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Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial

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ABSTRACT

Purpose
To prospectively compare standard radiation therapy (RT) with an abbreviated course of RT in older patients with glioblastoma multiforme (GBM).

Patients and Methods
One hundred patients with GBM, age 60 years or older, were randomly assigned after surgery to receive either standard RT (60 Gy in 30 fractions over 6 weeks) or a shorter course of RT (40 Gy in 15 fractions over 3 weeks). The primary end point was overall survival. The secondary end points were proportionate survival at 6 months, health-related quality of life (HRQoL), and corticosteroid requirement. HRQoL was assessed using the Karnofsky performance status (KPS) and Functional Assessment of Cancer Therapy-Brain (FACT-Br).

Results
All patients had died at the time of analysis. Overall survival times measured from randomization were similar at 5.1 months for standard RT versus 5.6 months for the shorter course (log-rank test, $P = .57$). The survival probabilities at 6 months were also similar at 44.7% for standard RT versus 41.7% for the shorter course (lower-bound 95% CI, −13.7). KPS scores varied markedly but were not significantly different between the two groups (Wilcoxon test, $P = .63$). Low completion rates of the FACT-Br (45%) precluded meaningful comparisons between the two groups. Of patients completing RT as planned, 49% of patients (standard RT) versus 23% required an increase in posttreatment corticosteroid dosage (χ^2 test, $P = .02$).

Conclusion
There is no difference in survival between patients receiving standard RT or short-course RT. In view of the similar KPS scores, decreased increment in corticosteroid requirement, and reduced treatment time, the abbreviated course of RT seems to be a reasonable treatment option for older patients with GBM.

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common glioma and accounts for 40% of primary CNS malignancies. Among older patients, GBM accounts for the majority of primary brain tumors. The age-adjusted incidence of brain tumors in older patients (≥ 60 years old) has been increasing steadily (ie, independent of the increase in the number of older patients) and will continue to do so.[1] The most significant prognostic factor in GBM is age, followed by Karnofsky performance status (KPS), histology, and mental status.[2] Older patients with a limited functional status do particularly badly and have median survivals of only a few months, and there are no long-term survivors.[3,4] Current treatment for patients with GBM, including surgical resection, radiation therapy (RT), and chemotherapy, is partially effective; rarely patients are cured of their disease. As yet, no clinical, radiographic, pathologic, or molecular alteration in GBM predicts a favorable response to either RT or chemotherapy.

In recent years, there has been considerable uncertainty about the management of older patients with GBM, because their survival tends to be short but the standard treatment is lengthy. Accordingly, many have questioned whether the inconvenience and morbidity associated with 6 weeks of RT outweigh the modest benefits of such treatment in older patients. Furthermore, the value of aggressive therapy in older patients has been difficult to determine, because large clinical trials have often excluded older patients. Several single-armed studies of accelerated hypofractionated RT schedules are reported in the literature in older patients with GBM. Results of shorter overall treatment schedules may be equivalent to standard (6 to 7 week) courses of RT, with median survival times ranging from 4 to 10 months.[4-10] There is no consensus with respect to the dose recommendation for older patients with GBM.

To date, there has been no randomized trial examining the effectiveness of an abbreviated treatment schedule for older patients with GBM. This issue led our group to undertake a randomized controlled clinical trial comparing standard versus a shorter RT course. Patients with GBM, age 60 years or older, were randomly assigned to receive standard RT (60 Gy in 30 fractions over 6 weeks) versus a biologically similar shorter course (40 Gy in 15 fractions over 3 weeks). The experimental schedule was selected because it was well tolerated by patients with brain metastases.[11]

PATIENTS AND METHODS

Participants

Patients were enrolled at four Canadian regional cancer centers: the Cross Cancer Institute (Edmonton, Alberta), the Tom Baker Cancer Center (Calgary, Alberta), the London Regional Cancer Center (London, Ontario), and the Northwestern Ontario Regional Cancer Center (Thunder Bay, Ontario). The principal eligibility criteria included age $\geq$ 60 years, histologically confirmed GBM, and KPS $\geq$ 50. Any of the following features rendered patients ineligible: previous cranial RT, concomitant or prior invasive cancer (except nonmelanomatous skin cancer and carcinoma-in-situ), failure to commence RT for GBM within 6 weeks of surgical diagnosis, and inability to comply with follow-up requirements. Patients were also ineligible if pre- and postoperative imaging studies were unavailable for review. Approval to conduct the study was obtained independently from an internal review board at each participating institution. Each participant was required to consent in writing.

Pathologic Evaluation

The diagnosis of GBM was confirmed centrally on all cases.

Interventions

Patients were randomly assigned to standard adjuvant RT (60 Gy in 30 fractions over 6 weeks) or short-course regimen (40 Gy in 15 fractions over 3 weeks). RT started within 6 weeks of surgery. Patients receiving standard RT were treated in two phases. In the first phase, the prescribed dose was 46 Gy in 23 daily fractions. The planning target volume (PTV) was based on preoperative computed tomography and magnetic resonance imaging studies and included the enhancing tumor plus peritumoral edema with a 2-cm margin or a 2.5-cm margin if there was no peritumoral edema. In the second phase, the prescribed dose was 14 Gy in seven daily fractions, and the PTV was preoperative enhancing tumor with a 2.5-cm margin. Patients who were randomly assigned to shorter-course treatment received a total dose of 40 Gy in 15 daily fractions to a PTV that was identical to that used in the first phase of standard treatment. A photon energy of 4 MV or higher was used. Treatment plans included opposed lateral fields, wedge pair fields, rotation, or multiple field techniques. Computer-aided treatment planning was recommended but not required. The absorbed dose was to be within 10% of the prescribed dose. Attempts were made to limit the dose of RT to the optic chiasm (54 Gy), retina (50 Gy), and brainstem (54 Gy), provided this could be accomplished without shielding gross tumor. If the location of the tumor was such that these critical structures would inadvertently receive higher doses, the patient was advised in advance of the potential for radiation toxicity. Chemotherapy was not prescribed before or during RT but could be given at the time of disease recurrence.

Randomization

An independent statistician at the coordinating center (Cross Cancer Institute) produced computer-generated randomization lists. Patients were stratified by extent of resection (biopsy *v* any degree of resection, as defined by the operative report) and KPS (< 70 *v* ≥ 70). Strata-specific, sequentially numbered, sealed opaque envelopes containing the treatment assignment were supplied by the statistician to the research nurse at the coordinating center. Once patient eligibility had been determined and consent was obtained, participating centers contacted the coordinating nurse by fax to request randomization. The next envelope in the appropriate strata was opened to determine treatment assignment.

Outcomes and Patient Assessments

The primary end point of the study was overall survival, measured from the date of randomization to death from any cause. The secondary end points were overall survival from the date of diagnosis, the proportion of patients alive at 6 months, health-related quality of life (HRQoL), and the corticosteroid requirement of the two groups. HRQoL was assessed using the KPS and Functional Assessment of Cancer Therapy–Brain (FACT-Br; version 3) at baseline, 3 weeks after starting RT, at the conclusion of RT, and at 3-month intervals thereafter. At each assessment, the oncologist determined the KPS and the patient completed the FACT-Br. Corticosteroid use was recorded in the format of total daily dexamethasone dose. To compare with the Radiation Therapy Oncology Group (RTOG)–established recursive partitioning analysis class survival, study patients were also classified retrospectively as class IV, V, and VI according to the published criteria for possible concordance.[2]

Statistical Considerations

The target sample size was calculated following the method of Makuch and Simon.[12] We expected 50% of the patients receiving standard RT would be alive at 6 months, and we considered the clinical efficacy of the shorter course to be equivalent if the proportion surviving at 6 months was at least 35%. For an 80% probability that the one-sided 90% CI for a difference at 6 months did not exceed 15% when in reality the treatments were equivalent, 101 patients would be required in each treatment arm. Allow-

ing for a 10% loss to follow-up rate, we intended to randomly assign 224 patients. In October 2001, the steering committee met after having recruited 100 patients and decided to close the trial. It became apparent that to prove statistical equivalence between two treatments of similar outcomes and exclude a small difference in survival (eg, of 5%), the target sample size would render further study not feasible.[13] Survival curves were generated using the Kaplan-Meier method. Relative risk was calculated using a proportional hazards model. A one-sided 95% CI for the difference in the proportion of patients surviving at 6 months was calculated. Both survival analyses based on patients who began (but may not have finished) their assigned treatment, and intent-to-treat, were performed. Interquartile range was used to describe variability in KPS.

RESULTS

Between 1996 and 2001, 100 patients were randomly assigned: 51 to standard RT and 49 to shorter-course treatment. Among those assigned to receive treatment over 6 weeks, two withdrew after randomization: one chose to receive the short-course treatment and one pursued alternative therapy. Two other patients died before their RT could be started. Among those randomly assigned to receive RT over 3 weeks, one patient withdrew from the study and declined further treatment. Twelve (26%) of 47 patients began their assigned standard 6-week course of RT but did not complete the treatment. Five (10%) of 48 patients did not complete the shorter 3-week course of treatment. In all instances, RT was discontinued because of the patient had deteriorated clinically. Chemotherapy was given for disease progression in eight patients, four in each treatment group. At the time of final analysis, all patients had died.

The treatment groups were balanced in terms of pretreatment characteristics (Table 1). The median survivals (measured from randomization) were similar for the two groups: 5.1 months for the 6-week group and 5.6 months for the 3-week group (hazard ratio, 0.89; 95% CI, 0.59 to 1.36; $P = .57$; Fig 1). The survival probabilities at 6 months were also similar in the two groups: 44.7% and 41.7% for the 6-week and 3-week treatment arms, respectively. The lower bound of the one-sided 95% CI for the difference in survival at 6 months was −13.7%. In other words, with 95% confidence, we ruled out a difference of greater than 13.7% in terms of the proportion of patients in the two groups surviving to 6 months. The median survivals measured from the time of diagnosis were also similar for the two groups (5.9 *v* 6.1 months for the 6- and 3-week groups, respectively; hazard ratio, 0.90; 95% CI, 0.60 to 1.35; $P = .61$). Survival analysis on the intent-to-treat population yielded similar results.

In case of any imbalance in the two arms with respect to the number of patients with total resection, the models were refit excluding those patients. In this case, the median survival (measured from randomization) was 5.0 months in both groups (hazard ratio, 1.0; 95% CI, 0.65 to 1.53; $P = .99$). Stratified analysis on extent of resection yielded similar results. Moreover, our patients were retrospectively regrouped as class IV (n = 10), V (n = 43), and VI (n = 42) according to the RTOG recursive partitioning analysis.[2] Their median survival times were 8.8, 6.9, and 4.8 months, respectively.

The secondary end point of HRQoL was measured by the KPS and FACT-Br. The KPS data are summarized in Table 2 and Figure 2. These scores show marked variability between patients. KPS was similar at first follow-up, 70 for the 6-week group and 65 for the 3-week group (Wilcoxon test, $P = .63$). There were no differences in the KPS scores averaged over time ($P = .99$) or in the change in KPS scores over time ($P = .15$) between the two groups. The completion rates for the FACT-Br scores (173 of 383, 45%) were

Table 1. Patient Characteristics

Baseline Characteristics	6-Week Regimen (n = 47)	3-Week Regimen (n = 48)
Sex, n		
Female	22	18
Male	25	30
Age, years		
Mean	72.4	71.0
Standard deviation	5.4	5.5
KPS		
Median	70	70
IQR	60-80	60-80
FACT-Br		
Mean	75.1	77.7
Standard deviation	15.5	15.6
Extent of surgery		
Biopsy		
No.	20	17
%	42.5	35.4
Subtotal resection		
No.	25	24
%	52.3	50.0
Total resection		
No.	2	7
%	4.2	14.6
Days to beginning RT		
Median	34	33
IQR	25-41	26-41
Outcomes		
Median survival, months	5.1	5.6
P	.57*	
Patients alive at 6 months, %	44.7	41.7
KPS at first follow-up		
Median	70	65
IQR	50-70	50-80
P	63†	

Abbreviations: KPS, Karnofsky performance status; IQR, interquartile range; FACT-Br, Functional Analysis of Cancer Therapy–Brain; RT, radiation therapy.
*Log-rank test.
†Wilcoxon test.

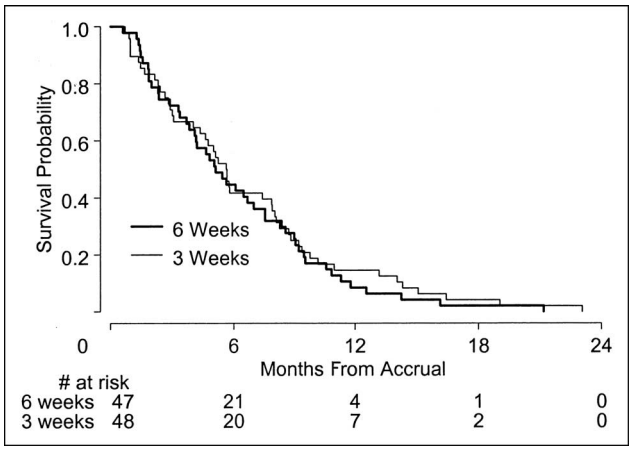

Fig 1. Overall survival from randomization by treatment group. There was no difference in the overall survival between the standard 6-week (thick line) versus abbreviated 3-week (thin line) course of radiation therapy (Log-rank test, $P = .57$).

too low to provide meaningful comparisons between the standard and abbreviated RT groups (Table 2).

Corticosteroid requirement at the start and completion of RT was available for the 78 patients who completed the treatment. Seventeen (49%) of 35 patients in the 6-week group required a posttreatment increase in total daily dose from the beginning of treatment compared with 10 (23%) of 43 patients in the 3-week group (χ^2 test, $P = .02$).

DISCUSSION

Shorter courses of RT are commonly used in older patients with GBM despite the fact that there have been no prospective randomized trials comparing different RT approaches. In this randomized controlled trial, we found no significant differences in overall survival, survival at 6 months, or HRQoL between standard RT versus shorter-course treatment in older patients with GBM. Although the study was not sufficiently powered to conclude that the two treatments are equivalent, a greater than 14% difference in the proportion of patients surviving 6 months or longer was confidently excluded. Similarly, we did not see any significant difference in KPS over time between the two groups. The FACT-Br questionnaire applied in this study was originally designed to assess quality of life for patients with brain tumors but proved to be impractical in this specific patient population. On the other hand, patients who were treated with the shorter RT course required less increment in posttreatment corticosteroid dosage. For the purposes of our clinical practice, we now regard the shorter course of RT as a reasonable treatment option for older patients with GBM.

These findings are important in two respects. First, they provide clinicians with data justifying the option of using less-intensive RT schedules for older adults with aggressive GBMs. Short-course RT might be especially appropriate for those with poor performance status where survival after standard RT is known to be extremely short. Moreover, these results set the stage for clinical trials that compare RT with other management strategies that may be substantially less intensive, such as selective chemotherapy, judicious corticosteroid use only, or palliative care only. Future comparisons between radically different management strategies would be difficult to contemplate without our trial comparing two active radiation treatments, one of which was administered over a shorter time. Health maintenance organizations or governments might be especially interested in sponsoring these types of clinical trials in neuro-oncology, where the goal is not to enhance survival per se, but instead to determine whether management approaches that con-

Table 2. Health-Related Quality of Life

	Baseline	3 Weeks	6 Weeks	First Follow-Up	Second Follow-Up
KPS*					
6-week regimen					
Completion rate, n	47/47	42/45	34/38	25/34	13/21
Median	70	65	70	70	60
IQR	60-80	50-80	60-80	50-70	60-70
3-week regimen					
Completion rate, n	48/48	43/45	8/40	34/38	21/27
Median	70	70	70	65	60
IQR	60-80	60-80	50-80	50-80	40-70
FACT-Br†					
6-week regimen					
Completion rate, n	44/47	6/45	8/38	18/34	12/21
3-week regimen					
Completion rate, n	43/48	7/45	2/40	23/38	10/27

Abbreviations: KPS, Karnofsky performance status; IQR, interquartile range; FACT-Br, Functional Assessment of Cancer Therapy–Brain.
*There was no difference in either average KPS over time or change in KPS over time between the two groups ($P = .99$ and .15, respectively).
†Completion rates for the FACT-Br were too low to compare the two groups.

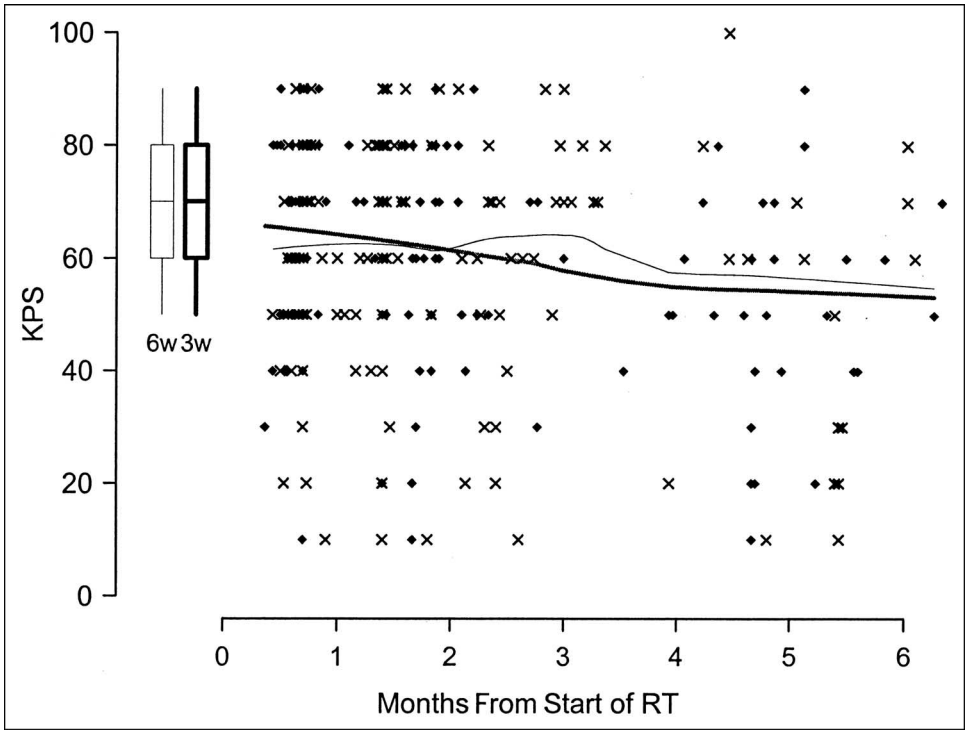

Fig 2. Karnofsky performance status (KPS) for the 6-week (×) versus 3-week course (♦) of radiation therapy (RT). Box plots depict the KPS scores at baseline. The thin and thick lines represent smoothed estimates. There were no differences in the averaged or change in KPS scores over time.

sume fewer health care resources give similar outcomes without compromising HRQoL.

Our findings are consistent with other data. Although there is no randomized controlled trial similar to our own, others have compared different radiation schedules in adults with GBM. Bleehen et al[14] (1991) randomized 474 adults (aged 18 to 70 years) with astrocytomas, grade 3 or 4, to 60 Gy (30 fractions over 6 weeks) or 45 Gy (20 fractions over 4 weeks) in a 2:1 ratio. Adjuvant chemotherapy was not prescribed. In this trial, there were 45 patients 60 years of age or older with GBMs. Twenty-nine patients received 60 Gy over 6 weeks, and 16 received 45 Gy over 4 weeks. The survival hazard ratio for these two subset of cases was 1.0 (95% CI, 0.54 to 1.89; S. Stenning, personal communication, November, 1998), with the wide CIs reflecting small number of cases in each group. The corresponding survival hazard ratio in our study was 0.89, favoring the short-course treatment (95% CI, 0.59 to 1.34).

Data from several prospective but nonrandomized studies have suggested that the survival of patients receiving shorter-course RT is similar to that of historical controls treated conventionally. Bauman et al (1994) examined the use of a short course of RT (30 Gy in 10 fractions over 2 weeks) in 29 patients with GBM ≥ 65 years of age. The study patients were compared with historical controls of older patients with GBM treated with longer courses of RT (≥ 50 Gy in 25 fractions over 5 weeks). The short-course treatment seemed to be equally effective in controlling symptoms; 60% of patients alive at 1 month had stable or improved quality of life and KPS, stable disease on computed tomography scan, and stable or reduced dexamethasone requirements.[5] The 11 patients with KPS greater than 50 in this study achieved a median survival of 5 months. Ford et al[10] reported their treatment results of patients with poor-prognosis GBM, more than half of whom were 60 years of age or older, as defined by the Medical Research Council prognostic score of greater than 25. Patients were treated with 36 Gy in 12 fractions over 3 weeks. The median survival of these patients was 16 weeks, which was similar to patients with similar prognostic signs who received 60 Gy of RT over 6 weeks. Thomas et al[6] (1994) reported a single-arm prospective study in a similar group of patients (KPS ≤ 50, age ≥ 70 years; or KPS 50 to 70, age 50 to 70 years) who were treated with 30 Gy in six fractions over 2 weeks. The median survival was 6 months, which again compared favorably with that of conventionally treated older patients with GBM. Quality of life (measured by the Barthel index) was improved or stabilized in 77% of patients at 1 month. Retrospective case series suggest the survivals of older GBM patients receiving RT is only approximately 5 months.[4] Finally, Curran et al[2] (1993) used a recursive partitioning technique to analyze survival in 1,578 patients entered onto three RTOG malignant glioma trials from 1974 to 1989 that used several RT regimens. The median survival time of our patients identified retrospectively as class IV (n = 10), V (n = 43), and VI (n = 42) according to the RTOG recursive partitioning analysis was 8.8, 6.9, and 4.8 months, respectively. This was in contrast to the

reported RTOG class survival of 11.1, 8.9, and 4.6 months, respectively. The inclusion of astrocytomas with anaplastic or atypical foci into class IV by the RTOG study may partly explain the difference.

With respect to HRQoL, patients receiving standard RT and those given shorter-course treatments had similar KPS evaluations. Unfortunately, a more comprehensive evaluation tool like the FACT-Br had limited practical value in this setting. Too few patients were alive, capable, or willing to complete the detailed FACT-Br questionnaire at the prescribed time points. This finding reflects the challenges of complete and detailed quality-of-life data in cancer clinical trials.[15] Completion rate of the tool may be improved with deliberate encouragement and assistance from the clinical research staff. Our experience in this regard will need to be considered in the planning of future studies. In the setting of a rapidly fatal illness, patients and families will be especially attuned to treatments and management strategies that preserve and respect their quality of life. Judging by our own experience, measuring this important outcome in older patients with GBM may prove to be a significant research challenge.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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