

**TITLE:** A Prospective Trial of Neural Progenitor Cell Sparing Radiation Therapy Plus Temozolomide for Newly Diagnosed Glioblastoma Multiforme

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## SCHEMA

### **Patient Eligibility: (See Section 3)**

Newly diagnosed, histologically confirmed glioblastoma multiforme.

Radiation and medical oncologist recommends adjuvant radiation plus temozolomide.

Must begin therapy within 12 weeks of biopsy or surgery.

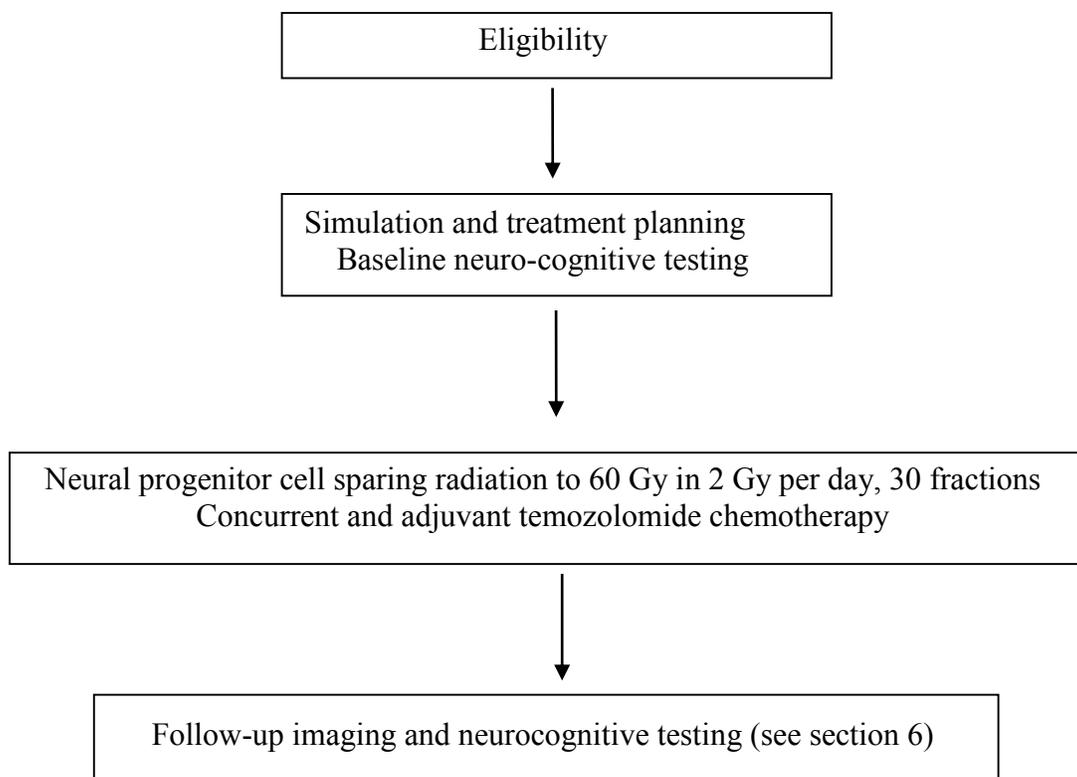
No prior brain radiation.

Age  $\geq$  18 years.

KPS > 60%.

Signed informed consent.

### **Treatment Plan: (See Section 5)**



**Required sample size: 30 patients**

**Anticipated accrual: 4-5 patients per month**

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## 1. OBJECTIVES

### 1.1. Primary Objectives

To estimate the local recurrence (LR) rate at 1 year in the spared neural progenitor cell (NPC) containing niches of the brain in patients treated with NPC sparing radiation therapy (RT) plus temozolomide for newly diagnosed glioblastoma multiforme (GBM).

### 1.2. Secondary Objectives

1.2.1 To quantify the extent of radiation dose sparing to the NPC containing regions that is possible without compromising tumor coverage in patients with newly diagnosed GBM

1.2.2 To examine the relationship between radiation dose to the NPC-containing niches and the proximity of the planning tumor volume to the NPC-containing regions.

1.2.3 To assess feasibility of evaluating cognitive function prospectively in patients undergoing NPC sparing RT for newly diagnosed GBM.

1.2.3 To explore if the potential change from baseline to six months in neurocognitive function as measured by the Mini Mental State Exam, Trail Making Test, Controlled Oral Word Association test (COWAT), Hopkins Verbal Learning Test-Revised, Digit Symbol Substitution Test is related to radiation dose to the NPC containing regions in patients treated with NPC sparing radiation for newly diagnosed GBM.

## 2. BACKGROUND

### 2.1 Study Disease and Rationale

The current standard of care in treatment of newly diagnosed GBM is based on the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada Clinical Trials Group (EORTC/NCIC) phase III clinical trial (1). This study randomized patients to surgical resection followed by radiation therapy plus or minus concurrent and adjuvant temozolomide and demonstrated an improvement in median survival from 12.1 months with standard radiation therapy to 14.6 months with the addition of temozolomide. This marked a significant improvement in 2 year overall survival from 10% to 27% with an improvement in five year overall survival from 1.9% to 9.8% (2), representing the first report of long term survivals of GBM.

As long term survival from GBM improves, minimizing long term toxicities of therapy becomes increasingly important. Animal studies have shown that new neurons and glia are produced throughout adult life from neural stem cell precursors in the subventricular zone of the lateral ventricles and the subgranular zone of the hippocampal dentate gyrus (3-5). These cells play an important role in injury repair within the central nervous

system (6,7). Similarly, these cells migrate to the site of inflammation caused by irradiation or brain injury (7).

Multiple animal studies have shown that neural progenitor cells are extremely sensitive to radiation (8-11). Tada et al. showed that 2 Gy of radiation effectively killed proliferating cells in both the SVZ of the lateral ventricles (8) and the subgranular zone of the dentate gyrus (9). The anti-proliferative effects last for up to 15 months after a single radiation treatment (12) and are dose dependent (8,9).

There is an association between radiation-induced neural progenitor cell impairment and neurocognitive decline after central nervous system irradiation in rodents. Cranial irradiation significantly decreases hippocampal neurogenesis and is associated with impaired performance of hippocampal-dependent tasks (13-16), indicating that newly born cells may be essential for normal hippocampal functioning.

Several studies suggest that neurogenic areas similar to those described in the rodent brain exist in the human brain as well. For example, Eriksson et al. (17) demonstrated that progenitor cells in the human dentate gyrus divide to form new neurons, while Sanai et al. (18) found that astrocytes in the human SVZ of the lateral ventricles divide in vivo and act as multipotent progenitor cells in vitro. Human studies have likewise demonstrated cognitive deficits following cranial irradiation, most notably in children (19-22). This decline includes diminished capability to learn and memorize new tasks and information, as well as a dramatic reduction in full-scale IQ (23).

The relationship between neural precursor cells and the development of GBM remains unclear. There is some evidence that neural progenitor cells may act as precursor cells in the development of GBM. Several animal studies have suggested that gliomas, including GBM may be induced from the neural progenitor cells in the subventricular zone (24,25). It is therefore possible that sparing these regions during radiation therapy may actually result in a worse overall tumor control.

On the other hand, contradictory data suggests that neural progenitor cells may play a role in inhibiting tumor growth. NPCs have been shown to track along and inhibit growth of migrating tumor cells and to mitigate tumor-related damage (26-28). Increased NPC attraction to the tumor is associated with decreased tumor size and increased overall survival (29). Recent studies also suggest that radiation may enhance the migration of exogenous or endogenous stem cells to site of the tumor. For example, Tabatabai et al. (30) showed that 8 Gy of irradiation increased the tropism of intravenously injected adult human hematopoietic progenitor cells to the site of a glioma tumor implanted orthotopically in the striatum of a mouse. Less migration was observed in control mice. In combination, these data raise the possibility that, in addition to improving long term radiation associated toxicity, NPC sparing radiation techniques may potentially contribute to improved local control for brain tumors.

Recent human studies have demonstrated that it is possible to use intensity modulated radiation therapy (IMRT) to reduce the radiation dose to NPC containing regions during radiation therapy for brain tumors (31-33). In addition, preliminary data using a mouse

model has suggested that NPC sparing radiation may allow improved survival of neural progenitor cells compared to conventional radiation treatment plans, at least at an early time point (34).

Given the potential benefit of NPC in reducing the neurocognitive toxicity of radiation, but the unclear relationship between radiation dose to the NPC containing niches and tumor control, the purpose of this trial is to examine local recurrence at 1 year using a modified radiation technique which attempts to spare the NPC containing niches of the brain as much as possible without compromising tumor coverage during adjuvant radiation therapy plus temozolomide for GBM. If this study demonstrates that NPC-sparing radiation does not adversely influence local recurrence in the spared region of the brain, we plan to design a randomized controlled trial to evaluate neurocognitive outcomes in brain tumor patients treated NPC-sparing RT versus conventional RT.

## 2.2 **Temozolomide**

Temozolomide is an oral alkylating agent that interferes with DNA replication in a schedule-dependent manner. The therapeutic benefit of the drug depends on its ability to alkylate or methylate DNA at the N-7 or O-6 position of guanine residues, which results in DNA damage and cell death. Some tumor cells produce an enzyme called O-6-methylguanine methyltransferase (MGMT) which repairs the DNA damage and decreases the therapeutic benefit of temozolomide (35). Epigenetic silencing of MGMT by some tumor cells prevents synthesis of the enzyme resulting in tumors that are more sensitive to killing by temozolomide. Similarly, MGMT presence in GBM cells predicts for poor response to the drug. Toxicities associated with temozolomide include nausea, vomiting, infertility, teratogenicity, alopecia, fatigue, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenias, fever, dizziness, coordination abnormal, viral infection, amnesia, insomnia, lymphopenia, thrombocytopenia, neutropenia, and leucopenia, allergic reactions.

## 2.3 **Correlative Studies Background**

Correlative studies include a neurocognitive function test battery that has been validated in a multi-institutional phase III study by the Radiation Therapy Oncology Group (RTOG) in the context of brain metastases (36,37), plus 1 additional test. The tests will be performed by a trained examiner. The tests utilized in this protocol are described briefly below:

### 2.2.1 Mini Mental State Examination

The Mini Mental State Examination (38) is designed to evaluate global function. It consists of six tasks designed to evaluate short term memory retention and recall, attention, and language (see Appendix A). The maximum score is 30. Scores fall into 4 categories:

- 24-30: “Normal” range
- 20-23: Mild cognitive impairment
- 10-19: Moderate cognitive impairment
- 0-9: Severe cognitive impairment

### 2.2.2 Trail Making Test

The Trail Making Test A is designed to evaluate visual motor scanning speed and the Trail Making Test B is designed to evaluate executive function (39,40). These tests require patients to connect circles in numerical (part A) or alternating numerical and alphabetical sequence (part B) within a timed interval of less than 5 minutes for each test (see Appendix B). Results are reported as the number of seconds required to complete the task with higher scores reflecting higher degrees of impairment.

	<b>Average</b>	<b>Deficient</b>	<b>Rule of Thumb</b>
<b>Trail A</b>	29 seconds	>78 seconds	Most in 90 seconds
<b>Trail B</b>	75 seconds	>273 seconds	Most in 3 minutes

### 2.2.3 Controlled Oral Word Association Test

The Controlled Oral Word Association Test (COWAT) is designed to evaluate verbal fluency. It requires patients to name words beginning with a specific letter with increasing associated activity, in three 1-minute periods. Scoring is based on the number of words named during the 1 minute periods, with adjustments for education and age. Individual scores are categorized as intact, low average, borderline, deficient, or seriously deficient, based on their scores after these adjustments (41).

### 2.2.4 Hopkins Verbal Learning Test-Revised

The Hopkins Verbal Learning Test-Revised is designed to evaluate memory. It requires patients to memorize a list of 12 items for three consecutive tests (recall), to identify the same 12 items from a list of semantically related or unrelated items (recognition), and to recall the same 12 items after a 15 minute delay (delayed recall). Scoring and interpretation are simple, and outlined in a professional manual (42).

### 2.2.5 Digit Symbol Substitution Test

The Digit Symbol Substitution Test (WAIS-IV) is designed to measure attention, perceptual speed, motor speed, visual scanning and memory. The subject is given a piece of paper with nine symbols corresponding with nine digits. Next on this piece of paper are three rows of digits with empty spaces below them. The subject is asked to fill in as many corresponding symbols as possible in 120 seconds.

## 3. PATIENT SELECTION

### 3.1 Eligibility Criteria

- 3.1.1 Patient must have newly diagnosed, histologically confirmed GBM.
- 3.1.2 Patient must have undergone gross total resection, subtotal resection, or biopsy with the extent of resection determined by the treating neurosurgeon, and must begin radiation within 12 weeks of this procedure.
- 3.1.3 Patients must not have received previous irradiation to the brain.
- 3.1.4 Patient must be at least 18 years of age since the diagnosis of GBM in patients younger than 18 is rare and accurate evaluation of neurocognitive function would require a different battery of examinations than employed in this study.
- 3.1.5 ECOG performance status 0–2 (Karnofsky > 60%; see Appendix A).
- 3.1.6 Patient must be scheduled to receive temozolomide concurrent with and following radiation (temozolomide may be started late due to insurance reasons, insufficient counts, or other reasons)
- 3.1.7 If a woman is of child-bearing potential, a negative urine or serum pregnancy test must be demonstrated prior to treatment. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of study participation and for up to 12 weeks following the study. Should a woman become pregnant or suspect she is pregnant while participating in this study she should inform her treating physician immediately.
- 3.1.8 Patient must have the ability to understand and the willingness to sign a written informed consent document.
- 3.1.9 All patients must be informed of the investigational nature of this study and must be given written informed consent in accordance with institutional and federal guidelines.

### 3.2 Exclusion Criteria

- 3.2.1 Patients may not receive any approved or investigational agents to treat their glioblastoma besides temozolomide.

Note: Exceptions may be made for non-therapeutic intervention at the discretion of the Principal Investigator.

- 3.2.2 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, cervical carcinoma in situ, or other cancer from which the patient has been disease free for at least 2 years.
- 3.2.3 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements will be excluded.
- 3.2.4 Pregnant and breastfeeding women are excluded. Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control to avoid pregnancy for the entire study period and up to 12 weeks after the study are excluded. This applies to any woman who has not experienced menarche and who has not undergone successful surgical sterilization or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months). Male subjects must also agree to use effective contraception for the same period as above.

### 3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

## 4. REGISTRATION PROCEDURES

Patients will be accrued from Johns Hopkins Medical Institutes in Baltimore, MD. Contact information for the Principal Investigator is listed on the cover page.

To register the patient, the following documents must be completed and faxed to 410-502-2821 or emailed to Katharine Oteiza, the Study Coordinator at [koteiza1@jhmi.edu](mailto:koteiza1@jhmi.edu).

- Copy of operative note and pathology report
- Source documentation verifying eligibility
- Eligibility checklist
- Signed patient consent form
- HIPAA authorization form

If the patient is deemed eligible for the study, the Study Coordinator will register the patient and assign a study number.

Adjuvant radiation therapy must begin within 12 weeks of surgery.

## **5. TREATMENT PLAN**

### **5.1 Surgery and Chemotherapy**

#### **5.1.1 Surgical considerations**

As an eligibility requirement patients must undergo maximal safe resection, with the extent of resection determined by the treating neurosurgeon.

#### **5.1.2 Chemotherapy**

Patients will be scheduled to receive continuous daily temozolomide (75 mg per square meter of body surface area per day, 7 days per week from the first to the last day of radiation therapy), followed by 6 cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28 day cycle). Temozolomide may be started later than the first day of radiation therapy due to insurance reasons, insufficient counts, or other reasons. Temozolomide may be held, discontinued, or modified at the discretion of the treating medical oncologist. Laboratory studies such as CBC with differential and comprehensive metabolic panels will be performed at the discretion of the patient's medical oncologist. At the time of tumor progression or after one year of follow-up, further chemotherapy or biologic therapy is permitted at the provider's discretion. Therapy will be recorded, but the patient will not be removed from the study.

### **5.2 Radiation**

#### **5.2.1 Radiation Simulation and Prescription**

Patients will be treated to a total dose of 60 Gy with a once daily fractionation schedule of 2 Gy per fraction, administered five days per week. All patients will undergo CT simulation with intravenous contrast. In addition they will undergo MRI simulation with both T1 with gadolinium as well as FLAIR sequences. They will be treated in a supine position using an aquaplast mask system for immobilization. CT image data will be reconstructed in approximately 3 mm slice thickness and manually coregistered with T1 post-gadolinium and FLAIR sequence MRI.

#### **5.2.2 Target Delineation**

Delineation of the tumor and treatment margins will follow the Johns Hopkins institutional standard and will not be altered in any way for the purpose of this study. The gross tumor volume-1 (GTV-1, initial field) will be contoured using the simulation CT scan and fused T1 with gadolinium and FLAIR

sequence MRI. The gross tumor volume-2 (GTV-2, cone down field) will be contoured using the simulation CT scan and the T1 with gadolinium sequence MRI. The clinical tumor volume (CTV) will include the respective GTV plus approximately 0.5 to 1 cm margin. The planning tumor volume (PTV) will include the respective CTV plus approximately 0.5 cm margin.

### 5.2.3 Normal Tissues

Organs at risk including the eyes, lens, optic nerves, optic chiasm, brainstem, spinal cord, and inner ears will be contoured on the planning CT scan. Target dose constraints on these organs will follow the institutional standards at Johns Hopkins:

<b>Organ</b>	<b>Volume</b>	<b>Dose Constraint</b>
<b>Spinal Cord</b>	0.1 cc	Max 50 Gy
<b>Brainstem</b>	0.1 cc	Max 62 Gy
<b>Chiasm</b>	0.1 cc	Max 55 Gy
<b>Optic Nerve</b>	0.1 cc	Max 55 Gy

### 5.2.4 Neural Progenitor Cell Containing Niches

The NPC containing niches will be defined as a 5 millimeter region adjacent to the lateral wall of the lateral ventricle and the entire hippocampus. These areas will be contoured on the simulation CT scan using a manually coregistered MRI as a reference. A portion of the NPC-containing niches which is >2 cm from the PTV will be contoured as a region of interest and labeled as “NPC\_for\_sparing”. A radiation treatment plan will be generated in which we attempt to limit the RT dose to the “NPC\_for\_sparing” region as much as possible without compromising the radiation dose coverage of the tumor. Specifically, using inverse planning, the dose constraint and weight of the “NPC\_for\_sparing” region will be progressively tightened until additional iterations would result in compromised tumor coverage or unacceptable dose to another organ at risk. The extent of NPC sparing that is possible will be recorded for each patient in terms of the volume of the “NPC\_for\_sparing” region, and the mean, minimum, and maximum dose to this area. .

### 5.2.5 Equipment, Radiation Technique, and Dosimetry

Patients will be treated using a megavoltage linear accelerator with nominal beam energy of 6 MV and cone beam CT guidance for precise localization. Dosimetric indicators of plan quality such as the minimal dose to the PTV, conformity index, D50 to the whole brain as a measure of integral dose, and dose to the normal structures will be recorded.

### 5.2.6 Beam Verification

Either daily on-line cone beam CT guidance or weekly portal imaging will be

used for precise patient setup.

### **5.2.7 Therapy Interruption**

For radiation therapy interruptions of up to and including 14 days, irradiation should be completed to the full prescribed dose. On the last day, the total number of fractions and the reasons for interrupting therapy must be documented.

If radiation therapy interruption goes beyond 14 days, the patient will be removed from the protocol treatment. Resumption and completion of treatment will then be at the discretion of the radiation oncologist in consultation with the principal investigator. All patients who initiate protocol treatment will be followed per the study calendar.

### **5.2.8 Risks of Radiation**

Short term toxicities of radiation therapy include fatigue, alopecia, erythema or irritation of the skin, dry skin, headaches, worsening of current symptoms, edema of brain requiring steroids, ear pain or discomfort, damage to the baby if patient is or becomes pregnant, seizures, neurologic deficits depending on tumor location, edema of brain requiring surgery, death. Long term toxicities include memory loss, cataracts, edema of the brain requiring steroids, vision loss, hearing loss, necrosis of brain requiring surgery second tumor or cancer caused by radiation.

## **5.3 Duration of Follow Up**

Patients will be followed either at Johns Hopkins Hospital or an outside facility until death or the time of data analysis. It is preferred that MRIs be performed at Johns Hopkins Hospital but they may also be performed at outside facilities as necessary for insurance, scheduling, or other reasons.

## **5.4 Criteria for Removal from Study**

Patients will be removed from the study for the following reasons:

- 5.4.1 Unacceptable toxicity from therapy. Toxicity must be appropriately documented.
- 5.4.2 Development of intercurrent, non-cancer related illness that prevents either continuation of therapy or regular follow-up.
- 5.4.3 The patient may decide to discontinue enrollment in the protocol at any time and for any reason.

All reasons for discontinuation of treatment must be documented. The decision to

continue either treatment modality while discontinuing the other (i.e.: discontinue radiation while continuing temozolomide) must be discussed with the principal investigator and treating physician(s).

## 6. STUDY CALENDAR

Baseline evaluations are to be conducted prior to initiation of adjuvant radiation therapy. Patients will be evaluated with a toxicity assessment at least weekly during the course of radiation therapy. Note that the study calendar is based on the ideal subject. The schedule should be followed as closely as realistically possible, but may be modified due to problems such as scheduling delays, conflicts such as clinic closure or poor weather conditions, or other unforeseeable events. Neurocognitive testing will be obtained after 12 months only if funding allows. Follow-up MRIs will be obtained as medically indicated by the patient's provider.

	Baseline <sup>1</sup>	Treatment (Weeks)						Follow-Up (Post-RT)		
		1	2	3	4	5	6	6 Mo	12 Mo	24 Mo
Demographics	X									
Medical history	X									
Physical Exam	X							X	X	X
Vital signs <sup>11</sup>	X									
Weight	X									
Pregnancy Test <sup>2</sup>	X									
Performance status	X	X	X	X	X	X	X	X	X	X
Labs <sup>3</sup>	X	X	X	X	X	X	X			
Neurocognitive testing <sup>4</sup>	X							X	X	X
Toxicity Assessment		X	X	X	X	X	X	X	X	X
Acute toxicity <sup>5</sup>	X	X	X	X	X	X	X			
Late toxicity <sup>6</sup>								X	X	X
Brain MRI								X	X	X <sup>7</sup>
CT Scan <sup>8</sup>	X									
Chemotherapy <sup>9</sup>		X	X	X	X	X	X	X		
Radiation <sup>10</sup>		X	X	X	X	X	X			
<sup>1</sup> Baseline evaluations are to be conducted prior to initiation of adjuvant radiation therapy										
<sup>2</sup> If a woman is of child-bearing potential, a negative urine or serum pregnancy test must be demonstrated prior to treatment.										

<sup>3</sup> Laboratory tests to be performed at baseline include CBC with differential and CMP. Week 1-6 laboratory tests include CBC with differential and CMP will be performed at the discretion of the patient's medical oncologist.
<sup>4</sup> The Mini Mental State Examination, Trail Making Test A&B, Controlled Oral Word Association Test, Hopkins Verbal Learning Test Revised Digit Symbol Substitution Test
<sup>5</sup> RTOG Acute Morbidity Scoring Criteria
<sup>6</sup> RTOG Late Morbidity Scoring Criteria
<sup>7</sup> After 12 months follow-up MRI will be obtained only as deemed medically indicated by the patients provider
<sup>8</sup> CT simulation with intravenous contrast, data will be reconstructed in 3 mm slice thickness and manually coregistered with T1 post-gadolinium and FLAIR sequence MRI
<sup>9</sup> Patients will be scheduled to receive continuous daily temozolomide (75 mg per square meter of body surface area per day, 7 days per week from the first to the last day of radiation therapy), followed by 6 cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28 day cycle). Temozolomide may be started later than the first day of radiation therapy due to insurance reasons, insufficient counts, or other unknown reasons. Temozolomide may be held, discontinued, or modified at the discretion of the treating medical oncologist.
<sup>10</sup> Patients will be treated with a total dose of 60 Gy with a once daily fractionation schedule of 2 Gy per fraction
<sup>11</sup> BP, P, R, Temperature

## 7. MANAGEMENT OF TOXICITY

### 7.1 Acute Toxicity

Acute morbidity potentially associated with therapy will be monitored and recorded on the Radiation Oncology On-Treatment Evaluation Form for all patients from baseline to 3 months after completion of radiation therapy. Grading will be according to the RTOG Acute Morbidity Scoring Criteria as follows:

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<b>Skin</b>	No change over baseline	Faint erythema, epilation, dry desquamation, or decreased sweating	Tender or bright erythema, patchy moist desquamation, moderate erythema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
<b>Eye</b>	No change over baseline	Mild conjunctivitis with or without scleral	Moderate conjunctivitis with or without keratitis	Severe keratitis with corneal ulceration, objective decrease in	Loss of vision (unilateral or bilateral)

<b>Organ</b>	<b>Grade 0</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
		injection, increased tearing	requiring steroids and/or antibiotics, dry eye requiring artificial tears, iritis with photophobia	visual acuity or in visual fields, acute glaucoma, panopthalmitis	
<b>Ear</b>	No change over baseline	Mild external otitis with erythema, pruritis, secondary to dry desquamation not requiring medication. Audiogram unchanged over baseline.	Moderate external otitis requiring topical medication, serous otitis media, hypoacusis on testing only	Severe external otitis with discharge or moist desquamation, symptomatic hypoacusis, tinnitus, not drug related	Deafness
<b>CNS</b>	No change over baseline	Fully functional status with minor neurologic findings, no medications needed	Neurologic findings present sufficient to require home care. Nursing care may be required. Medications including steroids and/or anti-seizure agents	Neurologic findings requiring hospitalization for initial management	Serious neurologic impairment which included paralysis, coma, or seizures, despite medications. Hospitalization required
<b>Hematologic WBC (x1000)</b>	≥ 4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
<b>Platelets (x 1000)</b>	≥ 100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
<b>Neutrophils</b>	≥ 1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
<b>Hematocrit (%)</b>	≥ 32	28 - <32	<28	Packed cell transfusion required	N/A



## 7.2

**Late Toxicity**

Late toxicity will be recorded on the Radiation Oncology Follow-up form at each follow-up visit greater than 3 months post completion of radiation therapy. Grading will be according to the RTOG Late Radiation Morbidity Scoring Schema as follows:

<b>Organ</b>	<b>Grade 0</b>	<b>Grade 1</b>	<b>Grade 2</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 5</b>
Skin	None	Slight atrophy, pigmentation change, some hair loss	Patchy atrophy, moderate telangiectasia, total hair loss	Marked atrophy, gross telangiectasia	Ulceration	Death directly related to late radiation effect
Subcutaneous Tissue	None	Slight induration and loss of subcutaneous fat	Moderate fibrosis but asymptomatic . Slight field contracture. <10% linear reduction	Severe induration and loss of subcutaneous tissue. Field contracture >10% linear measurement	Necrosis	
Spinal Cord	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurologic findings at or below cord level treated	Mono-, para-, quadra-plegia	
Brain	None	Mild headache, slight lethargy	Moderate headache, great lethargy	Severe headaches, severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures, paralysis, coma	
Eye	None	Asymptomatic cataract, minor corneal ulceration of keratitis	Symptomatic cataract, moderate corneal ulceration, minor retinopathy or glaucoma	Severe keratitis, severe, retinopathy or detachment, severe glaucoma	Panophthalmitis, blindness	

## 8. STATISTICAL CONSIDERATIONS

### 8.1 Study Design/Endpoints

#### 8.1.1 Study Design

This is a single arm prospective investigation to evaluate the local recurrence rate in the spared NPC-containing regions of the brain after NPC-sparing radiation therapy plus temozolomide for newly diagnosed GBM.

#### 8.1.2 Primary Endpoint

Site of local recurrence at 1 year post radiation therapy will be recorded for each patient. Sites will be classified as follows: 1) Recurrence within the spared NPC-containing region, defined as a recurrence within the avoidance structure contoured on the simulation CT scan; 2) Recurrence outside of the spared NPC-containing region, defined as a recurrence that is not within this avoidance structure; 3) No local recurrence.

#### 8.1.3 Secondary Endpoints

8.1.3.1 The extent of NPC-sparing will be recorded for each patient. Patients will be binned into 4 groups according to the volume of NPC region that receives a certain dose as follows: 1)  $V_{5Gy} \leq 50\%$ ; 2)  $V_{5Gy} \leq 20\%$ ; 3)  $V_{10Gy} \leq 20\%$ ; 4) Doses higher than levels 1-3.

8.1.3.2 The X-, Y-, and Z- coordinate distances in centimeters will be recorded from the most proximal point of the planning tumor volume to the closest point of the spared NPC-containing niche. The mean, minimum, and maximum radiation dose to the spared NPC-containing region will be recorded for each patient. In addition, the volume of the “NPC\_for\_sparing” region will be recorded.

8.1.3.3 Completion of neurocognitive testing and Neurocognitive function will be assessed at baseline, and at six, twelve, and twenty-four months from baseline using the Mini Mental State Exam, Trail Making Test A & B, Controlled Oral Word Association Test, Hopkins Verbal Learning Test-Revised and the Digit Symbol Substitution Test.

## **8.2 Sample Size/Accrual Rate**

### **8.2.1 Sample Size**

The required sample size is based upon the primary study hypothesis which is the rate of local recurrence within the spared NPC-containing region at 1 year post radiation therapy in patients treated with NPC sparing RT plus temozolomide for newly diagnosed GBM. Using conventional RT, approximately 20% of GBM recur outside of the tumor bed or radiation field margin (48). We hypothesize that there will be  $\leq 25\%$  LR rate in the designated NPC avoidance region using our modified radiation technique, which is clinically acceptable. This is the first study to estimate the LR rate in the spared NPC containing region following NPC sparing RT for GBM. Given the clinically meaningful control LR rate in this region of 25% and a moderate variation among the patients, the 30 patients will have the optimal information gain (relative certainty) based on empirical information entropy to estimate the LR rate in the spared region (49).

### **8.2.2 Accrual**

We anticipate enrollment of approximately 3-4 patients per month to the protocol with accrual completed in approximately 1-2 years.

## **8.3 Stratification Factors**

There will be no stratification factors upon initial enrollment in the protocol.

## **8.4 Statistical Methods of Analysis**

All analysis will be based on the Intend-To-Treat (ITT) principle. Per-protocol will be allowed after ITT analyses.

The proportion of patients with LR in the avoidance region of the NPC will be estimated along with the exact 95% confidence interval. The lower bound 95% confidence interval of exact binomial distribution will be used to determine the acceptance of the LR rate of 25%.

All patients will count towards assessment of all objectives. However, if no patient relapses in the spared NPC containing region, we recognize that the present study will not definitively demonstrate that sparing of the NPC regions does not impact the pattern of recurrence since this is a pilot study and 2 patients received mebendazole following completion of radiation therapy but prior to relapse. Given that no intervention to date including systemic agents, radiation dose escalation, and hypofractionation has ever impacted the site of recurrence we feel it is exceedingly unlikely that mebendazole would impact our primary endpoint. However, we will evaluate if the analysis of the primary endpoint would yield different results with or without inclusion of these patients. If there is a difference both analyses will be presented in the manuscript. Even if there is no statistically significant difference

between the groups we will clearly state in our publications that 2 patients received mebendazole with their adjuvant temozolomide following completion of radiation therapy but prior to relapse.

To quantify the extent of radiation dose sparing to the NPC containing regions that is possible, patients will be binned into 4 groups according to the volume of NPC region that receives a certain dose as follows: 1)  $V_{5Gy} \leq 50\%$ ; 2)  $V_{5Gy} \leq 20\%$ ; 3)  $V_{10Gy} \leq 20\%$ ; 4) Doses higher than levels 1-3. The proportion of overall patients who meet at least the dose constraint will be estimated using a binomial distribution along with 95% confidence intervals, as well as the individual group.

To assess the feasibility of evaluating cognitive function prospectively in this patient population, we will evaluate the six month post radiation therapy protocol compliance in terms of neuropsychological evaluations. The proportion of patients completing the planned neurocognitive assessments at both baseline and 6 months post radiation therapy will be calculated, along with the 95% confidence interval. If  $\geq 40\%$  of patients did not complete at least 1 of these planned assessments, the testing will be considered not feasible.

The change in neurocognitive function from baseline to 6 months post radiation therapy will be explored by using the 5 instruments measuring neurocognitive function. The change will be summarized graphically (using, for example, boxplots) and using mean, median or score shifting etc. This will be done for each instrument separately. Correlation coefficients will be calculated to explore potential correlation between the change in neurocognitive function from the baseline and the radiation dose to the NPC-containing region.

Spearman's rank correlation coefficient will be calculated to explore an association between the closest distance (either X-, Y-, or Z-) of the planning tumor volume to the spared NPC-containing niche and the mean, minimum, and maximum radiation dose to this region.

## 8.5 Interim Disease Progression Monitoring

Based on the unpublished data from the New approaches to Brain Tumor Therapy Consortium, the median time of progression was 8.5 months among the newly diagnosed GBM treated by RT+TMZ (standard). The progression area outside radiation bed was about 20%. This study does not anticipate an above 30% progression rate in the spared NPC containing region. We expect a less than 30%, about 20% progression rate in the spared NPC containing region. However, we plan to monitor the progression rate throughout the trial. The progression rate in the spared NPC containing region will be monitored continuously throughout the cohort using the Bayesian stopping rule at patient numbers 10 and 20, after patients have a minimum of 6 months follow-up. We consider a 30% progression rate the highest limit that permits to continue this study and will stop early if there are excesses. The number of patients experiencing progression in the spared NPC containing region was assumed to follow a binomial distribution. Given the planned sample size of 30, a

stopping boundary would be reached if the proportion of patients experiencing progression in the spared NPC containing region exceeds 30% with a posterior probability  $\geq 0.6$ . A recommendation for early stopping if 4 or more out of 10, or 7 or more out of 20 patients had disease progression in the spared NPC containing region. The probability of meeting the stopping boundary is 0.56 under a true probability of progression is 0.3.

## 9. ADVERSE EVENTS AND RECORDING

### 9.1 Definition of Adverse Event (AE)

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition during or following an exposure to a treatment, whether or not considered causally related to the treatment. An undesirable medical condition may be symptoms (headache, nausea), signs (tachycardia, enlarged liver), or abnormal results of an investigation (MRI, laboratory finding). In clinical trials, from the time of signing an informed consent, an AE may include an undesirable medical condition, occurring at any time, even if no trial treatment has been administered.

### 9.2 Radiation Related Adverse Events

Risks Associated with Brain Radiation Therapy:

#### **Very Likely**

- Scalp redness or soreness
- Hair loss
- Dry mouth or altered taste
- Fatigue, sleepiness
- Skin redness or soreness in the ear canal

#### **Less Likely, But Serious**

- Permanent hair loss
- Hearing loss
- Eye injury resulting in vision loss or even blindness
- Mental slowness, behavioral changes
- Severe damage to normal brain tissue that may require additional surgery
- Brain damage, which could affect judgment, memory, sensation, or ability to control movement

#### **Less Likely**

- Fever, chills, heavy sweating
- Upset stomach, nausea and/or vomiting
- Loss of appetite
- Headaches, seizure, weakness

All radiation related adverse events will be recorded on the local toxicity case report forms.

### 9.3 Chemotherapy Related Adverse Events

#### **Risks associated with Temozolomide:**

##### **Very Likely**

- Nausea and/or vomiting
- Headache
- Constipation
- Drowsiness/Fatigue
- Insomnia (trouble sleeping)
- Skin rash
- Swelling

##### **Less Likely, But Serious**

- Decrease in blood counts that may cause infection and bleeding
- Decreased ability to carry out daily activities
- Pneumonia
- Increased blood sugar
- Pain when swallowing
- Internal bleeding
- Seizure
- Subsequent development of leukemia

##### **Less Likely**

- Loss of appetite
- Diarrhea
- Fever
- Weight loss
- Weakness
- Sores in your mouth
- Hair loss
- Weakness of hands and feet
- A temporary elevation in the blood tests that show how your liver is functioning
- Shortness of breath
- Confusion
- Blurred vision
- Allergic reactions
- Chills
- Body aches
- Coughing

The adverse events (both hematologic and non-hematologic) that patients experience due to chemotherapy will be recorded on appropriate case report forms only if they are greater than or equal to grade 3, result in a delay in treatment, or are required to be reported per institutional guidelines.

## **10. SERIOUS ADVERSE EVENTS (SAE) AND REPORTING**

### **10.1 Serious Adverse Event**

#### **10.1.1 Definition of Serious Adverse Event**

A serious adverse event is an AE occurring at any point during a clinical trial that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Is a congenital abnormality or birth defect.
- Unexpected event that cause harm or place person at a greater risk of harm than was previously known or recognized, and which was possibly related to the research. Unexpected means that the event was not described in the consent form or the event exceeded the expected severity.
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

### **10.2 SAE Reporting Guidelines for Johns Hopkins Hospital**

All SAE, with the exception of death, must be reported to the Johns Hopkins Hospital Institutional Review Board (JH-IRB) within 10 working days of the principal investigator learning of the event. Reporting for the death of a patient which was unexpected (i.e.: not related to a risk of participation that was listed in the protocol or the consent document, and was more likely than not to be caused by the research procedure/intervention, must be reported to the JH-IRB within 3 working days of when the principal investigator receives the report of the death. Reporting for death of a participant that was expected due to the nature of the patient's underlying disease or condition, or identified as caused by a possible risk of the study procedure/intervention as described in this protocol or consent form, must be reported to the JH-IRB within 10 working days from the time the principal investigator learns of the event. If death occurs 30 days after the participant has stopped or completed their study treatment, the principal investigator does not have to report the death until the time of continuing review.

## **11. DATA AND SAFETY REPORTING/ REGULATORY CONSIDERATIONS**

### **11.1 Data Quality Monitoring**

In addition to the ongoing quality assurance evaluations for each individual at the time of treatment, there will be regular internal monitoring meetings between the principal investigator, a medical oncologist, and the study coordinator to assess the data quality. These meetings will occur annually and a monitoring report of the findings will be submitted to the Data Safety Monitoring Committee on an annual basis. Any protocol deviations or violations will be documented in the monitoring reports. The review will include: consent forms, eligibility criteria, protocol compliance, treatment administration, toxicity reports, response, regulatory compliance, case report forms (completeness as well as verifying that information coded on the case report forms are supported by source documents), and all other materials related to the trial. This is a Level I study under the SKCCC Data Monitoring Plan (6/26/2010). The Clinical Research Office QA group will assume external auditing responsibilities by performing an audit at the end of the first year and then periodically thereafter depending on the rate of accrual and prior audit results. The Safety Monitoring Committee will review this trial for safety and data quality annually.

### **11.2 Data Safety Monitoring**

All SAE's and major protocol deviations that occur at Johns Hopkins Hospital will be submitted to the IRB of record. Once in the IRB these reports of SAEs and major protocol deviations will be reviewed by the Sidney Kimmel Comprehensive Cancer Center Data Monitoring Committee (SMC) for review per Institutional guidelines. In addition, the overall study safety and potential activation of the study's early stopping rules will be assessed at the time of every SAE. The Data Safety Monitoring Committee will review this trial for safety annually.

### **11.3 Data Reporting**

#### **11.3.1 Method**

Data will be collected on Case Report Forms (CRFs). These CRFs will be completed by the study coordinator. The CRFs for each subject will be kept in a separate research binder. Along with each completed CRF there will be corresponding source documentation filed for verification. The Principal Investigator, Research Study Nurse, and Study Coordinator will informally meet on a regular basis to make sure that the trial is progressing as mandated by the protocol. The CRO will audit this trial per their standards to ensure and verify that the protocol is being carried out according to specs as well as to verify that data included on subject CRFs are accurate. Exit reports generated as a result of these CRO audits will be forwarded to both the Safety Monitoring Committee as well as to the adjudicating IRB of record for review.

**11.3.2 Responsibility for Submissions**

Not applicable.

**11.4 CTEP Multicenter Guidelines**

Not applicable.

**11.5 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)**

Not applicable

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**APPENDIX A**

**Performance Status Criteria**

<b>ECOG Performance Status Scale</b>		<b>Karnofsky Performance Scale</b>	
<b>Grade</b>	<b>Descriptions</b>	<b>Percent</b>	<b>Description</b>
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.