

RADIATION THERAPY ONCOLOGY GROUP

RTOG BR-0021

**A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY PLUS HIGH DOSE
TAMOXIFEN FOR THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA
MULTIFORME (*GBM*)**

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Activation Date:

December 6, 2000

Closure:

December 28, 2001

Version Date:

**January 21, 2003 (Broadcast 2/10/03)
Includes Revision 1**

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A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY PLUS HIGH DOSE TAMOXIFEN FOR THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA MULTIFORME (GBM)

SCHEMA

- R** 60.0 Gy/30 fractions x 2.0 Gy. For the first 46 Gy/23 fractions the treatment volume should include the volume of contrast enhancing lesion and surrounding edema on pre-operative CT/MRI scan plus a 2 centimeter margin. If no edema is present, the margin should be 2.5 cm. After 46.0 Gy, the tumor volume should include the contrast enhancing lesion (*without edema*) on the pre-surgery MRI/CT scan plus a 2.5 centimeter margin.
- E**
- G**
- I**
- S**
- T** Tamoxifen must begin day 1 of radiotherapy; dose to be escalated 20 mg per day until target dose established; target dose 80 mg/m² p.o. (*in 4 divided doses, 20 mg/m² q 6 hours*). Tamoxifen will
- E**
- R** continue until disease progression.

Eligibility (See Section 3.0 for details)

- Histopathologically confirmed glioblastoma multiforme (*with areas of necrosis*); recurrent GBM is not eligible
- Diagnosis must be made by surgical biopsy or excision
- The tumor must be supratentorial in location
- Patient must have recovered from the effects of surgery, or post-operative infection and other complications
- Therapy must begin \leq five weeks after surgery
- Estimated survival of at least 8 weeks
- KPS \geq 70 (*Zubrod 0 and 1*)
- A contrast-enhanced MRI or CT scan must be performed preoperatively and postoperatively prior to initiation of RT.
- Absolute neutrophil count \geq 1500, platelets \geq 100,000, BUN \leq 25, Creatinine \leq 1.5, Bilirubin \leq 2.0, Hgb \geq 10 gm, SGPT or SGOT \leq 2 x normal range
- No metastases below the tentorium or beyond the cranial vault
- No major medical illnesses or psychiatric impairments
- No active connective tissue disorders or active thrombophlebitis
- No malignancy (*within the past five years*) except non-melanomatous skin cancer or carcinoma *in-situ* of the cervix, no prior endometrial cancer or atypical endometrial hyperplasia.
- No prior radiation therapy to head or neck area, chemotherapy or radiosensitizer.
- No patients with Acquired Immune Deficiency (*AIDS*)
- No pregnant or lactating women; tamoxifen is contraindicated in pregnancy
- Signed study-specific consent form prior to registration

Required Sample Size: 72

Institution # _____

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ELIGIBILITY CHECK (1/21/03)

Case # _____

(page 1 of 2)

- _____(Y) 1. Does the patient have histologically-confirmed supratentorial glioblastoma multiforme with areas of necrosis?
- _____(Y) 2. Was diagnosis made by surgical biopsy or excision?
- _____(N) 3. Is the tumor recurrent?
- _____(Y) 4. Has the patient recovered from the effects of surgery, post-operative infection or other complications?
- _____(Y) 5. Has a diagnostic contrast enhanced MRI or CT of the head been performed pre-operatively?
- _____(Y/N) 6. Has a diagnostic contrast enhanced MRI or CT of the head been performed post-operatively?
_____(Y) If no, did the patient have only a stereotactic biopsy performed?
- _____(Y) 7. Do the patient's laboratory values meet the criteria in Section 3.1.10?
- _____(N) 8. Has the patient received any prior radiotherapy to the head and neck area, chemotherapy, or radiosensitizer?
- _____(N) 9. Is the patient known to have Acquired Immune Deficiency Syndrome?
- _____(Y/N) 10. Has the patient had prior malignancies, except for non-melanomatous skin cancers, or carcinoma *in-situ* of uterus, cervix or bladder? (*prior endometrial cancer or atypical endometrial hyperplasia is ineligible*)
_____(Y) If yes, has the patient been disease free for ≥ 5 years?
- _____(N) 11. Does the patient have any detected metastases below the tentorium or beyond the cranial vault or tumor?
- _____(Y) 12. Is the patient's KPS ≥ 70 (*Zubrod 0 and 1*)?
- _____(Y) 13. Does the patient have an estimated survival of at least 8 weeks?
- _____(N) 14. Does the patient have any major medical or psychiatric illness which in investigator's opinion will prevent administration or completion of the protocol therapy?
- _____(N/NA) 15. Is the patient pregnant or lactating?

(cont'd on next page)

RTOG Institution # _____

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ELIGIBILITY CHECK (12/1/00)

Case # _____

(page 2 of 2)

- _____(Y/NA) 16. If the patient is of childbearing potential, has she agreed to use an approved method of contraception?
- _____(N) 17. Does the patient have any active connective tissue disorder or active thrombophlebitis?
- _____(Y) 18. Will treatment start \leq 5 weeks after surgery?

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Medical Oncologist's Name
- _____ 18. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 GBM Prognosis

Results with all present methods of treatment for glioblastoma multiforme has been disappointing. The combination of surgical resection, radiation therapy, and chemotherapy produces a median survival of less than one year.^{1,2} Surgery and radiation have probably reached maximal effectiveness. Chemotherapy has the potential to improve survival, but significant increase has been marginal using either intravenous or intra-arterial administration of conventional agents.^{1, 2}

1.2 Protein Kinase C, GBM and Tamoxifen

A series of studies have suggested that the proliferation of high grade gliomas is in part dependent on the activation of protein kinase C (PKC) mediated pathways.³⁻⁸ Thus, blocking this enzyme, i.e., PKC, known to be involved in signal transduction, provides a novel approach to inhibiting glioma cell growth. Beyond this, recent investigations have suggested that inhibition of PKC can result in enhancement of the ionizing effects of irradiation.^{9,10} Relevant to this, the antiestrogen tamoxifen is a significant PKC inhibitor.³⁻⁶ At concentrations several fold higher than that used in its traditional role as a breast cancer agent, tamoxifen can block glioma cell line *in vitro*. By extrapolation, serum concentrations in excess of 80 mg/m² p.o. can achieve serum concentration in a putative therapeutic range. In this regard, Couldwell et al. reported both safety and efficacy (*i.e., responses in 4/20 GBM patients*) in a small series at a tamoxifen dose of 160 to 200 mg per day.¹¹ This study, as well as smaller series, and anecdotal reports, are consistent with continued investigation of tamoxifen in this patient population.^{3, 12-15}

1.2.1 Laboratory Correlates

Tissue blocks will be collected on all patients enrolled on this study; an analysis of the expression of various isoforms of PKC will be performed using immunohistochemical methods. This information will be correlated with survival outcome.

1.3 Potential Toxicities

1.3.1 Thrombophlebitis and GBM and/or Tamoxifen

1.3.1.1 GBM: Brain tumor patients are highly predisposed to thromboembolic phenomena¹⁶ and have demonstrated an 8.4% incidence to pulmonary emboli, (*which is almost 3 times the incidence seen in nonmalignant neurosurgical patients*). Similarly the incidence of DVT's in such patients is 27.5% compared to 17% in a controlled neurosurgical group¹⁷ Sawaya et al.¹⁸, using ¹²⁵I-fibrinogen scanning demonstrated DVT's in 60% of patients with GBM. Interestingly, the presence of DVT's did not correlate with time of surgery, length of operation, ambulatory status or occurrence in a paretic limb. It has been suggested malignant brain tumors release a factor responsible for this predisposition to coagulopathy.¹⁹ Earlier work suggested increased platelet adhesiveness in malignant brain tumors is consistent with this supposition.^{20, 21} More recent work further supports the concept of an increased coagulable state of brain tumor patients.²²⁻²⁴

1.3.1.2 Tamoxifen: There is a defined increase risk of thromboembolic diseases in patients receiving tamoxifen.²⁵ Thus, it is logical to assume there may be an increased risk if this drug is introduced in high doses to a patient population predisposed to thromboembolic disease. Nevertheless, this has not been observed in the aforementioned studies or anecodated by the principal investigators in over 20 patients, or by other workers in larger series (*Louisa Thordan, Jefferson University, personal communication*). It is of parenthetical interest to note that Love et al. studied antithrombin III levels, fibrinogen levels and platelet count changes with adjuvant tamoxifen therapy in breast cancer patients.²⁶ These authors noted: decreased in tamoxifen-treated subjects at 6 months, but no subject exhibited a drop to clinically significant levels. Fibrinogen levels decreased 15 % (*0.4 g/L*) in tamoxifen-treated subjects at 6 months. Platelet counts decreased 7% to 9% from baseline to evaluations at 3, 6, 12, 18 and 24 months in tamoxifen-treated subjects. While these changes do not explain the possible small thrombophlebitis-promoting effect of tamoxifen, the decrease in fibrinogen levels might be expected to be associated with a decreased risk of arterial thrombosis. In this regard, we do not believe that we will observe an increase in thromboembolic disease. Consistent with this recent report by Broniscer et al.³⁰ regarding brainstem gliomas in high dose tamoxifen did not show an increase in the expected incidence of thromboembolic disease in a series of 29 patients.

2.0 OBJECTIVES

2.1 To determine if tamoxifen given orally on a daily basis starting at the time of conventional RT may improve the overall survival time of adults with newly diagnosed supratentorial glioblastoma.

- 2.2 To determine, in a multi-institutional setting, the feasibility and toxicity of prescribing tamoxifen at 80 mg/m²/day (*total*) in 4 divided doses.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

- 3.1.1 Histopathologically-confirmed glioblastoma multiforme (*with areas of necrosis*).
- 3.1.2 Diagnosis must be made by surgical biopsy or excision.
- 3.1.3 Tumor must be supertentorial in location.
- 3.1.4 The patient must have recovered from the effects of surgery, or post-operative infection and other complications before entry into the study.
- 3.1.5 Therapy must begin \leq five weeks after surgery.
- 3.1.6 Patients must have an estimated survival of at least 8 weeks.
- 3.1.7 Karnofsky Performance Status of ≥ 70 (*Zubrod 0 and 1*).
- 3.1.8 A diagnostic contrast-enhanced MRI or CT scan must be performed preoperatively and postoperatively prior to the initiation of radiotherapy. Preoperative and post operative scans must be the same type.
- 3.1.8.1 Patients diagnosed only by stereotactic biopsy do not require the post-op scan.
- 3.1.9 Hematologic, renal, and hepatic status should be documented. If anemia is present to the extent that the hemoglobin is less than 10 grams and the hematocrit is less than 30%, then correction by transfusion is indicated before entry into the study.

Hematologic: Hemoglobin \geq 10 grams
Absolute neutrophil count \geq 1500 (*ANC*) per mm³
Platelets \geq 100,000 per mm³
Hematocrit \geq 30%

Renal: BUN \leq 25 mg
Creatinine \leq 1.5 mg

Hepatic: Bilirubin \leq 2.0 mg
SGPT or SGOT \leq twice normal range

- 3.1.10 The patient must give written study-specific informed consent prior to study entry. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the responsible family member.

3.2 Conditions for Patient Ineligibility

- 3.2.1 Recurrent malignant gliomas.
- 3.2.2 Patients in whom metastases are detected below the tentorium or beyond the cranial vault.
- 3.2.3 Major medical illnesses or psychiatric impairments which in the investigator's opinion will prevent administration or completion of the protocol therapy.
- 3.2.4 Previous radiotherapy to the head or neck, chemotherapy, or radiosensitizer.
- 3.2.5 Active connective tissue disorders, such as lupus or scleroderma.
- 3.2.6 Previous malignancies, except for non-melanomatous skin cancers and carcinoma *in situ* of the uterine cervix or bladder, unless disease-free for \geq 5 years.
- 3.2.7 Patients with known Acquired Immune Deficiency (*AIDS*) which may alter the interpretation of the study results. Patients treated on this study will be compared to the established historical control which did not include AIDS patients.
- 3.2.8 Pregnant or lactating women; tamoxifen is contraindicated in pregnancy.
- 3.2.9 Prior tamoxifen unless completed at least 12 months before study entry.
- 3.2.10 Active thrombophlebitis, history of endometrial cancer, or atypical endometrial hyperplasia.

4.0 PRETREATMENT EVALUATIONS

4.1 Mandatory Studies

- 4.1.1 Complete history and general physical examination.
- 4.1.2 Contrast-enhanced MRI or CT scan performed preoperatively and postoperatively prior to the initiation of radiotherapy (*mandatory for eligibility*). The postoperative scan is not required if the patient was diagnosed by stereotactic biopsy.
- 4.1.3 CBC with differential, platelet count, BUN, serum creatinine, bilirubin, and SGOT or SGPT.
- 4.1.4 Steroid doses must be documented.

- 4.1.5 Detailed neurological examination and Mini-mental status exam immediately prior to beginning protocol treatment course. Request a forms pack from RTOG Headquarters in advance.

5.0 REGISTRATION PROCEDURES

- 5.1 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 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY PARAMETERS

6.1 Dose Definition and Schedule

Radiotherapy must begin within 5 weeks after surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over six weeks. All portals shall be treated during each treatment session. Doses are specified as the target dose which shall be to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

- 6.1.2 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
6.1.3 For an arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.
6.1.4 For complete rotation or arc therapy: in the plane of rotation at the center of rotation.
6.1.5 Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.
6.1.6 The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However, if this technique is utilized, the dose shall be specified at the center of the target area.
6.1.7 Other or complex treatment arrangements: at the center of the target volume.

6.2 Physical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from Cobalt 60 up to and including 10 MV photons. Selection of the appropriate photon energy(*ies*) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies, >10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy <10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines, secondary collimation is required. Electron, particle or implant boost is not permissible.

6.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. The initial target volume shall include the contrast-enhancing lesion and surrounding edema (*if it exists*) demonstrated on CT/MRI plus a 2.0 centimeter margin. If no surrounding edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5 centimeter margin.

This initial target volume will be treated to 46.0 Gy in 23 fractions. After 46 Gy the conedown tumor volume should include the contrast enhancing lesion (*without edema*) on the pre-surgery CT/MRI scan plus a 2.5 centimeter margin.

6.4 Treatment Planning

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. CT/MRI-guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores during RTOG HQ Dosimetry reviews.

Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to < 10%.

The minimum dose to the target volume should be kept within 10% of the dose at the center of the volume. The use of vertex fields requires either a diagram or photograph of treatment position to be submitted to RTOG Headquarters.

6.5 Dose Limitations 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 54 Gy, the retina of at least one eye (*but preferably both*) to 50 Gy, and the brain stem to 60 Gy. When the optic chiasm must be included in the full dose, then there may be a finite unknown risk of developing blindness.

6.6 Documentation Requirements

A copy of the pretreatment CT/MRI, the treatment prescription form, treatment calculation form, simulation films and representative portal films of each initial field must be forwarded to RTOG Headquarters according to Section 12.1. At the completion of treatment, the following shall also be forwarded to Headquarters: daily treatment record, all isodose distributions, simulation and portal films of the reduced fields, and the radiotherapy summary.

6.7 Acute Radiation Toxicities

6.7.1 Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically. If significant increase in reaction of the normal tissue occurs, it should be noted and reported to the Study Chairman.

6.7.2 Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation.

6.7.3 Hematologic toxicities should be rated on a scale of 0-5 as defined in the revised NCI Common Toxicity Criteria, Version 2.0.

6.8 Treatment Interruptions

Treatment will be delivered daily for all radiation fractions except for weekends. Up to three days of treatment interruptions are permitted for any reason. Interruptions of 3 to 5 treatment days will require notification to the radiotherapy study chair and patients will be regarded as eligible for evaluation. Treatment breaks of more than five treatment days will be considered a protocol violation.

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 Tamoxifen (Nolvadex)

7.1.1 Formulation

Tamoxifen is supplied in 20 mg tablets.

7.1.2 Storage and Stability

Tamoxifen is stable for at least five years under normal storage conditions and should be protected from light and moisture. Minimal shelf-life appears to be two years.

7.1.3 Administration and Modification (1/21/03)

Tamoxifen will be started on day 1 of radiotherapy. The **target** dose will be 80 mg/m². Before drug therapy starts, the target dose should be calculated. The **starting** dose will be 20 mg orally. The dose will be escalated 20 mg per day to a final dose of 80 mg/m². By the fourth day, the drug should be administered in four divided doses (*one with each meal and one at bedtime*). Patients not tolerating a given dose, e.g. secondary to \geq grade 2 nausea, should decrease dose by 20 mg/day until stable. Then there should be an attempt within 1-2 days to re-escalate by 20 mg/day to target dose. Each change in dosage, i.e., modification (*escalation, reduction, hold, etc.*) and the date must be recorded in the research record. Each cycle is three months (*90 days*). Tamoxifen will continue until disease progression, unless the patient develops thromboembolic disease (*see Section 7.1.7*).

7.1.4 Supplier

The drug is commercially available under the trade name Nolvadex®.

7.1.5 Animal Studies

In the rat, mouse, beagle dog, and rhesus monkey, maximal blood levels of tamoxifen are seen 1-6 hours and 24-44 hours after an oral dose. The drug is hydroxylated in the liver to a number of different compounds and excreted in the bile. After a conjugation, an extensive enterohepatic circulation exists, and the conjugated metabolites are hydrolyzed to the unhydrolyzed metabolite, reabsorbed, and re-conjugated. Eventually, the drug is excreted in the feces in the metabolized form. Very little drug is excreted in the urine. Biophasic half-lives of 5-12 hours and 62-170 hours were seen in the animal experiments. The antiestrogenic properties of the metabolite are unknown; however, the monohydroxyl metabolite is thought to have activity. Tamoxifen has been shown to cause liver tumors in rats, when they receive doses 20-100 times the human dose.

7.1.6 Human Studies

Using a method incorporating ion pair extraction, photochemical activation, and chromatographic analysis, maximal blood levels of tamoxifen and metabolite are found to occur within 3-12 hours after a single dose of tamoxifen of 10 mg. Preliminary data indicate a half-life after a single dose in excess of 24 hours. Metabolism in humans is similar to animals but with extensive enterohepatic circulation. Half-life after prolonged 10 mg b.i.d. dosage is variable but appears to be between 4 and 14 days.

7.1.7 Human Toxicity (1/21/03)

Toxicity attributable to tamoxifen is minimal and consists mainly of hot flashes (20%), transient nausea (10%), and vaginal discharge (9%). Vaginal bleeding, skin rash, and edema occur rarely. A mild leukopenia or thrombocytopenia will develop in up to 20% of the patients, usually during the second week of therapy, which resolves spontaneously within a week and does not require discontinuation of the drug. Hypercalcemia developed in approximately 1% of patients.

Analysis of data from NSABP P-1E, an ancillary study to NSABP B-14 designed to evaluate ocular toxicity in women taking tamoxifen, and the Breast Cancer Prevention Trial suggests that women taking tamoxifen may be at a slightly increased risk for developing cataracts. In addition, women who have a cataract prior to tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients.

An association between tamoxifen therapy and thromboembolic events has been supported by case reports, and the findings of decreased antithrombin levels in patients receiving tamoxifen in some, but not all studies. Data from a large prospective placebo-controlled adjuvant tamoxifen trial shows that the incidence of thromboembolic events was 0.9% in tamoxifen-treated patients versus 0.2% in patients receiving placebo. **Tamoxifen should be discontinued if the patient develops thromboembolic disease.**

In placebo-controlled adjuvant tamoxifen trials, no hepatocellular tumors have been observed in over 3000 tamoxifen-treated patients and over 3000 patients who received placebo. In a Swedish adjuvant trial in which patients received 40 mg/day of tamoxifen, 2/931 (0.2%) cases of liver cancer were observed in contrast to 0/915 cases in patients treated with placebo.

Tamoxifen has an estrogenic effect on the endometrium and cases of endometrial cancer in women on tamoxifen have been reported. Some of these resulted in death. The incidence of endometrial cancer is 0.3% (9/3097) in patients receiving 20 mg/day of adjuvant tamoxifen, in contrast to 0.1% (4/3091) in patients treated with placebo. The incidence of endometrial cancer was higher (1.4% versus 0.2%) in a Swedish adjuvant study which treated patients with 40 mg/day of tamoxifen.

Other adverse reactions reported infrequently include distaste for food, depression, dizziness, and light-headedness. Unpublished data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving tamoxifen, and there have been a few reports of liver cancer that have occurred in women taking tamoxifen.

7.2 Adverse Drug Reaction Reporting Guidelines

7.2.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTC version 2.0.

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.2.2 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to this protocol and attributed to the commercial agent should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days and telephoned to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery:

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

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

7.2.2.3 Any death on study if clearly related to the commercial agent.

7.2.2.4 The ADR report should be documented on form FDA 3500 and mailed to:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone: (24 hours) (301) 230-2330
Fax: (301) 230-0159**

7.2.3 Any death, regardless of cause, which occurs during protocol treatment must be reported to RTOG Headquarters by telephone within 48 hours of discovery.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

All patients should be maintained on the lowest steroid dose necessary for neurological stability.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank

- 10.1.1 Patients entered on this study must submit materials to the RTOG Tissue Bank.
- 10.1.2 The following must be provided:
 - 10.1.2.1 One H&E stained slide.
 - 10.1.2.2 A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.
 - 10.1.2.3 Pathology report documenting that submitted block or slides contain tumor.
 - 10.1.2.4 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.
- 10.1.3 RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).
- 10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).
- 10.1.5 Materials will be sent to:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
Ldafurne@ihc.com**

11.0 PATIENT ASSESSMENTS (1/21/03)

11.1 Study Parameters Table

Assessment	Prior to Study Entry	During Radiotherapy	During F/U
Neurological Exam, H&P	X		X ^d
Anti-seizure levels	X	Weekly	X ^d
Steroid Dose Documentation	X	X	X ^d
CBC and differential, platelets, coagulation studies	X		X ^d
BUN, Serum Creatinine, Bilirubin, & SGOT or SGPT,	X		X ^d
Contrast-enhanced Brain CT or MRI	X ^b		X ^{b,e}
MMSE	X ^a		X ^c
Toxicity Evaluation		Weekly	X ^c

- a. Prior to start of treatment
- b. Both preoperatively and postoperatively prior to RT. Post-operative scan not required if patient diagnosis was by stereotactic biopsy only. Six weeks post RT then q 2 months.
- c. At each follow-up evaluation.
- d. Monthly x 9 months then q 3 months.
- e. **Important: It is mandatory that patients are followed with the same study (CT vs. MRI) as the baseline study**

11.2 Evaluation During Study

- 11.2.1 A neurologic examination shall be performed once a week during radiation therapy.
- 11.2.2 The contrast-enhanced CT/MRI of the brain shall be obtained prior to surgery, post-surgery, six weeks post RT, every two months, and at the time of neurologic deterioration. Attention is drawn to the occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.
- 11.2.3 Anticonvulsant levels will be monitored weekly during RT, then monthly for nine months, then every three months.

11.3 CT/MRI Review

The serial CT/MRI shall be examined at the institution by an independent reviewer, a neuroradiologist. The evaluation of the scans will be compared to and correlated with the patient's clinical course.

11.4 Overall Response

- 11.4.1 ***Complete Response (CR)***: shall be defined as the circumstance when the tumor is no longer seen by neuroimaging provided the patient is not receiving any corticosteroids (*or only adrenal replacement doses as required*).
- 11.4.2 ***Partial Response (PR)***: Decrease of >50% in the product of two diameters provided that the patient has not had his/her dose of steroids increased since the last evaluation period.
- 11.4.3 ***Minor Response (MR)***: Decrease in diameter products of < 50% provided that the patient has not had his/her dose of steroids increased since the last evaluation period.
- 11.4.4 ***Stable Disease (SD)***: shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids.
- 11.4.5 ***Progression (P)***: shall be defined as a > 25% increase in tumor area (*two diameters*) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation at this point.

11.5 Instructions For Administration of Mini-Mental Status Examination (MMSE)

The Mini-Mental Status Exam could be administered by the physician, a nurse or an assistant trained in the administration of such tools. The person administering the Mini-Mental Status Exam needs to be sensitive to when the patient shows embarrassment of their inability to answer these questions. Patients should be assured by telling them that this is another way of telling how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to get this type of information directly from them. The person administering the test needs to understand that either the correct answer is given or not. There should be no partial credit for answers short of the mark.

11.6 Criteria for Evaluation of Therapy Effectiveness

- 11.6.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and CT/MRI scans may provide a guide to the actual course. Time interval to progression will be measured from the first day of treatment until deterioration is documented by the individual Investigator using these guides. The patient should consistently be followed with the same diagnostic imaging study (*CT or MRI*).
- 11.6.2 Overall survival will be measured from the time of first surgery until death.
- 11.6.3 The quality of survival will be measured by neurological functional classification and performance status.
- 11.6.4 Post mortem examination of the cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on malignant and normal brain tissue.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

(RTOG, 1101 MARKET STREET, PHILADELPHIA, PA 19107, FAX: 215/928-0153)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within two weeks of registration
On-study Form (I1)	
Pretreatment MRI/CT scan (<i>both pre- and post-surgery</i>) (C1) and reports (C3)	
Pathology report (P1)	
Pathology Slides/Blocks (P2)	
Mini Mental Status Exam (MS)	
<u>Preliminary Dosimetry Information:</u>	Within one week of treatment start
Radiotherapy prescription (T2)	
Simulation & Portal Localization films (T3)	
Calculation Form (T4)	
Radiotherapy Form (T1)	Within one week of completing radiotherapy
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5),	
Isodoses (T6),	
Simulation & Port Boost Films (T8)	
Initial Followup Form (FS)	
Mini Mental Status Exam (MS)	Week 13 from start of RT
Study Specific Flow Sheet (SF) then with every F1.	Week 13 from start of RT and
Post Treatment MRI(CT) (C2) and Report (C3)	6 weeks post XRT; for grade ≥ 3 RT toxicity and for progression. See Section 12.2 for submission details.
Follow-up Form (F1)	Every 3 months for year 1; q 4 months x 1
Mini Mental Status (MS)	year; q 6 months x 2 years, then annually. Also at progression/ relapse and at death (<i>F1 only</i>).
Operative reports (S2), surgical reports (S5) (<i>for subsequent surgery</i>)	As applicable
Autopsy Report (D3)	As applicable

12.2 CT/MRI Documentation

The contrast-enhanced MRI/CT taken before surgery and after-surgery-before-radiotherapy begins must be submitted within two weeks of registration. The post RT scan must also be submitted to RTOG Headquarters. A MRI/CT must be done at the time of neurologic deterioration, suggestive of tumor recurrence and not related to lowered steroid dose, unless the last MRI/CT had been done within one month and was compatible with recurrence. Other causes of neurological deterioration, such as metabolic imbalance, anticonvulsant, should be considered and properly investigated. The patient should consistently be followed with the same diagnostic study. Subsequent scans and reports, other than the pre-entry and post-RT scans, should be forwarded to RTOG Headquarters only in the event of a suspected grade ≥ 3 RT toxicity.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Overall survival

13.1.2 Acute and late toxicities associated with conventional RT with concurrent tamoxifen.

13.2 Background

RTOG recursive partitioning analysis (*RPA*) has found that the survival of malignant glioma patients is highly influenced by prognostic factors (*age, histology, mental status, KPS, symptom duration, extent of surgery, neurological class, and RT dose*).²⁷ The RTOG, and many groups in the brain cancer research community, use the RPA classes to stratify patients for study eligibility, treatment assignment at randomization, and for analytic purposes. GBM patients on this study must have a KPS of at least 70, and therefore will fall into RPA classes III, IV, or V, which historically have a median survival time (*MST*) of 17.9, 11.1, and 8.9 months, respectively. The RTOG GBM data base (*historical control*) contains 1027 RPA class III through V patients, with a breakdown of 20%, 49%, 31%, respectively.

13.3 Sample Size

The primary objective of this study is to estimate the median survival time (*MST*) for glioblastoma multiforme (*GBM*) patients treated with conventional RT with concurrent tamoxifen. Historically, GBM patients with RPA class of III, IV, and V have an estimated MST of 17.9, 11.1, and 8.9 months, respectively.²⁷ Using the Dixon-Simon method of calculating sample size for the comparison of survival against a historical control, a sample size of 68 evaluable RPA class III, IV, and V patients followed over 18 months will ensure at least 80% probability of detecting a minimum of 50% improvement in MST compared to the RTOG glioma database at the 0.05 significance level (*one-sided*).²⁸ In addition, see following table for equivalent statements regarding power, alpha, and detectable improvement. Adjusting for a 95% eligibility/ evaluability rate results in 72 patients needed in order to accrue 68 eligible patients. In summary, **this study requires a total sample size of 72 patients.**

68 Evaluable Patients		
Detectable Improvement (MST)	Alpha (<i>1-sided</i>)	Statistical Power
50%	0.05	80%
40%	0.10	80%
38%	0.15	84%
35%	0.20	86%

13.4 Inclusion of Women and Minorities

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into glioma trials failed to show any treatment interaction with gender.²⁷ The RTOG found no difference in survival of glioblastoma multiforme patients by race.²⁹ Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races. The projected gender and minority accruals are shown below:

	White, not of Hispanic Origin	Hispanic	Black, not of Hispanic Origin	Native Hawaiian or other Pacific Islander	Asian	American Indian or Alaskan Native	Other or Unknown	Total
Female	23	2	3	0	0	0	0	28
Male	35	3	4	1	0	1	0	44
Total	58	5	7	1	0	1	0	72

13.5 Patient Accrual

The patient accrual is projected to be 14 cases per month, based upon the monthly accrual for prior RTOG GBM studies. At this rate, it will take six months to reach the required total accrual of 72 cases. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.6 Analyses Plans

13.6.1 Interim Analyses

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

- a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;
- b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of the toxicities.

Through examining the above items, the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for this study, and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.6.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting of institutional accrual;
- c) distribution of important prognostic baseline variables – (*age, KPS, neurologic function, extent of surgery, time from first symptom, location of primary, and site of tumor*);
- d) observed results with respect to the endpoints described in Section 13.2.
- e) Overall survival of patients will be compared to the same proportion of RPA class III, IV, and V patients from the historical control using a one-sided log-rank test with a significance level of 0.05.

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APPENDIX I

RTOG BR-0021

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE II TRIAL OF CONVENTIONAL RADIATION THERAPY PLUS HIGH DOSE TAMOXIFEN FOR THE TREATMENT OF SUPRATENTORIAL GLIOBLASTOMA MULTIFORME (GBM)

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. You are being asked to take part in this study because you have a brain tumor called a supratentorial glioblastoma multiforme (GBM).

Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *Taking Part in Clinical Trials: What Cancer Patients Need to Know*, is available from your doctor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) Tamoxifen has on patients with your type of brain tumor. Studies suggest that tumor growth may be partly dependent on an enzyme. Tamoxifen is known to inhibit this enzyme and also helps the anti-tumor effect of radiation. The researchers also want to find out the effects (good and bad) of tamoxifen at high doses in patients with your disease.

This research is being done because currently, the standard treatment for your type of cancer is not very effective.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 72 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (1/21/03)

Radiation therapy treatments will be given once a day, five days a week, for six weeks. You will also take tamoxifen, while receiving radiation treatments, until your doctor tells you to stop.

- If you take part in this study, you will have the following tests and procedures that are part of regular cancer care. These may be done even if you do not join the study.

Procedure
Physical and Neurological Exam

Schedule
Prior to study entry, weekly during radiation, then every month for 9 months then every 3 months

Anti-seizure drug levels and coagulation levels

As medically necessary

Brain CT or MRI

Prior to study entry, six weeks after completion of radiation, then every 2 months and/or as medically necessary

Blood Counts and Chemistries

Prior to study entry, then every 3 months

- Standard procedures being done because you are in this study:

Procedure

Schedule

Mini Mental Status Exam

Every three months for 1 year, then with every follow-up visit. This exam will evaluate your thought process. You will be asked to follow short instructions and to draw a few patterns.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue will be sent to a central office for review and research investigation associated with this protocol.

HOW LONG WILL I BE IN THE STUDY?

You will receive radiation therapy to the brain for six weeks. Your tamoxifen treatments will begin with your radiation therapy and they will continue as long as the tumor remains stable or gets smaller. Follow-up visits will continue for the rest of your life according to the above schedule.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drug or radiation therapy is stopped, but in some cases side effects can be serious or long-lasting or permanent.

Risks Associated with Radiation Therapy:

Very Likely

Scalp redness or soreness
Hair loss
Dry mouth or altered taste
Fatigue, sleepiness
Headaches, seizure, weakness

Less Likely But Serious

Hearing loss
Eye injury resulting in blindness
Mental slowness, behavioral changes
Severe damage to normal brain tissue that may require additional surgery
Thrombophlebitis (blood clots)

Less Likely

Fever, chills, heavy sweating
Permanent hair loss
Upset stomach, nausea and/or vomiting
Loss of appetite, taste changes

Risks Associated with Tamoxifen:

Most data regarding tamoxifen has been learned from its use in women with breast cancer. Many the following side effects relate to those seen in women.

Frequent Side Effects: hot flashes, nausea and/or vomiting, menstrual irregularities including vaginal bleeding, vaginal discharge, and dryness.

Secondary Cancers

1. Endometrial Cancer - Tamoxifen may cause changes in the lining of the uterus. An early sign of these changes may be abnormal vaginal bleeding or pelvic pain. You should report such symptoms to your physician immediately. The level of increased risk of uterine cancer associated with tamoxifen is still uncertain. After an average of 8 years of

follow-up, the annual (*per year*) risk observed in a large-scale trial of breast cancer patients taking 20 mg of tamoxifen daily is about 2 per 1,000 women. This means that on the average, two cases of endometrial cancer were diagnosed among every 1000 women receiving tamoxifen during each year of the study and follow-up. This level of risk is approximately three times greater than that of a similar group of women in the general population. Uterine cancer may be life-threatening illness. Some breast cancer patients who develop uterine cancer while taking tamoxifen in the above studies have later died from uterine cancer. However, most of these cancers have been diagnosed at an early stage when treatment is highly effective. The treatment is surgical removal of the uterus, fallopian tubes, and ovaries. Radiation therapy may also be necessary. In view of this risk, it is recommended that all patients receiving tamoxifen have a pelvic exam before starting treatment and at least yearly thereafter. If you have already had a total hysterectomy, there is no risk of getting uterine cancer.

2. Other Cancers - One large U.S. study showed no increase in other (*non-uterine*) cancers in women taking tamoxifen. However, other unpublished data suggest a possible increase in second cancers of the gastrointestinal tract among women receiving the drug. There have been rare reports of liver cancer in women taking tamoxifen. It is not clear if these were due to the tamoxifen. Although tamoxifen can cause liver cancer in rats, it is not known to be a cause of liver cancer in humans. Whether an increased risk for other (*non-uterine*) cancers is associated with tamoxifen is still uncertain and continues to be studied.

Infrequent But Serious Side Effects:

1. Blood Clots - Some studies have shown that tamoxifen causes an increase in blood clots in the vein and pulmonary embolism (*loss of blood flow to the lungs*). Rarely, death has occurred from such events. Patients with an existing history of such problems should discuss tamoxifen treatment carefully with their physician.
2. Liver Toxicity - Abnormal liver function tests including rare cases of more severe liver abnormalities such as fatty liver, cholestasis (*back up of bile*), hepatitis, and hepatic necrosis (*destruction of liver cells*) have been observed. A few of these serious cases resulted in death but whether tamoxifen was the cause of these problems is uncertain.
3. Eye Changes - Women taking tamoxifen may be at a slightly increased risk for developing cataracts (*a clouding of the lens inside the eye*). As women age, they are more likely to develop cataracts whether or not they take tamoxifen. Cataracts may lead to a decrease in vision. Eye surgery may be required to remove the cataract and improve vision. Women who have a cataract before beginning to take tamoxifen may be more likely to have cataract surgery. Other eye problems, such as corneal scarring or retinal changes, have been reported in a few patients. You must report any changes in your vision, or other eye problems, to your physician.
4. Endometrial (uterine lining) Changes including polyps, hyperplasia (*tissue thickening*), and endometriosis (*endometrial cells outside the uterus*), or a decrease in platelet counts making you more prone to bleeding. Bone and tumor pain and sometimes high calcium occurred in those patients treated for metastatic disease. Patients with increased pain

require more or stronger pain relievers. Often such symptoms signaled a good response to treatment and these symptoms usually went away quickly.

5. Other infrequent side effects include skin rash, swelling of your hands or feet, genital itching, depression, dizziness and light-headedness, headache, hair thinning and/or partial hair loss. Ovarian cysts have been noted in premenopausal women.

Reproductive Risks: Because the drug in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask your doctor about counseling and more information about preventing pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with brain tumors in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy alone; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI’s Cancer Information Service at
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

Visit the NCI’s Web sites for comprehensive clinical trials information
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date

TISSUE AND BLOOD TESTING (RTOG BR-0021)

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

Yes No

Patient Signature (*or legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (<i>Karnofsky 90-100</i>).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (<i>Karnofsky 70-80</i>).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (<i>Karnofsky 50-60</i>).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (<i>Karnofsky 30-40</i>).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (<i>Karnofsky 10-20</i>).

APPENDIX IV

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

- | | |
|---|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days | As above |

of termination of the agent.

- All life threatening (*grade 4*) events which may be due to agent. As above

- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)**

- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. ****A written report to follow within 10 working days.**

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. ****Report in writing** to RTOG Headquarters and IDB within 10 working days.

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