60 Gy in 30 fractions. It is hypothesized that accelerated hypofractionated radiation of 52.5 Gy in 15 fractions (BED equivalent to Stupp) is safe and efficacious. **METHODS:** Elderly or frail patients with GBM treated with 52.5 Gy in 15 fractions were pooled from 3 phase 1/2 studies and a prospective observational study. Overall survival (OS) and progression-free survival (PFS) were defined time elapsing between surgery/biopsy and death from any cause or progression of disease. **RESULTS:** Sixty-two newly diagnosed patients were eligible for this pooled analysis of individual patient data. The majority (66%) had a Karnofsky performance status (KPS) score <70. The median age was 73 years. The median OS and PFS were 10.3 and 6.9 months, respectively. Patients with KPS scores ≥70 and <70 had a median OS of 15.3 and 9.5 months, respectively. Concurrent chemotherapy was an independent prognostic factor for improved PFS and OS. Grade 3 neurologic toxicity was seen in 2 patients (3.2%). There was no grade 4/5 toxicity. **CONCLUSIONS:** This is the only analysis of elderly/frail patients with GBM prospectively treated with a hypofractionated radiation regimen that is isoeffective to the Stupp regimen. Treatment was well tolerated and demonstrated excellent OS and PFS compared with historical studies. This regimen gives the elderly/frail population an alternative to regimens with a lower BED. Randomized trials are needed to validate these results. ***Cancer* 2022;128:2367-2374**. © *2022 American Cancer Society*.

KEYWORDS: elderly, frail, glioblastoma, hypofractionation, radiation.

INTRODUCTION

High-grade gliomas are the most common malignant brain tumor, encompassing approximately 70% of the 23,000 malignant brain tumors diagnosed in the United States each year.[1] The majority of these cases are glioblastoma multiforme (GBM). Early randomized trials demonstrated that maximal safe resection followed by adjuvant radiation therapy was more effective compared with resection alone with a doubling of overall survival (OS).[2,3] Prior Brain Tumor Study Group studies show a significant dose-response relationship that revealed an increase in OS when incrementally increasing the radiation dose from 50 to 60 Gy.[4] Thus, radiation therapy to 60 Gy in 30 fractions became the preferred adjuvant therapy until the Stupp trial defined the current standard of care by demonstrating a significant OS benefit (27.2% vs 10.9% at 2 years) with the addition of concurrent and adjuvant temozolomide when compared with adjuvant radiotherapy alone.[5]

The incidence of GBM increases with age with a median age at diagnosis of 64 years.[6] In the Stupp trial, elderly patients (>60 years old) had a median overall survival of 10.9 to 11.8 months.[5] For elderly patients, radiation offers a 4-month survival benefit versus supportive care alone.[7] Recent studies have shown that hypofractionated deescalated radiation therapy to 40 Gy in 15 fractions could be a reasonable alternative for elderly patients or those with a poor performance status.[8-10] The International Atomic Energy Agency (IAEA) trial including elderly (age ≥65 years) or frail (Karnofsky performance status [KPS] score, 50-70) patients showed a median OS of 6.4 months (radiation alone), and the Canadian Cancer Trials Group (CCTG) study showed a median OS of 7.6 months (radiation alone) versus 9.3 months (radiation plus temozolomide).[9,10] However, this regimen has a lower biological effective dose (BED) than the Stupp regimen, and

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patients in these cohorts had inferior survival outcomes compared with elderly patients in the Stupp trial. Thus, we hypothesize that radiation therapy to 52.5 Gy in 15 fractions (isoeffective to the Stupp regimen of 60 Gy in 30 fractions) may be safe and show improved efficacy for elderly and frail patients. We performed a pooled analysis of 4 prospective studies to investigate this hypothesis.

MATERIALS AND METHODS

Four studies prospectively treating elderly or frail patients were identified and included in this pooled analysis. Trial authors were individually contacted and patient-level demographic, radiation and chemotherapy, toxicity, and follow-up data were extracted from each study and pooled for analysis. These data include patients with GBM treated with 52.5 Gy in 15 fractions, an isoeffective dose compared with the Stupp trial. Toxicity was scored using the Common Terminology Criteria for Adverse Events (version 5.0).[11]

Three phase 1 and 2 studies and a prospective observational study were included in this analysis (Table 1).[12-15] For each study, an appropriate institutional review board and ethics committee approved the project; informed consent was obtained as detailed in the earlier publication.[12-14] Eligible patients had a new diagnosis of GBM and were either elderly (age ≥65 years old) or had a poor performance status (KPS score <70). Generally, patients were treated at a total dose of 52.5 Gy in 15 fractions, although Scoccianti et al treated patients with a simultaneous integrated boost,[14] the clinical target volume (CTV) for the simultaneous integrated boost (CTV, 67.5 Gy) was defined as the gross tumor volume plus a 5-mm margin. The radiation CTV was defined by the borders of the surgical cavity, residual tumor, and T2 fluid-attenuated inversion recovery seen on magnetic resonance imaging scan in each study with a 0- to 1-cm expansion. Additional details about radiation treatment planning and patient characteristics in each study are shown in Table 1.

Statistics

The primary end point of this study was the median OS for patients treated with 52.5 Gy in 15 fractions. We defined OS as the time elapsed between the surgery/biopsy and death from any cause and progression-free survival (PFS) as the time elapsed between surgery/biopsy and progression or death from any cause. Patients were right-censored if lost to follow-up. Summary statistics were used to describe patient demographics and clinical characteristics. The Fisher exact test was used to determine relationships

TABLE 1. Studies Pooled for Analysis

Study	No.	Median Age, y	Median KPS	Median OS, mo	Radiation Dose and Fractionation	GTV Delineation	CTV Delineation	PTV Expansion	TMZ Administration
Ammirati, 2014[12]	5	72	70	8.4	5250 cGy/15 fractions	T1 postcontrast enhancement and/or surgical cavity	GTV + T2-weighted abnormality	CTV + 2 cm	Concomitant TMZ, 100% of patients; adjuvant TMZ, 40% of patients
Navarria, 2019[13]	30	75	60	8.0	5250 cGy/15 fractions	T2-weighted FLAIR and/or surgical cavity	GTV + 0.5 cm	CTV + 0.5 cm	Concomitant TMZ, 27% of patients; adjuvant TMZ, 41% of patients
Perlow, 2022[15,a],	20	69	70	10.6	4005 cGy/15 fractions with SIB to 5250 cGy	T1 postcontrast enhancement and/or surgical cavity	4005, T2 FLAIR + 1 cm; 5250, GTV + 0-0.5 cm	4005, CTV + 0.3 cm; 5250, CTV + 0-0.3 cm	Concomitant TMZ, 95% of patients; adjuvant TMZ, 70% of patients
Scoccianti, 2018[14]	7	69	80	11.6	5250 cGy/15 fractions with SIB to 6750 cGy	T1 postcontrast enhancement and/or surgical cavity	5250, CTV6750 + 1 cm; 6750, GTV + 0.5 cm	5250, CTV + 0.3 cm; 6750, CTV + 0.3 cm	Concomitant TMZ, 100% of patients; adjuvant TMZ, 86% of patients

Abbreviations: CTV, clinical target volume; FLAIR, fluid-attenuated inversion recovery; GTV, gross tumor volume; KPS, Karnofsky performance status; OS, overall survival; PTV, planning target volume; SIB, simultaneous integrated boost; TMZ, temozolomide.
Eligible patients had a new diagnosis of glioblastoma and were either elderly (age ≥65 years) or had a poor performance status (KPS <70); patient-level data meeting criteria were extracted from each study.
[a]The patient population overlaps with Ammirati et al.[12] Eligible Ammirati patients are not included in this row.

between categorical variables. The Kaplan-Meier method was used to generate survival curves with corresponding log-rank tests for difference by stratification group. Last, we used Cox proportional hazards regression to estimate adjusted hazard ratios. The multivariable model was chosen by preselecting age, sex, and O6 methylguanine-DNA methyltransferase (MGMT) as clinically relevant estimates of interest and allowing a fourth explanatory variable based on effect size from univariable OS analysis. All analyses were conducted in R version 4.0.5.

RESULTS

Sixty-two patients were eligible for analysis. These patients had a median follow-up of 10 months. The majority of patients (66%) had a KPS score <70, and the median age was 73 years. Fifty-eight percent of patients were male (Table 2). There was an even split between MGMT unmethylated (49%) and methylated (51%) patients, not including 5 patients whose MGMT status was unavailable. Most patients (97%) had surgical resection, with two-thirds undergoing subtotal resection. Concurrent temozolomide was prescribed to 66% of patients.

The median OS for this cohort was 10.3 months (95% CI, 8.6-14.2 months) (Fig. 1). Patients with a KPS score ≥70 had a median OS of 15.3 months (95% CI, 9.3 months to not available), whereas patients with a KPS score <70 had a median OS of 9.5 months (95% CI, 7.8-12.8 months). No survival difference was seen between MGMT unmethylated and methylated patients with a median OS of 10.2 months (95% CI, 8.1-19.8 months) and 10.3 months (95% CI, 8.3-19.9 months), respectively.

The median PFS for the study population was 6.9 months (95% CI, 6.0-9.2 months) (Fig. 2). Patients with a KPS score ≥70 had a median PFS of 9.3 months (95% CI, 6.8-20.0 months), whereas patients with a KPS score <70 had a median PFS of 6.3 months (95% CI, 4.6-7.4 months). MGMT unmethylated and methylated patients had a median PFS of 7.8 months (95% CI, 6.5-11.4 months) and 6.8 months (95% CI, 4.1-9.2 months), respectively.

Univariable analysis demonstrated that younger age (hazard ratio [HR], 1.06; 95% CI, 1.01-1.1; P = .018), concurrent chemotherapy (HR, 0.3; 95% CI, 0.17-0.55; P < .001), and gross total resection (HR, 0.49; 95% CI, 0.25-0.95; P = .036) were associated with improved OS. For PFS, concurrent chemotherapy (HR, 0.5; 95% CI, 0.29-0.88; P = .015), gross total resection (HR, 0.45; 95% CI, 0.25-0.83; P = .010), and smaller planning treatment volume (HR, 1.003; 95% CI, 1.00-1.01; P = .008) were associated with improved outcomes. Multivariable analysis demonstrated that concurrent chemotherapy was an independent prognostic factor for improved PFS and OS (Supporting Tables 1 and 2). Patients with concurrent chemotherapy were more likely to have ≥70 KPS score (4.8% vs 50%; P < .001) and more likely to have gross total resection (14% vs 41%; P = .034), although because of the small sample size, we chose not to fit a larger model taking into account these confounders. Younger age and MGMT methylation status were not significant on multivariable analysis for improved PFS or OS.

Overall, 2 patients experienced a grade 3 or higher neurological toxicity. One patient was hospitalized for multiple breakthrough seizures but with questionable compliance to a prescribed anticonvulsant medication. The second patient was hospitalized for 2 subsequent breakthrough seizures despite being on Keppra during the radiation treatment course. No grade 4 or 5 toxicities were observed. Five additional patients experienced grade 1 or 2 seizures. Alopecia was documented in 63% of patients; 8% of patients experienced nausea; and headaches

TABLE 2. Patient Characteristics (N = 62)

Characteristic	Value
Sex	
Male	36 (58%)
Female	26 (42%)
Age	73 (69, 77)
MGMT status	
Unmethylated	26 (46%)
Methylated	31 (54%)
Unknown	5
Multifocal	
No	51 (82%)
Yes	11 (18%)
Surgery	
No	2 (3.2%)
Yes	60 (97%)
Extent of resection	
Subtotal	41 (68%)
Gross total	19 (32%)
Unknown	2
PTV volume, cc	263 (179-352)
Unknown	5
Concurrent chemotherapy	
No	21 (34%)
Yes	41 (66%)
Prognostic group	
KPS <70; age ≥70 y	31 (51%)
KPS ≥70; age ≥70 y	13 (21%)
KPS <70; age <70 y	9 (15%)
KPS ≥70; age <70 y	8 (13%)
Unknown KPS	1
KPS	
<70	40 (66%)
≥70	21 (34%)
Unknown	1

Abbreviations: KPS, Karnofsky performance status; MGMT, O6 methylguanine-DNA methyltransferase; PTV, planning treatment volume.
Data are presented as No. (%) or median (interquartile range).

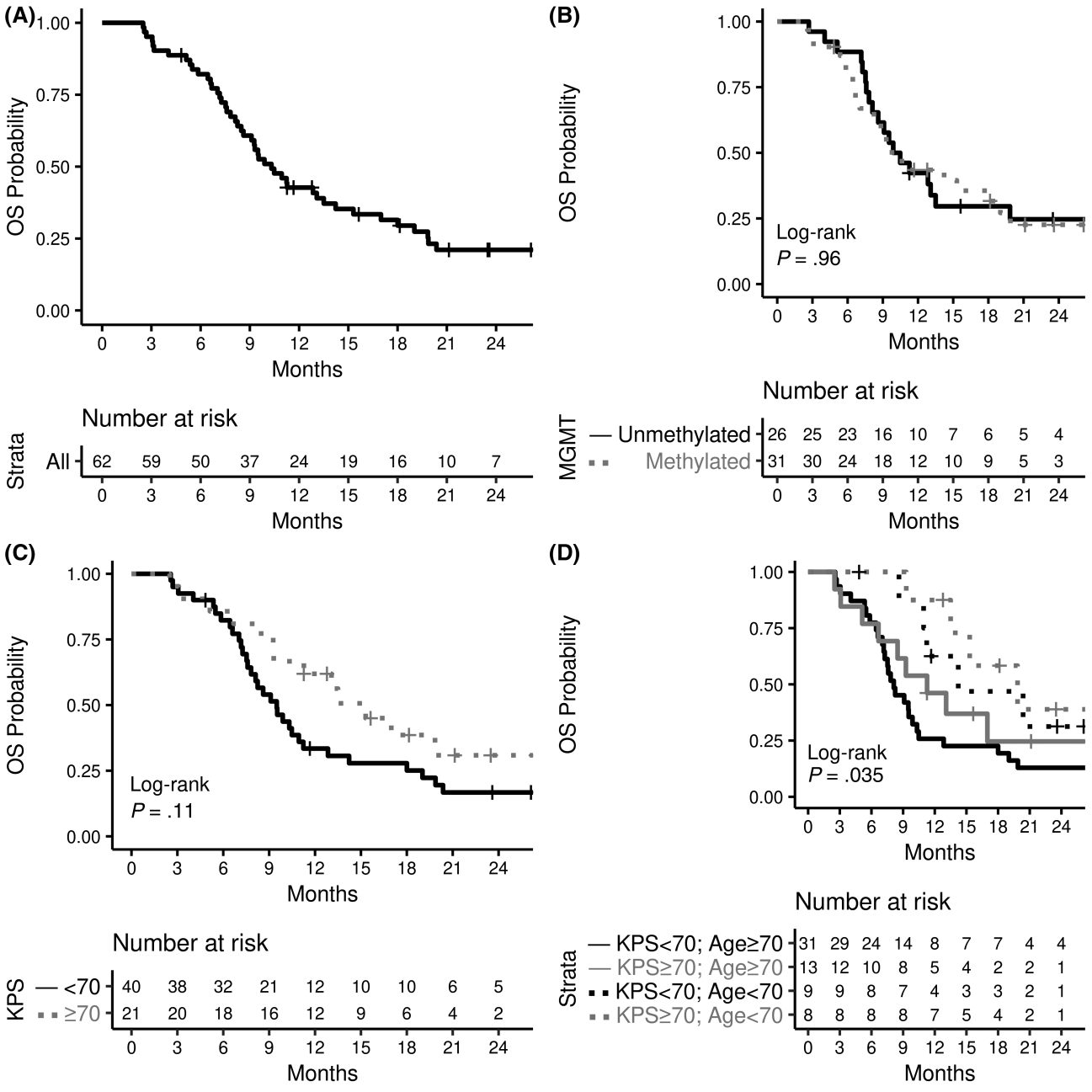

FIGURE 1. Kaplan-Meier curves evaluating OS. (A) OS for entire cohort, (B) OS stratified by MGMT methylation status, (C) OS stratified by performance status, and (D) OS stratified by prognostic group. KPS indicates Karnofsky performance status; MGMT, O6 methylguanine-DNA methyltransferase; OS, overall survival.

were reported by 8%. There were no reported events of cerebral hemorrhage.

DISCUSSION

This is the first pooled, prospective analysis of elderly and frail patients with GBM treated with accelerated hypofractionated radiation, which is isoeffective to the Stupp regimen. Within our cohort, median OS (10.3 months) was improved when compared with the IAEA trial (6.4 months) and CCTG studies (7.6-9.3 months). Concurrent temozolomide was an independent prognostic factor for improved PFS and OS. This was a well-tolerated treatment, with only 2 patients experiencing grade 3 neurologic toxicity during or after radiation.

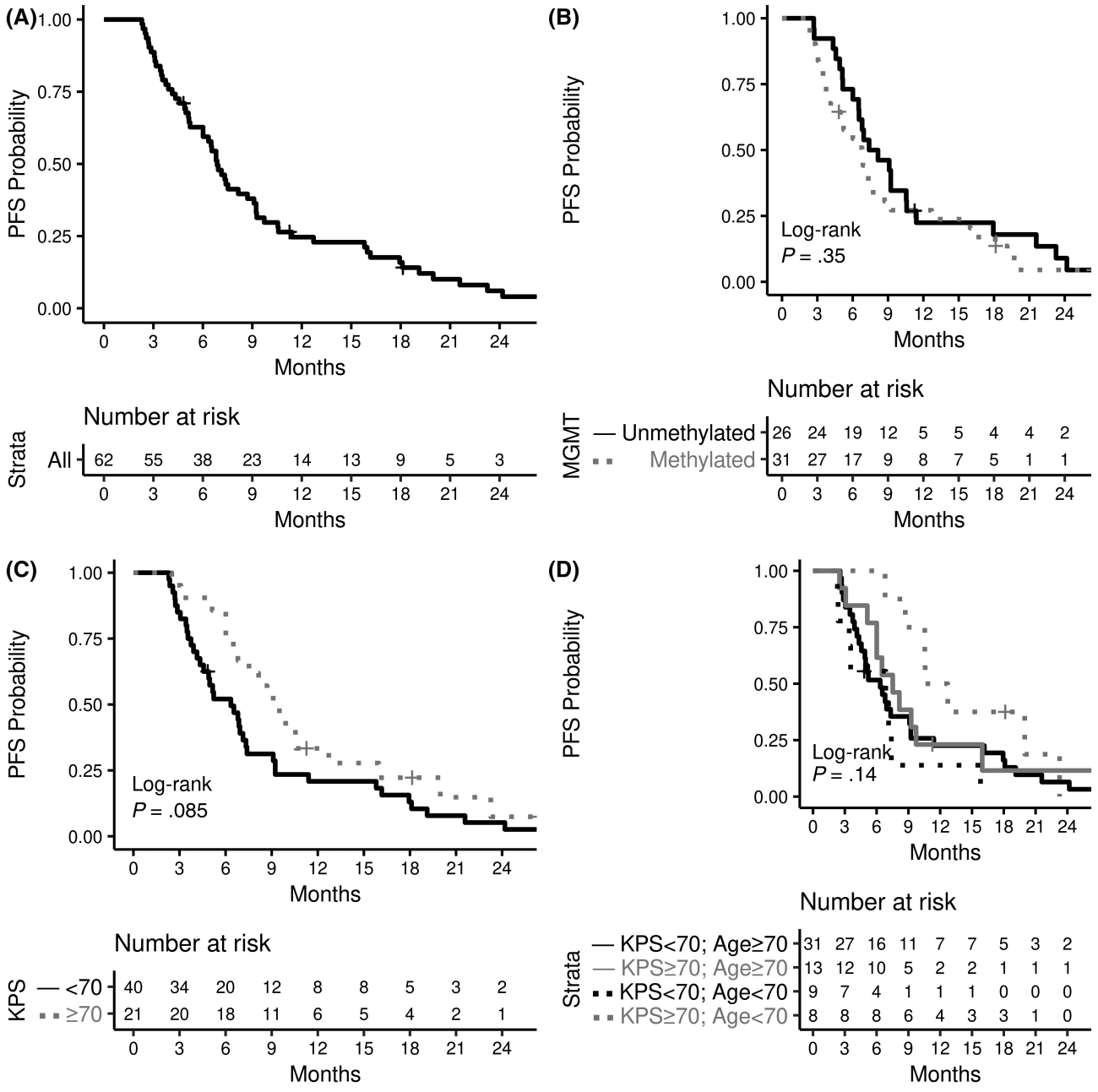

FIGURE 2. Kaplan-Meier curves evaluating progression-free survival. (A) PFS for entire cohort. (B) PFS stratified by MGMT methylation status. (C) PFS stratified by performance status. (D) PFS stratified by prognostic group. KPS indicates Karnofsky performance status; MGMT, O6 methylguanine-DNA methyltransferase; PFS, progression-free survival.

A key historical randomized trial included patients >60 years old treated with 60 Gy in 30 fractions or 40 Gy in 15 fractions.[8] This trial was designed as a superiority trial and was not adequately powered to determine that the short course arm was noninferior. However, because OS was similar (5.1 vs 5.6 months), the authors suggested that short-course radiation should be implemented for elderly patients. This study was notable because a large proportion of patients in the long-course arm that did not complete radiotherapy as prescribed (26% vs 10% in the short-course arm), which may have obscured the potential survival benefit of higher BED treatment. This is similarly seen in the Nordic study, in which a larger percentage of patients in the standard radiotherapy arm did not complete radiation compared with patients in the hypofractionated group (28% vs 5%).[16] This higher

rate of noncompliance shows the need for an isoeffective treatment that does not increase treatment burden for this patient population.

The improved outcomes in our pooled analysis are particularly notable considering the relatively low performance status of our enrolled patients when compared with patients enrolled in historical studies. The Minniti study (79% of patients had a KPS score ≥70) demonstrated a median OS of 9.3 months for patients >70 years old treated with 30 Gy in 6 fractions over 2 weeks.[17] The Nordic trial (80% of patients with a World Health Organization performance status of 0-1) demonstrated a median OS of 7.0 to 8.8 months for patients treated with hypofractionated radiation therapy of 34 Gy in 10 fractions over 2 weeks.[16] The IAEA trial (40% of patients had a KPS score ≥70) demonstrated a median OS of 7.9 months for patients treated with 25 Gy in 5 daily fractions and 6.4 months for patients treated with 40 Gy in 15 daily fractions.[9] The CCTG trial (77% of patients had an Eastern Cooperative Oncology Group score of 0-1) demonstrated a median OS of 7.6 to 9.3 months for patients treated with 40 Gy in 15 daily fractions and temozolomide.[10] In our analysis, only 34% of patients had a KPS score ≥70, yet the median OS of 10.3 months remains higher than previous hypofractionation studies. Our subset of patients with a KPS score ≥70 (comparable to Minniti, Nordic, and CCTG study populations with median OS from 7.0 to 9.3 months) had a median OS of 15.3 months (Table 3). Even poor performing patients (KPS score <70) in our cohort had a median OS of 9.5 months that compares favorably to outcomes in the IAEA trial population (median OS, 6.4 months with 40 Gy in 15 fractions).

Prior studies have demonstrated that MGMT methylated patients have improved outcomes because methylation is prognostic and predictive for response to temozolomide therapy.[18] There is evidence that temozolomide is less effective in elderly patients compared with younger patients.[19] However, concurrent chemotherapy was the only factor that independently predicted improved PFS and OS in our cohort of elderly and frail patients. Even MGMT unmethylated patients had favorable outcomes in our cohort with a median OS of 10.3 months. In the CCTG study, which included patients with a good performance status, unmethylated patients had a median OS of 7.9 months (radiation alone) or 10.0 months (radiation plus temozolomide). When Brandes et al treated elderly patients with a good performance status (KPS score ≥70) with 60 Gy in 30 fractions with temozolomide, the median OS was 13.7 months for unmethylated patients (compared with 10.0 months for the CCTG trial).[20] Unmethylated patients treated in NOA-08 (KPS ≥60) who received radiation (60 Gy for all patients) without temozolomide had a median OS of 10.4 months (compared with 7.9 months in the CCTG trial).[21] The lower BED in the CCTG dosing may have contributed to survival differences. Notably, our unmethylated cohort had a similar overall survival to Brandes and NOA-08 despite having a lower median performance status, suggesting that treating to a radiation dose isoeffective to 60 Gy in 30 fractions improves outcomes even in patients with multiple poor prognostic factors (Table 4).

Walker et al successfully showed that when increasing the dose from ≤45 to 50, 55, and 60 Gy in 1.8- to 2.0-Gy fractions, the median survival progressed from 13.5 to 28, 36, and 42 weeks, respectively.[4] These data guided the radiation prescription for the seminal Stupp trial to be 60 Gy in 30 fractions, which had a median overall of 10.9 to 11.8 months for elderly patients. However, the IAEA and the CCTG studies used prescriptions with a lower BED (53 Gy) in comparison to Stupp dosing (BED = 75 Gy). As a caveat, the surrounding normal brain (factoring an

TABLE 3. Overall Survival and Performance Status in Glioblastoma Studies

	Median Overall Survival, mo	Performance Status
KPS ≥70 in the current study	15.3	Good
Minniti et al, 2009[17]	9.3	Good
Malmström et al (Nordic), 2012[16]	7.0-8.8	Good
Perry (CCTG), 2017[10]	7.6-9.3	Good
KPS <70 in current study	9.5	Poor
Roa et al (IAEA), 2015[9]	6.4	Poor

Abbreviations: CCTG, Canadian Cancer Trials Group; IAEA, International Atomic Energy Agency; KPS, Karnofsky performance status; NOA-08, NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society.

TABLE 4. Unmethylated Patients in Glioblastoma Studies

	Overall Survival, mo	Receipt of TMZ	Performance Status
Unmethylated patients in current study	10.3	Mixed	Poor
Brandes, 2009[20]	13.7	Yes	Good
Perry (CCTG), 2017[10]	10.0	Yes	Good
Wick et al (NOA-08), 2012[21]	10.4	No	Mixed
Perry et al (CCTG), 2017[10]	7.9	No	Good

Abbreviation: TMZ, temozolomide.

α/β of 2) would have a BED of 60 Gy in 30 fractions of 120 Gy and a BED of 52.5 Gy in 15 fractions is 144 Gy. In comparison, 40 Gy in 15 fractions has a BED of 94 Gy to brain tissue. It is important to consider concerns for adjacent normal tissue when dose escalating, although this may be an ideal population of patients with a prognosis that allows for benefit of dose escalation without sufficient longevity and survival to realize normal tissue late toxicities. Our prospective cohort has superior outcomes when compared with the IAEA and CCTG studies for both good performers (median OS, 15.31 vs 7.6-9.3 months) and poor performers (median OS, 9.5 vs 6.4 months). We hypothesize that this is due to using isoeffective dosing similar to Stupp but using a hypofractionated regimen to avoid the compliance issues seen with conventional fractionation.

One notable strength of this study is that these pooled prospective data encompass the largest known collection of elderly or frail patients treated with 52.5 Gy and include representation from a diverse population around the world. These data included patients with both a good and poor performance status. Additionally, this radiation prescription does not increase the treatment burden for elderly or frail patients because it requires the same number of treatment visits when compared with the IAEA and CCTG studies without any evidence of increased treatment toxicity. However, limitations of this study include a relatively small sample size of 62 patients, restricting our ability to estimate confounding adjusted HRs. It is challenging to diagnose pseudoprogression in the absence of dedicated perfusion magnetic resonance imaging scans; more prospective data are needed to assess pseudoprogression with this fractionation regimen. A pooled analysis of 4 studies causes heterogeneity of radiation and chemotherapy regimens and may confound any conclusions. Information about neurocognitive function was not collected in these trials. Toxicity data were collected and attributed to each therapy; however, the nature of the data in this study makes it challenging to provide a complete picture on the toxicity of this treatment regimen. In addition, all of these studies were single arm without randomization. A large, randomized controlled trial is needed to validate these results.

In conclusion, this pooled analysis of individual patient-level data represents the only analysis of elderly/frail patients with GBM prospectively treated with a hypofractionated isoeffective radiation regimen. This regimen has favorable OS and PFS without any evidence of increased toxicity, and this suggests that this dose and fractionation may give the elderly/frail population a safe and effective alternative to regimens with a lower BED. A randomized, prospective trial directly comparing this regimen to standard of care is warranted.

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CONFLICT OF INTEREST DISCLOSURES

Paul D. Brown reports personal fees from UpToDate outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Haley K. Perlow: Data acquisition, formal analysis, and writing–review and editing. **Rahul N. Prasad:** Formal analysis and writing–review and editing. **Mike Yang:** Data acquisition and writing–review and editing. **Brett Klamer:** Statistical analysis and writing–review and editing. **Jennifer Matsui:** Formal analysis and writing–review and editing. **Livia Marrazzo:** Writing–review and editing. **Beatrice Detti:** Writing–review and editing. **Marta Scorsetti:** Writing–review and editing. **Elena Clerici:** writing–review and editing. **Andrea Arnett:** Writing–review and editing. **Sasha Beyer:** Writing–review and editing. **Mario Ammirati:** Writing–review and editing. **Arnab Chakravarti:** Writing–review and editing. **Raju R. Raval:** Writing–review and editing. **Paul D. Brown:** Writing–review and editing. **Pierina Navarria:** Writing–review and editing. **Silvia Scoccianti:** writing–review and editing. **John C. Grecula:** Writing–review and editing. **Joshua D. Palmer:** Data acquisition, formal analysis, and writing–review and editing.

DATA AVAILABILITY

Research data are stored in an institutional repository and will be shared on request to the corresponding author.

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