VOLUME 33 · NUMBER 35 · DECEMBER 10 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme

Wilson Roa, Lucyna Kepka, Narendra Kumar, Valery Sinaika, Juliana Matiello, Darejan Lomidze, Dalenda Hentati, Douglas Guedes de Castro, Katarzyna Dyttus-Cebulok, Suzanne Drodge, Sunita Ghosh, Branislav Jeremić, Eduardo Rosenblatt, and Elena Fidarova

See accompanying editorial on page 4129

Wilson Roa, Suzanne Drodge, and Sunita Ghosh, University of Alberta, Alberta Health Services-Cancer Control, Edmonton, Alberta, Canada; Lucyna Kepka, Warmia and Mazury Oncology Center, Olsztyn; Katarzyna Dyttus-Cebulok, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; Narendra Kumar, Postgraduate Institute of Medical Education and Research, Chandigarh, India; Valery Sinaika, N.N. Alexandrov National Cancer Centre of Belarus, Minsk, Belarus; Juliana Matiello, Irmandade da Santa Casa de Misericórdia de Porto Alegre, Porto Alegre; Douglas Guedes de Castro, Castro DG, AC Camargo Cancer Center, São Paulo, Brazil; Darejan Lomidze, High Technology Medical Center, University Clinic, Tbilisi, Georgia; Dalenda Hentati, Institut National de Cancer Salah Azaiz, Ministère de la Santé Publique, Bab Saadoum, Tunisia; Branislav Jeremić, Institute of Lung Diseases, Institutski put 4, Sremska Kamenica, Serbia; and Eduardo Rosenblatt and Elena Fidarova, International Atomic Energy Agency, Vienna, Austria.

Published online ahead of print at www.jco.org on September 21, 2015.

Supported by the International Atomic Energy Agency (IAEA) under the IAEA Coordinated Research Activities.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Clinical trial information: NCT01450449.

Corresponding author: Wilson Roa, MD, Section of Radiation Oncology, Cross Cancer Institute, 11560 University Ave, Edmonton, Alberta, Canada T6G 1Z2; e-mail: wilson.roa@albertahealthservices.ca.

0732-183X/15/3335w-4145w/$20.00

DOI: 10.1200/JCO.2015.62.6606

ABSTRACT

Purpose
The optimal radiotherapy regimen for elderly and/or frail patients with newly diagnosed glioblastoma remains to be established. This study compared two radiotherapy regimens on the outcome of these patients.

Patients and Methods
Between 2010 and 2013, 98 patients (frail = age ≥ 50 years and Karnofsky performance status [KPS] of 50% to 70%; elderly and frail = age ≥ 65 years and KPS of 50% to 70%; elderly = age ≥ 65 years and KPS of 80% to 100%) were prospectively randomly assigned to two arms in a 1:1 ratio, stratified by age (< and ≥ 65 years old), KPS, and extent of surgical resection. Arm 1 received short-course radiotherapy (25 Gy in five daily fractions over 1 week), and arm 2 received commonly used radiotherapy (40 Gy in 15 daily fractions over 3 weeks).

Results
The short-course radiotherapy was noninferior to commonly used radiotherapy. The median overall survival time was 7.9 months (95% CI, 6.3 to 9.6 months) in arm 1 and 6.4 months (95% CI, 5.1 to 7.6 months) in arm 2 (P = .988). Median progression-free survival time was 4.2 months (95% CI, 2.5 to 5.9) in arm 1 and 4.2 months (95% CI, 2.6 to 5.7) in arm B (P = .716). With a median follow-up time of 6.3 months, the quality of life between both arms at 4 weeks after treatment and 8 weeks after treatment was not different.

Conclusion
There were no differences in overall survival time, progression-free survival time, and quality of life between patients receiving the two radiotherapy regimens. In view of the reduced treatment time, the short 1-week radiotherapy regimen may be recommended as a treatment option for elderly and/or frail patients with newly diagnosed glioblastoma.

J Clin Oncol 33:4145-4150. © 2015 by American Society of Clinical Oncology

INTRODUCTION

The median age of patients with glioblastoma multiforme (GBM) is 64 years, and the highest incidence is observed in those age 75 to 84 years.[1] Over the last 50 years, there has been an observed increase in the age-standardized incidence of GBM coupled with an increase in brain tumor mortality.[2-6] Newer diagnostic imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) may have impacted the apparent increase in incidence, but the overall incidence was increasing before their introduction.[3,6] There is a need for standardized improvements in the care of older and/or frail patients to uphold quality of life (QoL) in a cost-effective manner.

Standard treatment for GBM is based on the trial by Stupp et al[7,8] and entails surgery, postoperative radiotherapy (RT) to a total tumor dose of 60 Gy in 30 fractions, and concurrent and adjuvant temozolomide (TMZ) chemotherapy as permitted. However, the Stupp trial design only included patients younger than 70 years of age with an Eastern Cooperative Oncology Group performance status of 0 to 2, and a subgroup analysis illustrated a decreased benefit with increasing age. In addition, elderly and/or frail individuals fare worse than younger and healthier patients, with a median survival time of approximately 6 months.[9-11] Controversies in the standard of care for these patients remain with limited phase III data to support treatment choices.

Treatment of elderly patients with GBM was studied in a prospective, randomized trial by Keime-Guibert et al,[12] which assessed supportive care versus supportive care plus RT (50 Gy in 25 daily fractions) in patients age ≥ 70 years. The study demonstrated that supportive care plus RT fared better, with a median survival time of 29.1 weeks compared with 16.9 weeks with supportive care alone. To improve the treatment of elderly patients and curtail lengthy RT treatments, Roa et al[13] prospectively demonstrated no difference in the survival results in elderly patients with GBM receiving 60 Gy in 30 fractions versus 40 Gy in 15 fractions (overall survival, 5.1 *v* 5.6 months, respectively; $P = .57$). This study established a viable alternative for elderly patients, and the abbreviated course of RT reduced active treatment time, benefiting both patients and health resource utilization.

Underlying the selection of appropriate treatment, however, is the understanding of how treatment will impact health-related QoL (HRQOL). QoL in patients with GBM is greatly impacted by and correlated with overall survival, leading to dependency and loss of global QoL.[14] A phase II prospective trial assessing HRQOL in 65 elderly patients (≥ 70 years) treated with an abbreviated course of RT (40 Gy in 15 fractions) plus concomitant and adjuvant TMZ illustrated that HRQOL was maintained until time of disease progression, with significant improvements in global QoL as well as social and cognitive function.[15]

We hypothesized that further shortening of RT time alone can provide an attractive treatment alternative with no difference in overall survival, especially in the current global setting of limited health care resources. This trial compared a commonly used RT regimen of 40 Gy in 15 fractions to a short-course RT regimen for elderly and/or frail patients with GBM.

PATIENTS AND METHODS

Study Design and Random Assignment

This is a phase III, randomized, international, multicenter, prospective, noninferiority trial (ClinicalTrials.gov identifier: NCT1450449). Patients were randomly assigned to one of two groups in a 1:1 ratio and stratified by age (< and ≥ 65 years), Karnofsky performance status (KPS), and extent of surgery (near total/complete/gross total or incomplete/partial resection). Patients were randomly assigned to either short-course RT (25 Gy in five fractions delivered in 1 week) or commonly used RT (40 Gy in 15 fractions delivered in 3 weeks). Random assignment was performed using Excel with the RAND option function (Microsoft, Redmond, WA). All eligible patients admitted to the trial were observed until death.

The median overall survival time of elderly patients with GBM treated by RT alone is approximately 6 months.[9-12] It was expected that changing the RT regimen from 1 week to 3 weeks would improve survival by 15%. One hundred forty-four deaths were needed to detect a hazard ratio of 1.61 between the two treatment arms, with a power of 80% and a significance level of 5%. A preplanned interim analysis with respect to the primary end point was conducted when two thirds of the planned total number of patients had been accrued for observed events (ie, approximately 96 patients).

Patients

The trial population included elderly and/or frail patients diagnosed with GBM. Frail patients were defined as ≥ 50 years old with a KPS of 50% to 70%; elderly and frail patients were defined as ≥ 65 years old with a KPS of 50% to 70%; and elderly patients were defined as ≥ 65 years old with a KPS of 80% to 100%. Before trial admission, patients were screened and required to meet all of the following eligibility criteria: histopathologically confirmed newly diagnosed GBM (WHO grade 4); initial surgery/biopsy at diagnosis performed ≤ 6 weeks before random assignment; age ≥ 50 years at time of entry; KPS ≥ 50%; no previous chemotherapy or RT exposure; ability and willingness to complete QoL questionnaires; ability and willingness to give informed consent; accessibility for treatment and follow-up; and delivery of protocol beginning within 2 weeks of patient random assignment. Patients fulfilling either of the following criteria were not eligible for the study: history of other malignancy or history of a serious infection or underlying medical condition.

All patients completed a pretreatment evaluation within 14 days before random assignment that included history, physical examination, KPS, clinical tumor status, blood work with a CBC, and a Mini-Mental State Examination (MMSE). After surgery, patients were imaged with contrast-enhanced CT or MRI of the brain. If imaging was not available postoperatively, a preoperative contrast-enhanced CT or MRI was admissible if completed within 14 days before surgery.

QoL Evaluation

QoL was evaluated in all patients at baseline and during follow-up. Assessments consisted of the self-administered European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and EORTC Quality of Life Questionnaire Brain Cancer Module (QLQ-BN20). The QLQ-C30 questionnaire includes five functional scales, three symptom scales, and six single-item scales. The QLQ-BN20 includes 20 items within four domains and seven single items. All scales and single items are scored categorically and linearly transformed to 0 to 100 scales.

Treatment

Patients were to start treatment within 2 weeks of random assignment and were treated in a position deemed appropriate by the treating physician with immobilization devices. A postoperative diagnostic contrast-enhanced CT and/or MRI was required for simulation. Patients were treated on megavoltage equipment and cobalt-60 or linear accelerator beams with a minimal nominal energy of 1.25 MV. Electrons, particles, implants, and stereotactic radiosurgery were not permissible.

Treatment volumes were to be covered with various field arrangements, accepting dose homogeneity assessed to the limit of a single voxel within the volume of ± 10%. Three-dimensional conformal RT planning was a minimum requirement for the study. A parallel-opposed pair beam arrangement was not allowed except for the rare large central tumors that could not be treated otherwise with comparatively improved dosimetry. Only one volume was considered with no cone-down or boost volume. Gross tumor volume was defined as the entire postoperative enhancing tumor and surgical cavity. The clinical target volume added a 2.0-cm margin to the gross tumor volume with no expansion beyond anatomic boundaries (eg, skull). The planning target volume (PTV) equaled the clinical target volume plus 0.5 cm in all directions. Specified organs at risk, such as optic nerves, chiasm, and brainstem, were delineated for all treatments.

Treatment consisted of a total dose of 25 Gy in five daily fractions (dose/fraction = 5.00 Gy) over 1 week in arm 1 and 40.05 Gy in 15 daily fractions (dose/fraction = 2.67 Gy) over 3 weeks in arm 2. Verification of all treatment fields on the first day of treatment was mandatory and was then performed weekly. PTV deviation was defined as failure to meet PTV criteria; a minor deviation occurred when PTV received 85% to 90% and/or 110% to 115% of prescription dose, and a major deviation occurred when PTV received less than 85% and/or higher than 115% of prescription dose. An organ-at-risk (OAR) major violation was defined as failure to meet OAR criteria, where any OAR received higher than 100% of the prescription dose. Any unspecified normal tissue (eg, scalp and contralateral cerebrum) receiving greater than 105% of the prescription dose was recorded as a major deviation.

A central RT quality assurance (RTQA) process was introduced at trial initiation. Each participating center had two benchmark cases reviewed by the RTQA committee before patient accrual. These were treatment plans of protocol-compliant in-house nontrial patients. In addition, each center provided two randomly selected patients for review by the committee. Centers enrolling two or fewer patients submitted all patients for review. A final RTQA report on the center-by-center audit was examined and approved in 2013 by

the scientific trial committee, ensuring that any individual shortcoming in the primary treatment modality used in this trial was prevented. No center was required to resubmit patients based on the set criteria or was precluded from entering patients after review.

Monitoring/Follow-Up

Patients were assessed weekly during treatment and then 4 weeks after completing RT with repeat history, physical examination, imaging of the brain, and MMSE; patients were then assessed every 3 months thereafter until death. At disease progression, patients were required to complete a physical examination and adverse event evaluation. Acute and late adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). AEs were evaluated weekly during RT, at 4 weeks after RT, and every 3 months until tumor progression; after this period, AEs were only reported in case of grade ≥ 3 toxicity. EORTC QLQ-C30 and QLQ-BN20 questionnaires were completed 4 weeks after RT and then every 3 months. Serious AEs were carefully monitored.

Table 1. Patient Characteristics (categorical variables)

Characteristic	No. of Patients (%)		P
	Arm 1 (n = 48), Short-Course Radiotherapy	Arm 2 (n = 50), Regular Radiotherapy	
Country			.777
Belarus	10 (21)	12 (24)	
Brazil (PA)	4 (8)	3 (6)	
Brazil (SP)	0 (0)	1 (2)	
Chile	1 (2)	0 (0)	
Georgia	2 (4)	4 (8)	
Greece	0 (0)	1 (2)	
India	12 (25)	10 (20)	
Indonesia	0 (0)	1 (2)	
Ireland (Dublin)	1 (2)	0 (0)	
Poland	16 (33)	14 (28)	
Thailand	1 (2)	1 (2)	
Tunisia	1 (2)	3 (6)	
KPS*			.853
50%	12 (25)	11 (22)	
60%	17 (35)	16 (32)	
70%	11 (23)	10 (20)	
80%	6 (13)	9 (18)	
90%	2 (4)	4 (8)	
Sex			.830
Male	22 (46)	24 (48)	
Female	26 (54)	26 (52)	
Age, years*			.106
50-65	22 (46)	15 (30)	
> 65	26 (54)	35 (70)	
Imaging modality			.063
CT	12 (25)	21 (43)	
MRI	36 (75)	28 (57)	
Data missing	0 (0)	1 (2)	
Surgical procedure			.549
Stereotactic biopsy	4 (8)	9 (18)	
Partial resection	34 (71)	30 (61)	
Total macroscopic resection	8 (17)	8 (16)	
Tumor location			.534
Frontal lobe	10 (21)	9 (18)	
Occipital lobe	5 (10)	6 (12)	
Parietal lobe	10 (21)	13 (26)	
Temporal lobe	15 (31)	11 (22)	
Multilobar	8 (17)	8 (16)	
Other†	0 (0)	3 (6)	
Corticosteroid therapy			.990
Yes	22 (47)	23 (47)	
No	25 (53)	26 (53)	

Abbreviations: CT, computed tomography; KPS, Karnofsky performance status; MRI, magnetic resonance imaging; PA, Porto Alegre; SP, São Paulo.
*These characteristics stratified patients at time of random assignment.
†Other includes one tumor in corpus callosum and one tumor in basal ganglia.

Statistical Analysis

Analysis was conducted as per protocol as well as per intent to treat, as recommended for a noninferiority trial.[16] Detailed results of intent-to-treat analysis were not included in this report, but the analysis did not show any difference in the outcomes. Descriptive statistics were used to report baseline characteristics. Mean and standard deviation (SD) were used for normally distributed continuous variables; median and range were used for non–normally distributed continuous variables. The *t* test was used to compare the continuous variables of the two study arms, and χ^2 tests were used to compare the categorical variables. Overall survival was calculated from the date of random assignment to the date of death, and the patients who were alive at the date of last follow-up were censored from the analysis. Progression-free survival was calculated from the date of treatment to the date of progression or death. Patients who did not have any documented disease progression and were alive at the last follow-up were censored. Kaplan-Meier estimates were used to obtain the median survival time and the corresponding 95% CI. Log-rank tests were used to compare the survival of the two study arms. An independent *t* test was used to compare the mean QoL between the two arms. $P < .05$ was used for all statistical significance and two-sided tests for the study. SAS version 9.3 (SAS Institute, Cary, NC) was used to conduct all statistical analysis.

RESULTS

A total of 98 patients from 12 institutions worldwide were randomly assigned in a 1:1 fashion. Both groups were similar in baseline characteristics at study entry (Table 1), with no significant differences in

Table 2. Patient Baseline Characteristics (continuous variables)

Characteristic	Arm 1	Arm 2	P (significant at P < .05)
Treatment time*			.904
No. of patients	48	50	
Mean (± SD), days	32.9 (± 9.8)	33.2 (± 9.9)	
KPS†			.349
No. of patients	48	50	
Mean (± SD), %	64.0 (± 11.2)	65.8 (± 12.5)	
Largest tumor diameter			.828
No. of patients	44	45	
Mean (± SD), cm	5.8 (± 3.5)	5.6 (± 3.7)	
MMSE baseline‡			.878
No. of patients	47	49	
Mean (± SD), score	20.7 (± 7.0)	20.9 (± 6.8)	
Hemoglobin			.925
No. of patients	46	49	
Mean (± SD), g/dL	12.4 (± 1.3)	12.4 (± 1.3)	
Corticosteroid dose			.598
No. of patients	21	21	
Mean (± SD), mg/d	8.6 (± 6.4)	10.2 (± 12.4)	

Abbreviations: KPS, Karnofsky performance status; MMSE, Mini-Mental State Examination; SD, standard deviation.
*Treatment time is time between surgery and start of radiotherapy.
†This characteristic stratified patients at time of random assignment.
‡Maximum score is 30; scores above 26 are defined as normal mental status.

Table 3. Global Health Status (QoL)

Global Health Status/QoL*	Arm 1	Arm 2	*P*
Baseline			.042
No. of patients	44	49	
Mean (± SD), score	42.6 (± 22.5)	51.2 (± 17.6)	
4 weeks after treatment			.99
No. of patients	36	27	
Mean (± SD), score	49.6 (± 20.0)	49.7 (± 23.8)	
8 weeks after treatment			.60
No. of patients	20	17	
Mean (± SD), score	51.3 (± 22.5)	54.9 (± 19.6)	

Abbreviations: QoL, quality of life; SD, standard deviation.
*QoL measured using European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and EORTC Quality of Life Questionnaire Brain Cancer Module. Categorical scales are transformed to linear 0 to 100 scale.

country, KPS, sex, age, imaging modality (CT *v* MRI), tumor location, surgical procedure, and the use of corticosteroids. Time between surgical resection/biopsy and RT start, continuous KPS, MMSE, and hemoglobin were all similarly distributed between arm 1 and arm 2 at baseline (Table 2).

There was no grade ≥ 3 acute toxicity. The mean dexamethasone doses in arm 1 and arm 2 were not statistically different at baseline or 1 or 3 months after treatment.

Global health status/QoL scores were measured at baseline and at 4 and 8 weeks after treatment. The mean global QoL scores at baseline for arm 1 (n = 44) and arm 2 (n = 49) were 42.6 (SD, 22.5) and 51.2 (SD, 17.6), respectively ($P = .04$). Mean global QoL scores at 4 weeks after treatment for arm 1 (n = 36) and arm 2 (n = 27) were 49.6 (SD, 20.0) and 49.7 (SD, 23.8), respectively ($P = .99$). Mean global QoL scores at 8 weeks after treatment for arm 1 (n = 20) and arm 2 (n = 17) were 51.3 (SD, 22.5) and 54.9 (SD, 19.6), respectively ($P = .60$; Table 3). Detailed HRQOL data will be conveyed in a future report.

After study entry, two patients were lost to follow-up as a result of unavoidable situations (one patient each in arms 1 and 2; Fig 1) and were not included in the overall survival (Fig 2) and progression-free survival (Fig 3) analyses. Hence, the survival analysis was conducted as a per-protocol analysis on a total of 96 patients (47 patients in arm 1 and 49 patients in arm 2). At the time of statistical analysis, 96% of patients (45 of 47 patients) in arm 1 and 96% of patients (47 of 49 patients) in arm 2 had

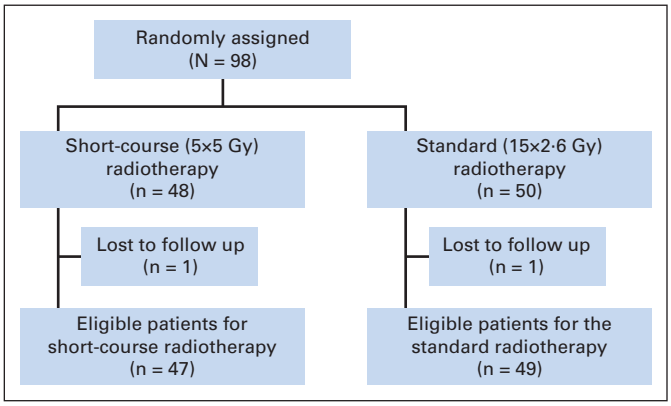

Fig 1. CONSORT diagram.

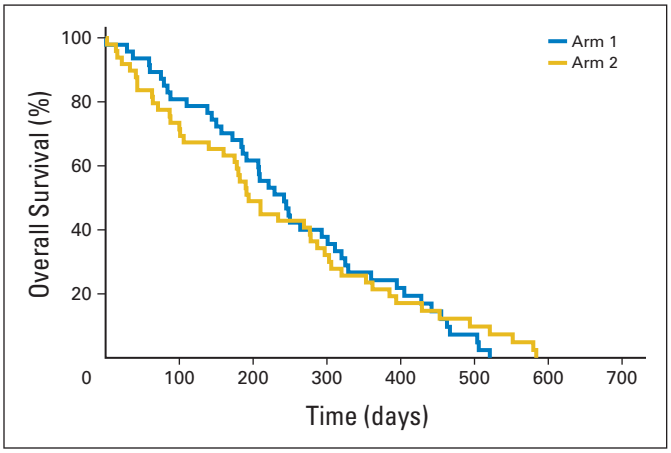

Fig 2. Overall survival (OS). Kaplan-Meier plots of OS according to the treatment arm (arm 1 = short-course radiotherapy: 25 Gy in five daily fractions; arm 2 = commonly used radiotherapy: 40 Gy in 15 daily fractions). Comparison of median OS showed no statistically significant difference between arms (7.9 *v* 6.4 months in arms 1 and 2, respectively; $P = .988$).

died, and 100% (47 of 47 patients) and 100% (49 of 49 patients) of patients in arms 1 and 2, respectively, had experienced disease progression. Median overall survival was not inferior in patients receiving short-course RT (arm 1; 7.9 months; 95% CI, 6.3 to 9.6 months) compared with patients receiving commonly used RT (arm 2; 6.4 months; 95% CI, 5.1 to 7.6 months; $P = .988$). Median progression-free survival was also not inferior in arm 1 versus arm 2 (4.2 months [95% CI, 2.5 to 5.9 months] *v* 4.2 months [95% CI, 2.6 to 5.7 months]; $P = .716$). Analyses were conducted per intent to treat as well, with no difference in median overall survival or progression-free survival.

DISCUSSION

This prospective phase III study demonstrates that short-course RT (25 Gy in five fractions) in elderly and/or frail patients is noninferior to a commonly used 3-week course of RT. An approximate median overall

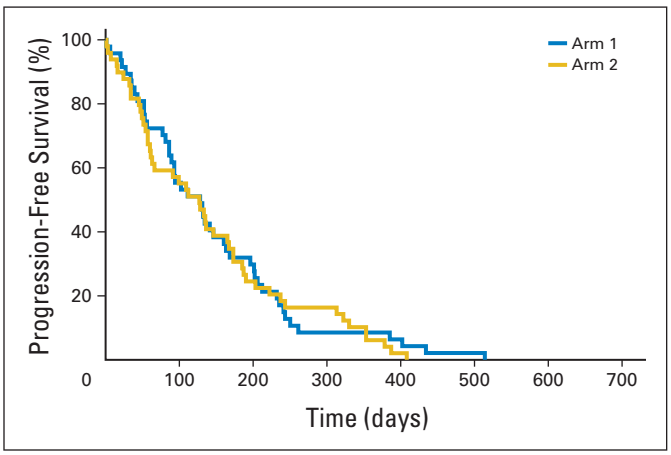

Fig 3. Progression-free survival (PFS). Kaplan-Meier plots of PFS according to the treatment arm (arm 1 = short-course radiotherapy: 25 Gy in five daily fractions; arm 2 = commonly used radiotherapy: 40 Gy in 15 daily fractions). Comparison of median PFS showed no statistically significant difference between arms (4.2 *v* 4.2 months in arms 1 and 2, respectively; $P = .716$).

survival time of 7 months and progression-free survival time of 4 months were seen in both arms, with similar global QoL at 4 and 8 weeks after treatment. These data provide an evidence-based justification for physicians to offer shorter RT courses to elderly and/or frail patients.

Although there is no direct randomized trial to compare with this trial, other trials have compared different RT schedules. Bleehen and Stenning[17] randomly assigned 474 adults with grade 3 or 4 astrocytomas to either 60 Gy in 30 fractions or 45 Gy in 20 fractions, showing a median survival time of approximately 9 months. A subgroup of patients older than 60 years (n = 45) was analyzed, with a survival hazard ratio of 1.0 (95% CI, 0.54 to 1.89). Furthermore, a phase II study by Jeremic et al[18] evaluated the efficacy of short-course RT in elderly (≥ 60 years old) and frail (KPS 50% to 70%) patients with GBM, treating the tumor volume with 45 Gy in 15 daily fractions. The overall response rate reported in this study was 60%, with a median survival of 9 months. A study by Newall et al[19] in 18 patients with GBM older than age 50 years and treated with whole-brain RT with 30 Gy in 10 daily fractions reported a mean survival time of 44 weeks. Our current trial results demonstrate similar global QoL in both arms at 4 and 8 weeks after treatment, strengthening the argument to support short-course RT (25 Gy in five fractions) for elderly and/or frail patients with GBM.

Treatment of this population over a shorter time frame not only provides the opportunity to improve the survival-to-treatment time ratio, but also allows increased cost effectiveness and improved resource utilization. Given the global challenge of limited health care resources, providing prolonged treatment can become a challenge. Analysis by Konski et al[20] showed recently that shorter RT regimens in patients older than age 50 years with high-grade astrocytomas produced the longest quality-adjusted survival. Cost-utility analysis also illustrated an advantage for a shorter versus longer RT regimen in patients older than age 50 years. In addition, short-course RT may allow more patients to receive treatment with decreased wait times, which is particularly important for centers struggling to maintain acceptable RT start times.

In a review by Bauchet et al,[21] elderly patients with GBM were highlighted as a challenging and heterogeneous cohort with respect to optimizing management. In this study, factors related to patient characteristics, study design, treatment delivery, and evaluation of outcomes could all influence clinical outcomes.[22-24] For example, potential morbidity that might follow from hypofractionated RT with hotter spots in treatment arm 1 of this study could lead to a higher rate of RT-induced brain necrosis. However, the radiobiologic advantage of higher doses inside irradiated tumor within the PTV could lead to improved progression-free and overall survival. In addition, the MMSE might not be considered optimal for evaluating RT-related neurocognitive decline, given the lack of sensitivity to early cognitive changes. Therefore, the EORTC QoL questionnaires (core and brain modules) and National Cancer Institute Common Terminology Criteria for Adverse Events monitoring for AEs could be used to complement the MMSE.

In a recent reanalysis of the original Radiation Therapy Oncology Group recursive partitioning analysis database, of 1,672 patients with GBM between the ages of 18 and 83 treated by various regimens, the most important prognostic factors identified included age, KPS, extent of surgical resection, and neurologic function.[25] Within this analysis, class V and VI patients, which included patients with KPS less than 70%, biopsy alone, or poor neurologic function, had a median overall survival time of 7.5 months. Such findings are consistent with the median overall survival of approximately 8 months in this study.

Our study did not address the possible benefit of TMZ chemotherapy in the elderly and/or frail GBM population. Current research not yet reported by the National Cancer Institute of Canada Clinical Trials Group CE·6/EORTC 26062-22061/TransTasman Radiation Oncology Group 08.02 Elderly Glioblastoma Trial will provide information on the possible benefit of adjuvant chemotherapy in addition to RT (40 Gy in 15 fractions). Taken together, the data presented in our current trial comparing short-course RT of 25 Gy in five fractions versus 40 Gy in 15 fractions support an opportunity to provide a standard of care comparable to current practice using 40 Gy in 15 fractions for the treatment of GBM in the elderly.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Wilson Roa, Sunita Ghosh, Branislav Jeremić, Eduardo Rosenblatt, Elena Fidarova
Administrative support: All authors
Provision of study materials or patients: Wilson Roa, Lucyna Kepka, Narendra Kumar, Valery Sinaika, Juliana Matiello, Darejan Lomidze, Dalenda Hentati, Douglas Guedes de Castro, Katarzyna Dyttus-Cebulok, Suzanne Drodge, Sunita Ghosh, Branislav Jeremić, Elena Fidarova
Collection and assembly of data: Wilson Roa, Lucyna Kepka, Narendra Kumar, Valery Sinaika, Darejan Lomidze, Douglas Guedes de Castro, Katarzyna Dyttus-Cebulok, Sunita Ghosh, Elena Fidarova
Data analysis and interpretation: Wilson Roa, Lucyna Kepka, Suzanne Drodge, Sunita Ghosh, Eduardo Rosenblatt, Elena Fidarova
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Dolecek TA, Propp JM, Stroup NE, et al: CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol 14:v1-v49, 2012 (suppl 5)
2. Ahlbom A, Rodvall Y: Brain tumor trends. Lancet 2:1272, 1989
3. Shugg D, Allen BJ, Blizzard L, et al: Brain cancer incidence, mortality and case survival: Observations from two Australian cancer registries. Int J Cancer 59:765-770, 1994
4. Boyle P, Maisonneuve P, Saracci R, et al: Is the increased incidence of primary brain tumors in the elderly real? J Natl Cancer Inst 82:1594-1596, 1990
5. Grieg NH, Ries LG, Yancik R, et al: Increasing annual incidence of primary malignant brain tumors in the elderly. J Natl Cancer Inst 82:1621-1624, 1990
6. Davis L, Ahlbom A, Hohl D, et al: Is brain cancer mortality increasing in industrial countries? Am J Ind Med 19:423-431, 1991
7. Stupp R, Hegi ME, Mason WP, et al: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5 year analysis of the EORTC-NCIC trial. Lancet Oncol 10:459-466, 2009
8. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-996, 2005
9. Iwamoto FM, Reiner AS, Panageas KS, et al: Patterns of care in elderly glioblastoma patients. Ann Neurol 64:628-634, 2008

10. Kita D, Ciernik IF, Vaccarella S, et al: Age as a predictive factor in glioblastomas: Population-based study. Neuroepidemiology 33:17-22, 2009

11. Paszat L, Laperriere N, Groome P, et al: A population-based study of glioblastoma multiforme. Int J Radiat Oncol Biol Phys 51:100-107, 2001

12. Keime-Guibert F, Chinot O, Taillandier L, et al: Radiotherapy for glioblastoma in the elderly. N Engl J Med 356:1527-1535, 2007

13. Roa W, Brasher PM, Bauman G, et al: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol 22:1583-1588, 2004

14. Henriksson R, Asklund T, Poulsen HS: Impact of therapy on quality of life, neurocognitive function and their correlates in glioblastoma multiforme: A review. J Neurooncol 104:639-646, 2011

15. Minniti G, Scaringi C, Baldoni A, et al: Health-related quality of life in elderly patients with newly diagnosed glioblastoma treated with short-course radiation therapy plus concomitant and adjuvant temozolomide. Int J Radiat Oncol Biol Phys 86:285-291, 2013

16. Shah PB: Intention-to-treat and per-protocol analysis. CMAJ 183:696, 2011

17. Bleehen NM, Stenning SP: A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma. Br J Cancer 64:769-771, 1991

18. Jeremic B, Shibamoto Y, Grujicic D, et al: Short-course radiotherapy in elderly and frail patients with glioblastoma multiforme: A phase II study. J Neurooncol 44:85-90, 1999

19. Newall J, Ransohoff J, Kaplan B: Glioblastoma in the older patient: How long a course of radiotherapy is necessary? J Neurooncol 6:325-327, 1988

20. Konski A, Bracy P, Weiss S, et al: Cost-utility analysis of a malignant glioma protocol. Int J Radiat Oncol Biol Phys 39:575-578, 1997

21. Bauchet L, Zouaoui S, Darlix A, et al: Assessment and treatment relevance in elderly glioblastoma patients. Neuro Oncol 16:1459-1468, 2014

22. Curran WJ Jr, Scott CB, Horton J, et al: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. J Natl Cancer Inst 85:704-710, 1993

23. Glatstein E, Makuch RW: Illusion and reality: Practical pitfalls in interpreting clinical trials. J Clin Oncol 2:488-497, 1984

24. Simon R: Importance of prognostic factors in cancer clinical trials. Cancer Treat Rep 68:185-192, 1984

25. Li J, Wang M, Won M, et al: Validation and simplification of the Radiation Therapy Oncology Group recursive partitioning analysis classification for glioblastoma. Int J Radiat Oncol Biol Phys 81:623-630, 2011

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Wilson Roa
No relationship to disclose

Lucyna Kepka
No relationship to disclose

Narendra Kumar
No relationship to disclose

Valery Sinaika
No relationship to disclose

Juliana Matiello
No relationship to disclose

Darejan Lomidze
No relationship to disclose

Dalenda Hentati
No relationship to disclose

Douglas Guedes de Castro
No relationship to disclose

Katarzyna Dyttus-Cebulok
No relationship to disclose

Suzanne Drodge
No relationship to disclose

Sunita Ghosh
No relationship to disclose

Branislav Jeremić
No relationship to disclose

Eduardo Rosenblatt
No relationship to disclose

Elena Fidarova
No relationship to disclose

Acknowledgment

We thank Xanthoula Kostaras and Natalie Estabrooks for their professional assistance with the article preparation.