ARTICLES

Recursive Partitioning Analysis of Prognostic Factors in Three Radiation Therapy Oncology Group Malignant Glioma Trials

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Background: **Despite notable technical advances in therapy for malignant gliomas during the past decade, improved patient survival has not been clearly documented, suggesting that pretreatment prognostic factors influence outcome more than minor modifications in therapy. Age, performance status, and tumor histopathology have been identified as the pretreatment variables most predictive of survival outcome. However, an analysis of the association of survival with both pretreatment characteristics and treatment-related variables is necessary to assure reliable evaluation of new approaches for treatment of malignant glioma.** ***Purpose:*** **This study of malignant glioma patients used a nonparametric statistical technique to examine the associations of both pretreatment patient and tumor characteristics and treatment-related variables with survival duration. This technique was used to identify subgroups with survival rates sufficiently different to create improvements in the design and stratification of clinical trials.** ***Methods:*** **We used a recursive partitioning technique to analyze survival in 1578 patients entered in three Radiation Therapy Oncology Group malignant glioma trials from 1974 to 1989 that used several radiation therapy (RT) regimens with and without chemotherapy or a radiation sensitizer. This approach creates a regression tree according to prognostic variables that classifies patients into homogeneous subsets by survival. Twenty-six pretreatment characteristics and six treatment-related variables were analyzed.** ***Results:*** **The most significant split occurred by age (<50 versus ≥50 years). Patients younger than 50 years old were categorized by histology (astrocytomas with anaplastic or atypical foci [AAF] versus glioblastoma multiforme [GBM]) and subsequently by normal or abnormal mental status for AAF patients and by performance status for those with GBM. For patients aged 50 years or older, performance status was the most important variable, with normal or abnormal mental status creating the only significant split in the poorer performance status group. Treatment-related variables produced a subgroup showing significant differences only for better performance status GBM patients over age 50 (by extent of surgery and RT dose). Median survival times were 4.7-58.6 months for the 12 subgroups resulting from this analysis, which ranged in size from 32 to 256 patients.** ***Conclusions:*** **This approach permits examination of the interaction between prognostic variables not possible with other forms of multivariate analysis.** ***Implications:*** **The recursive partitioning technique can be employed to refine the stratification and design of malignant glioma trials. [J Natl Cancer Inst 85:704–710, 1993]**

Patients with malignant glial neoplasms, specifically glioblastoma multiforme (GBM) and astrocytomas with anaplastic or atypical foci (AAF), constitute a particularly difficult challenge for clinicians charged with their care. The high fatality-to-case ratio among the 6000-8000 patients diagnosed each year in the United States has prompted efforts to improve both surgical and postoperative oncologic care. Despite notable technical advances in both the surgical and radiotherapeutic treatment approaches to malignant gliomas during the past decade, improved patient survival has not been clearly documented. The benefit of optimal surgical resection and postoperative external beam radiation therapy (RT) in prolonging survival has been established

*See "Notes" section following "References."

since the 1970s in selected subgroups, as has the additional benefit of nitrosourea chemotherapy (*1,2*). Since that time, however, further improvement in patient outcome by such treatment approaches as radiation sensitizers, more intensive chemotherapy, or altered fraction RT has not been conclusively documented (*3-6*). It would appear that pretreatment prognostic factors influence outcome more strongly than any minor modifications in therapeutic approach.

Several cooperative group trials in malignant glioma (*4,7,8*) have identified patient age, tumor histopathology (AAF versus GBM), and performance status as the pretreatment variables most predictive of patient outcome. These trials have generally included all malignant glioma patients meeting specified performance status or neurologic function criteria and have not allowed for an analysis of the full interaction between treatment factors and all important patient and tumor-related variables. While novel treatment approaches to selected patients (including interstitial brachytherapy, stereotactic radiosurgery, and certain radiosensitizing agents) have produced encouraging results in pilot studies (*9-11*), it is often difficult to identify an appropriate comparison group treated with standard therapy.

The goals of the present study, which uses an interactive, nonparametric statistical technique known as recursive partitioning analysis, are as follows: 1) to analyze the relative contributions of pretreatment variables to the survival of patients with malignant glioma, 2) to define the influence of treatment variations on survival among patients enrolled in three consecutive Radiation Therapy Oncology Group (RTOG) randomized trials, and 3) to identify patient subgroups with survival rates that are sufficiently different as to influence the design and stratification of future clinical trials.

Patients and Methods

Patient Population

Patients entered in three consecutive RTOG trials for biopsy-proven, supratentorial malignant gliomas constitute the study group for this article. These trials, as shown in Table 1, were RTOG 74-01/Eastern Cooperative Oncology Group (ECOG) 1374, RTOG 79-18, and RTOG 83-02; they accrued a total of 1743 patients from 1974 to 1989. Central pathology review was conducted on 93% of the cases by one of the authors (J. S. Nelson). Primary treatment outcome reports of these trials have been previously published (*2,3,7,8*). Eligibility criteria were consistent in all three studies and included the following: histologically confirmed supratentorial GBM or AAF; age 18-70; an interval of 4 weeks or less from surgery to registration; and normal hepatic, renal, and bone marrow function. Ineligibility criteria included prior malignancies except skin carcinomas and prior chemotherapy or head and neck irradiation. In RTOG 79-18 and RTOG 83-02, patients were required to have a Karnofsky performance status of 40 or greater, and both preoperative and postoperative computerized tomography scans were required.

Table 1. RTOG malignant glioma trials

Study	No. of patients	Treatment arms
74-01	538	60 Gy
		70 Gy
		60 Gy and carmustine
		60 Gy, semustine, and dacarbazine
79-18	293	60 Gy and carmustine
		60 Gy, misonidazole, and carmustine
83-02	747	Hyperfractionated RT and carmustine
		64.8-81.6 Gy
		Acccelerated hyperfractionated RT and carmustine
		48.0 and 54.4 Gy
Total	1578	

Protocol Summaries

The treatment regimens of these three trials, as summarized in Table 1, are described below. One hundred sixty-five of the 1743 cases were considered nonanalyzable for this study for the following reasons: (*a*) failure to meet protocol eligibility requirements (34 patients), (*b*) inadequate information submitted (59 patients), and (*c*) removal from study prior to initiation of therapy (72 patients).

The RTOG 74-01/ECOG 1374 trial was a phase III randomization study among 1) 60-Gy whole-brain RT, 2) 60-Gy whole-brain RT plus a 10-Gy RT boost dose, 3) 60-Gy whole-brain RT plus carmustine chemotherapy, and 4) 60-Gy whole-brain RT plus semustine and dacarbazine. Carmustine dosing in all three studies was 80 mg/m^2 during days 1-3 and then 80 mg/m^2 once every 8 weeks for 1 year. Because of hematologic toxicity, dacarbazine doses were reduced from 175 mg/m^2 to 150 mg/m^2 for 5 days every 4 weeks after 9 months of accrual, and semustine doses were reduced from 150 mg/m^2 to 125 mg/m^2 at the same time. A total of 639 patients were entered (including 13 nonrandomized cases not previously reported), and 538 were analyzable for this study (*2*)

The RTOG 79-18 study was a phase III trial. In it, outcome from treatment with 60-Gy whole-brain RT and carmustine with the radiosensitizing agent misonidazole at a dose of 2.5 mg/m^2 prior to RT each Monday was compared with outcome from the same treatment without misonidazole. The daily RT fraction size was 1.7-2.0 Gy in the RTOG 74-01/ECOG 1374 trial and in the nonmisonidazole arm of the RTOG 79-18 trial; in the misonidazole arm, the fraction sizes were 4.0 Gy on Mondays and 1.5 Gy on Tuesdays, Thursdays, and Fridays. For the RTOG 79-18 trial, 318 patients were randomized, and 293 were available for this analysis (*3*).

The third trial, RTOG 83-02, was a phase I–phase II randomized dose escalation trial of hyperfractionated partial brain RT and accelerated hyperfractionated partial brain RT with carmustine. Four total RT dose levels of hyperfractionated partial brain RT were studied in 1.2-Gy twice-daily fractionation with an interfraction interval of 4-8 hours. These dose levels were 64.8, 72.0, 76.8, and 81.6 Gy. A total of 474 patients were enrolled (including eight nonrandomized cases), and 444 were analyzable (*7*). The final portion of this study was a randomization between the total accelerated hyperfractionated partial brain RT doses of 48.0 and 54.4 Gy in 1.6-Gy twice-daily fractionation with the same interfraction interval requirements. Three-hundred twelve patients were entered, and 303 were analyzable (*8*).

In both RTOG 79-18 and RTOG 83-02, patients were stratified by age, institutional histopathology, and Karnofsky performance status prior to randomization In those studies, the randomization scheme described by Zelen (*12*) to achieve institutional balance of treatment assignments was utilized with the three patient-related stratification variables. In RTOG 74-01/ECOG 1374, an institutional option design was used in which an institution could choose a subset of two or three treatment arms from which treatment assignment would be made.

Prognostic Factors

A number of patient-related variables were available from the data set created at the time of protocol enrollment. Those that were tested in this analysis included the following: age; race; gender; Karnofsky performance status; neurologic functional classification (class 1, able to work; class 2, able to be at home; classes 3 and 4, hospitalized); duration of neurological signs and symptoms; the presence of coexisting medical conditions, including diabetes mellitus, cardiac disease, and hypertension; and 13

neurologic signs and symptoms. These neurologic signs and symptoms were listed as being "present" or "absent," and they were visual disturbance, headache, cerebral deficit, sensory deficit, motor deficit, papilledema, seizure history, somnolence, speech impairment, memory lag, personality change, cranial nerve deficit, and changes in mental status. The three tumor-related variables analyzed were tumor location (frontal, parietal, temporal, or other), tumor size (<5 cm or ≥5 cm), and histology (GBM or AAF). Treatment-related factors considered in the analysis were extent of resection (total, partial, or biopsy), total RT dose received, interfraction RT interval (for hyperfractionated RT), RT fraction size, use of chemotherapy (carmustine, semustine and dacarbazine, or none), and use of the RT sensitizer misonidazole. For continuous variables such as age, RT dose, or tumor size, several break points were analyzed, ranging from 2 for RT fraction size up to 6 for duration of neurologic symptoms. This analysis resulted in a total of 58 variables to test in the first operation in the recursive partitioning algorithm.

Statistical Methods

All survival data were updated to November 1991. A recursive partitioning technique was used to establish prognostic groups. Recursive partitioning is a method of building decision trees to model predictors (*13*). The entire data set was considered as the primary node. Given any node in the tree, the product-limit estimate (*14*) of the survival function was computed for each variable within that node (*15*). The node was split if the modified Wilcoxon statistic was significant for any variable beyond the .05 probability level (*16,17*); the significance level was adjusted for the number of multiple comparisons (*18,19*). The Wilcoxon statistic was used instead of the logrank statistic because of its greater power when hazard ratios between prognostic factors decrease substantially over time, as is the case among malignant glioma patients. Each splitting resulted in the definition of two homogeneous subgroups with respect to survival outcome. Only patients with complete data for a particular variable were used to define a particular split. Terminal nodes were defined as those with fewer than 25 patients or when no possible partitions exceeded the adjusted minimum chi-square value.

Terminal node populations were tested by the modified Wilcoxon test to determine whether any two groups were similar enough in survival to be merged. This final classification would be made by "amalgamating" terminal node subsets with a similar survival profile into distinct classes.

A stepwise Cox proportional hazards model was also performed on this database using the 25 variables common to all three clinical trials (*20*). This model tested whether the proportionality of the hazards (death rates) between two groups of a covariate remained constant. Without such constancy (i.e., the death rate ratio of men to women must be constant), the assumptions of the Cox model may be spurious.

Results

Patient and Treatment Demographics

Of the 1743 patients enrolled in these studies, 1578 were sufficiently evaluable for inclusion in this analysis. Table 2 lists the patient and tumor-related characteristics of these patients pertinent to this study. Tumor size was less than 5.0 cm in 40% of patients, and 82% had GBM histology. Seventy-three percent of all patients had a Karnofsky performance status of 70 or greater, and 86% had a neurologic functional class of 1 or 2. Nearly two thirds of patients were 50 years old or older. Among the 13 neurologic signs and symptoms evaluated, the most commonly identified deficits were disturbances in motor function (53%), altered mental status (43%), headache (39%), and memory disturbance (38%). Table 3 lists the treatment-related characteristics, with 80% of patients undergoing either a partial or total resection and 75% of patients receiving carmustine chemotherapy.

Table 2. Patient and tumor-related characteristics

Variable	% of assessable patients
Age, y	
<40	17
40-49	17
50-59	32
≥60	34
Gender	
Men	63
Women	37
Race	
White	92
Other	8
Symptom duration, mo	
<2	38
2-4	36
>4	26
Neurological class	
1 (Work)	42
2 (Home)	44
3 (Hospital)	14
Karnofsky performance status	
<70	27
70-80	39
90-100	34
Tumor size, cm	
<5.0	40
≥5.0	60
Tumor histology	
GBM	82
AAF	18
Tumor location	
Frontal	44
Parietal	22
Temporal	30
Other	4

Recursive Partitioning Analysis: First Node

With the use of the modified Wilcoxon test for the entire group, the most significant split was by age, with age 50 as the most prominent break point ($P<.000001$; age was partitioned by decade of life). The median survival time

Table 3. Treatment-related characteristics

Characteristic	% of assessable patients
Extent of surgery	
Total resection	20
Partial resection	60
Biopsy	21
Total RT dose, Gy	
≤54.4	32
54.5-59.9	26
60-72.0	24
>72.0	17
RT fraction size, Gy	
1.2	26
>1.2	74
Interfraction interval (for RT two times daily), hours	
<4.5	36
≥4.5	63
Systemic agents used	
Carmustine	75
Semustine and/or dacarbazine	9
Misonidazole	9

(MST) of the entire group was 11.3 months, and the MSTs for the 541 patients under age 50 and the 1037 patients over 50 were 18.0 and 8.8 months, respectively. Of the 58 individual modified Wilcoxon tests performed on the entire patient group, 35 achieved a significance level (i.e., $P<.05$) even when adjusted for multiple comparisons. These univariate results included a survival difference according to Karnofsky performance status, tumor histology, neurologic class, and mental status. Among these factors are four significant treatment-related variables associated with better survival: more extensive surgery, an RT dose received in excess of 54.4 Gy, treatment with carmustine, and treatment with semustine and dacarbazine (P = .00006, .00016, .00025, and .00028, respectively).

Recursive Partitioning Analysis: Patients Under Age 50

Among the 541 patients under age 50, the most significant split was by histology, with an MST of 49.4 months for the 172 AAF patients and 13.7 months for the 324 GBM patients ($P<.000001$). Only normal versus abnormal mental status created an additional split among the AAF patients under age 50, with MSTs of 18.4 and 58.6 months, respectively. The GBM patients under age 50 were split only by Karnofsky performance status, with MSTs of 17.6 months for those with a Karnofsky performance status of 90-100 and 10.7 months for those with a Karnofsky performance status of less than 90 (Fig. 1 and Table 4).

Recursive Partitioning Analysis: Patients Over Age 50

The 1037 patients age 50 and older were first split by Karnofsky performance status at 70 or more versus less than 70, with MSTs of 10.3 and 5.3 months, respectively. Among the 330 patients with a Karnofsky performance status of less than 70, the terminal nodes were partitioned between those with mental status changes (MST, 4.7 months) and those without identified mental status changes (MST, 8.1 months).

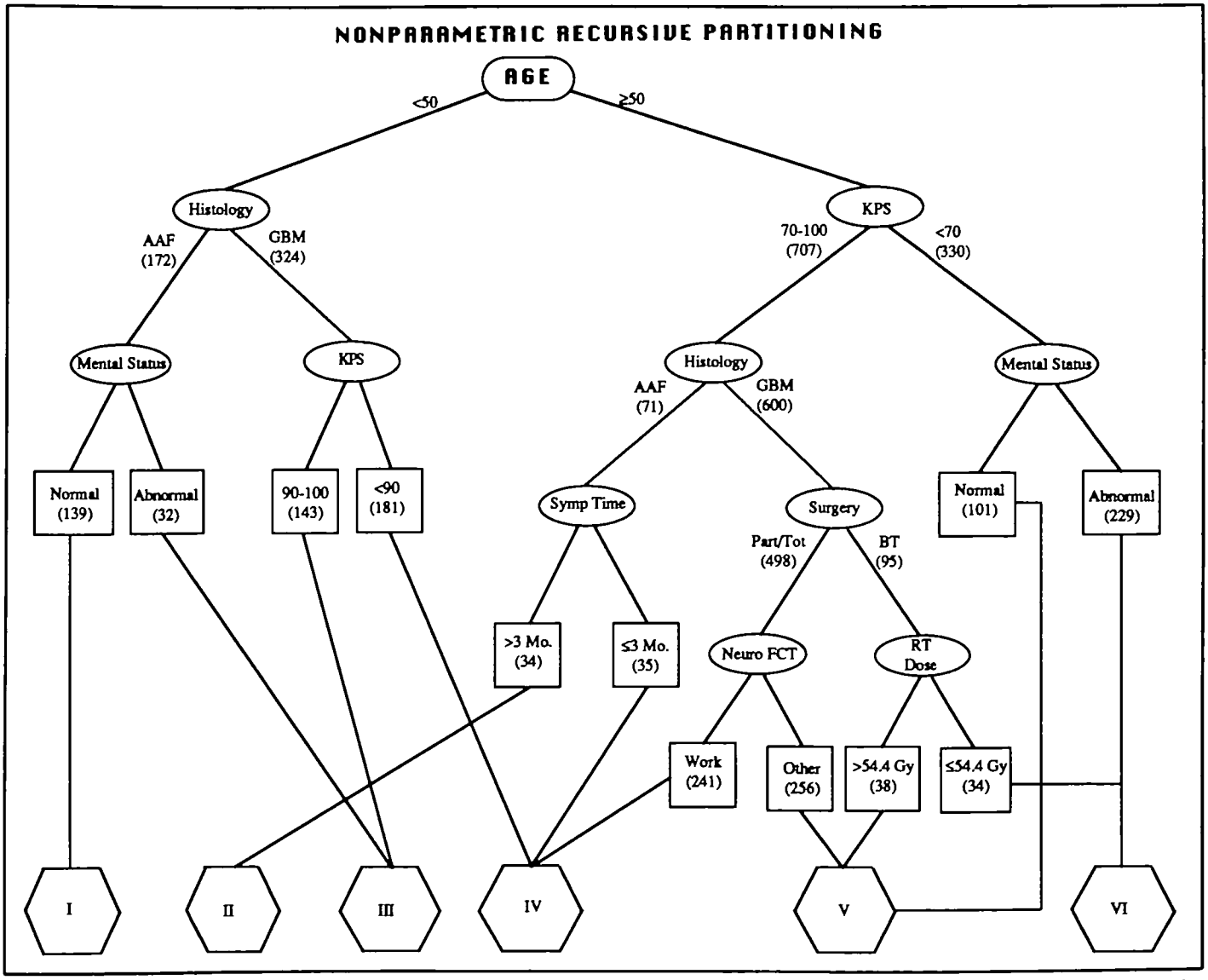

Fig. 1. Results of the recursive partitioning analysis and amalgamation displaying the 12 terminal nodes and their amalgamation into six classes. KPS = Karnofsky performance status; BT = biopsy; Neuro FCT = neurologic function.

Table 4. Survival outcome for patients under age 50 by terminal node

	No. of patients*	Median survival, mo	25% survival, mo
AAF			
Normal mental status	139	58.6	121.0
Abnormal mental status	32	18.4	34.1
GBM			
Karnofsky performance status ≥90	143	17.6	33.5
Karnofsky performance status <90	181	10.7	17.7

*Complete information was available for 495 of the 541 patients.

Histology split the 707 patients with a Karnofsky performance status of 70 or more, with MSTs of 21.7 months for the 71 patients with AAF and 9.7 months for the 600 GBM patients. These AAF patients were divided into the terminal nodes by the duration of symptoms. MSTs were 37.5 and 11.2 months and favored patients with more than 3 months of symptoms. The 600 GBM patients were divided by extent of surgery, with MSTs of 10.3 months for the 498 undergoing partial or total resection and 6.2 months for those undergoing biopsy. The biopsied patients were split by RT dose received, with the break point at 54.4 Gy (MST, 8.3 versus 4.3 months). Finally, patients with more extensive surgery were divided into terminal nodes by neurologic functional classification, with an MST of 11.4 months for class 1 patients and 9.2 months for class 2 and 3 patients (Fig. 1 and Table 5).

Recursive Partitioning Analysis: Overall

A total of 12 terminal nodes was created, ranging in size from 32 to 256 patients. The MSTs of these groups range from 4.3 months (for the GBM patients over age 50 with a Karnofsky performance status ≥70 and a "biopsy only" tumor receiving ≤54.4 Gy) to 58.6 months (for AAF patients under age 50 without mental status changes). The survival results of all 12 terminal groups are displayed in Tables 4 and 5.

Table 5. Survival outcome for patients age 50 and older by terminal node

	No. of patients*	Median survival, mo	25% survival, mo
	Karnofsky performance status ≥70		
AAF			
Symptoms >3 mo	34	37.5	66.3
Symptoms ≤3 mo	35	11.2	22.5
GBM			
Partial or total resection "Work" status	241	11.4	15.6
Partial or total resection "Home" or "hospital" status	256	9.2	13.8
Biopsy only RT >54.5 Gy	38	8.3	13.8
Biopsy only RT ≤54.4 Gy	34	4.3	6.8
	Karnofsky performance status <70		
Mental status			
Normal	101	8.1	13.1
Abnormal	229	4.7	9.1

*Complete information was available for 968 of the 1037 patients.

Amalgamation

Although the recursive partitioning method ensures that right and left terminal nodes from the same parent are significantly different, it is possible that terminal nodes from the distinct parents may have similar survival profiles. This possibility was tested among the 12 terminal nodes by the modified Wilcoxon test in order to determine whether sufficiently homogeneous outcome existed to merit merging selected subgroups. As shown in Fig. 1, the 12 terminal nodal groups were amalgamated into six classes (designated by Roman numerals), ranging in size from 34 to 457 patients. The 2-year survival rates of these patient classes ranged from 4% to 76% (Fig. 2 and Table 6).

Cox Model

The Cox proportional hazards model requires complete data for all variables, and only 751 of 1578 patients (48%) had complete data on all 25 variables examined. Eight of 25 variables were significantly predictive of survival among those 751 cases; they are histology, age, neurologic function, prior surgery, mental status, time from first symptom, motor deficit, and memory lag. There were 1396 patients with complete data on those eight covariates, and in a Cox model on that subset, memory lag was not significant at the .05 probability level. The same 1396 patients were then examined by the Cox model for those eight variables plus the four additional covariates for which these patients had

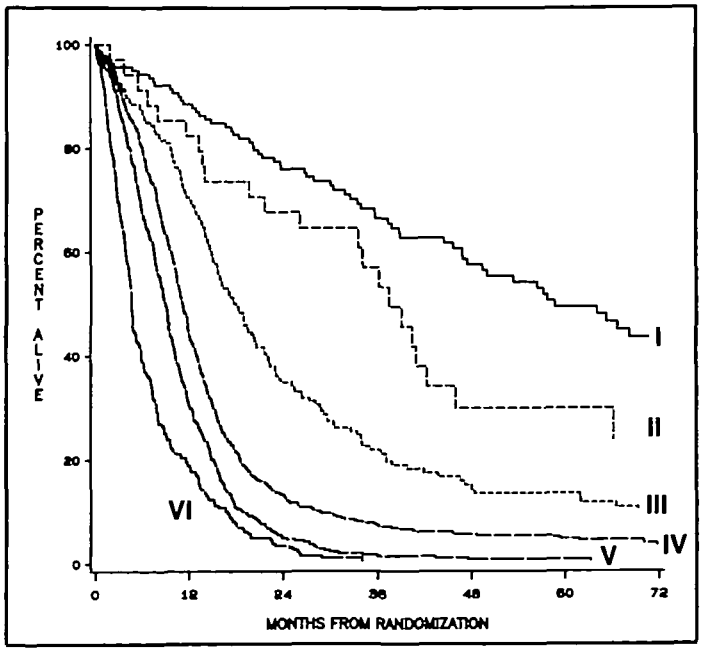

Fig. 2. Survival of the six patient classes created by the recursive partitioning and amalgamation technique.

Table 6. Survival by patient class

Class (No. of patients)	Median survival, mo	2-year rate, %
I (139)	58.6	76
II (34)	37.4	68
III (175)	17.9	35
IV (457)	11.1	15
V (395)	8.9	6
VI (263)	4.6	4

complete data (gender, treatment with carmustine, speech impairment, and performance status). Eleven of 12 covariates were significant, with only speech impairment not achieving significance.

Discussion

The goal of this statistical analysis of an existing malignant glioma database was to increase our understanding of the relative influence that specific variables have on patient outcome. While this study confirms the importance of age, histology, and performance status among these patients, several additional observations have been made that might not have been possible with other statistical approaches. The recursive partitioning technique employed in this analysis allows for an exploratory approach to a large number of variables without requiring guidance as to the most important interactions (*21*). Examination of the hazards (death rates) within prognostic groups, such as the GBM patient population, revealed a nonconstant proportionality, a feature which violates the underlying assumption of constant proportionality of the proportional hazards model of Cox. The effect of this lack of constancy on the validity of a Cox model remains difficult to determine. The observation that 11 of 12 variables tested by the Cox model in the present analysis achieved significance underscores the difficulty in using this model to discriminate the relative importance of prognostic factors in patient subgroups. The Cox model also requires specification of all interactions, while the recursive partitioning technique can utilize cases without complete data. In this study, 1578 patients were used in the recursive partitioning approach, compared with 1396 patients in the Cox model.

The 12 terminal node patient groups and the six classes created through amalgamation can be valuable in future clinical research in several ways. Among the most favorable patient subsets (classes I and II), future clinical trials should use the extended survival rates (MSTs of 59 and 37 months, respectively) achieved in these three trials during the 1970s and 1980s with external beam RT with or without chemotherapy as the standard against which outcomes with investigational approaches should be compared. It is worth restating that the patients in classes I and II represent 11% of the entire database and have a 2-year survival rate of over 70%. The encouraging results from certain institutional studies may, in part, be due to the inclusion of a large number of such favorable patients. A recent example may be found in the report on a phase II experience with a radiosurgery boost in newly diagnosed malignant glioma patients by Loeffler et al. (*10*) in which the MST exceeded 2 years. In that trial, 38% of the 37 malignant glioma patients had AAF tumors, the median age was 51, and the median Karnofsky performance status was 85. Many of these patients would probably meet the criteria of class I or II as defined in this article, and an appropriate historical comparison for such a trial should acknowledge the extended survival of such patients seen with standard therapy.

For the substantial number of patients with intermediate prognosis (classes III and IV), the MSTs of 11 and 18 months represent the disappointing results upon which current neuro-oncology research should attempt to improve. Of note is the fact that the statistical difference in survival between classes III and IV would not have been accounted for by the stratifying variables of age, histology, and performance status currently employed in cooperative group malignant glioma trials (*22*).

The poor prognosis patients in classes V and VI account for 45% of the patients enrolled in these trials, and the MSTs of 8.9 and 4.6 months and 2-year survival rates of 6% and 4%, respectively, raise important philosophical issues regarding the most appropriate treatment approach for such patients. It is likely that these studies underrepresent this unfavorable patient cohort, in part because of the upper age limit of 70 in these trials and also because of the recent increase in the incidence of brain tumors among the elderly (*23*). The brief survival of these patients following a 6- to 7-week course of cranial RT and long-term chemotherapy, particularly in class VI, should encourage further trials with short courses of accelerated fractionation RT as well as a supportive care-only arm (*24,25*). Inclusion of such patients in a trial designed to seek improvement in the median survival of all malignant glioma patients may obscure the potential benefit of aggressive therapy for more favorable patients.

The notable survival differences among terminal nodal groups and patient classes would suggest that treatment approaches and clinical trial design for adult malignant glioma patients be tailored to several more homogeneous patient subgroups. Such an approach is already in place in the Brain Tumor Cooperative Group, within which current trials are designed for either brachytherapy-eligible or brachytherapy-ineligible patients (*26*), and in the Brain Tumor Research Center at the University of California at San Francisco, which is currently conducting independent trials for GBM and AAF patients (*27*). The Brain Tumor Research Center has separated GBM and AAF patients into independent trials because of a lack of apparent benefit of brachytherapy for AAF patients (*9*). While the survival of the 268 AAF and 1206 GBM patients in the RTOG trials analyzed here differs significantly, other pretreatment and treatment-related variables are also equally influential in the present analysis. The development of independent research programs for AAF and GBM patients must allow for consideration of these other important variables.

The only treatment-related variables that partitioned patients in this recursive analysis were extent of surgery and RT dose delivered. The split by extent of surgery occurred

among the 600 GBM patients over age 50 with a good performance status (Karnofsky performance status 70-100), and the split by RT dose was among the subset of this group receiving a biopsy only. Since 84% of patients on these three studies received chemotherapy, this database may be somewhat limited in its ability to determine the value of chemotherapy. Any potential benefit of either higher doses of RT or chemotherapy may be obscured by the power of the pretreatment variables to influence patient survival. Newer investigative therapies would be expected to substantially influence survival only if appropriate patient subgroups can be identified.

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