Effect of the Addition of Chemotherapy to Radiotherapy on Cognitive Function in Patients With Low-Grade Glioma: Secondary Analysis of RTOG 98-02

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ABSTRACT

Purpose

The addition of PCV (procarbazine, lomustine, and vincristine) chemotherapy to radiotherapy (RT) for patients with WHO grade 2 glioma improves progression-free survival (PFS). The effect of therapy intensification on cognitive function (CF) remains a concern in this population with substantial long-term survival.

Patients and Methods

A total of 251 patients with WHO grade 2 glioma age ≥ 40 years with any extent of resection or age < 40 years with subtotal resection/biopsy were randomly assigned to RT (54 Gy) or RT plus PCV. We observed 111 patients age < 40 years with gross total resection. CF was assessed by Mini-Mental State Examination (MMSE) at baseline and years 1, 2, 3, and 5.

Results

Overall, few patients experienced significant decline in MMSE score. There were no significant differences in the proportion of patients experiencing MMSE score decline between the randomized study arms at any time point. Both study arms experienced a significant gain in average MMSE score longitudinally over time, with no difference between arms.

Conclusion

The MMSE is a relatively insensitive tool, and subtle changes in CF may have been missed. However, the addition of PCV to RT did not result in significantly higher rates of MMSE score decline than RT alone through 5 years of follow-up. Patients in both randomly assigned arms experienced a statistically significant average MMSE score increase over time, with no difference between arms. The addition of PCV chemotherapy to RT improves PFS without excessive CF detriment over RT alone for patients with low-grade glioma.

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INTRODUCTION

Low-grade gliomas (LGGs) are defined by the WHO as grade 1 or 2 primary brain neoplasms.¹ Over the last 15 years, several phase III randomized trials have investigated different paradigms of therapy intensification for this disease.²⁻⁵ These include immediate adjuvant radiation therapy (RT), increased dose of adjuvant RT, and addition of chemotherapy to adjuvant RT. The primary end point of each of these trials was overall survival (OS), but all demonstrated either no difference between arms or a progression-free survival (PFS) benefit without an OS benefit. Patients with LGGs generally have a favorable prognosis, with 5-year OS rates consistently between 60% and 70%. The effect of therapy intensification on cognitive function (CF) remains a concern in this population with substantial long-term survival.

Neurocognitive outcomes after oncologic therapy for a variety of cancer locations and types have been the subject of increasing attention both as a formal study subject and among the lay press and patient population. The term “chemo-brain” has been adopted by patients to describe the potential detrimental effects of chemotherapy predominantly on concentration and short-term memory. Meta-analyses primarily of studies examining local therapy only versus local therapy plus chemotherapy for patients with breast cancer have demonstrated statistically significant chemotherapy-associated CF detriment, primarily in executive functioning, verbal ability, and visuospatial ability, albeit with a relatively small absolute effect size in each of these domains.⁶

RTOG (Radiation Therapy Oncology Group) 98-02 is a prospective phase II/III trial that

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investigated the addition of PCV (procarbazine, lomustine, and vincristine) chemotherapy to RT for patients with WHO grade 2 LGGs.⁵ The initial results of this trial have been published, and the addition of adjuvant PCV chemotherapy was found to provide a PFS benefit, but not an OS benefit, in the intention-to-treat analysis. However, the effect of therapy intensification through the addition of PCV to RT on cognitive functioning has not been well studied in this patient population.

In an attempt to answer this question, CF evaluations were collected prospectively for 362 patients with LGGs as part of the RTOG 98-02 trial. CF was measured using the Folstein Mini-Mental State Examination (MMSE), an extensively used and well-validated screening test for dementia and cognitive impairment.⁷⁻¹⁰ The purpose of this secondary analysis was to characterize the pattern of CF changes after therapy and determine if there is a detrimental effect on CF associated with the addition of chemotherapy to RT versus RT alone for patients with LGGs.

PATIENTS AND METHODS

Patients

In this analysis, 362 patients were enrolled onto a prospective, multicenter clinical trial (RTOG 98-02) investigating the effects of observation alone for low-risk LGG and the addition of PCV chemotherapy to RT for high-risk LGG. The phase II observation arm for low-risk LGG included 111 patients; the phase III component for high-risk LGG included 251 randomly assigned patients. Detailed information on primary study outcomes has been previously published.^{5,11} Patients were considered high risk and eligible for the phase III study if they had histologically confirmed grade 2 astrocytoma, oligodendroglioma, or mixed oligoastrocytoma based on central pathology review. Other eligibility criteria included age 18 to 39 years with less than gross

total resection or age ≥ 40 years with any extent of resection, Karnofsky performance status $\geq 60\%$, neurologic functioning score ≤ 3 , and supratentorial location. Eligibility criteria for the low-risk phase II arm were largely the same, except all patients were required to be age 18 to 39 years with a neurosurgeon-defined gross total resection.

Treatment

All patients in the high-risk phase III study were treated with the same RT regimen. The radiation dose was 54 Gy administered in 30 fractions of 1.8 Gy each (prescribed to isocenter) over 6 weeks. Patients randomly assigned to receive chemotherapy were treated with six cycles of postradiation procarbazine (60 mg/m² orally per day on days 8 to 21 of each cycle), lomustine (110 mg/m² orally on day 1 of each cycle), and vincristine (1.4 mg/m² [maximum 2 g] intravenously on days 8 and 29 of each cycle). The cycle length was 8 weeks. Patients in the low-risk phase II study were observed after surgery until time of progression. Salvage treatment at the time of tumor progression was permitted on an individual basis.

Patient Evaluation and Follow-Up

After completion of RT, patients were observed with serial clinical evaluations and magnetic resonance imaging scans every 4 months for 1 year, every 6 months for 2 years, and every year thereafter. The follow-up schedule was the same for patients enrolled onto the low-risk phase II arm, except intervals were based on the date of study enrollment. The MMSE was collected as part of the patient clinical evaluation at each study follow-up date and discontinued at the time of tumor progression.

Statistical Considerations

Key evaluations were designated as baseline and years 1, 2, 3, and 5 from the start of RT. Follow-up information, including MMSE score, was included in the analysis if the date of patient evaluation was within ± 60 days of the year-1 specified time, ± 90 days of the year-2 specified time, and ± 120 days for the year-3 and -5 specified time. At each key evaluation, patients were classified as either experiencing progression or not according to whether they met the criteria for disease progression by the end of the interval. Patients were included in the analysis until the time of progression, meaning MMSE scores

Fig 1. CONSORT diagram of the randomized phase III component of RTOG (Radiation Therapy Oncology Group) 98-02. MMSE, Folstein Mini-Mental State Examination; NA, not assessed; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

Table 1. Characteristics of Randomly Assigned Patients From RTOG 98-02

Characteristic	RT Alone (n = 126)	RT + PCV (n = 125)
Age, years		
Median	40	41
Range	22-79	18-82
Median tumor size, cm	5	4.7
KPS 90% to 100%, %	74	75
Gross total resection, %	9	11
Histology, %		
Astrocytoma	23	29
Oligodendroglioma	45	40
Mixed astrocytoma/oligodendroglioma	32	31
Enhancement	60	65

Abbreviations: KPS, Karnofsky performance status; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group.

were included through the key evaluation preceding the evaluation documenting progression. This was done to minimize the potential confounding effect of tumor progression on the association of intensified LGG therapy and CF change.¹²

Significant MMSE score decline was defined as a decrease of > three points⁸; significant gain was defined as an increase of > three points; no change was defined as any MMSE score change ≤ three points. All MMSE score changes were a comparison of baseline MMSE score and key evaluation MMSE score. The primary analysis was a comparison between the randomly assigned arms of the phase III component (RT v RT plus PCV). Patients were categorized by baseline MMSE score (< 27 and 27 to 30) because those with baseline MMSE score > 26 were by definition not eligible for a significant MMSE gain because of a maximum MMSE score of 30 (ceiling effect), and patients with baseline MMSE score < 27 were in the lowest quartile of MMSE scores compared with an age-matched reference group.¹³ Proportions were compared using the χ^2 test of independence for categorical variables. Fisher's exact test was used when expected counts were ≤ five. With MMSE score as a continuous variable, average MMSE score over time was analyzed using a linear mixed-effects model, with intercept and coefficients of time (linear and quadratic terms) as random effects and treatment and other prognostic baseline characteristics as fixed effects.¹⁴ An interaction term between treatment arm and time was used to assess if mean MMSE score change over time was statistically different between the two randomly assigned arms, accounting for the effects of known prognostic factors. The final multivariable model was determined based on clinical relevance, results from univariable models, and

likelihood-based model selection criteria. For the PFS and OS end points, the Kaplan-Meier method¹⁵ was used to estimate the rates, and the log-rank test¹⁶ was used to compare differences between groups. OS was defined as the interval from random assignment to death resulting from any cause, and PFS was defined as the interval from random assignment to progression or death, whichever occurred first. The significance threshold was a *P* value < .05. All analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

The patient characteristics and CONSORT diagram (Fig 1) for the randomly assigned arms of the phase III component of RTOG 98-02 have been previously published.⁵ In brief, 251 patients were randomly assigned, 126 to the RT alone arm and 125 to the RT plus PCV arm. Patient and tumor characteristics were well balanced between arms (Table 1). Baseline MMSE score was collected for 238 (95%) of 251 randomly assigned patients, and these patients made up the population for the primary analysis. Baseline MMSE score was collected for 105 (95%) of 111 patients in the observation phase II arm. At each key evaluation, the percentage of patients with MMSE score collected of the total eligible patient population (defined as patients alive and not experiencing progression by that key evaluation) was calculated. There were no significant differences in compliance rates between arms at any key evaluation time point except for year 1 (Table 2). To detect potential selection bias in MMSE response, patient and tumor characteristics for eligible patients with and without an MMSE score at all key evaluation time points were compared. Results of the year-1 comparison are listed in Table 3. There was no significant difference in any patient or tumor characteristic between those with an MMSE score available and those eligible patients without one at any time point except for patients with an MMSE having a higher proportion of right-sided tumors versus those without at year 2 (57% v 39%; *P* = .005). To detect potential selection bias for eligible patients (patients alive and without progression) between treatment arms, patient and tumor characteristics for eligible patients between the RT and RT plus PCV randomly assigned arms at all key evaluation time points were compared. Results of the year-1 comparison are listed in Table 4. There was no significant difference in any patient or tumor characteristic for eligible patients between the randomly assigned arms at any

Table 2. MMSE Assessment Compliance

Treatment Arm	Baseline		Year 1		Year 2		Year 3		Year 5	
	No.	%	No.	%	No.	%	No.	%	No.	%
Observation										
Expected*	111		97		89		77		61	
Received	105	95	62	64	49	55	44	57	27	44
RT alone										
Expected*	126		99		89		75		54	54
Received	122	97	74	75	60	67	48	64	22	41
RT + PCV										
Expected*	125		91		85		81		72	
Received	116	93	51	56	50	59	43	53	25	35
χ^2 <i>P</i>		.36		.004		.51		.10		.11

Abbreviations: MMSE, Folstein Mini-Mental State Examination; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

*Patients alive and without progression at key evaluation.

Table 3. Characteristics of Eligible Patients With and Without MMSE at Year 1

Characteristic	MMSE (n = 187)		No MMSE (n = 100)		P*
	No.	%	No.	%	
Age, years					.32
< 40	124	66	72	72	
≥ 40	63	34	28	28	
Sex					.81
Male	102	55	56	56	
Female	85	45	44	44	
KPS, %					.32
60-80	39	21	16	16	
90-100	148	79	84	84	
Extent of surgery					.46†
Biopsy	52	28	32	32	
Partial resection	59	32	26	26	
Total resection	76	41	42	42	
Neurologic function					.09‡
No symptoms	89	48	58	58	
Minor symptoms	83	44	38	38	
Moderate (fully active)	11	6	3	3	
Moderate (not fully active)	4	2	1	1	
Histology					.28§
Astrocytoma	36	19	16	16	
Oligodendroglioma	94	50	44	44	
Oligoastrocytoma (astrodominant)	19	10	22	22	
Oligoastrocytoma, (astro = oligo)	8	4	2	2	
Oligoastrocytoma (oligodominant)	30	16	16	16	
Lateralization of tumor					.15
Right	99	53	44	44	
Left	85	45	50	50	
Bilateral	1	1	6	6	
Unknown	2	1	0	0	
Contrast enhancement on preoperative scan					.47
Present	102	55	59	59	
Absent	85	45	41	41	

NOTE. Percentages may not sum to 100% because of rounding.
Abbreviations: MMSE, Folstein Mini-Mental State Examination; KPS, Karnofsky performance status.

* χ^2 test.

†Biopsy v other.

‡No symptoms v other.

§Oligodendroglioma and oligoastrocytoma (oligodominant) v other.

||Right v left/bilateral.

Table 4. Characteristics of Eligible Patients With MMSE by Treatment Arm at Year 1

Characteristic	RT alone (n = 74)		RT + PCV (n = 51)		P*
	No.	%	No.	%	
Age, years					.64
< 40	38	51	24	47	
≥ 40	36	49	27	53	
Sex					.09
Male	46	62	24	47	
Female	28	38	27	53	
KPS, %					.66
60-80	20	27	12	24	
90-100	54	73	39	76	
Extent of surgery					.94†
Biopsy	31	42	21	41	
Partial resection	36	49	23	45	
Total resection	7	9	7	14	
Neurologic function					.16‡
No symptoms	27	36	25	49	
Minor symptoms	43	58	19	37	
Moderate (fully active)	2	3	6	12	
Moderate (not fully active)	2	3	1	2	
Histology					.96§
Astrocytoma	11	15	13	25	
Oligodendroglioma	38	51	25	49	
Oligoastrocytoma (astrodominant)	9	12	3	6	
Oligoastrocytoma (astro = oligo)	5	7	1	2	
Oligoastrocytoma (oligodominant)	11	15	9	18	
Lateralization of tumor					.96
Right	35	47	25	49	
Left	36	49	26	51	
Bilateral	1	1	0	0	
Unknown	2	3	0	0	
Contrast enhancement on preoperative scan					.33
Present	47	64	28	55	
Absent	27	36	23	45	

NOTE. Percentages may not sum to 100% because of rounding.
Abbreviations: KPS, Karnofsky performance status; MMSE, Folstein Mini-Mental State Examination; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.

* χ^2 test.

†Biopsy v other.

‡No symptoms v other.

§Oligodendroglioma and oligoastrocytoma (oligodominant) v other.

||Right v left/bilateral.

time point. Patient and tumor characteristics for patients with an MMSE score < 27 or from 27 to 30 at baseline are listed in Appendix Table A1 (online only). The subset with MMSE score from 27 to 30 had significantly higher proportions of patients who were age < 40 years, were women, had Karnofsky performance status from 90% to 100%, had no or minor neurologic symptoms, and had right-sided tumor location.

Change in MMSE Score Over Time

Categorical change in MMSE score by baseline MMSE score group is listed in Appendix Table A2 (online only). Because of the small patient and event numbers, inferential statistics were not performed. Significant MMSE score decline was a rare event regardless of baseline MMSE score, and > 50% of patients with baseline MMSE

score < 27 did experience/sustain significant MMSE score gain at each key evaluation time point.

Categorical change in MMSE score by treatment arm is summarized in Table 5. Inferential statistics were comparisons between the randomly assigned RT and RT plus PCV arms. The low-risk observation results are included, but it must be noted that these patients were not randomly assigned and, by definition of their low-risk status, had more favorable prognostic characteristics. No patient in the observation arm experienced significant MMSE score decline, with the vast majority experiencing no change in MMSE score. MMSE decline was a rare event in either of the randomized arms as well, with the overwhelming majority of patients experiencing no change in MMSE score over time. There was no significant difference in the proportion of

Table 5. Categorical Change in MMSE Score by Treatment Arm

MMSE Score Change*	Observation		RT Alone		RT + PCV		P†
	No.	%	No.	%	No.	%	
Year 1	n = 62		n = 74		n = 51		.99
Decline	0	0	5	7	2	4	
No change	60	97	66	89	44	86	
Gain	2	3	3	4	5	10	
Year 2	n = 49		n = 60		n = 50		.5
Decline	0	0	1	2	0	0	
No change	49	100	58	97	43	86	
Gain	0	0	1	2	7	14	
Year 3	n = 44		n = 48		n = 43		.5
Decline	0	0	1	2	0	0	
No change	44	100	45	94	38	88	
Gain	0	0	2	4	5	12	
Year 5	n = 27		n = 22		n = 25		.99
Decline	0	0	0	0	2	8	
No change	27	100	21	96	20	80	
Gain	0	0	1	5	3	12	

NOTE. Percentages may not sum to 100% because of rounding.
 Abbreviations: MMSE, Folstein Mini-Mental State Examination; PCV, procarbazine, lomustine, and vincristine; RT, radiation therapy.
 *MMSE decline, > three-point decline; MMSE gain, > three-point gain; MMSE no change, ≤ three-point change.
 †Fisher's exact test performed for decrease v no change/increase, comparing RT-alone and RT + PCV arms.

patients experiencing MMSE score gain, no change, or decline at any of the key evaluation time points between treatment arms.

MMSE score change over time was also analyzed as a continuous variable to increase the sensitivity of detecting change over time between randomly assigned arms as well as to account for the nonindependence of MMSE score over time for individual patients. The multivariable linear mixed-effects model results are listed in Table 6. MMSE score increased over time ($P < .001$) for both randomly assigned arms. There was no difference in MMSE score change over time between randomly assigned arms ($P = .57$). In addition, patients with good neurologic function score ($P = .01$) and right lateralization ($P = .04$) had significantly better MMSE scores over time than those without.

Table 6. Multivariable Linear Mixed-Effects Model for MMSE Score Change Over Time for All Randomly Assigned Patients

Parameter (reference level)	Estimate	SE	P
Time, years	0.58	0.15	<.001
Time ²	-0.08	0.03	.003
RT-alone treatment arm	0.19	0.24	.44
Neurologic function score (minor/moderate symptoms)	0.55	0.21	.01
KPS 60% to 80%	0.27	0.24	.26
Left/bilateral lateralization	0.50	0.24	.04
Male sex	0.24	0.19	.23
Age ≥ 40 years	0.29	0.19	.13
Time × treatment arm	-0.05	0.09	.57
Time × lateralization	-0.16	0.09	.10

Abbreviations: KPS, Karnofsky performance status; MMSE, Folstein Mini-Mental State Examination; RT, radiation therapy.

There were not enough MMSE score decline events to allow investigation of the association between potential baseline characteristic predictors and change in CF. We were also unable to determine if an association existed between tumor progression and CF change because of the lack of MMSE scores available at the time of documented tumor progression.

Disease Progression, Death, and Baseline MMSE Score

The median follow-up time for living patients was 9.7 years. PFS and OS were compared for patients with baseline MMSE score < 27 versus from 27 to 30. Median PFS was 4.4 and 5.8 years, respectively. There was no significant difference in PFS based on baseline MMSE score ($P = .93$). Median OS was 9.5 and 10.1 years, respectively, with no significant difference between groups ($P = .7$).

DISCUSSION

CF has become an increasingly important topic, both in patients with brain tumors as well as in patients with nonbrain malignancies. This issue is especially germane for patients with LGGs. These patients have a long expected survival, with a median OS of 9 to 10 years, which is an extended period of time to potentially manifest neurocognitive toxicity from oncologic therapies. In addition, the major phase III studies that are currently informing our treatment decisions for LGGs have largely been negative for their primary end points, with some demonstrating a PFS benefit without an OS benefit in intention-to-treat analyses.²⁻⁵ The establishment of improved PFS, but with a lack of improvement in OS, makes the decision of whether to adopt a new, more intensive therapy regimen difficult. More information is necessary to make an informed decision, specifically more evidence about the toxicity of therapy versus the toxicity of disease progression/recurrence, to put the benefits of improved PFS into context.

We sought to better inform the decision about intensifying therapy with the addition of PCV chemotherapy to RT by investigating the association between PCV use and CF. When MMSE score gain or decline was analyzed as a categorical variable, it was demonstrated that the vast majority of patients maintained their baseline CF. Significant MMSE score decline was a rare event. Patients who had a baseline MMSE score < 27 were numerically more likely to experience significant MMSE score gain than decline, suggesting that at least some of the baseline deficits in CF caused by the tumor itself can be reversed with effective therapy. However, caution should be used when interpreting these results because of the small patient numbers in the group with MMSE score < 27. Although patient numbers and MMSE compliance did fall over time, there was no indication that more intensive therapy was associated with higher rates of CF decline at any key evaluation time point through 5 years post RT. When MMSE score was analyzed as a continuous variable, it was demonstrated that average MMSE score actually increased over time, albeit with a magnitude of minor clinical significance, again with no significant difference between treatment arms.

It has been previously demonstrated that therapy intensification with higher doses of RT does not have a detrimental effect on CF. Brown et al¹⁷ analyzed MMSE score as a categorical variable for patients enrolled onto an intergroup study, in which patients were randomly assigned to 50.4 versus 64.8 Gy. Their results are similar to those of our study, in that

significant MMSE score decline was a rare event, and the vast majority of patients maintained their baseline CF. There were no differences in CF change detected between the higher-dose and standard-dose arms. RTOG 98-02 was initiated in 1998, and at the time, the standard CF measure employed in RT trials was the MMSE. The MMSE was originally developed and validated as a screening tool for dementia.⁷⁻¹⁰ Although it has been extensively used in RT trials, it has never been validated for use in patients with brain tumors undergoing cranial RT. There is also growing literature that MMSE score, especially when analyzed as a categorical variable, is an insensitive measure. The MMSE can determine accurately if gross CF decline has occurred, but it has poor sensitivity for more subtle neurocognitive changes. A study comparing the MMSE with other neurocognitive tests of specific domains found the MMSE to have a sensitivity of 50%.¹⁸

We attempted to increase the sensitivity of the MMSE as a global measure of CF by analyzing MMSE score as a continuous variable and adjusting for potential confounders. There was no indication of MMSE score decline as a continuous variable in either randomly assigned arm, suggesting at least no major or gross cognitive detriment. The current standard battery of neurocognitive tests is both sensitive and specific for several cognitive domains. However, this battery only began to be widely used after the initiation of RTOG 98-02, with the feasibility study of using these tests for patients with brain tumors in a prospective multi-institutional setting only being published in 2004.¹⁹ Although we acknowledge that a major limitation of this analysis is the use of the MMSE alone as a measure of CF, these data do represent the best available level of evidence as a secondary analysis of a prospective multi-institutional phase III randomized trial.

The study of CF in patients with cancer is becoming an increasingly complex field, and more rigorous analyses will be required in future studies to determine causal relationships. We have attempted to adjust for known prognostic factors such as age, tumor size, and extent of resection, but many other factors play a role in CF. Our data demonstrated that good pretreatment neurologic function and right tumor lateralization were associated with better MMSE score over time. We did not have information on other potentially important factors, including measures of cognitive reserve (eg, detailed education, occupation, and cognitive stimulation information), medication use (eg, antiepileptic, antidepressant, or anxiolytics), or genetic susceptibility factors (eg, apolipoprotein E allele type²⁰).

In conclusion, the MMSE is a relatively insensitive tool that has not been validated in patients receiving cranial RT, and subtle changes

in CF may have been missed. However, the addition of PCV to RT for LGGs did not result in significantly higher rates of MMSE score decline than RT alone through 5 years post RT. Patients in both randomly assigned arms experienced a statistically significant average MMSE score increase over time, with no difference between arms. More sensitive neurocognitive assessments may detect changes not apparent through use of the MMSE alone as a measure of CF.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix**Table A1.** Patient Characteristics by Baseline MMSE Score

Characteristic	MMSE Score < 27 (n = 32)		MMSE Score 27 to 30 (n = 311)		P*
	No.	%	No.	%	
Age, years					.02
< 40	14	44	200	64	
≤ 40	18	56	111	36	
Sex					.02
Male	24	75	165	53	
Female	8	25	146	47	
KPS, %					< .001
60-80	15	47	58	19	
90-100	17	53	253	81	
Prior surgery					.89†
Biopsy	11	34	103	33	
Partial resection	13	41	87	28	
Total resection	8	25	121	39	
Neurologic function					< .001‡
No symptoms	4	13	165	53	
Minor symptoms	17	53	127	41	
Moderate (fully active)	5	16	16	5	
Moderate (not fully active)	6	19	3	1	
Histology					.93§
Astrocytoma	11	34	65	21	
Oligodendroglioma	11	34	139	45	
Oligoastrocytoma (astrodominant)	2	6	49	16	
Oligoastrocytoma (astro = oligo)	0	0	10	3	
Oligoastrocytoma (oligodominant)	8	25	48	15	
Lateralization of tumor					.006
Right	8	25	164	53	
Left	19	59	140	45	
Bilateral	3	9	7	2	
Unknown	2	6	0	0	
Contrast enhancement on preoperative scan					.15
Present	22	69	173	56	
Absent	10	31	138	44	

NOTE. Percentages may not sum to 100% because of rounding.

Abbreviations: KPS, Karnofsky performance status; MMSE, Folstein Mini-Mental State Examination.

* χ^2 test.

†Biopsy v other.

‡No symptoms v other.

§Oligodendroglioma and oligoastrocytoma (oligodominant) v other.

||Right v left/bilateral.

Table A2. Categorical Change in MMSE Score by Baseline MMSE Score

MMSE Score Change*	MMSE Score < 27		MMSE Score 27 to 30	
	No.	%	No.	%
Year 1	n = 17		n = 170	
Decline	0	0	7	4
No change	7	41	163	96
Gain	10	59	—	—
Year 2	n = 10		n = 149	
Decline	0	0	1	1
No change	2	20	148	99
Gain	8	80	—	—
Year 3	n = 11		n = 124	
Decline	0	0	1	1
No change	4	36	123	99
Gain	7	64	—	—
Year 5	n = 7		n = 67	
Decline	1	14	1	2
No change	2	27	66	99
Gain	4	57	—	—

NOTE. Percentages may not sum to 100% because of rounding.

Abbreviation: MMSE, Folstein Mini-Mental State Examination.

*MMSE decline, > three-point decline; MMSE gain, > three-point gain; MMSE no change, ≤ three-point change.