The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

A Phase 3 Trial of Chemo-Radiotherapy for Anaplastic Oligodendroglioma: Long Term Results of RTOG 9402

Cairncross, et al

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INT 0149
RADIATION THERAPY ONCOLOGY GROUP

RTOG 94-02

PHASE III INTERGROUP RANDOMIZED COMPARISON OF RADIATION ALONE VS PRE-RADIATION CHEMOTHERAPY FOR PURE AND MIXED ANAPLASTIC OLIGODENDROGLIOMAS

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INT 0149
RADIATION THERAPY ONCOLOGY GROUP

RTOG 94-02
ECOG R9402
NCCTG 92-72-52
SWOG 9402

PHASE III INTERGROUP RANDOMIZED COMPARISON OF RADIATION ALONE VS PRE-RADIATION CHEMOTHERAPY FOR PURE AND MIXED ANAPLASTIC OLIGODENDROGLIOMAS

SCHEMA

STRATIFY

Age
1. < 50
2. ≥ 50

KPS
1. 60-70
2. ≥ 80

Tumor Grade
1. Moderately Anaplastic
2. Highly Anaplastic

RANDOMIZE

Arm 1
I-PCV[a] x 4 cycles *(q 6 weeks)* followed by RT[b]

Arm 2
RT alone[b]

a. Intensive-PCV *(I-PCV)*
Day 1 CCNU 130 mg/m^2 p.o.
Day 8 - Vincristine 1.4 mg/m^2 i.v.
Days 8-21 - Procarbazine 75 mg/m^2 p.o.
Day 29 - Vincristine 1.4 mg/m^2 i.v.

b. External Beam RT 59.4 Gy *(1.8 Gy x 33 fractions, 5 days a week)* to MR defined tumor volume.

Treatment (PCV or RT) must begin within two weeks of randomization.

Eligibility: *(See Section 3.0 for details)*

- Supratentorial pure or mixed anaplastic oligodendrogliomas confirmed by central pathology review.
- Age ≥ 18.
- KPS ≥ 60.
- Randomization must take place within 8 weeks of surgery/tissue diagnosis.
- No prior RT or chemotherapy
- No chronic lung disease unless PFTs demonstrate DCO ≥ 60% of predicted.
- Platelets ≥ 150,000, serum creatinine ≤ 1.5 x normal
- Absolute granulocyte count ≥ 1500
- Bilirubin, SGOT *(AST)*, alkaline phosphatase ≤ 2 x normal
- Study-specific consent form

Required Sample Size: 292

RTOG Institution # _____ INT 0149 RTOG Case # _____

RTOG /ECOG/SWOG 94-02 **ELIGIBILITY CHECK** Int. Seq.# _____

NCCTG 92-72-52

_____(Y) 1. Was central pathology review done and histology determined to be eligible by the central neuropathology reviewer?

_____(N) 2. Is the tumor located predominantly in the posterior fossa?

_____(N) 3. Is there evidence of spinal drop metastasis or spread to non-contiguous meninges?

_____(N) 4. Does the tumor originate in the spinal cord?

_____(≥ 18) 5. Report the patient's age.

_____(≥ 60) 6. Report the KPS.

_____(≥ 1.5) 7. Report the absolute granulocyte count *(x 1000)*.

_____(≥ 150) 8. Report the platelet count *(x 1000)*.

_____(Y) 9. Is the serum creatinine ≤ 1.5 times normal?

_____(Y) 10. Is the bilirubin, SGOT *(AST)* and alkaline phosphatase ≤ 2 times normal?

_____(Y/N) 11. Prior malignancy other than *in situ* carcinoma of the cervix or non-melanomatous skin cancer?

_____(Y) If yes, has the patient been disease-free for at least 5 years?

_____(Y/N) 12. Any chronic lung disease?

_____(Y) If yes, do PFT'S demonstrate a DCO ≥ 60% of predicted?

_____(N) 13. Does the patient have an active infectious process?

_____(Y) 14. Has a study-specific informed consent form been signed?

_____(Y/N/NA) 15. Does the patient have child-bearing potential? *(If no, skip to "patient name")*

_____(N) If yes, is the patient pregnant?

_____(Y) Has the patient been advised regarding contraception and avoiding pregnancy during treatment?

_____	Patient's Name	_____	Sex
_____	Verifying Physician	_____	Race
_____	Patient ID #	_____	Social Security Number
_____	Referring Institution	_____	Zip Code *(9-digit if avail.)*
_____	Tumor Grade *(moderately or highly anaplastic)*	_____	Method of Payment
_____	Medical Oncologist	_____	Treatment Start Date
_____	Birthdate	_____	Treatment Assignment

Completed by _____ Date _____

1.0 INTRODUCTION

Surgery and RT are the principle treatments for anaplastic glioma. Surgery is essential for diagnosis and improves symptoms in many instances. External beam RT prolongs life for most patients with malignant glioma, a benefit demonstrated conclusively in randomized trials.[1] The merits of chemotherapy are less clear. The nitrosoureas, procarbazine, cisplatin and other alkylating agents have anti-tumor activity but most randomized trials have either failed to demonstrate that adjuvant chemotherapy significantly prolongs median survival or have shown only modest survival benefit.[2-4] Some patients seem to have sensitive tumors, and live longer as a result of adjuvant treatment, but clinicians are unable to predict who will benefit and who won't, and treat accordingly. While the search for more effective anti-glioma chemotherapy must continue, investigators are increasingly aware of the need to identify subsets of patients with malignant glioma for whom adjuvant treatment with currently available cytotoxic drugs is of unequivocal benefit. The rational allocation of expensive and toxic therapies for cancer will be an increasing priority in western medicine. It is in this context that recent reports of "successful" chemotherapy for pure and mixed anaplastic oligodendrogliomas have appeared .[5-9]

Oligodendrogliomas are uncommon tumors thought to arise from the oligodendrocyte or its precursors. They represented 4.2% of primary brain tumors in a 25-year survey of the Norweigan Cancer Registry.[10] The typical oligodendroglioma is a slowly growing, partially calcified, non-enhancing tumor. There are different approaches to initial treatment of non-anaplastic tumors, anticonvulsants and follow-up are recommended for some, surgery and RT for others. Some oligodendrogliomas, probably the minority, are clinically aggressive, contrast enhancing and histologically anaplastic. Anaplastic oligodendrogliomas represented 3.5% of new malignant gliomas seen at a Canadian cancer center over 5.5 years.[11] Anaplastic tumors may evolve from benign ones or appear *de novo*. Unlike typical oligodendrogliomas, anaplastic ones have some or all of the following microscopic features: high cellularity, nuclear pleomorphism, mitotic figures, endothelial proliferation and necrosis. Based on these histologic characteristics oligodendrogliomas can be graded A*(low)*,B,C, or D*(high)* as proposed by Smith et al.[12] or I*(low)*, II,III, or IV*(high)* using the Kernohan or St. Anne-Mayo systems.[13,14] Anaplastic features may not be as reliable an indicator of rapid growth as they are in astrocytic gliomas, but nevertheless, anaplastic oligodendrogliomas usually behave more aggressively than non-anaplastic ones as illustrated in the following table of median survivals measured in months for tumors of different grades.

	A/I	B/II	C/III	D/IV	
Smith et al. [12]	94	51	45	17	Smith scale
Kros et al. [13]	113	77	83	15	Smith scale
Kros et al. [13]	122	67	71	35	Kernohan scale
Shaw et al. [14]	116		38		Kernohan scale
Shaw et al. [14]	117		47		St. Anne-Mayo

Like other gliomas, the survival of patients with oligodendrogliomas is determined by multiple factors, tumor grade being one. Age, performance status, extent of resection, and postoperative RT also appear to be important prognostic factors.[14] Younger patients, those with good function, those whose tumors have been completely removed, and those who receive RT after partial removal, live longer. Generally speaking, surgery and RT are regarded as standard initial treatment for anaplastic oligodendrogliomas.

Until recently there was little information about the natural history and response to treatment of anaplastic mixed gliomas, that is anaplastic tumors containing both oligodendroglial and astroglial elements. This is not surprising given the infrequent occurrence of oligoastrocytomas as compared to glioblastomas and anaplastic astrocytomas and the absence of uniform diagnostic criteria distinguishing them from anaplastic astrocytomas on the one hand, or anaplastic oligodendrogliomas

on the other. Two recent retrospective studies have compared the median durations of survival of patients with anaplastic mixed gliomas to other types of anaplastic glioma. These analyses have yielded conflicting results; Winger et al.[11] found the median survival for patients with anaplastic oligoastrocytomas to be inferior to anaplastic oligodendrogliomas and identical to anaplastic astrocytic tumors, *(i.e., 12 months)* while Shaw et al.[15] found the median duration of survival of patients with anaplastic mixed tumors to be identical to anaplastic oligodendrogliomas and significantly longer than anaplastic astrocytomas *(i.e., 34 months using the Kernohan system, 52 months using the St. Anne-Mayo System)*. Accepting that diagnostic criteria vary, oligoastrocytomas appear to be at least as common as "pure" oligodendrogliomas and either the oligodendroglial or astroglial element may be anaplastic. Standard initial treatment for anaplastic oligoastrocytomas includes surgery and RT.

There is a growing body of evidence to suggest that pure and mixed anaplastic oligodendrogliomas are chemosensitive tumors. In 1988, based on a small series of consecutive cases, Cairncross and Macdonald[5] reported that recurrent anaplastic oligodendrogliomas responded predictably to nitrosourea-based chemotherapy, especially PCV *(procarbazine, CCNU [lomustine] and vincristine)*, a regimen described eight years earlier by Levin et al.[16] Two years later, Macdonald et al.[6] reported responses to chemotherapy prior to RT in a small series of patients with newly diagnosed aggressive oligodendrogliomas. By aggressive they meant either histologically anaplastic tumors or non-anaplastic oligodendrogliomas that were symptomatic, enlarging and enhancing. In 1990, Brown et al.[7] for the Duke-based CNS Cancer Consortium reported that recurrent anaplastic oligodendrogliomas were more likely to respond to intravenous melphalan than non-oligodendrogliomas. This finding, and a case report by Saarinen et al.[8] in 1990, describing a complete response to high-dose thiotepa in a child with a recurrent, heavily pre-treated tumor, provided further evidence that aggressive oligodendrogliomas were chemosensitive solid tumors. Glass et al.[9] in 1992 made the important observation that anaplastic oligoastrocytomas also responded to PCV. They observed durable responses in recurrent tumors and responses prior to RT in new cases. The National Cancer Institute of Canada completed a multicenter phase II trial of intensive-PCV (I-PCV) for new or recurrent anaplastic oligodendrogliomas observing a 75% response rate and substantial numbers of complete responses *(~40%) (personal communication, E.Eisenhauer)*. These observations suggest that anaplastic tumors with oligodendroglial differentiation are a chemosensitive subset of gliomas and set the stage for a study designed to evaluate the role of adjuvant chemotherapy in the treatment of newly diagnosed pure and mixed anaplastic oligodendrogliomas.

Critical evaluation of treatment toxicity must be a component of any study evaluating the treatment of pure and mixed anaplastic oligodendrogliomas, particularly in light of their better natural history. Patients with these tumors will live longer and are at risk for late side effects. Radiation and chemotherapy have toxic effects some of which are severe, life threatening, or even fatal. Shaw et al.[14,17] observed dementia or necrosis in 5-11% of patients with pure or mixed oligodendrogliomas receiving RT, most had whole brain treatment . Shaw et al.[14,17] noted that partial brain RT was associated with improved survival, perhaps as a result of fewer serious radiation-related toxic effects. In NCI Canada's recent phase II study, I-PCV produced mild to moderate nausea and vomiting in 70-80% of treatment cycles, grade 3 or 4 neutropenia in 41% of cycles, and grade 3 or 4 thrombocytopenia in 17%. There were no instances of nadir sepsis or bleeding. Rash consistent with procarbazine allergy occurred in 30% of patients and mild to moderate sensory neuropathy developed in 70%. One steroid dependent ineligible patient died as a result of pneumocystis pneumonia after the first cycle of I-PCV and a second ineligible patient developed a subdural hematoma after cycle one *(nadir platelet count >100,000)*.

This is a non-blinded randomized Intergroup trial approved by the National Cancer Institute-United States *(NCI-US)* and coordinated by the Radiation Therapy Oncology Group *(RTOG)*. This study is different from other randomized trials for malignant glioma in three respects. First, it will evaluate the role of adjuvant chemotherapy in a recognizable subset of patients with malignant glioma, those with oligodendroglial differentiation. Second, the RT treatment volume will be based on a postoperative pre-randomization MR image, rather than the customary preoperative diagnostic CT or

MR. Third, in the experimental arm of this study, chemotherapy will be given prior to RT. This departure from standard management can be justified based on the high rate of response of pure and mixed oligodendrogliomas to PCV, and successful piloting of this approach at several centers.[6,9] There are potential advantages to pre-RT PCV: chemotherapy may be more effective when given prior to radiation; effective chemotherapy may result in substantial reductions in tumor size prior to RT; and RT may control smaller tumors more effectively than larger ones. Patients whose tumors progress on chemotherapy will proceed to RT immediately. Several other important features of this study are central pathology review prior to randomization, central radiology review to assess response to PCV and to substantiate tumor progression, and a quality of life assessment to document the acute and chronic toxicities of chemotherapy and radiation including effects on cognitive function.

Surgery and radiotherapy plus or minus PCV may adversely affect a patient's physical and emotional functioning. Karnofsky performance status *(KPS)* measures physical well-being primarily. To complement KPS, the Mini-Mental Status exam[21] (MMSE) will be administered to patients to assess cognitive ability. Neither of these tools measures emotional well-being or global quality of life. An examination of the available quality of life questionnaires indicated no questionnaire specifically designed for patients with primary malignant gliomas.[22,23] The evaluation of quality of life in this patient group required the modification of either a questionnaire intended for patients with chronic neurologic diseases, or appending a general questionnaire for oncologic patients. Mackworth, et al.[24] chose the latter. The European Organization for Research and Treatment of Cancer *(EORTC)* developed a core quality of life questionnaire *(QLQ)*. These core questions have established psychometric properties for cancer patients.[25,26] The reliability for subsections energy, leisure, cognition, socializing, work, symptoms, sex life, depression, and well being range from 0.61 to 0.85, while the memory section has a reliability of 0.84. Mackworth et al.[24] modified the QLQ for brain patients *(B-QLQ)* and applied it to 200 malignant glioma patients. The B-QLQ was shown to provide significant information on patients' global quality of life and emotional well-being.[24]

Patients with oligodendrogliomas have a median survival of approximately three years. The long-term effects of treatment on a patient's cognitive, physical, and emotional functioning is not well understood in this patient group. The KPS, MMSE, and B-QLQ will be administered at baseline and each follow-up visit in order to document changes in each of the three domains. These tools will permit us to assess the effect of therapy and disease on these domains in both the acute and long-term settings. Assessment of differences in quantitative survival between the two therapeutic regimens supplemented with qualitative survival by the assessment of KPS, MMSE, and B-QLQ.

2.0 OBJECTIVES

2.1 The primary endpoint of this trial is overall survival.

2.2 This study will compare time to tumor progression between the two arms.

2.3 The frequency of severe *(≥ grade 3)* toxicities will be examined.

2.4 This study will compare quality of life and neurologic function between the two arms.

2.5 This study will identify the key histopathologic criteria necessary to make the diagnosis of anaplastic oligodendroglioma and mixed oligo-astrocytoma; evaluate the diagnostic and prognostic relevance of chromosomal alterations; evaluate the diagnostic and prognostic relevance of DNA ploidy and indices of proliferation including percent S and percent G2M; study the diagnostic and prognostic relevance of immunohistochemical markers of cellular function and/or glial development; and evaluate the translational relevance of tumor suppressor genes and oncogenes. These objectives will be studied utilizing the tissues and peripheral blood samples obtained from the patients entered on this trial and funded by a grant to Dr. Robert Jenkins, Pathologist and Molecular Geneticist, Mayo Clinic, Rochester, MN 55905.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Pathologic evidence of unifocal or multifocal supratentorial pure or mixed anaplastic oligodendroglioma *(see Section 10.0)*. Patients with prior suspected or proven low grade glioma are eligible provided they now have a biopsy-proven pure or mixed anaplastic

oligodendroglioma and have not been treated previously with either RT or chemotherapy.

3.1.2 Age ≥ 18 years.

3.1.3 KPS ≥ 60.

3.1.4 Absolute granulocyte count ≥ 1500/mm^3.
Platelet count ≥ 150,000/mm^3.
Serum creatinine ≤ 1.5 x normal.
Bilirubin, SGOT *(AST)*, alkaline phosphatase ≤ 2 x normal.

3.1.5 Signed study-specific informed consent.

3.2 Ineligibility Criteria

3.2.1 Equivocal oligodendroglial element *(see Section 10.0)*.

3.2.2 Tumor that is predominantly located in the posterior fossa *(i.e. brain stem or cerebellum)*.

3.2.3 Spinal cord tumors.

3.2.4 Evidence of spinal drop metastasis or spread to non-contiguous meninges **(MR of the spine is not required in asymptomatic patients and patients will not be excluded based on pathologic evidence of local meningeal infiltration by underlying tumor)**.

3.2.5 Prior malignancy *(excluding in situ carcinoma of the cervix or non-melanomatous skin cancer)* unless disease free for at least five years.

3.2.6 Prior radiotherapy to the brain or head/neck.

3.2.7 Prior chemotherapy.

3.2.8 Chronic lung disease unless pulmonary function tests *(PFTs)* demonstrate a DCO ≥ 60% of predicted.

3.2.9 Active infectious process.

3.2.10 Pregnant or nursing.

3.2.11 Inability or unwillingness to consider effective contraception.

4.0 PRETREATMENT EVALUATIONS *(all tests and scans must be performed within two weeks prior to randomization)*.

4.1 Central pathology review is mandatory prior to randomization to confirm eligibility. Stereotactic biopsies are permitted but the tissue sampled must be adequate for unequivical pathologic diagnosis.

4.2 History and physical examination *(including neurological examination)* with documentation of all symptoms and signs.

4.3 Laboratory Evaluation

Hematology:
- hemoglobin
- WBC with differential *(absolute granulocyte count)*
- platelet count

Biochemistry:
- electrolytes
- glucose
- creatinine
- bilirubin
- SGOT *(AST)/SGPT*
- alkaline phosphatase

Pulmonary:
- full screening PFTs as necessary *(see Section 3.2.8)*

Radiology:
- chest x-ray
- CT or MR scan without and with contrast. Note: Patients may be followed by either CT or MR but must have an MR scan for RT treatment planning.
- **Postoperative MR scan for RT planning.** RT for both treatment arms will be planned with an MR scan obtained ≤ 2 weeks prior to randomization. If the tumor progresses on I-PCV, the RT planning MR may need to be repeated

Pregnancy test for women of child-bearing age.

4.4 Mini-Mental Status Examination

4.5 Quality of Life Assessment

5.0 REGISTRATION PROCEDURES

5.1 **Central pathology review *(see Section 10.0)* must be completed prior to randomization.**

Randomization must take place within 8 weeks of 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 Note: A signed HHS 596 Form for this protocol must be on file at the ECOG Operations Office before any ECOG institution may enter a patient.

5.3.2 To register a patient, the investigator will telephone the Central Randomization Desk at the ECOG Statistical Center Data Management Office (617) 632-2022 from 8:30 a.m. to 5:00 p.m. ET Monday-Friday. The following information will be requested:

- Protocol Number
- Investigator Identification
  Institution name and/or affiliate
  Investigator's name
- Patient Identification
  Patient's name or initials and chart number
  Patient's Social Security number
  Patient Demographics: sex, birthdate*(MM/YY)*, race, nine-digit zip code, and method of payment.
- Treatment Start Date

5.3.3 Patients must meet all of the eligibility requirements listed in the protocol document. The randomization specialist will verify eligibility by asking questions from the checklist. Upon confirming eligibility, the ECOG Statistical Center will place a call to RTOG Headquarters to receive an RTOG case number and treatment assignment which will be relayed to the ECOG member.

5.3.4 RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group will forward a copy of the calendar to the participating institution.

5.3.5 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 and confirm all eligibility criteria and information as per Section 5.1, 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 three working days prior to the planned start of treatment)*. The information listed on the RTOG Eligibility Check must be provided at the time of registration. 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 596 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 4 p.m. central standard time 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 4 p.m. central standard time to register a patient. NCCTG will also verify that both a radiation oncologist and a medical oncology 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

Treatment will be delivered with megavoltage machines of energy ≥ 4 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. The patient will be treated in the supine or other appropriate position. There must be at least two shaped treatment fields with each field treated daily. Treatment with a single beam is not acceptable. Port films of each field will be taken weekly, except for opposed fields with identical blocking where one film from each of the opposed fields should be taken weekly.

6.1.1 *Treatment Volumes*

For both groups of patients the target volumes will be based on an MR scan *(T2 and T1 gadolinium-enhanced images)* obtained within two weeks of randomization. The initial target volume will include the T2 abnormality plus a 2 cm margin. The boost volume will include all tumor visible on the T1 gadolinium-enhanced scan plus a 1 cm margin. If the tumor has been completely resected and the MR scan for RT planning is normal, the initial volume will be the surgical defect plus a 2 cm margin. The boost volume will be the surgical defect plus a 1 cm margin. The target volumes are to receive 95-105% of the prescribed dose.

6.1.2 *Dose and Schedule*

Treatment will be given in 1.8 Gy fractions *(to isocenter)*, 1 fraction per day, 5 days per week, to a total dose of 59.4 Gy in 33 fractions. The initial 50.4 Gy in 28 fractions will include the initial target volume *(T2-MR plus 2 cm margin)*. The final 9 Gy in 5 fractions will include the boost volume *(T1 enhanced MR plus 1 cm margin)*. For patients receiving RT alone, RT must begin within two weeks after randomization. For those receiving I-PCV + RT, RT must begin no later than 6 weeks after completing the final cycle of I-PCV, *(i.e., within 6 weeks of day 29 of the final cycle of I-PCV)* blood counts permitting (see Section 6.1.7).

6.1.3 *Treatment Summary*

Volume	Includes	Daily Dose	No. of fractions	Total Dose
Initial	T2-MR + 2 cm	1.8 Gy	28	50.4 Gy
Boost	T1 *(Gad)* MR + 1 cm	1.8 Gy	5	9 Gy
Total	-	-	33	59.4 Gy

6.1.4 *Dosimetry*

Two central access isodose plots *(Appendix VII)* one showing the initial tumor volume and one showing the boost tumor volume should be submitted with the following isodose lines in Gy. 25.2 Gy, 45.4 Gy, 47.9 Gy, 50.4 Gy, 52.9 Gy, 53.5 Gy, 55.4 Gy, 56.4 Gy, 59.4 Gy, 62.4 Gy, and 65.3 Gy. The following quality assurance guidelines will apply:

6.1.4.1 If the initial target volume receives < 45.4 Gy or > 55.4 Gy *(i.e.., < 90% or > 110% of the prescribed total dose)* a major deviation will be scored. If the boost volume receives < 53.5 Gy or > 65.3 Gy *(i.e., < 90% or > 110% of the prescribed total dose)*, a major deviation will

be assigned.

6.1.4.2 If the initial target volume receives 45.4-47.8 Gy or 53.0-55.4 Gy *(i.e., 90-94% or 106-110% of the prescribed total dose)* a minor deviation will be scored. If the boost volume receives 53.5-55.8 Gy or 63.0-65.3 Gy *(i.e., 90-94% or 106-110% of the prescribed total dose)* a minor deviation will be assigned.

6.1.4.3 If the initial target volume receives 47.9-52.9 Gy *(i.e.. 95-105% of the prescribed total dose)* no deviation will be scored. If the boost volume receives 56.4 -62.4 Gy *(i.e., 95-105% of the prescribed total dose)* no deviation will be assigned.

6.1.5 *Dose Specification*

Doses are specified as the target dose which shall be the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

6.1.5.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.1.5.2 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.1.5.3 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

6.1.5.4 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.

6.1.5.5 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots due to unacceptable tissue inhomogeneity. However, if this technique is utilized the dose shall be specified at the center of the target area.

6.1.5.6 Other or complex treatment arrangements: at the center of the target area

6.1.6 *Dose Limitation to Critical Structures*

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 60 Gy, the retina of at least one eye *(but preferably both)* to 50 Gy, and the brain stem to 60 Gy.

6.1.7 *Treatment Delays*

RT will be delayed or interrupted if the absolute granulocyte count is < 500 or the platelet count is < 20,000. RT will not begin or resume until the absolute granulocyte count is ≥ 500 and the platelet count is ≥ 20,000.

6.1.8 *Toxic Reactions*

Expected RT toxic reactions include hair loss, scalp redness or soreness, dry mouth or altered taste, hearing impairment, fatigue, or temporary aggravation of brain tumor symptoms such as headaches, seizures, or weakness. Unusually severe reactions should be noted and reported to the study chair. All early delayed or late delayed neurotoxicities *(eg. transient demyelination syndromes, dementia, or brain necrosis)* must be documented and reported.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Procarbazine Hydrochloride

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.

7.2 Lomustine (CCNU)

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 tablets. Its major toxicities include delayed myelosuppression, both leucopenia 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

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 Lily and available commercially in 1, 2 and 5 mg vials. Its major toxicities include sensorimotor and autonomic neuropathy. Myelosuppression is rare.

7.4 Treatment Prescription

7.4.1 *Intensive-PCV (I-PCV) Regimen*

Patients assigned to the pre-RT chemotherapy arm will receive four cycles of I-PCV at six week intervals. I-PCV must start within two weeks after randomization. Procarbazine, CCNU and vincristine will be prescribed as follows:

DRUG	DOSE	ROUTE	SCHEDULE
CCNU	130 mg/m^2	p.o.	day 1
Vincristine	1.4 mg/m^2	i.v.	day 8
Procarbazine	75 mg/m^2	p.o.	days 8-21
Vincristine	1.4 mg/m^2	i.v.	day 29

Each cycle is defined as the period of therapy plus 2 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 over days 8-21 will be calculated as follows: (75 x surface area in m^2 x 14) + 50 rounded to the nearest whole number *(eg. 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: 50 mg p.o. day 8, 50 mg p.o. b.i.d day 9, etc. Vincristine doses will be rounded to the nearest tenth of a milligram *(e.g. 2.12 give 2.1 mg, 2.15 or 2.18 give 2.2 mg)*. **There will be no 2 mg limit on each dose of Vincristine.**

7.4.3 *Dose Modifications*

There will be no dose escalations. Doses will be reduced for hematologic and other toxicities and scored using the Common Toxicity Criteria *(Appendix IV)*. 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 as follows:

Absolute Granulocyte Count *(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)*	decrease 25% *(last dose)*

Doses of vincristine will not be delayed or reduced for low treatment-day blood counts.

7.4.3.2 Neurotoxicity

Vincristine will be stopped for grade 3 or grade 4 toxicity *(Appendix IV)*. CCNU and procarbazine continue as per protocol.

7.4.3.3 Nausea/Vomiting

If grade 3 or grade 4 nausea or vomiting persist despite antiemetics, the doses of CCNU or procarbazine may be reduced as described for "other toxicity" in Section 7.4.3.6.

7.4.3.4 Skin Toxicity

Procarbazine will be discontinued should a urticarial rash develop on I-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 continue as 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 DCO is <60% of predicted. Procarbazine and vincristine continue as per protocol.

7.4.3.6 Other Toxicity

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

7.4.4 *Treatment Delays*

Doses of vincristine will not be delayed for hematologic toxicity. Cycles 2, 3 or 4 will be delayed for low treatment day counts as outlined below:

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

7.4.5 *Duration of Treatment*

Toxicity permitting, there will be four cycles of I-PCV. **I-PCV will be discontinued *(and RT started)* for:**

- treatment delays in excess of 8 weeks between cycles.
- any reason at the request of the patient or guardian.
- CT or MR documented tumor progression *(see Sections 11.3 and 11.6)*.
- 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 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.**

7.5 Adverse Reaction Reporting

7.5.1 The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol which 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).

7.5.2 The ADR report should be documented on Form FDA 1639 (Appendix V) and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone (301) 230-2330
available 24 hours

7.6 Adverse Drug Reaction Reporting/ECOG Members

The following adverse reactions must be reported to ECOG and NCI in the manner described. In addition, your local IRB should be notified.

7.6.1 *Deaths*

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related must be reported as follows:

Commercial Agents - An Adverse Drug Reaction *(ADR)* Form for Investigational Drugs *(#391R)* must be sent to the ECOG Statistical Center Data Management Office *(ATTN: ADR)* within 10 working days of the event. Upon receipt, the ECOG Statistical Center will fax the ADR form to RTOG Headquarters. This form must be signed by the treating investigator.

Mailing address for ECOG ADR reporting is:
ECOG Statistical Center
Data Management Office
303 Boylston Street
Brookline, MA 02146-7215
ATT: ADR

7.6.2 *Unexpected Toxicities*

Commercial Agents - For any unexpected toxicity (not reported in the literature or the package insert) an Adverse Drug Reaction *(ADR)* Form for Investigational Drugs *(#391R)* must be submitted to the NCI and to the ECOG Statistical Center Data Management Office *(ATTN: ADR)* within 10 working days of the event. Upon receipt, the ECOG Statistical Center will fax the ADR form to RTOG Headquarters. This form must be signed by the treating investigator.

7.6.3 *Expected Toxicities*

Commercial Agents - Expected grade ≤ 4 toxicities need not be reported.

7.6.4 *Non-Treatment Related Toxicities*

If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the Flow Sheets submitted to the ECOG Statistical Center Data Management Office *(ATTN: DATA)* to be forwarded to RTOG Headquarters according to the protocol.

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.

7.7.2 **Within 10 days the investigator must send the completed *(original)* DCT form *(for regimens using investigational agents)* or the FDA 1639 form *(for regimens using only commercial agents)* to the NCI:**

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

7.7.3 **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 78245-3218

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

Not applicable to this study.

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 will be recorded at randomization and at specific time points during and after treatment *(see Section 11.0)*. Investigators should avoid radical changes in steroid dose during periods critical for response evaluation so as not to complicate the assessment of response to I-PCV in the experimental arm.

10.0 PATHOLOGY

10.1 **Central pathology review is mandatory prior to study entry to confirm eligibility.** It should be initiated as soon as the diagnosis has been made. Central pathology review will be performed by Dr. Bernd Scheithauer, Mayo Clinic. All slides for pre-entry review will be sent directly to the Mayo Clinic *(see Section 10.3.3)* and not through Group Headquarters.

10.2 To be eligible for this study, the patient's tumor must contain an unequivocal *(at least 25%)* oligodendroglial element and have two or more anaplastic features. For mixed tumors, the non-oligodendroglial element must be astrocytic and either the oligodendroglial or astroglial component may be anaplastic. The "home" pathologist will assess the tumor and complete the Pathology Checklist *(Appendix III)*. First, the tumor will be designated a pure anaplastic

oligodendroglioma or a mixed anaplastic glioma, and if mixed, further described as oligodendroglioma-dominant, astrocytoma-dominant, or equally mixed. For subsequent analyses and reporting, pure oligodendrogliomas and oligodendroglioma-dominant mixed tumors will be considered "pure" and the others considered "mixed". The degree of anaplasia will be based on the presence or absence of high cellularity, nuclear pleomorphism, frequent mitoses, vascular proliferation, and necrosis. For stratification, tumors with 2 or 3 anaplastic features will be considered moderately anaplastic and those with 4 or 5 features considered highly anaplastic.

10.3 The following materials will be couriered to the Mayo Clinic for central review:

- Pathology Checklist *(Appendix III)* with the left hand side completed by the "home" pathologist and Specimen Transmittal Form.
- representative slides *(H& E sections)*
- paraffin blocks
- your fax number

10.3.1 The data manager will initiate the Pathology Checklist. The top and bottom right-hand corner of the form are to be filled out and submitted along with the operative and pathology reports, when requesting the slides.

10.3.2 The primary pathologist will complete the Pathology Checklist and return it to the data manager, along with the slides, blocks and pathology and operative reports.

10.3.3 The data manager will check the form for completeness and send all materials *(Section 10.3)* to the central neuropathology reviewer in care of :

Jane Milburn
Clinical Trials Office
Mayo Clinic/Div. of Radiation Oncology
Desk R; Charlton Building
Rochester, MN 55905
(507) 284-9549
FAX (507) 284-0079
Please alert Mrs. Milburn prior to sending the materials

10.3.4 After the pathology materials have been reviewed, a call will be made to the institution notifying them whether or not the case is eligible and confirmed by fax.

10.3.4.1 If the patient enters the study, the patient's RTOG case number will be added to the Pathology Checklist by the data manager and a copy of the completed form will be sent to RTOG. A copy of the Specimen Transmittal Form must be included. All materials will be returned to the submitting institution along with all slides except the one(s) selected by the neuropathologist for the study files.

10.3.4.2 If the patient does not enter the study, *all* slides, blocks and forms will be returned to the participating submitting institution.

10.4 At the time of confirmation of eligibility, the institution entering the patient will be required to send two tubes of peripheral blood, 15 cc, one in EDTA and the other in Heparin.

Note: A specimen mailing kit will be sent from the Mayo Clinic to the institution with specific instructions on how to properly ship the blood samples. Do not ship blood samples until the kit has been received.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

PARAMETER	ON STUDY	I-PCV +	RT ARM	BOTH ARMS		F/U
		Pre-cycles 2,3,4	Weekly on I-PCV	Pre-RT	≥ End of RT	per Sec. 12.0
Clinical Assessment, KPS, NF[d]	X	X		X	X	X

PARAMETER	ON STUDY	I-PCV +	RT ARM	BOTH	ARMS	F/U
Hematology HGB, WBC, AGC[a], plt. count	X	X	X	X	X	X
Biochemistry Electrolytes, Glucose, Creat, SGOT *(AST)*/SGPT, Alk phos, bili	X	X		X	X	X
CT or MR without/with contrast	X[b,c]	X		X	X	X
Pregnancy Test	X					
Chest X-ray	X					
PFT's	X					
Record Steroid Dose	X	X		X	X	X
Mini-Mental Status Exam	X			X[e]		X
Quality of Life Assessment	X					X
Toxicity Evaluation		X	X	X	X	X

a. absolute granulocyte count
b. the baseline and all follow-up scans to assess response/progression must be of the same type, that is either CT or MR
c. MR *(T2 and T1 gad)* to plan RT, within 2 weeks of randomization for both arms.
d. See Appendix II
e. Arm 1 only

11.2 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 randomization and the date of death.

11.3 Time to Progression

Patients will be followed clinically and radiologically as outlined in Section 11.0. The date at which the tumor is documented to have first enlarged by 25% *(steroid dose stable or increased, neurologically stable or worse [see Section 11.6])* will be considered the date of tumor progression. Time to progression will be the interval between the date of randomization and the date of tumor progression. Tumor progression will be confirmed by central radiology 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 tumor progression by stereotactic biopsy or other surgical procedure is encouraged, particularly for patients who receive RT alone and then recur. Thallium-SPECT or PET imaging of all "recurrent lesions" is recommended for patients at centers with access to these technologies.

11.4 Response Assessment

11.4.1 Definition of response to I-PCV adapted from Macdonald et al.[18] For patients with unequivocal measurable disease after surgery, and randomized to I-PCVx 4 then RT, response to I-PCV will be evaluated. Two sets of response criteria will be used, one set for tumors that are predominantly enhancing and the other for tumors that contain small enhancing regions or are non-enhancing.

11.4.2 *Residual enhancing tumor:*

Complete response (CR) - disappearance of all enhancing tumor on consecutive CT or T1*(gad)* MR scans at least one month apart, off steroids, and neurologically stable or improved.

Partial response (PR) - 50% or greater decrease in enhancing tumor size on consecutive CT or T1 *(gad)* MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.

Tumor regression (TR) - A substantial decrease in enhancing tumor size on consecutive CT or T1 *(gad)* MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.

Note: Responses will be confirmed by central radiology review. For the purposes of response assignment: surgical defects and areas of calcification will be ignored; tumor size will be the

maximum cross-sectional area of the enhancing tumor; and for tumors of peculiar shape, response *(here, called regression)* will be based on the central RT reviewer's visual interpretation, rather than a measured maximum cross-sectional area *(the tumor must still be at least 50% smaller to have responded).*

11.4.3 *Residual non-enhancing or minimally enhancing tumor:*
Complete response (CR) - disappearance of all tumor on consecutive CT or MR scans at least one month apart, off steroids, and neurologically stable or improved.
Partial response (PR) - 50% or greater decrease in tumor size on consecutive CT or MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.
Tumor regression (TR) - A substantial decrease in tumor size on consecutive CTor MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.
Note: Responses will be confirmed by central radiology review. For the purposes of response assignment: surgical defects and areas of calcification will be ignored; tumor size will be the maximum cross-sectional area of the non-enhancing tumor; and for tumors of peculiar shape, response *(here, called regression)* will be based on the central RT reviewer's visual interpretation, rather than a measured maximum cross-sectional area *(the tumor must still be at least 50% smaller to have responded).*

11.5 Definition of Stable Disease
Stable disease (SD) - all other situations.

11.6 Definition of Tumor Progression
For all patients, tumor progression will be defined as follows:
Progressive disease (PD) - 25% or greater increase in enhancing or non-enhancing tumor size on consecutive CT or MR scans, or any new areas of tumor, steroid dose stable or increased, and neurologically stable or worse. *(Note: Under exceptional circumstances disease progression may be declared in the absence of an increase in tumor size - see Section 7.4.5)*

11.7 Toxicity Evaluation

11.7.1 *Acute Toxic Reactions*
Patients randomized to pre-RT chemotherapy will have a complete blood count on a weekly basis while receiving I-PCV and screening biochemical evaluation prior to each cycle of I-PCV. PFTs and other tests 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 a mini mental status examination prior to the start of protocol treatment, prior to RT *(Arm 1)*, and subsequently in followup and with CT or MR scans to assess response.

11.7.3 *Quality of Life Assessment (B-QLQ)*
All patients will be asked to complete a quality of life questionnaire prior to the start of protocol treatment, and subsequently in followup and with CT or MR scans to assess response.

11.7.4 *Other Toxicities*
All second malignancies, myelodysplastic syndromes, respiratory illnesses, neuromuscular disorders, dementias and other illnesses probably or possibly related to I-PCV or RT will be reported.

11.8 Treatment at Progression
See Section 11.6 for the definition of tumor progression.

11.8.1. *I-PCV + RT Arm*

11.8.1.1 Progression during I-PCV
Immediate external beam RT is strongly recommended for tumor progression during I-PCV phase of the I-PCV + RT, but other therapies are permitted. The MR scan for RT treatment planning may need to be repeated.

11.8.1.2 Progression during RT
Those whose tumors progress during the RT phase of I-PCV + RT will be treated at the discretion of the investigator. All subsequent treatments will be recorded.

11.8.1.3 Progression after treatment
Those whose tumors progress after completing I-PCV + RT will be treated at the discretion of the investigator. Tissue confirmation of recurrent tumor should be considered. All

subsequent treatments will be recorded.

11.8.2 *RT Arm*

11.8.2.1 Progression during RT

I-PCV x four cycles is strongly recommended for tumor progression during RT but other therapies are permitted. All treatments will be recorded.

11.8.2.2 Progression after treatment

I-PCV x four cycles is strongly recommended for tumor progression after RT but other therapies are permitted. Tissue confirmation of recurrent tumor should be considered. All subsequent treatments will be recorded.

Note: The investigator must be careful to exclude causes of clinical or radiologic deterioration that mimic tumor progression *(ie. pseudoprogression)* such as acute radiation reactions, precipitous steroid withdrawal, intratumoral hemorrhage, etc.

11.9 Film Review

Baseline and follow-up scans will be reviewed on all patients who have responsed, progressed, experienced an unexpected CNS toxicity, or died.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Medical Oncology Treatment Planning Form **(M2)** *(Arm 1)* Pathology Checklist **(P4)** *(copy, original to reviewer)* Specimen Transmittal Form *(ST)* *(copy, original to reviewer)*	Within 1 week of study entry
Initial Evaluation Form **(I1)** Pathology Report **(P1)** Brain Tumor Quality of Life Questionnaire **(QL)** Initial Mini-Mental Status Evaluation **(MS)** Pre-op and pre-entry CT/MR scan **(C1)** and reports **(C3)** Treatment planning MR **(MR)**	Within 2 weeks of study entry
CT/MRI Reports **(C3)***	After cycles 1-4 and at followup, within 2 weeks of scan date
Interim Report **(F9)** *(Arm 1)*	At 3 and 6 months or at end of chemotherapy
Chemotherapy Flowsheet **(M1)** *(Arm 1)*	At the end of each cycle and 3 months after day 29 of last cycle.
Mini-Mental Status Evaluation **(MS)** *(Arm 1)*	At the end of chemotherapy
Radiotherapy Form **(T1)**	Within 2 weeks of RT end
Follow-up Form **(F1)** Mini-Mental Status Evaluation **(MS)** Brain Tumor Quality of Life Questionnaire **(QL)**	Arm 1: At 9 and 12 months Arm 2: Every 3 months from treatment start in year 1 ; Both Arms: then q 4 months in year 2, q 6 months in years 3, 4, and 5, then annually. Also at progression/relapse. At death *(F1 only)*.

Autopsy Report (D3) As applicable

* CT/MR reports must be submitted on all patients who respond or progress on I-PCV and on all patients at progression. These must be submitted to RTOG within 2 weeks of scan date.

12.2 Dosimetry and Film Submission

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

Pre-op Scans with and without contrast (C1)	Due within 2 weeks of RT end
Pre-op scan report (C3)	
Post-op MR scan with contrast for treatment planning (C2)	
Post-op MR scan report (C3)	
Calculation data form for all fields (TL)	
Simulation and portal films for all fields (TP)	
Complete treatment record (T5)	
Isodose Distributions (T6) *(see Section 6.1.4 for details)*	
FollowUp Scan (C2)	Due 4 months from the end of RT
Follow Up Scan Report (C3)	

12.3 ECOG, SWOG AND NCCTG DATA SUBMISSION

12.3.1 *ECOG*: The required forms must be submitted to the ECOG Statistical Center Data Management Office, 303 Boylston Street, Brookline, MA 02146-7215 *(ATTN: DATA)*. They will be forwarded to RTOG by the ECOG Statistical Center.

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, 1124 Columbia Street, 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 **Rapid Review Items**: Time critical data which requires rapid submission must be sent directly to RTOG:

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

Send to:
Radiation Therapy Oncology Group (RTOG)
ATT: Dosimetry
1101 Market Street
Philadelphia, PA 19107

12.2.5 **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

12.2.6 **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.

13.1.2 This study will compare time to tumor progression between the two arms.

13.1.3 The frequency of severe *(≥ grade 3)* toxicities will be examined.

13.1.4 This study will compare quality of life and neurologic function between the two arms.

13.1.5 Tumor tissue and blood will be collected for companion basic science studies to be reported separately.

13.2 Sample Size

It is estimated that the median survival for patients on the RT arm will be 3.8 years. The difference to be detected is a relative 50% increase in median survival which corresponds to a 5.7 median suvival for patients on the I-PCV + RT arm. The Lachin and Foulkes[19] sample size method assumes exponential survival and that comparisons will be performed by the logrank statistic. Assuming an ineligibility/inevaluability *(no data)* rate of 5%, then **292 patients will be needed** *(146 per arm)* to ensure 80% *(b=0.20, type II error)* probability of detecting a 50% improvement in five-year survival, while rejecting the null hypothesis at the 95% level *(a=0.05, one-sided type I error)*.

13.3 Noncompliance

The anticipated survival difference assumes full compliance to the I-PCV + RT arm, defined as a minimum of 3 cycles of I-PCV. If I-PCV is given for less than 3 cycles for reasons other than tumor progression or death, then the patient will be considered non-compliant. The following table indicates the effect of non-compliance to I-PCV on the sample size, assuming that non-compliant patients respond like patients on the RT arm.

% Non-Compliance	Total Sample Size
5%	296
10%	310
15%	328

Therefore, compliance to I-PCV will be monitored during the accrual phase. The sample size will be adjusted if non-compliance is greater than or equal to 5%.

13.4 Patient Accrual

The patient accrual is projected to be 4.5 patients per month. This trial should complete the accrual phase in 5.4 years. If the monthly accrual is less than two cases per month, the study will be re-evaluated with respect to feasibility.

13.5 Randomization Scheme

The treatment allocation will be one using a randomized permuted block within strata to balance for patient factors other than institution. The stratifying variables are age *(< 50 vs. ≥50)*, KPS *(60-70 vs. 80-100)*, tumor grade *(moderately anaplastic vs. highly anaplastic)*.

13.6 Analyses 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 has 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 and stratification variables;
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 two interim analyses of the primary study endpoints *(survival and time to tumor progression)*. The interim analyses will proceed according to the following table[20]

Total Accrual	Significance Level
50%	0.00250

100% 0.00296

If any of the interim analyses exceeds the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be terminated. The results of these interim analyses will be reported, in a blinded fashion, to the RTOG Data Monitoring Committee *(DMC)* as privileged communications. The recommendation from the DMC, based upon the interim analysis report, will be given to the Brain Committee which is responsible for this study and, if necessary, to 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 each patient has been followed for a minimum of three years. The usual components of this analysis are:

1) tabulation of all cases entered and any excluded from the analysis together with 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.

The α-level of 0.04831 will be used, thus correcting for previous interim tests. Ineligible patients will be excluded from all outcome analyses, but will be included in toxicity analyses (if applicable). Inevaluable patients will be excluded from all analyses. Correlation between results of MMSE and clinical and toxicity evaluation will be performed. Comparisons of treatment arms with respect to MMSE and B-QLQ will utilize analyses of variance[21], principal component methodologies.

REFERENCES

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APPENDIX I

RTOG 94-02/INT 0149
Phase III Intergroup Randomized Comparison of Radiation Alone vs. Pre-Radiation Chemotherapy for Pure and Mixed Anaplastic Oligodendroglioma

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply 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 cancerous brain tumor that is wholely or partly an oligodendroglioma. Pure and mixed malignant oligodendrogliomas are considered incurable illnesses but treatment is usually beneficial. Standard treatment is local radiation after surgical removal or biopsy *(sampling)*. Although most tumors eventually regrow, radiation treatments often delay regrowth for extended periods, sometimes years. Some tumors never regrow after standard treatment but this is uncommon. Doctors have noticed that brain cancers containing an oligodendroglial element often respond to chemotherapy. Response means shrinkage or disappearance of the tumor on a CT scan or MRI. These tumors are sensitive to a number of chemotherapy drugs but the combination of procarbazine, CCNU, and vincristine *(PCV)* seems particularly effective. PCV shrinks most newly diagnosed tumors when given prior to radiation, and also shrinks those that regrow after radiation.

My doctors are studying the best way to use chemotherapy in the treatment of these tumors. Should chemotherapy be given at an early stage together with radiotherapy, or only given if the tumor regrows after radiation? Early aggressive treatment that is chemotherapy and radiation, may cause more side effects than radiation alone, but more side effects may be an acceptable price to pay if intense treatment at diagnosis controls the tumor more effectively. If early aggressive treatment does not control the tumor more effectively than standard treatment, then chemotherapy can be held in reserve until the tumor recurs, or omitted altogether should it never regrow. For the future, my doctors want to know which treatment approach is better.

DESCRIPTION OF PROCEDURES

This study involves at random *(by chance)* assignment to one of two treatment arms. It is not clear at the present time which of the two regimens is better. For this reason the therapy which is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the two regimens by computer. The chance of my receiving one of the two therapies is approximately equal. I will be assigned to one of two treatments: chemotherapy and radiation or radiation alone.

Radiation will be prescribed in a similar fashion for both groups, but one group will begin radiation soon after surgery and the other will begin radiation after approximately six months of chemotherapy. Radiation will be given daily, Monday to Friday, for six weeks. The chemotherapy regimen to be used in this study is called Intensive PCV *(I-PCV)*. I-PCV is 25% stronger than standard PCV. I-PCV is given in four week cycles every six weeks. (P) Procarbazine is given orally by capsule daily for two weeks each cycle. During this time, minor dietary and medication restrictions are required. (C) CCNU is given orally by capsule on the first day of each cycle. (V) Vincristine is given as an intravenous *(in my vein)* injection over several minutes on two separate days each cycle. These are usual chemotherapy drugs and they can be given on an outpatient basis. Should I be assigned to the chemotherapy arm of this study, I will receive four cycles of I-PCV prior to radiation.

As part of this study my doctors are asking me to fill out a questionnaire to assess the impact of cancer on my

quality of life (QOL).

The QOL study will require an assessment at the time of study entry, at the end of my radiation treatments, and on some follow-up visits to my doctor. Assessment will be made using a one and a half page questionnaire which should take several minutes to complete. I will answer the questions myself to the best of my ability. If I am unable to fill out the questionnaire, I understand that my doctor would ask a close friend or family member to do so for me. The questionnaire would be completed as if I were answering the questions.

I understand that my tissue slides, additional sections of my brain tumor tissue, and two samples of my peripheral blood will be studied in a pathology and molecular genetics laboratory for the purpose of identifying features 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 which 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-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.

Participation in the QOL study may cause some emotional distress when describing the impact of cancer on my quality of life. I understand that my participation in the QOL study is voluntary and that I am free at any time to decline participation in this aspect of the study with no effect on my future care.

The success of my treatment and all its side effects will be carefully monitored. I will have follow-up examinations, CT scans or MRIs, and blood tests at regular intervals during and after treatment. My doctor will also evaluate memory, concentration and other brain functions at each visit, and ask me to complete a quality of life questionnaire at each visit.

My doctor may prescribe medication to keep any 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 receive early chemotherapy and radiation, and my tumor regrows, I will be offered other treatment as appropriate. This may include re-operation, re-irradiation, other chemotherapy, or promising experimental treatment. If I receive radiation alone, and my tumor regrows, I may be given I-PCV chemotherapy as outlined above, or any treatment thought to be superior to I-PCV.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement 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 notify Dr. _____ the investigator in charge at _____. In addition, I may contact _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include surgery or radiation therapy alone, chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. 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. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at headquarters of the Radiation Therapy Oncology Group (RTOG). 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 the conduct of this study may have access to medical records which 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 and research investigation associated with this protocol.

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

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

NF	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	Severe neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

APPENDIX III

PATHOLOGY CHECKLIST (P4)

RTOG 94-02
ECOG R9402 Seq # _____
NCCTG 92-72-52 Seq.# _____
SWOG 9402 Seq.# _____
PT. Name _____
Institution _____

Central pathology review is required prior to study entry.

Eligibility: To be eligible for this study, tumors must contain an unequivocal *(at least 25%)* oligodendroglial component and have two or more of the following anaplastic features: high cellularity, nuclear pleomorphism, frequent mitoses, endothelial proliferation, or necrosis. For mixed tumors, the non-oligodendroglial element must be astrocytic *(either element may be anaplastic).*

"HOME" PATHOLOGY REVIEW			CENTRAL PATHOLOGY REVIEW		
Tumor Type:			**Tumor Type:**		
Oligodendroglioma	_____		Oligodendroglioma	_____	
Mixed Glioma	_____		Mixed Glioma	_____	
If mixed,	oligo dominant	_____	If mixed,	oligo dominant	_____
	oligo = astro	_____		oligo = astro	_____
	astro dominant	_____		astro dominant	_____
Anaplastic Features:			**Anaplastic Features:**		
	Yes	No		Yes	No
High cellularity	_____	_____	High cellularity	_____	_____
Nuclear pleomorphism	_____	_____	Nuclear pleomorphism	_____	_____
Frequent mitoses	_____	_____	Frequent mitoses	_____	_____
Endothelial proliferation	_____	_____	Endothelial proliferation	_____	_____
Necrosis	_____	_____	Necrosis	_____	_____
Total # of anaplastic features	_____		Total # of anaplastic features	_____	

Stratification: For the purposes of subsequent analysis, pure oligodendrogliomas and oligodendroglioma-dominant mixed tumors will be considered "pure" whereas oligodendroglioma = astrocytoma and astrocytoma-dominant mixed tumors will be considered "mixed". For stratification, tumors with 2 or 3 anaplastic features and will be considered **moderately anaplastic** and those with 4 or 5 features will be considered **highly anaplastic.**

Cooperative Group Common Toxicity Criteria

INSTRUCTIONS

1. Toxicity grade should reflect the most severe degree occurring during the evaluated period, not an average.
2. When two criteria are available for similar toxicities, the one resulting in the more severe grade should be used.
3. Toxicity grade = 5 if that toxicity caused the death of the patient.
4. Refer to detailed toxicity guidelines in the protocol, or to RTOG Headquarters for toxicity not covered on this table.
5. The evaluator must attempt to discriminate between disease/treatment and related signs/symptoms.
6. An accurate baseline prior to start of therapy is necessary.

	TOXICITY	- 0 -	- 1 -	- 2 -	- 3 -	- 4 -
Blood/Bone Marrow	WBC	=> 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
	Platelets	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
	Hemoglobin	WNL	10.0 - normal	8.0 - 10.0	6.5 - 7.9	< 6.5
	Granulocytes/Bands	=> 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Lymphocytes	=> 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Hemorrhage (Clinical)	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive > 4 units transfusion per episode
	Infection	None	Mild	Moderate	Severe	Life-threatening
Gastrointestinal	Nausea	None	Able to eat/reasonable intake	Intake significantly decreased but can eat	No significant intake	- - - - - -
	Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hrs	> 10 episodes in 24 hours or requiring parenteral support
	Diarrhea	None	Increase of 2-3 stools per day over pre-Rx	Increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools/day or incontinence or severe cramping	Increase of => 10 stools/day or grossly bloody diarrhea, or need for parenteral support
	Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema or ulcers but can eat	Painful erythema, edema or ulcers and cannot eat	Requires parenteral or enteral support
Liver	Bilirubin	WNL	- - - - - -	< 1.5 X N	1.5 - 3.0 X N	> 3.0 X N
	Transaminase (SGOT, SGPT)	WNL	=< 2.5 X N	2.6 - 5.0 X N	5.1 - 20.0 X N	> 20.0 X N
	Alkaline Phosphatase or S'nucleotidase	WNL	=< 2.5 X N	2.6 - 5.0 X N	5.1 - 20.0 X N	> 20.0 X N
	Liver/clinical	No change from baseline	- - - - - -	- - - - - -	Precoma	Hepatic coma
Kidney/Bladder	Creatinine	WNL	< 1.5 X N	1.5 - 3.0 X N	3.1 - 6.0 X N	> 6.0 X N
	Proteinuria	No change	1 + or < 0.3 g% or < 3 g/l	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/l	4+ or >1.0 g% or >10 g/l	Nephrotic syndrome
	Hematuria	Negative	Micro only	Gross/no clots	Gross + clots	Requires transfusion

TOXICITY		- 0 -	- 1 -	- 2 -	- 3 -	- 4 -
	Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	- - - - - -	- - - - - -
	Pulmonary	None or no change	Asymptomatic with abnormality in PFT's	Dyspnea on significant exertion	Dyspnea at normal level of activity	Dyspnea at rest
Heart	Cardiac dysrhythmias	None	Asymptomatic/transient/ requiring no therapy	Recurrent or persistent/ no therapy required	Requires treatment	Requires monitoring or hypotension or ventricular tachycardia or fibrillation
Heart	Cardiac function	None	Asymptomatic/decline of resting ejection fraction by <20% of baseline value	Asymptomatic/decline of resting ejection fraction by >20% of baseline value	Mild CHF, responsive to therapy	Severe or refractory CHF
Heart	Cardiac/ischemia	None	Non-specific T-wave flattening	Asymptomatic/ST and T wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
Heart	Cardiac/pericardial	None	Asymptomatic effusion/no intervention required	Pericarditis (rub, chest pain, ECG changes)	Symptomatic effusion: drainage required	Tamponade/ drainage urgently required
Blood Pressure	Hypertension	None or no change	Asymptomatic/transient increase by > 20mm Hg (D) or to > 150/100 if previously WNL/No treatment required	Recurrent or persistent increase by > 20mm Hg (D) or to > 150/100 if previously WNL/No treatment required	Requires therapy	Hypertensive crisis
Blood Pressure	Hypotension	None or no change	Changes requiring no therapy/including transient orthostatic hypotension	Requires fluid replacement or other therapy but not hospitalization	Requires therapy and hospitalization/resolves within 48 hours of stopping the agent	Requires therapy and hospitalization for >48 hrs after stopping the agent
Neurologic	Neurological/sensory	None or no change	Mild paresthesias/loss of deep tendon reflexes	Mild or moderate objective sensory loss/ moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	- - - - - -
Neurologic	Neurological/motor	None or no change	Subjective weakness/no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
Neurologic	Neurological/cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence, agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic psychosis
Neurologic	Neurological/cerebellar	None	Slight incoordination/ dysdiadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
Neurologic	Neurological/mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
Neurologic	Neurological/headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	- - - - - -

APPENDIX IV

	TOXICITY	- 0 -	- 1 -	- 2 -	- 3 -	- 4 -
Neurologic	Neurological/constipation	None or no change	Mild	Moderate	Severe	Ileus > 96 hours
	Neurological/hearing	None or no change	Asymptomatic/hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
	Neurological/vision	None or no change	- - - - - -	- - - - - -	Symptomatic subtotal loss of vision	Blindness
	Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritis or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
	Allergy	None	Transient rash/drug fever < 38°C, 100.4°F	Urticaria, drug fever = 38°C, 100.4°F/mild bronchospasm	Serum sickness, bronchospasm, requiring parenteral medication	Anaphylaxis
	Fever in absence of infection	None	37.1 - 38.0°C 98.7 - 100.4°F	38.1 - 40.0°C 100.5 - 104.0°F	> 40.0°C/> 104.0°F for less than 24 hours	> 40.0°C/104.0°F for more than 24 hrs or fever accompanied by hypotension
	Local	None	Pain	Pain and swelling with inflammation or phlebitis	Ulceration	Plastic surgery indicated
	Weight gain/loss	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	=> 20.0 %	- - - - - -
Metabolic	Hyperglycemia	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
	Hypoglycemia	> 64	55 - 64	40 - 54	30 - 39	< 30
	Amylase	WNL	< 1.5 X N	1.5 - 2.0 X N	2.1 - 5.0 X N	> 5.1 X N
	Hypercalcemia	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	=> 13.5
	Hypocalcemia	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	=< 6.0
	Hypomagnesemia	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	=< 0.5
Coagulation	Fibrinogen	WNL	0.99 - 0.75 X N	0.74 - 0.50 X N	0.49 - 0.25 X N	=< 0.24 X N
	Prothrombin time	WNL	1.01 - 1.25 X N	1.26 - 1.50 X N	1.51 - 2.00 X N	> 2.00 X N
	Partial thromboplastin time	WNL	1.01 - 1.66 X N	1.67 - 2.33 X N	2.34 - 3.00 X N	> 3.00 X N

RTOG Acute Radiation Morbidity Scoring Criteria

APPENDIX IV

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
MUCOUS MEMBRANE	No change over baseline	Injection / may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
EYE	No change	Mild conjunctivitis with or without scleral injection / increased tearing	Moderate conjunctivitis with or without keratitis requiring steroids &/or antibiotics / dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panopthalmitis	Loss of vision (unilateral or bilateral)
EAR	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/ serous otitis medius/ hypoacusis on testing only	Severe external otitis with discharge or moist desquamation / symptomatic hypoacusis/ tinnitus, not drug related	Deafness
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness / thick, sticky saliva / markedly altered taste	———	Acute salivary gland necrosis
PHARYNX & ESOPHAGUS	No change over baseline	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesics/ may require soft diet	Moderate dysphagia or odynophagia/ may require narcotic analgesics/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss (>15% from pre-treatment baseline) requiring N-G feeding tube, I.V. fluids or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
LARYNX	No change over baseline	Mild or intermittent hoarseness/ cough not requiring antitussive/ erythema of mucosa	Persistent hoarseness but able to vocalize / referred ear pain, sore throat, patchy fibrinous exudate or mild arytenoid edema not requiring narcotic/cough requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fibrinous exudate, marked arytenoid edema.	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
UPPER G.I.	No change	Anorexia with <= 5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/ nausea &/or vomiting requiring antiemetics/abdominal pain requiring analgesics	Anorexia with >15% wt loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/ abdominal pain, severe despite medication/ hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/ abdominal pain requiring tube decompression or bowel diversion.

RTOG Acute Radiation Morbidity Scoring Criteria

	[0]	[1]	[2]	[3]	[4]
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication / rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil) / mucous discharge not necessitating sanitary pads / rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support / severe mucous or blood discharge necessitating sanitary pads / abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
LUNG	No change	Mild symptoms of dry cough or dyspnea on exertion	Persistent cough requiring narcotic, antitussive agents / dyspnea with minimal effort but not at rest	Severe cough unresponsive to narcotic antitussive agent or dyspnea at rest / clinical or radiologic evidence of acute pneumonitis / intermittent oxygen or steroids may be required	Severe respiratory insufficiency / continuous oxygen or assisted ventilation
GENITOURINARY	No change	Frequency of urination or nocturia twice pretreatment habit / dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g. Pyridium)	Frequency with urgency and nocturia hourly or more frequently / dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic / gross hematuria with / without clot passage	Hematuria requiring transfusion / acute bladder obstruction not secondary to clot passage, ulceration or necrosis
HEART	No change over baseline	Asymptomatic but objective evidence of EKG changes or pericardial abnormalities without evidence of other heart disease	Symptomatic with EKG changes and radiologic findings of congestive heart failure or pericardial disease / no specific treatment required	Congestive heart failure, angina pectoris, pericardial disease responding to therapy	Congestive heart failure, angina pectoris, pericardial disease, arrhythmias not responsive to non-surgical measures
CNS	No change	Fully functional status (i.e., able to work) with minor neurologic findings, no medication needed	Neurologic findings present sufficient to require home care / nursing assistance may be required / medications including steroids/ anti-seizure agents may be required	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which includes paralysis, coma or seizures > 3 per week despite medication / hospitalization required
HEMATOLOGIC WBC (X 1000)	=> 4.0	3.0 - < 4.0	2.0 - < 3.0	1.0 - < 2.0	< 1.0
PLATELETS (X 1000)	> 100	75 - < 100	50 - < 75	25 - < 50	< 25 or spontaneous bleeding
NEUTROPHILS (X 1000)	=> 1.9	1.5 - < 1.9	1.0 - < 1.5	0.5 - < 1.0	< 0.5 or sepsis
HEMOGLOBIN (GM %)	> 11	11 - 9.5	< 9.5 - 7.5	< 7.5 - 5.0	----------
HEMATOCRIT (%)	=> 32	28 - < 32	< 28	Packed cell transfusion required	----------

GUIDELINES: The acute morbidity criteria are used to score/grade tocity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects are to be utilized.

The evaluator must attempt to discriminate between disease and treatment related signs and symptoms

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3,4 or 5* must be verified by the Principal Investigator

* ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.

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	Market atrophy; Gross telangiectasia	Ulceration	DEATH DIRECTLY RELATED TO RADIATION LATE EFFECTS
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 quadraplegia	
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 tachychardia >110 (at rest)	Moderate angina on effort Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes; Low QRS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade / Severe heart failure / Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fribrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilatation 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 albuminaria; Severe hypertension Persistent anemia (<10g%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance <50%	Malignant hyprtension 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	

APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).

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

3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.

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.

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.

7. See the specific protocol for criteria utilized to grade the severity of the reaction.

8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.

9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.

10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had 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. Form 1639 is to be used in reporting details (see attached). All relevant data forms must accompany the RTOG copy of Form 1639.

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 and 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 only a reasonable suspicion.

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

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 NCI Adverse Drug Reaction Reporting Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION (HFN-730)
ROCKVILLE, MD 20857

ADVERSE REACTION REPORT
(Drugs and Biologics)

Form Approved: OMB No. 0910-0230. RTOG 9402 Case#

FDA CONTROL NO. INT 0149

ACCESSION NO.

I. REACTION INFORMATION

1. PATIENT ID/INITIALS (*In Confidence*)	2. AGE YRS.	3. SEX	4.-6. REACTION ONSET MO.	DA.	YR.

7. DESCRIBE REACTION(S)

13. RELEVANT TESTS/LABORATORY DATA

8.-12. CHECK ALL APPROPRIATE:

- ☐ PATIENT DIED
- ☐ REACTION TREATED WITH Rx DRUG
- ☐ RESULTED IN, OR PROLONGED, INPATIENT HOSPITALIZATION
- ☐ RESULTED IN PERMANENT DISABILITY
- ☐ NONE OF THE ABOVE

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (*Give manufacturer and lot no. for vaccines/biologics*)

15. DAILY DOSE

16 ROUTE OF ADMINISTRATION

17. INDICATION(S) FOR USE

18. DATES OF ADMINISTRATION (*From/To*)

19 DURATION OF ADMINISTRATION

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐ YES ☐ NO ☐ NA

21. DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐ YES ☐ NO ☐ NA

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (*Exclude those used to treat reaction*)

23. OTHER RELEVANT HISTORY (*e.g. diagnoses, allergies, pregnancy with LMP, etc.*)

IV. ONLY FOR REPORTS SUBMITTED BY MANUFACTURER

24. NAME AND ADDRESS OF MANUFACTURER (*Include Zip Code*)

24a. IND/NDA. NO. FOR SUSPECT DRUG

24b MFR CONTROL NO.

24c. DATE RECEIVED BY MANUFACTURER

24d. REPORT SOURCE (*Check all that apply*)
☐ FOREIGN ☐ STUDY ☐ LITERATURE
☐ HEALTH PROFESSIONAL ☐ CONSUMER

25 15 DAY REPORT?
☐ YES ☐ NO

25a. REPORT TYPE
☐ INITIAL ☐ FOLLOWUP

NOTE: Required of manufacturers by 21 CFR 314.80

V. INITIAL REPORTER (*In confidence*)

26.-26a. NAME AND ADDRESS OF REPORTER (*Include Zip Code*)

26b. TELEPHONE NO. (*Include area code*)

26c. HAVE YOU ALSO REPORTED THIS REACTION TO THE MANUFACTURER?
☐ YES ☐ NO

26d. ARE YOU A HEALTH PROFESSIONAL?
☐ YES ☐ NO

Submission of a report does not necessarily constitute an admission that the drug caused the adverse reaction.

INSTRUCTIONS FOR COMPLETING FORM FDA 1639

Attachment 4 (continued)

Use a separate report form for each case. If more space is needed, additional pages may be attached.

I. Patient/Reaction Information (Items 1-12)

1. Patient ID/Initials: Record patient's identification (i.e. medical record number, initials, etc). *(This information is kept in confidence by the FDA.)*
2. Age: Record the age of the patient. When reporting a congenital malformation, record the age of the mother.
3. Sex: Record the sex of the patient. When reporting a congenital malformation, record the sex of the baby.
4. Weight: Record the weight of the patient in pounds. When reporting a congenital malformation, record the weight of the mother.
5. Height: Record the height of the patient in inches. When reporting a congenital malformation, record the height of the mother.
6. Reporting Date: Record the date when the report was initially communicated to the manufacturer.
7. Reaction Onset Date: Record the date on which the reaction was first observed or detected.
8. Suspected Reaction(s): Describe the signs, symptoms and course of the drug related event in the terminology used by the original observer of the reaction. (Coding terms e.g. COSTART, SNOMED, etc. may also be noted, but only in addition to original description.)
9. Outcome of Reaction: Indicate the status of the patient as of date indicated in Item 23. If the patient died, give the cause and date of death. Include discharge summary and/or autopsy findings, if available.
10. Tests/Laboratory Data: Describe the results of all diagnostic tests and exams (e.g. biochemical tests, x-rays, endoscopy, biopsy, etc.) which were done as a result of the event described in Item 8. Pertinent base line values and laboratory normals should be included with each test or exam reported. If this information is not available at the time of the initial report, a follow up report should be submitted.
11. Treatment Required: If "yes", a short description of treatment should be included in Item 8.
12. Hospitalization Required: If "yes", a short description of the treatment should be included in Item 8.

II. Suspect Drug Information (Items 13-20)

13. Suspect Drug(s): Record the trade name. The generic name should be used only when the trade name is not known. Include IND/NDA number of the drug as well as the lot number, when available.
14. Total Daily Dose: Record the total daily dose as of the date recorded in Item 7. If drug(s) was given in a different dose or form on a previous occasion, include dates and total daily dose for each drug exposure.
15. Route of Administration: Record the route of administration (i.e. po, IM, IV) as of the date recorded in Item 7.
16. Indication(s) for use: Record intended use in accepted medical terminology.
17. Therapy Dates: Give starting and stopping dates of administration for each drug listed in Item 13.
18. Therapy Duration: Give duration of therapy in days.
19. Dechallenge:
    (a) Applicable if the suspect drug(s) was either reduced in dosage or discontinued.
    (b) If 19(a) is checked, indicate whether the reaction subsided upon reduced dosage or discontinuation of the drug.
20. Rechallenge:
    (a) Applicable if the suspect drug was reintroduced to the patient's therapy after dechallenge.
    (b) If 20(a) is "yes", indicate whether or not the reaction reappeared upon rechallenge with the drug.

III. Recent/Concomitant Drugs and Medical Problems (Items 21-22)

21. List all recent or concomitant drugs. Include the total daily dose(s), indication(s) for use, route(s) of administration and dates of administration and/or duration of therapy for each drug.
22. Describe other relevant medical conditions or problems which could have contributed to the reaction. Include pertinent medical history such as allergies, occupation, industrial hazards, diet, smoking, climate, ethnic origin, cosmetics and biologicals. When reporting a congenital malformation, include the date of the last menstrual period of the mother, gravidity, parity and previous abortions.

IV. Other Information (Items 23-26)

23. Manufacturers Information: Include manufacturer's name, address, control number and date report is sent to FDA. This control number is the identifying number assigned by the manufacturer to the report for internal record control.
24. Indicate if this is an initial submission to FDA or a follow-up of a previously submitted Form FDA 1639. If this is a follow-up attach copy of initial report.
25. Record the name, title and address of the practitioner originating the report. *(This information is kept in confidence by the FDA.)*
26. Check "yes" or "no", if the source of this report may or may not be released to the Armed Forces Institute of Pathology for further study and follow-up. This is encouraged whenever possible.

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 which 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 which are not forms (CAT 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:** Forms packages may be obtained from the participating Cooperative Group office. Attached is a list (Forms Package Index) of all data collection forms used in the study, the toxicity criteria for this study, if applicable and a sample of the data collection forms.

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:** Preprinted labels are available for source document data items (radiographic reports, etc.) Supplied white labels are to be used for film identification.

The blank 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.

Data managers 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 cancelled, 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.

VI. **RAPID REVIEW ITEMS:** Time critical data which requires rapid submission must be sent directly to RTOG (See Section V). These items are:

M2 - Medical Oncology Treatment Planning Form (if required by the Protocol)
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:

Randomization/Registration	Registration Secretary (215) 574-3191
Pathology	Pathology Coordinator (215) 574-3161
Data/Eligibility/Treatment/ Adverse Reactions	Data Manager (215)574-3214
Data Management Procedures	Data Manager (215)574-3214
Protocols/Amendments	Protocol Administrator (215) 574-3195
Radiotherapy data items (films, radiographs, isodose summations, treatment records, scans, reports and calculations)	Dosimetry Clerk (215) 574-3219

If you are unable to reach the person noted, and your call is urgent, ask to speak to any data manager.

XI. ADVERSE REACTIONS/AND TOXICITY

From Radiotherapy: Unusual toxicities, and all grade 4-5 toxicities are to be reported by telephone to RTOG Headquarters, the Group Chairman Dr. James Cox and to the Study Chairman. If the Chairman is unavailable, ask to speak to the Data Manager for this study.

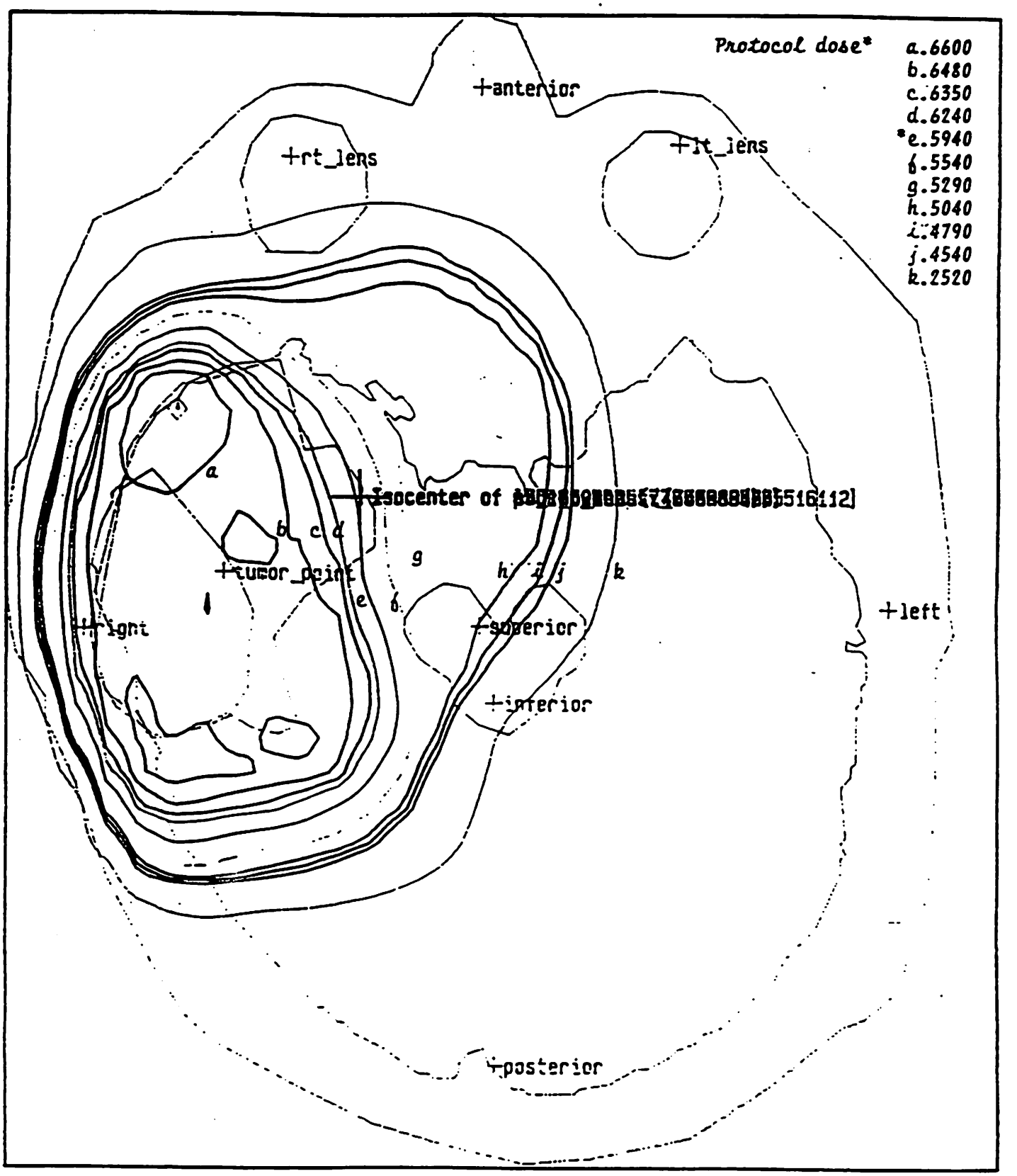
From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters and the Study Chairman are to receive notification as outlined by the NCI procedures, i.e. if telephone notification is necessary, RTOG and the Study Chairman must also be called.

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.

APPENDIX VII

SAMPLE ISODOSE PLAN



SUMMARY OF CHANGES
Update, February 11, 2005

RTOG 9402, "Phase III Intergroup Randomized Comparison of Radiation Alone VS Pre-Radiation Chemotherapy for Pure and Mixed Anaplastic Oligodendrogliomas"

Study Chair: Gregory Cairncross, M.D., (519) 685-8640, FAX (519) 685-8624

RTOG 9402 been updated as follows:

Title Page: Corrected Edward Shaw, M.D.'s contact information.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as "Update Date".

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/

#4

SUMMARY OF CHANGES

RTOG 94-02 Oligodendroglioma *(INT 0149)* September 8, 1998

The following changes are in effect:

Cover Page - Dr. Shaw's new area code is 336.

Dr. Schomberg's new phone number is (507) 284-3551.

Eligibility Checklist - Updated to show all questions asked at randomization.

Section 10.3 and 10.5 Central review requires one representative H&E stained slide and one representative paraffin block. If a paraffin block is not available, submit 10 representative unstained slides.

Section 10.3.3 Pathology will be mailed to Pam Fain-Pribyl.

Section 12.1 The M2 Form is no longer required. The C1, C3 and MR were deleted from this section (duplicates of requirements in Section 12.2).

Section 12.2 The code type for the post-op MR scan was corrected to "MR' (not C2)

Section 12.3.2 SWOG's mailing address was updated.

Section 13.2, line 7 "five-year" was corrected to median"

Appendix VI was updated for phone numbers

#3

SUMMARY OF CHANGES

RTOG 94-02 Oligodendroglioma *(INT 0149)* October 15, 1996

The following changes are in effect:

NCIC CTG has joined. This affects the Cover Page, the Schema and Eligibility Checklist (group number was added), Sections 5.6, 7.9, 12.3, and Appendices I&II (group number, and line 2 of *Confidentiality)*

Other Changes

Section 7.1 Paragraph 2 was added to discuss risk of drug interactions. This is also now stated in paragraph 3 of *Risks and Discomforts* (p.22).

A replacement protocol through page 26A is attached.

SUMMARY OF CHANGES

#2

RTOG 94-02 Oligodendroglioma *(INT 0149)* January 31, 1996

The following changes are in effect:

Cover Page The NCCTG neuro-oncologist is Dr. Jan C. Buckner.

Fax numbers were added for RTOG.

A replacement cover page is attached.

SUMMARY OF CHANGES

#1

RTOG 94-02 Oligodendroglioma *(INT 0149)* June 30, 1995

The following changes are in effect:

Cover Page Dr. Hellman's new phone number is (203) 444-3744

Dr. Shaw's new number is (910) 716-4981

Section 5.3 ECOG's participation requirements have been updated, also affects Sections 7.6, 10.5 and 12.3.1.

Section 7.5.2 Form 3500 replaces 1639. This also affects Appendix V, p.34 and pp. 36-37.

Section 10.2 Add to the first sentence and to top of p. 26 (Appendix III)

. . .(one of which must be . . .)

Section 12.3 Deleted Section 12.3.4, rapid review does not apply to this study. Subsequent sections were renumbered.

A revised protocol is attached.