

RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-02

**A PHASE II TRIAL OF WEEKLY PACLITAXEL AND CONVENTIONAL
RADIOTHERAPY FOR SUPRATENTORIAL
GLIOBLASTOMA MULTIFORME**

(NSC # 125973)

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CONVENTIONAL RADIOTHERAPY FOR SUPRATENTORIAL
GLIOBLASTOMA MULTIFORME
(NSC # 125973)**

SCHEMA

R	<u>Age</u>	R	60 Gy/30 fractions/2 Gy once daily
	1. 18 to < 50		
E	2. ≥ 50	E	Plus
C	<u>Karnofsky Performance Status</u>	G	Paclitaxel 225 mg/m ² /3 hr infusion (to be completed 1-3 hours prior to RT)
	1. 90-100	I	once a week x 6 weeks
O	2. 60-80		
R		S	
D		T	
		E	
		R	

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 cm margin (2.5 cm when no edema is visualized). After 46 Gy the tumor volume should include the contrast enhancing lesion (without edema) on the pre-surgery CT/MRI scan plus a 2.5 cm margin.

Eligibility: (See Section 3.0 for details)

- Histopathologically-confirmed glioblastoma multiforme
- Supratentorial location
- Age ≥ 18
- KPS ≥ 60
- Life expectancy ≥ 3 months
- Neurologic functional status 0, 1, 2, or 3.
- Hgb ≥ 9 absolute neutrophils ≥ 1500, platelets ≥ 100,000, BUN ≤ 30, creatinine ≤ 1.5.
- Study-specific consent form
- Therapy must begin within six weeks of surgery
- No prior chemotherapy or radiation above the supraclavicular areas

Required Sample Size: 53

Institution # _____
RTOG 96-02 _____
Case # _____

ELIGIBILITY CHECK
(page 1 of 2)

- _____(Y) 1. Does patient have histopathologically confirmed supratentorial glioblastoma multiforme diagnosed by surgical biopsy or resection?
- _____(Y) 2. Will therapy begin within six weeks of surgery?
- _____(Y/N) 3. Was a diagnostic contrast-enhanced CT or MRI performed pre-operatively and post-operatively? (If no, skip to Q5)
- _____(Y) 4. Does the tumor enhance on the post-op study? (Skip to Q6)
- _____(Y) 5. Was the patient diagnosed by stereotactic biopsy only?
- _____(N) 6. Has the patient had any prior radiotherapy above the supraclavicular area?
- _____(N) 7. Has the patient had any prior chemo?
- _____(≥ 18) 8. Patient's age?
- _____(Y) 9. Does the patient have life expectancy of ≥ 3 months?
- _____(≥ 60) 10. What is the KPS?
- _____(0-3) 11. What is the neurologic function status?
- _____(≥ 9) 12. What is HGB?
- _____(≥ 1.5) 13. What is the ANC (x 1000)?
- _____(≥ 100) 14. What is the platelet count (x 1000)?
- _____(≤ 30) 15. What is BUN?
- _____(≤ 1.5) 16. What is the creatinine?
- _____(≤ 2) 17. What is the bilirubin?
- _____(Y) 18. Are the SGPT and SGOT ≤ 3 x normal?
- _____(Y) 19. Is the patient on anticonvulsants?
- _____(Y) 20. Has a study-specific informed consent been signed?
- _____(Y/N) 21. Has the patient had a previous malignancy other than non-melanomatous skin cancer or carcinoma *in-situ* of the uterine cervix?
- _____(Y) If yes, has the patient been disease free for at least 3 years?

Institution # _____
RTOG 96-02 _____
Case # _____

ELIGIBILITY CHECK
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- _____(N) 22. Any active angina or uncontrolled arrhythmia?
- _____(N) 23. Any medical illness or psychiatric impairments which would prevent administration or completion of protocol therapy or interfere with followup?
- _____(N) 24. Does the patient have AIDS?
- _____(Y/N) 25. Is the patient eligible for RTOG 93-05?
 _____(N) If yes, does your facility have radiosurgery capabilities?

_____ Patient's Name
 _____ Verifying Physician
 _____ Patient ID #
 _____ Referring Institution # (*if different*)
 _____ Medical Oncologist's Name
 _____ Birthdate
 _____ Sex
 _____ Race
 _____ Social Security Number
 _____ Zip Code (*9 digit if available*)
 _____ Method of Payment
 _____ Treatment Start Date
 _____ Treatment Assignment

Completed by _____ Date _____

1.0 INTRODUCTION

- 1.1** Malignant gliomas constitute the most common group of primary brain tumors, more than one-half of over 15,000 primary CNS tumors diagnosed in the United States each year. Even when managed with the best available therapeutic modalities, including surgery, radiation therapy, and chemotherapy, treatment of these astrocytic tumors remains difficult and frustrating. Patients with malignant gliomas have an extremely poor prognosis, with median survival of 10-12 months and few long term survivors.
- 1.2** Radiation therapy remains the most effective adjuvant modality in the management of malignant gliomas,¹ and the overall patient survival time is directly correlated with the total dose delivered.² However, further increase in the total dose is limited by rapid increase of late normal tissue damage.
- 1.3** Chemotherapy to date has had only a modest effect on survival with nitrosureas the most effective agent(s).^{3,4,5,6} Current standard therapy with RT (60 Gy) +/- BCNU yields a median survival and 18-month survival of 35 weeks and 4-19% respectively.⁷ Therefore in good performance status patients we need to evaluate new agents with intrinsic activity in GBM as well as radiosensitizing properties.
- 1.4** Paclitaxel, a chemotherapeutic approved for use in advanced breast and ovarian cancer, has demonstrated evidence of radiosensitization in pre-clinical models⁴ with radiation enhancement ratio of 1.5-1.8 in astrocytoma cell lines.^{8,9,10} By causing polymerization of microtubules, paclitaxel substantially increases the fraction of cells in G2 or M, the optimal time period for radiosensitization during the cell cycle.¹¹ Paclitaxel has also been shown to inhibit division of G18 glioma cell cultures. Choy and Glantz et al. in a phase I study have determined a maximal tolerated dose (MTD) of paclitaxel of ~ 250 mg/m²/3 hrs weekly x 6, in combination with conventional RT for GBM.¹² 3-hour infusion schedule has an advantage over 24-hour schedules in terms of reduced myelosuppression,^{13,14} and improved cost and patient convenience (*outpatient vs inpatient therapy*). The MTD obtained is substantially higher than that obtained in single agent trials in other disease sites with or without radiation. Pharmacokinetic studies refute the contention that steroids or anti-convulsants accelerate the clearance of paclitaxel, although there is a strong possibility based on the work of Fettell, et al.,¹⁵ and Chang et al.¹⁶ that activation of p450 cytochrome system enzymes by anticonvulsant or corticosteroids might potentially affect drug metabolism.
- In addition, unpublished data (*telecommunication-Dr. Rhodes; presentation at RTOG 7/95 meeting*) suggest that increased p53 expression by immunohistochemistry (IHC) in GBM patients correlates with improved prognosis in patients receiving concurrent RT and paclitaxel and that in p53 (+) patients, survival outcome is superior in those receiving paclitaxel doses ≥ 200 mg/m² weekly. These observations merit formal, prospective verification. Although data from previous RTOG experience shows that central pathology review in phase II trials of GBM patients is unnecessary,¹⁷ the adjunctive p53 IHC assessment(s) will require the efforts of RTOG HQ to facilitate the process.
- 1.5** The purpose of this study is to determine the feasibility and efficacy of conventional external beam irradiation combined with weekly paclitaxel at its maximal tolerated dose (MTD) in GBM patients. The possibility that a combination of paclitaxel and RT is particularly useful in patients whose tumor is p53(+) by IHC will be examined at the time of data analysis.

2.0 OBJECTIVES

- 2.1** To determine the freedom from progression, median, 1-year, and 2-year survival in patients treated with conventional radiotherapy and weekly paclitaxel.
- 2.2** To determine the frequency and severity of toxicities of concurrent RT and paclitaxel.
- 2.3** To record p53 status (*immunopositivity*) and correlate with response and survival.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1** Histopathologically confirmed supratentorial glioblastoma multiforme. Patients with astrocytoma with atypical or anaplastic features (AAF) are not eligible.
- 3.1.2** Diagnosis must be made by surgical biopsy or resection.
- 3.1.3** Therapy must begin within six weeks of surgery.

- 3.1.4 Except for cases diagnosed only by stereotactic biopsy, a diagnostic contrast enhanced CT or MRI scan must be performed preoperatively and postoperatively prior to initiation of radiotherapy.
 - 3.1.5 No previous radiotherapy to regions above the supraclavicular area; no prior chemotherapy.
 - 3.1.6 Age \geq 18 years.
 - 3.1.7 Life expectancy \geq 3 months.
 - 3.1.8 Karnofsky performance status \geq 60 (*Appendix II*).
 - 3.1.9 Neurologic Function Status 0, 1, 2, or 3 (*Appendix II*).
 - 3.1.10 Adequate bone marrow reserve (*hemoglobin \geq 9 grams, absolute neutrophil count \geq 1500/mm³, platelets \geq 100,000/mm³*) and acceptable renal (*BUN \leq 30 mg, creatinine \leq 1.5 mg*) and hepatic function (*bilirubin \leq 2.0 mg, SGPT and SGOT \leq 3 x normal range*).
 - 3.1.11 Patients must be on anticonvulsant(s).
 - 3.1.12 Patient must have signed a study-specific informed consent form. If the patient's mental status precludes his/her giving informed consent, written informed consent may be given by the patient's legal representative.
- 3.2 Ineligibility Criteria**
- 3.2.1 Well differentiated astrocytomas
 - 3.2.2 Astrocytoma with atypical or anaplastic features (*AAF*).
 - 3.2.3 Infratentorial tumors.
 - 3.2.4 Recurrent malignant glioma.
 - 3.2.5 Patients whose residual tumors do not enhance on a postoperative CT or MRI study. (**1/31/97**)
 - 3.2.6 Patients with previous malignancies, except for non-melanomatous skin cancers and carcinoma *in situ* of the uterine cervix, unless disease-free for \geq 3 years.
 - 3.2.7 Active angina or uncontrolled arrhythmias.
 - 3.2.8 Major medical illnesses or psychiatric impairments which in the investigator's opinion will prevent administration or completion of the protocol therapy and would interfere with follow-up.
 - 3.2.9 Inability to obtain histologic proof of GBM.
 - 3.2.10 Patients with Acquired Immune Deficiency Syndrome (*AIDS*).
 - 3.2.11 Eligible for RTOG 93-05 in an institution with radiosurgery capabilities. In a facility without radiosurgery capacity, patients otherwise eligible for RTOG 93-05 may be enrolled on this study.

4.0 PRETREATMENT EVALUATIONS

- 4.1 Complete history and physical examination with a detailed neurologic exam.
- 4.2 CT or MRI scan with contrast performed preoperatively and postoperatively within 2 weeks prior to the initiation of radiotherapy.
- 4.3 CBC with differential, platelet count, blood chemistries to include SGOT, SGPT, total bilirubin, BUN and creatinine (*SMA-12*).
- 4.4 Anticonvulsant serum level and steroid dosage.
- 4.5 Chest x-ray.
- 4.6 Electrocardiogram: 12 lead with rhythm strip.
- 4.7 Mini-Mental Status Exam (*MMSE*).

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 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

6.0 RADIATION THERAPY PARAMETERS

6.1 Standard Radiotherapy

- 6.1.1** Dose
Radiotherapy must begin within 6 weeks of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy. All portals shall be treated during each treatment session.
- 6.1.2** Physical Factors
Treatment shall be delivered with megavoltage machines of energy ranging from 4-10 MV photons. Selection of 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 used only in dual energy beam arrangements using at least one beam with energy \leq 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle or implant boost is not permissible.
- 6.1.3** 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 cm margin. If no surrounding edema is present, the initial target volume should include the contrast enhancing lesion plus a 2.5 cm margin. For the first 46 Gy/23 fractions the target volume should include the volume of contrast enhancing lesion and surrounding edema on preoperative CT/MRI scan plus a 2 cm margin. After 46 Gy the target volume should include the contrast enhancing lesion (*without edema*) on the pre-surgery CT/MRI scan plus a 2.5 cm margin. Should significant change in anatomic architecture occur postoperatively then the postoperative scans should be used for planning (*if questions occur, please contact the radiation oncology chairperson*).
- 6.1.4** Treatment Planning
Treatment plans may include a wedge pair of fields, arcs, or multiple field techniques. Straight opposed lateral fields are not recommended and should be avoided. CT or 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 at headquarters reviews. Isodose distribution for the initial target volume and conedown target volume are required on all patients, including those treated with parallel opposed fields. The inhomogeneity across the target volume should be kept to a minimum. The use of a vertex fields require either a diagram or photograph treatment position to be submitted to RTOG Headquarters.
- 6.1.4.1** Two central access isodose plots one showing the initial tumor volume and one showing the boost tumor volume should be submitted with the following isodose lines in Gy: 23.0, 41.1, 43.7, 48.3, 50.6, 54.0, 57.0, 63.0, and 66.0.
- 6.1.4.2** If the initial target volume receives < 41.4 Gy or > 50.6 Gy (*i.e., < 90% or > 110% of the prescribed dose*) a major deviation will be scored. If the boost volume receives < 54.0 Gy or > 66.0 Gy (*i.e., < 90% or > 110% of the prescribed total dose*) a major deviation will be assigned.
- 6.1.4.3** If the initial target volume receives 41.4-43.2 Gy or 48.76-50.6 Gy (*i.e., 90-94% or 106-110% of the prescribed dose*) a minor variation will be scored. If the boost volume receives 54.0-56.4 Gy or 63.6-66.0 Gy (*i.e., 90-94% or 106-110% of the prescribed total dose*) a minor variation will be assigned.
- 6.1.4.4** If the initial target volume receives 43.7-48.3 Gy (*i.e. 95-105%*) no deviation will be assigned. If the boost volume receives 57.0-63.0 Gy, no deviation will be assigned.
- 6.1.5** Dose Specification
Doses are specified as the target dose which shall be at the center of the target volume. For the following portal arrangements the point of dose specifications shall be specified as follows:
- 6.1.5.1** For the 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.

6.2 Acute Radiation Toxicities

6.2.1 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.

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

6.2.3 Hematologic toxicities should be rated on a scale of 0-5 as defined in the RTOG Toxicity Criteria.

6.3 Adverse Reaction Reporting

6.3.1 All fatal toxicities resulting from radiation and chemotherapy must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the Study Chairman within 24 hours of discovery.

6.3.2 All life threatening (*grade 4*) toxicities from radiation must be reported by telephone to the Group Chairpersons, to RTOG headquarters Data Management Staff and to the Study Chairpersons within 24 hours of discovery.

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

6.3.4 Additional information is detailed in Appendix IV.

7.0 DRUG THERAPY

7.1 Paclitaxel (NSC #125973)

7.1.1 Formulation (1/31/97)

Paclitaxel is a poorly soluble plant product from the western yew, *Taxus brevifolia*. It is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (*30 mg/vial*) in polyoxyethylated castor oil (*Cremophor EL*) 50% and dehydrated alcohol, USP, 50%. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

7.1.2 Supplier (1/31/97)

Paclitaxel is commercially available. Bristol-Myers-Squibb will not routinely provide taxol. Instances of extreme hardship (*low income, noninsured, low liquid asset patients*), contact Carol Wirtz at Bristol (812-429-8054) for patient-specific consideration.

7.1.3 Solution Preparation

Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP (*D5W*). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexylphthalate (*DEHP*) plasticizer from polyvinyl chloride (*PVC*) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration.

NOTE: Formulation of a small number of fibers in solution (*within acceptable limits established by the USP Particulate Matter Test for LVPs*) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (*e.g.: Millex-GV, Millipore Products*) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

7.1.4 Storage

The intact vials should be stored under refrigeration ($2-8^{\circ}\text{C}$).

7.1.5 Stability

Commercial paclitaxel vials will bear an expiration date on the label. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (*0.3-1.2 mg/ml*) are physically and chemically stable for 24 hours.

7.1.6 Administration of Paclitaxel (10/25/96)

Paclitaxel will be administered at a dose of 225 mg/m² to be infused over three hours weekly x 6 wks. Paclitaxel will be administered via an infusion control device (*pump*) using non-PVC tubing and connectors, such as the IV administration sets (*polyethylene or polyolefin*) which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered. Vital signs will be monitored closely (*q 15 minutes*) during the 1st hour of the 1st

infusion, then every 30 minutes until the infusion is completed. It must be completed 1-3 hours prior to RT.

7.1.6.1 Paclitaxel will be administered on an outpatient basis by 3-hr infusion mixed in 1000 cc D5W or NSS in non PVC containing plastic containers and infused via polyethylene-1 med NTG tubing with a 0.22 u in-line filter.

7.1.6.2 Hypersensitivity prophylaxis will consist of single doses of dexamethasone 20 mg, diphenhydramine 50 mg, and cimetidine 300 mg given intravenously ~ 30 min prior to initiation of paclitaxel. There will be no empiric reduction in patient's chronic oral steroid dose on the days paclitaxel is administered. Individual treating physicians may substitute Ranitidine, Famotidine, or oral dexamethasone at their discretion.

7.2 Dosing and Modifications (10/25/96)

7.2.1 There will be no dose escalation.

7.2.2 Blood counts will be drawn each week. The dose modifications will be as follows:

7.2.2.1 At scheduled time of administration:

<u>Absolute Neutrophil Count</u>		<u>Platelets</u>	<u>Modification</u>
≥ 1500	and	≥ 100,000	Full dose
1000- < 1500	or	75,000- < 100,000	50% dose
< 1000	or	< 75,000	Hold dose for one week

7.2.2.2 After one week delay:

<u>Absolute Neutrophil Count</u>		<u>Platelets</u>	<u>Modification</u>
≥ 1500	and	≥ 100,000	75% dose
1000-< 1500	or	75,000- < 100,000	50% dose
< 1000	or	< 75,000	Contact chemotherapy Chairman before further chemotherapy administration

7.2.3 Dose will be permanently reduced to 75% if neutropenic fever has occurred.

7.2.4 If paclitaxel dose has been modified the previous week, but can be given the following week, use criteria stipulated in Section 7.2.2.1, with attempt to return paclitaxel to full dose, if possible.

7.2.5 In the event of both treatment delay and neutropenic fever, paclitaxel will be dosed at 50%.

7.2.6 Paclitaxel will be discontinued if irreversible symptomatic arrhythmias or cardiac dysfunction occurs.

7.2.7 Patients with grade 0 or grade 1 neuropathy will undergo no dose adjustment. For grade 2 neuropathy, the doses will be reduced by 50%. If neuropathy level returns to grade 0 or grade 1, full dose (100%) will be resumed. Grade 3 neuropathy will mandate withholding paclitaxel; it will be resumed at 50% dose once neuropathy returns to grade ≤ 2. For those experiencing grade 3 neuropathy, the 50% dose reduction will be maintained.

7.3 Known Potential Adverse Effects

7.3.1 Hematologic: Myelosuppression

7.3.2 Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhilitis; ischemic colitis; neutropenic enterocolitis

7.3.3 Heart: Atrial arrhythmia, brachycardia, heart block, ventricular tachycardia, myocardial infarction (*MI*); hypotension; hypertension possibly related to concomitant medication dexamethasone).

7.3.4 Neurologic: Sensory (*taste*), peripheral neuropathy, seizures, mood; hepatic encephalopathy; encephalopathy

7.3.5 Allergy: Anaphylactoid and urticarial reactions (*acute*), flushing, rash, pruritus.

7.3.6 Skin: infiltration (*erythema, induration, tenderness, rarely ulceration*) radiation recall, rash, nail changes (*discoloration of finger nails, separation from nail bed*).

7.3.7 Liver: Increased SGOT, SGPT, bilirubin, alkaline phosphatase, hepatic failure, hepatic necrosis.

7.3.8 Pulmonary: pneumonitis

7.3.9 Other: Alopecia, fatigue, arthralgia, myalgia; lightheadedness; myopathy; sensation of flashing lights; blurred vision; scintillating scotoma.

7.4 Adverse Drug Reaction Reporting Guidelines

7.4.1 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:

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

- 7.4.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.4.1.3 Any death on study if clearly related to the commercial agent(s).
- 7.4.1.4 Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.4.2 The ADR report should be documented on the FDA form 3500 (*Appendix IV*) and mailed to:

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

7.5 Off-Protocol Criteria

- 7.5.1 Disease: progression or decline in performance status due to disease precluding continued protocol treatment.
- 7.5.2 Intolerable toxicity, which in the investigator's opinion, precludes continued safe therapy.
- 7.5.3 Patient request.

8.0 SURGERY

The extent of surgical resection prior to protocol entry shall be documented as a) biopsy, or b) subtotal resection as described by both the operative report and/or postoperative imaging.

9.0 OTHER THERAPY

- 9.1 Steroids and anti-seizure medications should be given as clinically indicated. The total dose must be recorded pre-treatment, and at the time of each treatment evaluation. Steroids will be used at a dosage which will afford the patient satisfactory neurologic function and the best possible quality of life. It is recommended that steroids at some dosage be continued until radiation is completed.
- 9.2 Infections are to be treated with appropriate antibiotics and recorded.
- 9.3 Corticosteroid and anticonvulsants and any other medications are to be specified, and their dose recorded, throughout the course of concurrent radiation and paclitaxel.

10.0 PATHOLOGY

- 10.1 The initial histologic diagnosis will be made by the pathologist at the institution where the patient is entered on the therapeutic protocol. *Paraffin blocks, two H&E stained slides and 5 unstained (silanized) slides along with a copy of the surgical pathology report and a Pathology Submission Form will be sent to RTOG Headquarters:*

RTOG Headquarters
ATT: Pathology Coordinator
1101 Market Street, 14th Floor
Philadelphia, PA 19107

- 10.2 RTOG headquarters will forward the pathologic material to Dr. Harker Rhodes who will review the H&E stained slides to confirm the diagnosis. Using a standardized immunohistochemistry protocol, unstained slides will be stained for p53 immunoreactivity by Dr. Rhodes who will grade the degree of staining as -, +, ++, or +++. Immunohistochemical staining will be done in batches and duplicate slides from cases stained in early batches will be repeated in later batches to assess the batch-to-batch consistency of the immunohistochemistry.
- 10.3 Review will be based in part on the results of a phase I study of paclitaxel and concurrent RT which was done at Brown (*Glantz et al. A Phase I Study of Weekly, Out-Patient Paclitaxel and Concurrent Cranial Irradiation in Adults with Astrocytomas. J. Clin. Onc. in press*). The biopsy specimens from those patients have been stained using a commercially available polyclonal anti-p53 antiserum and the survival data re-analyzed including p53 status as a potential prognostic factor (*Rhodes et al, personal communication*). Although, paclitaxel dose and p53 positivity were confounding prognostic variables, that study suggested that p53 immunopositivity may predict response to treatment with paclitaxel and RT. If that is true, then the subset of patients whose tumors are p53 positive would be expected to show a greater response to the therapy proposed here than the study patient population taken as a whole. Analysis of the p53 positive patients separately may show a statistically significant response to this treatment even if the increase in survival does not reach a level of statistical significance when the p53 positive and negative populations

are combined. We will, therefore, examine the biopsies of patients in this study using the same p53 immunohistochemical protocol that was used previously.

10.4 Statistical analysis to determine whether p53 status is an independent predictor of survival time will be done at the RTOG Statistical Unit. If appropriate, the patients will be divided into two subpopulations on the basis of their p53 status and the statistical analysis described in Section 13.0 repeated on the subgroups separately. Pathologic material will be retained to allow for re-review of the material or for additional immunohistochemical studies if appropriate.

A univariate analysis on the difference in survival by -, +, ++, or +++ will be performed. If there is sufficient incidence of p53 mutation then aside from the univariate analysis then p53 mutation will also be incorporated in a Cox regression model. This method will assess the relative importance of p53 in relation to previously established prognostic factors.

10.5 In addition, representative H&E stained tumor sections and a copy of the institutional surgical pathology report will be forwarded by RTOG to Dr. James S. Nelson to be stored in the RTOG malignant glioma archive.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessment	Prior to Therapy	During RT	At each Follow-up
History and PE ^a	X		X
Neurological exam, KPS	X	weekly	X
Evaluation of skin within RT treatment portals	X	weekly	X
CBC including differential	X	weekly ^d	X
Serum chemistries including serum creatinine, BUN, SGPT, SGOT, & total bilirubin	X		X
Chest x-ray	X		As indicated
ECG (12 lead and rhythm strip)	X		
CT scan with contrast and/or gadolinium enhanced and T2 weighted MRI	X (both pre-op. and post-op. ^e pre-radio-therapy)		q 4 mos ^c in yrs 1 +2, q 6 mos yrs 3-5 , then annually Also at time of neurologic deterioration unless the last CT/MRI had been done within 1 mo and was compatible with recurrence
Mini-Mental Status Exam	X	X ^b	X

- a. To include record of steroid and anticonvulsant dose.
- b. At six weeks, 3 months, then at each followup.
- c. 4 mo follow-up post initiation of RT (~ 2 1/2 months post-completion of RT).
- d. CBC may be repeated weekly for 2 to 3 weeks at individual physician's discretion, although it is anticipated that paclitaxel at this dose in this schedule will not prove myelosuppressive.
- e. Post-op scan not required for cases diagnosed only by stereotactic biopsy.

11.2 Evaluation During Study

11.2.1 A neurologic examination shall be performed once a week during radiation (prior to each paclitaxel cycle), then at each followup thereafter.

11.2.2 The contrast enhanced CT or MRI of the brain shall be obtained prior to surgery, pre- and post-treatment, every four months for 2 years, every six months for 3 years, then annually and at the time of neurologic deterioration unless the last CT/MRI done was within one month and was compatible with recurrence. 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 may spontaneously improve without therapy. They are considered to be due to transient

demyelination.¹⁵ Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.

11.2.3 While a patient is receiving paclitaxel, weekly blood counts are required.

11.3 Criteria for Evaluation of Therapy Effectiveness

11.3.1 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.**

11.3.2 Considering that radionecrosis is usually indistinguishable from tumor progression by CT or MRI imaging, Thallium-SPECT imaging should be attempted in all cases at the time of suspected progression/necrosis.

11.3.3 Overall survival should be measured from day treatment is initiated.

11.3.4 The quality of survival will be measured by the MMSE.

11.4 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.

11.5 Ineligible and Inevaluable Patients

11.5.1 Patients who receive no paclitaxel will be cancelled, removed from the study, and will be excluded from all analyses. No data will be required by RTOG.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 1 wk of study entry
Medical Oncology Treatment Planning Form (M2)	
Baseline Mini-Mental Status Evaluation (MS)	
Pretreatment CT/MRI scan both pre- and post-surgery (C1) and reports (C3)	
Initial Evaluation Form (I1)	Within 2 wks of study entry
Pathology Report (P1)	
Pathology Slides/Blocks (P2)	
<u>Preliminary Dosimetry Information:</u>	Within 1 wk of start of RT
RT Prescription (Protocol Treatment Form) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
Mini-Mental Status Exam (MS)	Within 1 wk of RT completion
Radiotherapy Form (T1)	
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films (<i>simulation and portal</i>) (T8)	
Study-Specific Flowsheets (SF)	At one week for pre-study labs, then to be completed for each day of the six week course of therapy and submitted at 3 weeks and at 7 weeks
Follow-up Form (F1)	Every 4 mos from treatment start for 2 yr; q 6 mos x 3 yrs, then annually. Also at progression/relapse. An F1 will be due at death.
Mini-Mental Status Exam (MS)	
Autopsy Report (D3)	As applicable

12.2 CT/MRI Submission

The CT (*with contrast*)/MRI taken after-surgery-before-radiotherapy begins must be submitted within one week of randomization. The calendar specifies CT or MRI PRE-RX, this means all sets of scans (*films*) with corresponding reports. A subsequent scan (*and report*) four months from the date of the start of external beam RT must also be submitted to Headquarters. CT/MRI must also be done and submitted (*scan and report*) for documentation of initial progression, neurologic deterioration (*unless the last CT/MRI had been done within one month and was compatible with recurrence*) and/or suspected toxicity. **The patient should consistently be followed with the same diagnostic study.**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Progression free survival; median, 1-year and 2-year overall survival.

13.1.2 Acute and late toxicities associated with paclitaxel and radiotherapy.

13.2 Sample Size

The primary objective of this study is to estimate the median survival time (MST) for glioblastoma multiforme (*GBM*) patients treated with paclitaxel and radiotherapy. The MST for GBM patients is highly influenced by prognostic factors.^{18,19} Patients enrolled onto this trial should not be eligible for RTOG 93-05, thus the majority of patients will have a maximum tumor diameter greater than 40 mm. Historically GBM patients with tumor sizes 5 cm or larger have an estimated MST of 9.6 months.¹⁹ Although, prognostic factors such as age, neurologic function, surgical resection, and Karnofsky performance status will impact upon this estimate.¹⁸

Using the 9.6 month MST for sample size calculation and a one-sample test of significance the following table is produced assuming minimum power of 80% and 50 evaluable patients.

Baseline MST	Type I Error	Type II Error	Detectable MST	
6	0.20	0.20	8.1	
		0.10	8.8	
	0.15	0.20	8.4	
		0.10	9.1	
	0.10	0.20	8.8	
		0.10	9.6	
Baseline MST	Type I Error	Type II Error	Detectable MST	
9.6	0.05	0.20	9.3	
		0.10	10.4	
	0.20	0.20	13.5	
		0.10	14.9	
	0.15	0.20	14.3	
		0.10	15.8	
	0.10	0.20	14.9	
		0.10	16.8	
	0.05	0.20	16.6	
		0.10	18.6	
	12.0	0.20	0.20	17.4
			0.10	20.0
0.15		0.20	18.6	
		0.10	20.7	
0.10		0.20	20.0	
		0.10	22.4	
0.05	0.20	22.4		
	0.10	26.4		

Therefore, this sample size will ensure a 80% probability of detecting a clinically significant difference in MST, depending upon the significance level chosen. Assuming a 5% ineligibility/inevaluability rate, **the total sample size required will be 53 patients.**

13.3 Patient Accrual

The patient accrual is projected to be 9 cases per month, based upon the monthly accrual for RTOG 94-17. At that rate, it will take 6 months to reach the **required total accrual of 53 cases**. If the average monthly accrual rate is less than 3 patients, the study will be re-evaluated with respect to feasibility.

13.4 Suspension of Accrual Due to Morbidity

If there is any fatal treatment morbidity the accrual will be suspended and all data pertaining to the event will be reviewed by the study chair and reported to the RTOG data monitoring committee for review.

13.5 Analyses Plans

13.5.1 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 data for the accrual phase;
- 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 study chair and 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 executive committee, so that corrective action can be taken.

13.5.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of one year. 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 institutional accrual;
- c) distribution of important prognostic baseline variables by treatment arm;
- d) observed results with respect to the endpoints described in Section 13.1. The estimated median survival from this sample will be tested against the historical control presented in Section 13.2 using a one-sample test.²⁰ Median survival estimates will also be calculated for patient subgroups according to the subgroups identified in Curran et al.¹⁸ Furthermore, survival comparisons will be made between patient subgroups defined by the results of molecular studies defined in Section 10. The Brookmeyer-Crowley confidence interval for median survival will be provided for all estimates.²¹ An improvement in MST of at least 35% dependent upon appropriately identified baseline comparison, will be encouraging for further study.

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APPENDIX I

RTOG 96-02

A PHASE II TRIAL OF WEEKLY PACLITAXEL AND CONVENTIONAL RADIOTHERAPY FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME (NSC# 125973)

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 I have an opportunity to decide whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand my diagnosis is malignant glioma, a brain tumor, and further treatment is recommended. The standard treatment in cases as mine is radiotherapy with or without chemotherapy. Radiotherapy is the treatment of tumors by means of x-rays. It is usually administered once daily, 5 days per week for 6-8 weeks. Chemotherapy is the treatment of tumors by means of chemicals which destroy tumor tissue. Recent research has shown that the drug paclitaxel may increase the effectiveness of radiotherapy.

The purpose of this research study is to evaluate the results of radiation therapy along with the drug paclitaxel given weekly over 3 hours just before radiation.

DESCRIPTION OF PROCEDURES

I will receive radiation treatment once daily, five days per week for six weeks. I will also receive paclitaxel by vein usually over 3 hours prior to radiation as an outpatient on a weekly basis for six weeks. Prior to paclitaxel, I will receive the medications dexamethasone, diphenhydramine and cimetidine to prevent allergic reactions. During paclitaxel therapy, my blood pressure and pulse will be monitored.

I will be followed throughout treatment and then every four months for the first two years, and then every six months for the next three years then annually. I may be seen more often, if necessary.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. The radiation 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. Radiation therapy may result in simply reddening and tanning of the skin, but might also involve skin blisters. Other side effects of radiation therapy include hair loss that may be permanent, possible nausea, headaches, plugging of the ears with decreased hearing, fatigue, and increased sleepiness. The major risk of these doses of radiation is damage to adjacent brain tissue, the most serious cases of this damage leading to radiation necrosis. Radiation injury or radiation necrosis can lead to neurologic problems. The symptoms of radiation necrosis can mimic those of recurrent tumor or those of a stroke. In some instances, these changes may require surgical treatment or may prove irreversible. Cataracts can be caused by one of the medications that is usually used to treat my condition, dexamethasone (*Decadron*), a steroid. Cataracts can be removed surgically if they become symptomatic.

Paclitaxel (*Taxol*) commonly causes a lowering of blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need treatment with antibiotics, require hospitalization, or need transfusions if these problems are severe. Other common side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, and fatigue. There is the possibility of skin irritation if paclitaxel leaks from the my vein into the surrounding skin. Rarely, paclitaxel can cause a severe allergic reaction resulting in a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If I am treated with a high dosage or for a prolonged period, I may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or irregular heart rhythm, but only rarely does it cause symptoms that I would notice. In addition, paclitaxel may

increase radiation risks. In addition, paclitaxel may increase any or all of the previously described radiation risks. This may include an increased risk of radiation-related injury to adjacent brain tissue.

It is unknown what side effects paclitaxel may have on an unborn child. For this reason, I will be asked to practice an effective method of birth control, during the course of this study if I or my partner are of child-bearing potential.

In the event of death, permission will be asked of the surviving family members to perform an autopsy. Permission for an autopsy may be refused; however, information gained from an autopsy is usually very beneficial to the physicians and other patients participating in the study.

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

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 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 significant new findings develop 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, radiation therapy, or chemotherapy alone or in any combination. 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. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

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.

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 the 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

<u>N F</u>	<u>Definition</u>
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 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 supercede 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 of termination of the agent. | As above |
| - All life threatening (<i>grade 4</i>) 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