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The 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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By

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M.D., University of Florida, 2008

B.A., University of Florida, 2005

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Abstract

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

By Roshan S. Prabhu, MD

Purpose: The addition of PCV (procarbazine, CCNU, vincristine) chemotherapy to radiotherapy (RT) for patients with WHO grade II glioma improves progression free survival (PFS), without a significant improvement in overall survival (OS). The effect of therapy intensification on cognitive function (CF) remains a concern in this population with substantial long term survival.

Methods: Two hundred fifty-one patients with World Health Organization (WHO) grade II glioma and age >40 with any extent of resection, or age < 40 with subtotal resection/biopsy were randomized to RT (54 Gy) or RT + PCV. One hundred eleven patients with age <40 and gross total resection were observed on a related phase II study. CF was assessed by mini-mental status exam (MMSE) at baseline and years 1, 2, 3, and 5. The primary analysis was between the RT and RT + PCV randomized arms. All MMSE score changes were comparisons between the key evaluation score to baseline MMSE score. The proportion of patients with MMSE decline (defined as score decrease >3 points) as a categorical variable was analyzed using the Fisher exact test. MMSE score change over time as a continuous measure was analyzed using linear mixed effects model, utilizing both univariate and multivariate models to adjust for potential confounding variables.

Results: Overall, very few patients experienced significant decline in MMSE score, with a median follow-up time of 9.7 years for alive patients. There were no significant differences in the proportion of patients experiencing MMSE decline between study arms at any time point or longitudinally over time. Patients in both randomized arms experienced a statistically significant average MMSE score increase over time, with no difference between arms. Patients with baseline MMSE score <27 were numerically more likely to experience significant MMSE gain than decline.

Conclusions: 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 decline than RT alone. The addition of PCV chemotherapy to RT significantly improves PFS without excessive CF detriment over RT alone for patients with low grade glioma.

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INTRODUCTION

Low grade gliomas are defined by the World Health Organization (WHO) as grade 1 or 2 primary brain neoplasms (1). The most common histologies included in studies of adult low grade glioma are grade 2 astrocytoma, oligodendroglioma, and mixed oligoastrocytoma. Over the last 15 years, several phase III randomized trials have investigated different paradigms of therapy intensification for this disease (2-5). These paradigms included immediate adjuvant radiation therapy (RT), increased dose of adjuvant RT, and addition of chemotherapy to adjuvant RT. The primary endpoint of each of these trials was overall survival, but all demonstrated either no difference between arms or a progression free survival benefit without an overall survival benefit in the intention to treat population. Patients with low grade glioma generally have a favorable prognosis, with 5 year overall survival rates consistently between 60 – 70%. The effect of therapy intensification on cognitive function remains a concern in this population with substantial long term survival.

An analysis of cognitive performance data from a phase III randomized intergroup trial (NCCTG 86-72-51), in which both study arms received RT, demonstrated that cognitive deterioration as measured by the mini-mental status exam (MMSE) after RT is a rare event and not influenced by the higher radiation dose given in the experimental arm (6). Radiation Therapy Oncology Group (RTOG) 98-02 is a prospective phase II/phase III trial that investigated the addition of PCV (procarbazine, CCNU, vincristine) chemotherapy to RT for patients with WHO grade 2 glioma (5). The initial results of this trial have been published, and the addition of adjuvant PCV chemotherapy was found to provide a progression free survival benefit, but not an overall

survival benefit in the intention to treat analysis. An exploratory analysis of conditional overall survival for patients surviving at least 2 years did demonstrate a significant benefit with the addition of PCV. However, the effect of therapy intensification by 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, cognitive functioning evaluations were collected prospectively on 362 patients with low grade glioma as part of the RTOG 98-02 trial. Cognitive functioning 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 cognitive functioning changes after therapy and determine if there is a detrimental effect on cognitive functioning associated with the addition of chemotherapy to RT versus RT alone for patients with low grade glioma until the time of tumor progression, if tumor progression occurs.

BACKGROUND

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 and chemotherapy for patients with breast cancer have demonstrated statistically significant chemotherapy-associated cognitive functioning detriment primarily in executive functioning, verbal ability, and visuospatial ability, albeit with a relatively small absolute effect size in each of these domains (11). The current model for patients with non-central nervous system (CNS) tumors is that patients have maximal cognitive functioning prior to therapy and can only experience either no effect or detriment due to the addition to chemotherapy (12).

Patients with CNS tumors may not fit this model because these patients can have cognitive functioning detriment due to the tumor itself at the time of presentation and effective therapy can relieve these symptoms, allowing for an increase in cognitive functioning with therapy. In a large randomized phase III study of patients with brain metastases examining whole brain radiation therapy with or without the radiosensitizing agent motexafin gadolinium, 91% of patients were found to have baseline impairment in at least 1 cognitive domain and 42% were found to be impaired in ≥ 4 cognitive domains (13). From this same study, it was found that response to therapy, in terms of brain metastases shrinkage, was significantly associated with prolonged time to cognitive functioning deterioration in several cognitive domains (14). These data indicate that, as

opposed to patients with non-CNS tumors, more intensive therapy regimens that are more efficacious could lead to higher rates of improved or stable cognitive functioning in patients with CNS malignancies.

Since there is no screening program for intracranial malignancies, most patients with low grade glioma present with symptoms directly attributable to their tumors. Effective therapy, including surgery, radiation therapy, and potentially chemotherapy, reduces the tumor burden and significantly decreases the risk of tumor relapse/progression. Patients with low grade glioma have excellent prognosis among patients with primary brain tumors, with median overall survival times in the 9 – 10 year range. This represents ample time to be able to manifest potential long term toxicity in cognitive functioning from oncologic therapies. The addition of PCV chemotherapy to RT has been shown to improve progression free survival without a benefit in overall survival for patients with “high risk” low grade glioma (5). However, the effect of therapy intensification by the addition of PCV to RT on cognitive functioning has not been well studied in this patient population.

METHODS

The null hypothesis for this study was that there is no detrimental effect on neurocognitive functioning associated with the addition of chemotherapy to RT compared with standard of care RT for patients with low grade glioma until the time of tumor progression, if progression occurs.

Patients

Three hundred sixty-two patients in this analysis were from a prospective, multicenter clinical trial (RTOG 98-02) investigating the effects of observation alone for low risk low grade glioma and the addition of PCV chemotherapy to RT (RT + PCV) for high risk low grade glioma. One hundred eleven patients were included in the phase II observation arm for low risk low grade glioma, while 251 patients were randomized on the phase III component for high risk low grade glioma. Detailed information on the primary study outcomes has previously been published (5, 15). Patients were considered high risk and eligible for the phase III study if they had histologically confirmed grade II astrocytoma, oligodendroglioma, or mixed oligoastrocytoma based on central pathology review. Other eligibility criteria included age 18 - 39 status post subtotal resection or age ≥ 40 with any extent of resection, Karnofsky performance status (KPS) $\geq 60\%$, 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 – 39 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 given in 30 fractions of 1.8 Gy each (prescribed

to isocenter) over 6 weeks. The treatment fields included the T2 or FLAIR MRI-defined tumor volume plus a 2-cm margin to block edge, resulting in an approximate 1-cm dosimetric margin. Patients randomly assigned to receive chemotherapy were treated with six cycles of post-radiation procarbazine (60 mg/m2 orally per day on days 8 through 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 individualized basis.

Patient Evaluation and Follow-Up

Baseline assessment prior to therapy included a history and physical (including neurologic) examination, evaluation of neurologic symptoms and signs, medications, KPS, neurologic function score, and MMSE. Pre- and postoperative MRI scans with and without contrast were also required. The extent of surgical resection was neurosurgeon defined and detailed in the operative report. After completion of RT, patients were followed with serial clinical evaluations and MRI 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 on the low risk phase II arm, except the follow-up dates 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. Tumor progression was defined as a 25% or greater increase in the cross-sectional area of enhancing or nonenhancing tumor on consecutive MRI scans, or any new area(s) of tumor.

Statistical Considerations

Key evaluations were designated as baseline and years 1, 2, 3 and 5. 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. The window period for key evaluations increased because by year 2, the interval between patient follow-up appointments had increased from 4 months to 6 months, and this further increased to 1 year by year 3. At each key evaluation, patients were classified as either having progressed 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 were included through the key evaluation preceding the key evaluation documenting progression. This was done to minimize the potential confounding effect of tumor progression on the association of intensified low grade glioma therapy and cognitive functioning change (16).

Significant MMSE score decline was defined as a decrease of > 3 points (8); significant gain was defined as an increase of > 3 points, and no change for any MMSE score change ≤ 3 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 randomized arms of the phase III component of RTOG 98-02 (RT vs. RT + PCV). Patients were categorized by baseline MMSE score (< 27 and 27 – 30) because those with baseline MMSE score > 26 were by definition not eligible for a significant MMSE gain and patients with baseline MMSE scores < 27 are in the lowest quartile of MMSE scores compared with an age-matched reference group (17). Proportions were compared

using the chi-square test of independence for categorical variables. Fisher exact test was used when expected counts were ≤ 5. MMSE score over time as a continuous variable was analyzed using a mixed effects linear regression model, with time and baseline MMSE score as random variables, in order to increase the sensitivity of detecting change over time between randomized arms as well as account for the non-independence of MMSE scores over time for individual patients (18). A univariate model was constructed with treatment arm and a time*treatment group interaction term to determine any difference in MMSE over time by treatment arm. The univariate model was as follows: Key evaluation MMSE score = β_0 + β_1(treatment arm) +β_2(time) +β_3(time*treatment arm). A multivariate mixed effects model was constructed to adjust for known prognostic factors including age, Karnofsky performance status, pre-op tumor size, extent of surgery, neurologic function score, and tumor histology. The multivariate model was as follows: key evaluation MMSE score = β_0 + β_1(treatment arm) +β_2(time) + β_3(time*treatment arm) + β_4(age) + β_5(KPS)+ β_6(tumor size) + β_7(surgery) + β_8(neurologic function)+ β9(histology). All covariates besides time were from the baseline assessment and dichotomized as follows: age (≥ 40 years), KPS (90 – 100%), tumor size (≥ 5 cm), surgery (gross/subtotal resection), neurologic function (minor/moderate symptoms), histology (astrocytoma, oligoastrocytoma (astrocytoma dominant) or oligoastrosytoma (astrocytoma=oligodendroglioma)). Time was in years with range 0 to 5 years. Treatment arm was RT + PCV vs. RT alone.

The parameter of interest in both models is the time*treatment group interaction term, which indicates if there is a difference in MMSE score over time by treatment arm. For the progression free survival and overall survival endpoints, the Kaplan-Meier

method (19) was used to estimate the rates, and the log-rank test (20) was used to compare differences between the two treatment arms. Time to event was calculated from the date of randomization. An event for overall survival was death due to any cause. An event for progression free survival was the first reported occurrence of tumor progression or death.

All statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC). No baseline covariate information was missing. Eligible patients without a MMSE score at a key evaluation time point were not included in the categorical analysis for that key evaluation time. All patients with at least 2 key evaluation MMSE scores were included in the linear mixed effects model analysis.

RESULTS

Patient characteristics

Patient characteristics and CONSORT diagram for the randomized arms of the phase III component of RTOG 98-02 have been previously published (5). In brief, 251 patients were randomized, 126 to the RT alone arm and 125 to the RT + PCV arm. Patient and tumor characteristics were well balanced between arms. Patient characteristics for each treatment arm are provided in Table 1. Baseline MMSE score was collected in 238 of 251 randomized patients (95%), and these patients make up the population for the primary analysis. Baseline MMSE was collected 105 of 111 patients (95%) in the observation phase II arm. At each key evaluation, the percentage of patients with MMSE scores collected of the total eligible patient population (defined as patients alive and not progressed at that key evaluation) was calculated. MMSE assessment compliance at each key evaluation is provided in Table 2. There were no significant differences in compliance rates between arms at any key evaluation time point except for year 1. The RT + PCV arm had the lowest MMSE compliance rate of 56% compared with 75% in the RT alone arm ($p=0.004$).

In order 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. The comparisons for year 1, year 2, year 3, and year 5 are demonstrated in Tables 3, 4, 5, and 6, respectively. There was no significant difference in any patient or tumor characteristic between those with an MMSE available and those eligible patients without at any time point except for lateralization of tumor at year 2. In order 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 + PCV randomized arms at all key evaluation time points were compared. The comparisons for year 1, year 2, year 3, and 5 are demonstrated in Tables 7, 8, 9, and 10, respectively. There was no significant difference in any patient or tumor characteristic for eligible patients between the randomized arms at any time point. Patient and tumor characteristics for patients with an MMSE score < 27 and MMSE 27 – 30 at baseline are available Table 11. The MMSE score 27 – 30 subset had significantly higher proportions of patients with age < 40, female gender, KPS 90 – 100%, no or minor neurologic symptoms, and right sided tumor location.

Change in MMSE Score Over Time

Categorical change in MMSE score by baseline MMSE score group is presented in Table 12. Due to small patient and event numbers, inferential statistics were not performed. Significant MMSE decline was a rare event regardless of baseline MMSE score, and patients with baseline MMSE score < 27 were more likely to experience MMSE gain than no change or decline. However, caution should be used when interpreting these results due to the small patient numbers in the MMSE < 27 group.

Categorical change in MMSE score by treatment arm is presented in Table 13. Inferential statistics are a comparison between the randomized RT and RT + PCV arms. The low risk observation results are included, but it must be noted that these patients were not randomized and by definition of their low risk status, have more favorable prognostic characteristics. No patient in the observation arm experienced MMSE decline, with the vast majority experiencing no change in MMSE. 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 patients experiencing MMSE decline at any of the key evaluation time points between treatment arms.

MMSE score change over time was also analyzed as a continuous variable. The mixed effects linear regression model results are presented in Table 14. The modeled average change in MMSE score per year was 0.2 for the RT + PCV arm and 0.14 for the RT alone arm. This slope is significantly different than 0, indicating a statistically significant increase in average MMSE score over time for both randomized arms. There was no significant difference in MMSE score change over time between the RT + PCV and the RT alone arms (p=0.52). The results were similar when a multivariate model adjusting for known prognostic factors was used. The adjusted mixed effects linear regression model results are presented in Table 15.

There were not enough MMSE decline events to be able to investigate the association between potential baseline characteristic predictors and changes in cognitive functioning. We were also unable to determine if an association exists between tumor progression and cognitive change due to 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 alive patients was 9.7 years. Progression free survival and overall survival were compared for patients with baseline MMSE score < 27 versus 27 – 30. Median progression free survival was 4.4 years and 5.8 years, respectively. There was no significant difference in progression free survival based on

baseline MMSE score (p=0.93). The median overall survival period was 9.5 years and 10.1 years, respectively, with no significant difference between groups (p=0.7).

DISCUSSION

Cognitive function has become an increasingly important topic, both in patients with brain tumors as well as in patients with non-brain malignancies. This issue is especially germaine for patients with low grade glioma. These patients have a long expected survival, with a median overall survival period of 9 – 10 years, which is an extended period of time to be able to manifest late neurocognitive toxicity from oncologic therapies. In addition, the major phase III studies that are currently informing our treatment decisions for low grade glioma have largely been negative for their primary endpoints, with some demonstrating a progression free survival benefit without an overall survival benefit in the intention to treat analysis (2-5). The establishment of improved progression free survival, but with a lack of improvement in overall survival, makes the decision of whether or not to adopt a new, more intensive, therapy regimen very difficult. More information is necessary in order to make an informed decision, specifically more evidence about the toxicity of therapy and toxicity of disease progression/recurrence in order to put the benefits of improved progression free survival in context. The European Organization for Research and Treatment of Cancer (EORTC) "Non-Believers" study is an example of this difficulty, where early RT was associated with improved progression free survival, but there was little information as to how this translated to patient performance and functioning and whether prolonged time to progression was equivalent to a prolonged time to clinical deterioration (4).

We sought to better inform the decision of intensifying therapy with the addition of PCV chemotherapy to RT by investigating the association between PCV use and cognitive functioning. When MMSE gain or decline was analyzed as a categorical

variable, it was demonstrated that the vast majority of patients maintained their baseline cognitive functioning. Significant MMSE decline was a rare event. Patients who had a baseline MMSE score of < 27 were more likely to experience MMSE gain than decline, suggesting that at least some of the baseline deficits in cognitive functioning caused by the tumor itself can be ameliorated with effective therapy. Though patient numbers and MMSE compliance did fall over time, there was no indication that more intensive therapy was associated with higher rates of cognitive functioning decline at any key evaluation time point through 5 years post-RT. When MMSE 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 cognitive functioning. Brown et al. analyzed MMSE score as a categorical variable for patients enrolled on an intergroup study, which randomized patients to 50.4 Gy vs. 64.8 Gy (6). Their results are similar to that of the current study, in that significant MMSE decline was a rare event and the vast majority of patients maintained their baseline cognitive functioning. There were no differences in cognitive functioning change detected between the higher dose and standard dose arms. An analysis by Kiebert et al. came to a different conclusion when quality of life data from the EORTC dose escalation trial was analyzed (21). This trial randomized patients to 45 Gy vs. 59.4 Gy and a 47 item quality of life questionnaire measuring several domains including physical, psychological, social, and symptoms was included as part of the follow-up evaluation. The authors found that fatigue/malaise and insomnia immediately

after RT and leisure time and emotional functioning at 7–15 months after randomization were significantly worse in the higher dose arm. However, there were no formal measures of cognitive functioning recorded as part of this trial.

RTOG 98-02 was initiated in 1998 and at the time the standard cognitive functioning measure employed in radiation trials was the MMSE. The MMSE was originally developed and validated as a screening tool for dementia (7-10). Though 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 a growing literature that the MMSE, especially when analyzed as a categorical variable for significant change, is an insensitive measure. MMSE can determine accurately if gross cognitive functioning decline as occurred, but it has poor sensitivity for more subtle neurocognitive changes. A study comparing the MMSE to other neurocognitive tests of specific domains found the MMSE to have a sensitivity of 50% (22). Douw et al. reported the results of an observational study of 65 patients with low grade glioma at a mean follow-up period of 12 years (23). Approximately half had been treated with RT and all were followed with an extensive battery of neurocognitive tests. Patients who had received RT were significantly more likely to experience decline in attentional function, executive function, and information processing speed, though the authors were unable to control for other potential confounders such as age, medication use, extent of surgery, and lateralization of the tumor. We attempted to increase the sensitivity of the MMSE as a global measure of cognitive functioning by analyzing MMSE score as a continuous variable and adjusting for potential confounders. There was no indication of MMSE decline as a continuous variable in either randomized 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 was only begun to be widely used well after the initiation of RTOG 98-02, with the feasibility study of employing this battery for patients with brain tumors in a prospective multi-institutional setting only being published in 2004 (24).

The strengths of this study include that fact that the data was derived from a prospective multi-institutional phase III randomized trial with the randomized exposure (PCV chemotherapy) intact. Patient numbers are also large, especially for a relatively rare tumor. Limitations include the potential for selection bias, with 2 levels of selection occurring. The first level of selection was that only patients who were alive and without progression at each key evaluation date were eligible. However, we did not detect any evidence of group imbalance indicative of selection bias for eligible patients at any key evaluation time point between the randomized arms. The second level of selection was that only eligible patients with an MMSE score available at each key evaluation were included in the analysis. Again, we did not detect any evidence of group imbalance indicative of selection bias for eligible patients with and without a MMSE score at any key evaluation time point. Patient numbers also were significantly reduced in the later years of this study due to a reduction in both eligible patients over time and the proportion of those patients with MMSE scores available. This limited the power to detect a difference between arms in the later years, however utilization of the linear mixed effects model allows full use of the available data, and no difference in MMSE score change over time between arms over the entire study period was detected.

The study of cognitive functioning 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 cognitive functioning. We did not have information on other potentially important factors such as education level (17), medication use such as anti-epileptic, anti-depressant, or anxiolytics, or genetic susceptibility factors such as apolipoprotein E (APOE) allele type (25).

In conclusion, the MMSE is a relatively insensitive tool that has not been validated in patients receiving cranial RT, and subtle changes in cognitive functioning may have been missed. However, the addition of PCV to RT for low grade glioma did not result in significantly higher rates of MMSE decline than RT alone. Patients in both randomized 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 cognitive functioning.

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Table 1. Randomized Patient Characteristics from RTOG 98-02

Characteristic	RT alone	RT + PCV
Number	126	125
Median age, years (IQR)	40 (18)	41 (19)
Median tumor size, cm (IQR)	5 (2.5)	4.7 (2.2)
KPS 90 – 100%	74%	75%
Gross total resection	9%	11%
Histology		
Astrocytoma	23%	29%
Oligodendroglioma	45%	40%
Mixed astrocytoma/oligodendoglioma	32%	31%
Enhancement: yes	60%	65%

KPS = Karnofsky performance status, RT = radiation therapy,
PCV = procarbazine, lomustine, vincristine chemotherapy
IQR = interquartile range

Table 2. MMSE Assessment Compliance

Treatment Arm	Evaluation Status	Baseline	Year 1	Year 2	Year 3	Year 5
Observation	Expected (No.)*	111	97	89	77	61
	Received (%)	105 (95%)	62 (64%)	49 (55%)	44 (57%)	27 (44%)
RT alone	Expected (No.)*	126	99	89	75	54
	Received (%)	122 (97%)	74 (75%)	60 (67%)	48 (64%)	22 (41%)
RT + PCV	Expected (No.)*	125	91	85	81	72
	Received (%)	116 (93%)	51 (56%)	50 (59%)	43 (53%)	25 (35%)
Chi-square p-value		0.36	0.004	0.51	0.10	0.11

* Patients alive and without progression at key evaluation
RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy

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

Characteristic	MMSE (n=187)	No MMSE (n=100)	Chi-square Test
Age			0.32
< 40	124 (66%)	72 (72%)	
≥ 40	63 (34%)	28 (28%)	
Gender			0.81
Male	102 (55%)	56 (56%)	
Female	85 (45%)	44 (44%)	
KPS			0.32
60-80%	39 (21%)	16 (16%)	
90-100%	148 (79%)	84 (84%)	
Extent of Surgery			0.46*
Biopsy	52 (28%)	32 (32%)	
Partial Resection	59 (32%)	26 (26%)	
Total Resection	76 (41%)	42 (42%)	
Neurologic function			0.09[#]
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			0.28[a]
Astrocytoma	36 (19%)	16 (16%)	
Oligodendroglioma	94 (50%)	44 (44%)	
Oligoastrocytoma, astro dominant	19 (10%)	22 (22%)	
Oligoastrocytoma, astro=oligo	8 (4%)	2 (2%)	
Oligoastrocytoma, oligo dominant	30 (16%)	16 (16%)	
Lateralization of tumor			0.15[b]
Right	99 (53%)	44 (44%)	
Left	85 (45%)	50 (50%)	
Bilateral	1 (1%)	6 (6%)	
Unknown	2 (1%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.47
Present	102 (55%)	59 (59%)	
Absent	85 (45%)	41 (41%)	

MMSE = Folstein mini-mental status exam, KPS = Karnofsky performance status
* Biopsy vs. other, [#] No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other

[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 4. Characteristics for Eligible Patients With and Without MMSE at Year 2

Characteristic	MMSE (n=159)	No MMSE (n=104)	Chi-square Test
Age			0.08
< 40	103 (65%)	78 (75%)	
≥ 40	56 (35%)	26 (25%)	
Gender			0.52
Male	92 (58%)	56 (54%)	
Female	67 (42%)	48 (46%)	
KPS			0.66
60-80%	31 (19%)	18 (17%)	
90-100%	128 (81%)	86 (83%)	
Extent of Surgery			0.51*
Biopsy	43 (27%)	32 (31%)	
Partial Resection	52 (33%)	28 (27%)	
Total Resection	64 (40%)	44 (42%)	
Neurologic function			0.31[#]
No symptoms	85 (53%)	49 (47%)	
Minor symptoms	66 (42%)	48 (46%)	
Moderate (fully active)	7 (4%)	4 (4%)	
Moderate (not fully active)	1 (1%)	3 (3%)	
Histology			0.75[a]
Astrocytoma	30 (19%)	16 (15%)	
Oligodendroglioma	78 (49%)	52 (50%)	
Oligoastrocytoma, astro dominant	21 (13%)	13 (13%)	
Oligoastrocytoma, astro=oligo	4 (3%)	5 (5%)	
Oligoastrocytoma, oligo dominant	26 (16%)	18 (17%)	
Lateralization of tumor			0.005[b]
Right	91 (57%)	41 (39%)	
Left	63 (40%)	61 (59%)	
Bilateral	4 (3%)	1 (1%)	
Unknown	1 (1%)	1 (1%)	
Contrast Enhancement on Pre-operative Scan			0.66
Present	90 (57%)	56 (54%)	
Absent	69 (43%)	48 (46%)	

MMSE = Folstein mini-mental status exam, KPS = Karnofsky performance status

* Biopsy vs. other, [#] No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 5. Characteristics for Eligible Patients With and Without MMSE at Year 3

Characteristic	MMSE (n=135)	No MMSE (n=98)	Chi-square Test
Age			0.40
< 40	88 (65%)	69 (70%)	
≥ 40	47 (35%)	29 (30%)	
Gender			0.88
Male	73 (54%)	54 (55%)	
Female	62 (46%)	44 (45%)	
KPS			0.15
60-80%	31 (23%)	15 (15%)	
90-100%	104 (77%)	83 (85%)	
Extent of Surgery			0.23*
Biopsy	37 (27%)	34 (35%)	
Partial Resection	43 (32%)	25 (26%)	
Total Resection	55 (41%)	39 (40%)	
Neurologic function			0.80[#]
No symptoms	68 (50%)	51 (52%)	
Minor symptoms	58 (43%)	43 (44%)	
Moderate (fully active)	6 (4%)	3 (3%)	
Moderate (not fully active)	3 (2%)	1 (1%)	
Histology			0.71[a]
Astrocytoma	22 (16%)	18 (18%)	
Oligodendroglioma	72 (53%)	53 (54%)	
Oligoastrocytoma, astro dominant	17 (13%)	12 (12%)	
Oligoastrocytoma, astro=oligo	2 (1%)	2 (2%)	
Oligoastrocytoma, oligo dominant	22 (16%)	13 (13%)	
Lateralization of tumor			0.07[b]
Right	75 (56%)	43 (44%)	
Left	58 (43%)	52 (53%)	
Bilateral	1 (1%)	3 (3%)	
Unknown	1 (1%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.90
Present	76 (56%)	56 (57%)	
Absent	59 (44%)	42 (43%)	

MMSE = Folstein mini-mental status exam, KPS = Karnofsky performance status
* Biopsy vs. other, [#] No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 6. Characteristics for Eligible Patients With and Without MMSE at Year 5

Characteristic	MMSE (n=74)	No MMSE (n=113)	Chi-square Test
Age			0.88
< 40	47 (64%)	73 (65%)	
≥ 40	27 (36%)	40 (35%)	
Gender			0.76
Male	39 (53%)	57 (50%)	
Female	35 (47%)	56 (50%)	
KPS			0.99
60-80%	15 (20%)	23 (20%)	
90-100%	59 (80%)	90 (80%)	
Extent of Surgery			0.23*
Biopsy	20 (27%)	40 (35%)	
Partial Resection	20 (27%)	30 (27%)	
Total Resection	34 (46%)	43 (38%)	
Neurologic function			0.13[#]
No symptoms	43 (58%)	53 (47%)	
Minor symptoms	25 (34%)	54 (48%)	
Moderate (fully active)	5 (7%)	4 (4%)	
Moderate (not fully active)	1 (1%)	2 (2%)	
Histology			0.22[a]
Astrocytoma	10 (14%)	20 (18%)	
Oligodendroglioma	43 (58%)	60 (53%)	
Oligoastrocytoma, astro dominant	5 (7%)	16 (14%)	
Oligoastrocytoma, astro=oligo	3 (4%)	1 (1%)	
Oligoastrocytoma, oligo dominant	13 (18%)	16 (14%)	
Lateralization of tumor			0.34[b]
Right	40 (54%)	53 (47%)	
Left	33 (45%)	58 (51%)	
Bilateral	1 (1%)	2 (2%)	
Unknown	0 (0%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.87 .
Present	41 (55%)	64 (57%)	
Absent	33 (45%)	49 (43%)	

MMSE = Folstein mini-mental status exam, KPS = Karnofsky performance status
* Biopsy vs. other, [#] No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 7. Characteristics of Eligible Patients with MMSE by Treatment Arm at Year 1

Characteristic	RT alone (n=74)	RT + PCV (n=51)	Chi-square Test
Age			0.64
< 40	38 (51%)	24 (47%)	
≥ 40	36 (49%)	27 (53%)	
Gender			0.09
Male	46 (62%)	24 (47%)	
Female	28 (38%)	27 (53%)	
KPS			0.66
60-80%	20 (27%)	12 (24%)	
90-100%	54 (73%)	39 (76%)	
Extent of Surgery			0.94*
Biopsy	31 (42%)	21 (41%)	
Partial Resection	36 (49%)	23 (45%)	
Total Resection	7 (9%)	7 (14%)	
Neurologic function			0.16[#]
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			0.96[a]
Astrocytoma	11 (15%)	13 (25%)	
Oligodendroglioma	38 (51%)	25 (49%)	
Oligoastrocytoma, astro dominant	9 (12%)	3 (6%)	
Oligoastrocytoma, astro=oligo	5 (7%)	1 (2%)	
Oligoastrocytoma, oligo dominant	11 (15%)	9 (18%)	
Lateralization of tumor			0.96[b]
Right	35 (47%)	25 (49%)	
Left	36 (49%)	26 (51%)	
Bilateral	1 (1%)	0 (0%)	
Unknown	2 (3%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.33
Present	47 (64%)	28 (55%)	
Absent	27 (36%)	23 (45%)	

RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy
KPS = Karnofsky performance status
* Biopsy vs. other, # No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 8. Characteristics of Eligible Patients with MMSE by Treatment Arm at Year 2

Characteristic	RT alone (n=60)	RT + PCV (n=50)	Chi-square Test
Age			0.55
< 40	31 (52%)	23 (46%)	
≥ 40	29 (48%)	27 (54%)	
Gender			0.17
Male	39 (65%)	26 (52%)	
Female	21 (35%)	24 (48%)	
KPS			0.15
60-80%	11 (18%)	15 (30%)	
90-100%	49 (82%)	35 (70%)	
Extent of Surgery			0.32*
Biopsy	26 (43%)	17 (34%)	
Partial Resection	29 (48%)	23 (46%)	
Total Resection	5 (8%)	10 (20%)	
Neurologic function			0.25[#]
No symptoms	27 (45%)	28 (56%)	
Minor symptoms	33 (55%)	16 (32%)	
Moderate (fully active)	0 (0%)	5 (10%)	
Moderate (not fully active)	0 (0%)	1 (2%)	
Histology			0.77[a]
Astrocytoma	7 (12%)	14 (28%)	
Oligodendroglioma	32 (53%)	23 (46%)	
Oligoastrocytoma, astro dominant	10 (17%)	4 (8%)	
Oligoastrocytoma, astro=oligo	3 (5%)	0 (0%)	
Oligoastrocytoma, oligo dominant	8 (13%)	9 (18%)	
Lateralization of tumor			0.43[b]
Right	34 (57%)	25 (50%)	
Left	23 (38%)	23 (46%)	
Bilateral	2 (3%)	2 (4%)	
Unknown	1 (2%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.86
Present	37 (62%)	30 (60%)	
Absent	23 (38%)	20 (40%)	

RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy
KPS = Karnofsky performance status
* Biopsy vs. other, [#] No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 9. Characteristics of Eligible Patients with MMSE by Treatment Arm at Year 3

Characteristic	RT alone (n=48)	RT + PCV (n=43)	Chi-square Test
Age			0.74
< 40	24 (50%)	20 (47%)	
≥ 40	24 (50%)	23 (53%)	
Gender			0.64
Male	28 (58%)	23 (53%)	
Female	20 (42%)	20 (47%)	
KPS			0.55
60-80%	15 (31%)	11 (26%)	
90-100%	33 (69%)	32 (74%)	
Extent of Surgery			0.14*
Biopsy	23 (48%)	14 (33%)	
Partial Resection	21 (44%)	22 (51%)	
Total Resection	4 (8%)	7 (16%)	
Neurologic function			0.36[#]
No symptoms	20 (42%)	22 (51%)	
Minor symptoms	26 (54%)	17 (40%)	
Moderate (fully active)	0 (0%)	4 (9%)	
Moderate (not fully active)	2 (4%)	0 (0%)	
Histology			0.14[a]
Astrocytoma	6 (13%)	11 (26%)	
Oligodendroglioma	29 (60%)	20 (47%)	
Oligoastrocytoma, astro dominant	5 (10%)	6 (14%)	
Oligoastrocytoma, astro=oligo	1 (2%)	0 (0%)	
Oligoastrocytoma, oligo dominant	7 (15%)	6 (14%)	
Lateralization of tumor			0.83[b]
Right	24 (50%)	21 (49%)	
Left	23 (48%)	21 (49%)	
Bilateral	0 (0%)	1 (2%)	
Unknown	1 (2%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.14
Present	33 (69%)	23 (53%)	
Absent	15 (31%)	20 (47%)	

RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy
KPS = Karnofsky performance status
* Biopsy vs. other, # No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 10. Characteristics of Eligible Patients with MMSE by Treatment Arm at Year 5

Characteristic	RT alone (n=22)	RT + PCV (n=25)	Chi-square Test
Age			0.71
< 40	10 (45%)	10 (40%)	
≥ 40	12 (55%)	15 (60%)	
Gender			0.45
Male	13 (59%)	12 (48%)	
Female	9 (41%)	13 (52%)	
KPS			0.82
60-80%	5 (23%)	5 (20%)	
90-100%	17 (77%)	20 (80%)	
Extent of Surgery			0.12*
Biopsy	12 (55%)	8 (32%)	
Partial Resection	10 (45%)	10 (40%)	
Total Resection	0 (0%)	7 (28%)	
Neurologic function			0.49[#]
No symptoms	11 (50%)	15 (60%)	
Minor symptoms	11 (50%)	7 (28%)	
Moderate (fully active)	0 (0%)	3 (12%)	
Moderate (not fully active)	0 (0%)	0 (0%)	
Histology			0.80[a]
Astrocytoma	3 (14%)	4 (16%)	
Oligodendroglioma	14 (64%)	13 (52%)	
Oligoastrocytoma, astro dominant	1 (5%)	2 (8%)	
Oligoastrocytoma, astro=oligo	2 (9%)	0 (0%)	
Oligoastrocytoma, oligo dominant	2 (9%)	6 (24%)	
Lateralization of tumor			0.18[b]
Right	8 (36%)	14 (56%)	
Left	14 (64%)	10 (40%)	
Bilateral	0 (0%)	1 (4%)	
Unknown	0 (0%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.83
Present	13 (59%)	14 (56%)	
Absent	9 (41%)	11 (44%)	

RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy
KPS = Karnofsky performance status
* Biopsy vs. other, # No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 11. Patient Characteristics by Baseline MMSE Score

Characteristic	MMSE < 27 (n=32)	MMSE 27 – 30 (n=311)	Chi-square Test
Age			0.02
< 40	14 (44%)	200 (64%)	
≥ 40	18 (56%)	111 (36%)	
Gender			0.02
Male	24 (75%)	165 (53%)	
Female	8 (25%)	146 (47%)	
KPS			<0.001
60-80%	15 (47%)	58 (19%)	
90-100%	17 (53%)	253 (81%)	
Extent of Surgery			0.89*
Biopsy	11 (34%)	103 (33%)	
Partial Resection	13 (41%)	87 (28%)	
Total Resection	8 (25%)	121 (39%)	
Neurologic function			<0.001[#]
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			0.93[a]
Astrocytoma	11 (34%)	65 (21%)	
Oligodendroglioma	11 (34%)	139 (45%)	
Oligoastrocytoma, astro dominant	2 (6%)	49 (16%)	
Oligoastrocytoma, astro=oligo	0 (0%)	10 (3%)	
Oligoastrocytoma, oligo dominant	8 (25%)	48 (15%)	
Lateralization of tumor			0.006[b]
Right	8 (25%)	164 (53%)	
Left	19 (59%)	140 (45%)	
Bilateral	3 (9%)	7 (2%)	
Unknown	2 (6%)	0 (0%)	
Contrast Enhancement on Pre-operative Scan			0.15
Present	22 (69%)	173 (56%)	
Absent	10 (31%)	138 (44%)	

MMSE = Folstein mini-mental status exam, KPS = Karnofsky performance status
* Biopsy vs. other, # No symptoms vs. other, [a] Oligodendroglioma and Oligoastrocytoma, oligo-dominant vs. other
[b] Right vs. Left/bilateral
Percentages may not sum to 100% due to rounding

Table 12. Categorical Change in MMSE Score by Baseline MMSE

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

MMSE = Folstein mini-mental status exam
MMSE decline: > 3 point decline, MMSE gain: > 3 point gain, MMSE no change: ≤ 3 point change
Percentages may not sum to 100% due to rounding

Table 13. Categorical Change in MMSE Score by Treatment Arm

	Observation[#]	**RT alone**	**RT + PCV**	**Fisher's Exact Test***
MMSE change year 1	(n=62)	(n=74)	(n=51)	0.99
Decline	0 (0%)	5 (7%)	2 (4%)	
No Change	60 (97%)	66 (89%)	44 (86%)	
Gain	2 (3%)	3 (4%)	5 (10%)	
MMSE change year 2	(n=49)	(n=60)	(n=50)	0.5
Decline	0 (0%)	1 (2%)	0 (0%)	
No Change	49 (100%)	58 (97%)	43 (86%)	
Gain	0 (0%)	1 (2%)	7 (14%)	
MMSE change year 3	(n=44)	(n=48)	(n=43)	0.5
Decline	0 (0%)	1 (2%)	0 (0%)	
No Change	44 (100%)	45 (94%)	38 (88%)	
Gain	0 (0%)	2 (4%)	5 (12%)	
MMSE change year 5	(n=27)	(n=22)	(n=25)	0.99
Decline	0 (0%)	0 (0%)	2 (8%)	
No Change	27 (100%)	21 (96%)	20 (80%)	
Gain	0 (0%)	1 (5%)	3 (12%)	

[#]Observation group are those age < 40 and with gross total resection on phase II observational arm
*Fisher's exact test performed for decrease vs. no change/increase comparing RT alone and RT+PCV arms
RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy
MMSE = Folstein mini-mental status exam
MMSE decline: > 3 point decline, MMSE gain: > 3 point gain, MMSE no change: ≤ 3 point change
Percentages may not sum to 100% due to rounding

Table 14. Univariate Mixed Effects Model for MMSE Change Over Time for Randomized Patients (n=238)

Variable	Estimate	Standard Error	p-value
Difference in baseline MMSE score (RT + PCV vs. RT)	-0.07	0.28	0.81
Change in MMSE score per year (RT)	0.14	0.07	<0.045
Difference in change in MMSE score change per year (RT + PCV vs. RT)	0.06	0.98	0.52

MMSE = Folstein mini-mental status exam
RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy

Table 15. Multivariate Mixed Effects Model for MMSE Change Over Time for Randomized Patients (n=238)

Variable	Estimate	Standard error	p-value
Difference in baseline MMSE score (RT + PCV vs. RT)	0.09	0.2	0.63
Change in MMSE score per year (RT)	0.17	0.05	p<0.001
Difference in change in MMSE score change per year (RT + PCV vs. RT)	0.04	0.93	0.6
Age (≥ 40 years)	0.29	0.19	0.13
KPS (90 – 100%)	0.42	0.24	0.08
Pre-operative tumor size (≥ 5 cm)	0.07	0.19	0.71
Surgery (gross/subtotal resection)	0.08	0.19	0.72
Neurologic Function (minor/moderate symptoms)	-0.47	0.21	0.02
Histology (astrocytoma/ oligoastrocytoma, astro-dominant/ oligoastrocytoma, astro=oligo)	0.07	0.2	0.72

MMSE = Folstein mini-mental status exam
RT = radiation therapy, PCV = procarbazine, lomustine, vincristine chemotherapy
KPS = Karnofsky performance status
Astro = astrocytoma, Oligo = oligodendroglioma