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Joint NCCTG and NABTC prognostic factors analysis for high-grade recurrent glioma

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The purpose of this study is to determine prognostic factors in patients with high-grade recurrent glioma for 3 outcome variables (overall survival, progression-free survival [PFS], and PFS rate 6 months after study registration [PFS6]). Data from 15 North Central Cancer Treatment Group (NCCTG) trials ($n = 469$, 1980–2004) and 12 North American Brain Tumor Consortium (NABTC) trials ($n = 596$, 1998–2002) were included. Eighteen prognostic variables were considered including type of treatment center (community/academic) and initial low-grade histology (yes/no). Recursive partitioning analysis (RPA), Cox proportional hazards, and logistic regression models with bootstrap resampling were used to identify prognostic variables. Longer survival was associated with last known grade (Grade) of III, younger age, ECOG performance score (PS) of 0, shorter time from initial diagnosis (DxTime), and no baseline steroid use. Factors associated with longer PFS were Grade III and shorter DxTime. For patients without temozolomide as part of the treatment regimen, the only factor associated with better PFS6 was Grade III, although DxTime was important in RPA and PS was important in logistic regression. Grade was the most important prognostic factor for all three endpoints regardless of the statistical method used. Other important variables for one or more endpoints included age, PS, and DxTime. Neither type of treatment center nor initial low-grade histology was identified as a major predictor for any endpoint.

Keywords: brain tumors, high grade, prognostic factors, recurrent glioma

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There is limited information available on prognostic factors associated with outcomes frequently used to assess the efficacy of experimental therapies for patients with recurrent high-grade gliomas, and current findings are inconsistent. For patients with recurrent gliomas, Wong et al.[1] noted that the histologic diagnosis at study registration (glioblastoma vs anaplastic astrocytoma) was a dominant predictor for response, overall survival (OS), progression-free survival (PFS), and PFS rate 6 months after study registration (PFS6), and prior treatments (≤ 2 vs > 2 surgeries or chemotherapy regimens) and the Karnofsky performance score (KPS) were associated with survival. Carson et al.[2] noted that initial histology (GBM vs all other), age, KPS, and baseline corticosteroid use were prognostic factors for survival.

This study was designed to utilize data from North Central Cancer Treatment Group (NCCTG) and North American Brain Tumor Consortium (NABTC) prospective clinical trials to determine prognostic factors in patients with high-grade recurrent glioma (GBM, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma) for 3 outcome variables (OS, PFS, and PFS6). Few responses were seen in those trials so predictors of response were not evaluated.

Materials and Methods

Pooled individual patient data from 15 NCCTG and 12 NABTC consecutive trials (Table 1) for recurrent glioma were included. For all 27 trials, each patient's last histologic diagnosis based on the central neuropathology review was determined. Tumors were classified by cell type and grade according to World Health Organization (WHO) criteria. Since glioma patients' histologic grades remain the same or higher at relapse, patients with (a) initial diagnoses of high-grade glioma

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Table 1. Summary of individual studies included in this analysis[a]

Sponsor	Study number	Regimens	Study size	Endpoint
NABTC	97-01	Temozolomide + carmustine	36	PFS6
	97-05	Thymidine + carboplatin	45	Response
	98-01	Irinotecan	64	PFS6
	98-03	Temozolomide + 13-*cis*-retinoic acid	87	PFS6
	99-01	Zarnestra	92	PFS6
	99-04	Temozolomide + thalidomide	44	PFS6
	99-05	Fenretinide	42	PFS6
	99-07	Temozolomide + irinotecan	35	PFS6
	99-08	Imatinib	42	PFS6
	00-01	Gefitinib	50	PFS6
	01-01	Temsirolimus	41	PFS6
	01-03	Erlotinib	18	PFS6
NCCTG	797251	Etoposide vs teniposide	86	Response
	847251	Fludarabine	7	Response
	867202	Interferon-α + difluoromethylornithine	22	Response
	867253	Interferon-α + carmustine	17	Response
	867254	Etoposide + cisplatin	16	Response
	887251	Ifosfamide + sodium 2-mercaptoethane sulfonate	14	Response
	897251	5-Fluorouracil + leucovorin	28	Response
	897252	Amonafide	20	Response
	917251	Mechlorethamine + vincristine + procarbazine	45	Response
	927251	Topotecan	29	Response
	937251	2-Chlorodeoxyadenosine	9	Response
	957253	Dacarbazine	29	Response
	967251	Irinotecan	53	Response
	987254	Pyrazoloacridine + carboplatin	34	Response
	N997B	Temsirolimus	60	PFS6

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; PFS6, progression-free survival rate at 6 months.
[a]All patients on these studies or their designated surrogates signed an approved institutional review board consent form.

plus evidence of progression by computed tomography (CT)/magnetic resonance imaging (MRI) at recurrence, or (b) confirmation of high-grade malignancy at recurrence, or (c) initial diagnoses of low-grade tumor but pathology confirmed high-grade tumor at recurrence were included in this study.

The NABTC data set included 596 patients treated on Phase II trials between February 1998 and December 2002. Some studies included both Phase I and Phase II components. For the purpose of this analysis, all patients who met the eligibility entry criteria for the Phase II component and were treated on the recommended Phase II dose were included even if they were enrolled in the Phase I portion. Patients treated on other Phase I dose levels were excluded.

The NCCTG data set included 583 patients treated on Phase II trials between June 1980 and October 2004. Of those, the 469 patients with last known grade (Grade) of III or IV were included in this analysis. One trial included both a primary and a recurrent brain tumor component, and only patients enrolled on the recurrent component ($n = 86$) were included. Excluded were patients with (a) both initial and recurrent diagnosis of low grade, (b) initial diagnosis of low grade and recurrent diagnosis missing, or (c) no tissue left for regrading when NCCTG switched from the Kernohan system to the WHO grading system in the mid-1990s. Overall, 1065 patients from NABTC and NCCTG were included in this analysis.

Prognostic Factors

We defined 18 patient, disease, treatment, and time-interval variables (Table 2). With the combined data set, we had a sufficient number of patients to evaluate four new factors not usually studied: prior temozolomide (TMZ) use, type of treatment center (academic vs community), number of prior relapses, and initial low-grade histology. No distinction was made as to whether the patients with prior TMZ had received the therapy at the time of initial diagnosis or at the time of progression since it was felt that the primary consideration was whether or not the patients had previously failed TMZ. Since TMZ is currently an approved treatment for recurrent grade-3 tumors and 4 of the 12 NABTC trials included in this report included TMZ as one the treatment agents, we considered TMZ as part of the treatment regimen (current TMZ) as a potential confounding factor and adjusted for its effect in all our analyses.

For some variables, data were missing from some of the studies. Of the 15 NCCTG trials, 12 did not collect baseline anticonvulsant use, 1 did not collect baseline steroid use, 4 did not collect prior nitrosourea use, and none noted prior TMZ use. For some NABTC patients, grade at initial diagnosis was missing.

For some variables, transformations were required to combine the two data sets. KPS (used by NABTC) was translated to ECOG PS (used by NCCTG) using KPS 90–100 = ECOG 0, KPS 70–80 = ECOG 1, and KPS

Table 2. Baseline demographic and clinical characteristics for all patients

Variable	NCCTG (n = 469; No. [%])	NABTC (n = 596; No. [%])	All (n = 1065; No. [%])
Patient			
Age (years) median (range)	52.2 (18.2–81.2)	49.3 (20.2–84.5)	50.9 (18.2–84.5)
Gender			
Male	294 (63)	382 (64)	676 (64)
Female	175 (37)	214 (36)	389 (36)
Race/ethnicity			
White	416 (99)	556 (93)	972 (95)
Nonwhite	6 (1)	40 (7)	46 (5)
Missing	47	0	47
Baseline ECOG performance score			
$\leq$1	278 (59)	565 (95)	843 (79)
$\geq$2	190 (41)	31 (5)	221 (21)
Missing	1	0	1
Year of study entry			
1980–1989	152 (32)	0 (0)	152 (14)
1990–1999	223 (48)	188 (32)	411 (39)
2000–2004	94 (20)	408 (68)	502 (47)
Disease			
Time since initial diagnosis (weeks) Mean (range)	87 (9–1233)	95 (10–814)	91 (9–1233)
Initial grade			
II	35 (8)	55 (11)	90 (9)
III	74 (17)	88 (17)	162 (17)
IV	339 (76)	372 (72)	711 (74)
Missing	21	81	102
Last known grade			
III	90 (19)	159 (27)	249 (23)
IV	379 (81)	437 (73)	816 (77)
Last known histology			
Anaplastic astrocytoma	59 (13)	101 (17)	160 (15)
Anaplastic oligodendroglioma	18 (4)	39 (7)	57 (5)
Anaplastic oligoastrocytoma	19 (4)	19 (3)	38 (4)
Glioblastoma multiforme	341 (74)	437 (73)	778 (74)
Grade IV oligoastrocytoma	26 (6)	0 (0)	26 (2)
Missing	6	0	6
Treatment			
Extent of primary resection			
None	3 (1)	0 (0)	3 (0)
Biopsy	86 (20)	128 (24)	214 (22)
Subtotal resection	216 (51)	245 (47)	461 (48)
Gross total resection	123 (29)	154 (29)	277 (29)
Missing	41	69	110
Baseline steroid use			
Yes	279 (75)	326 (55)	605 (63)
No	92 (25)	270 (45)	362 (37)
Missing	98	0	98
Baseline anticonvulsant use			
Yes	103 (60)	461 (77)	564 (73)
No	70 (40)	135 (23)	205 (27)
Not defined/unknown	296	0	296
Prior chemotherapy			
Yes	388 (83)	459 (77)	847 (80)

Continued

Table 2. *Continued*

Variable	NCCTG ($n = 469$; No. [%])	NABTC ($n = 596$; No. [%])	All ($n = 1065$; No. [%])
No	79 (17)	136 (23)	215 (20)
Missing	2	1	3
Prior nitrosoureas			
Yes	240 (62)	220 (37)	460 (47)
No	149 (38)	376 (63)	525 (53)
Missing	80	0	80
New Factors			
Prior TMZ use			
Yes	NA	292 (49)	292 (49)
No	NA	304 (51)	304 (51)
Type of treatment center			
Academic	131 (28)	596 (100)	727 (68)
Community	338 (72)	0 (0)	338 (32)
Number of prior relapses			
≤ 1	412 (100)	475 (90)	887 (94)
≥ 2	0 (0)	56 (10)	56 (6)
Missing	57	65	122
Initial low-grade histology			
Yes	35 (8)	55 (10)	90 (9)
No	413 (92)	476 (90)	889 (91)
Missing	21	65	86
Current TMZ			
Yes	0 (0)	202 (34)	202 (19)
No	469 (100)	394 (66)	863 (81)

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; TMZ, temozolomide.

60 = ECOG 2. NCCTG did not collect the exact number of relapses, but ≤ 1 prior relapse was an eligibility criterion for most NCCTG trials. Thus, the number of prior relapses was dichotomized to ≤ 1 vs > 1.

Endpoints

OS was defined as the time from the study registration date to the date of death due to any cause. Patients still alive or lost to follow-up were censored at the last follow-up date.

PFS was defined as the time from study registration to the first observation of disease progression or death due to any cause.

All NCCTG patients were evaluated with a neurologic examination and an imaging study (CT or MRI) every 8 weeks while receiving study treatment. The same imaging modality was used consistently to monitor a patient throughout the trial. For all NCCTG trials, tumor progression was determined by a combination of changes in neurologic status, steroid doses, and imaging results. Specifically, progression was defined as $>25\%$ increase in the product of perpendicular diameters of the contrasting lesion or mass for bidimensionally measurable disease, or otherwise unequivocal increase in the size of contrast enhancement or mass effect, or development of new lesions, as agreed upon by both the primary and quality control physicians for evaluable disease (ie, contrast enhancing mass on MRI and/or CT which is not bidimensionally measurable but clearly evaluable for response to therapy). Patients deemed to have a worsened neurological exam on two consecutive evaluations ($\geq$ 4 weeks apart) compared with base were deemed to have disease progression regardless of scan findings. Patients with surgical resection of recurrent tumor were excluded from trial participation unless serial scans revealed further evidence of tumor growth.

All NABTC patients were evaluated with MRI scans and neurological examinations every 8 weeks as well. The primary tool used to determine patient progression was MRI scans. When there was doubt about the MRI scan, a combination of the neurological examination, changes in steroid doses used, and MRI scan was used to make a final determination. For all NABTC studies, progression was defined using the Macdonald criteria. Because the primary endpoint for these studies was PFS6, evaluable (unidimensionally measurable lesions with margins not clearly defined) or measurable (bidimensionally measurable lesions with clearly defined margins) disease was allowed, and patients having a recent resection for progressive tumor were permitted to enroll if that resection indicated the presence of tumor. In the latter situation, there was no requirement that residual tumor be present after resection. Progression was determined by the local institutional investigator and was defined as an increase in tumor

size of 25% or greater for measurable disease and clear worsening, or a −2 response, for evaluable disease. Failure to return for evaluation due to death or deteriorating condition was considered to represent progression.

For this analysis, patients who did not progress on the study were assumed to have progressed at their progression date if it was within 30 days after the off-study date. Otherwise, their PFS was censored at their off-study date. Patients were considered positive for PFS6 if they were known to be alive and progression-free 6 months (26 weeks) after registration.

Statistical Considerations

For each of the endpoints, OS, PFS, and PFS6, a recursive partitioning analysis (RPA) described by Breiman et al.[3] was used to identify the subsets of patients with different outcome distributions. A minimum final node size of 20 was used in the classification and pruning procedure. All prognostic factors were included as possible factors for RPA.

To obtain prognostic models independent of effective treatment, OS and PFS were adjusted for the effect of current TMZ using Cox proportional hazard (Cox PH) models. Predicted values from the Cox PH model were treated as Poisson variables for splitting.[4] For binary endpoint PFS6, RPA was conducted separately for patients who were and were not receiving TMZ in the recurrent trials.

Kaplan–Meier curves were used to estimate the distributions of OS and PFS for the terminal groups defined by RPA, and log-rank tests were used to confirm the differences. Similar analyses were conducted for PFS6 using chi-squared tests. Terminal nodes that did not reach the $P < .01$ criterion in the log-rank test (or chi-squared test) were combined.

All variables selected by RPA to define terminal groups were included in multivariate Cox PH analyses to test for associations with OS or PFS by backward stepwise selection ($P \leq .05$). Because some patients with initial low-grade diagnoses had very long times from initial diagnosis to study registration, the logarithm of time since initial diagnosis (DxTime) was used for the PH analyses to prevent these data points from dominating the analysis. Similar analyses were conducted for PFS6 using multivariate logistic regression ($P \leq .05$).

Bootstrap analyses were used to confirm the significance of the multivariate logistic and Cox PH models. In each bootstrap analysis, 500 samples using sampling with replacement were created, and all variables identified as significant ($P \leq .05$) in at least 350 samples (70%) were considered to be significant prognostic factors.

To look for differences in prognostic factors in patients with Grade III vs Grade IV disease, RPAs were performed separately for patients with Grade III and Grade IV. To assess the sensitivity of the prognostic models to different data sets, above analyses were repeated separately in the NCCTG and NABTC data sets.

Results

Patient Characteristics

Demographic and clinical characteristics for all patients are presented in Table 2. NCCTG and NABTC patients have similar distributions in: age, gender, race, initial grade, last known histology, extent of primary resection, number of prior relapses, and initial low-grade histology. Higher percentages of NCCTG patients had poor performance score (PS), Grade IV, required steroids, received prior nitrosoureas, and had shorter DxTime.

Patient Outcomes

In all 1065 patients, the median OS was 28 weeks and the median PFS was 9 weeks. Overall, 59 patients were censored for progression but not for death, 30 were censored for both progression and death, and 26 were censored for death only. In addition, 866 (81%) had progressed or died within 6 months of study entry, 35 (3%) were censored before 6 months, and 164 (15%) were alive and progression free at 6 months. Data distributions by Grade for the 3 endpoints are shown in Tables 3 and 4.

Prognostic Factors for OS

Prognostic factors for OS based on the pooled data using RPA and Cox PH models are presented in Tables 5 and 6, respectively. Prognostic factors for OS based on individual data sets are presented in Table 7.

For the pooled data, RPA identified 5 groups with substantial survival differences based on 5 variables: Grade, age, PS, DxTime, and baseline steroid use (steroids; Table 5). The most important factors for longer survival were Grade III and PS of 0. Younger age was important for longer OS, but the cut points for Grade III and

Table 3. Data distribution for endpoints (Grade III)

	NCCTG ($n = 90$)	NABTC ($n = 159$)	Total ($n = 249$)	Total (current TMZ = no) ($n = 193$)
Median OS (wk)	40.9	38.9	40.9	38.0
Median PFS (wk)	15.1	10.7	12.0	10.6
% PFS >6 mo	36.7	23.9	28.5	23.8

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; PFS, progression-free survival; OS, overall survival.

Table 4. Data distributions for endpoints (Grade IV)

	NCCTG ($n = 379$)	NABTC ($n = 437$)	Total ($n = 816$)	Total (current TMZ = no) ($n = 670$)
Median OS (wk)	21.6	30.1	25.1	23.4
Median PFS (wk)	8.0	8.3	8.1	7.9
% PFS >6 mo	10.3	12.4	11.4	8.7

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; PFS, progression-free survival; TMZ, temozolomide; OS, overall survival.

Table 5. Prognostic factors for OS: RPA results

Group	Median survival (wk)	*n* (1065)	Variables				
			Grade	Age	PS	DxTime (wk)	Steroids
1	57	47	III	<34			
		85	III	≥34	0		
2	37	117	III	≥34	>0		
		228	IV	<71	0		
3	26	189	IV	<71	>0	< 33	
		142	IV	<71	>0	≥ 33	No
4	19	218	IV	<71	>0	≥ 33	Yes
5	12	39	IV	≥71			

Abbreviations: DxTime, time from initial diagnosis; PS, performance score.

Table 6. Prognostic factors for OS: Cox PH model results

	Grade[a]	Age[a]	PS[a]	Ln (DxTime)	Male	Steroids	Current TMZ[a]
Hazard ratio	1.76	1.02	1.41	1.13	1.17	1.19	0.69
P-value	<.0001	<.0001	<.0001	.006	.03	.03	<.0001

Abbreviations: TMZ, temozolomide; DxTime, time from initial diagnosis; PS, performance score; Cox PH, Cox proportional hazard.
[a]Variables identified as significant (≤.05) in at least 70% of 500 bootstrap samples.

Table 7. Prognostic factors for OS: cross group comparisons by analysis methods

RPA		Cox PH	
NCCTG	NABTC	NCCTG	NABTC
PS	PS	PS	PS
Age	Age	Grade	Grade
DxTime	DxTime		Age
Grade	Steroids		Steroids
	Gender		Gender
			Number of prior relapses
			Current TMZ

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; TMZ, temozolomide; OS, overall survival; DxTime, time from initial diagnosis; PS, performance score; RPA, recursive partitioning analysis; Cox PH, Cox proportional hazard.

Grade IV patients were different: age 34 years for Grade III and age 71 years for Grade IV patients. For Grade IV patients, longer OS was also associated with shorter DxTime and no baseline steroid use.

The 5 variables that were identified by RPA as important prognostic factors, that is, Grade, age, PS, DxTime, and baseline steroid use, plus Gender were included in the Cox PH model backward selection procedures. To adjust for the TMZ effect, the variable current TMZ was also included in the model. All 7 variables were significant in the final Cox model (Table 6). The most important factors for longer survival were Grade III and lower PS. Younger age, shorter DxTime (log), being a female, and no baseline steroid use were important for longer OS as well. When the 4 new factors (prior TMZ, type of treatment center, number of prior relapses, and initial low-grade histology) were added to the final model, none showed significant prognostic effect.

Separate RPAs in the Grade III and Grade IV patients generated the same patient groups as in the pooled data.

Sensitivity analyses conducted using the NABTC and NCCTG data sets separately produced some differences in prognostic models for each analysis method used (Table 7). However, in both data sets, RPA identified PS, age, and DxTime as important, whereas Cox PH analyses identified PS and Grade as important.

Prognostic Factors for PFS

Prognostic factors for PFS based on the pooled data using RPA and Cox PH models are presented in Tables 8 and 9, respectively. Prognostic factors for PFS based on individual data sets are presented in Table 10.

For the pooled data, RPA identified 3 prognostic factors for longer PFS: Grade III, year of study entry <1994, and shorter DxTime. These 3 variables plus 4 additional variables, age, PS, Gender, and baseline steroid use, used by RPA in defining groups with different PFS distributions were included in the Cox PH model backward selection procedures. Current TMZ was included to adjust for its effect. Five variables, Grade, PS, current TMZ, DxTime (log), and year of study entry were significant in the final Cox model (Table 9). The most important factors for longer PFS were Grade III and lower PS. Longer PFS was also associated with shorter DxTime. None of the 4 new factors showed significant prognostic effect for PFS.

Separate RPA in Grade III patients generated the same results as in the pooled data, but selected 2 additional variables, PS and number of prior relapses, as important factors in Grade IV patients.

Sensitivity analyses for individual data sets are reported in Table 10. Both RPA and Cox PH analyses identified DxTime as important for PFS in both data sets. Both methods also identified Grade, PS, and year of study entry as important for the NCCTG data and age as important for the NABTC data.

Prognostic Factors for PFS6

In the pooled data, RPA immediately split the patients with current TMZ = yes from those with current TMZ = no. Prognostic factors for PFS6 in the latter group are presented in Tables 11 and 12.

RPA identified 3 prognostic factors for better PFS6: Grade III, DxTime ≤26 weeks, and year of study entry <1992. These 3 variables plus 5 additional variables (age, PS, Gender, prior chemotherapy, and extent of primary resection) were included in the logistic model. Grade, PS, and year of study entry were significant in the final logistic model (Table 12). Grade III and lower PS were important for better PFS6. None of the 4 new factors showed significant prognostic effect for PFS6.

Separate analyses by Grade generated the same results in the Grade III data as in the pooled data but selected 2 additional variables, type of treatment center and age, as important factors in the Grade IV patients.

Sensitivity analyses in the patients with current TMZ = no (Table 13) found that PS and Grade were selected in both RPA and logistic regression analysis in the NCCTG data but only age was selected in the NABTC data.

Table 8. Prognostic factors for PFS: RPA results

Group	Median PFS (wk)	*n* (1065)	Variables		
			Grade	Year of study entry	DxTime (wk)
1	19	58	III	<1994	
2	10	191	III	≥1994	
		225	IV		< 29
3	8	591	IV		≥ 29

Abbreviations: PFS, progression-free survival; DxTime, time from initial diagnosis; RPA, recursive partitioning analysis.

Table 9. Prognostic factors for PFS: Cox PH model results

	PS[a]	Current TMZ[a]	Grade[a]	Ln (DxTime)[a]	Year of study entry[a]
Hazard ratio	1.28	0.62	1.82	1.17	1.02
P-value	<.0001	<.0001	<.0001	.0004	.008

Abbreviations: TMZ, temozolomide; DxTime, time from initial diagnosis; PS, performance score; Cox Ph, Cox proportional hazard.
[a]Variables identified as significant (≤.05) in at least 70% of 500 bootstrap samples.

Table 10. Prognostic factors for PFS: cross group comparisons by analysis methods

RPA		Cox PH	
NCCTG	NABTC	NCCTG	NABTC
DxTime	DxTime	DxTime	DxTime
PS	Age	PS	Age
Grade	Number of prior relapses	Grade	Grade
Year of study entry		Year of study entry	Current TMZ

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; TMZ, temozolomide; DxTime, time from initial diagnosis; PS, performance score; RPA, recursive partitioning analysis; Cox PH, Cox proportional hazard.

Table 11. Prognostic factors for PFS6 (current TMZ = no): RPA results

Group	% PFS ≥6 mo	*n* (863)	Variables		
			Grade	DxTime (wk)	Year of study entry
1	42	54	III		<1992
2	15	140	III		≥1992
		125	IV	<26.1	
3	5	544	IV	≥26.1	

Abbreviations: PFS6, progression-free survival rate at 6 months; DxTime, time from initial diagnosis; RPA, recursive partitioning analysis.

Table 12. Prognostic factors for PFS6 (current TMZ = no): logistic model results

	Grade[a]	PS[a]	Year of study entry[a]
Odds ratio	0.32	0.63	0.93
P-value	<.0001	.002	<.0001

Abbreviations: PFS6, progression-free survival at 6 months; PS, performance score.
[a]Variables identified as significant (≤.05) in at least 70% of 500 bootstrap samples.

Table 13. Prognostic factors for PFS6: cross group comparisons (current TMZ = no), by analysis methods

RPA		Logistic Regression	
NCCTG	NABTC	NCCTG	NABTC
PS	Age	PS	Age
Grade		Grade	
Age		Year of study entry	
DxTime			
Extent of primary resection			

Abbreviations: NABTC, North American Brain Tumor Consortium; NCCTG, North Central Cancer Treatment Group; PFS6, progression-free survival rate at 6 months; DxTime, time from initial diagnosis; PS, performance score; RPA, recursive partitioning analysis.

Only the NABTC data set included trials where TMZ was part of the treatment regimen and so provided information on patients treated with TMZ at progression (current TMZ). RPA of the NABTC data selected current TMZ for the first split, thus confirming the importance of adjusting for this factor in prognostic factor assessment. For patients with current TMZ, PS was important in RPA and PS and age were important in logistic regression analysis.

Discussion

The primary goal of these 27 clinical trials in recurrent glioma patients was to identify effective treatments that improve patients' PFS, and eventually, extend their OS. Identifying factors unrelated to treatment that predict outcome will allow investigators to better identify effective treatments by distinguishing between study outcome differences related to patient selection and those related to clinical trial treatment.

In the combined data set, Grade was the most important prognostic factor for all three endpoints no matter which statistical analysis was used. These results are consistent with those of Wong and Carson, suggesting that the measure of histologic grade, whether at initial diagnosis or recurrence, is a critical determinant of disease course following tumor recurrence.

PS is consistently associated with OS in all reports thus far. Like Carson but unlike Wong, we identified age as a prognostic variable for OS. Given known differences in genetic alterations based on age,[5,6] as well as potential comorbidities and physiologic effects of aging, this observation is not surprising.

Shorter DxTime was associated with longer PFS and greater PFS6. There are 3 possible explanations for this observation. First, pseudoprogression may occur relatively quickly after completion of radiation therapy. Although the eligibility criteria for all NCCTG and NABTC trials prohibited the entry of patients who had terminated radiation therapy less than 1 month before, it is likely that some patients still had not achieved true tumor progression at the time of study enrollment. Second, shorter DxTime may be related to fewer prior therapies and fewer prior relapses. Indeed, Wong demonstrated that more than two prior treatments predicted shorter OS, and more relapses were associated with poorer survival in the NABTC data set from this analysis. Third, the impact of DxTime may simply reflect differing points of entry into clinical trials along the continuum of disease progression for individual patients. For example, if two patients truly have identical outcomes, the patient whose qualifying progression is identified first may have a perceived longer time to their next progression even if the disease course is the same.

None of the 4 new factors (low grade at initial diagnosis, number of prior relapses, prior TMZ use, and type of treatment center) was identified as a major predictor. The absence of impact of initial diagnosis of low-grade glioma suggests that once patients had transformation to high-grade glioma, characteristics of treatment responsiveness are similar to those diagnosed initially as high-grade glioma. Number of relapses, which was significant for OS in the NABTC data set but was not collected in the NCCTG data set, may provide some additional prognostic information not entirely captured by DxTime. It is noteworthy that prior TMZ was not

associated with outcome after recurrence, since most patients now have received TMZ as a component of adjuvant therapy. Similarly, it is noteworthy that patients selected for clinical trial participation and managed according to trial guidelines had similar outcomes regardless of academic or community practice setting. It is also important to point out that this analysis was limited to outcomes in the clinical trial setting and was not designed to assess referral bias or population-biased differences in outcomes. Such an analysis would require the inclusion of a representative sample of all patients treated in the academic and community settings, not just those enrolled in clinical trials.

It is interesting that year of study entry was a significant prognostic factor for PFS6 and PFS. The cut points were 1992 and 1994, respectively. A possible explanation is that around 1992–1994, MRI replaced CT as the standard medical imaging tool to demonstrate pathological or other physiological alterations in brain tumor patients. Since CT is less sensitive in detecting progression, it is not surprising that patients enrolled in studies conducted with CT monitoring had longer times to progression.

In conducting prognostic factors analyses, it is important to take into account any substantial treatment differences. For instance, current TMZ was significantly associated with all three endpoints in this analysis. Failure to adjust for this factor would result in misleading prognostic models. It is also important to keep in mind that prognostic models may differ based on different data sets, even relatively large ones, and on different analysis methods. For instance, for the NABTC data, baseline steroid use was important for OS and age was important for PFS6 (for current TMZ = no) no matter which method was used. But those results were not confirmed in the NCCTG data. So, even though we utilized identical analytical methods, the results were not identical, likely reflecting that variability in eligibility criteria, definition of data variables, measurements of outcomes, and somewhat heterogeneous cohorts of patients as well as chance may produce differing results.

Molecular or epigenetic features are important prognostic factors in addition to knowledge of patient clinical history. Owing to the difficulties obtaining tissue for recurrent glioma appropriate for assessing these markers, molecular and epigenetic features of the tumor are often not available. On the other hand, clinical prognostic factors are readily available and therefore especially important for evaluation of therapies for treating patients at the time of progression, thus the focus of this paper is on prognostic clinical factors predicting outcome when patients are treated at the time of progression.

Nevertheless, we propose that the careful analysis of these 2 well-characterized cohorts of patients provides strong evidence that future trials should collect and report the significant variables identified, including Grade, age, baseline performance score, and DxTime.

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