RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-05

A PHASE III TRIAL COMPARING THE USE OF RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH BCNU TO CONVENTIONAL RADIOTHERAPY WITH BCNU FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-05

A PHASE III STUDY COMPARING STEREOTACTIC EXTERNAL BEAM IRRADIATION FOLLOWED BY CONVENTIONAL RT WITH BCNU TO CONVENTIONAL RT WITH BCNU FOR SUPRATENTORIAL GLIOMABLASTOMA MULTIFORME

SCHEMA

STRATIFY

Age

1. ≥ 18 to < 50
2. ≥ 50

Performance Status

1. Karnofsky 90-100
2. Karnofsky 60 to 80

RANDOMIZE

Arm 1: 60 Gy/30 fractions/2 Gy once daily, BCNU 80 mg/m^2 i.v. days 1,2,3 of RT then q 8 weeks for a total of 6 cycles.

Arm 2: Radiosurgery followed by 60 Gy/ 30 fractions/2 Gy once daily, BCNU 80 mg/m^2 i.v. days 1,2,3 of RT then q 8 weeks for a total of 6 cycles

Arm 1: For the first 46 Gy/23 fractions, the treatment volume should include the volume of contrast enhancing lesion and surrounding edema on pre-operative CT/MRI scan plus a 2 cm margin. After 46 Gy the tumor volume should include the contrast enhancing lesion *(without edema)* on the presurgery CT/MRI scan plus a 2.5 cm margin.

Arm 2: Radiosurgery dose will be prescribed to the isodose surface *(³ 50% to £ 90% of the maximum dose)* which encompasses the margin of the tumor. Radiosurgery doses will be tumor size dependent. *(See Section 6.2.2.1)*. Conventional radiotherapy will begin within one week of the date of radiosurgery.

BCNU will be given to both arms for a total of 6 cycles (maximum dose = 1440 mg/m^2).

ELIGIBILITY *(See Section 3.0 for details)*

- Histopathologically confirmed glioblastoma multiforme or gliosarcoma
- Supratentorial, well-circumscribed lesions, ≤ 4 cm
- Age ≥ 18
- KPS ≥ 60
- Life expectancy > 3 months
- No prior irradiation
- Hgb ≥ 10, absolute neutrophils ≥ 1500, platelets ≥ 100,000
- BUN ≤ 25, creatinine ≤ 1.5, bilirubin ≤ 2.0, SGOT ≤ 2 x normal
- Study-specific consent form
- Therapy must begin within five weeks of surgery.

Required sample size: **200**

Institution # _____

RTOG 93-05 **ELIGIBILITY CHECK (9/8/98)**

Case # _____ *(page 1 of 2)*

_____(Y) 1. Is there histologically-confirmed supratentorial glioblastoma multiforme or gliosarcoma?

_____(Y) 2. Diagnosis made by surgical biopsy or resection?

_____(N) 3. Does the tumor originate in the brain stem?

_____(N) 4. Is the tumor located within 10 mm of the optic chiasm?

_____(N) 5. Is the tumor recurrent or multifocal?

_____(Y) 6. Has a pre-surgical and a post-surgical CT *(with contrast)*/MRI *(with contrast)* been done?

_____(≤ 40) 7. Report the maximum diameter *(in mm)* of the tumor on the post-surgical contrast-enhanced scan.

_____(Y) 8. Will protocol therapy begin within 5 weeks of surgery?

_____(N) 9. Any prior radiotherapy to the head or neck?

_____(N) 10. Any prior chemotherapy?

_____(Y) 11. Has the patient recovered from the effects of surgery or any post-op complication?

_____(≥ 18) 12. Report the patient's age.

_____(Y) 13. Estimated survival of at least 3 months?

_____(≥ 60) 14. Report the Karnofsky.

_____(0-3) 15. Report the neurological function status.

_____(≥ 10) 16. Report the hemoglobin *(gms)*.

_____(≥ 1500) 17. Report the absolute neutrophil count *(per mm^3)*

_____(≥ 100) 18. Report the platelet count *(x 1000)*

_____(≤ 25) 19. Report the BUN *(mg%)*

_____(≤ 1.5) 20. Report the creatinine *(mg%)*

_____(≤ 2) 21. Report the bilirubin *(mg%)*

_____(Y) 22. Is the SGOT or SGPT less than twice the normal range?

_____(Y/N) 23. Is the chest x-ray abnormal and/or is there a history of pulmonary disease?

_____(Y) If yes, have pulmonary studies been performed and found to be within the range specified in the protocol?

Institution # _____

RTOG 93-05 **ELIGIBILITY CHECK (9/8/98)**

_____(N/Y) 24. Has the patient had a prior or concurrent second malignancy except for non-melanomatous skin cancers or carcinoma in situ of the uterine cervix?

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

_____(N) 25. Does the patient have AIDS?

_____(N) 26. Any major medical illness or psychiatric impairments which in the investigator's opinion will prevent administration or completion of protocol therapy or would interfere with follow-up?

_____(Y) 27. Has the patient signed a study-specific informed consent?

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # *(if different)*

_____ Medical Oncologist's Name

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code *(9 digit if available)*

_____ Method of Payment

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

_____ Treatment Start Date

_____ Treatment Assignment

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Malignant gliomas constitute the most common group of primary brain tumors. Even when managed with the best available therapeutic modalities, including surgery, radiation therapy, and chemotherapy, treatment of these astrocytic tumors remains difficult and frustrating. Patients with malignant gliomas have an extremely poor prognosis.

1.2 Radiation therapy remains the most effective adjuvant modality in the management of malignant gliomas[1] and the overall patient survival time is directly correlated with the total dose delivered.[2] However, further increase in the total dose is limited by rapid increase of late normal tissue damage. Recently, there has been a growing interest in alternative forms of radiation treatment, such as hyperfractionation[3-5] and accelerated fractionation.[6] Both strategies use multiple daily fractions of radiotherapy in smaller than conventional daily dose fractions, enabling the delivery of higher total doses with late toxicity no different from that of conventional radiotherapy. An ongoing RTOG phase III trial is presently comparing hyperfractionation with conventional radiation therapy *(RTOG 90-06)*.

1.3 Considering that 90% of recurrences in malignant gliomas are located within 2 cm of the enhancing edge of the original tumor on CT scans,[7,8] and that the occurrence of multicentric disease or metastatic spread is rare,[9-11] treatments that irradiate a localized tumor to a high dose with a minimal irradiation of adjacent normal brain tissues are an attractive alternative that may improve the therapeutic ratio.

1.4 *Interstitial brachytherapy* has been shown to improve local control and survival in selected patients with malignant gliomas. Gutin et al.[12] from the University of California, San Francisco, treated 41 patients with recurrent malignant gliomas *(18 glioblastoma multiforme)* using stereotactic interstitial implants. The median survival times were 52 weeks and 153 weeks for patients with glioblastoma multiforme and anaplastic astrocytoma, respectively. Despite the prolonged median survivals, the high incidence of focal radiation necrosis with 41% of the patients requiring reoperation is of concern. Gutin et al.[13] have also recently reported their experience in a non-randomized trial on the use of brachytherapy as a boost to external irradiation in patients with newly diagnosed high grade gliomas. Of the 101 evaluable patients with unifocal, well-circumscribed lesions, 63 received the combined approach. From the authors' analysis, it appears that a brachytherapy boost may improve median survival of some patients with glioblastoma multiforme but its value for anaplastic astrocytomas remains uncertain. Nearly 50% of the patients in the combined modality treatment group required reoperation for tumor progression and/or necrosis.

1.5 Another possible approach to higher dose treatment is *stereotactic external beam irradiation* (SEBI), also called "radiosurgery". The term radiosurgery has been used to describe a variety of radiotherapy techniques characterized by the accurate delivery of high doses of radiation, usually in a single session, to stereotactically defined small intracranial targets *(usually £ 40 mm in maximum diameter)* in such a way that the dose fall-off outside the targeted volume is very sharp. Radiosurgery is a relatively simple, non-invasive treatment technique, usually performed on an out-patient basis. Reviews articles dealing with the physical and clinical aspects of radiosurgery have been published.[14-16] Since a large number of patients are not eligible for brachytherapy because of tumor location, radiosurgery may prove to be an excellent alternative to brachytherapy as a way to deliver a boost following external beam radiotherapy for patients with malignant gliomas.

1.6 The RTOG is presently conducting a phase I dose escalation study of SEBI *(RTOG 90-05)* for the treatment of recurrent primary brain tumors and CNS metastases *(maximum tumor diameter £ 40 mm)* in patients who have previously received irradiation to the brain. SEBI doses are dependent on the maximum tumor diameter and will be escalated in increments of 1.5 Gy to 3.0 Gy based on incidence of ≥ grade III CNS toxicity. The frequency of patients developing ≥ grade 3 acute CNS toxicity is the primary endpoint of the study. At the first dose level, treatments were well tolerated and SEBI dose has been escalated from 12 Gy to 15 Gy in patients with 31-40 mm tumors, from 15 Gy to 18 Gy for patients with 21-30 mm tumors and from 18 Gy to 21 Gy in patients with tumors diameters of ≤ 20 mm.

1.7 Recently, Loeffler et al.[17] reported their preliminary results of radiosurgery used in the initial management of patients with malignant gliomas. Selected patients with performance status ≥ 60% and with small, circumscribed lesions, not otherwise eligible for brachytherapy because of tumor location, received conventional external beam irradiation *(59.40 Gy/33 fractions)* followed 2 to 4 weeks later by radiosurgery. Radiosurgery doses were tumor size dependent and ranged from 11 Gy for a 40 mm diameter tumor to 20 Gy for a 15 mm diameter lesion. Doses were prescribed at the edge of the enhancing lesion, as seen on imaging studies, with a 2 to 4 mm margin on each planar contour. Of the 37 patients who entered the study, 28 *(75.5%)* were alive and clinically stable at a median follow-up time of 19 months. Seven patients *(19%)* underwent a reoperation at a median time of 5 months after radiosurgery. Histologic findings of necrosis were seen in only 2 of these patients, whereas the other 5 patients had viable tumor cells. Four of the reoperated patients were alive at 10 to 16.5 months post-surgery.

1.8 Considering that a large proportion of patients *(37.5%)* are unable to undergo interstitial implantation following external beam irradiation, usually because of disease progression,[13] the upfront use of radiosurgery followed by conventional irradiation may prove to be a better strategy in the management of these tumors, allowing for treatment of all eligible patients.

1.9 The purpose of this study is to compare the use of radiosurgery followed immediately by conventional external beam irradiation to conventional external irradiation, with BCNU delivered in both arms of the study.

1.10 Mini-Mental Status Examination *(MMSE)* and the Spitzer Quality of Life Index *(SQLI)* have been piloted at the Joint Center for Radiation Therapy, Harvard Medical School, Boston, MA in glioma patients and are presently being assessed.
The MMSE can be done in less than five minutes during follow-up visits and has been administered in the medical community to test cognitive ability for many years.
The SQLI was selected for its brevity, reliability, extensive use and the fact that it is a global instrument that captures the three components of health outlined in the World Health Organization definition. The use of this simple self-report measure which can be used by clinicians allows comparison across a variety of cancer trials. Although reliability and validity have been demonstrated, response variation on social functioning items is limited[24] and the total score correlates more with physical rather than psychosocial functioning.[25] Therefore it provides a more global measure of physical functioning.

1.11 **(1/31/96)** 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 21 24	12 18 10	0 0 0	0 6 10	0 6 10
21-30	15 18 21 24	15 15 13 12	7 0 7 33	7 20 31 8	14 20 38 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 use of radiosurgery given prior to conventional radiotherapy with BCNU improves upon the overall survival of conventional radiotherapy plus BCNU.

2.2 To determine and compare the frequency and severity of toxicities of these approaches.

2.3 To compare the effect of treatment regimens on neurologic function and quality of life.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (1/31/96)

3.1.1 Histopathologically confirmed supratentorial glioblastome multiforme or gliosarcoma. Patients with astrocytoma with atypical or anaplastic features *(AAF)* are not eligible.

3.1.2 Diagnosis must be made by surgical biopsy or resection.

3.1.3 The patient must have recovered from the effects of surgery or any post-operative complication before entry into the study.

3.1.4 Therapy must begin within five weeks of surgery.

3.1.5 A diagnostic contrast enhanced CT or MRI scan must be performed preoperatively and post-operatively prior to initiation of radiotherapy, including radiosurgery.

3.1.6 The contrast enhancing tumor must be well circumscribed with a maximum diameter *(in any direction)* on the enhanced scan of ≤ 40 mm. Patients whose contrast enhancing tumor are rendered ≤ 40 mm after surgical resection are also eligible.

3.1.7 No previous radiotherapy to the head and neck area or chemotherapy.

3.1.8 Age ≥ 18 years.

3.1.9 Life expectancy ≥ 3 months.

3.1.10 Karnofsky performance status ≥ 60 *(Appendix II)*

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

3.1.12 Adequate bone marrow reserve *(hemoglobin ³ 10 grams, absolute neutrophil count ³ 1500/mm^3, platelets ³ 100,000/mm^3)* and acceptable renal *(BUN £ 25 mg, creatinine £ 1.5 mg)* and hepatic function *(bilirubin £ 2.0 mg, SGPT or SGOT £ twice normal range).*

3.1.13 Normal chest x-ray. If the chest x-ray is abnormal and/or there is a history of pulmonary disease, the pulmonary studies should be performed including D_LCO *(diffusion - lung carbon monoxide)* should be more than 75% of predicted value. If anemia is present to the extent that the hemoglobin is less than 10 grams, correction by transfusion is allowed before entry into the study.

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

3.2 Ineligibility Criteria (6/30/95)

3.2.1 Well differentiated astrocytomas

3.2.2 Astrocytoma with atypical or anaplastic features *(AAF).*

3.2.3 Patients with tumors that originate in the brain stem or are located adjacent*(within 10 mm)* to the optic chiasm.

3.2.4 Infratentorial tumors.
3.2.5 Multifocal malignant glioma.
3.2.6 Recurrent malignant glioma.
3.2.7 Patients whose tumors are > 40 mm, as measured on a postoperative CT/MRI study.
3.2.8 Patients whose tumors do not enhance on a postoperative CT or MRI study.
3.2.9 Patients with previous malignancies, except for non-melanomatous skin cancers and carcinoma *in situ* of the uterine cervix unless disease-free for ≥ 5 years.
3.2.10 Major medical illnesses or psychiatric impairments which in the investigator's opinion will prevent administration or completion of the protocol therapy and would interfere with follow-up.
3.2.11 Start of therapy more than five weeks after surgery.
3.2.12 Inability to obtain a histologic proof.
3.2.13 Patients with Acquired Immune Deficiency Syndrome *(AIDS)*.

4.0 PRETREATMENT EVALUATIONS

4.1 Complete history and physical examination with a detailed neurologic exam
4.2 CT or MRI scan with contrast performed preoperatively and postoperatively prior to the initiation of radiotherapy. Only patients with tumors ≤ 40 mm postoperatively are eligible.
4.3 CBC with differential, platelet count, blood chemistries to include AST, total bilirubin and creatinine *(SMA-12)*.
4.4 Chest x-ray.
4.5 MMSE and SQLI

5.0 REGISTRATION PROCEDURES

5.1 A RTOG Stereotactic Facility Questionnaire must be received at RTOG Headquarters for each institution prior to entering any patients on this study *(Appendix IX)*.
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
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY PARAMETERS

6.1 Standard Radiotherapy

6.1.1 **Conventional Radiotherapy must begin within 5 weeks of surgery**. **(2/14/95)** One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy. All portals shall be treated during each treatment session. This conventional external beam irradiation regimen will be identical for both arms. For those patients receiving radiosurgery, conventional radiotherapy must begin within one week from the date of radiosurgery.

6.1.2 *Physical factors*
Treatment shall be delivered with megavoltage machines of energy ranging from 4-10 MV photons. Selection of appropriate photon energy(ies) should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies >10 MV should be used only in dual energy beam arrangements using at least one beam with energy ≤ 10 MV.[19] Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Electron, particle or implant boost is not permissible.

6.1.3 *Localization, Simulation, and Immobilization*
The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy

and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative CT/MRI. The initial target volume shall include the contrast enhancing lesion and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0 cm margin. **If no surrounding edema is present, the initial target volume in both treatment arms should include the contrast enhancing lesion plus a 2.5 cm margin.**

Arms 1 and 2: For the first 46 Gy/23 fractions the treatment volume should include the volume of contrast enhancing lesion and surrounding edema on preoperative CT/MRI scan plus a 2 cm margin. After 46 Gy the tumor volume should include the contrast enhancing lesion *(without edema)* on the presurgery CT/MRI scan plus a 2.5 cm margin.

6.1.4 *Treatment Planning*

Treatment plans may include a wedge pair of fields, rotation, or multiple field techniques. Straight opposed lateral fields are not recommended and should be avoided. CT or MRI guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores at headquarters reviews. Isodose distribution for the initial target volume and conedown target volume are required on all patients, including those treated with parallel opposed fields. The inhomogeneity across the target volume should be kept to a minimum. The minimum dose to the target volume should be kept within 5-10% of the dose at the center of the volume *(see Appendix VI)*.

The use of a vertex fields require either a diagram or photograph of treatment position to be submitted to RTOG Headquarters.

6.1.5 *Dose Specification*

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

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

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

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

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

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

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

6.1.6 *Dose Limitation to Critical Structures*

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

6.2 Radiosurgery

6.2.1 **Radiosurgery must be performed within 5 weeks of surgery**. **(2/14/95)** Only those patients whose tumors are ≤ 40 mm, as measured by a post-operative CT/MRI, are eligible to enter the study. Conventional radiotherapy must begin within one week from the date of radiosurgery.

6.2.2 *Total Dose Determination*

6.2.2.1 The total dose will depend on the size of the target volume and will be defined as follows:

Maximum Tumor Diameter	Dose **(1/31/96)**
≤ 20 mm	24 Gy
21-30 mm	18 Gy
31-40 mm	15 Gy

6.2.3. There are a variety of SEBI techniques which all have similar goals and include treatment of small volumes, use of a high dose in a single session, high dose gradients at the field edges, and intersection of multiple beams at a commom intracranial point. All institutions participating in this study must:

6.2.3.1 Fill out the RTOG stereotactic radiotherapy facility questionnaire prior to enrolling patients in the study *(see Appendix IX)*.

6.2.3.2 Utilize stereotactic frame placement for imaging procedures and treatment delivery.

6.2.3.3 Perform target localization using stereotactic CT scan or MRI.

6.2.3.4 Have a treatment planning system capable of generating isodose distributions in three dimensions for a given treatment.

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

6.2.4.1 Target volume and isocenter determination will be based on a CT scan with contrast or MRI with the patient's head in a stereotactic frame. The imaging study used to deliver the radiosurgical treatment must be the same imaging study used to determine the post-operative tumor size.

6.2.4.2 Stereotactic CT slice thickness may not exceed 5 mm.

6.2.4.3 The target volume will include the enhancing portion of the biopsied or residual primary brain tumor without margin. Surrounding areas of edema will not be considered part of the target volume.

6.2.4.4 The target volume *(mm^3)* will be determined on serial CT or MRI images.

6.2.5 *Dose Prescription and Dosimetry Requirements*

6.2.5.1 The dose will be prescribed to the isodose surface *(50% to 90%)* which encompasses the margin of the tumor, as defined by the imaging studies. For multiple isocenters, the maximum dose must be normalized to 100% and dose prescribed to the 50% to 90% isodose surface. The 100% *(maximum)* dose will be recorded for each patient. The prescription dose shall be delivered to the 50% to 90% *(maximum = 100%)* isodose surface, and is defined as the minimum dose to the target volume. This 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.

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

6.2.6.1 Submit either of the following:

a. Isodose distributions calculated at the center of the target in the transverse, coronal, and sagittal planes.

b. Isodose distributions calculated through the target in at least three transverse plnes including:

i. through the isocenter for single isocenter treatments, and through the target center for multiple isocenter treatments.

ii. through a plane halfway between the superior aspect and center of the target.

iii. through a plane halfway between the inferior aspect and the center of the target volume.

6.2.6.2 The isodose distributions on the three planes required shall be superimposed on CT or MR anatomy, and shall include isodose lines *(in % dose or dose)* that correspond to 100%, 90%, 80%, and 50% of the prescription dose *(for examples, see Appendix VII).* It is intended that these data are of sufficient quality that the physician reviewer can judge the adequacy of target coverage by the dose distribution.

6.2.6.3 Submit dose-volume data in tabular form, showing the accumulated volumes of those elements within the target volume receiving dose in 1 or 2 Gy dose intervals. If prescription dose is 15 Gy and 2 Gy dose intervals are used to report dose-volume data, then the volume receiving 15 Gy should additionally be reported. These data may either be differential or cumulative dose-volume statistics. State the dose matrix voxel size *(for example, see Appendix VIII).*

6.2.6.4 Submit dose-volume data in tabular form, showing the accumulated volumes of those elements within the *treated* volume receiving dose in 1 or 2 Gy dose intervals. If prescription dose is 15 Gy and 2 Gy dose intervals are used to report dose-volume data, then the volume receiving 15 Gy should additionally be reported. These data may either be differential or cumulative dose-volume statistics, and shall be for the global treatment volume, including the target volume. State the dose matrix voxel size and also state the lower dose cutoff for the data, as limited by the size of the calculation matrix or the cranium *(for example see Appendix VIII).*

6.3 Radiosurgery Quality Assurance Review

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.

6.3.1 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.

6.3.2 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 deviation*.

6.3.3 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.

6.3.4 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.

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

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

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

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

6.4 Acute Radiation Toxicities

6.4.1 Expected toxicities include loss of hair and erythema of the scalp. Reactions in the ear canals and on the ear should be observed and treated symptomatically.

6.4.2 Both acute and delayed or late reactions to radiotherapy are to be recorded and included in the complete toxicity evaluation *(see Appendix IVb).*

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

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

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

6.5.2 All life threatening *(grade 4)* toxicities from the radiosurgery arm must be reported by telephone to the 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 if requested a written report, must be submitted to Headquarters within 10 working days of the reported incident.

6.5.3 Additional information is detailed in Appendix V.

7.0 CHEMOTHERAPY

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

7.1 BCNU Administration

7.1.1 *BCNU (bis-chlorethyl nitrosourea)* is available commercially.

7.1.2 *Schedule*

7.1.2.1 BCNU dose is calculated upon actual weight.

7.1.2.2 BCNU *(80 mg/m^2)* will be administered on days 1, 2, and 3 of the first week of radiotherapy and repeated on days 56, 57, 58. It will then be administered every 8 weeks for four cycles for a total of six cycles *(maximum BCNU dose 1440 mg/m^2).* The BCNU administered on days 1, 2, and 3 of the first week of radiotherapy can be given any time those days.

7.1.2.3 BCNU will be given as an intravenous infusion over 1-2 hours at a dose of 80 mg/m^2 per day per each 3 day course.

7.1.2.4 BCNU should be reconstituted by adding 3 ml of accompanying diluent *(absolute ethanol),* then 27 ml of sterile water for injection, USP. This results in a concentration of 100 mg/30 ml. For

infusion, dilute total dose in 250 ml of 5% Dextrose in water, USP, or Sodium Chloride injection, USP in glass bottle. Severe local discomfort can occur especially during infusion in less than 100 ml of fluid. The final dosage form prepared in glass at 0.2 mg/ml is stable for 48 hours at 4° C and for 8 hours at room temperature.

7.1.3 *Discontinuation of BCNU*

At documentation of progress, BCNU is discontinued. At the discretion of the investigator, the patient may be treated with additional chemotherapy, surgery, or supportive care. Such therapy shall be documented in detail and reported to RTOG on the appropriate data forms.

7.2 BCNU Toxicity

7.2.1 Possible progressive pulmonary toxicity may occur with BCNU chemotherapy. The risks of developing pulmonary toxicity appear to increase sharply above a total cumulative dose of 1200-1500 mg/m^2. Pulmonary toxicity usually presents as progressive interstitial pneumonitis and interstitial fibrosis on chest x-ray. Worsening pulmonary function tests or progressive pulmonary symptoms should alert the investigator to consider stopping BCNU. It is mandatory that BCNU be stopped at a maximum of 1440 mg/m^2 *(6 cycles at 80 mg/m^2 x 3 days)* or one full year of therapy. If symptoms or signs of BCNU toxicity occur, chest x-ray and pulmonary function studies including D_LCO should be obtained to document toxicity.

7.2.2 Toxicities may include myelosupression which may be delayed and severe; mild to moderate nausea and vomiting 2-12 hours after administration; mild and reversible liver enzymes changes; alopecia; pain along the vein of injection; pulmonary impairment; and very rarely renal impairment.

7.3 Dose Modification

7.3.1 There will be no dose escalation.

7.3.2 Dose reduction due to hematologic toxicity: The blood counts immediately prior to the next cycle of chemotherapy and the nadirs from the weekly CBC and platelets recorded in the previous cycle will both be examined to determine whether the next cycle of chemotherapy is to be given at a reduced dose. The dose modifications will be as follows:

7.3.2.1 **Nadir:**

Absolute Neutrophil Count *(ANC)*		Platelets	Modification
≥ 750	and	≥ 75,000	100% dose
250 to < 750	or	25,000 to < 75,000	75% dose
< 250	or	< 25,000	50% dose

7.3.2.2 **At scheduled time of administration**:

Absolute Neutrophil Count	Platelets	Modification
≥ 1500	and	≥ 100,000	Dose modified for nadir only
< 1500	or	< 100,000	Hold dose for two weeks* and repeat

7.3.2.3 ***After 2 weeks:**

Absolute Neutrophil Count		Platelets	Modification
≥ 1500	and	≥ 100,000	Dose modified for nadir
1000 to < 1500	or	75,000 to < 100,000	75% dose
< 1000	or	< 75,000	Contact chemotherapy Chairman before further chemotherapy administration

7.3.3 Repetition of severe marrow depression, persistent neutropenia *(< 1500)* or thrombocytopenia *(< 25,000)* at time of treatment and after dose reduction shall require contacting the chemotherapy chairman before any further chemotherapy. Further chemotherapy shall be given only if there is joint agreement between the Chemotherapy Study Chairman and the individual Investigator.

7.3.4 When liver enzyme *(AST, or total bilirubin)* level is greater than 3 times the upper limit of the institutional normal value, BCNU should be held until AST drops to less than 2 times the upper limit of normal and bilirubin drops within the normal range. Then, BCNU should be administered at 50% of previous dose level.

7.3.5 All dose modifications made for nadir counts or counts at the time of administration must be maintained in all subsequents cycles of chemotherapy. Any subsequent modifications must be made on already reduced dose levels.

7.4 Adverse Drug Reaction Reporting Guidelines (7/1/94, 2/14/95)

7.4.1 The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

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

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

7.4.1.3 Any death on study if clearly related to the commercial agent(s).

7.4.1.4 Acute myeloid leukemia *(AML)*. The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogentics, etc. and protocol identification.

7.4.2 The ADR report should be documented on FDA Form 3500 *(Appendix V)* and mailed to:

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

8.0 SURGERY

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

9.0 OTHER THERAPY

9.1 Steroids and anti-seizure medications may be given as clinically indicated. The total dose must be recorded pre-treatment, and at the time of each treatment evaluation. Steroids will be used in the smallest dose which will afford the patient satisfactory neurologic function and the best possible quality of life.

9.2 Local anesthetic during stereotactic frame placement.

9.3 Infections are to be treated with appropriate antibiotics and recorded.

9.4 Analgesics and any other medications are to be specified, and their dose recorded.

10.0 PATHOLOGY (6/30/95, 9/8/98)

10.1 RTOG Tissue Bank

10.1.1 Patients entered on this study are eligible for the RTOG Tissue Bank.

10.1.2 The following must be provided:

10.1.2.1 One paraffin block of tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.

10.1.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the RTOG Tissue Bank.

10.1.3 To encourage compliance, your Pathology Department will be reimbursed for obtaining blocks or cutting slides. Contact RTOG Administration.

10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request *(pathology blocks belong to the patient from whom tissue has been removed).*

10.1.5 Materials will be sent to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (7/1/94, 3/1/96)

Assessment	Prior to Therapy	During RT	Prior to each chemo cycle	At each Follow-up
History and PE	X		X	X
Neurological exam[a], KPS	X	weekly	X	X
Evaluation of skin within RT treatment portals	X	weekly		X
CBC including differential	X	weekly	X[c]	X
Serum chemistries including serum creatinine, AST, & total bilirubin	X		X	
Chest X-ray	X		As ind.	As indicated
CT scan with contrast and/or gadolinium enhanced and T2 weighted MRI	X *(Both pre-operat. and post-operat. pre-radiotherapy)*			q 4 mos through year 2, q 6 mos. in yrs. 3-5, then annually. Also at time of neurologic deterioration unless the last CT/MRI had been done within 1 mo. and was compatible with recurrence *(11.2.2)*
Quality of Life	X	X[b]		X

a. To include recording of steroid and anticonvulsant dose.
b. At six weeks, 3 months, then at each followup.
c. Also weekly per Section 7.3.2.

11.2 Evaluation During Study

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

11.2.2 The contrast enhanced CT or MRI of the brain shall be obtained prior to surgery, and post-operatively *(prior to radiotherapy, including radiosurgery)*, every four months through year 2,every six months for 3 years, then annually and at the time of neurologic deterioration unless the last CT/MRI done was within one month and was compatible with recurrence. Note: the first post RT scan must be done **4 months from beginning of RT.** Attention is drawn to the ocurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post treatment and last up to 6-8 weeks. These transient adverse signs and symptoms may spontaneously improve without therapy. They are considered to be due to transient demyelination.[18] Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation **(7/1/94)**.

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

11.3 Criteria for Evaluation of Therapy Effectiveness

11.3.1 Tumor response and regrowth can frequently be difficult to measure directly. Serial neurological exams and CT/MRI scans may provide a guide to the actual course. Time interval to progression will be measured from the first day of treatment until deterioration is documented by the individual investigator using these guides. **The patient should consistently be followed with the same diagnostic imaging study.**

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

11.3.3 Overall survival will be measured from randomization until death.

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

11.4 Post-mortem examination of the cranial contents should be obtained at death whenever possible to evaluate effects of this therapy on malignant and normal brain tissue.

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

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

11.5.1 *Orientation*

1. Ask for the year, season, date, day, month: Then ask specifically for parts omitted, e.g., "Can you also tell me what season it is?" One point for each correct.
2. Ask in turn, "Can you tell me the name of this department?" (state, county, town, hospital, floor). One point for each correct.

11.5.2 *Registration*

Ask the patient if you may test his memory. Then say the names of 3 unrelated objects, clearly and slowly, about one second for each. After you have said all 3, ask him to repeat them. This first repetition determines his score (0-3) but keep saying them until he can repeat all 3, up to 6 trials. If he does not eventually learn all 3, recall cannot be meaningfully tested.

11.5.3 *Attention and Calculation*

Ask the patient to begin with 100 and count backward by 7. Stop after 5 subtractions *(93, 86, 79, 72, 65)*. Score the total number of correct answers. If the patient cannot or will not perform this task, ask him to spell the word "world" backward. The score is the number of letters in correct order, e.g., dlrow=5, dlorw=3.

11.5.4 *Recall*

Ask the patient if he can recall the 3 words you previously asked him to remember in the registration section. Score 0-3.

11.5.5 *Language*

NAMING: Show the patient a wrist watch and ask him what it is. Repeat for pencil. Score 0-2.
REPETITION: Ask the patient to repeat the sentence after you. Allow only one trial. Score 0-1.

11.5.6 3-Stage Command

Give the patient a piece of plain blank paper and ask him to follow your instructions. Score 1 point for each part correctly executed.

11.5.7 *Reading*

On a blank piece of paper, print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask him to read it and do what it says. Score 1 point only if he actually closes his eyes.

11.5.8 *Writing*

Give the patient a blank piece of paper and ask him to write a sentence for you. Do not dictate a sentence. It is to be written spontaneously. It must contain a subject and a verb and be sensible. Correct grammar and punctuation are not necessary.

11.5.9 *Copying*

On a clean piece of paper, draw two intersecting pentagons, each side about 1 inch, and ask him to copy it exactly as it is. All 10 angles must be present and 2 must intersect to score 1 point. Tremor and rotation are ignored.

11.5.10 Estimate the patient's level of sensorium along a continuum, from alert on the left to coma on the right, by drawing a vertical line at the appropriate point in the horizontal line.

11.6 Instructions for Completing the Spitzer Quality of Life Index *(SQLI)*

11.6.1 This form is given to the patient to be completed. If the patient cannot come in for followup, the form may be mailed to him/her for completion. If the patient cannot complete the form at all, the reason must be recorded.

11.6.2 Review the questionnaires and instructions with the patient and significant other or family.

11.6.3 Review the scheduled intervals at which the questionnaire is required.

11.7 Ineligible and Inevaluable Patients

11.7.1 Patients that are randomized and retrospectively found to be ineligible for this trial may discontinue forms submission upon notification of ineligiblity from HQ. Data until that point, however, must be submitted to RTOG.

11.7.2 Patients that are cancelled and removed from the study will be excluded from all analyses. No data will be required by RTOG.

12.0 DATA COLLECTION (6/30/95, 9/8/98)

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Initial Mini-Mental Status Evaluation **(MS)** Initial Spitzer Questionnaire **(PQ)** Pretreatment CT/MRI scan *(both pre-and post-surgery)* **(C1)** and reports **(C3)**	Within 1 week of study entry
Initial Evaluation Form **(I1)** Pathology Report **(P1)** Block/Slides **(P2)**	Within 2 wks of study entry
Preliminary Dosimetry Information: RT Prescription (Protocol Treatment Form) **(T2)** Films *(simulation and portal)* **(T3)** Calculations **(T4)**	Within 1 wk of start of RT
Mini-Mental Status Evaluation **(MS)** Spitzer Questionnaire **(PF)** Radiotherapy Form **(T1)** Final Dosimetry Information: Daily Treatment Record **(T5)** Isodose Distribution **(T6)** Boost Films *(simulation and portal)* **(T8)** Radiosurgery Calculations and Isodose **(TL)** *(Arm 2)* Radiosurgery Placement Scans **(TP)** *(Arm 2)*	Within 1 week of RT end
Medical Oncology Flowsheet **(M1)**	Monthly for first 3 months, then q 3 months x 3 to 1 year
Follow-up Form **(F1)** Mental Status Evaluation **(MS)** Spitzer Questionnaire **(PF)** relapse. An F1 will be due at	Every 3 months from treatment Mini-start for 1 year; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/ death.
Autopsy Report **(D3)**	As applicable

12.2 CT/MRI Submission

The CT *(with contrast)*/MRI taken before surgery and after-surgery-before-radiotherapy begins must be submitted within one week of randomization. The calendar specifies CT/MRI PRE-RX, this means both set of scans with corresponding reports. For those patients randomized to Arm 2 *(radiosurgery arm)* the stereotactic CT/MRI performed for target volume determination must also be submitted. A subsequent scan four months from the date of the start of external beam RT must be submitted to Headquarters. CT/MRI must also be done and submitted for documentation of initial progression, neurologic deterioration *(unless the last CT/MRI had been done within one month and was compatible with recurrence)* and/or suspected toxicity. **The patient should consistently be followed with the same diagnostic study.**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is overall survival.

13.1.2 The frequency and severity of toxicities will be examined and compared 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) and on quality of life via the Spitzer Index *(SQLI)*.

13.2 Sample Size

The primary endpoint of this trial is survival. The standard arm (1) is radiotherapy plus BCNU *(RT+BCNU)*, and the experimental arm (2) is radiosurgery followed by radiotherapy plus BCNU *(RS+ RT+BCNU)* . An analysis of patients with glioblastoma multiforme *(GBM)* malignant glioma from RTOG 83-02[20] provides a median survival of 12.5 months for the RT+BCNU arm. Loeffler, et al.[17] used a treatment regimen similar to RS+ RT+BCNU and observed a median survival of 26 months in GBM patients. However, a greater than 100% improvement in median survival may not extend to a multi-institutional setting; therefore, this trial will test for a 50% improvement to 18.75 month median survival. The estimated sample size[22] is 95 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, one-sided type I error)*. Assuming a 5% ineligibility/inevaluability rate, **the total sample size required is 200 patients.** Quality of life and neurologic function will be assessed by the instruments listed in Section 13.1.3. It is estimated that approximately 75% of all randomized cases will participate in the quality of life component. Therefore, there should be a sufficient number of patients to detect a clinically significant difference in quality of life or change in neurologic function between the two arms.

13.3 Patient Accrual

The patient accrual is projected to be 5 patients per month, based upon the accrual of this patient group to RTOG 90-05 and RTOG 83-02. This trial should complete the accrual phase in 3 years. If the monthly accrual is less than 3 cases per month, the study will be re-evaluated with respect to feasibility.

13.4 Randomization Scheme

The treatment allocation will be one using a randomized a permuted block within strata to balance for patient factors other than institution. The stratifying variables, which have been identified in a previous database analysis[26] are age *(< 50 versus = 50)*, and KPS *(60-80 versus 90-100)*.

13.5 Analyses Plans

13.5.1 *Interim analyses of accrual and toxicity data*

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results 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 status of patients with repect to evaluability; c) the distribution of patients with respect to pretreatment characteristics; d) compliance rate of treatment delivery with respect to the protocol prescription; e) the frequency and severity of the toxicities.

13.5.2 *Interim analyses of study endpoints*

There will be two interim analyses of the primary study endpoint *(survival)*. The interim analyses will proceed according to the following table[23]

Total Accrual	Significance Level
50%	0.00250
100%	0.00296

If any of the interim analyses exceeds the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be terminated. The results of these interim analyses will only be reported, in a blinded fashion, to the RTOG Data Monitoring Committee *(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 responsible for this study and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.5.3 *Analysis and reporting of initial treatment results*

This major analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. 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 sizes within the subgroups)* for the purpose of identifying patterns of treatment responses. The p-value of 0.04831 will be used, thus correcting for previous interim tests. Inevaluable patients will be excluded from all analyses. Ineligible patients who completed radiosurgery and/or external radiation therapy will be evaluated for toxicity. All ineligible cases will be excluded from outcome analyses. The analyses of quality of life data will utilize principal components, analysis of variance, and regression procedures to assess differences in the treatment groups and relationship with other clinical measures.

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*** 1/31/96**

APPENDIX I

A PHASE III TRIAL COMPARING THE USE OF RADIOSURGERY FOLLOWED BY CONVENTIONAL RADIOTHERAPY WITH BCNU TO CONVENTIONAL RADIOTHERAPY WITH BCNU FOR SUPRATENTORIAL GLIOMABLASTOMA MULTIFORME

RTOG 93-05

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

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

Recent research has shown that alternate ways of administering radiotherapy, given as a "boost" to the initial standard radiotherapy course, may benefit some patients with malignant glioma. Stereotactic external beam irradiation (also known as radiosurgery) is a radiotherapy technique which allows the delivery of a single high dose of radiation to the tumor-bearing part of the brain, while sparing most of the adjacent normal brain.

BCNU is a chemotherapy drug which has been found to be beneficial in the treatment of patients with brain tumors such as mine. This drug is, therefore, considered to be potentially helpful for controlling my disease.

The purpose of this research study is to compare results of standard radiation therapy against standard radiation therapy, preceded by radiosurgery, along with the chemotherapy drug BCNU. As part of this study my doctors are asking me to fill out a questionnaire to assess the impact of cancer on me and my quality of life (QOL).

DESCRIPTION OF PROCEDURES (6/30/95)

It is not clear whether the use of radiosurgery first followed by standard radiotherapy is better than standard radiotherapy alone. For this reason, the therapy which will be offered to me will be based upon a method called randomization. Randomization means that my doctor will call an office which will assign one of the therapies to me. The chances of my receiving either of the two therapies is equal.

If I am assigned to Treatment 1, I will receive radiation treatment once daily, five days per week for six weeks. On the first three days of radiation, I will receive BCNU chemotherapy by vein as an outpatient. The BCNU will be repeated every eight weeks for up to six cycles.

If I am assigned to Treatment 2, I will receive radiosurgery first followed by the same radiotherapy and chemotherapy regimen as in treatment 1, that is, radiation treatment once daily, five days per week for six weeks and BCNU during the first three days of radiation and then every eight weeks for up to six cycles.

Radiosurgery consists of delivering a single high dose of radiation to the tumor-bearing part of the brain. This will require the application of an apparatus, called stereotactic head frame, to the head. This entails making four perforations in the outer part of the skull under local anesthesia. Following placement of the head frame, brain scans, such as CT or MRI scans, are done in order to localize the tumor. After all the treatment planning is completed, the stereotactic radiation treatment is given. The stereotactic frame is removed after the treatment.

The QOL study will require an assessment once at the beginning of treatment, at 6 weeks and three months, then when I see my doctor for checkups. Assessments will be made with two one-page questionnaires which should take a few minutes to complete. The questionnaires will be completed independently by me. If I am unable to fill out the questionnaire, my doctor would ask my spouse, a family member, or significant other to fill it out. This questionnaire is to be filled out as if I were answering the questions **(7/1/94)**.

Also, at the time of my diagnosis by biopsy, all or some of my tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds to treatment, can be identified.

RISKS AND DISCOMFORTS (7/1/94, 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.

The side effects of BCNU which may occur are: lowering of the white cell count and platelet count which may increase the risk of infection and bleeding; nausea and vomiting; hair loss; lung impairment, such as a cough, fever, or shortness of breath may develop, pain or increase in pigmentation along the vein of injection; a slight burning sensation at the site of injection, and rarely, reversible kidney, liver impairment, or acute leukemia.

Participation in the QOL study may cause some emotional distress when describing the impact of cancer on myself. Participation is voluntary. If I choose not to participate in the QOL study, it will not effect my treatment. The results of the QOL study may be published but individual patients their spouses, family members, and significant others will not be identified by name in these publications.

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

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

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr._____ _____ the investigator in charge at_____. In addition, I may contact_____ _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

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

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

ALTERNATIVES

Alternatives which could be considered in my case include surgery, radiation therapy, or chemotherapy alone or in any combination, or treatments to make me feel better. 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 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 III

NEUROLOGICAL FUNCTIONAL CLASSIFICATION

A neurological evaluation and assignment to a functional class will be performed for each patient in the study. The patient will be classified as below:

Class I - Able to work, neurological findings minor or absent.
Class II - Able to be at home although nursing care may be required. Neurological findings present but not serious.
Class III - Requiring hospitalization and medical care with major neurological findings.
Class IV - Requiring hospitalization and in serious physical or neurological state including coma.

Class	Ability to Work	Hospital *(bed)*	Neurologically Impaired
I	+	-	0,1
II	-	- to ±	2
III	-	+ to +	3
IV	-	-	4

NEUROLOGICAL PERFORMANCE

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

Headache
Visual Disturbance
Speech Impairment
Sensory Symptoms
Motor Symptoms
Memory Lag
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 IV-A

NEUROLOGIC TOXICITY CRITERIA

	0	1	2	3	4
SKIN					
a) Acute	None	Slight erythema: Dry desquamation	Brisk erythema folliculitis	Moist desquamation	Ulceration
b) Chronic	None	Minimal pigmentation	Predominantly depigmentation mild fibrosis	Telangiectasia atrophy, severe symptomatic fibrosis	Necrosis ulceration
NEURO					
CNS					
a) Mental status (Mood Ideation Memory Consciousness)	No change	Transient alteration and/or minimal lethargy	Alteration substantially affecting function	Alteration substantially affecting function < 50% of time or of function	Comatose
b) Motor Paresis	None	Mild or transient	Substantially affects function < 50% decrement in baseline capabilities	Substantially affects function > 50% decrement in baseline capabilities	Paralysis
c) Cerebellar Function	No change	Mild or transient alteration	Substantially affects function < 50% decrement in baseline capabilities	Substantially affects function > 50% decrement in baseline capabilities	Confined to bed
d) Seizures	None		Transient or satisfactorily controlled by medical therapy	Seizure disorder not controlled by medical therapy	Status epilepticus
HAIR	None	Limited hair loss	Total alopecia		

APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates.

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

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

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

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

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

A copy of all correspondence (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.

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

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

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

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

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

Adverse Drug Reactions - Drug and Biologics

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

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

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

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

ii. Unknown adverse reactions (≥ grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. Form 1639 is to be used in reporting details (see attached). All relevant data forms must accompany the RTOG copy of Form 1639.

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

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

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

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

ii. Phase II, III Studies Utilizing Investigational Agents

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

**** See attached NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

RADIATION THERAPY PARAMETERS

The 2.5 cm margins (for the boost fields) are three-dimensional: superiorly, inferiorly, medially and laterally as well as anteriorly and posteriorly. (See Diagrams A & B)

Please note that it is important that the dose inhomegeneity be minimized particularly between the central axis dose and the tumor minimum dose. The protocol dose should be prescribed at the center of the target volume.

The inferior margin of the temporal lobe follows the outline of the sphenoid sinus. In order to encompass a 2.5 cm margin around most temporal lobe tumors, the entire temporal fossa usually needs to be included. In order to deliver a full dose to the inferior portion of the temporal fossa, the inferior border of the treatment portals should be below the bottom of the sphenoid sinus. (See Diagram B).

APPENDIX VI
(continued)

Diagram 1 illustrates that even with 6 MV photons utilizing parallel opposed portals, if the treatment portal encompasses the posterior occiput or the frontal region, it is obvious that without wedges the target minimum dose is 10% lower than the prescribed central axis dose, and there is a hot spot in the thinner portion that can be 10% to 15% hotter. These differences can be minimized with the use of wedges as in Diagram 2. The tumor minimum is only 2% lower than the central axis dose, and the hot spots are smaller and of lower dose. Isodose distributions are required for parallel opposed fields.

APPENDIX VI
(continued)

Diagram 3 is an example of a composite plan for an anteriorly located lesion with significant edema. By combining large 15 wedged parallel opposed fields to 57.60 (Diagram 4), it was possible to even out hot spots and treat the target volume to a high dose throughout with minimal gradient. Optimization of individual plans and the submission of composite plans is an essential requirement of this study.

APPENDIX VI
(continued)

APPENDIX VII

EXAMPLES OF QA GUIDELINES FOR RADIOSURGERY

Gamma Knife: Consider treatments with a specified prescription dose of 18Gy for Gamma Knife procedures. The Gamma Knife planning computer normalizes dose as percent of maximum dose.

1. Suppose the optimized plan shows that on one axial CT level the minimum isodose that encompasses the target is 65% of maximum. The prescription would then be 18Gy to the 65% isodose. The homogeneity ratio *(MDPD)*, would be 100%/65% = 1.54. This ratio is acceptable.

   Isodose lines to be submitted would be the 65%, 59%, 52% and 32.5% *(or 18Gy, 16.2Gy, 14.4Gy, and 9Gy).*

   The volume encompassed by the 18Gy isodose surface is calculated to be 33,500mm^3. The target volume is determined to be 15,700mm^3. The PITV ratio is 2.1. This would be considered a minor deviation.

2. Suppose the treatment was delivered as 18Gy to the 50% isodose. The homogeneity ratio *(MDPD)* would be 2.0, which is acceptable.

   Isodose lines to be submitted would be the 50%, 45%, 40%, and 25% *(18Gy, 16.2Gy, 14.4Gy, and 9Gy).* Upon review, it is observed that the target is not completely covered by the 45% isodose, but is completely covered by the 40% isodose. This would be classified as a minor deviation.

   The volume encompassed by the 18Gy isodose surface is calculated to be 33,500mm^3. The target volume is determined to be 22,800mm^3. The PITV ratio is 1.5. This is acceptable.

Linac: Consider Linac treatments with a prescription dose of 18Gy. *(The particular planning system normalizes isodose lines as cGy)*

3. A plan is developed such that the 18Gy line completely covers the target on all axial levels.

   The maximum dose is determined by the institution to be 26Gy. The homogeneity ratio *(MDPD)* would be 26/18 = 1.44. This ratio is acceptable.

   Isodose lines to be submitted would be the 18Gy, 16.2Gy, 14.4Gy, and 9Gy. Upon review, the target is encompassed by the 18Gy line at all levels.

   The volume encompassed by the 18Gy isodose surface is calculated to be 33,500mm^3. The target volume is determined to be 15,300mm^3. The PITV ratio is 2.2. This would be considered a minor deviation.

4. Suppose a plan is developed such that the 18Gy line covers the target.

   The maximum dose is determined by the institution to be 47Gy. The homogeneity ratio *(MDPD)* would be 47/18 = 2.6. This would be classified as a major acceptable deviation.

   Isodose lines to be submitted would be the 18Gy, 16.2Gy, 14.4Gy, and 9Gy. Upon review, on one axial level the target is not encompassed by the 18Gy, but the target is encompassed by the 16.2Gy line. This would be considered acceptable.

   The volume encompassed by the 18Gy isodose is calculated to be 14,300mm^3. The target volume is determined to be 11,700mm^3. The PITV ratio is 1.2. This is acceptable.

APPENDIX VIII

DOSE-VOLUME DATA EXAMPLE

Prescription: 16Gy at 50% isodose. Maximum dose = 32Gy

Dose matrix: 2.0mm grid, voxel volume = $8mm^3$

*Isodose levels < 7Gy extend outside calculation matrix

Dose *(Gy)*	Incremental TARGET Volume *(mm)*	Cumulative TARGET Volume *(mm)*	Incremental TREATMENT Volume *(mm)*	Cumulative TREATMENT Volume *(mm)*
2	0	11856	*	*
4	0	11856	*	*
6	0	11856	*	*
8	0	11856	20056	59784
10	0	11856	10960	39728
12	0	11856	6984	28768
14	312	11856	5088	21784
16	1032	11544	3760	16696
18	1728	10512	3232	12936
20	1952	8784	2872	9704
22	2520	6832	2520	6832
24	1864	4312	1864	4312
26	1248	2448	1248	2448
28	816	1200	816	1200
30	336	384	336	384
32	48	48	48	48
34	0	0	0	0

Target Volume = 11856 mm^3
Volume encompassed by prescription isodose *(16 Gy)* = 16696 mm^3

PITV = 16696/11856 = 1.41

APPENDIX IX

STEREOTACTIC FACILITY QUESTIONNAIRE

Unless previously approved for other RTOG stereotactic protocols, this questionnaire, with the requested supporting physics dosimetry information must be submitted to RTOG headquarters before any patients can be placed on RTOG Stereotactic Radiotherapy protocols. These data will help assure the RTOG quality assurance office that each institution has committed proper facilities and effort to this modality. These data will also be used by the RTOG quality assurance office in their review of protocol treatment and verification. Please include additional descriptions when necessary.

I. **General Information**

Institution Name _____RTOG Inst. #*(required)*_____

Responsible Radiation Oncologist*(s)*_____Telephone #_____

Responsible Medical Physicist*(s)*_____Telephone #_____

Responsible Data Manager*(s)*_____Telephone #_____

II. **Stereotactic Equipment:**

A. *Radiation Unit*

Manufacturer, Make & Model_____

Nominal Beam Energy _____Nominal Accelerating Potential:_____

Nominal SSD/SAD_____

Describe method to determine the variation of isocenter over range of gantry and couch angles employed. Report the results of this determination._____

_____

_____

_____

B. *Treatment Fixation System(i.e., patient's head frame relative to treatment couch (isocenter).*

1. Describe commercial system *(Attach vendor descriptive literature)*:_____

_____

_____

_____

Describe "homemade" system _____

_____

_____

_____

C. *Head Frame System*

1. Vendor:_____

_____

2. If specially designed, please describe:_____

_____

3. Attach diagram showing dimensions of outer CT/MR fiducials.

D. *Treatment Planning System*

1. Vendor/Model:_____

If system is specially designed, please describe_____

_____

_____

2. State the ability of the system to outline the target and calculate the target volume:_____

_____

_____

3. State the ability of the system to calculate the required dose-volume data:_____

_____

_____

4. State the ability of the system to provide isodose lines superimposed on CT/MR images:____

_____

_____

E. *Other*

Please describe any additional devices or techniques used for the stereotactic radiotherapy procedures.

_____

_____

III. **Dosimetric Parameters for Stereotactic Radiotherapy**

Note: These data should be based on procedures and data in the AAPM Calibration Protocol *(Med Phy 10:741-771, (1983))* for basic machine calibration, and upon ICRU Report #24 for depth dose distributions.

PLEASE ATTACH THE FOLLOWING INFORMATION:

A. Statement of Unit Calibration.

B. Relative Dosimetric Parameters:

1. Applicator output: cGy/MU or output relative to calibration, for all cones. Describe measurement geometry *(i.e., SSD and depth).*

2. Central axis depth dose information: table of TPR's, TMR's or percent depth dose for largest, smallest, and intermediate cone/collimator sizes.

3. Tabulated widths of the 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, and 10% isodose or dose decrement lines on three orthogonal axes through isocenter, for largest, smallest, and intermediate cone/collimator sizes. State the measurement geometry and technique used to determine these data *(as examples: "diode scans for static field at 8cm depth," or "film dosimetry in 16cm diameter phantom for (specific) multiple arc technique").*

IV. **Additional Information**

The following are important clinical considerations for which there are no standard dosimetry procedures. Other institutions may benefit from this information.

A. Techniques for stereotactic verification of isocenter *(couch, gantry, and collimation)* and alignment of the head frame:_____

_____

_____

B. Techniques used to verify the treatment dose via phantom measurements:_____

_____

_____

C. Any other technical descriptions unique to your system:_____

_____

_____

V. **Required Before You Can Enter Cases on RTOG Radiosurgery Protocols**

Complete this form in its entirety. Review by the RTOG Physics team may take several weeks longer if the application is incomplete.

Submit completed documentation for a treated, non-protocol patient, including the Radiosurgery Procedure Summary Form, treatment records, required isodose distributions on CT or MR anatomy, and dose-volume data.

Send this form and required documentation to:

Michael Gillin, Ph.D.
Medical College of Wisconsin
Radiation Physics
8700 West Wisconsin Ave.
Milwaukee, WI 53226

(414) **805-4360**

Radiosurgery Procedure Summary Form

Radiation Therapy Oncology Group

Institution_____RTOG INSTITUTION NUMBER_____

Patient's Name_____Patient's I.D. Number_____

Instructions: COMPLETE FOR A TREATED, NON PROTOCOL PATIENT
Include treatment record, isodose distributions on CT or MR anatomy, and dose-volume data for target and treatment volumes.

---

1. _____/_____/_____ DATE OF RADIOSURGERY

2. _____ TREATMENT UNIT
   1. Linear accelerator, multiple arcs
   2. Linear accelerator, dynamic rotation
   3. Gamma knife
   4. Other, specify:_____

3. _____ Beam Energy (MV)

4. _____ Number of Isocenters

TARGET DIMENSIONS

5. _____ X (Transverse) mm

6. _____ Y (AP/PA) mm

7. _____ Z (Superior/Inferior) mm

8. _____ Maximum (if other than X,Y,Z) mm

TARGET VOLUME (Based on the actual volume as determined from serial CT or MRI images)

9. _____ mm^3

. PRESCRIPTION DOSE

10. _____ Gy

11. _____ % Prescription Isodose Line (maximum=100%)

12. _____ Volume of Prescription Isodose (mm^3)

MAXIMUM DOSE (100%)

13. _____ Gy

RATIOS

14. _____ Radio of Maximum Dose/Prescription Dose (MDPD)

15. _____ Ratio of Prescription Isodose Volume/Target Volume (PITV)

PROTOCOL COMPLIANCE

16. _____ Treatment Completed
    1. No
    2. Yes

17. _____ If no, reason not completed
    1. Toxicity or surgical complication
    2. Refusal
    3. Progression or Death
    4. Technical limitations (comment)
    5. Other (Specify in comment section)
    6. Unknown

COMMENTS:_____

_____

_____ _____

SIGNATURE DATE