RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-02

A PHASE II STUDY OF OBSERVATION IN FAVORABLE LOW-GRADE GLIOMA AND A PHASE III STUDY OF RADIATION WITH OR WITHOUT PCV CHEMOTHERAPY IN UNFAVORABLE LOW-GRADE GLIOMA

ECOG ***(R9802)***
Radiation Oncology
Minesh Mehta, M.D
(608) 263-8500
FAX (608) 263-9167

Medical Oncology
Mark R. Gilbert, M.D.
(404) 778-2190
FAX (404) 778-2191

NCCTG ***(R9802)***
Radiation Oncology
Paul D. Brown, M.D.
(507) 284-2949
FAX (507) 284-0079

Medical Oncology
Jan C. Buckner, M.D.
(507) 284-4320
FAX (507) 284-1803

SWOG ***(R9802)***
Radiation Oncology
Keith J. Stelzer, M.D., Ph.D.
(206) 548-4115
FAX (206) 548-6218

Medical Oncology
Geoffrey R. Barger, M.D.
(313) 577-1242
FAX (313) 745-4216

Study Chairs
RTOG *(98-02)*
(Coordinating Group)

Radiation Oncology	Edward G. Shaw, M.D Wake Forest University School of Medicine Medical Center Blvd. Winston-Salem, NC 27157-1030 *(336)* 713-6506 **(3/1/05)** F*AX (336) 713-6512* **(3/1/05)**
Medical Oncology	Jan C. Buckner, M.D. *(507)* 284-4320 *FAX (507) 284-1803*
Neuro-Oncology	Geoffrey R. Barger, M.D. *(313)* 577-1242 *FAX (313) 745-4216*
Neuropathology	Stephen W. Coons, M.D. *(602)* 406-7088 *FAX (602) 406-7169*
Neuroradiology	Peter E. Ricci, MD. (*303)* 788-8734 *FAX (303)* 788-6546
Neurosurgery	Dennis E. Bullard, M.D. *(919)* 785-3500 *FAX (919) 783-7810*
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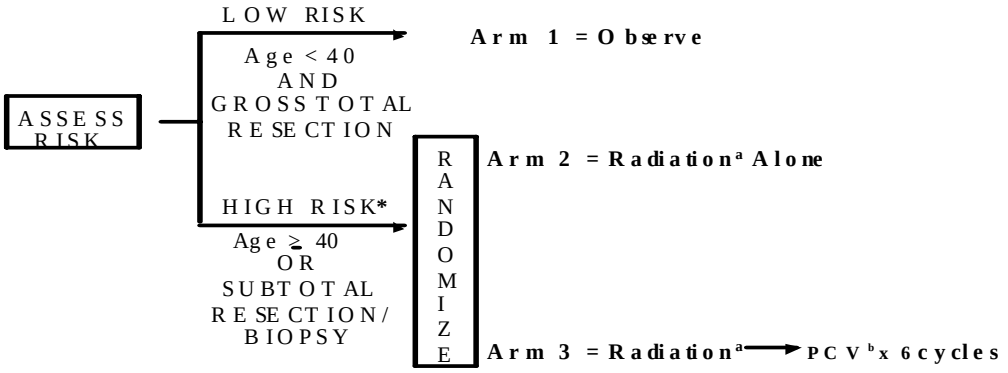
A PHASE II STUDY OF OBSERVATION IN FAVORABLE LOW-GRADE GLIOMA AND A PHASE III STUDY OF RADIATION WITH OR WITHOUT PCV CHEMOTHERAPY IN UNFAVORABLE LOW-GRADE GLIOMA

SCHEMA



***Stratify**: **(8/18/03)** Tumor Subtype *(astrocytoma [mixed-astro dominant] or equal (astro/oligo mix) vs. oligodendroglioma [mixed-oligo dominant])*; Age *(< 40 vs. ≥40);* KPS *(60-80 vs. 90-100)*; Contrast Enhancement on Pre-Op scan *(present vs. absent).*

Treatment *(must begin within 4 weeks after registration)*

a. Radiation - External Beam Radiation Therapy *(EBRT)*
   EBRT: 54 Gy/30 fractions over six weeks, 5 days a week to gross tumor volume defined by a T2 weighted post-op MRI scan *(pre-op MRI acceptable if biopsy only)* plus a 2 cm margin *(tumor edge to block edge.* There will be no boost volume.
b. PCV Chemotherapy - Procarbazine/CCNU/Vincristine
   Procarbazine 60mg/m^2 po, Days 8-21
   CCNU 110mg/m2 po, Day 1
   Vincristine 1.4mg/m^2 iv, Days 8,29 *(maximum dose 2 mg)*
   PCV must start within one month following last day of RT. Repeat PCV at 8 week intervals x 6 cycles

Eligibility *(See Section 3.0 for details)* **[8/18/03]**

- Histologic proof of supratentorial WHO grade II astrocytoma, oligodendroglioma, or oligoastrocytoma confirmed by central pathology review prior to randomization
- Age ≥ 18 years
- KPS ≥ 60
- Neurological Function Status ≤ 3
- Absolute granulocyte count ≥ 1500, platelets within institutional normal range, and serum creatinine ≤ 1.5 x normal *(Arms 2/3)*
- Total bilirubin and alkaline phosphatase ≤ 2 x normal, transaminases (SGOT [AST] or SGPT) ≦ 4x normal
- Pre- and post-op MRI scans with and without contrast must be available for patients on Arm 1; post-op MRI scans with and without contrast must be available for patients on Arms 2 & 3 *(not necessary on biopsy-only patients as long as pre-op MRI is available)*
- No chronic lung disease unless DLCO ≥ 60% of predicted
- Signed study-specific consent form

Required Sample Size: 252 ***(Arms 2 & 3)***

RTOG Institution # _____
RTOG 98-02
RTOG Case # _____

ELIGIBILITY CHECK ***(8/18/03)***
(page 1 of 2)

_____(Y) 1. Does the patient have a histologically proven supratentorial WHO grade II astrocytoma, oligodendroglioma, or oligoastrocytoma confirmed by central pathology review?

_____(Y) 2. Was the tissue used to make the histologic diagnosis obtained within the last 12 weeks?

_____(Y) 3. Does the patient's laboratory values meet the criteria specified in Section 3.1.5 of the protocol?

_____(Y/N) 4. Were both pre-operative and post-operative MRI scans with and without contrast obtained within 12 weeks of date of surgery?

_____(Y) If post-op MRI scan is not available, did the patient have a biopsy only?

_____(N) 5. Does the tumor location include the optic chiasm, optic nerve*(s)*, pons, medulla, cerebellum, or spinal cord?

_____(N) 6. Is there evidence of spread to spinal meninges or non-contiguous cranial meninges?

_____(Y) 7. Is the patient free of synchronous malignancies, except for *in situ* carcinoma of the cervix or non-melanomatous skin cancer?

_____(Y/N) 8. Any prior malignancies?

_____(Y) If yes, has the patient been disease free ≥ 5 years?

_____(N) 9. Has the patient received any prior radiation to the brain or head/neck or chemotherapy for any reason?

_____(Y/N) 10. Does the patient have any chronic lung disease?

_____(Y) If yes, did pulmonary function tests demonstrate a DLCO ≥ 60% of predicted?

_____(N) 11. Does the patient have an active infectious process?

(continued on next page)

The following questions will be asked at Study Registration:

_____(Y) 1. Has the Eligibility Checklist *(above)* been completed?

_____(Y) 2. Is the patient eligible for this study?

_____ 3. Date the study-specific Consent Form was signed? *(must be prior to study entry)*

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # *(if different)*

_____ Tumor Subtype *(astrocytoma or mixed astro/oligo [astro ≥ oligo component] vs oligodendroglioma or mixed astro/oligo [oligo > astro component].)*

_____ Age *(< 40 vs. ≥ 40)*

_____ KPS *(60-80 vs. 90-100)*

_____ Contrast Enhancement on Pre Op Scan *(present vs. absent)*

_____ Extent of Resection *(gross total resection vs. subtotal resection/biopsy)*

_____ Medical Oncologist

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code *(9 digit if available)*

_____ Method of Payment

_____ Will any component of the patient's care be given at a military or VA facility?

_____ Treatment Start Date *(must be within 4 weeks after randomization)*

_____ Treatment Assignment

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background

The low-grade gliomas *(LGG)* are a diverse group of glial tumors found throughout the central nervous system, including sites in the brain and spinal cord. The annual incidence is about 1800 cases. They occur in adults and children. Histologic subtypes of LGG include the diffuse fibrillary astrocytomas *(WHO grade II astrocytomas)*, oligodendrogliomas, mixed oligoastrocytomas, and pilocytic astrocytomas *(WHO grade I astrocytomas).* Pilocytic astrocytomas usually occur in the cerebellum of children. They are usually well circumscribed, often completely resectable, and associated with a 10-year survival rate of >80% *(Hayostek et al.).* For the purposes of this protocol, only supratentorial, non-pilocytic LGG in adults will be considered, including WHO grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas *(Zulch et al.)*, which are similar in prognosis to the St. Anne-Mayo grade I-II astrocytomas, oligodendrogliomas, and oligoastrocytomas *(Daumas-Duport et al.)*. Factors influencing survival in these tumors include histologic subtype, age, extent of surgical resection, and radiation therapy.
The table below shows the median survival time and 2-, 5-, 10-, and 15-year survival rates for the various histologic subtypes of supratentorial LGG:

Survival	**Astrocytomas**	**Oligo-Astros**	**Oligodendrogliomas**
Median (yr)	4.7	7.1	9.8
2-yr (%)	80	89	93
5-yr (%)	46	63	73
10-yr (%)	17	33	49
15-yr (%)	17	17	49

The differences in survival between astrocytomas, oligoastrocytomas and oligodendrogliomas are statistically significant *(Shaw et al.).* Age also has a significant impact on survival, as shown in the table below. Age 40, which is the most consistently used age cut-off for better versus worse survival, is also the median age at the time of tissue diagnosis for adults with supratentorial LGG.

Series	**Age**	**Survival Median *(Yrs.)***
Eyre et al.	< 30	Not Reached
	30-49	5.5
	≥ 50	1.6
Medberry et al.	< 40	6.75
	≥ 40	1.0
Piepmeier	< 40	8.7
	≥ 40	4.9
Shaw et al.	< 35.5	6.3
	≥ 35.5	4.2

The majority of series in the literature have identified more aggressive surgical resection as having a statistically significant beneficial effect on survival, as summarized in the table below:

Series	Extent of Resection	5-yr Survival	Mean Survival
Janny et al.	Gross Total Subtotal/Biopsy	88% 57%	
North et al.	Gross Total Subtotal Biopsy	85% 64% 43%	
Philippon et al.	Gross Total Subtotal Biopsy	80% 50% 45%	
Piepmeier	Gross Total Subtotal Biopsy		8.12 yrs 7.08 yrs 5.88 yrs

However, in the series of Shaw et al, and Shibamoto et al, survival was not significantly affected by the extent of surgical resection, with 5-year survival rates of 52-64% for patients undergoing biopsy, subtotal, or gross total resection. Of note, in all the quoted surgical series, the determination of the extent of resection was based on the neurosurgeon's assessment, without the potential benefit of postoperative imaging. In a more recent retrospective study by Berger et al, pre- and postoperative tumor volumes were estimated from magnetic resonance imaging *(MRI)* scans. Low-grade glioma patients with residual tumor volumes less than 10 cc's had a recurrence rate of 15% *(median time to recurrence 50 months)*, compared to a recurrence rate of 40 % *(median time to recurrence 30 months)* if the residual tumor volume was greater than 10 cc's.

The most controversial issue in the management of the adult patient with a supratentorial LGG is whether or not to administer immediate versus delayed *(until the time of recurrence)* radiation therapy. The literature to date, virtually all of which is retrospective, is quite split on the issue, as shown in the table below:

Series	Postoperative Radiation	5-yr Survival	10-yr Survival	Median Survival
Leighton et al.	No *(Surgery only)* Yes	84% 62%	70% 35%	13 yrs 8 yrs
Philippon et al.	No Yes	65% 55%		
Piepmeier	No Yes			8.76 yrs. 6.45 yrs
Shaw et al.	No Yes (< 53 Gy) Yes *(> 53 Gy)*	32% 47% 68%		
Shibamoto et al.	No Yes	37% 60%		

The difficulty in interpreting the above data is in the unknown bias that determines whether or not a patient receives postoperative radiation. For example, in the series by Leighton et al, patients who did not receive postoperative radiation were significantly more likely to have gross total resection and oligodendroglioma histology, in contrast to those receiving postoperative radiation, who were more likely to have subtotal resection/biopsy and astrocytoma histology. Over a decade ago, when the Brain Tumor Study Group tried to randomize adults with supratentorial LGG to immediate versus delayed postoperative radiation, the study failed due to poor accrual, in part because some physicians didn't want their good prognosis patients to potentially be randomized to receive immediate postoperative radiation, whereas other physicians with poor prognosis patients didn't want the possibility that postoperative radiation might not be given. Another controversial issue regarding radiation therapy is the appropriate dose to give. Despite Shaw et al's observation that doses >53Gy were associated with significantly better survival than doses < 53Gy, a recently published phase III prospective randomized trial from the European Organization for the Research and Treatment of Cancer *(EORTC)* failed to detect a significant difference in either overall or relapse-free survival between 45Gy/25 fractions and 59.4 Gy/33 fractions in adults with supratentorial LGG *(Karim et al.)*. A similar prospective study was completed in 12/94 by the North Central Cancer Treatment Group *(NCCTG)*, Radiation Therapy Oncology Group *(RTOG)*, and Eastern Cooperative Oncology Group

(ECOG), randomizing between 50.4Gy/28 fractions and 64.8Gy/36 fractions. Until results of this trial become available, the majority of radiation oncologists prefer to treat these patients with total doses in the mid-50Gy range. A recent poll of nearly 100 radiation oncologists showed that the preferred dose was 54Gy/30 fractions, when given the choice between 50.4, 54, 55.8, and 59.4Gy in 1.8Gy fractions *(Shaw et al, unpublished data, 5/9/97).*

The value of chemotherapy in patients with low-grade glioma has not been clearly demonstrated. Most studies have not reported response to treatment in relationship to tumor grade. There has been one randomized trial assessing the role of adjuvant chemotherapy in adult patients with supratentorial low-grade gliomas. The Southwest Oncology Group *(SWOG)* randomized 54 patients to either 55 Gy radiation *(RT)* alone *(n-19)* or RT plus CCNU *(n=35);* 1:2 randomization. Median survival was comparable between the two groups *(2.8-3.1 years)(Eyre et al.),* and was considerably lower than in other series *(Shaw et al.).*

More recently reported studies suggest a potentially beneficial role of chemotherapy. In a multi-institutional phase II trial, Cairncross et al noted responses in 9 of 10 patients with recurrent oligodendroglioma who had presented initially with low-grade pure oligodendroglioma. Buckner et al reported responses in 5/15 *(33%)* patients with recurrent low-grade astrocytoma and 2/5 *(40%)* patients with recurrent low-grade oligoastrocytoma treated on a phase II North Central Cancer Treatment Group (NCCTG) trial with BCNU plus recombinant interferon alpha. In a subsequent NCCTG phase II trial using nitrogen mustard, procarbazine, and vincristine, Buckner et al reported responses in 4/20 *(20%)* patients with recurrent low-grade glioma. In both NCCTG trials, patients with recurrent low-grade glioma had higher response rates to the investigational regimen than those with any other histologic type, including anaplastic oligodendroglioma. As a group, these studies suggest modest chemosensitivity of recurrent low-grade gliomas.

Less is known about chemoresponsiveness of previously untreated low-grade glioma patients. Mason et al reported a case series of 8 low-grade oligodendroglioma patients treated with procarbazine, CCNU, and vincristine. All responded to treatment with either standard or intensified dosing regimens *(Mason et al.).* In preliminary data from an ongoing NCCTG phase II trial of chemotherapy *("Intensive" PCV for 6 cycles every 8 weeks*) followed by radiation for patients with newly-diagnosed low-grade glioma, Buckner et al have noted responses in 5 of 15 patients who have completed the chemotherapy portion of the trial *(unpublished data).* Patients with astrocytoma, oligodendroglioma, and oligoastrocytoma have experienced tumor regression. Unfortunately, five patients have developed MRI scan evidence of tumor progression prior to radiation. In one, only necrosis was noted at resection post radiation, so interpretation of progression is problematic. In another patient who progressed, the clinical scenario was consistent with gliomatosis cerebri, distinctively different from most low-grade glioma patients. Two patients developed delayed myelosuppression, requiring initiation of radiation per protocol prior to completion of chemotherapy. At this point, the actual response rate and progression rate remain uncertain. Six out of the twelve planned additional patients have been accrued to the study and remain on chemotherapy. While there is evidence of antitumor activity of PCV in some untreated low-grade glioma patients, the frequency and duration of response are unclear. Nevertheless, preliminary data suggest that these patients are at least as responsive to chemotherapy as high-grade glioma patients in which adjuvant chemotherapy confers modest but reproducible survival benefit, especially in younger patients and those with anaplastic astrocytoma *(Nelson et al.).* Given the uncertain frequency of tumor progression in patients receiving chemotherapy alone prior to radiation, we propose to administer radiation first, followed by PCV chemotherapy. Most of the efficacy information available to date *(Cairncross et al., Buckner et al [unpublished data], and in some patients by Mason et al.)* has been obtained using the higher dose schedule of PCV. This schedule is currently the one utilized as adjuvant therapy in RTOG 94-02. However, most investigators who will be participating in the proposed study prefer the lower dose schedule of PCV. For this reason, we would propose using the lower dose schedule for six cycles at eight week intervals to accommodate delayed and cumulative myelosuppression common in all PCV regimens.

Histologic grading systems for gliomas usually have acknowledged the importance of tumor proliferative activity on prognosis. Estimate of proliferation based on mitotic activity is a cornerstone of most grading systems for astrocytomas and oligodendrogliomas. There are two basic methods to evaluate mitotic activity: their presence or absence, or their frequency. The latter is either measured quantitatively or estimated. These approaches have specific advantages and disadvantages but also share common issues. Mitoses are present during only a very limited portion of the cell cycle. As a result, the number of mitoses

greatly underestimates the number of cells that are proliferating at any time. This fact may permit accurate comparisons of proliferative activity between tumors and even accurate estimates of overall proliferation. However, it does make mitosis estimates more susceptible to sampling errors, which are more of a problem when the event being measured is relatively rare. The result of these inherent and methodological problems is inconsistent estimates of mitotic activity in tumors with less proliferative activity and fewer mitoses. Unfortunately, this is precisely the situation in low-grade and borderline anaplastic gliomas, and explains why the tumor grade often fails to predict the outcomes of these tumors.

The limitations inherent in estimates of mitotic activity in regard to gliomas have led to interest in other proliferation markers. A number of molecular markers of proliferation have been identified and evaluated to varying degrees. The markers use a variety of approaches to estimate tumor proliferative activity, including nucleotide analog incorporation [3H-thymidine, bromodeoxyuridine *(BrdU)*; antibodies to nuclear proteins expressed during the proliferation Ki-67/MIB-1, proliferating cell nuclear antigen *(PCNA)/*cyclin, DNA polymerase α, cytometric cell analysis; and probes for in situ hybridization *(Histone 3).* These molecular markers evaluate different portions of the cell cycle, but all identify a broader range than microscopic identification of mitoses and promise to provide more accurate estimates of cellular proliferation.

Numerous studies involving all of the proliferation markers have shown an association between proliferative activity and patient survival that was significant after accounting for patient age and histological grade. In the first studies that documented the prognostic value of proliferation markers in low-grade tumors, Hoshino et al found BrdU LI prognostic thresholds of 5% in a series of low-grade astrocytomas, and 5% in a series of oligoastrocytomas. However, methodological and financial issues make BrdU unsuitable for general application.

Using flow cytometry, Coons et al found that median patient survival in a series of 232 astrocytomas was 49, 24, and 13 months for SPF of 0-2.9%, 3-5.9%, and > 6%, respectively. Similar results were obtained in a series of 60 oligodendrogliomas. Using the same thresholds, patient survival was significantly different among the three groups. Of particular importance, a similar significance was found when the problematic grade 2 and 3 tumors, which comprise the majority of oligodendroglial tumors, were considered alone. The SPF identified both more aggressive grade 2 tumors and less aggressive grade 3 tumors. Sallinen et al also has documented the prognostic usefulness of flow cytometry SPF measurements in astrocytomas. However, flow cytometry requires expensive equipment and a dedicated operator. Accurate results are dependent on meticulous attention to preparation techniques. Also, relatively large tissue samples are required compared to immunohistochemistry methods.

The most promising of the immunohistochemistry proliferation markers is Ki-67/MIB-1. This marker identifies cells in the proliferative *(G1, S, G2-M)* phases of the cell cycle, but does not label cells in G0 phase. The newer antibodies work in routinely prepared formalin-fixed paraffin-embedded tissue, and interpretation is less problematic than with PCNA, where non-cycling cells are sometimes stained. Using Ki-67/MIB-1 immunohistochemistry, Montine et al analyzed 36 astrocytomas and found an association between LI and patient survival. When only grade 2 tumors were considered, a LI>3% identified a group of more aggressive tumors. Ellison et al analyzed 123 astrocytomas, including 24 well differentiated astrocytomas and found that patients whose tumors had MIB-1 LI<2 had better survival. Coons et al evaluated the relationship between the MIB-1 and survival in a series of 96 low-grade[32] and anaplastic[64] astrocytomas. Patient survival was highly associated with the LI for all tumors. LI<1, LI=1-4, and LI>4 classified the tumors into prognostic groups with median survival of 1122, 603, and 199 days, respectively. Survival within each group was also associated with the LI. For the LGA, the same thresholds were identified, with median survivals or 1485, 688, and 404 days.

Due to their relative rarity, the evaluation of oligodendroglial tumors lagged behind that of astrocytomas. However, three recent series suggest that Ki-67/MIB-1 LI may be more useful in oligodendrogliomas. Heegaard et al analyzed 32 oligodendrogliomas and found an association between patient survival and the LI as a continuous variable. Kros analyzed 108 oligodendrogliomas. A multivariate analysis confirmed the prognostic usefulness of the MIB-1 LI, taking into account patient age at diagnosis and histologic grade. Three prognostic groups were found, with L1<10, 10-20, and >20. In a series of 81 oligodendrogliomas and oligoastrocytomas, Coons et al also demonstrated independent prognostic significance of the Ki-67/MIB-1 LI. Tumors with LI<5% and >5% were associated with significantly

different patient survival. The median survival of the high proliferation group was 452 days, whereas the median survival was at least 1718 days in the group with LI<5%. The LI more accurately predicted survival among grade 2 and 3 tumors than the grade itself. As a whole, the median survival of grade 2 tumors was 1420 days. The grade 2 tumors with LI>5 had a significantly different median survival of 612 days, which corresponded closely to the survival of grade 3 tumors as a whole *(575.5 days)*. Similarly, the four grade 3 tumors with LI<5 had survivals closer to those of grade 2 tumors.

Taken together, these data suggest that measurement of proliferative activity can identify a subset of low-grade glioma tumors that behave like anaplastic tumors. However, the prognostic usefulness of proliferation markers has never been evaluated in a prospective clinical trial. It is important that such a study be done at a single site where the methods will be consistent, as proposed in this study. Sallinen et al showed that antibody clone, immunohistochemistry method, and even the counterstain affect the LI. Other factors, including counting method, also affect the LI. These issues are reflected in the differences in LI thresholds in the retrospective studies that found proliferation markers to be prognostically significant. Flow cytometry measurements are even more subject to problems with inter-institutional reproducibility.

For contemporary CNS clinical trials in the RTOG, quality of life *(QOL)* is assessed by a combination of tools including Karnofsky Performance Status *(KPS)(Appendix II)*, Neurologic Function Status *(NFS)(Appendix II)* and the Mini-Mental Status Exam.

1.2 Rationale for Study Design

In this study, we propose to divide adult patients with supratentorial *LGG (astrocytoma, oligodendroglioma, or oligoastrocytoma)* into two risk groups, based on the known prognostic factors of age and extent of surgical resection, and treat accordingly. Patients who are < 40 years old and who undergo gross total resection of their tumor will be categorized as low-risk. Patients who are ≥ 40 years old or who undergo subtotal resection or biopsy will be categorized as high-risk. Low-risk patients will be observed as part of a phase II study, whereas high-risk patients will be randomized between localized external beam radiation therapy, 54Gy/30 fractions, alone or followed by 6 cycles of Procarbazine/CCNU/Vincristine *(PCV)* chemotherapy. As with prior and ongoing RTOG studies in LGG and non-GBM malignant glioma, central pathology review will be required. Both paraffin embedded tissue and peripheral blood will be collected for future molecular genetic, molecular epidemiological, and other correlative studies.

2.0 OBJECTIVES

2.1 To identify the overall *(and relapse-free)* survival of low-risk adult patients with supratentorial LGG *(<40 years old who undergo gross total resection of a WHO grade II astrocytoma, oligodendroglioma, or mixed oligoastrocytoma)* who are observed postoperatively.

2.2 To compare the overall *(and relapse-free)* survival of high-risk adult patients with supratentorial LGG *(≥ 40 years old regardless of the degree of surgical resection, or age ≥ 18 who undergo subtotal resection or biopsy, of a WHO grade II astrocytoma, oligodendroglioma, or oligoastrocytoma)* who receive postoperative external beam radiation therapy with or without PCV chemotherapy.

2.3 To compare the severe or worse toxicities *(≥ grade 3)* of unfavorable patients receiving postoperative radiation therapy alone or radiation therapy plus PCV chemotherapy.

2.4 To compare the neurosurgeon's assessment of gross total resection with that of a postoperative MRI scan interpreted by a neuroradiologist.

2.5 To collect and store archival, paraffin embedded tissue and peripheral blood samples for concomitant and future correlative studies which will be funded by other mechanisms.

3.0 PATIENT SELECTION *(8/18/03)*

3.1 Eligibility Criteria

3.1.1 Histologic proof of a unifocal or multifocal supratentorial WHO grade II astrocytoma *(diffuse fibrillary, protoplasmic, or gemistocytic)*, oligodendroglioma, or oligoastrocytoma. Patients with prior suspected or proven LGG are eligible provided they now have a histologically proven eligible histology. Patients with neurofibromatosis are eligible. Stereotactic biopsies are permitted providing the tissue sample is adequate to make an unequivocal histologic diagnosis. For all patients, tissue must be obtained no more than 12 weeks before the date of registration or randomization.

3.1.2 Age ≥ 18 years.

3.1.3 KPS ≥ 60.

3.1.4 Neurologic Function Score *(NFS)* ≤ 3.

3.1.5 For high risk patients *(Arm 2 and 3):*

- Absolute granulocyte count *(AGC)* ≥ 1500/mm^3.
- Platelet count within institutional normal range.
- Serum creatinine ≤ 2x institutional normal range.
- Total bilirubin, and alkaline phosphatase ≤ 2x institutional normal range; transaminases (SGOT [AST] or SGPT) ≤ 4x institutional normal;

3.1.6 Pre-operative and post-operative MRI scans with and without contrast obtained within 12 weeks of date of surgery are required for patients on Arm 1

3.1.7 Post-operative MRI scans with and without contrast must be available for patients on Arms 2 & 3 *(* not necessary on biopsy-only patients as long as pre-op MRI is available) obtained within 12 weeks of date of surgery. Post-op CT scans are not acceptable.

3.1.8 Signed study-specific informed consent prior to study entry.

3.2 Ineligibility Criteria

3.2.1 Other LGG histologies including pilocytic astrocytoma, subependymal giant cell astrocytoma of tuberous sclerosis, subependymoma, pleomorphic xanthoastrocytoma, presence of a neuronal element such as ganglioglioma, or DNET *(dysneuroembryoplastic epithelial tumor).* Presence of any high grade glioma including anaplastic astrocytoma, glioblastoma multiforme, anaplastic oligodendroglioma, or anaplastic oligoastrocytoma.

3.2.2 Tumors in non-supratentorial or other locations including optic chiasm, optic nerve*(s),* pons, medulla, cerebellum, or spinal cord.

3.2.3 Evidence of spread to spinal meninges or non-contiguous cranial meninges *(i.e., leptomeningeal gliomatosis)* based on a MRI scan of the spine or positive CSF cytology. **MRI of the spine/CSF cytology are not required in patients without symptoms of spinal/cranial meningeal spread.**

3.2.4 Gliomatosis cerebri.

3.2.5 Synchronous malignancy excluding *in situ* carcinoma of the cervix or non-melanomatous skin cancer; prior malignancy unless disease free ≥ 5 years.

3.2.6 Prior radiation to the brain or head/neck *(unless head/neck radiation clearly excluded the brain, e.g., radiation for localized vocal cord cancer).*

3.2.7 Prior chemotherapy.

3.2.8 Chronic lung disease unless pulmonary function tests demonstrate a DLCO ≥ 60% of predicted.

3.2.9 Active infectious process.

3.2.10 Pregnant or nursing women because of the potentially adverse effects of treatment on the developing fetus or newborn.

3.9.11 For premenopausal women or men of reproductive potential, inability or unwillingness to consider effective contraception until the completion of therapy.

4.0 PRETREATMENT EVALUATION [8/18/03] *(all tests and imaging studies must be obtained within 2 weeks prior to registration)*

4.1.1 Central pathology review *(Section 10.0)* is mandatory prior to randomization to confirm eligibility.

4.1.2 History and physical exam *(including neurologic exam)* with documentation of baseline signs, symptoms, and medications including steroids and anticonvulsants.

4.1.3 Assessment including KPS, NFS, Mini Mental Status Exam *(MMSE).*

4.1.4 *Laboratory Tests (for High Risk Patients)*

4.1.4.1 Hematology: hemoglobin, WBC with differential *(AGC),* and platelet count.

4.1.4.2 Biochemistry: sodium, potassium, creatinine, total bilirubin, glucose, SGOT *(AST),* SGPT, and alkaline phosphatase.

4.1.5 *Imaging Studies*:

4.1.5.1 Chest X-ray

4.1.5.2 Pre-op MRI with and without contrast

4.1.5.3 Post-op MRI scan with and without contrast. Post-op CT scan not acceptable. The MRI must include T1 weighted images with and without contrast, and T2 weighted images. Patients who undergo biopsy only do not need a post-op MRI.

4.1.6 *Pulmonary*

4.1.6.1 Pulmonary function tests including DLCO if patient has an abnormal CXR or a history of or active chronic lung disease.

4.1.7 For premenopausal women of childbearing potential: pregnancy test.

4.1.8 *Risk Group Determination*

- Low Risk: age < 40 years old and gross total resection

- High Risk: age ≥ 40 years old or subtotal resection/biopsy

5.0 REGISTRATION PROCEDURES

5.1 ***Central pathology review (see Section 10.0) must be completed prior to randomization. Registration must take place within 12 weeks after tissue diagnosis.***

5.2 RTOG Institutions

Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

5.3 ECOG Institutions

5.3.1 **A signed HHS 310 Form, a copy of the institution's IRB-approved informed consent document, and written justification for any changes made to the informed consent for this protocol must be on file at the ECOG Coordinating Center before an ECOG institution may enter patients.** These will be submitted to: ECOG Coordinating Center, Frontier Science, Attn: IRB, 303 Boylston Street, Brookline, MA 02445-7648. Patient must not start protocol treatment prior to registration. Treatment must begin within four weeks after randomization. See Section 10.0 for pre-randomization pathology requirements.

5.3.2 To register eligible patients on study, the investigator will telephone the Randomization Desk at the ECOG Coordinating Center at *(617)* 632-2022 Monday-Friday between the hours of 9:00 am and 4:30 pm ET, to allow time to call RTOG that same day. ECOG members should not call RTOG directly. The following information will be requested: Protocol Number; Investigator Identification (*including institution and/or affiliate name and investigator's name);* Patient identification *(including patient's name or initials and chart number, patient's social security number, patient demographics [sex, birth date, race, nine-digit zip code and method of payment]);* Treatment start date; Pathology block number*(s)* for diagnostic primary tumor; Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0. The randomization specialist will verify eligibility by asking questions from the checklist and will also verify IRB approval. The ECOG Randomization Desk will contact RTOG to enter the patient, after which the ECOG Coordinating Center will contact the institution to relay the treatment assignment for that patient.

5.3.3 RTOG will send a Confirmation of Registration and a Forms Due Calendar to ECOG for each case registered. ECOG will forward copies to the participating institution.

5.3.4 If a patient does not receive any protocol therapy, written notification and an explanation must be received at ECOG Headquarters *(who will route it to RTOG)* as soon as this has been determined. The Onstudy Form *(I1)* and Eligibility Checklist should also be submitted. RTOG will notify ECOG if the patient may be canceled. Once a patient has been given protocol treatment, all forms must be submitted.

5.3.5 On a case-by-case basis, patients entered through ECOG institutions may decline to participate in the Quality of Life component of the study.

5.3.6 Additional Intergroup information is in Appendix VI.

5.4 SWOG Institutions

5.4.1 Investigators will call the Southwest Oncology Group Statistical Center at *(206)* 667-4623 between the hours of 6:30 a.m. and 1:30 p.m. *(PT)* Monday through Friday, excluding holidays. This must be done in order for the Southwest Oncology Group Statistical Center to complete the registration with RTOG prior to the close of business. The Statistical Center will obtain information as per Section 5.2, RTOG Registration. In addition, the Statistical Center will request the date informed consent was obtained and the date of IRB approval for each entry. The Statistical Center will then contact RTOG to register the patient after which the Statistical Center will contact the institution to confirm registration and relay the treatment assignment and case number for that patient. RTOG will forward a confirmation of treatment assignment to the Statistical Center for routing to the participating institution.

5.4.2 Patients must be registered prior to the initiation of treatment *(no more than 4 weeks prior to the planned start of treatment).* The information listed on the RTOG Eligibility Checklist must be completed as well as the SWOG Registration Form. The caller must also be prepared to provide the date of Institutional Review Board approval for this study. Patients will not be registered if the IRB date is not provided or is > 1 year prior to the registration date.

5.5 NCCTG Institutions

A signed HHS 310 form is to be on file at the NCCTG Randomization Center before patient entry.

To register a patient, call the NCCTG Randomization Center *(507)* 284-4130 8 a.m. to 3 p.m. *(CT)* Monday through Friday. The NCCTG Randomization Center will verify eligibility by completing the eligibility checklist and will call the RTOG Headquarters at *(215)* 574-3191, Monday through Friday 8 a.m. to 3 p.m. *(CT)* to register a patient. NCCTG will also verify that both a radiation oncologist and a medical oncologist have consulted with the patient and verified that the patient is a suitable candidate for this study. The treatment assignment and case number will be relayed to the registering institution. RTOG will send a Confirmation of Registration and a Forms Due Calendar to NCCTG who will forward this information to the participating institution.

6.0 RADIATION THERAPY

6.1 General Requirements

- Megavoltage machines ≥ 6MV
- SAD ≥ 100 cm
- At least 2 fields, shaped, all fields treated daily; **the use of opposed lateral fields treating significant volumes of uninvolved contralateral normal brain is strongly discouraged**
- 2 or 2.5D *(i.e., coplanar)* or 3D *(i.e., coplanar or noncoplanar)* treatment planning approaches can be used
- Port films need to be taken per department routine but will not be submitted to RTOG for review.

6.2 Treatment Volumes

The target volume is based on the T2 weighted images from the postoperative MRI scan *(the preoperative MRI scan can be used in patients who underwent biopsy only)* and will include any T2 abnormality suspected of containing tumor plus a 2 cm margin *(to block edge).* If the tumor has been completely resected, the target volume will be the surgical defect and any T2 abnormality surrounding the surgical defect plus a 2 cm margin *(to block edge).* **There will be no boost volume.** The margin may be reduced to a 1 cm margin *(to block edge)* around critical structures *(See Section 6.4)* and/or natural barriers to tumor growth *(e.g. skull and tentorium).*

6.3 Dose, Schedule, Dosimetry, and Compliance Criteria

Treatment will be given in 1.8 Gy fractions *(to isocenter)*, 1 fraction per day, 5 days per week and must begin within four weeks after randomization. The total dose will be 54 Gy in 30 fractions over approximately 6 weeks. The target volume must receive 95-105% of the prescribed total dose to be per protocol *(encompassed by the 51.3 to 56.7 Gy isodose line).*

If the target volume receives 90-94% or 106-110% of the prescribed total dose, an acceptable variation will be assigned.

If the target volume receives < 90% or >110% of the prescribed total dose, an unacceptable deviation will be assigned.

Other variances from protocol radiotherapy will be assigned as follows:

≤ 5% variation from protocol specifications-per protocol;

6-10% - acceptable variation;

>10% - unacceptable deviation.

The isodose distribution in the transverse *(axial)* plane through the geometric center of the target volume must be submitted to RTOG for review.

6.4 Critical Structures

Every attempt should be made to shield the globes *(including lenses and retinae)* from any direct radiation beams. A portion of one globe may receive ≤ 10 Gy. The pituitary gland, optic chiasm, or brainstem *(medulla, pons, midbrain)* may not receive > 105% *(56.7 Gy)* of the prescribed total dose of 54 Gy. Uninvolved contralateral normal brain may not receive > 36 Gy.

6.5 Radiation Toxicity (3/24/10)

Radiation toxicity was scored using the NCI Revised Common Toxicity Criteria Version 2.0 *(3/98)* for toxicities appearing ≤ 90 days after RT start and the RTOG/EORTC Late Radiation Morbidity Scoring Criteria *(Appendix IV)* will be used to score toxicities appearing or persisting > 90 days after start of RT.

Potential acute toxicities include: skin, eye, ear and CNS. Potential late toxicities include skin, subcutaneous tissue, brain, and eye.

7.0 DRUG THERAPY (3/24/10)

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual. All chemotherapy toxicities will be scored using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) beginning April 1, 2010. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE

7.1 Procarbazine Hydrochloride *(P)*

Procarbazine is an orally administered lipid soluble hydrazine-derivative. It freely crosses the blood-brain barrier. While its mode of action is not fully understood, procarbazine appears to inhibit both protein and nucleic acid synthesis. It is used to treat Hodgkin's disease, brain tumors and other cancers. Procarbazine is manufactured by Roche and available commercially in 50 mg capsules. Its major toxicities include myelosuppression, both leukopenia and thrombocytopenia, anorexia, nausea, vomiting, diarrhea, stomatitis, and allergic reactions *(rarely anaphylaxis).* Procarbazine produces mild monoamine oxidase inhibition necessitating a low tyramine diet. It may cause transient CNS side effects such as personality change, confusion, or somnolence and can evoke a disulfiram-like reaction. Food and beverages to avoid include alcohol, yogurt, ripe cheese, and bananas. Over-the-counter cold medications should be avoided. Since procarbazine may inhibit monoamine oxidase, a thorough review of concurrent medications for potential drug interactions should be undertaken prior to initiating procarbazine. Continued vigilance for drug interactions is necessary with the addition of medications during procarbazine therapy. Caution patients not to take any new medications *(including over-the-counter medications)* without consulting a physician or pharmacist during procarbazine therapy. Use of meperidine should be considered contraindicated during or within two weeks following procarbazine therapy.

7.2 Lomustine *(CCNU)(C)*

CCNU is an orally administered lipid soluble nitrosourea. It freely crosses the blood-brain barrier. CCNU exerts cytotoxic effects by alkylating DNA and RNA. It is used primarily to treat brain tumors. CCNU is manufactured by Bristol and available commercially in 100, 40 and 10 mg capsules. Its major toxicities include delayed myelosuppression, both leukopenia and thrombocytopenia, nausea and vomiting. Pulmonary fibrosis may occur at higher cumulative doses *(>1100 mg/m^2).* Hepatotoxicity and nephrotoxicity are uncommon side effects.

7.3 Vincristine *(V)*

Vincristine is a parenterally administered naturally occurring water soluble antineoplastic. It does not cross the blood-brain barrier. Vincristine is a mitotic spindle poison and arrests dividing cells in metaphase. It is used to treat a variety of hematologic and solid-tissue malignancies. Vincristine is manufactured by Eli Lilly and available commercially in 1, 2 and 5 mg vials. Its major toxicities include sensorimotor and autonomic neuropathy. Myelosuppression is rare. Fatal if given intrathecally; for intravenous use only. Syringes containing the product should be labeled "*Warning- for IV Use Only*". Extemporaneous prepared syringes containing Vincristine must be packaged in an overwrap labeled "*Do Not Remove Covering Until Moment of Injection. Fatal if Given Intrathecally. For Intravenous Use Only*"

7.4 Treatment Prescription (3/24/10)

7.4.1 *PCV Regimen*

Patients assigned to the chemotherapy arm will receive six cycles of PCV at eight week intervals. PCV must start within one calendar month following the last day of radiation therapy. Procarbazine, CCNU and Vincristine will be prescribed as follows:

DRUG	DOSE	ROUTE	SCHEDULE
Procarbazine	60 mg/m^2	p.o.	Days 8- 21
CCNU	110 mg/m^2	p.o.	Day 1
Vincristine	1.4 mg/m^2*	i.v.	Days 8,29

* Maximum dose 2 mg

Each cycle will last 8 weeks, i.e., will be defined as the period of therapy as outlined above plus 4 weeks.

7.4.2 *Dose Calculations*

Doses will be calculated using actual body weight. CCNU doses will be rounded to the nearest 10 mg *(e.g. 242 give 240 mg., 245 or 248 give 250 mg)*. The total number of procarbazine capsules to be administered on days 8 through 21 will be calculated as follows: *(60 x surface area in m^2 x 14)* ÷ 50 rounded to the nearest whole number *(e.g. 39.2 give 39 tabs, 39.5 or 39.8 give 40 tabs)*. To minimize nausea and vomiting, procarbazine may be introduced gradually as follows: e.g., 50 mg po day 8, 100 mg po day 9 and following. Vincristine doses will be rounded to the nearest tenth of a milligram up to 2.0 mg. **There will be a 2 mg limit on each dose of vincristine**.

7.4.3 *Dose Modifications*

Patients will have a complete blood count on a weekly basis while receiving PCV. **There will be no dose escalations**. Doses will be reduced for hematologic and other toxicities and scored using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events **beginning April 1, 2010.** The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.. All dose reductions will be maintained in subsequent treatment cycles.

7.4.3.1 Hematologic Toxicity

The doses of CCNU and **Procarbazine will be reduced based on nadir blood counts of the previous cycle as follows:**

Absolute Granulocyte ***(nadir)***		**Platelet Count** ***(nadir)***	**Dose Next Cycle CCNU & Procarbazine**
≥ 0.5 x 10^9/L *(≥ 500)*	**and**	≥ 50 x 10^9/L *(≥ 50,000)*	No change
≤ 0.5 x 10^9/L *(< 500)*	**or**	< 50 x 10^9/L *(< 50,000)*	Reduce previous cycle's dose by 25%

Vincristine dose will not be reduced for low treatment-day blood counts. Vincristine will be given days 8 and 29 of each cycle.

7.4.3.2 Neurotoxicity

Vincristine will be stopped for grade 3 or grade 4 neurosensory or neuromotor toxicity. CCNU and procarbazine continue as per protocol. For severe abdominal or jaw pain, reduce vincristine dose by 50% on all subsequent doses.

7.4.3.3 Nausea/Vomiting

If grade 3 or grade 4 nausea or vomiting persist despite antiemetics, the doses of CCNU and procarbazine may be reduced as described for "other toxicity" in Section 7.4.3.7.

7.4.3.4 Skin Toxicity

Procarbazine will be discontinued should an urticarial rash develop from PCV. Note: a generalized erythematous rash may be a manifestation of Dilantin, Tegretol, or other drug allergy. Procarbazine may be continued or stopped at the discretion of the investigator for non-urticarial rashes. CCNU and vincristine will continue per protocol.

7.4.3.5 Pulmonary Toxicity

CCNU will be stopped if cough, shortness of breath, or other pulmonary symptoms develop and if the DLCO is < 60% of predicted. Procarbazine and vincristine will continue per protocol.

7.4.3.6 Hepatic Toxicity

Hold all drugs for SGOT *(AST)* or SGPT >3x normal and resume with 25% dose reduction when SGOT or SGPT is ≤ 2x normal.

7.4.3.7 Other Toxicity

Doses will be reduced by 25% for grade 3 toxicity, and 50% for grade 4 toxicity. PCV may be discontinued for any grade 4 toxicity *(see Section 7.4.5)* but only after discussion with the medical oncology study co-chair.

7.4.4 *Treatment Delays*

Doses of vincristine will not be delayed for hematologic toxicity on days 8 or 29. Cycles 2 through 6 will be delayed for low treatment day counts as outlined below:

Absolute Granulocyte Count *(at retreatment)*		Platelet Count *(at retreatment)*	Dose This Cycle CCNU & Procarbazine
≥ 1.5 x 10^9/L *(≥ 1500)*	**and**	≥ 100 x 10^9/L *(≥ 100,000)*	Proceed – dose dictated by nadir counts
< 1.5 x 10^9/L *(< 1500)*	**or**	< 100 x 10^9/L *(< 100,000)*	Delay treatment until hematologic recovery

7.4.5 *Duration of Treatment*

Toxicity permitting, there will be 6 cycles of PCV. PCV will be discontinued for:

- treatment delays in excess of 12 weeks from day 1 of the present cycle.
- any reason at the request of the patient or guardian.
- MRI scan documented tumor progression *(see Section 11.8).*
- clinical deterioration, which in the judgement of the treating physician, is due to disease progression.

Note: if the scan is unchanged, the investigator should be careful to exclude causes of clinical deterioration that mimic tumor progression such as radiation effects, anticonvulsant or other drug toxicity, occult infection, pulmonary embolism with hypoxemia, precipitous steroid withdrawal, intratumoral hemorrhage, etc.

7.4.6 *Antiemetics*

Antiemetics may be prescribed as required but steroids may not be used as antiemetics. It is strongly recommended that patients receive either granisetron or ondansetron orally as prophylaxis for CCNU and at least the first 3 days of procarbazine *(e.g., granisetron 1 mg po or ondansetron 8 mg po TID beginning 1 hour before chemotherapy).*

7.5 Toxicity Reporting/RTOG Members (3/24/10)

7.5.1 The revised NCI Common Toxicity Criteria Version 2.0 *(3/98)* was used to score chemotherapy and acute radiation *(≤ 90 days)* toxicities. The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting **beginning April 1, 2010.** The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE. The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent*(s)* should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.5.1.1 Any ADR which is both serious *(life threatening, fatal)* and unexpected.

7.5.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.5.1.3 Any death on study if clearly related to the commercial agent*(s)*.

7.5.1.4 Acute myeloid leukemia *(AML)*. The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.5.2 The ADR report should be documented on Form FDA 3500 *(Appendix V)* and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
***(301)* 230-2330**
available 24 hours
FAX *(301)* 230-0159

7.6 Adverse Drug Reaction Reporting Requirements/ECOG Members (3/24/10)

The CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting **beginning April 1, 2010.** The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of the CTCAE.

7.6.1 The following adverse reactions must be reported to ECOG, the NCI, and your local IRB in the manner described below:

	Grades 4-5 unexpected[1]	**Death due to RX or within 30 days of RX[2]**
ECOG ADR Form to NCI within 10 days	X	
ECOG ADR Form to ECOG Coordinating Center within 10 days	X	X
Notify local IRB within 10 days	X	X

1. Any unexpected toxicity not reported in the literature or the package insert must be reported.
2. Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the protocol treatment has ended but which is felt to be treatment related, must be reported.

ECOG suggests ADRs be reported to on the Adverse Reaction *(ADR)* Form for Investigational Drugs *(Form 391RF)*. The form must be signed by the treating investigator.

7.6.2 *Reporting of All Second Primary Cancers*

	NCI/CTEP Secondary AML/MDS Report Form[1]	**ECOG Second Primary Form[2] *(Form #630)***
AML/MDS	X	
All other secondary cancers		X

1. To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and to the NCI, accompanied by copies of the pathology report *(and when available, a copy of the cytogenetic report).*
2. To be submitted to ECOG within 30 days of diagnosis of a new primary cancer during or after protocol treatment, regardless of relationship to protocol treatment. Not for use for reporting recurrence or metastatic disease. A copy of pathology report should be sent, if available.

7.6.3 **The ECOG Coordinating Center will call the RTOG Operations Office to report the telephone ADR calls. The ADR forms will be forwarded to the RTOG Operations Office by the ECOG Coordinating Center.**

NCI Telephone Number*: (301)* 230-2330
NCI FAX: *(301)* 230-0159
NCI Mailing Address
IDB
P.O. Box 30012
Bethesda, MD 20824

ECOG Telephone Number: *(617)* 632-3610
ECOG FAX: (617) 632-2990
ECOG Mailing Address:
ECOG Coordinating Center
ATTN: ADR
Frontier Science
303 Boylston Street
Brookline, MA 02445-7648

7.6.3 *Non-Treatment Related Toxicitie*s
Toxicites which fall within the definitions listed above must be reported as an ADR/second primary regardless if they are felt to be treatment or not. Toxicities unrelated to treatment that do NOT fall within the definitions above, must simply be clearly documented on the Data Forms which is submitted to the ECOG Coordinating Center *(ATTN: DATA)* according to the Data Collection Section *(Section 12.0).*

7.7 Adverse Drug Reaction Reporting/SWOG Members

7.7.1 All Southwest Oncology Group (SWOG) investigators are responsible for reporting of adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines. SWOG investigators must:

- **Call the SWOG Operations Office 210/677-8808 within 24 hours of any suspected adverse event deemed either drug-related, or possibly drug-related.** Instructions will be given as to the necessary steps to take depending on whether the reaction was previously reported, the grade *(severity)* of the reaction, study phase, and whether the reaction was caused by investigational and/or commercial

agent*(s)*. The SWOG Operations Office will immediately notify the RTOG Headquarters Data Management Staff as listed in the RTOG reporting guidelines.

- **Within 10 days the investigator must send the completed** *(original)* Adverse Reaction Form *(ADR)* for Investigational agents *(#391RF)* or FDA 3500 form *(for regimens using only commercial agents)* to the NCI:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824

- In addition, within 10 days the investigator must send:
  - a copy of the above report,
  - all data records for the period covering prestudy through the adverse event, and
  - documentation of IRB notification to the following address**:**

ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217

7.8 Adverse Drug Reaction Reporting/NCCTG Members

7.8.1 Fax, then report in writing to NCCTG Operations Office *(no telephone calls necessary)* within five working days:

1. Any ADR that is both serious and unexpected: life threatening *(grade 4)* or fatal *(grade 5)*.
2. Any increased incidence of a known ADR that has been reported in the package insert or the literature.
3. Any death on study, if clearly related to the commercial agent*(s)*.

7.8.2 The ADR report must be documented on the ADR form *(Form FDA 3500)* and the original mailed to:

North Central Cancer Treatment Group
Operations Office
200 First Street, SW
Rochester, MN 55905

7.8.3 The NCCTG Operations Office will immediately forward a copy of the ADR form to RTOG and IDB if deemed a reportable ADR.

8.0 SURGERY

8.1 Definitions of Extent of Surgical Resection

8.1.1 *Gross Total Resection (GTR)* - removal of all grossly abnormal tumor tissue **as defined by the neurosurgeon**. Patients <40 years old who underwent GTR will be registered to Arm 1, and will be observed with close follow-up. Patients ≥ 40 years old who underwent GTR will be randomized to either Arm 2 or 3, and will undergo radiation therapy +/- PCV chemotherapy.

8.1.2 *Subtotal Resection (STR)* - removal of less than all grossly abnormal tumor tissue as defined by the neurosurgeon. All patients who underwent STR, regardless of age will be randomized to either Arm 2 or Arm 3, and will undergo radiation therapy +/- PCV chemotherapy.

8.1.3 *Biopsy Only*- removal of a tissue specimen for the purpose of making a histologic diagnosis. May be performed stereotactically or via craniotomy. All patients who undergo biopsy only, regardless of age, will be randomized to either Arm 2 or Arm 3, and will undergo radiation therapy +/- PCV chemotherapy.

8.2 Postoperative Imaging

8.2.1 At the discretion of the clinician entering a patient to Arm 1 of this trial, if postoperative imaging strongly suggests the presence of significant residual tumor, the patient may be randomized to either Arm 2 or Arm 3 *(radiation therapy +/-PCV chemotherapy)*. For the purpose of stratification, such patients will still be considered to have undergone GTR.

9.0 OTHER THERAPY

9.1 Steroid Use

Steroids may be used as required to control CNS symptoms due to tumor-associated or RT-associated cerebral edema, but wherever possible, should be tapered and stopped. Steroid doses at study entry and at specific time points after treatment *(see Sections 11.0 and 12.0)* will be recorded. Investigators should avoid radical changes in steroid dose during periods critical for response evaluation so as not to complicate the assessment of response to PCV in the experimental arm.

9.2 Anticonvulsant Use

Anticonvulsants may be used as clinically indicated. Doses at study entry and at specific time points of the treatment must be recorded.

10.0 PATHOLOGY

10.1 Prerandomization Central Pathology Review for all Groups *(8/18/03)*

10.1.1 ***Central pathology review is mandatory prior to study entry to confirm eligibility***. It should be initiated as soon as a tissue diagnosis has been made. Central pathology review will be performed by Dr. Stephen Coons. Pathology materials must be sent directly to Dr. Coons *(Section 10.1.3)*.

10.1.2 To be eligible for this study, the patient's tumor must be a WHO grade II astrocytoma, oligodendroglioma, or oligoastrocytoma. The tumor may have atypia but not other histologic features such as mitoses, endothelial proliferation, and/or necrosis that would result in a designation of anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma, or GBM. Low grade glioma variants, such as pilocytic astrocytoma, subependymal giant cell astrocytoma of tuberous sclerosis, subependymoma, pleomorphic xanthoastrocytoma, ganglioglioma, or DNET *(dysneuroembryoplastic epithelial tumor)* are not eligible.

All pathology materials sent to Dr. Coons for central review must be accompanied by the "local" pathology report and a Pathology Checklist completed by the local pathologist.

10.1.3 The following materials will be sent by overnight mail to Dr. Coons:

- Pathology Checklist *(Appendix III)* completed by the local pathologist *(left side only)*
- PreRandomization Pathology Submission Form *(available from RTOG HQ)*
- Representative slides *(H&E sections)*.
- In the lower left hand corner of the address label or mailing envelope, write: *"LOW GRADE GLIOMA PROTOCOL"*.
- Name, phone and fax number of person to whom the results of the central pathology review should be transmitted. Notify Dr. Coons' office by phone or fax that a case is coming for review. Send to:

Stephen W. Coons, M.D.
Division of Neuropathology
Barrow Neurologic Institute
St. Joseph Hospital and Medical Center
350 W. Thomas Rd.
Phoenix, AZ 85013-4496
Phone *(602)* 406-7088
Fax (602) 406-7169

10.1.4 After the pathology materials have been reviewed, Dr. Coon's office will call the institution notifying them of whether or not the case is eligible. This will be confirmed by fax.

10.1.5 If the patient enters the study, the patient's RTOG case number will be added to the Pathology Checklist and a copy of the completed form will be sent to RTOG. Representative H&E slides will be retained by Dr. Coons. The remaining materials will be returned to the submitting institution *(or Group, for intergroup cases.*

10.1.6 If the patient does not enter the study, all slides and forms will be returned to the submitting institution.

10.1.7 ECOG Institutions: Please follow RTOG guidelines.

10.2 Peripheral Blood Samples *(8/18/03)*

10.2.1 Following confirmation of eligibility, the institution entering the patient will be required to send six tubes of peripheral blood. A specimen mailing kit will be sent to the institution by Mayo Medical Laboratories, Rochester, MN with specific instructions on how to properly return the blood samples. Blood should not be drawn until the mailing kit is received. **Do not ship blood samples without the special mailing kit.**

10.2.2 *Submission of Blood Samples*

Following confirmation of eligibility, the institution entering the patient will send six tubes of peripheral blood, 5 cc each, four in EDTA vacutainer tubes, and two in Heparin vacutainer tubes; the blood is to be received within 48 hours of collection. The registering institution will need to notify Mayo Medical Laboratories of the RTOG case number; this number must appear on all labels. If you have any

questions regarding specimen collection, processing, and/or courier arrangements, contact Darla Schletty *(Mayo Medical Laboratories)* at 1-800-826-5561.

Kits will be supplied through Mayo Medical Laboratories *(MML).* Participating institutions may obtain kits by submitting the attached FAX Supply Request Form *(Appendix VII)* to Darla Schletty *(fax: 507/266-0188)* who will then federal express the kit to you. **Do not ship blood samples until the kit has been received.**

The appropriate type and number of collection tubes and a three-part MML requisition form will be contained within each specimen collection kit. The RTOG case number must appear on the requisition form adjacent to the RTOG protocol number and on all specimen labels.

The pink copy of the form is for submitting institution's records, the remaining two copies of the form are to be returned with the specimens to MML. MML will forward one copy to the Operations Office of the appropriate Cooperative Group, upon receipt of the specimen.

If a site has a Mayo courier, use this courier to send in the specimens. If not, ship Federal Express according to the following instructions.

10.2.3 *Shipment of Peripheral Blood by Federal* Express *(for sites without Mayo courier)*

Federal Express may be either your primary courier service or backup to your regular courier service. However, shipments by Federal Express may be made at any time your regular courier service is unavailable.

10.2.3.1 Specimens must be completely packaged in shipping containers prior to Federal Express pickup.

- All specimens should be placed in the "refrigerate specimen" transport bag, as noted previously in instructions for each study visit.
- Place the refrigerate specimen transport bag, along with a solidly frozen cold pack, into the "Refrigerate Only" shipping container provided by Mayo Medical Laboratories. Seal the container.

NOTE: Freeze and store cold packs in the freezer, not on dry ice. Dry ice freezes the cold packs at a temperature that may cause samples to freeze more readily. Place the frozen cold pack in the bottom of the Styrofoam® container. Place a paper towel between the cold pack and the sample*(s)* to minimize the risk of freezing.

Between November 15 and March 15, use a refrigerated cold pack rather than a frozen cold pack if you are located North of the Mason-Dixon line. This will help to prevent the specimens from freezing during the Winter.

- Complete a pre-printed Federal Express airbill. Be sure to request Priority Overnight service and to indicate "Deliver Saturday" on the airbill if you ship on Friday.
- Write your return address on the shipping container.

10.2.3.2 Call **Federal Express** at 1-800-238-5355 by noon for same-day service. Provide the following information:

- Exact location of pick-up site.
- Number of refrigerate boxes in shipment.

10.2.3.3 Assist the **Federal Express** courier in finding the shipping box*(es)*, if requested.

Please contact **Mayo Laboratory Inquiry** at 1-800-826-5561 if you have questions regarding these arrangements.

10.3 RTOG Tumor Bank *(for RTOG, ECOG, and SWOG Institutions)*

10.3.1 Patients entered on this study should participate in the RTOG Tissue Bank.

10.3.2 The following must be provided:

10.3.2.1 One paraffin block of tumor or 15 unstained slides *(on "plus" coated slides).* Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.3.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.3.2.3 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.3.3 RTOG will reimburse pathologists from submitting institutions $100 per case if proper materials are submitted *(reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement).*

10.3.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request *(pathology blocks belong to the patient from whom tissue has been removed).*

10.3.5 Materials will be sent to:

LDS Hospital
Department of Pathology
E.M. Laboratory
8th Avenue and C Street
Salt Lake City, UT 84143
***(801)* 321-1314**
FAX *(801)* 321-5020

10.3.6 *ECOG Institutions*

One paraffin block of tumor or 15 unstained slides along with the completed ECOG Pathology Material Submission Form #638 and the institutional pathology report, should be submitted to the ECOG Pathology Coordinating Office *(PCO).* A copy of the completed submission form will be sent to the ECOG Study Chair and to the ECOG Coordinating Center by the Pathology Coordinating Office. The submitting pathologist should be informed that the blocks will not be returned unless requested. The blocks or slides and form should be sent to: ECOG Pathology Coordinating Office, Evanston Hospital Room B634, 2650 Ridge Avenue, Evanston, IL 60201-1797. The PCO will retain this material until requested by RTOG.

10.4 NCCTG Institutions

Per Section 10.1, central pathology review is mandatory prior to study entry and patient's tumor must meet the requirements as stipulated in Section 10.2. Central pathology review *(representative slides only)* will be performed by Dr. Stephen Coons.

10.4.1 *NCCTG Submission of Representative Slides*

Prior to study entry, confirmation of eligibility must be verified by submission of materials, listed below, overnight mail, to Dr. Coons at the address noted in Section 10.1.3. It should be initiated as soon as the diagnosis has been made.

- Pathology Checklist *(Appendix III)* completed by the local pathologist *(left side only)*
- PreRandomization Pathology Submission Form
- Representative slides *(H&E sections)*
- In the lower left hand corner of the address label or mailing envelope, write *"LOW GRADE GLIOMA PROTOCOL"*.
- Name, phone, and fax number of a person to whom the results of the central pathology review should be transmitted. Notify Dr. Coons' office by phone or fax that a case is coming for review.

10.4.2 *NCCTG Submission of Paraffin Blocks*

Within 30 days of registration, inform the submitting pathology department that the paraffin blocks will be forwarded to the NCCTG Operations Office where they will be catalogued and retained for future laboratory correlative studies. If there is an insufficient amount of tissue available, a letter from the pathologist stating such must be submitted to the NCCTG Operations Office. Submit the paraffin blocks, operative and pathology reports to:

NCCTG Operations Office
200 First Street, SW
Rochester, MN 55905
Attention: Pathology Coordinator

Each block should be placed in individual plastic bags and each bag labeled with the NCCTG membership name, study patient number, patient's initials, protocol number, surgical accession number and source *(e.g., tumor location)*, pathology and operative reports.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters - Arm 1 *(Observation) [8/18/03]*

Parameter	On-Study	q 4 mos x 1 yr	q 6 mos x 2 yrs	q year
Central Path Review *(pre randomization)*	X			
Clinical Assessment, incl. KPS & NFS	X	X	X	X
Record Steroid & Anticonvulsant Doses	X	X	X	X
MRI without and with Contrast	X[a,b]	X	X	X
Mini-Mental Status Exam	X	X	X	X

11.2 Study Parameters - Arm 2 *(Radiation Alone) [8/18/03]*

Parameter	On-Study	At Completion of RT	q 4 mos x 1 yr	q 6 mos x 2 yrs	q year
Central Path Review *(pre randomization)*	X				
Clinical Assessment, incl. KPS & NFS	X	X	X	X	X
Record Steroid and Anticonvulsant Doses	X	X	X	X	X
Hematology: Hgb, WBC, diff, AGC, plts	X				
Biochemistry: Na, K, creatinine, SGOT *(AST)*, SGPT, alk phos., total Bili, glucose	X				
MRI without and with Contrast	X[b]		X	X	X
Chest X-ray	X[c]				
Pulmonary Functions[d]	X				
Pregnancy Test[e]	X				
Mini-Mental Status Exam	X	X	X	X	X
Toxicity Evaluation		X	X	X	X

11.3 Study Parameters - Arm 3 *(Radiation + PCV) [8/18/03]*

Parameter	On-Study	At end of RT	Pre-cycles 1-6	Pre-cycles 3&5	4 mos after end of last cycle of chemo	q 6 mos x 2 yrs	q year
Central Path Review *(pre randomization)*	X						
Clinical Assessment incl KPS & NFS	X	X	X		X	X	X
Record Steroid & Anticonvulsant Doses	X	X	X		X	X	X
Hematology: Hgb, WBC, diff, AGC, plts	X		X *(and weekly during PCV)*		X	X	X
Biochemistry: Na, K, creatinine, SGOT *(AST)*, SGPT, alk phos., total Bili, glucose	X		X		X[c]	X[c]	X[c]
MRI without and with Contrast	X[b]			X	X	X	X
Chest X-ray	X[c]						
Pulmonary Functions[d]	X				X[d]		
Pregnancy Test[e]	X						
Mini-Mental Status Exam	X	X		X	X	X	X
Toxicity Evaluation		X	X	X	X	X	X

Key and Footnotes to Sections 11.1, 11.2, and 11.3:

KPS = Karnofsky Performance Status *(Appendix II)*, NFS = Neurologic Function Score *(Appendix II)*, AGC = Absolute Granulocyte Count, RT = Radiation Therapy

a. ***(8/18/03)*** Pre-op imaging study, suggested MRI technique: MRI should include the following: pre-contrast sagittal T1, axial T1 without and with contrast, axial T2 *(fast spin echo preferred, spin echo acceptable)*, coronal T1 post-contrast. Axial slice thickness should be 5 mm/skip 2.5 mm with 22 cm field of view, parallel to the AC/PC line. Sagittal slice thickness should be 6 mm/skip 33 mm with a 24 cm field of view. Coronal slice thickness should be 5 mm/skip 2 mm with a 22 cm field of view, perpendicular to the AC/PC line.
b. ***(8/18/03)*** Post-op and follow-up imaging studies: MRI with and without contrast *(patients who had biopsy only do not need post-op MRI if pre-op MRI with and without contrast was performed).*
c. As clinically indicated thereafter.
d. ***(8/18/03)*** Pulmonary function testing including DLCO is only needed at baseline in patients with an abnormal CXR or those symptoms suggesting CCNU toxicity, such as unexplained cough or dyspnea.
e. A pregnancy test is required for women of child-bearing potential.

11.4 Survival

Patients will be followed until death. The cause of death will be recorded for each patient and if possible the histologic type and extent of tumor reassessed at autopsy. Survival time will be the interval between the date of registration/randomization and the date of death.

11.5 Time to Progression

Patients will be followed clinically and radiologically as outlined in Sections, 11.1-11.3. The date at which the tumor is documented to have progressed *(see Section 11.6*) will be considered the date of tumor progression. Time to progression will be the interval between the date of registration/randomization and the date of tumor progression. Tumor progression will be confirmed by central review. In the event of a discrepancy and for the purposes of analysis, the treating physician's date of tumor progression will be deemed to be correct. Tissue confirmation of suspected tumor progression is encouraged. For patients suspected of having tumor progression in whom tissue confirmation is not possible, MRI spectroscopy, Thallium SPECT, or PET scanning is strongly recommended.

11.6 Response Assessment

11.6.1 The majority of supratentorial non-pilocytic low-grade astrocytomas, oligodendrogliomas, or oligoastrocytomas are non-enhancing on a MRI scan. Therefore, two sets of response data will be collected, one set for tumors that have an enhancing component and the second for tumors that are non-enhancing.

11.6.2 Responses will be confirmed by central review. For the purposes of classifying response, post-operative change, surgical defects, and areas of calcification will be ignored; tumor size will be the maximum cross-sectional area of the enhancing tumor on axial or coronal images. For tumors whose shape precludes maximum cross-sectional area measurement, the TR rather than PR response criterion should be used *(see below).* For patients who are deemed responders *(CR, PR, or TR*), response must be sustained on their consecutive imaging studies.

11.6.3 *Response Criteria for Tumors with an Enhancing Component*

Complete response **(CR)** - disappearance of all enhancing tumor on consecutive enhancing T1 MRI images on stable , decreasing, or no steroids, with a stable or improved KPS/NFS.

Partial response **(PR)** - 50% or greater decrease in enhancing tumor cross-sectional area on consecutive enhancing T1 MRI images on stable, decreasing, or no steroids, with a stable or improved KPS/NFS.

Tumor regression **(TR)** - A substantial *(~ 50% or greater)* decrease in enhancing tumor cross-sectional area on consecutive enhancing T1 MRI images on stable, decreasing, or no steroids, with a stable or improved KPS/NFS.

11.6.4 *Response Criteria for Tumors without an Enhancing Component*

Complete response (**CR**) - disappearance of all tumor on consecutive T2 MRI images on stable, decreasing, or no steroids, with a stable KPS/NFS.

Partial response (**PR**) - 50% or greater decrease in tumor cross-sectional area on consecutive T2 MRI images on stable, decreasing, or no steroids, with a stable KPS/NFS.

Tumor regression (**TR**) - A substantial decrease *(~ 50% or greater)* in tumor cross-sectional area on consecutive T2 MRI images on stable, decreasing, or no steroids, with a stable KPS/NFS.

11.6.5 *Definition of Stable Disease*

Stable disease **(SD)** - all situations other than those outlined in Sections 11.6.2, 11.6.3, 11.6.4, and 11.6.6.

11.6.6 *Definition of Tumor Progression*

For all patients, tumor progression will be defined as follows:

Progressive disease **(PD)** - 25% or greater increase in the cross-sectional area of enhancing or non-enhancing tumor on consecutive MRI scans, or any new area*(s)* of tumor. Under exceptional circumstances, disease progression may be declared in the absence of an increase in tumor size based on "clinical deterioration" including the need for increasing doses of steroid and/or a worsening KPS/NF.

11.7 Toxicity Evaluation

11.7.1 *Acute Toxic Reactions*

Patients randomized to post-RT PCV chemotherapy will have a complete blood count on a weekly basis while receiving PCV and a screening biochemical evaluation prior to each cycle of PCV *(see Section 11.3)*. Other tests such as CXR and pulmonary functions will be performed as necessary to assess pulmonary *(and other)* toxicity due to chemotherapy. All unexpected radiation reactions will be reported.

11.7.2 *Mental Status Evaluation*

All patients will be given the Mini Mental Status Examination prior to the start of protocol treatment, at the end of protocol treatment, and subsequently in followup.

11.7.3 *Other Toxicities*

All second malignancies, myelodysplastic syndromes, infections, neuromuscular disorders, dementias and other illnesses probably or possibly related to PCV or RT will be reported.

11.8 Documentation of Progression

Every attempt should be made to pathologically document tumor progression *(biopsy or resection)*. When this is not possible, an attempt should be made to obtain a physiological imaging study such as MRI spectroscopy, a PET scan, or a Thallium SPECT scan.

11.9 Treatment at Progression

Treatment*(s)* at the time of progression will be at the discretion of the treating physician*(s)*. The treatment*(s)* given should be recorded. Patients will be followed until death following documented progression.

11.10 Central Film Review *(8/18/03)*

Pre-op MRI scans and post-op/follow-up MRI scans will be reviewed on all patients who have responded, progressed *(Section 11.6)*, died, or experienced a grade 3, 4, or 5 neurotoxicity.

12.0 DATA COLLECTION

12.1 Summary of Data Submission *(8/18/03)*

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX# 215/928-0153)

Item	Due
Demographic Form **(A5)** Pathology Checklist **(P4)** *(copy, original to reviewer)* Specimen Transmittal Form **(ST)** *(copy, original to reviewer)* Initial Evaluation Form **(I1)** Pathology Report **(P1)** Pathology Slides/Blocks **(P2)** Initial Mini-Mental Status Evaluation **(MS)** Pre-op MRI and post-op MRI scans **(C1)** and reports **(C3)**	Within 2 weeks of study entry
Radiotherapy Form **(T1)** Complete treatment record **(T5)** Isodose Curves **(T6)** *(see Section 6.3 for details)*	Within 2 weeks of RT end *(Arms 2 & 3)*
Follow-up MRI scans **(C2)** and reports **(C3)**	At 4 months post RT
Chemotherapy Flowsheet **(M1)**	At the end of each cycle and 3 months after day 29 of last cycle
Initial Followup-Form **(FS)** Mini-Mental Status Evaluation **(MS)**	At end of RT and at 90 days from the start of RT *(Arms 2 and 3)*
Follow-up MRI scans **(C2)** and reports **(C3)**	At regression, progression, and at ≥ grade 3 neurotoxicity
Follow-up Form **(F1)** Mini-Mental Status Evaluation **(MS)**	q 4 mo x 1 yr, q 6 mo x 2 yr then annually. Also at progression /relapse and death *(F1 only).*
Autopsy Report **(D3)**	As applicable

12.2 Dosimetry and Film Submission

12.2.1 **Items will be sent directly to RTOG Headquarters by all Groups.**

12.2.2 MRI scans and reports must be submitted on all patients who respond, progress, die, or experience grade ≥ 3 neurotoxicity. These must be submitted to RTOG within 2 weeks of scan date.

12.3 ECOG, SWOG AND NCCTG DATA SUBMISSION

12.3.1 *ECOG*: The original data forms as listed in Section 12.1 should be submitted to the ECOG Coordinating Center 303 Boylston Street, Brookline, MA 02445-7648 *(ATTN: DATA).* Include the RTOG and ECOG study and case numbers. The ECOG Coordinating Center will forward the forms to RTOG. Do not use ECOG Forms for this study, with the exception of the Adverse Reaction *(ADR)* form *(Form #391RF),* the ECOG Second Primary Form *(Form #630),* the NCI/CTEP Secondary AML/MDS Report Form and the ECOG Pathology Materials Submission Form *(Form #638).*

12.3.2 *SWOG*: The original data forms as listed in this section should be submitted at the required intervals to the Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue, MP-557, Seattle, WA 98104-2092. Include the RTOG protocol number and patient case number as well as the Southwest Oncology Group study number and patient number. It is not necessary to submit extra copies.

12.3.3 *NCCTG*: All forms listed in Section 12.1 are to be submitted to the NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905. NCCTG will forward to RTOG.

12.3.4 **Both the ECOG, NCCTG, or SWOG and RTOG assigned case and study numbers must be recorded on all items submitted.** Unidentified data will be returned.

12.3.5 **Request for Study Information and Forms Request**:

Requests for additional information or clarification of data will be routed through ECOG/NCCTG/SWOG for distribution to the individual institution. The RTOG memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically *(generally three times per year)* computer generated lists identifying delinquent material are prepared and are routed through ECOG/NCCTG/SWOG for distribution.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is overall survival. Progression will also be examined.

13.1.2 The frequency and severity of toxicities will be examined.

13.1.3 Estimate overall survival and progression of low risk-patients when no adjuvant therapy is delivered.

13.1.4 Assess the agreement between neurosurgeon's and the central neuroradiologist's assessment of tumor resection.

13.2 Sample Size

The primary endpoint of this trial is survival. The standard arm is radiotherapy *(RT)* and the experimental arm is RT followed by PCV. Low-grade glioma patients classified as high-risk have an estimated five year survival of 70%. High-risk patients are defined as patients over age 40 or undergoing less than a gross total resection. This trial will test for a 21% improvement in five-year survival. The RT +PCV arm is expected to have an estimated 85% five-year survival rate.

The estimated sample size is 120 patients per arm. This sample size will ensure a 90% probability of detecting the specified improvement, if it exists, while rejecting the null hypothesis at the 95% level *(α=0.05, two-sided type I error).* This sample size is designed to test a difference between survival using a modified Wilcoxon statistic. The sample size of 240 patients is the maximum accrual assuming three interim analyses and an expected 80 deaths overall. Assuming a 5% ineligibility rate, **the total sample size required for Arms 2 and 3 is 252 patients.**

The grade 3 or worse toxicity from standard radiation therapy is expected to be 5% or less. A sample size of 126 patients per arm will provide at least 90% power to test a 19% or greater rate of grade 3 or worse toxicity on the RT + PCV arm. This assumes a two-sided statistical test. It is expected that 50 low risk patients will be accrued which will permit survival to be estimated within 8-11% error.

Assessing the agreement between the neurosurgeon's and the central neuroradiologist's assessments of resection will be performed using the kappa statistic. Assuming that 25% of the patients receive complete resection, a 0.05 level two-sided test that the intraclass kappa is 0.50 will have at least 89% statistical power to detect an alternative kappa of 0.70 when the sample size is 252.

13.3 Patient Accrual

The patient accrual is projected to be 4 patients per month. This trial should complete the accrual phase in 5 years. If the monthly accrual is less than 2 cases per month, the study will be re-evaluated with respect to feasibility.

13.4 Randomization Scheme

The randomization of high-risk patients will be stratified by tumor histologic subtype *(astrocytoma [mixed-astro dominant] vs. oligodendroglioma [mixed-oligo dominant]);* age *(< 40 vs. ≥ 40)*; KPS *(60-80 vs. 90-100);* and balance by accruing institution.

13.5 Other Stratification Factors

Contrast enhancement on pre-op scan: present vs. absent.

13.6 Analysis Plans

13.6.1 *Interim Analyses of Accrual and Toxicity Data*

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results have been submitted. In general, the interim reports will contain information about:

a) the patient accrual rate with projected completion date for the accrual phase;
b) the distribution of patients with respect to pretreatment characteristics including race and gender;
c) compliance rate of treatment delivery with respect to the protocol prescription;
d) the frequency and severity of the toxicities.

13.6.2 *Interim Analyses of Study Endpoints*

There will be three interim analyses of the primary study endpoint *(survival).* The interim analyses will proceed according to the following table:

Total Number of Deaths	Null Hypothesis	Alternative
20	0.00004	0.86
40	0.0026	0.336
60	0.011	0.0942

If a significance level is smaller than the values listed for the null hypothesis then the null hypothesis will be rejected. On the other hand, if a significance level is larger than the values listed for the alternative then the alternative will be rejected. These significance levels were calculated to ensure an overall significance level of 0.05. The results of these interim analyses will only be reported, in a blinded fashion to the Data Monitoring Committee. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the data monitoring committee, not results, will be reported to the brain committee, which is responsible for this study and, if necessary, the RTOG executive committee, so that corrective action can be taken.

13.6.3 *Analysis and Reporting of Initial Treatment Results*

This major analysis will be undertaken when every patient has been potentially followed for a minimum of five years or a maximum of 80 deaths have occurred. The usual components of this analysis are:

1) Tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
2) reporting institutional accrual;
3) distribution of the important prognostic factors by assigned treatment;
4) observed results with respect to the study endpoints.

Further subgroup analyses may be conducted *(depending upon the sizes within the subgroups)* for the purpose of identifying patterns of treatment responses. The p-value of 0.0478 will be used if all three interim analyses have been performed, thus correcting for previous interim tests.

13.7 Inclusion of Women and Minorities

In conformance with the National Institute of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observation. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender *(Curran et al.).* The RTOG found no difference in survival of glioblastoma multiforme patients by race *(Simpson et al.).* Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races. The projected accrual is shown below:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	0	1	6	6	80	0	93
Male	0	2	11	6	140	0	159
Unknown	0	0	0	0	0	0	0
Total	0	3	17	12	220	0	252

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APPENDIX I -A

RTOG 98-02

A PHASE II STUDY OF OBSERVATION IN FAVORABLE LOW-GRADE GLIOMA AND A PHASE III STUDY OF RADIATION WITH OR WITHOUT PCV CHEMOTHERAPY IN UNFAVORABLE LOW-GRADE GLIOMA

Sample Patient Consent Form

GROUP 1 PATIENTS

RESEARCH STUDY

I have the right to know about the procedures used in this research study. This form will tell me about the study so I can decide whether to be a part of this research study.

PURPOSE OF THE STUDY

I have an uncommon brain tumor called a low-grade glioma. Patients with this type of tumor can be divided into two groups based on their age and extent of surgical removal of their brain tumor:

1) patients who are < 40 years old and have had total removal of their tumor. The risk of regrowth is thought to be low. Patients in this group will not receive further therapy unless there is evidence of tumor regrowth on their follow-up brain scans after surgery.

2) patients 40 years of age or older, or those have had incomplete removal of their brain tumor. This second group of patients is thought to have a high risk of tumor regrowth if no further therapy is given after surgery. Patients in this group will receive 6 weeks of radiation therapy, with or without chemotherapy.

Since I am in the first, low risk, group my doctors want to see how I do after the surgery. They will also compare the results of my surgery according to my surgeon with the results of my surgery on MRI scans according to a radiologist.

DESCRIPTION OF PROCEDURES

No further therapy after surgery will be given. Therapy can be given if the tumor reappears. I will return for checkups and MRI scans every four months for one year, then twice a year for two years, then once a year.

With my permission, tissue slides, additional samples of my brain tumor tissue from the surgery and several small samples of my blood will be stored for future studies. These might be helpful to better understand and treat future patients with a similar kind of tumor.

RISKS AND DISCOMFORTS

There are no unpleasant or harmful side effects from taking part in this study. This is a no treatment study.

CONTACT PERSONS

Treatment will be available if needed; however, I will not be reimbursed for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research, I can contact Dr. _____ the investigator in charge at _____. In addition, I may contact _____ at _____ for information about patients' rights in research studies.

BENEFITS

The information obtained from this study will be used for scientific research. It may possibly be helpful to others.

I have been told that should my disease come back, or should developments occur that indicate the research program is not in my best interest, further treatment would be discussed.

ALTERNATIVES

I may decide to not join this research program. I can decide either way.

VOLUNTARY PARTICIPATION

I do not have to take part in this research study. I am free to withdraw at any time. If I refuse to participate, there will be no penalty.

CONFIDENTIALITY

Records of my progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG)*, and at ECOG, NCCTG, or SWOG, as applicable. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration *(FDA)*, the National Cancer Institute *(NCI)*, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review associated with this protocol.

I have read all the above, asked questions, received answers concerning areas I did not understand. I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

_____ _____

Patient Signature *(or Legal Representative)* Date

_____ _____

Investigator's Signature Date

TISSUE AND BLOOD TESTING

I agree to the use of my tissues/other samples for additional research studies.

☐ Yes ☐ No

_____ _____

Patient Signature *(or Legal Representative)* Date

APPENDIX I- B

RTOG 98-02

A PHASE II STUDY OF OBSERVATION IN FAVORABLE LOW-GRADE GLIOMA AND A PHASE III STUDY OF RADIATION WITH OR WITHOUT PCV CHEMOTHERAPY IN UNFAVORABLE LOW-GRADE GLIOMA

Sample Patient Consent Form

GROUP 2 PATIENTS

RESEARCH STUDY

I have the right to know about the procedures that are used in clinical research so I can decide whether to undergo the procedure after knowing the risks, benefits, and alternatives involved. This is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I have an uncommon brain tumor called a low-grade glioma. Standard treatment is surgery, radiation therapy to the brain, or a combination of both. Some of these tumors may regrow after standard treatment. Doctors have noticed that brain tumors like these respond *(shrink)* with chemotherapy. These tumors are sensitive to a number of chemotherapy drugs but the combination of procarbazine *(P),* CCNU *(C),* and vincristine *(V) (PCV)* seems the most promising. Combining chemotherapy and radiation may cause more side effects than radiation alone, but side effects may be acceptable if the more intense treatment controls the tumor more effectively. If radiation without chemotherapy does not control the tumor, chemotherapy can be given. It is not known which treatment approach is better, radiation alone or radiation plus chemotherapy.

For the purpose of this study, patients are divided into 2 groups based on their age and extent of surgical removal of their brain tumor: 1) patients who are < 40 years old and have had total removal of their tumor will not receive further therapy unless there is evidence of tumor regrowth on their follow-up brain scans since the risk of regrowth is thought to be low; 2) patients 40 years of age or older, or those have had incomplete removal of their brain tumor, will receive 6 weeks of radiation therapy, with or without chemotherapy, which will consist of 6 courses of PCV chemotherapy. These patients are thought to have a high risk of tumor regrowth if no further therapy is given after surgery.

DESCRIPTION OF PROCEDURES

My doctors are studying two groups of patients:

Patients in Group 1 are under 40 years old whose tumors have been completely removed. If I am in Group 1, no further therapy after surgery is being studied. Therapy can be given if the tumor reappears.

Patients in Group 2 are 40 years or older or have incomplete tumor removal. The therapy I get will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office that will assign me to one of two treatments by computer. The chance of getting one of the two therapies is approximately equal. I will get treated with one of the following:

- Radiation alone given once daily five days a week for six weeks.

- Radiation alone given once daily five days a week for six weeks. One month after I finish radiation treatments, I will start chemotherapy: CCNU on day one, vincristine on Days 8 and 29, and procarbazine for two weeks beginning at the same time as vincristine. These are usual chemotherapy drugs and can be given on an outpatient basis. I will receive up to 6 courses of PCV after radiation as shown below:

Drug	Method	Timing *(repeat up to 6 times [courses])*
CCNU	oral	Day 1
Procarbazine	oral	Days 8-21
Vincristine	i.v.	Days 8 and 29

Procarbazine is given orally by capsule daily. During this time, dietary and medication restrictions are required. I cannot drink alcoholic beverages while taking procarbazine. Combining alcohol and procarbazine will cause a hangover-like reaction. I must also avoid foods like yogurt, ripe cheese, and bananas. Over-the-counter medicines should also be avoided. I must check with my doctor before taking cold medications or any other kind of medication.

CCNU is given orally by capsule.

Vincristine is given as an intravenous *(in my vein)* injection over several minutes.

The typical length of one course is 8 weeks. During the first month of each course, I will receive the PCV chemotherapy. During the second month, I will have a break from chemotherapy.

After I finish treatment, I will return for checkups every four months for one year, then twice a year for two years, then once a year.

Summary of Treatment/Follow-up Schedules

Group	Age/Surgical Removal	Radiation	Chemotherapy	Follow-Up Schedules
1	< 40 and total removal	No	No	Every 4 months for one year then every 6 months for 2 years, then yearly; MRI scan & blood tests will be done each time.
2	≥ 40 or less than total removal	Mon-Fri for 6 weeks	No	
3		Mon - Fri for 6 weeks	Every other month for 1 year	

With my permission, tissue slides, additional samples of my brain tumor tissue from the surgery, and several small samples of my blood will be stored for future studies that might be helpful to better understand and treat future patients with a similar kind of tumor.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Risks: Radiation and chemotherapy have toxic effects that occasionally are severe, life threatening, or even fatal. During or shortly after radiation treatment I may experience some or all of the following side effects: scalp redness or soreness, hair loss, dry mouth or altered taste, hearing impairment, fatigue, or temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness. There may be other unexpected or unpredictable side effects, but these are uncommon. All toxic reactions will be treated in the best way possible and this may include steroid medications during radiation. Radiation sometimes causes late side effects such as mental slowing or behavioral change. Occasionally radiation causes severe local damage to normal brain tissue, a condition called necrosis *(tissue deterioration)*. Radiation necrosis can mimic recurrent brain tumor and may require surgery for diagnosis and treatment. I am encouraged to discuss this further with my doctor.

PCV chemotherapy may cause some or all of the following side effects: nausea or vomiting; infection or bleeding; numbness, tingling, or weakness of the hands or feet; severe constipation, abdominal pain, or jaw pain; allergic symptoms such as fever, rash, or blistering of the skin; or generalized weakness or fatigue. There may be other unexpected or unpredictable toxic reactions. All side effects will be treated in the best way possible and this may involve antinausea medications, hospitalization for antibiotics, platelet transfusions, stool softeners or laxatives, and steroids or antihistamines for allergic reactions. There are guidelines for reducing the doses of chemotherapy drugs or eliminating them altogether

should I experience serious or intolerable side effects. To avoid potential drug interactions, I should consult my physician or pharmacist before taking any new medications, including over the counter *(non prescription)* medications.

The success of my treatment and all its side effects will be carefully monitored. I will have checkups or MRI scans and blood tests at regular intervals *(every 4, 6, or 12 months)* during and after treatment. My doctor will evaluate my brain functions at each visit.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done to evaluate the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

If I agree to participate in this study and my tumor regrows, I will be offered other treatment as appropriate. This may include *(re)*operation, *(re)*irradiation, PCV chemotherapy, other chemotherapy, or other promising experimental treatment.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to pregnant women causes significant risks to the fetus. If I am a woman of childbearing age and have not been surgically sterilized *(tubal ligation or hysterectomy)*, I must have a pregnancy test before enrolling in this study. I must use adequate birth control measures to prevent pregnancy while participating in this study. If I am unwilling to use adequate birth control measures to prevent pregnancy, I should not participate in this study. If I should become pregnant while on this study, I must tell my doctor immediately.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

CONTACT PERSONS

If injury occurs as a result of this research, treatment will be available; however, I will not be reimbursed for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can contact Dr. _____ the investigator in charge at_____. In addition, I may contact _____ _____ at _____ for information about patients' rights in research studies.

BENEFITS

It is not possible to predict whether any personal benefit will result from the research program. The information obtained from this study will be used for scientific research. It may possibly be helpful to others. The possible benefits of this research program are greater shrinkage and control of my tumor and prolongation of my life.

I have been told that should my disease become worse, should side effects become very severe, or should developments occur that indicate the research program is not in my best interest the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

I may decide to not join this research program. I can decide either way.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I am free to withdraw my consent to participate in research at any time. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care**.**

CONFIDENTIALITY

Records of my progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group *(RTOG)*, and at ECOG, NCCTG, or SWOG, as applicable. The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration *(FDA)*, the National Cancer Institute *(NCI)*, qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review associated with this protocol.

I have read all the above, asked questions, received answers concerning areas I did not understand. I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature *(or Legal Representative)*	Date
Investigator's Signature	Date

TISSUE AND BLOOD TESTING

I agree to the use of my tissues/other samples for additional research studies.

☐ Yes ☐ No

Patient Signature *(or Legal Representative)*	Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

NEUROLOGIC FUNCTION (NF) STATUS

N F	Definition
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3.	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Sever neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

APPENDIX III

PATHOLOGY CHECKLIST for RTOG 98-02 ***(P4)***

PT Name: _____

Coop Grp: **RTOG, NCCTG, ECOG, SWOG**

Institution: _____

Case: _____

CENTRAL PATHOLOGY REVIEW MANDATORY PRIOR TO STUDY ENTRY.

Eligibility: WHO Grade II astrocytoma, oligodendroglioma, or oligoastrocytoma*****

Please indicate tissue source: Stereotactic biopsy *(date)* _____; Open biopsy/resection *(date)*_____.

LOCAL PATHOLOGY REVIEW	**CENTRAL PATHOLOGY REVIEW**
Tumor Grade/Type: WHO Grade II: Yes _____ No _____ Histologic Type: Astrocytoma* _____ Oligodendroglioma_____ Oligoastrocytoma‡ _____ * If Astrocytoma, Subtype: Diffuse Fibrillary _____ Gemistocytic _____ Protoplasmic _____ ‡ If Oligoastrocytoma: Astro dominant _____ Astro = Oligo _____ Oligo dominant _____	**Tumor Grade/Type**: WHO Grade II: Yes _____No _____ Histologic Type: Astrocytoma* _____ Oligodendroglioma _____ Oligoastrocytoma‡ _____ * If Astrocytoma,Subtype: Diffuse Fibrillary Gemistocytic _____ Protoplasmic _____ ‡ If Oligoastrocytoma: Astro dominant _____ Astro = Oligo _____ Oligo dominant _____
Features ***(check all that apply)*** _____ Atypia _____ Mitosis*(es)* _____ Endothelial Proliferation _____ Necrosis	**Features** ***(check all that apply)*** _____ Atypia _____ Mitosis*(es)* _____ Endothelial Proliferation _____ Necrosis

Completed by _____ Date _____

Telephone Number _____ FAX Number _____

***** Excluded are: Pilocyotic astrocytoma, subendymal giant cell astrocytoma of tuberous sclerosis, subependymoma, pleomorphic xanthoastrocytoma, ganglioglioma, and DNET *(dsyneuroembryoplastic epithelial tumor).*

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

APPENDIX IV

ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panopthalmitis/Blindness	
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/continuous O2/Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatitic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

DEATH DIRECTLY RELATED TO RADIATION EFFECTS

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff *(215/574-3214)* within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol *(FAX #215/928-0153).*

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute *(NCI)*, Investigational Drug Branch *(IDB)* or Food and Drug Administration *(FDA)*, the Principal Investigator should first call RTOG *(as outlined above)* unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group *(in the case of RTOG-coordinated intergroup studies)* must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities *(grade 5)* resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening *(grade 4)* toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal *(grade 5)* or life threatening *(grade 4)* adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions *(≥ grade 2)* resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities *(≥ grade 3)* from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch *(IDB)*
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(grade 4)* events which may be due to agent.	As above
- First occurrence of any toxicity *(regardless of grade)*.	Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. *Phase II, III Studies Utilizing Investigational Agents*

- All fatal *(grade 5)* and life threatening *(grade 4)* known adverse reactions due to investigational agent.	Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within working days with a copy to IDB. *(Grade 4 myelosuppression not reported to IDB)*
- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.	Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.	**Report **in writing** to RTOG Headquarters and IDB within 10 working days.

****** See attached *(if applicable to this study)* NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

I. REGISTRATION: RTOG will be responsible for all registration/ randomizations. The procedure is:
-Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
-The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
-RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forward a copy of the calendar to the participating institution.

II. PROTOCOL DISTRIBUTION: Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.

III. INSTITUTIONAL PARTICIPATION: It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.

IV. CONFIRMATION/CALENDARS: A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

The form identification code that appears on the Calendars in the "key" columns is found on the form in the lower right corner.

You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items that are not forms *(CT or MRI scan reports, pathology reports)* but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

Unless specified otherwise, all patients are followed until death or termination of the study.

V. FORMS: Other groups will attach a forms appendix to their members' version. It will be the responsibility of the other group's member to copy the attached forms and to maintain a supply of available forms for data submission.

The Demographic Data Form **(A5)** is required on all RTOG enrollments. This form is ideally completed by the patient. Instructions are found on the form.
The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review *(see below)*, data should be routed according to the mechanism set

up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to:

American College of Radiology
Radiation Therapy Oncology Group - 14th Floor
1101 Market Street
Philadelphia, PA 19107

VI. LABELS: Patient specific labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre op CT Brain Scan, "Large Photon Localization Film", "Follow-up Bone Scan", etc.

Research associates are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

VII. CANCELLATION/INELIGIBILITY: Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be canceled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission. RTOG requires all patients in randomized trials to be followed with data submission according to protocol schedule.

VI. RAPID REVIEW ITEMS: Time critical data that require rapid submission must be sent directly to RTOG. These items are:

T2 - Protocol Treatment Form
T3 - Photon Localization film *(for all fields treated initially)*
T4 - Photon dose calculations *(for all fields treated initially)*

IX. REQUEST FOR STUDY INFORMATION AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically *(generally three times per year)* computer-generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

Data/Eligibility/Treatment/ Adverse Events/Data Management Procedures	RTOG Research Associate *(215)* 574-3214
Forms Packets *(RTOG Members)*	Registration Secretary *(215)* 574-3191

Pathology	Pathology Clerk *(801)* 321-1929 *(unless specified otherwise in Section 10.0)*
Protocols/Amendments	Director, Protocol Development *(215)* 574-3195
Radiotherapy data items *(films, radiographs, isodose summations, treatment records, scans, reports and calculations)*	Dosimetry Clerk *(215)* 574-3219
Randomization/Registration	Registration Secretary (215) 574-3191

If you are unable to reach the person noted, and your call is urgent, ask to speak to any HQ Research Associate.

XI. ADVERSE EVENTS AND TOXICITY

From Radiotherapy: Unusual toxicities, all grade 5 toxicities, and grade 4 toxicities in altered fractionation studies are reported by telephone within 24 hours of discovery to RTOG Headquarters, to the Group Chairman Dr. Walter Curran, to the Study Chair*(s)*, and to the RTOG Research Associate for this study.

From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters, RTOG Data Management and the Study Chair*(s)* are to receive notification as outlined by the NCI procedures. If telephone notification is necessary, RTOG and the Study Chair*(s)* must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

From Commercial Drugs: Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.

Data Submission: Events that require telephone reporting will require current updating of data forms through the date of the event. Submit within 10 working days of the telephone call.

Second Malignancy: All second primary tumors that are diagnosed during or following protocol treatment must be reported on the study data collection forms. AML/MDS must be reported on the NCI/CTEP Secondary Reporting Form. Instructions for submission are on the data form.

APPENDIX VII ***(8/18/03)***

NCCTG SUPPLY REQUEST FORM

RTOG 98-02

To: Darla Schletty/Nadeen Keach Date: _____

Company: Mayo Medical Laboratories FAX: 1-507-266-0188

No. of Pages *(including cover sheet):* 1 Phone: 1-800-826-5561

Delivery Instructions: _____ X Routine _____ Urgent

Special Instructions:

From: Telephone:

RTOG 98-02 CT800688

Please complete the lower half of this form and the previous 2 lines.

Number of supplies needed:

_____ Kits: *(Kit includes: Requisition form, 4-5 ml EDTA tubes, 2-5 ml Heparin tubes, bubble bag, Refrigerate specimen bag.)*

_____ 5lb Frozen Mailer: *(Needed and used for Federal Express® courier service)*

_____ Federal Express® Domestic Air Bills

Date Needed at Site: _____ *(Please allow at least one week for delivery.)*

SHIP TO: *(Name)* _____

(Address) _____

_____

(no p.o. boxes)

(City) _____

(State, Zip) _____

NCCTG Member Number _____

Recipient's Phone Number _____