RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-08

A PHASE III TRIAL COMPARING WHOLE BRAIN IRRADIATION WITH VERSUS WITHOUT STEREOTACTIC RADIOSURGERY BOOST FOR PATIENTS WITH ONE TO THREE UNRESECTED BRAIN METASTASES

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SCHEMA

STRATIFY

Number of Metastases
1. Single
2. 2-3 *(discontinued 6/14/99)*

Extent of Extracranial Disease
1. None
2. Present

REGIONALIZE

REGISTER:

Arm 1: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/ week followed by radiosurgery to all *(1-3)* metastase*(i)s*

Arm 2: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/ week

Arm 1: All patients will receive whole brain radiation therapy delivered to 37.5 Gy in 15 daily fractions of 2.5 Gy followed by stereotactic radiosurgery *(SRS)* to all *(1-3)* known metastase*(i)*s. SRS dose will be tumor size dependent *(See Section 6.2.2)* and will be prescribed to the isodose surface *(³ 50% to £ 90% of the maximum dose [maximum = 100%])* which encompasses the margin of the tumor.

Arm 2: All patients will receive whole brain radiation therapy delivered to 37.5 Gy in 15 daily fractions of 2.5 Gy.

Eligibility *(See Section 3.0 for details)*
- Histologically confirmed systemic malignancy
- A diagnostic contrast enhanced MRI of brain demonstrating a single parenchymal brain metastasis
- Single brain metastasis is eligible only if surgery is refused or if surgery deemed inappropriate by the treating physician.
- Well circumscribed lesion with maximum tumor diameter ≤ 4.0 cm *(per lesion)*. If multiple lesions are present and one lesion is at the maximum diameter, the other*(s)* must not exceed 3.0 cm in maximum diameter *(multiple lesions were discontinued 6/14/99; see Section 13.2)*.
- No metastases to brain stem, midbrain, pons, or medulla or within 10 mm of the optic apparatus *(optic nerves and chiasm)*.
- No prior cranial irradiation
- Age ≥ 18 years
- Karnofsky performance status ≥ 70.
- Hgb ≥ 8, absolute neutrophil count ≥ 1000, platelets ≥ 50,000
- Study-specific consent form

Required Sample Size: 332

Institution # _____

ELIGIBILITY CHECK ***(6/14/99)***

(page 1 of 2)

RTOG 95-08
Case # _____

_____(Y) 1. Is there histologic proof of malignancy?

_____(Y) 2. Has a contrast enhanced, diagnostic brain MRI been done within the past 2 weeks?

_____(Y) 3. Does the imaging demonstrate the presence of a solitary unresected brain met?

_____(Y) 4. Has the patient refused complete resection or has the physician deemed complete resection inappropriate?

_____(Y) 5. Is the maximum tumor diameter ≤ 4.0 cm?

_____(N) 6. Has the patient had any previous cranial radiation?

_____(≥ 18) 7. What is the age of the patient?

_____(≥ 70) 8. What is the Karnofsky Performance Status?

_____(0-2) 9. What is the neurologic function status per Appendix II?

_____(≥ 8) 10. What is the hemoglobin in grams?

_____(≥ 1000) 11. What is the absolute neutrophil count?

_____(≥ 50) 12. What is the platelet count *(per 1000)*?

_____(N) 13. Has the patient had any clinical or radiographic evidence of progression other than the study lesion in the last month?

_____(N) 14. Any evidence of leptomeningeal metastases?

Institution # _____

ELIGIBILITY CHECK ***(6/14/99)***

(page 2 of 2)

RTOG 95-08
Case # _____

_____(N) 15. Are there any mets to the brain stem, midbrain, medulla, or within 10 mm of the optic apparatus?

_____(N) 16. Does the patient have leukemia or lymphoma?

_____(Y) 17. Has the patient signed a study-specific consent form?

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # *(if different)*

_____ Number of Metastases *(must be solitary)*

_____ Extent of Extracranial Disease *(none vs. present)*

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code *(9 digit if available)*

_____ Method of Payment

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

_____ Treatment Start Date *(must be within one week after registration)*

_____ Treatment Assignment

Completed by _____ Date _____

1.0 BACKGROUND (3/17/98)

Metastases to the cranium and intracranial contents are the most common malignancy affecting the brain.[6, 8,33] Of these, parenchymal brain metastases are the most common symptomatic lesions. Autopsy series have shown that as

many as 25% of patients who die of cancer will have intracranial metastases, involving brain substance in about 15%.[33] The majority of patients with intraparenchymal metastases have only one or two metastases, 49% and 21%, respectively, and the remaining 30% three or more. Approximently 80% of brain metastases are located supratentorially.[11]

Standard treatment for brain metastasis *(es)* include glucocorticoids and external beam whole brain irradiation *(WBRT)* which effectively relieve symptoms and restore neurological function in most patients.[34] Untreated patients have a median survival time *(MST)* of less than 7 weeks.[7] Three prospective randomized trials involving more than 1800 patients conducted by the Radiation Therapy Oncology Group *(RTOG)* evaluated 9 different radiation doses and schedules.[5] All doses up to 50 Gray *(Gy)* were equivalent with respect to toxicity, neurological improvement, and survival. Higher doses resulted in greater neurologic toxicity. MST of all patient subgroups were three to six months. Little difference was found between patients who received 20 Gy administered over one week and 40 Gy administered over four weeks. Furthermore, radiation boost treatment to the metastatic site did not improve on WBRT.[17] Currently, 30 Gy of WBRT delivered in 10 fractions is considered standard treatment in the United States.

The most common cancers to metastasize to brain are lung and breast, 34 and 30%, respectively. Of the approximately 200,000 patients with these malignancies who will die each year, 124,000 will have brain metastases.[6] The cause of death in almost 50% is persistence of lesions or recurrence following WBRT; however, 10 to 15% of patients will survive at least one year.[4, 10, 29] These data, along with the fact that brain metastases are so frequently single, provide the rationale for the development of treatment modalities that exceed current palliative measures to actually improve patient survival.

Surgical resection of brain metastases is increasingly performed on patients with favorable prognostic factors, accessible lesion*(s)*, and/or metastatic lesions from relatively radio-insensitive tumors such as renal cell carcinoma and melanoma.[14, 17, 28, 34, 38] Since metastases are usually well demarcated from surrounding brain, complete removal with a minimum of morbidity and mortality is often possible. Relief of symptoms of intracranial hypertension and focal brain dysfunction has been demonstrated. Patient survival is also dependent on the extent of extracranial disease. For patients who have undergone removal of solitary brain metastases, the addition of WBRT has been shown to result in a lower incidence of brain recurrence.[34] Intergroup #0124 was testing whether there is a major benefit with the addition of WBRT; however, this study closed due to poor accrual. Two prospective randomized trials in which surgical excision followed by radiation therapy compared to radiation therapy alone in patients with single metastases have been done.[29, 39] Patchell and colleagues randomized patients with single metastases to either surgical excision followed by WBRT *(25 pts)* or biopsy followed by WBRT *(23 pts)*. The MST of patients who underwent surgical resection rather than biopsy were 40 and 21 weeks, respectively; functional independent survival times were 38 and 8 weeks, respectively, and the intracranial recurrence rates 20 and 52%, respectively These results confirmed those of earlier uncontrolled studies showing the benefits of surgical resection.[14, 29, 31] Vecht et al. randomized 63 patients to the same regimens with similar results. Bindal et al., in a retrospective analysis of 56 patients with multiple resected metastases, 50% of whom received WBRT, reported a MST equivalent to that of patients with a single resected metastasis but longer than that of patients who had one or more lesions remaining after surgery.[4] Based on these reports, surgical removal in patients with a solitary accessible lesion followed by WBRT appears superior to WBRT alone for selected patients.

The post-operative delivery of WBRT for such patients is considered beneficial to sterilize residual disease in the tumor bed or other sites of occult disease in the brain. There are several retrospective studies involving relatively small numbers of patients in which surgery followed by WBRT has been compared to surgery alone.[35,16,12] Smalley and colleagues demonstrated a statistically significant difference in survival and fewer recurrences in 85 patients who received WBRT following surgery.[35] In a second retrospective analysis by the same investigators, the MST among 229 patients was 15 months for those who underwent surgery followed by adjuvant WBRT as compared to 8 months for patients who underwent surgery but did not receive WBRT.[36] On the other hand, Hagan et al. found no advantage to WBRT following surgery in patients with melanoma, a radioresistant tumor.[16] Likewise, Dorsoretz et al. found no survival advantage to low dose WBRT among 33 patients with resected solitary lesions and no active systemic cancer.[12]

Recent reports have suggested a role for stereotactic radiosurgery *(SRS)* in the treatment of metastatic brain tumor.[1,13,15,18,20-22,25,26] The recent development of linear accelerators modified to deliver focused irradiation has expanded the availability of SRS.[3,23,32] Advantages of SRS are ease of administration from the patient's viewpoint *(one-day treatment)*, the ability to treat metastases located in areas of the brain not amenable to complete surgical resection, and the potential to decrease neurosurgery and radiation related morbidity and mortality.[9, 24, 32, 37] SRS allows delivery of a high dose of focal irradiation in a single fraction to the tumor from multiple geometric positions.[19] Brain metastases are ideal targets for SRS because the majority are small *(< 3 cm in diameter)*, most are spherical with distinct tumor margins on contrast enhanced imaging studies and most displace rather than infiltrate normal brain.[3] SRS minimizes the amount of radiation received by the non-target regions of the brain, and the area targeted generally does not include functional brain.[15,32]

Retrospective analyses show that brain metastases from a large number of different types of malignancies including less radioresponsive malignancies such as colon cancer, renal cell carcinoma and melanoma respond to SRS.[26,32] Local control to complete radiographic obliteration has been achieved in 80 to 90% of cases.[32] Noordijk et al. treated 52 brain metastases in 33 patients with SRS.[28] At 5.5 months follow up, 10 *(29%)* patients' metastatic lesions had completely disappeared, 15 *(50%)* had decreased in size and four had stable intracranial disease. Mehta et al. recently reported the results of a prospective trial in which patients with single brain metastasis were randomized to undergo surgical resection of the metastasis followed by SRS to the preoperative tumor margins and/or residual tumor or SRS alone[25]. MST for patients who received surgery and SRS was 40 weeks compared to 15 weeks for patients who received SRS alone. There were fewer recurrences at the site of the original brain metastasis in patients who underwent surgery plus SRS compared to SRS alone, 20 vs 52%, respectively. The quality of life of patients in the former group was also markedly improved.

It has been demonstrated that SRS results in encouraging response rates for brain metastases. Furthermore, there may be improvement in the quality of life especially with respect to neurological status. The question addressed in this trial is whether such responses can translate into a prolongation of survival among patients with 1-3 untreated, unresected brain metastases.

The final results of RTOG 90-05 were presented at the 1995 ASTRO[27] 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.[43] 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 15 18	21 22 18	5 0 17	5 14 28	10 14 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.

2.0 OBJECTIVES

2.1 To determine if the delivery of stereotactic radiosurgery *(SRS)* boost treatment*(s)* after conventional whole brain radiation therapy improves upon the overall survival of radiotherapy alone in patients with 1-3 unresected brain metastases.

2.2 To compare site*(s)* of recurrence and cause of death between such patients receiving or not receiving SRS boost treatment*(s)* after whole brain radiation therapy.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (6/14/99)

3.1.1 Histologically confirmed malignancy with the presence of one intraparenchymal brain metastases. Patients with solitary metastasis are eligible only if a) they have refused surgery or b) surgical resection is deemed inappropriate by the patient's physician.

3.1.2 A diagnostic contrast enhanced MRI demonstrating the presence of one unresected brain metastases performed within two weeks prior to registration.

3.1.3 The contrast-enhancing tumor must be well circumscribed and must have a maximum diameter of ≤ 4 .0 cm in any direction on the enhanced scan. If multiple lesions are present and one lesion is at the maximum diameter, the other*(s)* must not exceed 3.0 cm in maximum diameter ***(multiple lesions were discontinued 5/26/99)*** (*delineate tumor under study by circling and numbering on the scan with wax pencil).*

3.1.4 No previous cranial radiation.

3.1.5 Age ≥ 18 years.

3.1.6 Karnofsky performance status ≥ 70 *(Appendix II)*.

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

3.1.8 Patients may have extracranial sites of metastastic disease.

3.1.9 Adequate bone marrow reserve *(hemoglobin ³ 8 grams, absolute neutrophil count ³ 1000/mm^3, platelets ³ 50,000/mm^3)*.

3.1.10 Patient must sign a study-specific informed consent form. If the patient's mental status precludes his/her giving informed concent, written informed consent may be given by the patient's legal representative.

3.2 Ineligibility Criteria

3.2.1 Major medical illnesses or psychiatric impairments which in the investigator's opinion will prevent administration or completion of the protocol therapy and/or interfere with follow-up.

3.2.2 All patients who have undergone a complete resection of all known brain metastase*(i)*s. Patients who have undergone subtotal resection are eligible providing residual disease is ≤ 4.0 cm in maximum diameter.

3.2.3 Inability to obtain histologic proof of malignancy.

3.2.4 Patients with leptomeningeal metastases documented by MRI or CSF evaluation.

3.2.5 Clinical or radiographic evidence of progression *(other than the study lesion(s))* within one month prior to registration.

3.2.6 Patients with metastases within 10 mm of the optic apparatus so that some portion of the optic nerve or chiasm would be included in the high dose SRS boost field.

3.2.7 Patients with metastases in the brainstem, midbrain, pons, or medulla.

3.2.8 Patients with leukemia or lymphoma are not eligible.

4.0 PRETREATMENT EVALUATION

4.1 Complete history and physical examination with a detailed neurological examination.

4.2 Contrast-enhancing MRI scan and measurement of size of brain metastasis within two weeks prior to initiation of treatment**. (6/14/99)**

4.3 Contrast-enhancing CT scans of the chest, abdomen and pelvis, and bone scan are strongly recommended to determine the extent of extracranial malignant disease.

4.4 CBC with differential, platelet count.

4.5 Patient evaluations must be obtained as part of the patient's clinical evaluation and will include the mini-mental status examination *(MMSE)*, and Karnofsky performance status.

4.5.1 Forms packets, including the MMSE forms, are available in advance from RTOG HQ. **The MMSE forms must be obtained pre-randomization** so that they may be completed by the patient at the appropriate time points *(see Section 11.1)*.

5.0 REGISTRATION PROCEDURES

5.1 The treating facility must complete and submit the RTOG stereotactic radiotherapy facility questionnaire *(Appendix VII)* 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.* Institutions without radiosurgery capability may refer a patient to an approved-RT facility if randomized to Arm 1.

5.2 Any RTOG facility without radiosurgery which seeks to enroll a patient on this study must have the patient evaluated by the RTOG radiosurgery institution for appropriateness for SRS treatment prior to randomization.

5.3 Patients can be randomized 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
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY

6.1 Whole Brain Radiation Therapy

6.1.1 *Total Dose*: Whole brain radiation therapy *(WBRT)* must begin within one week of randomization. One treatment of 2.5 Gy will be given daily 5 days a week for a total of 37.5 Gy. Both portals shall be treated during each treatment session. The WBRT regimen will be identical for both arms.

6.1.2 *Physical factors*: Treatment will be delivered using megavoltage machines with photon beams ranging from 4 to 8 MV. The minimum dose rate at the midplane in the brain on the central axis must be 0.50 Gy/minute. Electron, particle, or implant therapy is not permissible.

6.1.3 *Simulation, Immobilization, Localization*: The patient will be treated in the supine position. Adequate immobilization and reproducibility of position must be ensured. The target volume will cover the brain and the meninges to the foramen magnum.

6.1.4 *Treatment Planning*: Treatments must be delivered through parallel opposed fields that cover the entire cranial contents. There should be beam fall-off of at least 1 cm. The eyes will be excluded from the beam either by field arrangement or shielding.

6.1.5 *Dose Specification*: Doses will be specified at the central axis at midplane on the brain. For the following portal arrangments, the target dose shall be specified as follows:

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

6.2 Radiosurgery (3/17/98)

6.2.1 *Timing*: Radiosurgery must be delivered within seven days of completion of whole brain radiation in Arm 1. Only those patients assigned to Arm 1 are eligible to receive SRS as a component of initial therapy. It is possible that at the time of radiosurgery, one of these scenarios occur:

- An identified metastasis at the time of enrollment now exceeds the acceptable upper limit diameter *(4.0 cm for a solitary metastasis, or 3.0 cm for multiple metastases)*. If any one metastasis exceeds the limit at the time of radiosurgery, the lesion should not be treated.
- If a lesion disappears after the course of conventional radiation this lesion should not be targeted for radiosurgery.

- If more than three lesions exist at the time of radiosurgery, radiosurgery should be delivered to the three largest treatable lesions that meet the eligibility criteria. The physicians submitting the films should circle and number *(1-3)* with wax pencil, each lesion so each lesion can be uniformly identified and the response to treatment can be evaluated for each corresponding lesion.

6.2.2 *Total Dose Determination*: The total dose is dependent on the size of the metastastic lesion*(s)* as follows:

Maximum Tumor Diameter	*Assigned Dose*
≤ 2.0 cm	24 Gy
2.1-3.0 cm	18 Gy
3.1-4.0 cm	15 Gy

6.2.3 *SRS Technique*: All participating institutions must use stereotactic frame placement for imaging procedures and treatment delivery, perform target localization using CT or MRI data, and have a treatment planning system capable of generating isodose distributions in three dimensions for a given treatment. The Stereotactic Radiotherapy Guidelines *(Shaw et al.)* are available from the RTOG Dosimetry Department *(215/574-3219)*. The treating facility must complete and submit for RTOG approval the RTOG stereotactic radiotherapy facility questionaire. **The facility's questionaire must be approved by RTOG prior to enrollment of any patients.** Prior approval of this institution questionaire for RTOG 93-05 is sufficient.

6.2.4 *Target Volume Determination*: **(8/16/96)**

6.2.4.1 Target volume and isocenter determination will be based on a contrast enhanced CT scan with the patient's head in a stereotactic frame. The imaging study used to deliver the radiosurgical treatment must be the same as used to determine size of the metastatic lesion*(s)*.

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

6.2.4.3 The target volume will include the enhancing portion of the metastatic lesion. Surrounding areas of edema will not be considered part of the target volume.

6.2.5 *Dose Prescription and Dosimetry Requirements* **(3/17/98)**

6.2.5.1 The dose will be prescribed to the isodose surface *(50-90% [maximum = 100%])* which encompasses the margin of the metastasis, as defined by the imaging studies. The 100% *(maximum)* dose will be recorded for each patient. The prescription dose shall be delivered to the 50-90% *(maximum = 100%)* isodose surface, and is defined as the minimum dose to the target volume. The minimum dose shall be established by an examination of the dose distribution on each axial level on which the target volume has been defined, and/or by the target dose-volume histogram.

6.2.5.2 For patients with one, two, or three brain metastase*(i)*s, each lesion will be assigned to a SRS dose level according to its maximal diameter. If any two lesions are within 0.8 to 2 cm of each other, the intervening midplane dose will not exceed 13.0 Gy. This dose may represent a dose to each respective target that will be less than the dose prescription listed in Section 6.2.2. A second stipulation will involve size. If one lesion is > 3.0 cm the remaining two metastases may not exceed 3.0 cm each in diameter. This stipulation is designed to minimize toxicity in patients with larger volume multiple metastases. A review of patient and tumor criteria among patients entered into RTOG 91-04, a phase III trial for patients with unresected brain metastase*(i)*s, would suggest that the majority would meet the entry criteria of this trial.

6.2.6 *Radiosurgery Treatment Planning Data* **(8/16/96)**

6.2.6.1 Isodose distributions must be calculated, and the prescription isodose line clearly designated, for each target lesion in the transverse, coronal and sagittal planes.

6.2.6.2 The isodose distributions on the required three planes for each target lesion will include isodose lines *(in % dose)* that represent 10% dose increments.

6.2.6.3 Dose-volume data for accumulated volumes within the target and within the treated volume must be submitted. The data should be recorded in 1 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 be additionally reported.

6.3 Radiation Toxicities

6.3.1 *Acute, < 90 days from treatment start*: Expected toxicities include hair loss, erythema of the scalp, headache, nausea and vomiting. Reactions in the ear canals and on the ear should be observed and treated symptomatically.

6.3.2 Both acute and delayed, ≥ 90 days from treatment start *(lethargy, transient worsening of existing neurological deficits)* or late *(radiation necrosis, cognitive dysfunction, accelerated atherosclerosis, radiation-induced neoplasms*) effects of radiotherapy are to be recorded and included in the toxicity evaluation.

6.4 Radiosurgery Quality Assurance *(QA)* Review (3/17/98)

A final review of the stereotactic radiotherapy treatment will be performed by the protocol chairman and the protocol physicist. 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 *Lesion Identification*

The physicians submitting the films should circle and number *(1-3)*, with wax pencil, each lesion so the radiosurgery parameters can be evaluated for the corresponding lesion.

6.4.2 *Isodose QA*

Three isodose lines should be submitted: the prescription isodose line, 90% of the prescription isodose line *(not 90% of total dose)* and 80% of the prescription isodose line, should be submitted. See Appendix V.

6.4.3 *Target Coverage QA*

- Per protocol: The submitted 90% isodose line *(90% of the prescription dose, not total dose)* completely encompasses target.
- Acceptable variation: 80% isodose line covers the target.
  Unacceptable deviation: 80% isodose line does not cover target.

6.4.4 *Dose QA*

- Per protocol: If the maximum dimension of the tumor is
  > 2.0 cm: 24 Gy
  1-3 cm: 18 GY
  1-4 cm: 15 Gy
  prescribed to the is odose line that encompasses the target.
- Unacceptable deviation: Anything else

6.4.5 *Dose Homogeneity QA*

The ratio of the maximum dose to the prescribed dose *(MD/PD)* is:

- Per protocol if ≤ 2
- Acceptable variation if > 2 but ≤ 2.5
- Unacceptable deviation if > 2.5.

6.4.6 *Dose Conformity QA*

The ratio of prescription isodose volume to the target volume *(PI/TV)* is:

- Per protocol if between 1.0 and 2.0
- Acceptable variation if ≥ 0.9 but < 1.0 or >2.0 but ≤ 3.5.
- Unacceptable deviation if > 3.5.

(The prescription isodose volume may be obtained from the dose volume histogram which must be submitted in tabular, not graphic, form or by measuring the area of the prescription isodose on sequential levels. See Appendix V.)

6.4.7 ***Overall Radiosurgery Q/A Score***

The ration of prescription isodose volume to the target volume *(PI/TV)* is:

- Per protocol if no variations or deviations are scored.
- Acceptable if no variations are scored.
- Unacceptable if a deviation is scored.

6.5 Reporting Adverse Events *(fax #215/928-0153)*

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

6.5.2 All grade 3 *(severe)* and 4 toxicities *(life-threatening)* from the radiosurgery arm must be reported by telephone to Group Chairman, to RTOG Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.

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

6.5.4 Additional information is detailed in Appendix IV.

7.0 DRUG THERAPY

Not applicable.

8.0 SURGERY

Not applicable.

9.0 OTHER THERAPY

9.1 Dexamethasone

Patients should be placed on dexmethasone at the time of brain metastasis diagnosis. The starting dose should be 4-16 mg per day of dexamethasone in divided doses, or equivalent doses of other types of glucocorticoids. Steroids will be continued without taper throughout radiation therapy. At the completion of radiation therapy, a steroid taper will be initiated. In patient's who cannot tolerate taper and/or cessation of steroids, the steroid dose will be maintained at the lowest dose consistent with good medical practice.

9.1.1 *Chemistry*: Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, that are readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11, 17, 21-trihydroxy-16-methyl-pregna-1, 4-diene-3, 20-dione.

9.1.2 *Toxicity*: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, peptic ulcer, skin changes *(thinning)*, convulsions, vertigo, headache, endocrine abnormalities, ophthalmic changes, and metabolic changes.

9.1.3 *Formulation*: Dexamethasone is available in a variety of potencies in capsule or tablet form.

9.1.4 *Storage and stability*: Dexamethasone is to be stored at room temperature.

9.1.5 *Administration*: The drug is administered orally or intravenously.

9.2 Other Drugs

Other drugs including anticonvulsants and pain medications for treatment of systemic cancer may be given at the discretion of the patient's physician and must be recorded on the RTOG data forms. Hormonal therapy, including tamoxifen, is appropriate during protocol radiation therapy; however, chemotherapy for treatment of systemic cancers should be withheld during all phases of protocol treatment. No other treatment specifically for brain metastases should be given until a recurrence is detected.

10.0 PATHOLOGY (3/17/98)

Not applicable to this study.

11. 0 PATIENT ASSESSMENTS

11.1 Study Parameters (8/16/96)

Assessment	Pre Reg	WK 2	WK 4	MO 3	MO 6	MO 9	MO 12	MO 16	MO 20	MO 24+
History & Neuro Exam	X		X	X	X	X	X	X	X	X
MMSE	X[a]			X	X	X	X	X	X	X
Performance Status	X		X	X	X	X	X	X	X	X
CBC/differential, platelets	X		X	X	X	X	X	X	X	X
MRI of Head[b]	X[d]			X[d]	X[c,e]	X[c]	X[c,e]	X[c]	X[c]	X[c]
CTChest/Abdomen/Pelvis [c]	X									
Bone Scan[c]	X									

a. Pre treatment; obtain forms from HQ in advance.
b. Mandatory to establish number of brain metastases. Followup scans must also be MRI.
c. Strongly recommended *(must be MRI of the brain)*.
d. Submitted to RTOG for central review with lesion(s) delineated and numbered on the films.
e. Submitted to RTOG for central review *(if disease was stable at 3 months)* with lesion*(s) delineated and numbered on the films*.

11.2 Evaluation Points

11.2.1 All patients will receive general and neurological evaluations and a contrast-enhanced MRI two months following completion of radiation therapy *(3 months after randomization)* and at three month intervals to year one, then the interval will be increased to every four months.

11.2.2 Patient examinations at the completion of radiotherapy and thereafter at each interval evaluation as specified in Section 12.1. There will be a central review of the baseline and the three month post randomization imaging study.

11.3 Response rate for Central Review Only

11.3.1 *Complete response*: Total radiographic disappearance of brain metastasis *(es)* in conjunction with stabilization of the neurological examination and off glucocorticoids.

11.3.2 *Partial response*: Greater than 50% decrease in size of each metastatic lesion radiographically in conjunction with improvement or stabilition of the neurological examination without an increase in glucocorticoid dose.

11.3.3 *Stable disease*: A 0 to 50% decrease in size of each metastatic lesion radiographically in conjunction with improvement or stabilization of the neurological examination.

11.3.4 *Progressive disease*: A radiographic increase in the size in any metastatic lesion, the development of new intraparenchymal lesions or stable disease in conjunction with deterioration of the neurological examination. **All such patients should undergo further evaluation in an effort to distinguish radionecrosis from disease progression. If the distinction cannot be made, the Study Chair should be called and the imaging study submitted for central review.**

11.4 Recurrence

11.4.1 The reappearance of tumor on any MRI scan constitutes recurrent disease. The development of new intracranial metastatic foci or leptomeningeal disease also constitutes recurrent disease. Leptomeningeal disease must be documented by a positive CSF cytology, abnormal myelogram or spinal MRI.

11.4.2 All patients will be followed for evidence of neurological progression of symptoms and evidence of treatment failure. Patients who show 1) objective evidence of reappearance of the brain metastases, or 2) progression of hard neurological signs will be re-evaluated at that time. If a recurrence or new metastasis *(es)* is detected, further treatment may be given, consisting of chemotherapy, surgery, or additional radiation therapy including stereotactic radiotherapy at the discretion of the physicians involved in the patient's care.

11.5 Survival

The duration of survival will be from registration until death.

11.6 Cause of Death

Neurologic death verses non-neurologic death

11.6.1 *Neurologic death*: Patients will be considered to have died neurologic deaths if they had stable systemic disease and progressive neurologic disease consisting of expanding intracranial masses, CNS hemorrhages, hydrocephalus resulting in herniation or fulminant meningeal carcinomatosis.

11.6.2 *Non-neurologic death*: The systemic cancer, will be considered the cause of death, if in neurologically stable patients, fatal infections, extracranial hemorrhage, or vital organ failure develops.

11.7 Patient Assessment

11.7.1 Measures to be assessed will include the mini-mental status examination, changes in KPS, steroid dependence, radiographically documented recurrence of brain metastases, length of survival, and cause of death.

11.8 Criteria for Removal from Protocol Treatment

11.8.1 Unacceptable toxicity

11.8.2 The patient may withdraw from the study at any time for any reason.

12.0 DATA COLLECTION

12.1 Summary of Data Submission (3/17/98)

Item	Due
Demographic Form **(A5)**	Within 2 wks of study entry
Initial Evaluation Form **(I1)**	
Pathology Report **(P1)**	
Baseline Mini-Mental Status **(MS)**	
Treatment Planning MRI Scan **(MR)**	
Treatment Planning MRI Report **(ME)**	

Radiotherapy Form **(T1)**	Within 1 week of RT end
Final Dosimetry Information:	
Daily Treatment Record **(T5)**	
Isodose Distribution **(T6)**	
Calculation Form *(external beam)* **(TL)**	
External Beam Films *(simulation & portal)* **(TP)**	
Radiosurgery Calculations **(RS)** *(Arm 1)*	
Radiosurgery Placement Films **(RP)** *(Arm 1)*	
Post Treatment MRI Scan **(MR)**	At 2 months following completion of RT
Post Treatment MRI Report **(ME)**	
Follow-up Form **(F1)**	Every 3 months from treatment start for 1 Mini-year; q 4 months x 2 years, then annually.
Mental Status **(MS)**	
Also at progression/relapse and at death *(F1 only)*.	
Autopsy Report **(D3)**	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is overall survival.

13.1.2 Compare the site*(s)* of recurrence and cause of death between the two treatment regimens.

13.1.3 Compare the effect of the treatment regimens on neurologic function via the mini-mental status exam *(MMSE)*.

13.2 Sample Size (6/14/99, 11/13/00)

The primary endpoint of this trial is survival. The standard arm is WBRT, and the experimental arm is SRS+WBRT. An analysis of patients with brain metastases from four previous RTOG trials provides a median survival of 7.1 months for the WBRT arm. It is anticipated that the SRS+WBRT would provide a 50% improvement in median survival to 10.7 months. The estimated sample size[40] is 124 patients per arm. This sample size will ensure a 80% probability of detecting the specified improvement, if it exists, while rejecting the null hypothesis at the 95% level *(a=0.05, two-sided type I error)*. Assuming a 5% ineligibility/inevaluability rate, **the total sample size required is 262 randomized patients.**

This sample size assumes that no more than 5% of the patients randomized to SRS will not receive SRS. However, if more than 5% of the patients randomized to SRS do not receive SRS, then the sample size will be adjusted to account for the reduction in the observable difference. The subset of patients with solitary metastases are of interest to examine for treatment effect. Assuming 50% of the sample have solitary metastases, then 62 patients with a solitary metastasis will be sufficient per arm to detect a 75% improvement in median survival for patients treated with SRS + WBRT alone. This assumes exponential survival and a median survival of 8.9 months for patients with solitary metastases treated with WBRT alone.

In an interim analysis for the RTOG Data Monitoring Committee in January 1999, it was found that 10% of patients with solitary metastasis randomized to SRS did not receive SRS. In order to account for the reduced number of solitary metastases patient actually receiving SRS, then 85 solitary metastases patients actually receiving SRS, then 85 solitary metastasis patients per arm will be required. This adjusted sample is required to maintain at least 80% power to detect a 75% difference in median survival. **An additional 46 patients with a solitary brain metastasis will be accrued.**

Subsequently, in June of 2000, an interim analysis was performed for the RTOG Data Monitoring Committee and 15% of the patients with solitary metastases randomized to SRS did not receive SRS. Patients that are randomized to SRS but do not receive SRS will be analyzed in the SRS arm, but reduce the observable difference. In order to maintain at least 80% power to detect a 75% difference in median survival, then 188 patients *(94 patients per arm)* with solitary metastases will be required.

13.3 Inclusion of Women and Minorities (3/17/98)

There has been no suggestion an interaction beyond histology and tumor site; however the interaction will be examined in the final analysis. In conformance with the National Institute of Health *(NIH)* Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between gender/to race and treatments. The estimated accrual follows:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	0	1	15	3	85	1	105
Male	0	2	20	1	120	1	143
Unknown							
Total	0	3	35	4	205	2	248

13.4 Patient Accrual

The most recent RTOG phase III clinical trial *(RTOG 91-04)* in patients with brain metastases has accrued 8 patients per month and 11.5 patients per month in 1994. It is estimated that 75% of the RTOG 91-04 population will be eligible for this trial; therefore, a monthly accrual of 6 to 8.6 patients per month is expected. This trial should complete the accrual phase in 2.5-3.75 years. If the monthly accrual to this step is less than 3 cases per month, the study will be re-evaluated with respect to feasibility.

The rate of grade 3 or 4 CNS toxicities is expected to be 5-10%. If the rate of grade 3 or 4 CNS toxicities exceeds 15% or any grade 5 *(fatal)* CNS toxicities occur then the trial will be suspended for accrual. These adverse events will be reviewed by the Study Chair. The results will be reviewed by the RTOG Data Monitoring Committee *(DMC)* for consideration to re-open for accrual or to terminate accrual permanently.

13.5 Randomization Scheme

The treatment allocation will be one using a randomized permuted block within strata to balance for patient factors other than institution. The stratifying variables are number of CNS metastases *(single vs. two or three)* and extent of extracranial disease *(none vs. present)*.

13.6 Analyses Plans

13.6.1 *Interim Analyses of Phase III Data for Accrual and Toxicity*

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

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

13.6.2 *Interim Analyses of Study Endpoints*

There will be two interim analyses of the primary study endpoint *(survival)*. The interim analyses will be performed when all patients at the specified accrual have been on-study for at least six months. The interim analyses will proceed according to the following table[41]

Total Accrual	Significance Level
33%	0.00250
67%	0.00296

If any of the interim analyses exceeds the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be terminated. The results of these interim analyses will only be reported, in a blinded fashion, to the DMC. Through examining the above items, the DMC and the statistician can identify problems with the execution of the study. These will be reported to the Brain Committee, which is responsible for this study and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.6.3 *Analysis and Reporting of Initial Treatment Results* **(3/17/98)**

This major analysis will be undertaken when all patients have been on-study for a minimum of one year. The usual components of this analysis are:

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

Further subgroup analyses may be conducted *(depending upon the sample sizes within the subgroups)* for the purpose of identifying patterns of treatment responses. As specified in Section 13.2, an examination of outcome within patients with solitary metastases will be performed. Inevaluable patients *(do not start WBRT)* will be excluded from all analyses. Ineligible patients that receive either SRS or start WBRT will be analyzed for toxicity. The p-value of 0.04831 will be used, thus correcting for previous interim tests.

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APPENDIX I

RTOG 95-08

A PHASE III TRIAL COMPARING WHOLE BRAIN IRRADIATION WITH VERSUS WITHOUT STEREOTACTIC RADIOSURGERY BOOST FOR PATIENTS WITH ONE TO THREE UNRESECTED BRAIN 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 I have an opportunity to decide whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand that my diagnosis is a tumor in the brain which has spread from my previously diagnosed cancer and that further treatment is recommended. Radiation therapy is usually administered in daily doses 5 days per week for 2 to 4 weeks. Previous research studies have shown that different ways of administering the radiation therapy may produce greater tumor control or relief. Recent research has shown that administering radiotherapy as a boost *("sterotactic")* to the standard radiotherapy may help some patients with brain metastases. Stereotactic irradiation *(also known as radiosurgery)* is a radiotherapy technique which allows giving a single high dose of radiation to the tumor in the brain, while sparing most of the adjacent normal brain.

The purpose of this research study is to compare the results of radiation therapy followed by radiosurgery against radiation therapy alone.

DESCRIPTION OF PROCEDURES (9/8/98)

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

Treatment 1

I will receive radiation therapy once a day, five days a week for three weeks. Approximately one week later, I will receive radiosurgery. Radiosurgery will require wearing an apparatus, called stereotactic head frame, on my head which may remain in place 6-7 hours. This means having four perforations made in the outer part of my skull under local anesthesia. Following placement of the head frame, brain scans, such as CT or MRI scans, are done in order to pinpoint the tumor. After the treatment planning is completed, the stereotactic radiation treatment is given. The stereotactic frame is removed after the treatment. At the discretion of my treating physician, I may be admitted for overnight observation.

Treatment 2

I will receive radiation therapy once a day, five days a week for three weeks.

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.

Whole brain radiation therapy, frequently causes hair loss which may be permanent, nausea, alteration in taste, scalp irritation and fatigue. Occasionally, vomiting, headache, reddening and tanning of skin, drainage from ears, plugging of the ears with decreased hearing, memory loss and increased sleepiness *(lasting for several days up to 2 weeks, occurring 4-10 weeks after whole brain radiation therapy is complete)* occur. Rarely, cataracts and eye damage leading to blindness occur. A rare delayed effect of radiation to the brain is destruction of normal brain tissue with resulting effects including possible decrease in memory function.

If I am assigned to also receive stereotactic radiosurgery, I should be aware that stereotactic radiosurgery can cause the following side effects. 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)*. 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.

It is unknown what effects this treatment 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. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

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

My physician will explain any procedures related solely to research. 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	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 REACTION 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 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. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff *(215/574-3214)*. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the specific protocol for criteria to grade the severity of the reaction.

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

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

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 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.