RADIATION THERAPY ONCOLOGY GROUP

RTOG BR-0023

A PHASE II TRIAL OF ACCELERATED RADIOTHERAPY USING WEEKLY STEREOTACTIC CONFORMAL BOOSTS FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

Study Chairman

Radiation Oncology

Robert M. Cardinale, M.D.
MCV Hospitals
Dept. of Radiation Oncology
401 College Street
Richmond, VA 23298
(804) 828-7232
FAX # (804) 828-6042
BobCardinale@aol.com

Neurological Oncology

Ali Choucair, M.D.
(801) 408-1109
FAX # (801) 408-1943
ldachouc@ihc.com

Physics

Michael Gillin, Ph.D.
(713) 745-5777
FAX #(713) 794-5272
mgillin@mdanderson.org

Activation Date: March 5, 2001
Update Date: June 10, 2003
Closure: June 30, 2003
Terminated: February 19, 2009
Current Edition: March 5, 2001

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
INDEX

Schema

Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Pathology

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status
Appendix III - Toxicity Criteria
Appendix IV - Adverse Reaction Reporting Guidelines
Appendix V - Stereotactic Facility Questionnaire
A PHASE II TRIAL OF ACCELERATED RADIOTHERAPY USING WEEKLY STEREOTACTIC CONFORMAL BOOSTS FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

SCHEMA

TREATMENT:

**External Beam (EBXRT):** 50 Gy in 25 daily fractions of 2 Gy to preoperative contrast-enhancing lesion plus surrounding edema plus a 2 cm margin. No EBXRT will be given on the four SRT treatment days.

**Stereotactic Radiotherapy (SRT) Boost:** 4 treatments of 5 or 7 Gy, once per week during weeks 3-6. Patients will not receive EBXRT on the SRT treatment days.

GTV = Postoperative residual enhancing lesion *(including resection cavity)*

PTV = GTV + 5 mm

<table>
<thead>
<tr>
<th>Dose:</th>
<th>Maximum PTV Diameter</th>
<th>Dose Per Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 40 mm</td>
<td>7 Gy</td>
</tr>
<tr>
<td></td>
<td>&gt; 40 mm</td>
<td>5 Gy</td>
</tr>
</tbody>
</table>

**BCNU:** 80 mg/m² i.v. for 3 days, beginning within one month after the completion of RT then q 8 weeks for a total of 6 cycles

Eligibility: (See Section 3.0 for details)
- Histologically-confirmed supratentorial glioblastoma multiforme
- Postoperative enhancing tumor plus tumor cavity ≤ 60 mm
- Zubrod performance status 0,1
- Life expectancy > 3 months
- Hgb > 9 gm, absolute neutrophils > 1500 mm³, platelets > 100,000
- BUN < 30, creatinine < 1.8 mg, bilirubin < 2 mg, SGPT or SGOT < twice normal range
- Therapy must begin within five weeks after surgery
- Signed study-specific consent form prior to registration

Required sample size: 76
RTOG Institution #

RTOG BR-0023

ELIGIBILITY CHECK

Case #

(page 1 of 2)

1. (Y) Does the patient have histologically confirmed supratentorial glioblastoma multiforme?
2. (Y) Was diagnosis made by surgical biopsy or resection?
3. (N) Is the tumor recurrent?
4. (Y) Has a diagnostic contrast-enhanced MRI or CT of the head been performed preoperatively?
5. (Y/N) Has a diagnostic contrast-enhanced MRI or CT of the head been performed postoperatively?
   (Y) If no, did the patient have only a stereotactic biopsy done?
6. (Y) Does the postoperative residual contrast-enhancing tumor and the resection tumor cavity together (GTV) have a maximum diameter (in any direction) of ≤ 60 mm regardless of initial tumor size?
7. (Y/N) Does the patient have a normal chest x-ray?
   (Y) If chest x-ray is abnormal, was a DLCO performed and is it > 60% of predicted value?
8. (Y) Do the patient’s laboratory values meet the criteria in Section 3.1.8?
9. (Y) Is the Zubrod 0 or 1?
10. (Y) Is the neurologic function status 0, 1, 2, or 3? (See Appendix II)
11. (N) Does the tumor originate in the brainstem or have residual enhancing tumor within 10 mm of the optic chiasm?
12. (Y/N) Has the patient had prior malignancies with the exception of carcinoma in situ of the cervix or bladder, ductal carcinoma in situ of the breast or non-melanomatous skin cancer?
   (Y) If yes, has the patient been disease-free for ≥ 5 years?
13. (N/NA) Is the patient pregnant?
14. (Y) Will therapy begin within five weeks after surgery?

(continued on next page)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed? (Y)
3. Is the patient eligible for this study? (Y)
4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
5. Patient’s Name
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility?
16. Treatment Start Date
17. Treatment Assignment
18. What is the PTV? (mm)
19. Patient’s Age?
20. What is the Zubrod Performance Status? (0 or 1)

Completed by ____________________________ Date ________________
1.0 INTRODUCTION

It has been demonstrated that the survival duration in patients with malignant gliomas is correlated with the total radiation dose delivered.\(^1\) However, dose escalation beyond 60 Gy has resulted in a significant increase in late normal tissue damage\(^2\) due to the large amount of brain receiving high radiation doses with standard techniques. Since malignant gliomas have a propensity for local failure, investigators have explored various methods of local dose escalation by incorporating techniques such as interstitial brachytherapy\(^3,4\), and stereotactic radiosurgery (SRS)\(^5,6,7\) in an effort to improve local tumor control. However, these boost methods are restricted to patients with well circumscribed, focal tumors. A benefit of SRS boost to residual enhancing tumor preceding or following standard external beam irradiation was suggested for malignant glioma patients in a report comparing SRS treated patients with a recursive partitioning analysis of patients treated on prior RTOG protocols.\(^8\)

There is recognition that certain tumor types, including glioblastoma multiforme, undergo molecular changes during radiotherapy that lead to accelerated proliferation that counteracts the effectiveness of fractionated irradiation.\(^9,10\) Accelerated radiotherapy treatment schedules have been developed to shorten overall treatment time in order to decrease the opportunity for tumor cell repopulation while delivering a total dose near or greater than standard treatment courses.\(^11,12\) This can be achieved by using multiple treatments daily with a lower fraction size as compared to standard treatment or by employing concomitant boost schedules that give higher doses to the gross tumor volume on selected days during a treatment course.

RTOG trials for malignant gliomas using hyperfractionation and accelerated hyperfractionation (AHRT) to 70 Gy using standard RT techniques, have found no significant increase in survival.\(^13,14,15,16\) However, the authors concluded that the maximum tolerated dose of AHRT had not been reached and that further dose escalation using 3DXRT should be considered. Authors at the Massachusetts General Hospital reported on a trial that delivered accelerated fractionated proton/photon conformal radiation to a dose of 90 cobalt-Gy given in 1.8 Gy fractions twice per day.\(^17\) Most patients had either radiographic or pathologic findings at second surgery indicating treatment failure outside of the prescription isodose surface. Fifty-seven percent of patients underwent reoperation and those with necrosis had a median survival time of 29 months compared with 16 months for patients who had identifiable tumor.

Stereotactic radiotherapy (SRT) is a non-invasive method of delivering localized radiation in a similar fashion to SRS but uses relocatable immobilization which allows for fractionation that may be beneficial in treating malignancies.\(^18\) The non-invasive nature of SRT systems allows for simplified treatment delivery and SRT does not require sedation or hospital admission. An accelerated radiation schedule using SRT for boost delivery on a weekly basis combines the advantage of SRS by delivering a higher dose to the tumor with the potential benefit of fractionation. The Medical College of Virginia has treated patients on two prospective trials using an accelerated treatment schedule which employed 3-4 weekly stereotactic radiotherapy (SRT) boosts of 6-12 Gy each to the enhancing tumor and tumor resection cavity plus a small margin of adjacent brain tissue (3-5 mm) during a course of standard external beam radiotherapy to 44-50 Gy.\(^19,20\) Preliminary results of the most recent trial using more conformal SRT boosting techniques demonstrated a median survival time of 18 months on a cohort of RTOG-RPA group IV/V patients who had a median enhancing tumor diameter of 5 cm. The planning target volumes for SRT included all of the post resection enhancing lesion, identifiable resection cavity, and a small rim (5 mm) of adjacent brain tissue. The reoperation rate was 40% and 21% of patients had a distant brain failure as the site of first failure.

SRT treatment delivery relies on the use of highly precise, non-invasive, immobilization devices coupled with 3D treatment planning systems. It has been shown by several authors, that linear accelerator arc-based SRS/SRT dose distributions may not be ideal for non-spherically shaped targets because of the need for multiple isocenters. The use of multiple isocenters given with linear accelerators or gamma-knife units may improve conformity over linac-SRS single isocenter arc-based techniques, but dose inhomogeneity is significantly increased and this may lead to increased toxicity for selected lesion types.\(^24,25\) Conformality, homogeneity and normal tissue sparing can be significantly improved, especially for large irregularly
shaped targets with the use of multiple, static, noncoplanar beams shaped by custom-made blocks or multileaf collimators.

21, 22, 23, 24

The purpose of this study is to determine the feasibility and efficacy of an accelerated radiotherapy strategy that delivers highly conformal boosts to high-risk tissues on a weekly basis during a course of standard EBXRT. This tailored approach to treatment may achieve results similar to other dose escalation methods such as 3D photon or proton accelerated hyperfractionation schedules while limiting patient visits and departmental resources. The study will allow for a significant increase in dose intensity for some patients not well suited for brachytherapy or SRS and for those who have gross total resections.

2.0 OBJECTIVES
2.1 Evaluate overall and progression-free survival with an accelerated SRT-Boost treatment schedule.
2.2 Evaluate the short and long-term toxicity of the accelerated SRT-Boost treatment schedule.
2.3 Evaluate the feasibility of an accelerated radiotherapy treatment regimen using SRT-boosting in patients with glioblastoma multiforme.

3.0 PATIENT SELECTION
3.1 Eligibility Criteria
3.1.1 Histologically-confirmed supratentorial glioblastoma multiforme.
3.1.2 Diagnosis must be made by surgical biopsy or resection.
3.1.3 Therapy must begin within five weeks after surgery.
3.1.4 A diagnostic contrast-enhanced CT or MRI scan must be performed preoperatively and post-operatively. Patients undergoing stereotactic needle biopsy are not required to have a post-operative imaging study; however, a CT or MRI must be used for SRT treatment planning.
3.1.5 The postoperative residual contrast-enhancing tumor and the resection tumor cavity together (GTV) must have a maximum diameter (in any direction) of < 60 mm regardless of initial tumor size.
3.1.6 Zubrod performance status 0,1.
3.1.7 Neurologic Function status 0, 1, 2, or 3.
3.1.8 Adequate bone marrow reserve (hemoglobin > 9 grams, absolute neutrophil count > 1500/mm³, platelets > 100,000/mm³); acceptable renal (BUN < 30 mg and creatinine < 1.8 mg) and hepatic function (bilirubin < 2.0 mg and SGPT or SGOT < twice normal range).
3.1.9 Normal chest X-ray. If chest X-ray is abnormal, a DLCO should be performed and must be >60% of predicted value.
3.1.10 Life expectancy > 3 months.
3.1.11 Patients must have signed a study-specific informed consent form. If the patient’s mental status precludes his/her giving informed consent, written informed consent may be given by the patient’s legal representative.

3.2 Ineligibility Criteria
3.2.1 Well-differentiated or anaplastic astrocytomas.
3.2.2 Multifocal glioma.
3.2.3 Patients whose tumors originate in the brainstem, or who have residual enhancing tumor within 10 mm of the optic chiasm.
3.2.4 Recurrent glioblastoma multiforme.
3.2.5 Postoperative enhancing residual tumor and resection cavity together have a maximum diameter (in any direction) > 60 mm.
3.2.6 Patients with prior malignancies, except carcinoma in-situ of the cervix or bladder, ductal carcinoma in-situ of the breast or non-melanomatos skin cancer, unless disease free ≥ 5 years.
3.2.7 Inability to obtain histologic proof of glioblastoma.
3.2.8 Pregnancy. Teratogenic effects of radiation are well documented. Because SRT may involve noncoplanar or vertex beams, the fetus may be excessively irradiated if pregnant women were allowed on this study. To avoid this confounding/constraining treatment planning variable, pregnancy is an ineligibility criterion.

4.0 PRETREATMENT EVALUATION
4.1 Mandatory Studies
4.1.1 Complete history and physical examination including a detailed neurologic exam.
4.1.2 CT or MRI scan performed preoperatively and postoperatively. See Section 3.1.4.
4.1.3 Document extent of surgical resection as biopsy, subtotal resection or gross total resection as demonstrated by postoperative CT or MRI scan.
4.1.4 CBC with differential, platelet count, blood chemistries (SMA-12), liver profile.
4.1.5 Chest X-ray.
4.1.6 Pregnancy test for women of child-bearing potential.

5.0 REGISTRATION PROCEDURES

5.1 The treating facility must complete and submit the RTOG stereotactic radiotherapy facility questionnaire (Appendix V) for RTOG approval. The facility’s questionnaire for this study must be approved by RTOG prior to enrollment of any patients. Allow adequate time for processing by the RTOG Physics Committee. Prior approval for other RTOG studies is not acceptable for RTOG BR-0023.

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

6.0 RADIATION THERAPY

6.1 Standard Radiotherapy (EBXRT)

6.1.1 Dose
One treatment of 2 Gy will be given Monday through Friday except on the four SRT treatment days for a total dose of 50 Gy. All portals shall be treated during each treatment session.

6.1.2 Treatment 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. 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 the standard radiotherapy shall be based on the preoperative CT/MRI. The initial target volume shall include the contrast-enhancing lesion and surrounding edema (if it exists) demonstrated on CT/MRI plus a 2.0 cm margin. If no surrounding edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5 cm margin. Should significant change in anatomic architecture occur postoperatively then the postoperative scans should be used for planning.

6.1.4 Treatment Planning
Treatment plans may include a wedge pair of fields, arcs, or multiple field techniques. Straight opposed lateral fields are not recommended and should be avoided. CT or MRI guided treatment planning is necessary to assure accuracy in the selection of field arrangements. Inability to achieve field placement as defined by the protocol will result in variation scores at headquarter reviews. Isodose distribution for the initial target volume and conedown target volume is 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 target. The use of a vertex field requires either a diagram or photograph of the treatment position to be submitted to RTOG Headquarters. If possible, send a film of the vertex field portal (without the patient). This will ensure that the vertex field portal shape/blocks matches that drawn on the DRR.

6.1.5 Dose Specification
Doses are specified as the target dose which shall be at the center of the target volume; this normally will be the isocenter in an isocentric technique (ICRU 50).

6.2 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 dose to the optic chiasm to 55 Gy (including contribution from SRT), the retina of at least one eye (but preferably both) to 50 Gy, and the brain stem to 60 Gy.
Stereotactic Radiotherapy Boost (SRT)

SRT boost must start during week 3 of EBXRT. Patients will receive 4 total SRT treatments, one per week during weeks 3-6. Patients will not receive EBXRT on the SRT treatment days. Only those patients whose residual enhancing tumor plus tumor resection cavity is ≤ 60 mm are eligible to enter the study. The method of SRT delivery on this study must allow for a high degree of dose homogeneity and conformity. Treatment must be performed with 3D conformal radiotherapy techniques using multiple coplanar/noncoplanar static conformal beams (or other conformal treatment delivery method, see Section 6.3.4). The fields should be shaped by a multileaf collimator or by custom fabricated cerrobend blocks. Traditional SRS/SRT linear accelerator arc-based treatment delivery with circular collimators is not allowed. Gamma knife treatment is also not allowed due to significant dose inhomogeneity and the non-availability of relocatable frames.

Dose Specification

The dose prescribed to the PTV (see Section 6.3.3) will be based on the maximum diameter as follows:

<table>
<thead>
<tr>
<th>Maximum PTV Diameter</th>
<th>Dose Per Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 40 mm</td>
<td>7 Gy</td>
</tr>
<tr>
<td>&gt; 40 mm</td>
<td>5 Gy</td>
</tr>
</tbody>
</table>

Dose will be prescribed to 80-90% of maximum dose. The prescription isodose volume should encompass the entire PTV.

Equipment Requirements

Participating institutions must complete the RTOG stereotactic radiotherapy facility questionnaire (Appendix V) prior to enrolling any patients in the study. This is to ensure that RTOG participants understand the study and have the appropriate tools for delivery of SRT. Prior approval for other RTOG studies is not acceptable for RTOG BR-0023.

Immobilization/Relocalization: A non-invasive, stereotactic, relocatable immobilization system will be used for treatment simulation and delivery. These systems may include modified stereotactic frames, camera-based localization systems, etc. The immobilization/relocalization system should be capable of reproducing the patient setup to within 3 mm.

Treatment Planning: 3-D conformal radiation therapy capabilities. The ability to plan and deliver multiple non-coplanar fields, or other highly conformal dose conformity methods (see Section 6.3.4) is mandatory.

Image Acquisition: Precise delineation of residual tumor/resection cavity is greatly improved with MRI imaging. This may be accomplished with the use of MRI compatible immobilization devices and treatment planning systems or by MRI digital image registration procedures with the SRT treatment planning CT. If the later option is used then the MRI need not be performed with the headframe in place. If such an MRI is performed for image registration procedures, it must be done within 2 weeks of the treatment planning CT. If these options for MRI target delineation are unavailable and if the tumor treatment area is well visualized on CT, then CT only may be used.

Either the treatment planning CT or MRI should be acquired with the patient in the same position, immobilization device, and conditions as will be used during treatment delivery. Each patient will be immobilized in a relocatable stereotactic frame or with another precision, non-invasive stereotactic system. Standard thermal-plastic masks may not be used. The treatment planning CT/MRI scan should start at the top of the cranial vertex and proceed down to the neck to encompass the entire intracranial contents. The scan slice thickness should be ≤ 0.5 cm (preferably 0.3 cm) through the region that contains the target volume. The regions above and below the target volume may be scanned with a slice thickness of ≤ 1 cm. The GTV, PTV, and normal tissue structures must be outlined on all CT/MRI slices in which the structures exist.

Volume Definitions

The gross tumor volume (GTV) will include the contrast-enhancing residual tumor and the operative tumor resection cavity with no margin. The operative tumor resection cavity should be contiguous with or include the residual tumor although it may be difficult to distinguish between them because of postoperative rim-enhancing changes, etc. On occasion, a corticotomy tract is performed at the time of surgery to access deep seeded tumors; such tracts should not be included in the GTV. Surrounding areas of edema will also not be considered part of the GTV.
NOTE: If the GTV has increased in size beyond 60 mm since registration, the patient will not receive stereotactic boost and will be considered removed from study treatment even if the criterion for formal progression (Section 11.3.5) is not met. Radiotherapy will be at the discretion of the treating physician. (Please notify RTOG Headquarters and the study chairman if this occurs).

Gross total resection: GTV = tumor resection cavity
Partial resection: GTV = residual enhancing tumor + resection cavity
Biopsy only: GTV = enhancing tumor only

6.3.3.2 The planning target volume (PTV) will be equal to the GTV + 5 mm in all directions to incorporate adjacent high-risk disease and treatment set-up uncertainty. Note: The PTV does not necessarily indicate the block edge. An additional margin around the PTV to define the beam aperture may be needed to meet PTV dose homogeneity requirements because of the effect of beam penumbra.

6.3.3.3 Critical normal structures: Normal tissues to be contoured include the eyes, optic nerves, optic chiasm and brain stem.

6.3.4 Treatment Planning

6.3.4.1 3-D Conformal Radiotherapy Using Static Coplanar/Noncoplanar Beams (3DCRT): Multiple vertex and coplanar/noncoplanar beams should be used and arranged with the goal of excluding as much normal brain tissue as possible outside of the PTV at high and intermediate dose levels. The beam’s eye view displays must be used to design beam apertures. Wedges, compensators, and multileaf collimators may be used. Dynamic conformal arcs and other beam shaping techniques which modulate the field aperture to further improve dose conformality may be used as long as the dose homogeneity requirement is maintained.

6.3.5 SRT Treatment Planning Data

6.3.5.1 Submit isodose distributions calculated through the center of the target in the transverse, coronal, and sagittal planes. The isodoses shall be superimposed on MRI/CT anatomy and shall include isodose lines that correspond to 100%, 90%, 80% and 50% of the prescription dose. It is intended that these data are of sufficient quality that the reviewer can judge the adequacy of target coverage by the dose distribution.

6.3.5.2 Submit dose-volume data in tabular form, showing the accumulated volumes of those elements within the planning target volume and within the entire global treatment volume receiving dose in 1 Gy dose intervals. These data may be differential or cumulative dose-volume statistics.

6.3.6 SRT Quality Assurance Review

The protocol chairman and the protocol physicist will perform a final review of the stereotactic radiotherapy treatment. The review process will evaluate the SRT Summary Form, and the stereotactic CT/MRI with superimposed isodoses at required levels, and dose-volume data. Based on the evaluation and verification of data submitted, the following Quality Assurance scores will be assigned to each case.

6.3.6.1 The isodose line to which the dose is prescribed is considered the “prescription” or 100% isodose line. If the 90% isodose line completely encompasses the target, the case is considered per protocol. If the 90% isodose line does not completely cover the target, but the 80% isodose line does completely cover the target, this shall be classified as a minor variation. If the 80% isodose line does not completely cover the target, this shall be classified as a major deviation.

6.3.6.2 The maximum dose delivered shall be determined. Dose homogeneity within the planning target volume shall be determined as the maximum dose divided by the prescription dose (ratio MDPD). This ratio should be less than 1.25. MDPD ratio greater than 1.25 and less than 1.4 will be classified as a minor deviation. MDPD ratio greater than 1.4 will be classified as a major deviation.

6.3.6.3 The volume of the prescription isodose surface shall be determined from the dose volume histogram. A figure of merit for conformation of the prescription isodose surface divided by the target volume (ratio PITV). Every attempt should be made to keep the ratio as close to 1.00 as possible while maintaining target coverage and target homogeneity criteria. A value between 1.00 and 2.00, if achieved, will not be a minor deviation from protocol. PITV ratios > 2.00, but less than 2.5, shall be classified as a minor deviation. PITV ratios > 2.5 shall be classified as a major deviation.

6.3.6.4 Optic chiasm dose including contributions from all fields >55 Gy will be considered a major violation.

6.3.6.5 Overall quality assurance score will be as follows:
- Per protocol: One minor variation; no major deviation.
- Acceptable: > One minor variation but no major deviation.
**Unacceptable:** > One or more major deviations, regardless of whether minor variations were scored; optic chiasm dose including conventional and SRT contributions above 55 Gy.

### 7.0 DRUG THERAPY

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

#### 7.1 BCNU Administration

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

**7.1.2 Schedule**

**7.1.2.1** BCNU *(80 mg/m²)* will be administered on three consecutive days, beginning within one month after the completion of radiotherapy. It will then be administered every eight weeks for a total of 6 cycles *(maximum BCNU dose 1440 mg/m²)*.

**7.1.2.2** BCNU will be given as an intravenous infusion over 1-2 hours at a dose of 80 mg/m² per day for each 3-day course.

**7.1.2.3** 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 eight hours at room temperature.

**7.1.3 Discontinuation of BCNU**

At documentation of progression, BCNU will be discontinued. At the discretion of the investigator, the patient may be treated with additional chemotherapy, biological therapy, 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/m². 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/m² *(6 cycles at 80 mg/m² x 3 days)* or one full year of therapy. If symptoms or signs of BCNU pulmonary toxicities occur, chest x-ray and pulmonary function studies including DLCO should be obtained to document toxicity.

**7.2.2** Toxicities may include myelosuppression which may be delayed and severe; mild to moderate nausea and vomiting 2-12 hours after administration; mild and reversible liver enzyme changes; alopecia; pain along the vein of injection; increased pigmentation along the vein of injection; pulmonary impairment; and very rarely renal impairment. See Section 7.4 for reporting adverse drug reactions.

#### 7.3 Dose Modification

**7.3.1** BCNU dose is calculated upon actual weight provided it does not exceed 125% of ideal weight. Should the patient weigh more than 125% of ideal weight, the maximum BCNU dose is based on ideal body weight PLUS 25%.

**7.3.2** There will be no dose escalation.

**7.3.3** 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 modification will be as follows:

**7.3.3.1 Nadir:**

<table>
<thead>
<tr>
<th>Absolute Neutrophil Count (ANC)</th>
<th>Platelets</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 750</td>
<td>≥ 75,000</td>
<td>100% dose</td>
</tr>
<tr>
<td>250 to &lt; 750</td>
<td>or 25,000 to &lt; 75,000</td>
<td>75% dose</td>
</tr>
<tr>
<td>&lt; 250</td>
<td>or &lt; 25,000</td>
<td>50% dose</td>
</tr>
</tbody>
</table>

**7.3.3.2 At scheduled time of administration:**

<table>
<thead>
<tr>
<th>Absolute Neutrophil Count (ANC)</th>
<th>Platelets</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1500</td>
<td>≥ 100,000</td>
<td>Dose modified for nadir only.</td>
</tr>
<tr>
<td>&lt; 1500</td>
<td>or &lt; 100,000</td>
<td>Hold dose for two weeks and</td>
</tr>
</tbody>
</table>
7.3.3 After 2 weeks:

<table>
<thead>
<tr>
<th>Absolute Neutrophil Count (ANC)</th>
<th>Platelets</th>
<th>Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1500</td>
<td>≥ 100,000</td>
<td>Dose modified for nadir only.</td>
</tr>
<tr>
<td>1000 to &lt; 1500</td>
<td>75,000 &lt; 100,000</td>
<td>75% dose</td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>&lt; 75,000</td>
<td>Contact chemotherapy study chairman before further chemotherapy administration.</td>
</tr>
</tbody>
</table>

7.3.4 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.

7.3.5 When liver enzyme (SGOT, SGPT or bilirubin) level is greater than three times the upper limit of the institutional normal value, BCNU should be held until SGOT or SGPT drops to less than two times the upper limit of normal and bilirubin drops within the normal range. Then, BCNU should be administered at 50% of the previous dose level.

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

7.4 Adverse Drug Reaction Reporting

7.4.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for toxicity and Adverse Event Reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP Home page (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTC version 2.0. This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.4.2 The following guidelines for reporting adverse drug reactions (ADR’s) apply to any research protocol that uses commercial anticancer agents. The following ADR’s 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 ten working days:

7.4.2.1 Any ADR which is both serious (life-threatening, fatal) and unexpected.

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

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

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

7.4.3 The ADR report should be documented on FDA Form 3500 (Appendix V) and mailed to the address on the form, RTOG Data Management Department, and to:

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

7.4.4 Death from any cause while the patient is receiving protocol treatment, or up to 30 days after the last protocol treatment, must be reported to RTOG Headquarters Data Management department within ten days of discovery.

8.0 SURGERY

8.1 The extent of surgical resection prior to protocol entry shall be documented as a) biopsy, b) subtotal resection or c) gross total resection as described by the postoperative imaging study.
8.2 In the event that radiation necrosis is suspected based on imaging studies, a biopsy or repeat operation to remove the necrotic tissue is appropriate. An operative and pathology report from any reoperation procedure must be sent to RTOG Headquarters.

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 that will afford the patient satisfactory neurologic function and the best possible quality of life.
9.2 Infections are to be treated with appropriate antibiotics and recorded.
9.3 Analgesics and any other medications are to be specified and their dose recorded.

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

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

11.1 Study Parameters

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Prior to Registration</th>
<th>During RT</th>
<th>Prior to Each ChemoCycle</th>
<th>At Each Followup c</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and PE</td>
<td>X</td>
<td>weekly</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neurological exam a</td>
<td>X</td>
<td>weekly</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Evaluation of skin within RT treatment portals</td>
<td></td>
<td>weekly</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CBC including differential and platelets</td>
<td>X</td>
<td>weekly</td>
<td>weekly during chemo d</td>
<td>X</td>
</tr>
<tr>
<td>Blood chemistries (SMA-12, Liver Profile)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest X-ray</td>
<td></td>
<td></td>
<td>as indicated</td>
<td></td>
</tr>
<tr>
<td>Contrast enhanced CT or MRI of the Brain (Both pre-op &amp; post-op pre-radiotherapy)</td>
<td>X</td>
<td>X f</td>
<td>as indicated</td>
<td>X b</td>
</tr>
<tr>
<td>Physiologic Tumor Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>as applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. To include recording of steroid and anticonvulsant dose and performance status.
b. Every 4 months through year 2; every 6 months for year 3, then annually.
c. Every 3 months from end of treatment for 2 years; every 6 months for 3 years; then annually.
d. To be drawn prior to each chemo cycle and weekly after chemo treatment to capture nadir and toxicities.
e. PET, SPECT-Thallium, or MRI spectroscopy are encouraged if available.
f. As part of stereotactic treatment planning. See Section 6.3.2.1.

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 follow-up thereafter.

11.2.2 The contrast-enhanced CT or MRI of the brain shall be obtained prior to surgery, and post-operatively, and every four months through year 2, every six months for one year, then annually; also at the times 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 occurrence of "early delayed radiation reactions" that occur usually within the first 10 weeks post-treatment and last up to 6-8 weeks. These transient adverse signs and symptoms may spontaneously improve without therapy. They are considered to be due to transient demyelination. Caution is, therefore, urged in diagnosing and treating recurrent tumor during the first 2-3 months post irradiation.

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

11.3 Overall Response

11.3.1 Complete Response (CR): shall be defined as the circumstance when the tumor is no longer seen by imaging provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.3.2 Partial Response (PR): Decrease of >50% in the product of two diameters provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.3.3 Minor Response (MR): Decrease in diameter products of < 50% provided that the patient has not had his/her dose of steroids increased since the last evaluation period.

11.3.4 Stable Disease (SD): shall be defined as the circumstance when the scan shows no change. Patients should be receiving stable or decreasing doses of steroids.

11.3.5 Progression (P): shall be defined as a >25% increase in tumor area (two diameters) provided that the patient has not had his/her dose of steroids decreased since the last evaluation period. A concomitant decrease in steroid dose will rule out a progression designation at this point.
11.4 Criteria for Evaluation of Therapy Effectiveness

11.4.1 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.

11.4.2 Considering that radionecrosis is usually indistinguishable from tumor progression by CT/MRI imaging, Thallium-SPECT, PET or spectroscopic MRI imaging is encouraged in all cases at the time of suspected progression / necrosis.

11.4.3 Overall survival will be measured from registration until death.

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

11.5 Ineligible and Inevaluable Patients

11.5.1 Patients that are registered and retrospectively found to be ineligible for this trial may discontinue form submission upon notification of ineligibility from HQ. Data until that point, however, must be submitted to RTOG.

11.5.2 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

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Pretreatment CT/MRI both pre- and post-</td>
<td></td>
</tr>
<tr>
<td>surgery (C1) and reports (C3)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td></td>
</tr>
<tr>
<td>External Beam Films (simulation and portal) (TP)</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>External Beam Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>External Beam Calculations (TL)</td>
<td></td>
</tr>
<tr>
<td>Stereotactic Radiotherapy Calculation (RS)</td>
<td></td>
</tr>
<tr>
<td>Stereotactic Radiotherapy Films (RP) (if capability exists)</td>
<td></td>
</tr>
<tr>
<td>Initial Followup Form (FS)</td>
<td>At end of treatment and 3 months from start of RT</td>
</tr>
<tr>
<td>Follow-up CT/MRI (C2) and reports (C3)</td>
<td>4 months from beginning of RT then at regression, progression, and at ≥ grade 3 neurotoxicity.</td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3 months from end of treatment for 2 years; q 6 months x 3 years, then annually. Also at progression/relapse and at death.</td>
</tr>
<tr>
<td>Study-specific Flowsheet (SF)</td>
<td>Week 13 then every 8 weeks for 6 cycles</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Overall survival.

13.1.2 Acute and late toxicities associated with accelerated radiotherapy using stereotactic conformal boosts, followed by BCNU.

13.1.3 Progression-free survival.

13.2 Background

RTOG recursive partitioning analysis (RPA) has found that the survival of malignant glioma patients is highly influenced by prognostic factors (age, histology, mental status, KPS, symptom duration, extent of surgery, neurological class, and RT dose). The RTOG, and many groups in the brain cancer research community, use the RPA classes to stratify patients for study eligibility, treatment assignment at randomization, and for analytic purposes. GBM patients on this study must have a KPS of at least 70 (Zubrod 0 and 1), and therefore will fall into RPA classes III, IV, or V, which historically have a median survival time (MST) of 17.9, 11.1, and 8.9 months, respectively. The RTOG GBM database (historical control) contains 1027 RPA class III through V patients, with a breakdown of 20%, 49%, 31%, respectively.

13.3 Sample Size

The primary objective of this study is to estimate the median survival time (MST) for glioblastoma multiforme (GBM) patients treated with accelerated radiotherapy using stereotactic conformal boosts, followed by BCNU. Historically, GBM patients with RPA class of III, IV, and V have an estimated MST of 17.9, 11.1, and 8.9 months, respectively. Using the Dixon-Simon method of calculating sample size for the comparison of survival against a historical control, a sample size of 68 evaluable RPA class III, IV, and V patients followed over 18 months will ensure at least 80% probability of detecting a minimum of 50% improvement in MST compared to the RTOG glioma database at the 0.05 significance level (one-sided). In addition, see the following table for equivalent statements regarding power, alpha, and detectable improvement. Note that an ineligibility rate of 10% is assumed for this study, due to the possibility of tumor growth after registration. Adjusting for a 90% eligibility/evaluability rate results in 76 patients needed in order to accrue 68 eligible patients. In summary, this study requires a total sample size of 76 patients.

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

13.4 Inclusion of Women and Minorities

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

13.5 Patient Accrual

The patient accrual is projected to be 5 cases per month. At this rate, it will take fifteen months to reach the required total accrual of 76 cases. If the average monthly accrual rate is less than three patients, the study will be re-evaluated with respect to feasibility.

13.6 Suspension of Accrual Due to Morbidity

The accrual to this trial will be suspended if the expected grade 3 or 4 irreversible CNS toxicity rate is greater than 30%. Irreversible CNS toxicity is defined to be any CNS toxicity that does not respond to therapy or requires surgical intervention. This stopping rule is based upon Fleming’s design to reject if the true rate is greater than 30%. Therefore, suspension of accrual will occur if any of the following numbers of grade 3 or 4 irreversible CNS toxicity is exceeded.
Patients with Grade 3 or 4 Irreversible CNS Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Total Number of Evaluable Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>24</td>
<td>56</td>
</tr>
</tbody>
</table>

A Grade 5 toxicity will suspend accrual until the Study Chair reviews the case.

13.7 Analyses Plans

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

a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;

b) the quality of submitted data with respect to timeliness, completeness, and accuracy;

c) the frequency and severity of the toxicities.

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

13.7.2 Analysis for Reporting the Initial Treatment Results
This analysis will be undertaken when each patient has been potentially followed for a minimum of 18 months. The usual components of this analysis are:

a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;

b) reporting of institutional accrual;

c) distribution of important prognostic baseline variables – (age, performance status, neurologic function, extent of surgery, mental status);

d) observed results with respect to the endpoints described in Section 13.1.

e) Overall survival of patients will be compared to the same proportion of RPA class III, IV, and V patients from the historical control using a one-sided log-rank test with a significance level of 0.05.
REFERENCES


APPENDIX I

RTOG BR-0023

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE II TRIAL OF ACCELERATED RADIOTHERAPY USING WEEKLY STEREOTACTIC CONFORMAL BOOSTS FOR SUPRATENTORIAL GLIOBLASTOMA MULTIFORME

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know”, is available from your doctor.

You are being asked to take part in this study because you have brain cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) standard radiation therapy, stereotactic radiotherapy and the chemotherapy BCNU has on you and your brain cancer.

This research is being done to test the side effects and effectiveness of stereotactic radiotherapy in patients with this type of brain cancer when used with standard radiotherapy and BCNU.

Radiation therapy is the treatment of tumors by means of x-rays. Stereotactic radiotherapy is a radiation technique which allows for the delivery of higher doses of radiation to the tumor in your brain while sparing most of the surrounding normal brain tissue.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 76 people will take part in this study.
WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following treatment:

- All patients will receive:

  **Standard Radiation Therapy:** Standard radiation treatment to the brain will be for a total of 6 weeks: Once a day, 5 days a week, for 2 weeks, then 4 days a week for 3 weeks, then 3 days in the 6th and final week. This is a total of 25 treatments. All radiation therapy will be given as an outpatient at your institution.

  **Stereotactic Radiation Therapy:** Stereotactic radiation treatment to the brain will be given once a week during weeks 3, 4, 5, and 6 of standard radiation therapy for a total of four treatments. All radiation therapy will be given as an outpatient at your institution. Stereotactic radiation treatment delivers higher doses of radiation to the tumor in your brain. This will require the application of a removable mask or frame, *(stereotactic head frame)* to the head. This frame placement procedure does not require sedation or any invasive procedure. This frame will fit very snugly against your head and may also include a mouthpiece *(similar to a set of dentures)*. The purpose of this head frame is to hold your head very still during the planning and delivery of the stereotactic radiation treatment. Following placement of the head frame, brain scans, such as CT or MRI scans, are done in order to locate the tumor. After all the treatment planning is completed, the stereotactic frame is removed. It will be put back on for each of the four stereotactic treatment sessions and removed after each treatment. You will have the stereotactic radiation treatments *(with the head frame in place)* once a week for a total of four times.

  **Chemotherapy:** Within one month after completing the 6 weeks of radiation therapy, you will begin BCNU chemotherapy treatments. BCNU will be given once a day for 3 consecutive days every 8 weeks. This
will be given a total of 6 times (cycles). BCNU will be injected into a vein (intravenously) and will last for about 2 hours. Your chemotherapy treatments will be given as an outpatient at your institution.

If you take part in this study, you will have the following tests and procedures:

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to study entry</td>
<td>Physical exam with a medical history</td>
</tr>
<tr>
<td></td>
<td>Neurological exam</td>
</tr>
<tr>
<td></td>
<td>Blood tests called CBC and SMA-12</td>
</tr>
<tr>
<td></td>
<td>Chest X-ray</td>
</tr>
<tr>
<td></td>
<td>CT Scan or MRI of the brain – (before surgery, after surgery, and before radiation treatment starts.)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy test (as applicable)</td>
</tr>
</tbody>
</table>

During radiation treatment

- **Weekly**
  - Physical exam
  - Neurological exam
  - Blood test called CBC
  - Evaluation of skin within radiation treatment area

Prior to each chemotherapy treatment

- Physical exam
- Neurological exam
- Blood test called SMA-12
- Chest X-ray at physician discretion

During each chemotherapy treatment

- **Weekly**
  - Blood test called CBC

At each follow-up appointment

- Physical exam
- Neurological exam
- Blood test called CBC
- Evaluation of skin within radiation treatment area
- Chest X-ray at physician discretion
- CT scan or MRI of the brain – (every 4 months for 2 years, then every 6 months for year 3, then annually)

Additional imaging studies may need to be done during follow-up if necessary to evaluate your cancer.
Follow-up visits with your physician will be scheduled every three months from when your treatment ends for 2 years, then every 6 months for 3 years, and then annually for the rest of your life.

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

**HOW LONG WILL I BE IN THE STUDY?**

You will receive radiation therapy for 6 weeks. Then you will start the chemotherapy called BCNU for 3 consecutive days every 8 weeks. This will be repeated six times (cycles). The study treatment, including radiation and chemotherapy, will take just over one year to complete. Follow-up visits will continue for the rest of your life according to the schedule above.

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

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

**WHAT ARE THE RISKS OF THE STUDY?**

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

Very Likely
- Fatigue and sleepiness
- Hair loss which may be permanent
- Tanning, irritation and/or redness of skin within the treatment area which is temporary
- Skin in treatment area may remain permanently dry
- Dry mouth or altered taste, nausea
- Weakness
- Headaches

Less Likely
- Upset stomach and/or vomiting
- Loss of appetite
- Plugging of the ears with decreased hearing

Less Likely, But Serious
- Hearing loss
- Cataracts and eye damage leading to blindness
- Decrease in memory function
- Damage to normal brain tissue that may require additional surgery and treatment
- Seizures

Risks Associated with STEREOTACTIC Radiation Therapy

Very Likely
- Fatigue and sleepiness
- Hair loss which may be permanent
- Tanning, irritation and/or redness of skin within the treatment area which is temporary
- Skin in treatment area may remain permanently dry
- Weakness
- Headaches

Less Likely
- Upset stomach and/or vomiting

Less Likely, But Serious
- Difficulty with speech and/or balance
- Swelling within the brain, which is treated with anti-swelling medications
- Damage to brain tissue that may require additional surgery and treatment
- Seizures
Risks Associated with BCNU

Very Likely
Lower blood counts which can lead to a risk of infection or bleeding
Nausea and/or vomiting
Hair loss
Burning sensation at the site of injection
Facial flushing
Loss of appetite

Less Likely
Pain or increase in pigmentation along the vein of injection

Less Likely, But Serious
Low blood pressure
Scarring of the lungs resulting in coughing, fever, and/or shortness of breath
Temporary changes in your liver function which are reflected in liver function blood tests
Kidney damage

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

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

WHAT OTHER OPTIONS ARE THERE?

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

Another option may be to get the radiation and chemotherapy treatment as described in this study at this center and other centers even if you do not take part in the study.

Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**

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

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

**WHAT ARE THE COSTS?**

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

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

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

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

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.
We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

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

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

______________________________  ______________________________
Name  Telephone Number

For information about this study, you may contact:

______________________________  ______________________________
Name  Telephone Number

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

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

______________________________  ______________________________
Name  Telephone Number

WHERE CAN I GET MORE INFORMATION?

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

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

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

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

_________________________  ___________________________
Patient Signature (or legal Representative)  Date

TISSUE AND BLOOD TESTING (RTOG BR-0023)

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

☐  Yes  ☐  No

_________________________  ___________________________
Patient Signature (or authorized legal Representative)  Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

NEUROLOGIC FUNCTION (NF) STATUS

NF  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 EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

   a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

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

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).

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

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

C. ADVERSE DRUG REACTIONS DRUG AND BIOLOGICS

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

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

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

Commercial and Non Investigational Agents

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

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

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

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

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working
- 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 10 working days with a copy to IDB. (Grade 4 myelosuppression not reported to IDB)

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

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

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

STEREOTACTIC FACILITY QUESTIONNAIRE

This questionnaire, with the requested supporting physics dosimetry information must be submitted for approval 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 Research Associate(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): __________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
C. *Relocatable Stereotactic Head Frame or Other Immobilization/Localization 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:
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 Stereotactic Radiotherapy Protocols**

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

**Send this form and required documentation to (6/10/03):**

Michael Gillin, Ph.D.
Professor, Radiation Physics
The University of Texas M.D. Anderson Cancer Center
1515 Holcombe Boulevard – 94
Houston, TX 77030-4009
Phone: (713) 745-5777
Fax: (713) 794-5272