ORIGINAL ARTICLE

Radiotherapy for Glioblastoma in the Elderly

Florence Keime-Guibert, M.D., Olivier Chinot, M.D., Luc Taillandier, M.D., Stéphanie Cartalat-Carel, M.D., Marc Frenay, M.D., Guy Kantor, M.D., Jean-Sébastien Guillamo, M.D., Eric Jadaud, M.D., Philippe Colin, M.D., Pierre-Yves Bondiau, M.D., Philippe Meneï, M.D., Hugues Loiseau, M.D., Valérie Bernier, M.D., Jérôme Honnorat, M.D., Maryline Barrié, M.D., Karima Mokhtari, M.D., Jean-Jacques Mazeron, M.D., Anne Bissery, M.D., and Jean-Yves Delattre, M.D., for the Association of French-Speaking Neuro-Oncologists*

ABSTRACT

BACKGROUND

There is no community standard for the treatment of glioblastoma in patients 70 years of age or older. We conducted a randomized trial that compared radiotherapy and supportive care with supportive care alone in such patients.

METHODS

Patients 70 years of age or older with a newly diagnosed anaplastic astrocytoma or glioblastoma and a Karnofsky performance score of 70 or higher were randomly assigned to receive supportive care only or supportive care plus radiotherapy (focal radiation in daily fractions of 1.8 Gy given 5 days per week, for a total dose of 50 Gy). The primary end point was overall survival; secondary end points were progression-free survival, tolerance of radiotherapy, health-related quality of life, and cognition.

RESULTS

We randomly assigned 85 patients from 10 centers to receive either radiotherapy and supportive care or supportive care alone. The trial was discontinued at the first interim analysis, which showed that with a preset boundary of efficacy, radiotherapy and supportive care were superior to supportive care alone. A final analysis was carried out for the 81 patients with glioblastoma (median age, 73 years; range, 70 to 85). At a median follow-up of 21 weeks, the median survival for the 39 patients who received radiotherapy plus supportive care was 29.1 weeks, as compared with 16.9 weeks for the 42 patients who received supportive care alone. The hazard ratio for death in the radiotherapy group was 0.47 (95% confidence interval, 0.29 to 0.76; P=0.002). There were no severe adverse events related to radiotherapy. The results of quality-of-life and cognitive evaluations over time did not differ significantly between the treatment groups.

CONCLUSIONS

Radiotherapy results in a modest improvement in survival, without reducing the quality of life or cognition, in elderly patients with glioblastoma. (ClinicalTrials.gov number, NCT00430911.)

From Groupe Hospitalier Pitié–Salpêtrière, Assistance Publique–Hôpitaux de Paris; INSERM Unité 711; and Université Pierre et Marie Curie, Paris (F.K.-G., K.M., J.-J.M., A.B., J.-Y.D.); Hôpital de la Timone, Marseille, France (O.C., M.B.); Hôpital Saint-Julien, Nancy, France (L.T., V.B.); Université Claude Bernard Lyon 1, INSERM Unité 842, and Hospices Civils de Lyon, Lyon, France (S.C.-C., J.H.); Centre Antoine Lacassagne, Nice, France (M.F., P.-Y.B.); Institut Bergonie, Bordeaux, France (G.K.); Centre Hospitalo-Universitaire Côte de Nacre, Caen, France (J.-S.G.); Centre Paul Papin, Angers, France (E.J.); Polyclinique de Courlancy, Reims, France (P.C.); Centre Hospitalo-Universitaire, Angers, France (P.M.); and Centre Hospitalo-Universitaire, Bordeaux, France (H.L.). Address reprint requests to Dr. Delattre at Service de Neurologie Mazarin, Hôpital de la Salpêtrière, 47 Blvd. de l'Hôpital, 75013, Paris, France, or at jean-yves.delattre@psl.aphp.fr.

*Participants in the Association of French-Speaking Neuro-Oncologists Radiotherapy for Glioblastoma in the Elderly Study are listed in the Appendix.

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The incidence of malignant glioma is increasing among elderly patients,[1-3] whose advanced age has been associated not only with a poor prognosis but also with a reduced tolerance of treatment and a decreased efficacy of therapy.[4-6] Since the optimal management of malignant glioma in patients who are in their eighth or ninth decade of life has not been determined, we evaluated the efficacy of radiotherapy in this population.

METHODS

PATIENTS

Patients 70 years of age or older were eligible to participate in the study if they had histologically proven, newly diagnosed glioblastoma multiforme or anaplastic astrocytoma on the basis of the World Health Organization (WHO) classification and a Karnofsky performance score of 70 or more. Written informed consent was obtained from all patients, and the study was approved by the ethics committee of the Salpêtrière Hospital in Paris.

TREATMENT

After undergoing surgery, patients were randomly assigned to receive supportive care alone (the supportive care group) or supportive care in combination with radiotherapy (the radiotherapy group). Randomization was performed at the data center of the Delegation for Clinical Research of the Assistance Publique–Hôpitaux de Paris, and patients were stratified according to the treatment center. Randomization and initiation of assigned treatments were required within 4 weeks after surgery. Supportive care consisted of treatment with corticosteroids and anticonvulsant agents, physical and psychological support, and management by a palliative care team. Radiotherapy, delivered by means of linear accelerators with a nominal energy of 6 mV or more, consisted of fractionated focal irradiation, at a dose of 1.8 Gy per fraction, given once daily 5 days per week, for a total dose of 50 Gy. The dose was defined according to the guidelines of the International Commission on Radiation Units and Measurements. The clinical target volume included the area of contrast enhancement on magnetic resonance imaging (MRI) and a tumor margin of 2 cm.

SURVEILLANCE AND FOLLOW-UP

The baseline examination included computed tomographic (CT) or MRI studies; complete blood counts and blood chemical tests; neurologic examination; assessment of the Karnofsky performance status; evaluation of the health-related quality of life with the use of a questionnaire developed by the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30, version 2.0), which has a specific module for brain cancer (QLQ-BN20); and a neuropsychological evaluation that included the Mini–Mental State Examination (MMSE), the Mattis Dementia Rating Scale (MDRS), and the Neuropsychiatric Inventory. Patients were assessed every month during the first 3 months and then every 6 weeks by means of CT or MRI, neurologic examination, MMSE, and the health-related EORTC questionnaire (QLQ-C30). The MDRS and Neuropsychiatric Inventory were administered at days 60 and 135 and then every 3 months.

Tumor progression was defined as an increase in tumor size by 25% or more or the appearance of new lesions on CT or MRI. Patients with tumor progression received supportive care. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.

ASSESSMENT OF HEALTH-RELATED QUALITY OF LIFE

The QLQ-C30 questionnaire[7] comprises five scales that measure functioning (physical, role [work and household activities], emotional, cognitive, and social), three symptom scales (fatigue, vomiting, and pain), and six single-item scales (dyspnea, insomnia, anorexia, constipation, diarrhea, and financial difficulties). The QLQ-BN20 questionnaire[8] includes 20 items covering functional deficits, symptoms, toxic effects of treatment, and uncertainty about the future. The two questionnaires were scored according to the EORTC scoring manual.[9] For both questionnaires, scores can range from 0 to 100, with higher scores on the global health status and functioning scales and lower scores on the symptom scales and single-item measures indicating better performance.

NEUROPSYCHOLOGICAL EVALUATION

The MMSE was used as a measure of general cognitive status. Higher scores on this 30-point scale indicate better cognitive function. The Neuropsychiatric Inventory is a 12-item rating instrument that covers a range of psychological and behavioral symptoms (delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, euphoria or elation, apathy or indifference, dysinhibition, irritability or lability, aberrant motor

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behavior, and problems with sleeping or appetite).[10] The scores range from 0 to 144 for the patient's rating (obtained from the caregivers), with 0 indicating the optimal rating. The MDRS examines attention, memory, initiation and maintenance of verbal and motor responses, and conceptualization and construction (design copying).[11] Scores range from 0 to 144, with higher scores indicating better cognitive function.

STATISTICAL ANALYSIS

The primary end point was survival; the secondary end points were progression-free survival, tolerance of treatment, health-related quality of life, and cognitive functioning. Comparisons between the two groups were made on an intention-to-treat basis.

The trial was initially designed to have 80% statistical power to detect a 100% increase in the median overall survival from 16 to 32 weeks (hazard ratio for death, 0.5) in the radiotherapy group as compared with the supportive care group, with a two-sided significance level of 0.05. Seventy-four patients with a minimum follow-up of 1 year were required for this analysis. However, after the inclusion of the 72nd patient, an amendment to the protocol was made to permit an interim analysis. This was done because the investigators, who had no access to any part of the outcome data at that point, were concerned about the possibility of a premature, inconclusive termination of the study.

A procedure of sequential planning, associated with the continuation of recruitment, was instituted with a triangular sequential design for two-sided alternatives. This sequential design permitted discontinuation of the trial according to preset boundaries (Fig. 1) if radiotherapy was found to be significantly superior to supportive care (the upper boundary) or if there was no significant difference between the two groups (the lower boundary). After termination of the trial, we performed a final analysis, using the sequential method, of the data from all the patients who had undergone randomization by the time the efficacy boundary was crossed.

Secondary analyses were performed with the use of the Cox proportional-hazards regression model, with adjustments for relevant covariates. Survival curves were based on Kaplan–Meier estimates. The absolute health-related quality of life scores and all the cognitive scores were analyzed by means of a mixed-effects model for repeated measures; the method of empirical variances was used to estimate the standard error, with a first-order autoregressive covariance structure. A generalized estimating equation fitting the proportional-odds model for correlated ordinal data was used to analyze changes in the Karnofsky performance status over time.

Monitoring of the trial and data collection were performed by the Delegation for Clinical Research of the Assistance Publique–Hôpitaux de Paris. Site visits were performed at all centers. All histologic specimens were subject to a central review.

RESULTS

PATIENTS

From February 2001 to January 2005, a total of 85 patients from 10 institutions were randomly assigned to receive supportive care (the supportive care group) or supportive care plus radiotherapy (the radiotherapy group). The first interim analysis was carried out after inclusion of the 85th pa-

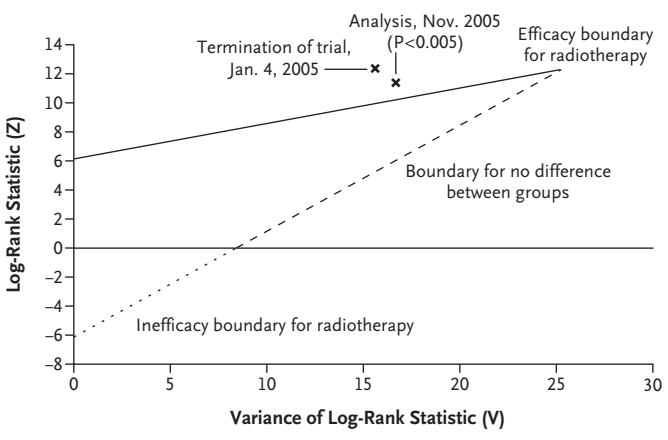


Figure 1. Design of the Triangular Test and Results of the Analysis.

The log-rank statistic (Z) summarizes the difference in survival between the group of patients who received radiotherapy plus supportive care and the group of patients who received supportive care only. The variance of the log-rank statistic (V) represents the quantity of information accumulated since the beginning of the trial, and it is closely related to the number of deaths. For each analysis, the two statistics Z and V were calculated and defined by a point shown on the graph. Three boundaries are shown: one indicating the inefficacy of radiotherapy plus supportive care as compared with supportive care alone (dotted line), one indicating no difference between the groups (dashed line), and one indicating the superiority of radiotherapy plus supportive care (the efficacy boundary for radiotherapy, solid line). The trial was discontinued at the first interim analysis, on January 4, 2005, after the upper boundary, indicating the superiority of radiotherapy, had been crossed. The analysis (in November 2005) incorporated the data from patients who had already been recruited when the trial was discontinued, and was continued for the specified length of time.

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Table 1. Baseline Characteristics of the Patients Who Underwent Randomization.

Characteristic	Supportive Care (N=42)	Supportive Care plus Radiotherapy (N=39)
Age — yr		
Median	73	75
Range	70–85	70–84
Sex — no.		
Male	28	23
Female	14	16
Karnofsky performance score — no.*		
70	23	20
80	14	15
90	3	4
100	2	0
Extent of surgery — no.		
Biopsy	22	20
Partial resection	7	7
Complete resection	13	12
Corticosteroid therapy — no. (%)		
Yes	36 (86)	32 (82)
No	6 (14)	7 (18)

* Higher Karnofsky performance scores indicate better performance.

Table 2. Outcomes in the Radiotherapy Group.

Variable	Patients (N=39)
Never started radiotherapy — no. (%)	1 (3)
Received ≤90% of planned dose — no. (%)	6 (15)
Dose — Gy	
Median	50
Range	10–52
Fraction size — Gy	
Median	1.8
Range	1.6–2.0
No. of fractions	
Median	28
Range	5–31
Duration of radiotherapy	
Median	5.9
Range	1.0–8.4
Time from diagnosis to radiotherapy — wk	
Median	5.3
Range	2.6–10.0
Interruption or delay in radiotherapy — no. (%)	11 (28)

tient (in January 2005). In this analysis, the log-rank statistic for the difference in survival between the two groups crossed the upper boundary for efficacy (Fig. 1), and the trial was discontinued because of the superiority of radiotherapy over supportive care.

Histologic slides were submitted for 84 of the 85 patients (99%), and a central pathological review confirmed the diagnosis of malignant astrocytoma in 83 of these patients (99%). The tumors included glioblastoma in 81 of the 84 patients (96%) and anaplastic astrocytoma in 2 patients (2%). On central review, one patient was found to have had a stroke. Owing to the very small number of anaplastic astrocytomas, this analysis focuses solely on the 81 patients with glioblastoma. The characteristics of the two groups of patients with glioblastoma were similar at baseline (Table 1). The median age in the supportive care group was 73 years and the median age in the supportive care plus radiotherapy group was 75, and 39 of the 81 patients (48%) had undergone debulking surgery.

TREATMENT

The median time from diagnosis to the start of radiotherapy was 5.3 weeks (range, 2.6 to 10.0) — about 1 week more than was expected. Table 2 summarizes the details of treatment. One patient who was assigned to the radiotherapy group did not receive radiation because another tumor (duodenal cancer) developed before the start of radiotherapy; this patient received supportive care only. Six patients received 90% or less of the planned radiation dose because of tumor progression (in five patients) and sudden death related to a pulmonary embolus (in one patient).

SURVIVAL AND PROGRESSION

At a median follow-up of 21 weeks, 73 patients (90%) had died. The hazard ratio for death in the radiotherapy group was 0.47 (95% confidence interval [CI], 0.29 to 0.76; P=0.002 by the log-rank test), indicating a 53% relative reduction in the risk of death for patients who received radiotherapy plus supportive care as compared with those who received only supportive care. The median survival benefit was 12.2 weeks; the median survival was 29.1 weeks (95% CI, 25.4 to 34.9) with radiotherapy plus supportive care and 16.9 weeks (95% CI, 13.4 to 21.4) with supportive care alone (Fig. 2). The median progression-free survival was

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14.9 weeks (95% CI, 10.9 to 22.1) with radiotherapy plus supportive care and 5.4 weeks (95% CI, 4.4 to 7.6) with supportive care alone (Fig. 3). The hazard ratio for disease progression in the radiotherapy group was 0.28 (95% CI, 0.17 to 0.47; P<0.001 by the log-rank test).

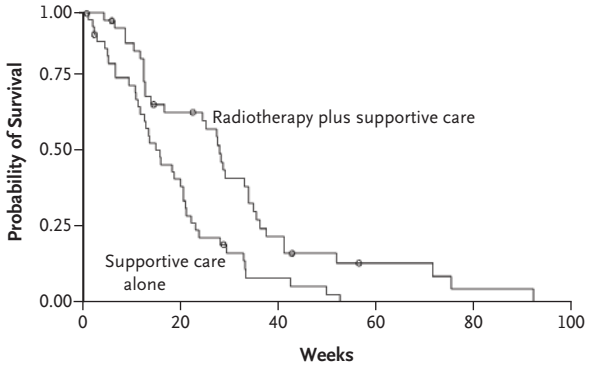
We used Cox proportional-hazard models to adjust the hazard ratio for death. In addition to the stratification factor (the treatment center to which the patient was assigned), other possible confounding factors — age, the extent of surgery, and performance status — were included. The adjusted hazard ratio for death in the radiotherapy group was 0.42 (95% CI, 0.25 to 0.68). The extent of surgery, according to the surgeon's report (complete resection vs. partial resection or biopsy), was associated with survival (hazard ratio for death among patients who underwent complete resection, 0.49; 95% CI, 0.29 to 0.81; P=0.005). The survival benefit of radiotherapy was independent of the extent of surgery.

PERFORMANCE STATUS AND QUALITY OF LIFE

The Karnofsky performance status declined over time, but there were no significant differences between the two groups (P=0.22). The rate of compliance with the health-related quality-of-life assessment decreased over time in both the group that received supportive care alone and the group that received radiotherapy plus supportive care, from 93% and 90% at baseline to 60% and 67% at day 135, respectively (see Tables 1 and 2 of the Supplementary Appendix, available with the full text of this article at www.nejm.org). Few patients were alive after the first four follow-up evaluations (up to day 135). For this reason, analyses of health-related quality of life were restricted to evaluations at days 1, 30, 60, 90, and 135. Table 3 shows changes in the mean health-related quality-of-life scores over time. In both groups, scores were significantly worse over time on the physical (P<0.001), cognitive (P=0.01), social (P=0.02), fatigue (P=0.008), and motor dysfunction (P=0.001) scales, whereas scores on the other scales, particularly the global score for health-related quality of life, did not change significantly (Fig. 1 of the Supplementary Appendix). Global assessments of deterioration over time also did not differ significantly between the two groups. Only the scale that assessed uncertainty about the future showed a different pattern of scores over time in the two groups, but no pattern exhibited a clear trend.

NEUROPSYCHOLOGICAL EVALUATION

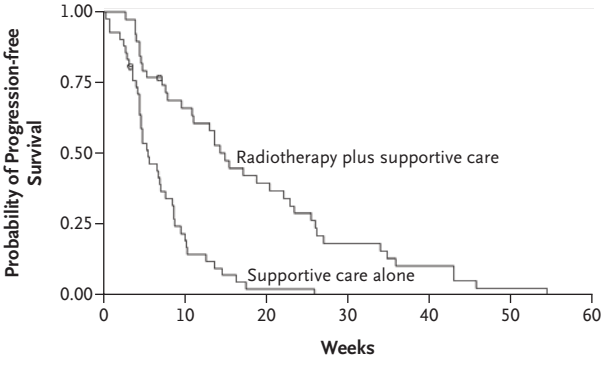
The MMSE scores declined over time in both groups (P=0.007), with no significant differences between the two groups (P=0.13). Analyses of the Neuropsychiatric Inventory and MDRS scores were



No. at Risk					
Supportive care alone	42	17	3	0	0
Radiotherapy plus supportive care	39	24	8	3	1

Figure 2. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients who received radiotherapy plus supportive care as compared with those who received supportive care alone was 0.47 (95% CI, 0.29 to 0.76; P=0.002).



No. at Risk			
Supportive care alone	42	2	0
Radiotherapy plus supportive care	39	15	4

Figure 3. Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.

The hazard ratio for disease progression among patients who received radiotherapy plus supportive care as compared with those who received supportive care alone was 0.28 (95% CI, 0.17 to 0.47; P<0.001).

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Table 3. Scores for Health-Related Quality of Life over Time.*

Measure	Score					P Value		
	Baseline	Day 30	Day 60	Day 90	Day 135	Treatment Effect	Time Effect	Interaction Effect
QLQ-C30								
Global						0.79	0.17	0.12
Supportive care	62.7±4.1	61.8±4.7	60.3±5.0	56.7±6.3	48.1±6.7			
Supportive care plus radiotherapy	62.9±3.4	57.6±3.5	55.6±3.9	49.1±4.0	58.8±4.47			
Functioning								
Physical						0.57	<0.001	0.97
Supportive care	75.4±4.6	64.9±6.3	53.8±7.6	51.9±7.9	37.2±15.9			
Supportive care plus radiotherapy	70.3±6.3	58.8±5.5	51.9±7.3	44.1±7.4	36.8±8.0			
Role (work and household activities)						0.29	0.07	0.90
Supportive care	66.3±5.7	59.1±6.8	61.8±8.5	56.6±7.8	45.1±14.5			
Supportive care plus radiotherapy	63.1±6.4	56.1±6.4	50.0±7.4	43.5±6.9	39.0±9.3			
Emotional						0.92	0.95	0.71
Supportive care	71.7±4.4	75.6±4.8	70.5±5.5	71.6±5.2	70.6±7.8			
Supportive care plus radiotherapy	75.6±4.3	70.5±5.0	70.5±5.2	69.7±5.2	71.1±5.7			
Cognitive						0.21	0.01	0.13
Supportive care	68.7±5.0	60.0±6.1	63.0±5.6	63.8±6.2	56.8±7.8			
Supportive care plus radiotherapy	66.8±4.7	59.6±4.9	57.4±6.7	42.8±7.1	43.8±6.7			
Social						0.49	0.02	0.83
Supportive care	73.7±6.1	66.1±6.0	63.8±7.3	67.8±8.2	43.6±16.2			
Supportive care plus radiotherapy	73.3±5.3	58.0±6.4	52.7±7.3	56.8±7.0	50.2±8.2			
Symptoms								
Fatigue						0.49	0.008	0.57
Supportive care	36.7±5.4	37.4±5.2	40.3±6.8	41.1±5.8	57.4±10.8			
Supportive care plus radiotherapy	33.0±4.0	39.5±4.9	48.9±6.3	52.8±5.0	57.9±5.3			
Nausea and vomiting						0.49	0.32	0.42
Supportive care	0.9±0.7	0.5±0.7	5.7±4.9	5.7±3.9	2.2±1.9			
Supportive care plus radiotherapy	3.3±1.3	4.3±2.7	5.1±2.7	10.7±5.5	0.9±1.0			
Insomnia						0.19	0.14	0.80
Supportive care	17.4±4.9	21.8±6.1	13.0±4.7	6.4±3.2	14.4±8.2			
Supportive care plus radiotherapy	25.9±5.4	24.4±5.2	15.9±5.1	18.9±5.6	21.3±6.2			

also restricted to 135 days of follow-up (Table 3 of the Supplementary Appendix). The global scores on the Neuropsychiatric Inventory did not change significantly over time (P=0.18), and there were no significant differences in these scores between the two groups (P=0.84). The MDRS score did not change significantly over time, except for progressive deterioration on the initiation (P=0.03) and construction (P=0.05) subscales in both groups (Table 4 of the Supplementary Appendix).

SAFETY

All patients in the radiotherapy group tolerated the treatment. One patient had transient early delayed somnolence (abnormal sleepiness) shortly after the completion of radiotherapy. Complications of corticosteroid treatment included diabetes in seven patients in the supportive care group and in two patients in the radiotherapy group and myopathy in three patients in the supportive care group and in six patients in the radiotherapy group.

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Table 3. (Continued.)

Measure	Score					P Value		
	Baseline	Day 30	Day 60	Day 90	Day 135	Treatment Effect	Time Effect	Interaction Effect
QLQ-BN20 (symptoms)								
Future uncertainty						0.85	0.67	0.002
Supportive care	33.3±4.7	31.3±4.5	36.4±6.0	28.6±5.5	32.5±8.0			
Supportive care plus radiotherapy	28.7±4.6	34.0±5.1	32.3±5.1	41.6±4.5	30.3±4.0			
Visual disorder						0.88	0.29	0.98
Supportive care	19.8±2.9	22.1±3.2	25.2±4.0	27.3±5.7	28.7±6.4			
Supportive care plus radiotherapy	21.9±2.7	22.2±2.8	26.1±3.9	27.1±3.3	28.8±2.8			
Motor dysfunction						0.50	0.001	0.46
Supportive care	20.2±4.1	23.6±5.8	27.6±7.2	29.6±6.8	54.0±16.4			
Supportive care plus radiotherapy	19.4±4.8	34.3±5.4	40.9±6.4	38.6±4.7	43.6±5.9			
Communication deficit						0.24	0.12	0.44
Supportive care	26.9±5.2	25.6±5.1	25.7±6.0	29.9±7.2	36.2±8.9			
Supportive care plus radiotherapy	27.9±5.5	39.6±6.6	36.6±7.0	41.1±7.0	44.8±8.0			
Bothered by hair loss						0.06	0.09	0.16
Supportive care	4.6±2.1	3.1±1.6	3.7±2.3	14.2±5.9	10.9±8.2			
Supportive care plus radiotherapy	7.9±4.1	16.5±6.0	22.6±5.9	26.2±7.7	16.2±6.5			

* Plus–minus values are means ±SD. Scores on both the QLQ-C30 and the QLQ-BN20 questionnaires can range from 0 to 100, with higher scores on the global health status and functioning scales and lower scores on the symptom scales and single-item measures indicating better performance.

TREATMENT AFTER DISEASE PROGRESSION

After disease progression, supportive care was given, with a few exceptions. Two patients in the radiotherapy group and one patient in the supportive care group received temozolomide. One patient in the supportive care group underwent reoperation.

DISCUSSION

This study shows that the addition of radiotherapy to supportive care prolongs survival and does not reduce the health-related quality of life or cognitive function of patients with newly diagnosed glioblastoma who are 70 years of age or older. The 16.9-week median survival of patients in our study who received only supportive care is consistent with the median survival reported more than two decades ago for younger patients treated with supportive care alone.[12,13] Conversely, the 12.2-week survival benefit with radiotherapy in the older patients in our study is about half the survival gain reported in the two earlier studies (22 and 24 weeks), which compared conventional radiotherapy (a total dose of 45 to 60 Gy, given in fractions of 1.7 to 2.0 Gy) with supportive care in a younger population.[12,13]

We selected a conventional 50-Gy schedule to minimize the age-related risk of radiation-induced neurotoxicity.[5] With this schedule, there were no cases of delayed neurotoxicity,[14] but the short survival of the patients in our study may have precluded the development of late toxicity. The optimal dose of radiotherapy in elderly patients remains undetermined. It is unclear whether a total dose of 60 Gy would increase the survival benefit of radiotherapy in older patients, as it does in younger patients.[15,16] In our trial, the 29.1-week median survival and 15% rate of discontinuation of radiotherapy compare favorably with the 22.1-week survival and 26% rate of discontinuation reported in a prospective study in which a dose of 60 Gy was delivered in 30 fractions over a period of 6 weeks in older patients.[17] In that study, an abbreviated course of radiotherapy (40 Gy in 15 fractions over a period of 3 weeks), as compared with the 60-Gy schedule, resulted in a similar median survival (24.3 weeks vs. 22.1 weeks), but

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a lower rate of premature discontinuation of radiotherapy (10% vs. 26%).[17]

Since the goal of the treatment of glioblastoma in older patients is palliation, the quality of life is relevant. The evaluation of health-related quality of life in patients with malignant glioma is notoriously difficult.[18-20] The main limitation is that severely ill patients with a rapidly progressive, fatal disease are not always compliant with such evaluations. To our knowledge, only one prospective study in the elderly attempted to evaluate health-related quality of life sequentially in patients with glioblastoma, but the data could not be analyzed because the compliance rate was too low (15 to 21% immediately after radiotherapy).[17] In our study, the rate of compliance with the questionnaires was similar to that in the few reported studies of patients with glioblastoma.[19-21] We were able to conduct a meaningful analysis of the data obtained from the first four follow-up evaluations (135 days of follow-up). Thereafter, the number of patients was too small for a reliable analysis.

At baseline, scores for the health-related quality of life did not differ significantly between the two groups and were similar to scores reported previously.[20] During and after treatment, scores on several evaluation scales (physical, cognitive, social, fatigue, and motor dysfunction) progressively declined in both groups, although the global score for health-related quality of life did not change significantly over time in either group. We did not observe the mild-to-moderate improvement on several scales that was reported in younger patients after radiotherapy, with or without chemotherapy.[20]

The evaluation of neuropsychiatric symptoms and cognitive function is associated with the same compliance limitation as the health-related quality-of-life analysis. The Neuropsychiatric Inventory did not show a time or treatment effect, particularly in the case of depression. In contrast, the cognitive evaluation (the MMSE and the initiation subscale of the MDRS) showed significant deterioration over time in both groups. However, as compared with supportive care alone, radiotherapy plus supportive care did not have a detrimental effect on cognitive function.

The population of elderly patients with cancer is underrepresented in clinical trials.[22,23] Likely causes of this underrepresentation are study-imposed restrictions, coexisting conditions, concern about the toxic effects of treatment, patient and family preferences, and the reluctance of physicians to enroll elderly patients in clinical trials.[24] Nevertheless, our study shows that these barriers may be overcome,[25] even in trials that involve a rapidly progressive, fatal disease, such as glioblastoma, and a palliative-care comparison group.

In conclusion, radiotherapy increases the median survival of elderly patients with glioblastoma who have a good performance status at the start of treatment. As compared with supportive care, radiotherapy in such patients does not cause further deterioration in the Karnofsky performance status, health-related quality of life, or cognitive functions, but the survival benefit is modest.

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This article is dedicated to each patient in this trial and to their families who went through the informed-consent process and agreed to participate in a study with a palliative care group. Knowing the situation, they chose to participate in solidarity with future patients.

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APPENDIX

In addition to the authors, the following investigators participated in the Radiotherapy for Glioblastoma in the Elderly Study: *Groupe Hospitalier Pitié–Salpêtrière, Paris* — L. Lacomblez, M. Levy-Soussan, A. Mallet, C. Houssard, D. Delgadillo, M. Poitou, K. Hoang-Xuan, M. Sanson, A.F. Carpentier, F. Laigle-Donadey, S. Taillibert, P. Cornu, A. Omuro, L. Capelle, A.-L. Boch, H. Duffau, J.-M. Simon; *Hôpital Européen Georges Pompidou, Paris* — J. Medioni; *Hôpital Paul Brousse, Villejuif* — P. Broet; *Hôpital de la Timone, Marseille, France* — A. Schmitt; *Hôpital Saint-Julien, Nancy, France* — E. Garat, P. Mathieu; *Institut Fédératif des Neurosciences, Hospices Civils de Lyon, Lyon, France* — N. Camille, J.-P. Collin; *Centre Antoine Lacassagne, Nice, France* — B. Bailet, C. Ciais, F. Fauchon, C. Lebrun; *Institut Bergonie, Bordeaux, France* — G. Guesdan, N. Stadelmaier, I. Lombard; *Centre Hospitalo-Universitaire Côte de Nacre, Caen, France* — P. Delassus, C. Lalevec; *Centre Hospitalo-Universitaire, Angers, France* — G. Aubin, D. Fournier, and G. Hayek.

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