RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-02

PHASE IB STUDY OF RADIOSURGERY AND ETANIDAZOLE *(SR-2508)* FOR THE TREATMENT OF RECURRENT PRIMARY BRAIN TUMORS OR CNS METASTASES

(NSC #301467)

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SCHEMA

REGISTER

Maximum Tumor Diameter	Treatment
1. ≤ 20 mm	Arm 1: 24 Gy/1 fraction plus SR-2508, 12 gm/m^2
2. 21-30 mm	Arm 2: 18 Gy/1 fraction plus SR-2508, 12 gm/m^2
3. 31-40 mm	Arm 3: 15 Gy/1 fraction plus SR-2508, 12 gm/m^2

RT dose will be prescribed at the tumor margin for the 50-90% isodose line.
SR-2508 will be administered as a rapid i.v. infusion over 15 minutes to begin 45 minutes before radiosurgery

Eligibility *(See Section 3.0 for details)*

- Recurrent primary brain tumors or CNS metastases, ≥ 3 months after prior localized or whole brain external beam irradiation
- Must be at least 3 months post-surgery *(not including biopsy)*
- Age ≥ 18
- KPS ≥ 60
- Neurologic function 0-3
- Maximum tumor diameter ≤ 40 mm on CT or MRI
- No systemic therapy < 1 month prior to protocol therapy
- No planned external beam irradiation within 3 months following radiosurgery
- Study-specific consent form
- Liver function tests < 2 x upper limit of normal, serum creatinine < 1.5

Required Sample Size: 18 per treatment arm

4/22/96
8/16/96

Institution # _____

RTOG 95-02 **ELIGIBILITY CHECK (8/16/96)**

Case # _____

_____(Y) 1. Is the lesion to be treated a recurrent primary or metastatic brain tumor?

_____(Y) 2. Is the maximum diameter *(in mm)* of the recurrent lesion as measured by CT/MRI scan ≤ 40 mm?

_____ Specify maximum diameter size *(£ 20 mm, 21-30 mm, 31-40 mm)*

_____(Y) 3. Has the patient received whole brain external beam irradiation ≥ 3 months ago?

_____(≥ 60) 4. What is the Karnofsky performance status?

_____(0-3) 5. What is the neurologic function classification?

_____(≥ 18) 6. What is the patient's age?

_____(Y) 7. Has a study-specific informed consent been signed?

_____(Y) 8. Are the liver function tests ≤ 2 times your institution's upper limit of normal?

_____(Y) 9. Is patient's life expectancy ≥ 3 months?

_____(N) 10. Has the patient had any systemic therapy in the last month?

_____(N) 11. Is fractionated external beam therapy or systemic therapy planned for the next 3 months?

_____(N) 12. Has the patient had prior radiosensitizer?

_____(Y/N) 13. Has the patient had prior radiosurgery?

_____(Y) If yes, is the current lesion > 2 cm from the previously treated lesion?

_____(Y) 14. Is the serum creatinine < 1.5?

_____(N) 15. Has the patient had surgery to the study area within the last 3 months *(excluding biopsy)*?

_____	Patient's Name	_____	Race
_____	Verifying Physician	_____	Social Security #
_____	Patient ID #	_____	Zip Code *(9 digit if avail)*
_____	Referring Inst *(# if different)*	_____	Method of Payment
_____	Birthdate	_____	Treatment Start Date *(must be after registration)*
_____	Sex	_____	Treatment Assignment

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background

1.1.1 *Radiosurgery*

The use of high dose, single fraction stereotactic external beam irradiation, also called radiosurgery is becoming an increasingly more common method of precisely treating small well-defined intracranial tumors *(usually £ 40 mm)*, of both benign and malignant types. A variety of beams *(gamma rays, x-rays, protons, neutrons, and helium-ions)* and equipment *(gamma-knife, linear accelerator, cyclotron)* have been used for stereotactic external beam irradiation. Review articles dealing with the technical aspects of Gamma-knife radiosurgery[1] and linear accelerator radiosurgery have been published.[18,19,20] Besides AVM's, radiosurgery has been used to treat several other CNS tumors including acoustic neuromas, meningiomas, and pituitary adenomas. Several authors have reported on the use of radiosurgery in patients with solitary brain metastases.[3,6,14]

The final results of RTOG 90-05 were presented at the 1995 ASTRO[29] meeting in Miami Beach, FL *(Shaw EG et al., unpublished data)*. The study entered 156 analyzable patients with recurrent previously irradiated primary brain tumors and brain metastases which were = 40 mm in maximum diameter. Patients received single fraction radiosurgery, with dose dependent on the maximum diameter of their tumor as follows:

Maximum Diameter *(mm)*	Initial Dose *(Gy)*
≤ 20	18
21-30	15
31-40	12

The main endpoint of the study was acute central nervous system toxicity, although chronic CNS toxicity was also assessed. Dose was escalated in 3 Gy increments providing the incidence of severe, life-threatening, or fatal acute CNS toxicity was ≤ 20%. Ten to 22 patients were entered per diameter/dose level.[28] The results are summarized in the following table:

Maximum Diameter *(mm)*	**Dose *(Gy)***	**n =**	**Incidence Bad CNS Toxicity***		
			Acute	**Chronic**	**Total**
≤ 20	18	12	0	0	0
	21	18	0	6	6
	24	10	0	10	10
21-30	15	15	7	7	14
	18	15	0	20	20
	21	13	7	31	38
	24	12	33	8	41
31-40	12	21	5	5	10
	15	22	0	14	14
	18	18	17	28	45

* Bad CNS toxicity = severe, life threatening or fatal per RTOG criteria *(grades 3,4,5)*

The maximum tolerable dose *(MTD)*, based on overall toxicity, was determined to be 24 Gy for ≤ 20 mm tumors *(investigators decided not to escalate the dose despite a lack of bad CNS toxicity at 24 Gy)*, 18 Gy for 21-30 mm tumors, and 15 Gy for 31-40 mm tumors.

1.1.2 *SR-2508 in Human Phase I Trials*

The RTOG completed RTOG 86-05, a phase I trial of SR-2508.[7-11] One hundred two patients with advanced disease not considered curable by conventional therapy, received SR-2508 in an intravenous infusion over 10 minutes, 30 to 60 minutes prior to planned standard fractionated radiation therapy. The interval between SR-2508 administration and radiotherapy subsequently was decreased to 30 minutes after tumor biopsy data was available. Initially, SR-2508 was given three times weekly for three weeks. 1.3 g/m^2 was the starting dose, this was increased by 0.39 g/m^2 per step. Three patients were entered per step. The individual maximum dose was 3.7 g/m^2 with a maximum total dose of 32.1 g/m^2. The second part of the trial involved a long schedule, over 5-6 weeks, as would be delivered with a curative course of radiotherapy. The starting dose was 2 g/m^2 given three times per week over a five

week course. Peripheral neuropathy was the dose limiting toxicity. SR-2508 can penetrate into brain tumors.[12,15,16]

On the short course with a higher daily dose the lowest total dose that produced toxicity was 21.6 g/m^2. Some patients tolerated 29.7 g/m^2. A dose of 30 g/m^2 produced toxicity in all patients. On the longer schedule with lower daily doses, no patients experienced toxicity with a total dose of 30 g/m^2. Two-thirds of patients experienced peripheral neurotoxicity at 36 g/m^2 over five weeks. Using a smaller individual dose size, split courses of radiation or an every-other day schedule, some patients were able to tolerate a dose of 40.8 g/m^2.
Other forms of toxicity were minimal. Six patients experienced nausea and vomiting. There was a drug rash in four, arthralgias in three and abnormal liver function tests in one patient. No central nervous system toxicity was observed. A phase III study in head and neck cancer has been completed.[13,17]

The RTOG has published quality assurance guidelines for radiosurgery. This is to insure appropriate equipment techniques, standard data set, and to properly define deviations in protocol treatment. These guidelines are implemented in the current protocol.[26] It appears that despite the experience with radiosurgery that failures within the field still remain, and that normal tissue toxicity is dose-limiting. Thus, the addition of a chemical modifier would likely improve the risk of in-field failure. SR-2508 is a better hypoxic cell sensitizer that SR-4233 when given in a single dose.

RTOG 89-06 accrued patients from June 1990 to June 1991 to evaluate the single-dose toxicity of SR-2508 in conjunction with IORT radiation. A total of 42 patients were entered on the study with dose escalation from 5.5 to 12 gm/m^2. Twenty-one patients were entered at the 12 gm/m^2 level. Toxicity at this level included nausea and vomiting in four of the 21 patients. No peripheral neuropathy was reported from the drug within the three day post drug period. The pharmacology data indicated that 12 gm/m^2 produced very satisfactory blood and tumor levels.

2.0 OBJECTIVES

2.1 To evaluate the acute, and chronic toxicity with etanidazole and high dose, single fraction irradiation utilizing stereotactic external beam in patients with recurrent or persistant primary brain tumors or CNS metastases who have received previous localized or whole brain irradiation.

2.2 To evaluate response *(clinical, radiographic)* utilizing serial neurologic histories and examinations, serial CT *(+ MRI)* scans, and autopsy data *(when available)*.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (4/22/96)

3.1.1 Prior whole brain or localized irradiation for a primary brain tumor or brain metastasis*(es)* which must be completed $\geq$ 3 months before entry to this study.

3.1.2 All data related to the previous radiation must be available including representative simulator and/or portal films, total dose, number of fractions, and dates treatment was given.

3.1.3 Pathologically and/or clinically *(CT/MRI)* confirmed recurrence; a patient with multiple recurrent lesions with a single dominant lesion will have only that lesion treated.

3.1.4 Maximum diameter *(in any dimension)* of the recurrence must be $\leq$ 40 mm as measured by CT/MRI scan.

3.1.5 Karnofsky Performance Status $\geq$ 60 *(Appendix II)*.

3.1.6 Neurologic Function Status 0, 1, 2, or 3 *(Appendix II)*.

3.1.7 Life expectancy $\geq$ 3 months.

3.1.8 Age $\geq$ 18 years.

3.1.9 Liver function tests must be $\leq$ 2 x upper limit of normal; serum creatinine must be < 1.5.

3.1.10 The patient must give written study-specific informed consent. 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 Ineligibility Criteria (4/22/96, 8/16/96)

3.2.1 Recurrent brainstem tumors *(midbrain, pons, medulla)*.

3.2.2 Planned standard fractionated external beam irradiation or systemic therapy *(cytotoxic chemotherapy, hormonal therapy or immunotherapy)* within 3 months following protocol treatment.

3.2.3 Systemic therapy within one month prior to treatment or prior RT to brain < 3 months prior to treatment.

3.2.4 Prior stereotactic RT *(unless current lesion is > 2 cm away)* or sensitizer.

3.2.5 Multiple separate lesions without a single dominant lesion may not be treated.

3.2.6 Not meeting institutional criteria in Section 6.2.

3.2.7 Pregnant or lactating women. Patients with child-bearing potential should agree to use an effective method of contraception.

3.2.8 Surgery to the study area *(excluding biopsy)* within 3 months prior to study entry.

4.0 PRETREATMENT EVALUATIONS (4/22/96)

4.1 Neurologic Exam and History *(Appendix III)*

4.2 CT Scan with contrast or MRI Scan with gadolinium.

4.3 Liver function tests(SGOT, SGPT, alkaline phosphatase), serum creatinine.

4.4 Mini-Mental Status Exam.

5.0 REGISTRATION PROCEDURES

5.1 The treating facility must complete and submit the RTOG stereotactic radiotherapy facility questionnaire *(Appendix IX)* for RTOG approval. **The facility's questionnaire must be approved by RTOG prior to enrollment of any patients.** *Allow adequate time for processing by the RTOG Physics Committee. Prior approval for RTOG 93-05 is acceptable.*

5.2 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
- Eligibility Criteria Information
- Tumor Size
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY

6.1 Total Dose Determination

6.1.1 The total dose will depend on the size of target volume *(i.e., its maximum diameter in any dimension).* Doses are based on the results of RTOG 90-05[20,21, 29] and will be as follows:

Maximum tumor diameter	*Dose (Gy)*
≤ 20 mm	24
21-30 mm	18
31-40 mm	15

6.1.2 Dose will be prescribed at the tumor margin to the 50-90% isodose line.

6.1.3 Whenever possible, ≥ 5 mm should separate the prescription isodose line from the critical structures such as optic nerve, optic chiasm, or brain.

6.1.4 Multiple isocenters to optimize conformal therapy are encouraged.

6.2 Institutional Requirements

6.2.1 There are a variety of radiosurgery techniques which all have similar goals, as outlined by Larson,[20] and include treatment of small volumes, use of a high dose in a single fraction, high dose gradients at the field edges, and intersection of multiple beams at a common intracranial point.

6.2.2 *All institutions participating in this study must*:

- Have previously completed the Stereotactic Facility Questionnaire *(Appendix IX).* See Section 5.1.
- Utilize a fixed stereotactic frame for imaging procedures and treatment delivery.
- Perform target localization utilizing a stereotactic contrast-enhanced CT or MRI scan.

6.3 Target Volume Determination (4/22/96)

6.3.1 Target volume and isocenter determination will be based on a CT scan with contrast or MRI scan with contrast *(e.g. gadolinium)* with the patient's head in a fixed stereotactic frame.

6.3.2 Stereotactic CT or MRI slice thickness may not exceed 5 mm.

6.3.3 The target volume will include the recurrent primary brain tumor or brain metastasis without margin. **Surrounding areas of "edema" will not be considered part of the target volume.**

6.3.4 The target volume will be calculated in mm^3 by taking the area of the tumor on serial transverse CT or MRI slices and multiplying the area by the slice thickness. Software is available for most CT or MRI scanners to accurately calculate the area of a given target on a given CT slice.

6.4 Radiosurgery Quality Assurance Review (4/22/96)

A final review of the stereotactic radiotherapy procedure will be performed by the protocol chairman and the Headquarters' physics staff. The review process will evaluate the Radiosurgery Summary Form, diagnostic CT, and the stereotactic CT/MRI *(or a hard copy thereof)* with superimposed isodoses at required levels. Based on the evaluation and verification of data submitted, the following Quality Assurance scores will be assigned to each case.

6.4.1 Required isodose lines will be the prescription isodose line, 90% of the prescription isodose line, and 80% of the prescription isodose line, e.g. if 15 Gy is given to the 50% isodose line, the 45% isodose line *(or 13.5 Gy isodose line)* and the 40% isodose line *(or 12 Gy isodose line)* should be submitted. See also Appendix VII.

6.4.2 If the 90% of prescription isodose line completely encompasses the target, the case is considered per protocol.

If the 90% of prescription isodose line does not completely cover the target, but the 80% of prescription isodose line does completely cover the target, this shall be classified as a minor variation.

If the 80% of prescription isodose line does not completely cover the target, this shall be classified as a major variation.

6.4.3 The maximum dose delivered by the treatment plan shall be determined. A figure of merit for dose homogeneity within the target volume shall be determined as the maximum dose divided by the prescription dose *(ratio MDPD)*. This ratio shall be less than or equal to 2.0, and if achieved, the case will be per protocol. MDPD ratio greater than 2 but less than 2.5 shall be classified as minor variation. MDPD ratio greater than 2.5 shall be classified as a major deviation.

6.4.4 The volume of the prescription isodose surface shall be determined *(this may be obtained from the dose volume histogram, or by measuring the area of the prescription isodose on sequential levels)*. A figure of merit for conformation of the prescription dose to the target shall be determined as the volume of the prescription isodose surface divided by the target volume *(ratio PITV)*.

- This ratio shall be between 1.0 and 2.0, and if achieved, there will be no deviation from the protocol.
- PITV ratios less than 1.0 but greater than 0.9, or PITV ratios > 2.0 but < 2.5, shall be classified as minor variations.
- PITV ratios less than 0.9 shall be classified as major deviations.
- PITV ratios ≥ 2.5 shall also be classified as major deviations.

6.4.5 *Overall quality assurance score will be as follows*:

6.4.5.1 Per Protocol: No minor variation or major deviation was scored.

6.4.5.2 Acceptable: ≥ 1 minor variation but no major deviation was scored.

6.4.5.3 Unacceptable: ≥ 1 major deviation was scored, regardless of whether minor variations were scored.

6.4.6 Dose-volume data for accumulated volumes within the target and within the treated volume must be submitted. The data should be recorded in 1 Gy or 2 Gy increments. If the prescription dose is 15 Gy and 2 Gy increments are used to report dose-volume data, then the volume receiving 15 Gy should additionally be reported.

7.0 DRUG THERAPY

7.1 Drug Information SR-2508 *(NSC# 301467)*

7.1.1 *Supply* **(1/31/96)**

SR-2508 is manufactured by Roberts Pharmaceuticals Corporation *(RPC)* and will be supplied to NCI by RPC for distribution. Drug may be requested by completing a Clinical Drug Request *(NIH-986)* and mailing it to Drug Management and Authorization Section, DCT, NCI, EPN Room 707, Bethesda, MD 20892, through the DMAS Electronic Clinical Drug Request system *(ECDR)*, or by FAX *(301/480-4612)*. For more information, call *(301)* 496-5725.

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCT, using the NCI Drug Accountability

Record Form. *(See the NCI Investigators Handbook for Procedures for Drug Accountability and Storage).*

7.1.2 *Chemical Characteristics*

SR-2508 is a 2-nitro-imidazole with a molecular weight of 214.

The electron affinity, measured as 1-electron reduction potential, is -388mV. The partition coefficient in octanol and water is .046. The solubility is 118 mg/ml in 22° water.

7.1.3 *Animal Tumor Data*

SR-2508 has been shown to be a potent radiosensitizer. It has a high LD_{50} than misonidazole as reported in three separate mouse studies from different laboratories. The half life of SR-2508 is shorter than misonidazole. The peak brain concentration in mice is lower than that of misonidazole. Pronounced radiosensitization has been demonstrated in three different tumors using the cell survival assay, regrowth delay assay, and the tumor control assay.

7.1.4 *Toxicity in Animals:*

LD_{50}/2 days in BALB/C mice is 4.9 mg/g or 22.9 mmole/kg for SR-2508. The lethal dose of SR-2508 in dogs is 48 gm/m^2 as a single dose.

7.1.5 *Sensitization by SR-2508*

Experiments using Chinese hamster ovary cells that have been rendered hypoxic have demonstrated sensitizer enhancement ratios which are identical to misonidazole for equimolar concentrations. Maximum sensitization occurs 30 minutes after infusion with an enhancement ration of 1.9. SR-2508 is thought to sensitize hypoxic cells via a free radical mechanism analogous to that of oxygen.Tumor regrowth delay assays using RIF-1 sarcoma cells in mice also demonstrated equivalent sensitization of hypoxic cells with misonidazole or SR-2508. Tumor control using the MDAF/MCa4 carcinoma irradiated after equitoxic doses of SR-2508 and misonidazole demonstrated a decrease of the TCD_{50} from 40.10 Gy with misonidazole to 30.20 Gy with SR-2508. The conclusion is that SR-2508 is as effective as misonidazole in sensitizing hypoxic cells but is less toxic. SR-2508 was felt to be 3.1 times less toxic. Thus it was felt that 3.1 times the obtainable dose of misonidazole could be given as the daily dose of SR-2508, to produce the equivalent degree of neurotoxicity.

7.1.6 *Pharmacokinetics of SR-2508*

Pharmacokinetics studies demonstrate that 2 g/m^2 of SR-2508 will produce a plasma level of approximately 100 ugm/ml at 30 minutes. The terminal half life is approximately 5.4 hours with 70% of the drug excreted unchanged in the urine in 24 hours. The area under the curve *(AUC)* of serum drug concentration versus time is predictive of neurotoxicity. In the short schedule drug study discussed above, there was no toxicity in 23 patients with an AUC less than 38 mM x hrs., while all 9 patients with greater than 39mM x hrs., developed neuropathy. The long schedule did not reveal a clear cut off, but suggested that the total drug tolerance could assessed by AUC.

Phase I trials are seeking the maximum tolerated single dose of SR-2508 given in conjunction with chemotherapy. Up to 12 gm/m^2 has been administrated as a single dose with cyclophosphamide. More profound pancytopenia was noted, and the dose of cytoxan was reduced. At 15 gm/m^2 a severe pain syndrome consisting of pain radiation from the hips down the legs and shoulder girdle down the arms, requiring narcotic analgesia, has been described. The maximum total dose is considered to be 12 gm/m^2.

7.1.7 *Storage*

SR-2508 is supplied as a sterile 30ml vial containing 1 gm of lyophilized powder. The sealed vials can be stored at room temperature *(22-25°C)*. The SR-2508 powder is reconstituted with 19.4 ml of 0.9% sodium chloride injection USP for a intravenous injection. Each ml will then contain 50 mg of SR-2508 at pH 5.5-7.5. This concentration of SR-2508 will exhibit little or no degradation over a 14 day storage period at room temperature. The reconstituted SR-2508 solution however should be discarded after 8 hours since there is no antibacterial preservative in the lyophilized dosage form.

7.2 Dosage of SR-2508 (1/31/96, 4/22/96)

7.2.1 The SR-2508 solution will be administered as a rapid intravenous infusion over a 15-30 minute period. The duration of drug infusion must be recorded. The start of the stereotactic radiation will be 45 minutes after the start of the drug infusion. Blood pressure must be carefully monitored during administration, as hypotension may be a side-effect.

7.2.2 12 gm/m^2 SR-2508 will be administered as a rapid intravenous infusion over a 15-30 minute period. SR-2508 infusion will begin 45 minutes before stereotactic radiation. The timing of drug administration starting with time zero as the start of the infusion shall be recorded. The interval between the completion of drug infusion and the stereotactic radiation will be recorded. The duration of drug infusion must be recorded as well.

7.3 Drug Toxicity

7.3.1 All attempts must be made to keep the patient well-hydrated. Dehydration potentiates neurotoxicity.

7.3.2 Toxicity may include peripheral neuropathy, hypotension, nausea and vomiting, and rarely, drug rash, joint pain, bronchospasm, arthralgias or abnormal liver function. May augment radiation-induced myelosuppression. Toxicity will be assessed as per Appendix IV.

7.3.3 Documentation of all toxicities will be recorded. An adequate *(pre-treatment)* blood pressure baseline must be recorded especially for patients with pre-existing nausea or vomiting.

7.3.4 The dose of SR-2508 employed in this protocol may cause nausea and occasional vomiting. If nausea is experienced, symptomatic relief can be obtained from antiemetic medications, as long as the dose and nature of such medications are documented on the study form. If the patient does experience vomiting, the time from drug dose to vomiting should be recorded.

7.4 Adverse Reaction Reporting

7.4.1 Patients must be evaluated for toxicity at one week and at one month after SR-2508 delivery and then as specified in Section 12.1.

7.4.2 All neurotoxicity *(central or peripheral)*, or ototoxicity of any grade or grade ≥ 3 nausea and vomiting which develops while under treatment or within 30 days of completion of drug must be reported by telephone within 24 hours to RTOG Headquarters and the Study Chair.

7.4.3 Patients with persistent or newly-developed neurotoxicity after the four week evaluation will be evaluated monthly until clearance.

7.4.4 Report by phone to RTOG Headquarters *(215/574-3214)*, the Study Chairman and to the Investigation Drug Branch (IDB) *(301/230-2330)* within 24 hours. A written report to IDB with a copy to the RTOG Headquarters is to follow within 5 working days *(fax # 215/928-0153)*.

a. All life-threatening *(Grade 4)* which may be due to drug administration.
b. All fatal events, during treatment and within 30 days of drug administration regardless of cause.
c. All first occurrence of any previously unknown toxicity *(regardless of grade)*

7.4.5 The form in Appendix VI is used to report ADRs to the Investigational Drug Branch and to RTOG.

Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
fax # 301/230-0159

7.4.7 Study data collection forms which document details of an adverse reaction must accompany copies of Adverse Reaction Reports sent to RTOG Headquarters.

7.4.8 Adverse events requiring telephone reporting are to be followed up within five working days with written documentation explaining the details. Failure to follow these guidelines as specified will lead to suspension of registration privileges for this study.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY (4/22/96, 8/16/96)

9.1 Premedication: Decadron 10 mg i.v. and Zofran 8 mg i.v. are recommended however, institutions may substitute their own anti-emetic regimen. Drugs and doses must be recorded on the data flowsheets. Patients with known seizure history require therapeutic levels of anti-seizure medication. The total dose must be recorded pre-treatment, and at the time of each treatment evaluation.

9.2 Anti-emetics may be given as clinically indicated. For patients at risk for experiencing significant nausea after treatment, a dose of 40 mg i.v. Solumedrol is recommended.

10.0 PATHOLOGY

A central pathology review is not required for this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (1/31/96, 4/22/96, 8/16/96)

Tests	Pre-Treatment [b]	Post-treatment at 2 months	At each followup *(see Section 12.1)*
Neurologic history and exam[a]	X	X	X

CT or MRI with contrast[c]	X	X	X[d]
SGOT, SGPT, alk phos.	X	X	X
Serum Creatinine	X		
Mini-Mental Status Exam	X	X	X

a) must include the neurologic signs and symptoms outlined in Appendix III, the name and daily dosage of steroids and anti-seizure medications, as well as an assessment of KPS and neurologic function score *(Appendix II).*
b) must be performed < 2 weeks prior to treatment.
c) CT or MRI scan with contrast. The maximum diameter *(--mm)* of the tumor in the transverse, coronal and sagittal planes must be recorded.
CT or MRI required pretreatment and at the 2 month post-treatment evaluation
d) also, at the time of suspected progression or toxicity ≥ 3. **Every attempt should be made to follow the patient with the same type of scan *(CT or MRI)* used at baseline.**

11.2 CNS toxicity will be defined as the development of any new neurologic symptoms or signs *(± CT and/or MRI abnormalities)* following the radiation treatment which are felt attributable to the treatment. CNS toxicity will be defined as immediate *(within 24 hours of treatment)*, acute *(within 3 months of treatment start)*, or chronic *(after 3 months).*

11.3 Reoperation should be considered:

11.3.1 In cases of suspected symptomatic radiation necrosis not responsive to steroids *(i.e., consider resection).*

11.3.2 In cases of suspected tumor recurrence or when a question of symptomatic recurrence versus necrosis arises *(i.e., consider stereotactic biopsy or resection).*

11.4 Post-mortem examination *(of the brain)* should be obtained at death whenever possible. If possible, the treating radiation oncologist should assist the pathologist with sectioning of the brain so that sections can be obtained in the same transverse planes as the isodose curves.

11.5 Patients will be followed until the time of death, at which time cause*(s)* of death should be determined according to:
- Due to progression of the treated tumor in the brain.
- Due to progression of disease, but not of the treated tumor *(specify site(s) of progression).*
- Due to toxicity of protocol treatment
- Due to intercurrent disease, unrelated to progression of the treated tumor, progression of disease, or toxicity of protocol treatment *(specify cause(s)).*
- Cause*(s)* unknown.

11.6 Response Assessment

11.6.1 Definition of response to RS+SR-2508 for patients with recurrent or persistent primary brain tumors: two sets of response criteria will be used, one set for tumors that are predominantly enhancing and the other for tumors that contain small enhancing regions or non-enhancing.

11.6.1.1 *Residual enhancing tumor*:
- Complete response *(CR)* - disappearance of all enhancing tumor on consecutive CT or T1 *(gad)* MR scans at least one month apart, off steroids, and neurologically stable or improved.
- Partial response *(PR)* - 50% or greater decrease in enhancing tumor size on consecutive CT or T1 *(gad)* MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.
- Tumor regression *(TR)* - A substantial decrease in enhancing tumor size on consecutive CT or T1 *(gad)* MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.

11.6.1.2 *Residual non-enhancing tumor*:
- Complete response *(CR)* - disappearance of all tumor on consecutive CT or T2 MR scans at least one month apart, off steroids, and neurologically stable or improved.
- Partial response *(PR)* - 50% or greater decrease in tumor size on consecutive CT or MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.
- Tumor regression *(TR)* - A substantial decrease on tumor size on consecutive CT or T2 MR scans at least one month apart, steroid dose stable or reduced, and neurologically stable or improved.

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

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

12.0 DATA COLLECTION

12.1 Data Due (8/16/96, 3/7/97)

Item	Due
Demographic Form **(A5)** On Study Form **(I1)** Pretreatment CT/MRI **(C1)** and report **(C3)** Mini Mental Status Exam **(MS)**	Within 1 week of registration.
Radiotherapy Form **(T1)** *(to include tumor and dose-volume data)* Isodose Distribution **(T6)** Calculation *(supplementary)*/radiosurgery **(RS)** Placement Films/radiosurgery **(RP)**	Within one week of stereotactic *volume* procedure
Radiosensitizer Form **(R1)**	1 week after radiosurgery; must contain pretreatment, treatment and week 1 assessments.
Follow-up form **(F1)** Mini-Mental Status Exam **(MS)** years then annually; at onset of	At 2 months post RT then q 3 months for 2 years, q 6 months for 3 toxicity ≥ grade 3, at progression/ relapse; at death *(F1 only).*
Follow-up CT/MRI **(C2)** and reports **(C3)** with tumor measurements in 3 dimensions	At 2 months post RT, and at onset of toxicity ≥ grade 3, and at progression/relapse.
Autopsy Report **(D3)**	When applicable

12.2 Prior and Protocol Treatment Data

Previous treatment data including copies of simulation/port films may be required by RTOG Headquarters and will be submitted upon request to RTOG. Pretreatment CT/MRI should be submitted within one week of registration. All data must be clearly identified with the RTOG study and case number, patient name and date of films.

12.3 Data Submission

Due to the study's objectives, timely submission of data is essential to toxicity evaluations in order to safely assign treatment to subsequent patients. Failure to comply with required assessments and timely data submission may lead to suspension of accrual privileges to this study.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Acute and late toxicities associated with RS + SR-2508.

13.1.2 Tumor response rate associated with Radiosurgery*(RS)* + Etanidazole*(SR-2508).*

13.1.3 Survival rates and time to tumor progression.

13.2 Sample Size

Sixteen patients will be required per tumor size. An additional 10% of the sample size will be added to guard against ineligible or unevaluable *(no data)* cases. **Therefore, 18 *(16+2)* cases will be required per tumor size, a maximum of 54 cases.**

13.3 Patient Accrual

The patient accrual is projected to be 1.5 cases per month per tumor size, based upon the monthly accrual for each tumor size in RTOG 90-05. At that rate, it will take 12 months to reach the required accrual of 18 cases per tumor size. When 18 patients are accrued for a tumor size then the accrual will be closed for that tumor size.

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 chairman and reported to the RTOG Data Monitoring Committee (DMC) 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 date for the accrual phase;
b) the quality of submitted date with respect to timeliness, completeness, and accuracy;
c) the frequency and severity of the toxicities.

Through examining the above items, the study chairs and the statistician can identify problems with the execution of the study. These will be reported to the RTOG DMC 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 3 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 institutional accrual;
c) distribution of important prognostic baseline variables by treatment arm and tumor size;
d) observed results with respect to the endpoints described in Section 13.1 by tumor size.

Further subgroup analyses will not be undertaken due to the small sample sizes. Ineligible cases treated according to the protocol will be evaluated for toxicity. Inevaluable cases will be excluded from all analyses.

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APPENDIX I

RTOG 95-02

PHASE IB STUDY OF RADIOSURGERY AND ETANIDAZOLE (SR-2508) FOR THE TREATMENT OF RECURRENT PRIMARY BRAIN TUMORS OR CNS METASTASES

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF STUDY

It has been explained to me that I have brain cancer. The purpose of this study is to evaluate the potential side effects of a single high dose of radiation given to a small area of the brain for patients with recurrent primary brain tumors or brain metastases following previous standard external beam radiation. Recent research has shown that there may be some benefit to giving patients a single, high-dose radiation therapy treatment *(stereotactic external beam therapy)* after standard radiation therapy treatment. Single dose radiation may not be as effective against cells which are low in oxygen. A potential way to improve the damage to these cells is to add a radiosensitizer, such as etanidazole *(SR-2508)*. My physicians believe that etanidazole may improve the effectiveness of the stereotactic radiosurgery. Approximately 60 patients will be treated on this study.

DESCRIPTION OF PROCEDURES

The treatment to be given to me is as follows: I will require application of a stereotactic head frame *(including the need to puncture my scalp under anesthesia and make four small holes in my skull)*, stereotactic imaging procedures such as CT and MRI scans, and stereotactic radiation treatment *(sometimes called "radiosurgery")*. Forty-five minutes before radiation, I will receive SR-2508 as an intravenous solution *(in my vein)* over a 15 minute period. An overnight hospital stay may be necessary. A series of regular follow-up visits and imaging procedures will be required.

The pharmaceutical company and the Division of Cancer Treatment, National Cancer Institute will provide me with the investigational agent free of charge for this study.

RISKS AND DISCOMFORTS (8/16/96)

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

Radiation Therapy: Redness or tanning of the skin and a small area of hair loss may occur. Placement of the headframe will result in pin-site soreness. There may also be some swelling within the brain which could cause any existing neurologic symptoms to become more severe, temporarily or occasionally permanently. Depending on the location of the tumor, different symptoms may result. They may include headache, nausea, vomiting, weakness, seizures, difficulty with speech or difficulty with balance. In most cases, these symptoms can be relieved with anti-swelling medication *(steroids)*. Blindness may occur if the tumor is located within or near the visual pathways. Six to 24 months after radiosurgery, I may develop radiation necrosis *(destruction of brain tissue)* which also results in swelling within the brain. This may cause similar symptoms and is treated the same way. Rarely, this condition may require surgery to relieve the swelling.

***SR-2508*:** Side effects include nausea, vomiting, tingling, numbness and/or pain in the extremities. Low blood pressure, drug rash, allergic reaction, shortness of breath, temporary joint pain or drug-induced abnormal liver enzyme levels or other blood counts have also been reported. All care will be taken to minimize these side effects, but they can be unpredictable both in nature and severity. It is unknown what effects this medication may have on an unborn child. For this reason, I will be asked to practice an effective method of birth control while I am participating in this study.

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

In the unforeseen event of death, permission will be asked of the family 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.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment for injury may be available. I understand, however, I will not be provided with reimbursement for medical care or receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. __
_____ the investigator in charge at._____
In addition, I may contact_____ at_____
for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.
I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

ALTERNATIVES

Alternatives which could be considered in my case include the use of medications alone *(possibly including steroids, anti-seizure medications)* chemotherapy, surgery alone or standard radiation therapy. 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.

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. In the event of a research-related injury, I understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at 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

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

APPENDIX III

CNS TOXICITY CRITERIA

Grade	Definition
0	No change
1	Fully functional status *(i.e., able to work)* with mild neurologic findings, no medication needed.
2	Moderate neurologic findings present, sufficient to require home care/nursing assistance may be required/meds. including steroids/anti-seizure agents may be required.
3	Severe neurologic findings present, requiring meds *(steroids, antiseizure agent)* and possibly hospitalization for initial management.
4	Life threatening neurologic impairment which includes paralysis, coma or seizures > 3 per week despite medication/hospitalization or nursing home care required. Radionecrosis requiring surgery.
5	Death

NEUROLOGICAL SIGNS AND SYMPTOMS

Neurological Symptoms

(to be scored as follows: 0-absent, 1-mild, 2-moderate, 3-severe)

Headache
Nausea
Visual Disturbance
Speech Impairment
Sensory Symptoms
Motor Symptoms
Memory Deficit
Personality Change
Seizures
Other (specify)

Neurological Signs

(to be scored as follows: 0-normal, 1-mildly impaired, 2-moderately impaired, 3-severely impaired)

Mental Status
Papilledema
Motor Deficit
Reflexes
Cranial Nerves *(specify abnormal one)*
Sensory Deficit
Cerebellar Deficit
Visual Fields
Other *(specify)*

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures 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 sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol *(FAX #215/928-0153).*

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

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

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

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

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

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

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

Investigational Agents

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

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

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(grade 4)* events which may be due to agent.	As above

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

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

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

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

APPENDIX VI

Stereotactic External Beam
Irradiation Techniques

A. Joint Center (Boston) technique for stereotactic external beam radiation therapy[19]

APPENDIX VI

Stereotactic External Beam Irradiation Techniques

B. Gamma-Knife Therapy