

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 98-03**

**PHASE I/II RADIATION DOSE ESCALATION STUDY APPLYING CONFORMAL  
RADIATION THERAPY IN SUPRATENTORIAL  
GLIOBLASTOMA MULTIFORME**

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Activation Date:                        September 8, 1998  
**Closure Date:                        September 3, 2003**  
**Update Date:                         July 14, 2003**  
**Current Edition:                      October 15, 2001**  
**Includes Revisions 1-5**

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**S C H E M A**

S		R	<u><b>DOSE TO PTV<sub>2</sub></b></u> <sup>a,c</sup>
T	<u><b>Group 1</b></u> PTV <sub>2</sub> < 75cc	E	Level 1    66 Gy (closed)
R	<u><b>Group 2</b></u> PTV <sub>2</sub> ≥ 75cc	G	Level 2    72 Gy (closed)
A		I	Level 3    78 Gy
T		S	Level 4    84 Gy
I		T	
F		E	<b>All patients receive BCNU<sup>b</sup></b>
Y		R	

- a. Radiation therapy to be administered in 2 Gy/day fractions. All patients will have a field reduction after 46 Gy.
- b. BCNU (80 mg/m<sup>2</sup>) on days 1,2, and 3 of the first week of radiotherapy repeated on days 56, 57 and 58. Then every eight weeks for four cycles for a total of six cycles (maximum BCNU dose 1440 mg/m<sup>2</sup>).
- c. PTV<sub>1</sub> = CTV<sub>1</sub> + 3mm, (CTV<sub>1</sub> = gross tumor + 15mm margin); PTV<sub>2</sub> = gross tumor + 3mm margin.

Dose escalation will be stratified by target volume. The treatment for each stratification group will be the same. Contact RTOG Headquarters prior to registration to know which dose level is currently open for each planning target volume (PTV<sub>2</sub>).

**Eligibility:** (See Section 3.0 for details)

- Newly diagnosed histologically-confirmed glioblastoma multiforme with areas of necrosis
- Supratentorial tumor
- Therapy beginning within 5 weeks after surgery but within one week after registration
- No prior chemotherapy or radiotherapy to the head and neck
- Age ≥ 18
- Karnofsky performance status ≥ 60
- Neurologic functional status 0, 1, 2 or 3
- Hemoglobin ≥ 9 gm, absolute neutrophil count ≥ 1500 mm<sup>3</sup>, platelets ≥ 100,000
- BUN ≤ 30 mg, creatinine ≤ 1.8 mg, bilirubin ≤ 2 mg, and SGPT or SGOT ≤ twice normal range
- Normal chest x-ray
- Signed study specific consent form prior to registration

**Required Sample Size: Dose tolerance dependent**

**11/13/00  
12/13/00  
10/15/01**

Institution # \_\_\_\_\_  
RTOG 98-03 \_\_\_\_\_  
Case # \_\_\_\_\_

**ELIGIBILITY CHECK (11/13/00)**  
*(page 1 of 2)*

- \_\_\_\_\_(Y) 1. Histologically-confirmed glioblastoma multiforme with areas of necrosis?
- \_\_\_\_\_(Y) 2. Was diagnosis obtained by excision, biopsy, or resection?
- \_\_\_\_\_(Y) 3. Is tumor supratentorial in location?
- \_\_\_\_\_(Y) 4. Will therapy begin within 5 weeks after surgery but within 1 week after registration?
- \_\_\_\_\_(≥ 18) 5. Patient's age?
- \_\_\_\_\_(≥60) 6. Karnofsky Performance Status?
- \_\_\_\_\_(0-3) 7. Neurologic Function Status?
- \_\_\_\_\_(≥ 9) 8. Hemoglobin?
- \_\_\_\_\_(≥ 1.5) 9. Absolute neutrophil count (*x 1000*)?
- \_\_\_\_\_(≤ 30) 10. BUN?
- \_\_\_\_\_(≥ 100) 11. Platelet count (*x 1000*)?
- \_\_\_\_\_(≤ 1.8) 12. Creatinine?
- \_\_\_\_\_(≤2.0) 13. Bilirubin?
- \_\_\_\_\_(Y) 14. Is the SGOT or SGPT ≤ twice your institution's top normal range?
- \_\_\_\_\_(N) 15. Is the patient's tumor multifocal or recurrent?
- \_\_\_\_\_(Y/N) 16. Is the chest x-ray normal?  
\_\_\_\_\_(Y) If no, has a DLCO been performed and found to be 60% or more of predicted value?
- \_\_\_\_\_(Y) 17. Was a preoperative CT with contrast or an MRI performed?
- \_\_\_\_\_(Y/N) 18. Has the post-operative MRI been performed in the last four weeks with gadolinium enhancement or other FDA-approved MR-compatible contrast agents?  
\_\_\_\_\_(Y) If no, was a stereotactic needle biopsy done, with an MRI scan still available for treatment planning or did the patient have a complete tumor resection?
- \_\_\_\_\_(N) 19. Any prior radiotherapy to the head and neck area?
- \_\_\_\_\_(N) 20. Any prior systemic chemotherapy for any malignancy?

*(cont'd on page 2)*

Institution # \_\_\_\_\_  
RTOG 98-03 \_\_\_\_\_  
Case # \_\_\_\_\_

**ELIGIBILITY CHECK (11/13/00)**  
*(page 2 of 2)*

- \_\_\_\_\_(Y/N) 21. Any prior malignancies except carcinoma *in situ* of the cervix, ductal carcinoma of the breast *in situ*, cancer *in situ* of the bladder, or non-melanomatous skin cancer?  
\_\_\_\_\_(Y) If yes, has the patient been disease-free for at least 5 years?
- \_\_\_\_\_(N) 22. Is the patient known to be pregnant?
- \_\_\_\_\_(Y/N) 23. Has the PTV been calculated on a planning 3D CT scan?

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_(Y) 1. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_(Y) 2. Is the patient eligible for this study?
- \_\_\_\_\_ 3. Date the study-specific Consent Form was signed? (*must be prior to study entry*)

\_\_\_\_\_ Patient's Name  
\_\_\_\_\_ Verifying Physician  
\_\_\_\_\_ Patient ID #  
\_\_\_\_\_ Referring Institution # (*if different*)  
\_\_\_\_\_ PTV2 (< 75cc vs. ≥ 75cc)  
\_\_\_\_\_ Medical Oncologist  
\_\_\_\_\_ Birthdate  
\_\_\_\_\_ Sex  
\_\_\_\_\_ Race  
\_\_\_\_\_ Social Security Number  
\_\_\_\_\_ Zip Code (*9 digit if available*)  
\_\_\_\_\_ Method of Payment  
\_\_\_\_\_ Will any component of the patient's care be given at a military or VA facility?  
\_\_\_\_\_ Treatment Start Date  
\_\_\_\_\_ Treatment Assignment

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION & BACKGROUND**

Glioblastoma is the most common primary brain tumor in adults. Nearly 12,000 cases are diagnosed annually in the United States. Despite aggressive therapy less than 5% of these patients are expected to live more than 5 years.<sup>1</sup> Conventional radiotherapy has demonstrated activity in prolonging median survival time in patients with glioblastoma multiforme, but it is generally unsuccessful at maintaining long-term tumor control. Most patients treated with standard radiation therapy have experienced in-field recurrences that inevitably lead to the patient's death because no adequate salvage therapy exists.<sup>2,3</sup> This predominant local failure has prompted some investigators to intensify the delivery of local radiation therapy treatments.

Many efforts at intensifying the local therapy of glioblastoma multiforme have involved radiation therapy dose escalation. This has been accomplished with technical modifications, (*i.e.* *brachytherapy or stereotactic radiosurgery*) or the use of biological modifications in treatment delivery such as altered fractionation schedules. Promising results in the use of brachytherapy in a prospective phase II trial have been reported. In these trials, patients receiving standard external beam radiotherapy and an interstitial boost have had an improved outcome relative to controls not receiving an implant. The encouraging results of phase II trials have prompted the evaluation with a phase III interstitial brachytherapy cooperative group trial (*BTCG 8701*).<sup>4,5</sup>

It has become customary to include peritumoral edema in the low dose radiation target volume. This practice is supported by the finding of infiltrating tumor cells in the edematous region around contrast-enhancing tumor on either MRI or CT scans.<sup>21</sup> Despite this elective radiation to these imaging abnormalities, the dominant pattern of treatment failure in high grade gliomas remains the region within or immediately adjacent to the contrast-enhancing mass on cross-section imaging.<sup>2,3</sup> Because radiation complications are a function of both dose and volume and large volume elective irradiation limits the conformality of 3D conformal radiation therapy, it makes good sense to eliminate elective irradiation of peritumoral edema and focus the radiation treatment to the dominant contrast-enhancing mass. As radiation dose is escalated to a central tumor mass, the adjacent tissue dose increases related to entrance and exit dose from multiple beam arrangements. This increased dose in regions juxtaposed to the primary tumor may contribute to local control of microscopic disease. An important objective of this study will be to determine whether the pattern of failure in patients with high dose 3D CRT with omission of elective edema radiation therapy is different from that of standard treatments.

Recently, stereotactic radiosurgery has been employed as a boost in selected patients with incompletely resected malignant gliomas. This is another method used to increase the local radiation dose above that which is safely delivered with conventionally planned and fractionated external beam radiation therapy. In a series from the Joint Center of Radiation Therapy in Boston, patients receiving stereotactic radiosurgery in addition to conventionally fractionated radiotherapy had improved outcome relative to historical controls.<sup>6</sup> Radiosurgery is currently being evaluated in the phase III clinical trial for patients with small glioblastomas multiforme.

Both brachytherapy and stereotactic radiosurgery are limited by the size and location of tumors that can be treated with these modalities. They cannot be universally applied to all patients with primary malignant brain tumors.

Attempts at dose escalation with standard external beam radiotherapy have been made. In an analysis of the Brain Tumor Study Group protocols, an improvement in median survival time was demonstrated with increasing radiation therapy doses: from 18 weeks without radiation to 28 weeks with 50 Gy, 36 weeks with 55 Gy and 42 weeks with 60 Gy.<sup>7</sup> In a randomized dose escalation study conducted jointly by the RTOG and ECOG, no benefit was demonstrated in patients receiving 70 Gy compared to those patients receiving 60 Gy.<sup>8</sup> The lack of benefit with doses above 60 Gy may be related to the increased toxicity associated with conventionally fractionated and standardly planned radiation therapy. Indeed, Marks et al. have reported that an 18% incidence of brain necrosis with doses higher than 64.8 Gy compared to 0% with radiation doses <57 Gy.<sup>9</sup>

Because of the risk of cerebral radionecrosis with increasing doses of conventionally fractionated radiation therapy, some investigators have employed hyperfractionated scheme to capitalize on the reduction of late effects associated with smaller fraction sizes. The Brain Tumor Study Group conducted a randomized study of whole brain radiation therapy with 66.0 Gy in 1.1 Gy twice daily fractions, compared to 60 Gy in conventionally fractionated 2 Gy per day fractions with BCNU chemotherapy, BCNU chemotherapy and misonidazole or streptozotocin. There was no significant improvement in patients receiving the hyperfractionated radiation therapy.<sup>10</sup> The lack of benefit may

have been related to the relatively small radiobiological differences between the two fractionation regimens for tumor control.

The Radiation Therapy Oncology Group has conducted a phase I/II dose escalation trial in patients with supratentorial malignant gliomas to determine the survival, and disease-free survival rates of patients treated with hyperfractionated or accelerated hyperfractionated regimens with progressively escalating doses of radiation. The rationale for employing accelerated fractionation is that tumor cell repopulation could be minimized by shortening overall treatment time thereby increasing the probability of tumor control for a given dose level.<sup>11</sup> In the most recent analysis, the subgroups of patients with glioblastoma multiforme who received higher hyperfractionated radiation therapy doses had a significantly superior survival than patients receiving lower doses in the accelerated hyperfractionated arms. This suggests that this group of patients may benefit even more from further dose escalation. Patients with anaplastic astrocytoma who received the higher hyperfractionated doses had worse survival than those receiving lower hyperfractionated doses. This suggests that at the highest hyperfractionation dose levels patients may experience radiation associated toxicity which contributes to a worse survival.<sup>12</sup> This hypothesis is supported by a radiographic analysis of the same patient population that demonstrated a higher rate of moderate to severe treatment related changes on follow-up CT or MRI at doses in excess of 72 Gy.<sup>13</sup>

In most normal tissues, late effects from radiation therapy correlate to cumulative radiation dose, fractionation, and treatment volume. A volume relationship for a CNS injury and conventionally fractionated radiation therapy has not been clearly established. In single fraction stereotactic radiosurgery, it is clear that there is an inverse relationship between volume irradiated and total radiation dose. As the volume of brain tissue irradiated in a single fraction increases, the radiation dose that causes radionecrosis decreases.<sup>14,15</sup> In clinical practice, this inverse relationship may not be apparent because the concern of late effects may prompt physicians to decrease dose and/or volume to avoid complications. RTOG study 94-11 tested the hypothesis that radiation therapy of smaller volumes would allow the safe administration of higher doses of radiation compared to patients with large volumes of tumor.

In this study, we hypothesize that late radiation CNS effects are dose and volume related and that the use of conformal radiation therapy may reduce the risk of late radiation associated necrosis by decreasing the volume of CNS tissue that receives a high dose with careful 3-D treatment planning. Data from the University of Michigan has demonstrated that there is significant saving of dose to normal brain with the use of conformal radiation therapy when compared to conventional treatment planned with parallel opposed lateral beams.<sup>16</sup> In the University of Michigan studies, a 3-D treatment plan reduced the volume encompassed by the 95% isodose by over 50% when compared with conventional opposed partial brain fields. A small series of patients with conformally planned fields to doses >70 Gy have been treated with no significant increase in morbidity.<sup>17</sup> An added indirect benefit of 3-D conformal radiation therapy is the adjacent normal brain is irradiated at a lower dose per daily fraction when all fields are treated than in conventional radiation therapy. Late CNS radiation effects are clearly related to dose per fraction and as a result it is expected that 3-D planned patients will tolerate higher doses to a central tumor and target volume because of the lower dose per fraction seen in the adjacent normal tissues.<sup>18</sup> Because the dominant pattern of failure of glioblastoma is within the contrast enhancing lesions seen on CT or MRI, it is the intent of this study to focus treatment exclusively at the enhancing residual mass following surgery. No treatment will be administered to the surrounding edema that is known to be at risk of containing microscopic tumor cells. By intensifying the dose of radiation therapy to the contrast enhancing lesion, we will learn whether the presence of microscopic tumor in the surrounding edema presents a risk of recurrence outside of the gross residual tumor.

If acceptable late toxicity is seen in this trial with high doses of conformally planned radiation therapy, it is expected that this modality may be tested in a future phase III trial for patients with radiosurgery ineligible glioblastoma multiforme treated to more conventional doses (60 Gy).

#### Diagnostic Follow-up Studies

One of the strengths of 3D conformal radiotherapy is the ability to analyze radiation and tumor related changes on follow-up MRI scans as they correlate to the original radiation dose distribution. Follow-up MRI scans will be correlated with the treatment plan to detect dose related changes at follow-up.

## **2.0 OBJECTIVES**

**2.1** Test feasibility and toxicity of escalating doses of conformal radiation therapy planned with 3D treatment planning in patients with glioblastoma multiforme.

- 2.2 Determine dose/volume and dose/anatomic characteristics that influence radiotherapy induced CNS toxicity. Dose information will be stored in a queryable image database similar to other 3D CRT trials.
- 2.3 Evaluate local control, survival, and failure patterns of patients treated with high doses of conformal radiation therapy to gross disease. Elective treatment to surrounding edema will not be used. Endpoints for data analysis will be "time off study" from any cause (*"early dropouts" from tumor progression and/or toxicity*) and survival.
- 2.4 Correlate changes on cross sectional diagnostic MRI imaging studies to clinical or biological endpoints (*tumor viability, cerebral radionecrosis, neurologic performance status*).

### **3.0 PATIENT SELECTION**

#### **3.1 Eligibility Criteria (11/13/00)**

- 3.1.1 Histologically confirmed glioblastoma multiforme with areas of necrosis.
- 3.1.2 Diagnosis must be made by surgical biopsy or subtotal excision; patients with a complete tumor resection of tumor are eligible.
- 3.1.3 The tumor must be supratentorial in location.
- 3.1.4 Therapy must begin within five weeks after surgery but within one week after registration.
- 3.1.5 Age  $\geq$  18 years.
- 3.1.6 Karnofsky performance status (*KPS*)  $\geq$  60 (*Appendix II*)
- 3.1.7 Neurologic Functional Status 0, 1, 2, or 3 (*Appendix II*)
- 3.1.8 Adequate bone marrow reserve (*hemoglobin  $\geq$  9 grams, absolute neutrophil count  $\geq$  1500/mm<sup>3</sup>, platelets  $\geq$  100,000/mm<sup>3</sup>*), and acceptable renal (*BUN  $\leq$  30 mg and creatinine  $\leq$  1.8 mg*) and hepatic function (*bilirubin  $\leq$  2.0 mg and SGPT or SGOT  $\leq$  twice normal range*).
- 3.1.9 Must be ineligible for RTOG 93-05 (*prior to study closure of RTOG 93-05 on 6/30/00*).
- 3.1.10 Normal chest X-ray. If chest X-ray is abnormal, a DLCO should be performed and must be  $\geq$ 60% of predicted value.
- 3.1.11 Either a diagnostic CT with contrast or MRI scan must have been performed preoperatively. A postoperative MRI with contrast enhancement must be performed within four weeks prior to registration. To minimize artifactual enhancement, post-operative imaging shall be done 48-72 hours after surgery when possible. Patients undergoing stereotactic needle biopsy are not required to have a post-operative imaging study; however, an MRI must be available for treatment planning. See Section 4.1.2.
- 3.1.12 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 (11/13/00)**

- 3.2.1 Well differentiated or anaplastic astrocytoma.
- 3.2.2 Multifocal glioma.
- 3.2.3 Recurrent glioblastoma multiforme.
- 3.2.4 Patients with prior malignancies, except carcinoma *in situ* of the cervix or bladder, ductal carcinoma of the breast *in situ* or non-melanomatous skin cancer, unless disease free  $\geq$  5 years.
- 3.2.5 Patients must not have received prior radiotherapy to the head and neck or prior systemic chemotherapy for any malignancy.
- 3.2.6 Major medical illness(es) or psychiatric impairment(s) that will prevent completion of protocol therapy or would interfere with follow-up.
- 3.2.7 Inability to obtain histologic proof of glioblastoma multiforme.
- 3.2.8 Pregnancy. Teratogenic effects of radiation are well documented. Because 3D CRT 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 general physical examination.
- 4.1.2 CT or MR scan performed preoperatively and MR postoperatively prior to the initiation of radiotherapy (*mandatory for eligibility*). Patients undergoing a stereotactic guided needle biopsy do not require a repeat MRI after the procedure if the prebiopsy MRI is suitable for treatment planning.
- 4.1.3 CBC with differential, platelet count, blood chemistries (*SMA-12*).
- 4.1.4 Chest x-ray.
- 4.1.5 Detailed neurological examination.



- 4.1.6 The extent of surgical resection prior to protocol entry shall be (a) biopsy, or (b) subtotal resection, as described by the operative report and/or post operative imaging.
- 4.1.7 Patients must complete the Spitzer quality of life index and mini-mental exam prior to starting therapy. Request forms pack from RTOG HQ in advance.
- 4.1.8 Pregnancy test for women of child-bearing potential.

**5.0 REGISTRATION PROCEDURES**

- 5.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in Appendix VII (3D Conformal Radiation Therapy Quality Assurance Guidelines) for Brain Tumors may enter patients to this study. The 3D Facility Questionnaire (Appendix VIII, one per institution) is to be sent to the Washington University (WU) 3D Quality Assurance (QA) Center for review prior to entering any cases. Upon review and successful completion of "Dry-Run" QA test, the WU 3D QA Center will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study.
- 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
- 5.3 After the patient is registered to a treatment arm, RTOG will notify the WU 3D QA Center (*by FAX*) providing the following information:
  - Case Number
  - Institution Name
  - Institution Number
  - Date of Registration
  - Treatment Option
  - Stratification Group
- 5.4 After the patient is registered to a treatment arm, the institution will submit the required data (*both hardcopy and digital*) to the WU 3D QA Center (*See Section 12.2*) and to the RTOG (*See Section 12.1*).

**6.0 RADIATION THERAPY**

**6.1 Dose Specification (11/13/00)**

- 6.1.1 Prescription dose is the ICRU reference point dose within the planning target volume, at or near the center of the target. The minimum dose to the planning target volume should not be less than 93% of the ICRU-50 reference point dose. PTV<sub>1</sub> represents the resection cavity and gross residual tumor plus 15 mm margin for subclinical disease (CTV<sub>1</sub>) and an additional 3 mm for treatment uncertainty. PTV<sub>2</sub> represents the resection cavity and gross residual tumor plus 3 mm for treatment uncertainty. The maximum dose to the PTV<sub>2</sub> should not exceed the ICRU reference point dose by more than 3%.
- 6.1.2 Prescription dose to PTV<sub>1</sub> and PTV<sub>2</sub> shall be according to the following dose escalation schema delivered in 2 Gy fractions, all fields treated once daily, 5 fractions/week.

Dose	Group 1		Group 2	Total Prescription Dose
	PTV <sub>2</sub> <75cc	PTV <sub>2</sub> ≥75cc	PTV <sub>2</sub> ≥75cc	
Level	Large Field (PTV <sub>1</sub> )	Boost (PTV <sub>2</sub> )	Boost (PTV <sub>2</sub> )	
1	46 Gy/23 fx	20 Gy/10 fx	20 Gy	66 Gy
2	46 Gy/23 fx	26 Gy/13 fx	26 Gy	72 Gy
3	46 Gy/23 fx	32 Gy/16 fx	32 Gy	78 Gy
4	46 Gy/23 fx	38 Gy/19 fx	38 Gy	84 Gy

PTV=CTV+3mm  
 CTV<sub>1</sub>=GTV+15mm  
 CTV<sub>2</sub>=GTV

Large ( $\geq 75cc$ ) and small ( $< 75cc$ ) targets will be treated identically. The volumes are stratified to determine if volume differences exist with respect to dose escalation. Contact RTOG Headquarters prior to registration to determine current dose level.

**6.1.3** The reported doses shall include the cumulative dose to the ICRU reference point (*Section 6.4*), the cumulative maximum point dose, and minimum point dose to the PTVs.

**6.1.4** Tissue heterogeneity corrections will not be used. Dose escalation will be based upon uncorrected dose distributions.

## **6.2 External Beam Equipment**

**6.2.1** Megavoltage equipment is required with effective photon energies  $\geq 4MV$ .

**6.2.2** 3-D conformal radiation therapy capabilities as defined and confirmed by the 3-D Quality Assurance Center. The ability to plan and deliver non-coplanar fields is mandatory. Digital merging of MRI and the treatment planning CT is recommended but not required. See Appendix VII for 3-D QA Guidelines.

## **6.3 Treatment Planning Imaging and Localization Requirements.**

**6.3.1** A treatment planning CT scan will be required to define tumor, clinical, and planning target volumes. The treatment planning CT should be acquired with the patient in the same position, immobilization device, and conditions as she/he will be for treatment. Each patient will be positioned and immobilized with an individualized thermoplastic cast or molded foam cradle on a flat table top. The CT scan should start at the top of the cranial vertex and down to the neck to encompass the entire cranial contents and the head. CT scan thickness should be  $\leq 0.5$  cm through the region that contains the target volumes. The regions above and below the target volume may be scanned with slice thickness of  $\leq 1$  cm.

The GTV, CTV and PTV and all normal tissues must be outlined on all CT slices in which the structures exist. The post-operative MRI will be used to define the GTV. If available, CT to MRI registration software should be used to assist in defining the MRI based GTV on the treatment planning CT. It is strongly encouraged that post operative MRI scanning is done  $\leq 72$  hours after surgery.

**6.3.2** A localization/immobilization system should be used. Generally, thermal-plastic masks are appropriate. Relocatable stereotactic head frames are acceptable. Other systems require approval of Dr. Michalski.

## **6.4 Volume and ICRU Reference Point Definitions**

The definitions of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

**6.4.1** The gross tumor volume (GTV) is defined by the physician as all known gross disease as defined by the treatment planning CT and/or postoperative MRI scan. CT to MRI image registration should be used when available. The GTV will encompass the residual gross tumor as seen on a contrast enhanced MRI scan of the head after surgery. Every attempt should be made to obtain postoperative MRI  $\leq 72$  hours after surgery.

**6.4.2** The clinical target volumes (CTV) are the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and for this study will be defined as follows: CTV<sub>1</sub> is the resection cavity or residual tumor plus at least a 15 mm margin. CTV<sub>2</sub> is the resection cavity or GTV (*post operative residual*) with no margin. Superior and inferior margins for CTV<sub>1</sub> should be at least 15 mm +/- 1 mm depending on the resolution of the CT scan slicing. The CTVs will be limited to the brain and adjacent nervous tissue. The CTVs need not extend beyond the cranial contents. The 15 mm margin refers to a margin of non-enhancing brain or nervous tissue adjacent to the GTV. (*See figure in Appendix VI*)

**6.4.3** The planning target volume (PTV) will provide a margin around the CTV to compensate for variability in treatment setup and patient motion. A minimum of 3 mm around the CTV is required to define each respective PTV. Note: The PTV does not indicate the block edge. Additional margin around the PTV to define the beam aperture is required to account for beam penumbra (*block margin in a BEV display*).

**6.4.4** The ICRU reference points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

**6.4.5** Critical Normal Structures. Normal tissues to be contoured will include the **cerebral hemispheres** (*ipsilateral and contralateral*), **brain stem**, **optic nerves** and **chiasm**, **eyes** (*ipsilateral and contralateral globes*), **cerebellum**, and **skin**. The tissue within the skin and outside all other critical normal structures and PTVs is designated as "unspecified tissue". In cases where the tumor crosses midline, the more involved side will be considered ipsilateral.

## **6.5 3-D Planning**

**6.5.1** Planning Target Volume (PTV): Treatment will be given only to the PTV(s) using a 3-D conformal fields shaped to exclude as much of the normal brain and other critical structures as possible. The beam's eye view displays must be used to design beam apertures. Field arrangements will be determined

by 3-D planning to produce the optimal conformal plan in accordance with the volume definition used. Vertex and other non-coplanar fields are often necessary to reduce dose to adjacent normal brain. The use of beam intensity modulation therapy is not allowed (*except for wedges, compensating filters, and static beam shaping devices, such as MLC*). The treatment plan used for each patient will be based on the treating physician's analysis of the volumetric dose including DVH analysis of the PTV and critical normal structures.

- 6.5.2** Critical Normal Structures: Custom shielding shall be used in conjunction with conformal planning to restrict the dose to normal structures. DVHs must be generated for all critical normal structures and the unspecified tissues. Portions of the adjacent normal brain will by necessity receive the full dose to the PTV; however, careful 3-D planning must be performed to ensure that the volume of normal brain and other critical structures receiving the full dose is kept to a minimum. DVHs for the following structures must be provided: Ipsilateral Cerebrum, Contralateral Cerebrum, Ipsilateral Optic Nerve, Contralateral Optic Nerve, Ipsilateral Eye (*globe*), Contralateral Eye (*globe*), Cerebellum, Brainstem, Spinal Cord, and Skin (*unspecified tissues*). Dose to the eyes, optic nerve or chiasm are recommended to be <55 Gy and spinal cord < 50 Gy. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

**6.6** Treatment Verification

First day port films or portal images of each field (*except where impractical*) must be obtained. In addition, there must be included a set of orthogonal setup megavoltage images (*AP and lateral*) from the first treatment. Thereafter, weekly verification films or images of orthogonal views (*anterior to posterior and lateral projections*) are required and will be reviewed by the treating physician.

**6.7** Quality Assurance for Target Volumes and Critical Structure Volumes

The 3-D QA Center will review PTV, CTV, GTV, and designated structures as appropriate (*see QA Guidelines, Appendix VII*).

**6.8** Quality Assurance of Field Placement

The 3-D QA Center will review the first day orthogonal setup and portal films or images (*see QA Guidelines, Appendix VII*).

**6.9** Quality Assurance of Dose Distribution

- 6.9.1** The 3D QA Center will display, and compare with hard copies, isodose distributions for the axial, sagittal, and coronal planes (*or multiple axial planes as outlined in Appendix VII, QA Guidelines*) through the isocenter to verify correct digital submission and conversion.
- 6.9.2** The PTV dose coverage and heterogeneity will be scored as specified in QA guidelines (*Appendix VII*).
- 6.9.3** For each treatment plan, a Conformity Index will be calculated and recorded by the 3D QA Center.

CONFORMITY INDEX

$$CF \text{ (cover factor)} = \frac{\# \text{ points } \geq \text{prescription dose in PTV}}{\text{Total \# points in PTV}}$$

$$SF \text{ (spill factor)} = 1 - \frac{\# \text{ points } \geq \text{prescription dose not in PTV}}{\text{Total of all points } \geq \text{prescription dose}}$$

$$CI \text{ (conformity index)} = CF \times SF$$

Perfect CI = 1.000

**6.10** Toxicity Reporting Guidelines

- 6.10.1** All fatal toxicities (*grade 5*) resulting from protocol treatment must reported by telephone to the group chairman, to RTOG Headquarters Data Management staff, and to the study chairman within 24 hours of discovery.
- 6.10.2** All life threatening (*grade 4*) toxicities from protocol treatment must be reported by telephone to group chairman, RTOG Headquarters Data Management staff, and to the study chairman within 24 hours of discovery.
- 6.10.3** Appropriate clinical data forms, and if requested, a written report, must be submitted to Headquarters within 10 working days of the telephone report by fax (215) 928-0153.

## **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 ( $80 \text{ mg/m}^2$ ) will be administered on days 1, 2, and 3 of the first week of radiotherapy and repeated on days 56, 57, and 58. It will then be administered every eight weeks for four more cycles for a total of 6 cycles (*maximum BCNU dose 1440 mg/m<sup>2</sup>*). The BCNU administered on days 1,2 and 3 of the first week of radiotherapy can be given any time on those days.

**7.1.2.2** BCNU will be given as an intravenous infusion over 1-2 hours at a dose of  $80 \text{ mg/m}^2$  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  $100 \text{ mg}/30 \text{ ml}$ . 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  $0.2 \text{ mg/ml}$  is stable for 48 hours at  $4^\circ\text{C}$  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  $1200\text{-}1500 \text{ mg/m}^2$ . 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  $1440 \text{ mg/m}^2$  (6 cycles at  $80 \text{ mg/m}^2 \times 3 \text{ days}$ ) or 1 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 reduce dose. The dose modification will be as follows:

<b>DOSE MODIFICATION TABLE</b>			
<b>Nadir:</b>			
<u>Absolute Neutrophil Count (ANC)</u>		<u>Platelets</u>	<u>Modification</u>
≥ 750	and	≥ 75,000	100% dose
250 < 750	or	25,000 < 75,000	75% dose
< 250	or	< 25,000	50% dose
<b>At scheduled time of administration:</b>			
<u>Absolute Neutrophil Count</u>		<u>Platelets</u>	<u>Modification</u>
≥ 1500	and	≥ 100,000	Dose modified for nadir only
< 1500	or	< 100,000	Hold dose for 2 weeks* and repeat
<b>* After 2 weeks:</b>			
<u>Absolute Neutrophil Count</u>		<u>Platelets</u>	<u>Modification</u>
≥ 1500	and	≥ 100,000	Dose modification for nadir only
1000 < 1500	or	75,000 < 100,000	75% dose
< 1000	or	< 75,000	Contact Chemotherapy Chairman before further chemo administration

**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.X for toxicity and Adverse Event Reporting. A copy of the CTC version 2.X 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.X.

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 (11/13/00)**

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

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**

Not applicable to this study.

**11.0 PATIENT ASSESSMENTS**

**11.1 Study Parameters**

Assessment	Prior to Registration	During RT	Prior to Each ChemoCycle	At Each Followup <sup>c</sup>
History and PE	X		X	X
Neurological exam <sup>a</sup> , KPS	X	weekly	X	X
Evaluation of skin within RT Treatment portals		weekly		X
CBC including differential and platelets	X	weekly	weekly during chemo	X
Blood chemistries (SMA12)	X		X	
Chest X-ray	X		as indicated	as indicated
Gadolinium enhanced and T2 weighted MRI	<i>(Both pre-op &amp; post-op pre-radiotherapy)</i>			Per Section 11.2.2 and sent directly to the QACenter at Washington University (WU)
Mini Mental Status	X <sup>d</sup>	X <sup>b</sup>	X	X
Quality of Life-SQLI	X <sup>d</sup>	X <sup>b</sup>	X	X
LENT Scales				X
Physiologic Tumor Imaging				At time of suspected recurrence or necrosis <sup>e</sup> and sent directly to the WU QA Center.
Pregnancy Test	as applicable			

a. To include recording of steroid and anticonvulsant dose.

b. At end of RT, at 4 months, then at each follow-up.

- c. Every 4 months in years 1 and 2, every 6 months in year 3, then annually.
- d. To be performed prior to protocol therapy.
- e. PET, SPECT-Thallium, or MRI spectroscopy are encouraged if available.

## **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 neuroimaging 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  $\geq 50\%$  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.

**11.3.3** *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** Mental status will be measured by the MMSE; the SQLI will measure quality of survival.

**11.4.5** 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.

## **11.6 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 follow-up 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 registered and retrospectively found to be ineligible for this trial may discontinue forms submission upon notification of ineligibility 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.

**11.8 Instructions for Completing the LENT Forms (LE)**

11.8.1 Assessment of late radiation effects will be made on all patients receiving any radiation therapy. This evaluation will be scored on the Follow Up Form (F1) using the RTOG/EORTC Late Radiation Morbidity Scheme. In addition, a LENT evaluation will be completed on the appropriate SOMA pages that are applicable for patients receiving irradiation to the brain. The applicable SOMA sites for this protocol are: Brain, Eye, Ear, Hypothalamic/Pituitary Axis (*Male and Female*), Skin/Subcutaneous Tissue, Mature Bone, and Cervical Spinal Cord. Instructions for completing this instrument are found on the LENT Cover Sheet (page one of the LE form). The Alytic portion of the SOMA scales may be omitted. The LENT Evaluation is **completed by the investigator** or his/her designee, i.e., not by the patient.

**12.0 DATA COLLECTION**

**12.1 Summary of Data Submission**

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

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Chemotherapy Flowsheet (M1) <i>(to include pretx labs)</i>	
Initial Mini-Mental Status Evaluation (MS)	
Initial Spitzer Questionnaire (PQ)	Within 1 week of RT end
Pathology Report (P1)	
Mini-Mental Status Evaluation (MS)	
Spitzer Questionnaire (PF)	
Radiotherapy Form (T1) <i>(copy, original to WU per Section 12.2)</i>	
Chemotherapy Flowsheets (M1)	Within 1 week of completing each chemotherapy cycle
Acute Toxicity Followup Form (F0)	3 months <i>(90 days)</i> from start of RT
Follow-up Form (F1)	Every 4 months from treatment start for 2 years; q 6 months x 1 year, then annually. Also at progression/relapse. An F1 will also be due at death.
LENT Scales (LE)	
Mini-Mental Status Evaluation (MS)	
Spitzer Questionnaire (PF)	As applicable
Autopsy Report (D3)	

**12.2 Summary of RT QA Requirements *(to Washington University)***

<b><u>Preliminary Dosimetry Information:</u></b>	Within 1 week of start of RT
Pretreatment CT/MRI scan <i>(both pre- and post-surgery)</i> (C1) and reports (C3)	
Digital Patient Submission Information Form (T2)	
CT data, critical normal structures, all GTV, CTV and PTV contours	
Films and/or digital film images for simulation, first day portals, and one orthogonal set-up pair	
Digital beam geometry for first set of beams <i>(required)</i> and for all additional beams <i>(optional)</i>	
Doses for first <i>(or all)</i> sets of concurrently treated beams are optional.	



**Final Dosimetry Information:**

Within 1 week of RT end

Radiotherapy Form (T1)

Digital Patient Submission Information Form (T2)

Daily Treatment Record

Digital dose data and beam geometry data for all beam sets is required

First day boost and orthogonal setup films and/or digital data (*simulation and portal, if any*)

Hard copy isodose distributions as defined in Section 6.9

Digital DVH data

MRI Scans

Per Section 11.2.2

**12.2.1** For Mail or Federal Express:

James A. Purdy, Ph.D.  
RTOG 3D QA Center  
Washington University School of Medicine  
510 S. Kingshighway  
St. Louis, MO 63110  
tel. 314/362-2631 Fax# 314/362-2682

**12.2.2** To send over Internet or using magnetic tape:

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the *ftp* account assigned to the submitting institution shall be used to and *e-mail* identifying the data set(s) being submitted shall be sent to:

**rtog3dqa@castor.wustl.edu**

For tape submission, please contact the 3D QA Center about acceptable tape types and formats.

**12.3** **Timely Data Submission for Toxicity Evaluation**

Timely data submission is critical in order to meet the study's objectives for toxicity evaluation and to safely assign treatment levels.

**13.0** **STATISTICAL CONSIDERATIONS**

**13.1** **Study Endpoint**

**13.1.1** The primary endpoint of this study is acute and late toxicity.

**13.1.2** Steroid dependency within the first three months of treatment.

**13.1.3** The incidence of treatment-related radionecrosis.

**13.2** **Sample Size**

In order to establish the maximum tolerated dose (*MTD*) of radiotherapy that can be delivered using three-dimensional conformal radiation treatment (*3D-CRT*), acceptable morbidity criteria must be defined. A 30% Grade 3 or Grade 4 irreversible CNS toxicity rate is determined to be dose limiting (*DLT*), a Grade 5 toxicity will suspend accrual until the Study Chair reviews the case. Irreversible toxicity is defined to be any CNS toxicity that does not respond to therapy or requires surgical intervention.

In this study, there are two separate groups determined by the amount of brain treated. The groups are: Group 1, < 75 cc in the boost planning target volume (*PTV<sub>2</sub>*), Group 2, > 75 cc in the *PTV<sub>2</sub>*.

The QA Center must approve each institution before they can begin accrual. This approval will consist of a submission of a "dry run", i.e., the demonstration of correct data exchange and the successful planning for one patient at the lowest dose level in that patient's registered group. When the QA Center has approved the institution, the Center will notify the Study Chair, Protocol Administrator, and Study Statistician in writing. A more detailed description of these procedures is provided within the QA Guidelines Section of this protocol.

When an institution is approved by the QA Center, that institution will be able to begin accruing to the highest available dose levels within the three groups, as described below.

Toxicity and accrual will be monitored continuously as each patient is accrued and the data accumulated. Twenty patients are required per dose arm to evaluate both acute DLT and late radionecrosis. Each patient must be evaluated for acute DLT, which may occur any time during the first 90 days from the start of therapy. If none of the first 9 patients develop a DLT, the additional 11 patients will be accrued then the dose arm will be escalated. If fewer than 3 patients in the first 14 develop a DLT, the additional 6 patients will be accrued then the dose arm will be escalated. If 3 or more DLTs in the first 14 cases are observed then the accrual will be halted. If the accrual is rapid and 20 patients are accrued prior to the assessment of the first 9 or 14 patients for acute DLT then accrual will be halted at 20. The DLT determines escalation, but an escalated dose may be halted if a prior dose is found to have either more than 2 patients with radionecrosis or if more than 9 of 14 progression-free patients are on steroids after 3 months from the start of therapy. **(10-15-01)**

### **13.3 Dose Escalation (1/8/99)**

Dose escalation is a three-step process within this study. Criteria for escalation are  $\leq 2$  grade 3 or 4 irreversible acute CNS toxicities and no grade 5 toxicities in the first 14 evaluable patients. If either of these criteria is exceeded then the dose will be deemed too toxic. In the first 14 progression-free patients fewer than 9 patients on steroids at 3 months from the start of therapy is acceptable for escalation. A dose may be de-escalated if more than 2 patients develop radionecrosis in the first year of follow-up.

### **13.4 Patient Accrual**

The patient accrual is projected to be 10 cases per month; however, since there are two separate groups, this translates to approximately 5 patients per month per group. At this rate, it will take a minimum of 5 months to accrue enough patients to determine each dose level for each group. If the average monthly accrual rate is less than two patients per group, the study will be re-evaluated with respect to feasibility.

### **13.5 Analysis Plans**

#### **13.5.1 *Interim Analyses***

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

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) compliance rate of treatment delivery with respect to protocol prescription; and,
- c) the frequency and severity of the toxicities.
- d) the cumulative incidence of radionecrosis.

Any problems will be reported to the RTOG committee responsible for this study and, if necessary, the Executive Committee, so that corrective action can be taken.

#### **13.5.2 *Analysis for Reporting the Initial Treatment Results***

This analysis will be undertaken when the MTD has been established for each group and each patient has been potentially followed for a minimum of 3 months following radiotherapy. The usual components of the analysis are:

- a) tabulation of all cases entered and any excluded from the analysis, with reasons for the exclusion;
- b) reporting institutional accrual;
- c) distribution of important prognostic baseline variables; and,
- d) observed results with respect to the endpoint described in Section 13.1. Further subgroup analyses will not be undertaken due to the small sample sizes.

### **13.6 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.<sup>19</sup> The RTOG found no difference in survival of glioblastoma multiforme patients by race.<sup>20</sup> Since there are no publications found to support a possible interaction between different radiation therapy schedule 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.

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## APPENDIX I

### RTOG 98-03

#### **PHASE I/II RADIATION DOSE ESCALATION STUDY APPLYING CONFORMAL RADIATION THERAPY IN SUPRATENTORIAL GLIOBLASTOMA MULTIFORME**

#### **Sample Consent Form**

#### **RESEARCH STUDY**

I have the right to know about the procedures that are used in my participation in clinical research so I can decide whether to undergo the procedure after knowing the risks, benefits, and alternatives involved. This is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

#### **PURPOSE OF STUDY**

It has been explained to me that I have a malignant brain tumor. The usual treatment for this disease is surgery, radiation therapy and chemotherapy. The Department of Radiation Oncology is involved in a research study using a radiation therapy planning technique call 3-Dimensional Conformal Radiation Therapy. This allows the radiation beams to treat an area shaped more closely like that of my tumor. The standard radiation treatments would normally treat a large area of normal brain tissue. Despite these large areas of treatment, most patients with tumors like mine will develop a recurrence near the original tumor. By using this new radiation therapy technique my doctor can prescribe a higher dose of radiation therapy to the remaining tumor in my brain in order to prevent or delay tumor growth. There is some evidence that a higher dose of radiation therapy may improve the chances of controlling my tumor. By using this new treatment planning technique my doctor can protect more of the normal brain while increasing the dose of radiation therapy to just the tumor.

The purpose of this research study is to determine the maximum tolerable dose of radiation therapy that can be given with this new treatment planning technology. It will provide my doctor and other radiation oncologists important information about how high doses of radiation therapy may be able to control a tumor such as mine. It will also give important information about radiation therapy related side effects in the brain. Because the area of radiation therapy is smaller than is used in similar patients with my disease, there is the possibility that my tumor could recur in other parts of my brain not treated to the high radiation dose.

#### **DESCRIPTION OF PROCEDURES**

If I agree to participate in this study I will need to have a magnetic resonance imaging (*MRI*) scan done after my surgery to determine how much tumor is remaining. I then will have a special CT scan of the brain for the radiation therapy treatment planning. I will wear a special custom-made face mask while I am lying in the treatment position on a flat table. This will ensure that I am placed in exactly the same position every day while receiving my radiation treatments. After this mask is made, the CT scan will be done for the 3 dimensional radiation treatment planning. This procedure generally takes one hour.

I will receive my radiation treatment once every day, Monday through Friday, for 6 to 8 weeks. Each treatment takes 15-30 minutes. The dose of radiation I receive will depend on the size of my tumor and how many patients have been entered on the study before me. The first few patients will receive a dose of radiation that previous experience suggests is safe. If they have no serious problems, the next group of patients will receive a higher dose. My doctor can tell me what dose I will receive before I make a decision about participating in this study. All patients in this study will receive at least 33 radiation treatments.

In addition to the radiation therapy, I will receive BCNU chemotherapy by vein as an outpatient. This commercially available drug is considered to be potentially helpful for controlling my disease. The BCNU chemotherapy will begin on the first three days of radiation. The BCNU chemotherapy will be repeated every 8 weeks for three days for up to six cycles. The BCNU chemotherapy treatment is given over 1-2 hours at each of these visits.

As part of this study my doctors are asking me to fill out a questionnaire to evaluate the impact cancer had on me and my quality of life (*QOL*). The QOL study will require an evaluation once at the beginning of treatment, at six weeks, at 3 months, and then when I see my doctor for checkups. Assessments will be made with short questionnaires that will take me

a few minutes to complete. The questionnaires will be completed independently by me. If I am unable to fill out the questionnaire, my doctor will ask my spouse, a family member, or significant other to fill it out as if I were answering the questions.

I will have follow-up examinations in the department of radiation oncology after finishing treatment. The follow-up examination will include a physical and neurologic examination, laboratory tests, x-rays, and scans. This schedule is similar to that of patients not participating in a research study.

In the event of death, an autopsy may be requested in order to better understand this type of tumor and its treatment. 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 helpful to the physicians and other patients participating in the study.

## **RISKS AND DISCOMFORTS**

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.

### **Risks of Radiation**

Radiation therapy may result in simply reddening and tanning of the skin, but might also involve skin blisters. The custom-made mask may be uncomfortably hot, or give me a feeling of being confined. Other side effects of radiation therapy include hair loss that may be permanent, possible nausea, headaches, plugging of the ears with decreased hearing, fatigue, and increased sleepiness lasting for several days or up to 1 to 2 weeks. This will happen 4 to 10 weeks after radiation therapy is complete. High doses of radiation may cause destruction of brain tissue ("*radiation necrosis*") and lead to neurologic problems. The symptoms of radiation necrosis can mimic those of recurrent tumor or those of a stroke. In some instance, these changes may require surgical treatment.

### **Risks of BCNU**

BCNU can cause nausea, a burning sensation at the injection site, facial flushing, and low blood pressure. Rarely liver and/or kidney abnormalities may develop. It also can lower blood counts, which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need antibiotics, hospitalization, and transfusions if these problems are severe. Rarely it may cause scarring of the lungs, resulting in cough or shortness of breath.

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, spouses, family members, and significant others will not be identified by name in these publications.

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 from chemotherapy 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.

This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant women causes significant risks to the fetus. If I am a woman of childbearing age and have not been surgically sterilized (*tubal ligation or hysterectomy*), I must have a pregnancy test before enrolling in this study. I must use adequate birth control measures to prevent pregnancy while participating in this study. If I am unwilling to use adequate birth control measures to prevent pregnancy, I should not participate in this study. If I should become pregnant while on this study, I must tell my doctor immediately. If I am a man, I must take adequate contraceptive precautions to avoid fathering a child.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

## **CONTACT PERSONS**

If injury occurs as a result of this research, treatment will be available. I understand, however, I will not be reimbursed 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 any personal benefit will result from the treatment program. I understand that the information obtained from this study will be used scientifically. It may 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.

Should my treatment cease to be of benefit and should my disease become worse, should side effects become very severe, should developments occur that indicate the treatment is not in my best interest, the treatment would be stopped. Further treatment would be discussed.

## **ALTERNATIVES**

Alternatives that could be considered in my case include radiation therapy performed off-study either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy. This 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 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. I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain procedures related to this protocol. 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 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. If there is 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 in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain my identity. However, no information by which I can be identified will be released or published.

**I have read all the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.**

\_\_\_\_\_  
Patient Signature *(or Legal Representative)*

\_\_\_\_\_  
Date



**APPENDIX II**

**KARNOFSKY PERFORMANCE SCALE**

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

**NEUROLOGIC FUNCTION (NF) STATUS**

<u>NF</u>	<u>Definition</u>
0	No neurologic symptoms; fully active at home/work without assistance.
1	Minor neurologic symptoms; fully active at home/work without assistance.
2	Moderate neurologic symptoms; fully active at home/work but requires assistance.
3	Moderate neurologic symptoms; less than fully active at home/work and requires assistance.
4	Sever neurologic symptoms; totally inactive requiring complete assistance at home or in institution-unable to work.

**APPENDIX III**

**NEUROLOGICAL FUNCTION 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 ( <i>bed</i> )	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 V

### ADVERSE EVENT REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures 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 ( $\geq$  *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities ( $\geq$  *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

#### Investigational Agents

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

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

#### i. Phase I Studies Utilizing Investigational Agents

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

- First occurrence of any toxicity (*regardless of grade*).

Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.  
\*\*A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent.

Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours  
\*\*A written report must be sent to RTOG within working days with a copy to IDB.  
(*Grade 4 myelosuppression not reported to IDB*)

- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent.

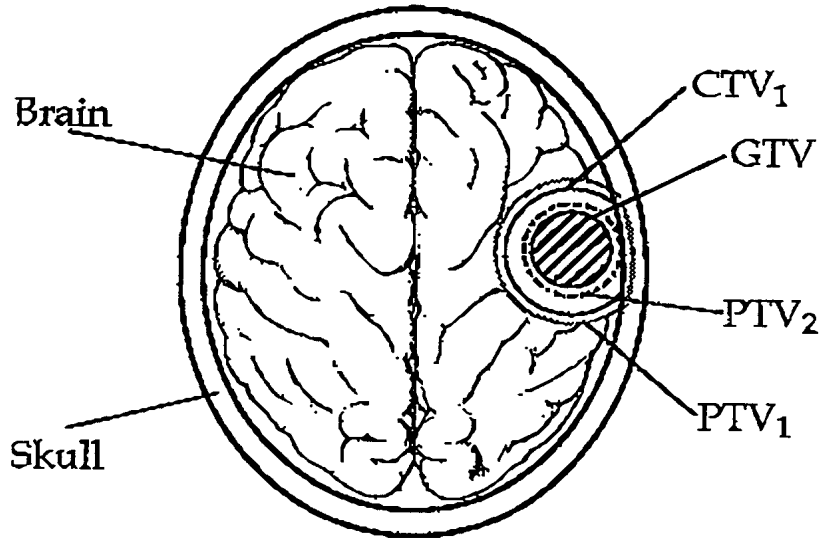
Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.  
\*\*A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.

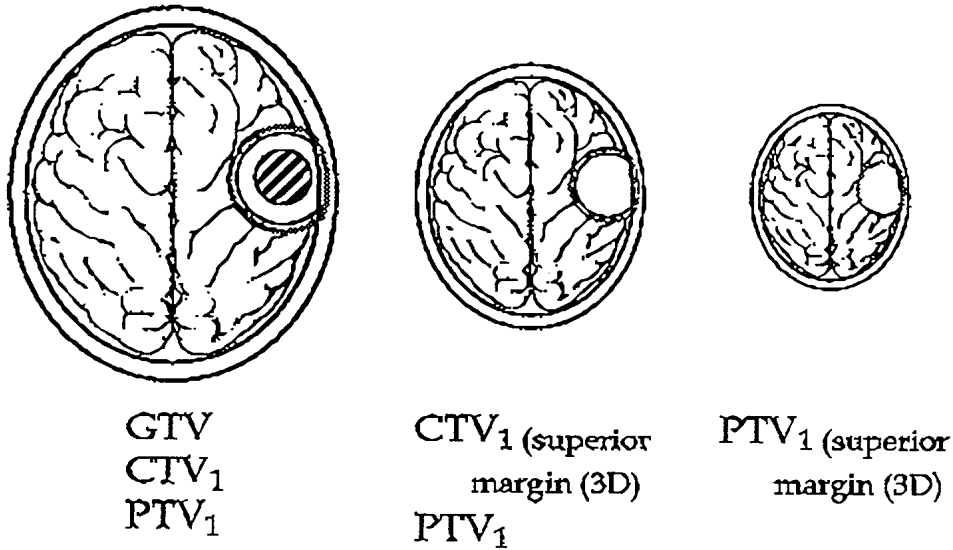
\*\*Report **in writing** to RTOG Headquarters and IDB within 10 working days.

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

APPENDIX VI  
ICRU Diagram for GTV, CTV, PTV



I. Asymmetric CTV margin remains within brain.  
 PTV is a symmetric margin around CTV.



II. A superior (3D) margin for both CTV and PTV are required.

## APPENDIX VII

### RTOG 3-D CONFORMAL RADIATION THERAPY QUALITY ASSURANCE GUIDELINES FOR BRAIN TUMORS

#### I. PURPOSE

To establish QA guidelines for the radiation oncologist, physicist, dosimetrist, technologist, and research associate pertaining to 3-D conformal radiation therapy (3-D CRT) studies.

#### II. BACKGROUND

The report of the Collaborative Working Group on the Evaluation of Treatment Planning for External Photon Beam Radiotherapy published in the May 15, 1991 issue of the International Journal of Radiation Oncology, Biology, Physics (Vol 21, No 1) should be referred to for background information regarding 3-D treatment planning.

#### III. CREDENTIAL REQUIREMENTS FOR PARTICIPATING INSTITUTIONS: TECHNOLOGY AND BASELINE PHYSICS INFORMATION

Facility questionnaire:

A. The following information must be submitted by each institution prior to enrolling patients in the protocol.

1. Treatment equipment: Documentation of linac model, energies to be used, and description of collimation to be used to define conformal fields, e.g. multileaf, cerrobend. Documentation of isocenter accuracy for gantry, collimator, and couch rotations.
2. Immobilization/repositioning system: Documentation of immobilization and repositioning system to be used.
3. Treatment verification system: Documentation of verification imaging system to be used, e.g., film, on-line imager.
4. Computer planning system: Documentation of 3-D RTP system to be used. To participate in Prostate 3-D CRT studies, the institution's 3-D RTP system must have the following capabilities:
  - a. CT data-system must be able to handle at least 40 axial CT slices.
  - b. Beam's-eye-view (BEV) display showing tumor and target volumes, critical structures, and beam aperture.
  - c. Calculate volumetric 3-D dose matrix for photon and electron beams. The minimum dose matrix size shall have a maximum dose point spacing of 3 mm or 10,000 points in axial planes (*whichever has least number of dose points*). The spacing between axial planes must be such that, at the minimum, a transverse distribution is computed for each axial slice.
  - d. Display and hard copy of superimposed isodose distributions on axial CT images (*sagittal and coronal planes, while desirable, are optional*).
  - e. Calculate dose-volume histograms (DVH) using dose-volume element sampling at least as fine as the dose calculation grid in axial planes and shall, at the minimum, use spacing in the orthogonal direction identical to the CT slice spacing. These DVHs must identify both absolute volume and absolute dose for the entire structure (*irradiated or not*).
  - f. Non-coplanar beams - system must provide capability of simulating each of the treatment machine motion functions including collimator length, width and angle, gantry angle, couch angle, and couch lateral, longitudinal and vertical position for both beam geometry definition and dose computation.
  - g. Calculate and display digital reconstructed radiographs (DRRs) with superimposed target volume, critical structure contours and treatment aperture.
5. Basic beam data: submit central axis dose ratios and dose profiles for 3 field sizes (*small, medium and large*), and corresponding isodose curves generated by 3-D RTP system for each beam modality and energy to be used.
6. Data transfer: Demonstrate capability of digital data exchange with the 3-D CRT QA Center for the data listed below. File formats will conform to the latest version of "*Specifications for Tape/Network Format for Exchange of Treatment Planning Information*" based on AAPM Report 10. All data will conform to treatment protocol requirements and these Quality Assurance Guidelines.
  - Patient CT data
  - Contours - gross tumor volume (GTV), clinical target volumes (CTV), planning target volumes (PTV) and critical normal tissues.
  - 3-D dose distribution data (*in absolute dose*) for multiple fraction groups (concurrently treated sets of fields)

- Beam modality/geometry and reference point dose specification
- Dose-volume histograms (in absolute dose and volume)
- Digital sim/portal images (*optional*)

B. Dry Run (*benchmark*) Test: A patient's complete data set as specified by the treatment protocol is to be submitted to the 3-D QA Center to demonstrate compliance with 3-D technical requirements.

#### **IV. PROTOCOL DATA AND QUALITY ASSESSMENT PARAMETERS**

A. The following information is to be submitted for each protocol patient at times specified in Section 12.2.

1. Hardcopy isodose distribution for the axial, sagittal, and coronal planes through the isocenter for the total dose plan must be submitted. If coronal and sagittal hard copy is a problem, five axial distributions may be substituted for them (*two cuts which are 2 slices superior and inferior of the superior and inferior slices containing the boost PTV, the superior and inferior cuts containing the boost PTV, and one through the center of the boost PTV*). These dose distributions must include
  - a. A reasonable number of isodose lines should be shown which can be used to determine that the digital dose and anatomy data are properly aligned relative to each other. The prescription dose for the boost PTV should be displayed. If the hard copy isodose lines are in percentage, the conversion factor to convert them to absolute dose (*Gy or cGy*) must be indicated.
  - b. The above isodoses should be superimposed over the treatment planning CT images. However, if such hard copy presents difficulties, similar plots without the gray scale image are acceptable if enough critical structure contours are identifiable on the hard copies to verify correct isodose curve positions relative to the digital data submitted.
2. First day portal films (*images*) for each portal and one set of orthogonal (*anterior-posterior and lateral*) films (*images*) for isocenter localization for each group of concurrently treated beams. If possible, these should be submitted in digital form as described below.
3. Dosimetry and imaging digital data. (*to be submitted via the Specifications for Tape/Network Format for Exchange of Treatment Planning Information where possible*):
  - a. Volumetric CT data for all cuts required by the protocol (required for the initial submission).
  - b. GTV, CTV, PTV and critical structure contours. They must be contoured on all slices in which each structure exists including skin on ALL CT cuts (*required for the initial submission*).
  - c. Postoperative contrast enhanced and T<sub>2</sub> weight MRI films used to define target volumes. Hard copy films are required.
  - d. Beam geometry specifications including ICRU 50 reference point doses (*for the purposes of this protocol, the isocenter dose should suffice*) in absolute dose units (*initial submission requires first set of beams with remaining beams sets optional, final submission requires **all** remaining beam sets*).
  - e. Volumetric 3-D dose distribution data in absolute dose for each set of concurrently treated beams computed without heterogeneity corrections.
  - f. Dose-volume histogram's for all PTV and critical normal structures (*including Unspecified Tissue - optional for initial submission, required for final submission*).
  - g. DRR or simulation verification radiograph (*initial submission only requires images for first set of beams, final requires remaining unsubmitted images*).
  - h. Portal radiograph or on-line image *initial submission only requires images for first set of beams, final requires remaining unsubmitted images*.
  - i. Any corrections to previously submitted digital data should be discussed with the RTOG 3D QA Center prior to such submission.

#### **V. QA REVIEW**

A. Quality Assurance of Target Volumes and Critical Structure Volumes

The 3-D QA Center will review PTV, CTV, GTV and designated critical structures on, at a minimum, the first 5 cases submitted by each institution. Subsequent cases will be spot checked only. Study Chair review will be performed on a semi-annual basis.

B. Quality Assurance of Field Placement

The 3-D QA Center will review initial placement films on, as a minimum, the first 5 cases submitted by each institution. At least one port film or pretreatment alignment film per field along with the digitally reconstructed radiograph from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation except where impractical. Subsequent cases will be spot checked only.



C. Quality Assurance of Dose Distribution

1. The 3-D QA Center will display, and compare with hard copies, isodose distributions for the planes submitted to verify correct interpretation and conversion of the digital patient and dose data.
2. The 3-D QA Center will calculate DVHs for the sum of all dose distributions submitted (*each submitted distribution is for one set of concurrently treated beams*). The QA center may compare them with the digitally submitted dose-volume histograms for the PTV, designated critical structures, and unspecified tissue.
3. Conformity Index - In each case a Conformity Index (*CI*) will be calculated for PTV<sub>2</sub>.

D. The following QA score will be assigned to each case:

- 1) No variation (*total coverage*). The 93% isodose surface (*relative to prescription dose*) completely contains the appropriate PTV.
- 2) Minor variation (*marginal coverage*). The 93% isodose surface (*relative to prescription dose*) contains <100% and  $\geq 95\%$  of the appropriate PTV.
- 3) Major variation (*miss*). The 93% isodose surface (*relative to prescription dose*) contains <95% of the appropriate PTV.

E. Dose Heterogeneity

1. Maximum dose to PTV should not exceed the prescription dose by >3% (*no variation,  $\leq 3\%$ ; minor variation,  $> 3$  to  $\leq 10\%$ ; major variation,  $> 10\%$ ). The maximum point dose to critical normal structures outside the PTV including the unspecified tissue should not exceed the prescription dose.*
2. Minor variation (*marginal coverage*); each prescription isodose surface coverage between  $\geq 95\%$  to < 100% of the appropriate PTV.
3. Major variation (*miss*); each prescription isodose surface coverage < 95% of the appropriate PTV.

**APPENDIX VIII**

**3D CRT QA  
FACILITY QUESTIONNAIRE**

This questionnaire with the requested supporting physics dosimetry information must be submitted to the RTOG 3D QA Center before any patients can be placed onto an RTOG 3D CRT protocol. These data will help assure the RTOG 3D Quality Assurance Center that each institution has committed proper facilities and effort to this modality. These data will also be used by RTOG 3D QA Center in their review of protocol treatment and verification. Please include additional descriptions when necessary.

**I. GENERAL INFORMATION**

Institution _____	RTOG# _____
Responsible Radiation Oncologist(s) _____	Telephone: _____
	FAX: _____
	Email: _____
Responsible Medical Physicist(s) _____	Telephone: _____
	FAX: _____
	Email: _____
Responsible Research Associate(s) _____	Telephone _____
	FAX: _____
	Email: _____

**II. 3D CRT EQUIPMENT (TO BE USED FOR PROTOCOL PATIENTS)**

A. Treatment 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, collimator, and couch angles employed (*attach description*). Report the results of this determination \_\_\_\_\_

Describe collimation to be used to define conformal fields \_\_\_\_\_

\_\_\_\_\_

B. Treatment Immobilization/Repositioning System

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

2. If developed “in-house”, please describe (*attach description*):

C. Treatment Verification System

1. Vendor/Model: \_\_\_\_\_

2. If developed “in-house”, please describe (*attach description*):

D. Treatment Planning System

1. Vendor/Model: \_\_\_\_\_

If developed "in-house", please describe (*attach description*):

2. State the ability of the system to contour the target and critical normal structures.
3. State the ability of the system to provide beam's-eye-view (*BEV*) display showing tumor and target volumes, critical structures, and beam aperture.
4. Describe the dose calculation algorithm.
5. State the ability of the system to calculate the required dose-volume data.
6. State the ability of the system to display and provide hardcopy of superimposed isodose distributions on 2D CT images (*axial, sagittal, and coronal planes*):
7. State the ability of the system to provide capability of simulating each of the treatment machine motion functions including collimator length, width and angle, gantry angle, couch angle, and couch lateral, longitudinal and vertical position for both beam geometry definition and dose computation.
8. State the ability of the system to calculate and display digital reconstructed radiographs (*DRRs*) with superimposed target volume, critical structure contours and treatment aperture.

E. Other

Describe any additional devices or techniques used for 3D CRT procedures.

**III. DOSIMETRIC PARAMETERS FOR 3D CRT**

Note: These data should be based on procedures and data in the AAPM Calibration *Protocol (Med Phys 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 treatment unit calibration.
- B. Relative Dosimetric Parameters.
  1. Output: cGy/MU or output relative to calibration, for all field sizes. Describe measurement geometry (*i.e., SSD and depth*).
  2. Central axis depth dose information: table of TPR's, TMR's, TAR's or percent depth dose for largest, smallest, and intermediate collimator sizes.
  3. Dose profiles for largest, smallest, and intermediate collimator sizes.

**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. Describe any special procedures (*beyond those required by protocol*) for treatment verification of 3D CRT.  
\_\_\_\_\_
- B. Describe techniques used to verify the treatment dose calculations via phantom measurements.  
\_\_\_\_\_
- C. Describe any other technical descriptions unique to your system \_\_\_\_\_  
\_\_\_\_\_

**V. REQUIRED BEFORE YOU CAN ENTER CASES**

- Complete this form
- Demonstrate capability of digital data exchange with the 3-D CRT QA Center.
  - a. Patient CT data
  - b. Contours – gross tumor volume (*GTV*), clinical target volumes (*CTV*), planning target volumes (*PTV*) and critical normal structures.
  - c. 3-D dose distribution data with fractionation information
  - d. Beam modality/geometry specification
  - e. Dose-volume histograms
  - f. DRR/Digital sim/portal images (*optional*)

Completed by \_\_\_\_\_ Date \_\_\_\_\_