RANDOMIZED COMPARISONS OF RADIOTHERAPY AND NITROSOUREAS FOR THE TREATMENT OF MALIGNANT GLIOMA AFTER SURGERY

MICHAEL D. WALKER, M.D., SYLVAN B. GREEN, M.D., DAVID P. BYAR, M.D., EBEN ALEXANDER, JR., M.D., ULRICH BATZDORF, M.D., WILLIAM H. BROOKS, M.D., WILLIAM E. HUNT, M.D., COLLIN S. MACCARTY, M.D., M. STEPHEN MAHALEY, JR., M.D., JOHN MEALEY, JR., M.D., GUY OWENS, M.D., JOSEPH RANSOHOFF, II, M.D., JAMES T. ROBERTSON, M.D., WILLIAM R. SHAPIRO, M.D., KENNETH R. SMITH, JR., M.D., CHARLES B. WILSON, M.D., AND THOMAS A. STRIKE, PH.D.

Abstract Within three weeks of definitive surgical intervention, 467 patients with histologically proved malignant glioma were randomized to receive one of four treatment regimens: semustine (MeCCNU), radiotherapy, carmustine (BCNU) plus radiotherapy, or semustine plus radiotherapy. We analyzed the data for the total randomized population and for the 358 patients in whom the initial protocol specifications were met (the valid study group). Observed toxicity included acceptable skin reactions secondary to radiotherapy and reversible leukopenia and thrombocytopenia due to chemotherapy. Radiotherapy used alone or in combination with a nitrosourea significantly improved survival in comparison with semustine alone. The group receiving carmustine plus radiotherapy had the best survival, but the difference in survival between the groups receiving carmustine plus radiotherapy and semustine plus radiotherapy was not statistically significant. The combination of carmustine plus radiotherapy produced a modest benefit in long-term (18-month) survival as compared with radiotherapy alone, although the difference between survival curves was not significant at the 0.05 level. This study suggests that it is best to use radiotherapy in the postsurgical treatment of malignant glioma and to continue the search for an effective chemotherapeutic regimen to use in addition to radiotherapy. (N Engl J Med. 1980; 303:1323-9.)

PRIMARY malignant brain tumors occur at an annual rate of approximately 4.5 cases per 100,000 population. Forty-three per cent of these cases are designated as malignant gliomas. Included within this group are glioblastoma multiforme, malignant astrocytoma, and anaplastic astrocytoma. These tumors are inevitably fatal, with a historical median survival of six months.[1]

The Brain Tumor Study Group (BTSG), a cooperative group of neurosurgeons, radiotherapists, neuropathologists, and oncologists working in conjunction with the National Cancer Institute, has previously reported the results of a clinical trial (BTSG 69-01) comparing the best conventional supportive care with carmustine — 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) — and radiotherapy, either alone or in combination.[2] The report concluded that the patients who received carmustine alone survived somewhat longer than did the group receiving only supportive care, although the difference was not statistically significant, and that each of the two groups receiving radiotherapy (with or without carmustine) had a significantly improved survival over that of each of the other two groups (one-tailed P value ≤ 0.001 for each comparison). The survival curves for the patients receiving radiotherapy alone and for those receiving carmustine plus radiotherapy were not significantly different; these two curves were practically superimposed during the first 12 months. However, there was a greater survival rate at 18 months among the patients receiving the combination of carmustine plus radiotherapy, with 15 to 20 per cent still alive at that time.

On completion of accrual to study 69-01, the BTSG began a subsequent prospective, randomized study (BTSG 72-01), reported here, to investigate further the relative benefits of radiotherapy and nitrosoureas. In addition to investigating carmustine, the study was designed to investigate a more recently developed nitrosourea, semustine, or 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (MeCCNU), which had been effective in a wide variety of experimental tumor models.[3] Early clinical trials had indicated the potential efficacy of semustine in the treatment of malignant glioma.[4]

With this background, study 72-01 was designed to compare four treatment regimens: semustine used as a single agent, radiotherapy alone, the combination of carmustine plus radiotherapy, and the combination of semustine plus radiotherapy.

Previous analyses[2,5] of data from study 69-01 identified variables that may have prognostic importance. In study 72-01, information on these and other potential prognostic factors has been collected for analysis.

From the National Cancer Institute, Landow Bldg., Rm. 4C-33, Bethesda, MD 20205, where reprint requests should be addressed to Dr. Strike.

This investigation was carried out by the following members of the Brain Tumor Study Group, in part under contract with the National Cancer Institute, National Institutes of Health: Eben Alexander, Jr., M.D., Bowman Gray School of Medicine, Contract No. N01-CM-67054; Collin S. MacCarty, M.D., Mayo Clinic, Grants PD-252921-5 and PD-222631-6; M. Stephen Mahaley, Jr., M.D., Duke University Medical Center, Contract No. N01-CM-67010; John Mealey, Jr., M.D., Indiana University School of Medicine, Contract No. N01-CM-67057; William R. Shapiro, M.D., Sloan-Kettering Memorial Hospital, Contract No. N01-CM-57019; Joseph Ransohoff, II, M.D., New York University Medical Center, Contract No. N01-CM-67059; William E. Hunt, M.D., Ohio State University Research Foundation, Contract No. N01-CM-67060; Kenneth R. Smith, Jr., M.D., St. Louis University School of Medicine, Contract No. N01-CM-57020; Guy Owens, M.D., University of Connecticut Health Center, Contract No. N01-CM-12181; Charles B. Wilson, M.D., University of California Medical Center at San Francisco, Contract No. N01-CM-67055; Ulrich Batzdorf, M.D., University of California at Los Angeles, Contract No. N01-CM-53752; William Brooks, M.D., University of Kentucky Medical Center, Contract No. N01-CM-67058; James T. Robertson, M.D., University of Tennessee Center for Health Sciences, Contract No. N01-CM-57021; and Michael D. Walker, M.D, Sylvan B. Green, M.D., David P. Byar, M.D., and Thomas A. Strike, Ph.D., National Cancer Institute.

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The study of prognostic factors is of interest in itself, and, in addition, such variables can be used in adjustment of statistical comparisons of the treatment groups.

Methods

Patient Accrual

Thirteen institutions participated in the design and conduct of this trial. Patients were entered into the study by the principal investigators at each institution within three weeks of definitive surgical intervention for the primary tumor. Eligibility criteria included histologically demonstrated supratentorial malignant glioma and an anticipated postoperative life expectancy of two months or more. Patients were required to have normal hematologic, hepatic, and renal function in addition to a reasonably good general medical condition. We informed all patients of the nature of the study, the therapeutic methods that might be employed, the toxicity that was reasonably anticipated to result from such therapy, the randomization procedure, and the availability of continued care if they declined to enter or remain in the study. Written informed consent was obtained from all patients.

Patients were randomized to one of the four treatment groups by means of a telephone call to the BTSG Operations Office, and all patients who were entered into the study were followed. Demographic, neurologic, and surgical information was collected for all patients, and a set of pathology slides from each patient's tumor was sent to the BTSG Operations Office for subsequent evaluation by the Neuropathology Review Committee, which made the final determination of eligibility on the basis of the histopathologic criteria given by Burger and Vogel.[6]

Treatment

The prescribed radiotherapy was a total dose of 6000 rads in 30 to 35 fractions of 171 to 200 rads, five days per week over six to seven weeks, delivered to the whole brain by parallel opposed ports with megavoltage equipment. The equipment at each institution was calibrated by the Radiologic Physics Center, Houston, Texas. For patients who were randomized to receive both chemotherapy and radiotherapy, the first course of chemotherapy was scheduled during the first few radiotherapy sessions.

Semustine was given in a single oral dose of 220 mg per square meter of body-surface area, repeated every six to eight weeks or when adequate bone-marrow function was demonstrated. The dose was reduced to 170 mg per square meter for patients with thrombocytopenia (platelet count below 50,000), leukopenia (white-cell count below 3000), or a decrease in hematocrit of more than 20 per cent of the initial value. An additional dose reduction to 130 mg per square meter was permitted if the same indicators of toxicity were observed after subsequent treatment. Carmustine was administered by vein at a dose of 80 mg per square meter per day on three successive days every six to eight weeks. A decrease in dosage to 60 or 45 mg per square meter per day on three successive days was employed for the same indications of toxicity used with semustine.

Before treatment, we evaluated patients by neurologic examination and rated them on performance status according to the Karnofsky scale[7] (100, normal: no complaints, no evidence of disease; 90, able to carry on normal activity: minor symptoms; 80, normal activity with effort: some symptoms; 70, cares for self: unable to carry on normal activity; 60, requires occasional assistance: cares for most needs; 50, requires considerable assistance and frequent care; 40, disabled: requires special care and assistance; 30, severely disabled: hospitalized, death not imminent; 20, very sick: active supportive treatment needed; 10, moribund: fatal processes are rapidly progressing). Patients receiving chemotherapy had complete blood and platelet counts and tests of hepatic and renal function performed before each course of treatment and repeated at appropriate intervals during the course of treatment. All investigators were aware of the profound delayed myelosuppression that is the hallmark of the nitrosoureas. After treatment, the performance status was evaluated bimonthly. Neurodiagnostic tests, particularly computerized-axial-tomographic scans, were obtained when indicated. It was expected that the usual procedures of medical and neurosurgical care would be afforded to all patients, but that after completion or termination of the prescribed treatment no extraordinary measures beyond those of standard medical practice would be undertaken to prolong a patient's life.

Corticosteroids greatly ameliorate symptoms in patients with brain tumors, although their effect on survival is not clearly understood. The protocol allowed the use of steroids (either dexamethasone, 3 to 4 mg every six hours, or methylprednisolone, 30 to 40 mg every six hours) for a period not to exceed one month during the preoperative and postoperative phases, including the period of radiotherapy. Corticosteroids could also be used during subsequent courses of chemotherapy for the control of life-threatening cerebral edema. However, their use was restricted to a one-week period during each course.

Statistical Methods

We calculated the probability of survival for a specified length of time by the life-table method,[8] and we compared the survival of different treatment groups with use of the Mantel–Haenszel test[9] or the Gehan test.[10,11] These two procedures are both commonly used in the analysis of survival data; they differ in that the Gehan test gives relatively more weight to earlier deaths. We compared the resulting statistics with critical values for a chi-square with one degree of freedom, always on the basis of two-tailed tests.

We investigated the prognostic effect of individual covariates by examining death rates, defined as the number of deaths divided by the total number of patient-months of follow-up for all patients in a specific category, and tested for significance with a chi-square test for linear trend. Such tests were only intended to serve as useful guides in the initial screening of variables. We considered the prognostic importance of multiple variables acting simultaneously by means of regression models, wherein the risk of death is modeled as a function of the specified variables. One such regression model, the Cox proportional-hazards model,[12] was used to compare the survival of the four treatment groups, adjusted for prognostic factors. Testing for significance of a treatment effect was based on the square of the standardized regression coefficient (the coefficient for the treatment variable in the Cox regression model, divided by its standard error), which was compared with two-tailed critical values for a chi-square with one degree of freedom. We formed risk groups on the basis of prognostic factors with a Weibull regression model, using the approach described by Byar et al.[13]

Results

Between October 1972 and December 1975, 467 patients were randomized to one of the four treatment groups as follows: 111 to semustine, 118 to radiotherapy, 120 to carmustine plus radiotherapy, and 118 to semustine plus radiotherapy. We first performed analyses on this total randomized population; for subsequent analyses we excluded certain patients to produce a valid study group. To minimize the danger of bias, we excluded patients from the valid study group only because of insufficient information for adjusted analyses or because of protocol violations that occurred near the time of randomization. The reasons for exclusion were as follows: 44 patients did not have malignant glioma on review of slides by the Neuropathology Review Committee; 15 patients did not receive any of the initial chemotherapy regimen to which they were randomized; seven patients did not receive even the initial dose of the radiotherapy course to which they were randomized; 11 patients received nonprotocol antineoplastic therapy within two weeks of randomization; three patients were randomized in

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error (i.e., they were ineligible because of therapy administered before randomization); four patients had either inadequate records or no follow-up information; and 25 patients had unknown values for prognostic variables needed for adjusted analyses. Any patient who was eligible for the study and who began the assigned treatment was included in the analysis of the valid study group, whether or not the patient's subsequent progress permitted delivery of the full course of therapy.

The valid study group assembled on the basis of these criteria consisted of 358 patients. The median age of these patients at the time of randomization was 55 years, and 59 per cent were men. The median duration of symptoms up to the time of operation was 2.5 months. The most common symptoms recorded were headache (present in 55 per cent of the patients), motor symptoms (45 per cent), seizures (36 per cent), personality change (35 per cent), and speech disorder (24 per cent). The tumor was entirely or predominantly located in the frontal lobe in 41 per cent of the patients, in the temporal lobe in 31 per cent, in the parietal lobe in 21 per cent, in the occipital lobe in 4 per cent, and in deeper areas in the remaining 3 per cent. A subtotal resection was performed in 47 per cent of the patients, subtotal resection plus lobectomy in 35 per cent, total (gross) resection in 10 per cent, and total resection plus lobectomy in 2 per cent; the remaining patients had only a biopsy. We also tabulated these characteristics for the total randomized population and found them to be substantially the same.

After review of histopathologic material, we classified 84 per cent of the patients in the valid study group as having glioblastoma multiforme, 11 per cent as having malignant (anaplastic) astrocytoma, and 5 per cent as having various other categories of malignant glioma. Important characteristics of the patients in the valid study group have been tabulated separately by treatment group (Table 1). Details of the treatment received by these patients are presented in Table 2.

We first performed an unadjusted analysis of survival in the total randomized population. Inspection of life-table survival probabilities (Table 3) and the corresponding survival curves (Fig. 1) suggested that the group receiving only semustine had the shortest survival and that the two groups receiving the combination of chemotherapy and radiotherapy had the longest. However, statistical tests for differences in survival (Table 4) showed only the comparison between semustine alone and carmustine plus radiotherapy to be significant at $P<0.05$; the similar comparison between semustine alone and semustine plus radiotherapy was not quite significant at the 0.05 level. Statistical significance was achieved with the Gehan test but not with the Mantel–Haenszel test; this observation implies that the early deaths among the patients receiving only semustine accounted for the difference. The significance levels reported here have not been corrected for the multiple comparisons performed; the probability that at least one significant result would occur by chance alone exceeds the nominal P value.

Table 1. Characteristics of Patients in the Valid Study Group.

Characteristic	Treatment Group				All Treatments
	Semustine	Radiotherapy	Carmustine + Radiotherapy	Semustine + Radiotherapy	
Number of patients	81	94	92	91	358
Median age at randomization (yr)	57	57	53	54	55
Symptoms before entry *					
Headache	60	53	58	51	55
Motor symptoms	42	48	47	42	45
Seizures	35	38	32	41	36
Personality change	38	34	25	42	35
Median duration of symptoms (mo)	2.4	2.4	2.5	2.9	2.5
Histopathologic category *					
Glioblastoma multiforme	86	87	81	82	84
Malignant (anaplastic) astrocytoma	10	10	11	14	11
Other †	4	3	8	3	5
Necrotic tumor *	53	49	51	45	49
Median initial performance status (Karnofsky scale)	60	60	65	60	60

*Figures denote percentages of the total number of patients.

†Includes the following categories: ependymal spongioblastoma, malignant ependymoma, astroblastoma, oligodendroblastoma, and other malignant glioma.

An unadjusted analysis of survival was also performed for the valid study group (Table 3 and Fig. 2). Here, statistical tests for the various comparisons of pairs (Table 4) showed that the survival of the patients receiving only semustine was significantly shorter than that of each of the other three groups, all of whom received radiotherapy, whereas the three groups who received radiotherapy did not differ significantly among themselves. These general conclusions were the same whether the Gehan test or the Mantel–Haenszel test was used. Inspection of the survival curves (Fig. 2) suggested a modest benefit for the combination of chemotherapy and radiotherapy as reflected in an increased number of long-term survi-

Table 2. Details of Treatment Received by Patients in the Valid Study Group.

	Semustine	Radiotherapy	Carmustine + Radiotherapy	Semustine + Radiotherapy
Chemotherapy courses				
Mean ±S.E.	3.6±0.4	—	4.9±0.4	4.5±0.4
Two or more *	77	—	78	78
Three or more *	48	—	60	65
Four or more *	33	—	51	47
Five or more *	23	—	40	40
Mean radiotherapy dose ±S.E. (rads)	—	5734±96	5708±106	5759±90

*Figures denote percentage of patients.

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Table 3. Life-Table Survival Probabilities by Treatment Group.

Treatment Group	Number of Patients	Median Survival	Percentage Surviving ±S.E.			
		weeks	*6 mo*	*12 mo*	*18 mo*	*24 mo*
Total randomized population						
Semustine	111	31	56.2±4.7	25.8±4.2	20.2±3.9	16.6±3.6
Radiotherapy	118	37	67.8±4.4	37.0±4.5	19.4±3.7	14.1±3.3
Carmustine plus radiotherapy	120	49	71.0±4.2	47.9±4.6	28.8±4.2	19.2±3.7
Semustine plus radiotherapy	118	43	68.8±4.3	40.9±4.6	29.6±4.3	19.2±3.7
Valid study group						
Semustine	81	24	47.6±5.6	15.0±4.0	10.0±3.4	7.5±3.0
Radiotherapy	94	36	69.1±4.8	34.6±4.9	15.1±3.7	9.7±3.1
Carmustine plus radiotherapy	92	51	70.7±4.7	50.0±5.2	27.2±4.6	15.2±3.7
Semustine plus radiotherapy	91	42	71.1±4.8	36.7±5.1	23.3±4.4	12.2±3.5

vors (e.g., 18 months); a difference in the later part of the observed survival curves may account for the significance level (P = 0.072) for the Mantel–Haenszel test comparing carmustine plus radiotherapy with radiotherapy alone (Table 4).

We analyzed data from the valid study group to investigate the prognostic importance of patient characteristics, symptomatology, tumor characteristics, and performance status at the time of randomization. We identified nine variables that had a significant effect on death rate when studied one at a time (Table 5). We then studied these variables by a multivariate analysis with the Cox proportional-hazards model and eliminated individual variables by a "step-down" procedure if they did not have a significant effect on survival, given the other variables in the model. In this multivariate analysis we used the reciprocal value of each patient's performance status, since the reciprocal value was found to be related to the death rate in an approximately linear fashion. Using the model, we identified five variables that were simultaneously important for predicting survival: age, personality change (as a symptom noted before entry into the study), duration of symptoms, histopathologic category, and performance status. In addition, the correspondence between the model and the data was significantly improved by the addition of an "interaction term" for personality change and performance status; this effect implies that the prognostic importance of personality change was greater for lower levels of performance status.

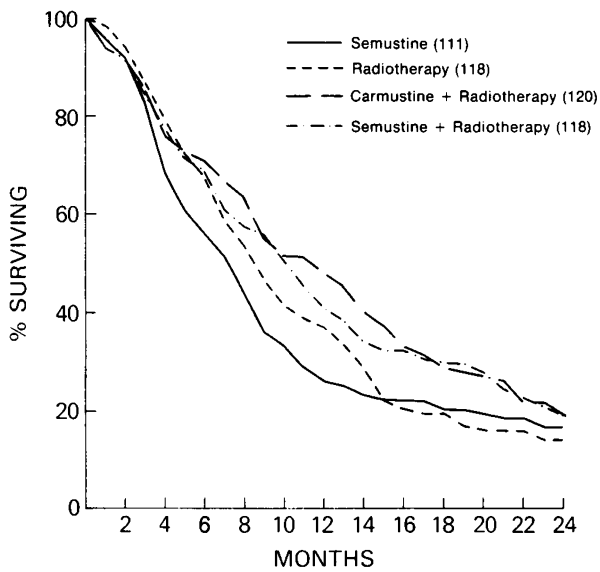


Figure 1. Survival Curves for Each Treatment Group in the Total Randomized Population.
The numbers of patients are shown in parentheses.

With these variables, we performed an adjusted analysis of survival for the valid study group, using the Cox model with indicator variables to represent the treatment groups. The results of significance tests (Table 4) did not affect the general conclusions reached after the corresponding unadjusted analysis of the valid study group.

To demonstrate the importance of the prognostic variables used for adjustment, we divided the patients into three risk groups on the basis of the percentage of patients surviving as predicted by the Weibull model. (Coefficients of the fitted model, with variables other than performance status categorized as in Table 5, were as follows: age, 0.33799; personality change, −0.38736; symptom duration, −0.19698; histopathologic category, −0.53351; reciprocal performance status, 47.222; interaction between personality change and reciprocal performance status, 34.645; intercept, −4.8155; and Weibull shape parameter, 1.4497.) On the basis of this model, 68 patients had a predicted 24-month survival greater than 25 per cent (Group 1), 163 patients between 2.5 and 25 per cent (Group 2), and 127 patients less than 2.5 per cent (Group 3). Characteristics of these three risk groups are presented in Table 6. Inspection of the observed life-table survival curves for these three groups and the predicted curves from the model (Fig. 3) shows that the model fits the data reasonably and demonstrates the marked importance of these prognostic factors at presentation.

Finally, we tabulated the toxicity reported for the various forms of treatment. Skin reactions due to ra-

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Table 4. Comparisons of Survival of Pairs Among the Four Treatment Groups.*

Treatment Comparison	Total Randomized Population		Valid-Study Group		
	Unadjusted		Unadjusted		Adjusted
	Gehan	*Mantel–Haenszel*	*Gehan*	*Mantel–Haenszel*	*Cox model*
Semustine vs. radiotherapy	0.146	0.623	0.003	0.048	0.016
Semustine vs. carmustine + radiotherapy	0.022	0.127	<0.001	0.001	<0.001
Semustine vs. semustine + radiotherapy	0.062	0.246	<0.001	0.006	0.006
Radiotherapy vs. carmustine + radiotherapy	0.201	0.181	0.139	0.072	0.108
Radiotherapy vs. semustine + radiotherapy	0.450	0.329	0.404	0.292	0.668
Carmustine + radiotherapy vs. semustine + radiotherapy	0.644	0.679	0.474	0.426	0.244

*Figures denote two-tailed P values.

diotherapy, graded according to degree of severity, were reported for the parietal scalp, the posterior-auricular area, and the auditory canal. The posterior-auricular area was the most sensitive, with 80 per cent of the patients having some degree of skin toxicity. The auditory-canal epithelium appeared to be the least sensitive, with reactions reported in 55 per cent of the patients. There was no difference in the degree or extent of reactions due to radiation that were observed with or without chemotherapy.

The hematologic toxicity of the two nitrosoureas was moderate and acceptable. About one quarter of the patients had mild thrombocytopenia (platelet count below 90,000) at some time during treatment, and 6 to 7 per cent had more severe thrombocytopenia (platelet count below 50,000). Leukopenia (white-cell count below 3000) was found in less than one quarter of the patients, with approximately 5 per cent having a white-cell count below 2000. Anemia (hematocrit decrease greater than 8 per cent) was observed in just under 5 per cent of the patients. The degree and extent of toxicity encountered in the different treatment groups indicated that the doses of chemotherapeutic agents used were nearly equal in toxicity.

Discussion

Several conclusions can be reached from the results of this clinical trial. First of all, the study confirms the benefits of radiotherapy in the treatment of malignant glioma. As in study 69-01, radiotherapy (whether alone or in combination with a nitrosourea) provided significant improvement in survival over nitrosourea alone.[2] In addition, the results suggest that carmustine remains the drug of choice for chemotherapy of malignant glioma. Semustine given alone was inferior to the regimens that included radiotherapy, as was carmustine in the previous study, and semustine in combination with radiotherapy clearly provided no advantage over carmustine plus radiotherapy.

The question of whether nitrosourea combined with radiotherapy offers an advantage over radiotherapy alone is less easily answered. If we consider the survival curve of each of the groups, the statistical tests that are appropriate for comparing survival curves (Gehan test and Mantel–Haenszel test) did not detect a significant improvement with combined-method therapy. However, the observed survival curves (Fig. 1 and 2) showed a pattern similar to that observed in study 69-01: a greater number of "long-term" survivors (e.g., at 18 months) in both combined-method groups as compared with the group receiving radiotherapy alone. It is important to note that only a small fraction of the patients were still alive at 18 months. Thus, if the effect is real and not due to chance, larger sample sizes may be required to produce statistically significant overall differences in the survival curves. Furthermore, if differences do exist, they represent a benefit only for patients who survive for at least one year.

The use of corticosteroids is virtually mandatory for the control of symptoms in patients with malignant brain tumors. An oncolytic effect of corticosteroids in the treatment of malignant glioma has yet to be demonstrated, although these agents do have a marked effect on neurologic findings and symptoms. A subsequent randomized trial, BTSG 75-01, has been evaluating the use of intermittent high-dose methylprednisolone with and without carmustine in comparison with carmustine or procarbazine. Preliminary results of this study do not show any survival benefit from high-dose steroids.

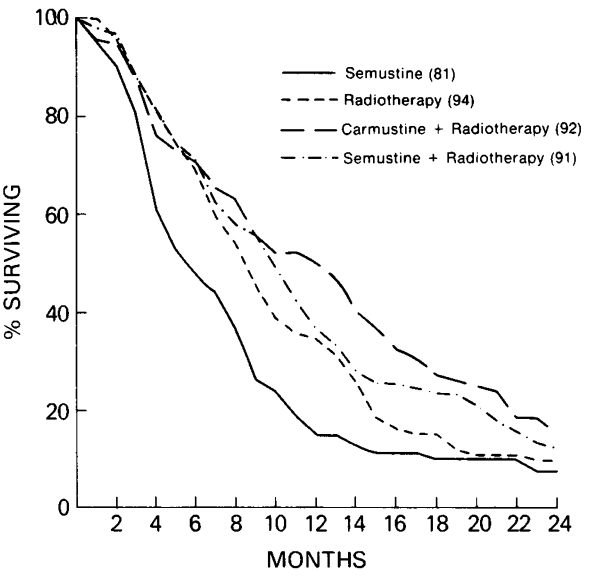


Figure 2. Survival Curves for Each Treatment Group in the Valid Study Group.
The numbers of patients are shown in parentheses.

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Any analyses performed on patient samples other than the total randomized population are open to some question, since bias may be introduced by the exclusion of patients. The conservative approach is to confine attention to the randomized population; therefore, we first presented the results of such an analysis. In the formation of the valid study group, the criteria for exclusion differed somewhat from those used in study 69-01 and resulted in a lower percentage of exclusions in study 72-01. It is highly unlikely that we introduced bias by excluding patients who were actually ineligible and should never have been randomized originally. On the other hand, we did not exclude patients in this analysis for such reasons as the need to institute additional nonprotocol therapy in patients faring poorly on the assigned regimen.

Table 5. Effect of Individual Prognostic Variables on Death Rate.

VARIABLE	CATEGORY	NUMBER OF PATIENTS	NUMBER OF DEATHS	DEATH RATE *	P VALUE
Age at randomization (yr)	<45	68	54	0.42	<0.00001
	45–54	108	104	0.76	
	55–64	110	106	1.20	
	≥65	72	72	1.41	
Headache	No	160	150	0.96	0.0186
	Yes	198	186	0.74	
Motor symptoms	No	198	182	0.73	0.0049
	Yes	160	154	0.99	
Seizures	No	228	219	0.92	0.0167
	Yes	130	117	0.70	
Personality change	No	234	215	0.76	0.0188
	Yes	124	121	0.99	
Duration of symptoms (mo)	<4	257	249	0.98	<0.00001
	4-6	25	25	0.96	
	>6	76	62	0.49	
Histopathologic category	Glioblastoma multiforme	302	292	0.96	<0.00001
	Other malignant glioma	56	44	0.44	
Necrotic tumor	No	181	164	0.71	0.0037
	Yes	177	172	0.98	
Performance status (Karnofsky scale)	10-40	66	65	1.52	<0.00001
	50-60	123	120	1.04	
	70-80	78	68	0.70	
	90-100	91	83	0.55	
All patients		358	336	0.83	

*Death rates are expressed as the number of deaths per 10 patient-months.

The analysis of prognostic factors presented here demonstrates the significant effect of several variables on survival and indicates that it is important to consider these factors in any comparison of treatment groups. In this study the conclusions remained unchanged after adjustment, implying that randomization produced groups that were well balanced prognostically. However, this result was not inevitable.

Because of the marked effect of some of these variables on prognosis, it is likely that they would be found to have similar prognostic importance in other studies. For example, initial performance status and age were also found to be important in analyses of study 69-01.[2,5] Not all variables previously reported as important for prognosis had a statistically significant effect in study 72-01. However, it is unlikely that the identical set of variables would be selected in repeated studies. One reason for this statement is that some results may appear significant by chance alone because of the multiple comparisons being performed. Our investigation of many variables for prognostic importance represents exploratory data analysis, and this investigation is unlikely to provide definitive answers unless significance levels are striking. For example, although personality change appeared to be prognosti-

Table 6. Characteristics of Risk Groups.*

CHARACTERISTIC	GROUP 1	GROUP 2	GROUP 3	ALL PATIENTS
Number of patients	68	163	127	358
Age at randomization				
Mean	36	53	63	53
<45 †	70.6	11.7	0.8	19.0
45-64 †	29.4	85.8	45.7	60.9
≥65 †	0	2.5	53.5	20.1
Personality change †	23.5	30.1	46.5	34.6
Duration of symptoms >6 mo †	58.8	14.1	10.2	21.2
Glioblastoma multiforme †	51.5	86.5	99.2	84.4
Performance status (Karnofsky scale)				
Mean	86	68	48	64
10-40 †	0	6.7	43.3	18.4
50-80 †	33.8	68.8	52.0	56.2
90-100 †	66.2	24.5	4.7	25.4
Survival at 24 mo †	46.3	4.3	1.6	11.3

*Risk groups are defined in the text. †Figures denote percentages.

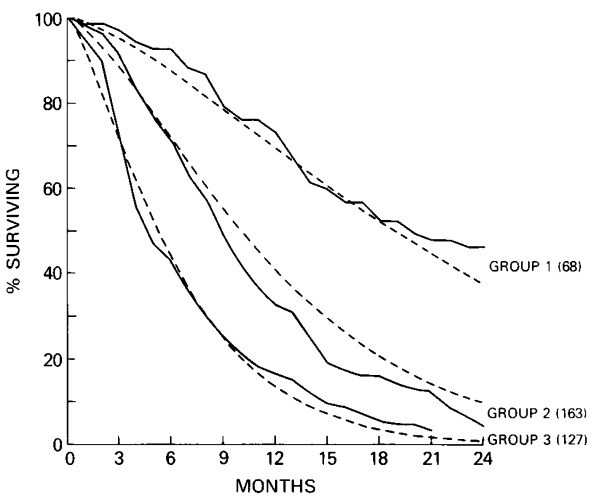


Figure 3. Survival Curves for Each Risk Group as Defined in the Text.

Solid lines represent the observed life-table survival rates. Dashed lines represent the predicted survival rates from the Weibull model. The numbers of patients are shown in parentheses.

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cally important in this study and demonstrated an interesting interaction with performance status, a preliminary analysis of a subsequent BTSG trial has failed to show a significant effect for this variable. Another important point is that some of these prognostic variables are highly correlated. Such relations may explain why the symptom of seizures, although significantly related to prognosis (the presence of seizures was favorable), was not needed in the regression-model analysis that considered multiple variables simultaneously, since the symptom of seizures correlated with symptom duration and patient age. It is to be expected that in various studies in which the same set of (correlated) variables are prognostically important, somewhat different subsets of these variables will be retained by a stepwise regression procedure.

On the basis of the results of this study, it appears best to use radiotherapy in the treatment of patients with malignant glioma and to continue the search for different chemotherapeutic regimens to combine with radiotherapy. Randomized clinical trials by the BTSG now in progress are designed to pursue this goal.

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