Mayo Clinic Radiation Oncology

MC167B: Phase-II study investigating the utility of ^{18}F-DOPA-PET in the treatment of recurrent high-grade glioma

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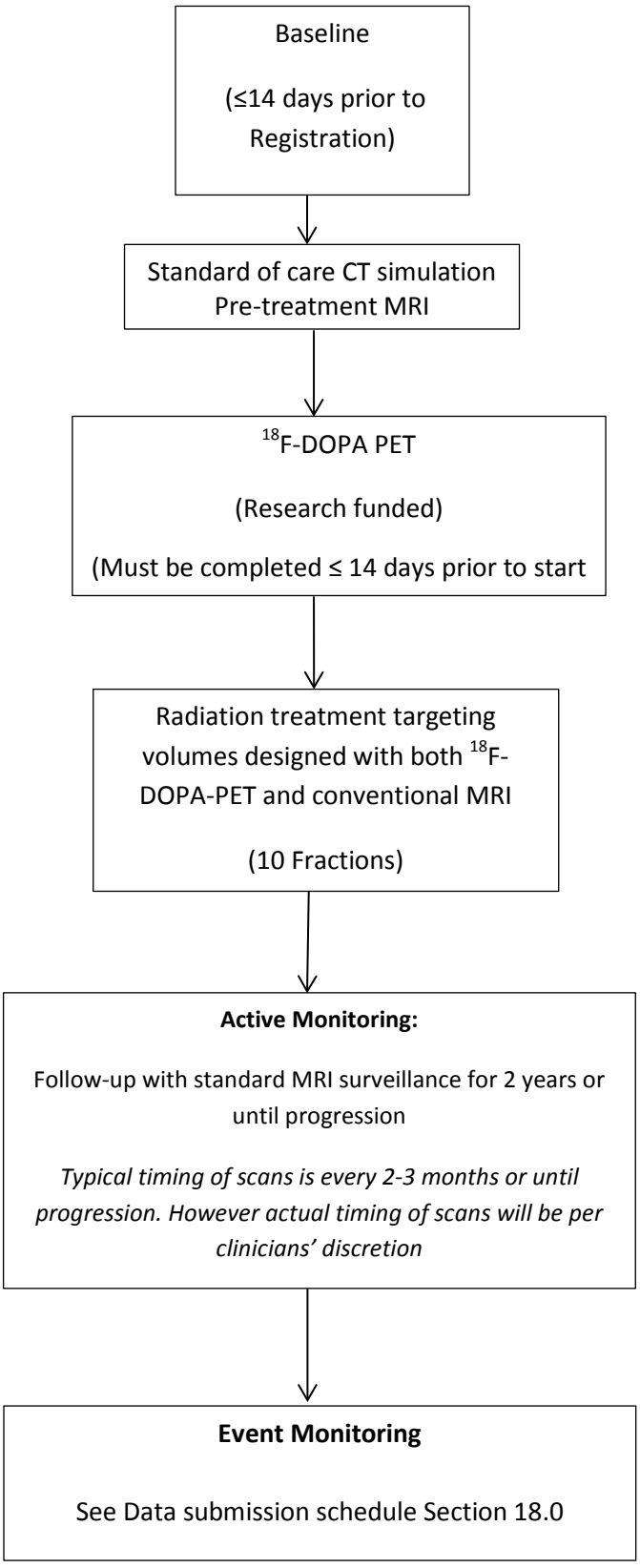
Document History	(Effective Date)
Version 1	April 17, 2017
Version 2	April 16, 2018
Version 3	May 22, 2019

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission, adverse events, forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]

Contents

Study Schema



List of Abbreviations

^{18}F-DOPA	3,4-dihydroxy-6-[^{18}F] fluoro-L-phenylalanine
AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computed Tomography
CTV	Clinical Target Volume
DICOM	Digital Imaging and Communication
DSMB	Data and Safety Monitoring Board
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
Gy	Gray (radiation dosing)
HIPAA	Health Insurance Portability and Accountability Act
MDASI-BT	MD Anderson Symptom Inventory Brain Tumor Module
MRI	Magnetic Resonance Imaging
NTD	Normal Tissue Dose
IRB	Institutional Review Board
PET	Positron emission tomography
PHI	Protected Health Information
PI	Principal Investigator
PS	Performance Score
PTRAX	Research Participant Tracking System
PTV	Planning target volume
QOL	Quality of Life
RANO	Response Assessment in Neuro-Oncology
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
T/N	Tumor to normal ratio
UPIRTSO	Unanticipated Problems Involving Risks to Subjects or Others
VEGF-A	Vascular endothelial growth factor- A

1.0 Background

Recurrent glioblastoma remains a problem despite modern treatment techniques despite advances in modern therapy; glioblastoma continues to portend a dismal prognosis. In modern trials, median progression-free survival remains short at around 7 months, with nearly all patients experiencing tumor progression by 36 months.[1, 2]

1.1 Many recurrences occur outside the high-dose radiotherapy volume:

The current standard for tumor delineation includes T1 contrast-enhanced and T2 FLAIR MRI. It is well established that high-grade gliomas infiltrate into peritumoral edema.[3] In a major prospective trial from the European Organization for Research and Treatment of Cancer (EORTC), the clinical target volume (CTV) included any residual tumor and resection cavity plus 2-cm margins.[1] Current Radiation Therapy Oncology Group (RTOG) protocols include the addition of postoperative edema plus 2-cm margins for CTV.[4] With these volumes, at least 75% of recurrences occur within the 95% isodose line of the 60 Gy volume.[5, 6] In addition, up to 20% of failures are located completely outside of the 95% isodose line.[6]

1.2 ^{18}F-DOPA-PET offers better localization of primary tumor than MRI alone:

While it is well established that regions of contrast enhancement and edema are likely to contain tumor, it is thought that infiltration of tumor may additionally occur along neuronal tracts.[7] Given that up to 20% of patients may experience progression outside the aforementioned MRI changes, a need exists to develop a complementary imaging modality. While standard 18-fluoro-deoxyglucose positron emission tomography (^{18}F-FDG-PET) is generally insufficient in visualizing brain tumors, amino acid PET tracers, such as 3,4-dihydroxy-6-[^{18}F] fluoro-L-phenylalanine (^{18}F-DOPA) offer several advantages.[8] ^{18}F-DOPA-PET shows high uptake in tumor tissue and low uptake in normal tissue. Unlike contrast enhancement, ^{18}F-DOPA-PET crosses the intact blood brain barrier freely via an amino acid transporter.[9] In a pilot study at Mayo Clinic, increased ^{18}F-DOPA-PET uptake was seen in 13 of 16 high-grade biopsy specimens, while MRI T1 contrast enhancement was only present in 6 of the 16 specimens.[10] With this knowledge, Mayo Clinic is currently enrolling patients with newly-diagnosed high-grade gliomas in a radiotherapy trial where dose-escalation is planned for regions of high ^{18}F-FDOPA uptake.

1.3 Pseudoprogression can be difficult to differentiate from true tumor progression:

Following treatment with radiotherapy, inflammatory changes are often seen on MRI. Thus, strict criteria are used to categorize the nature of the tumor's response. The historical standard criteria were published by Macdonald et al. and required >=25% increase in the sum of the products of perpendicular diameters of enhancing lesions, any new lesion, or clinical deterioration in order to declare progression.[11] These

criteria have come into question, as there can be significant interobserver variability, particularly in measuring irregularly shaped or cystic tumors. In addition, changes in contrast enhancement are typically nonspecific and simply represent a disrupted blood-brain barrier. Thus, fluctuations in contrast enhancement may be caused by inflammatory changes in the treated region, anti-angiogenic agents and radiation necrosis.[12] Pseudoprogression, defined as an increase in contrast enhancement that subsides without anti-neoplastic therapy, is common after standard treatment with radiotherapy and temozolomide.[13] This process is thought to be driven by radiation-induced increased permeability of the blood brain barrier. Because pseudoprogression typically occurs within 12 weeks of radiotherapy inside the high-dose region, the updated Response Assessment in Neuro-Oncology (RANO) criteria require new enhancement outside the 80% isodose line or viable tumor on histopathologic sampling for progression to be declared less than 12 weeks after radiotherapy.[14] These criteria help differentiate pseudoprogression from true progression, though challenges in interpreting changes in imaging after 12 weeks still remain.

1.4 Bevacizumab produces a moderately high response rate in glioblastoma:

While angiogenesis is common among a spectrum of tumors, it is particularly frequent in glioblastoma. Commonly, the tumor parenchyma produces vascular endothelial growth factor A (VEGF-A), which in turn up-regulates the VEGF pathway.[4] Bevacizumab is a humanized monoclonal antibody with activity against the VEGF-A ligand, which in turn reduces VEGF pathway up-regulation.[15] A randomized study comparing bevacizumab with or without irinotecan in patients with recurrent glioblastoma demonstrated moderately high response rates in the 30-35% range as determined by MRI.[16] A single-arm phase II study treating recurrent glioblastoma with bevacizumab followed by bevacizumab and irinotecan after further progression produced a response rate of 35% as defined by Macdonald criteria.[17] These trials led to FDA approval for bevacizumab use in the treatment of recurrent glioblastoma. This led to RTOG 0825, a randomized placebo-controlled trial comparing standard radiotherapy and temozolomide with or without adjuvant bevacizumab. This study revealed an improvement in progression-free survival but not overall survival.[4] A subsequent study compared concurrent radiotherapy, temozolomide and bevacizumab to radiotherapy and temozolomide alone, demonstrating a similar improvement in progression-free but not overall survival.[18] Responses were often measured radiographically, which may not be the most reliable indicator of response to anti-angiogenic agents.

1.5 MRI changes after bevacizumab may not accurately reflect tumor response:

While rapid responses in MRI contrast enhancement after initiation of treatment with VEGF pathway inhibitors are relatively common, it is not clear whether these changes truly reflect tumor regression or simply restoration of the blood-brain barrier.[19] Furthermore, increasing non-enhancing T2 FLAIR regions have been reported and may potentially represent tumor progression after bevacizumab.[20] This has driven

speculation that the improvement in progression-free but not overall survival with bevacizumab may be primarily driven by radiographic changes that do not fully correlate with true tumor response.

1.6 Reirradiation is often used for treatment of progression:

Repeat courses of radiotherapy are often considered for progressive disease refractory to systemic therapy. Conventionally fractionated doses between 36 and 46 Gy have been used with minimal neurologic toxicity.[21-23] Hypofractionated doses of 24-50 Gy in 3.5-5 Gy fractions have also been used with minimal toxicity when limiting doses to <40 Gy.[22, 24-29] Mayer and colleagues proposed a cumulative normal tissue dose limit (2 Gy per fraction equivalent) of <100 Gy to limit the risk of radionecrosis.[30] In general, the target volume includes a minimal expansion beyond MRI contrast enhancement.[21, 24-27, 29] Median survival after reirradiation ranges from 7 to 10 months.[21-27, 29] The best outcomes are seen when more time elapses between primary radiation and reirradiation and in patients with lower-grade histology.[24-26, 31] In an analysis of patterns of recurrence after reirradiation, 60-70% recurrences were located in-field with the remainder located out of field.[25, 32] Thus, MRI contrast enhancement may not accurately reflect tumor location potentially resulting in imprecise targeting of radiation target volumes.

1.7 ^{18}F-DOPA-PET may allow better localization of recurrent disease than MRI:

Because of the shortcomings of MRI in accurately differentiating tumor progression from pseudoprogression, in addition to the difficulty in truly assessing the response to bevacizumab, a novel imaging modality would prove useful in accurately classifying responses to treatment. In addition, more precise target delineation in the re-irradiation setting is particularly attractive; so as to allow for not only better target coverage but potentially reduced unnecessary coverage of normal tissue. The lack of dependence of ^{18}-FDOPA-PET uptake on blood-brain barrier breakdown is enticing, as many of these patients are currently receiving or recently received bevacizumab and may have alterations in the blood-brain barrier.

1.71 Preliminary results – ^{18}F-DOPA-PET identifies glioma outside conventional MRI in patients with imaging findings consistent with recurrent disease. In our two studies (MC1078 and MC1373), 13 patients with suspected recurrent disease had an ^{18}F-DOPA-PET/CT scan and MRI performed prior to stereotactic resection or biopsy. The PET scan was rigidly registered to the T1-weight scan using MIM Maestro (MIM Software Inc, Cleveland, OH). The registered PET images were transferred to the Stealth Station Neuronavigation System (Medtronic Sofamor Danek, Memphis, TN) and stereotactic biopsy locations were planned based on the PET SUVmax and locations of PET and MRI discordance (Figure 1). Of 45 biopsy specimens graded by Dr.

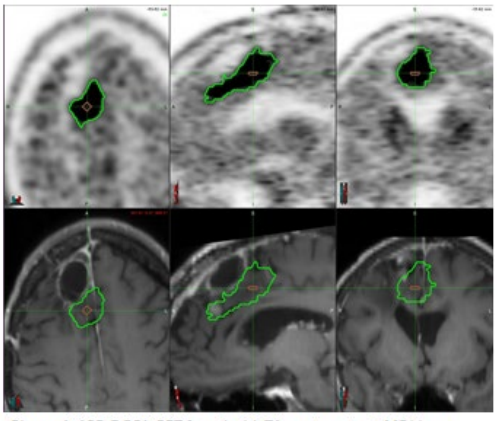


Figure 1. 18F-DOPA-PET fused with T1-post contrast MRI in a patient with recurrent high-grade glioma. Note 18F-DOPA avidity outside region of MRI contrast enhancement.

Caterina Giannini, 39 contained tumor. Fifteen samples were taken in regions of ^{18}F-DOPA avidity in the absence of MRI contrast enhancement (M-P+). Of these, 14 (93%) contained tumor and 10 (66%) were high-grade. Of the 33 specimens containing high-grade glioma, 20 (61%) were from regions of MRI contrast enhancement and 26 (79%) were from regions of ^{18}F-DOPA avidity.

2.0 Goals

2.1 Primary

2.11 Compare the progression-free survival rate at 3 months for recurrent high-grade glioma patients after reirradiation targeting volumes designed with both ^{18}F-DOPA-PET and conventional MRI with historical controls

2.2 Secondary

2.21 Compare overall survival from reirradiation and overall survival from initial diagnosis with historical controls

2.22 Prospectively evaluate toxicity and reoperation rates after reirradiation

2.23 Prospectively evaluate quality of life and fatigue using patient reported outcomes

2.3 Correlative Research

2.31 Compare volume of ^{18}F-DOPA-PET uptake with MRI contrast enhancement and T2 FLAIR for patients undergoing re-irradiation for recurrent high-grade glioma

2.32 Evaluate patterns of failure after reirradiation in relation to pre-treatment MRI and ^{18}F-DOPA-PET abnormalities

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age $\geq$ 18 years

3.12 ECOG PS $\leq$ 3

3.13 Histologically confirmed or radiographic evidence of recurrent/progressive glioma

3.14 History of radiation therapy to the brain for prior diagnosis of glioma

3.15 Planned radiation treatments at Mayo Clinic Rochester

3.16 Provide informed written consent

3.17 Willing to sign consent onto the Mayo Clinic Radiotherapy Patient Outcomes Registry and Biobanking study, IRB number 15-000136 (blood draw optional)

3.18 Willing to return to enrolling institution for follow-up during Active Monitoring Phase of the study.

3.2 Exclusion Criteria

3.21 More than one prior course of radiotherapy or prior prescription doses exceeding 60 Gy to re-irradiation target volumes

3.22 Unable to undergo MRI scans with contrast

3.23 Unable to undergo an ^{18}F-DOPA-PET scan (e.g., Parkinson's Disease, taking anti dopaminergic, or dopamine agonist medication or less than 6 half-lives from discontinuance of dopamine agonists.)

Note: Other potentially interfering drugs: amoxapine, amphetamine, benztropine, buproprion, buspirone, cocaine, mazindol, methamphetamine, methylphenidate, norephedrine, phentermine, phenylpropanolamine,selegiline, paroxetine, citalopram, and sertraline). If a patient is on any of these drugs, list which ones on the On-Study form.

3.24 Any of the following:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

4.0 Test Schedule

Tests and procedures	Baseline (<21 days prior to registration)	Radiation Treatment Planning	During Radiation Treatment	End of Radiation Treatment +/- 3 days	1 month post RT +/- 7 days	3 months post RT +/- 14 days	At every clinically indicated follow-up[8]
Physical examination, weight, ECOG PS	X			X	X	X	X
Neurologic history and examination	X[9]			X	X	X	X
Document current medications	X			X	X	X	X
Pregnancy test	X[1]						
QOL Assessment: MDASI-BT and BFI [10]	X[11]			X	X	X	X[11]
Standard Mayo glioma brain MRI with and without contrast		X[3]			X	X	X[5]
^{18}F-DOPA-PET		X[3, R]					
^{18}F-DOPA adverse event assessment		X[2]					
CT simulation for radiotherapy planning		X[3,4]					
Adverse event assessment[6]	X		X[7]	X	X	X	X

1. For women of childbearing potential only. Must be done ≤48 hours prior to injection of study drug. Note: For a positive pregnancy test prior to the pre-RT ^{18}F-DOPA injection the patient will not undergo the ^{18}F-DOPA PET scan and will instead be taken off study with no follow-up.

2. ^{18}F-DOPA post-injection AE assessment: done approximately 40-45 minutes post injection of ^{18}F-DOPA by the Nuclear Medicine technologist performing the study. If an AE was observed, a second AE assessment is required ≤24 hours post injection. This assessment will be completed by the study staff. This information will be used for MCCC DSMB review (Section 16.91) and reporting of any AEs under ^{18}F-DOPA IND (Section 10.0).

3. Must be completed ≤ 14 days prior to the start of radiotherapy.

4. CT simulation can be performed prior to or after registration.

5. All follow-up serial imaging after initial treatment will occur until progression or up to 2 years. Typical timing of scans is every 2-3 months or until progression. However, the actual timing of scans for protocol patients will be per the clinician's discretion.

6 To be assessed by Radiation Oncologist at baseline and during radiotherapy and Medical Oncologist for follow-up assessments for MCCC DSMB review (Section 16.91). Adverse events will be assessed weekly during routinely scheduled management visits (+/- 3 days)

7. Maximum grade of adverse events experienced during radiotherapy can be recorded at the end of treatment.

8. Follow up assessments will be completed as per clinician's discretion

9. Neurologic history and examination will be completed by treating Radiation Oncologist

10. Quality of Life (QOL) and cognitive function will be evaluated with MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) and the Brief Fatigue Index (BFI).

11. Patient will be asked to complete questionnaires at baseline and at each MRI evaluation for a maximum of 6 evaluations.

R. Research funded

5.0 Grouping/Stratification Factors:
None

6.0 Registration Procedures:

Patient will be registered to the study when they have consented, met eligibility criteria and have been logged into the Research Participant Tracking system (Ptrax).

6.1 Verify following procedures are complete prior to Registration to the study.

6.11 Prior to accepting the registration, verify the following:
6.12 IRB approval at the registering institution
6.13 Patient eligibility complete
6.14 Existence of a signed informed consent
6.15 Existence of a signed authorization for use and disclosure of protected health information (optional)

6.2 Radiation therapy on this protocol must be performed at Mayo Clinic Rochester under the supervision of a radiation oncologist.

6.3 Tests and procedures (Section 4.0) must be completed within the guidelines specified on the test schedule.

7.0 Protocol Treatment

7.1 CT simulation

The patient will be immobilized with a BrainLab mask and a CT dataset acquired of the patient for treatment planning as per standard of care during the CT simulation appointment.

7.2 ^{18}F-DOPA-PET

7.21 Timing of PET scanning:

The PET scan to be used for radiation treatment planning should be acquired no more than 14 days prior to beginning radiation treatments.

7.22 Patient preparation for PET scan

7.221 A negative pregnancy test must be done ≤48 hours prior to ^{18}F-DOPA injection for women of child-bearing potential only.

7.222 Patients will be instructed to follow a low-protein diet after the previous evening meal. Liberal hydration 24 hours before the exam will be encouraged. Carbidopa, used for Parkinson's patients to inhibit decarboxylation of the ^{18}F-DOPA tracer, is not necessary for brain tumor imaging.

7.23 Selection of patients for PET/CT or PET/MRI

7.231 PET/MRI is the planned method for obtaining anatomic correlation with ^{18}F-DOPA PET.PET/CT information is provided below in the circumstance that ^{18}F-DOPA/MRI is not possible/available. All requests to utilize ^{18}F-DOPA PET/CT will require approval from nuclear medicine and radiation oncology study chairs.

7.24 PET/CT

7.241 A total of 5.0 + 10% mCi of ^{18}F-DOPA will be intravenously injected. A scout image will be acquired in order to prescribe the scan range for the image acquisition. CT images will be obtained and used for attenuation correction of the PET data and, at 10 minutes after injection of ^{18}F-DOPA, a 20 minute 3D PET acquisition will be acquired. The PET data will also be acquired concurrently in list mode; this data will be used to salvage a scan should the patient move. The PET sinograms will be reconstructed with a fully 3D-OSEM algorithm into a 300 mm field of view with a pixel size of 1.17mm and slice thickness of 1.96mm. All images will be transferred to a Radiation Oncology workstation.

7.25 PET/MRI

7.251 The subject will undergo MRI screening for contraindications to scanning and contrast agent administration as per routine clinical protocol at Mayo Clinic. MRI will be acquired on a PET/MR scanner simultaneously during the 20 minute PET acquisition phase.

7.252 A total of 5.0 + 10% mCi of ^{18}F-DOPA will be intravenously injected. A scout image will be acquired in order to prescribe the scan range for the image acquisition. MR images will be obtained and used for attenuation correction of the PET data and, at 10 minutes after injection of ^{18}F-DOPA, a 20 minute 3D PET acquisition will be acquired. The PET data will also be acquired concurrently in list mode; this data will be used to salvage a scan should the patient move. The PET sinograms will be reconstructed with a time-of-flight algorithm into a 300 mm field of view with a pixel size of 1.17mm and slice thickness of 2.78mm. All images will be transferred to a Radiation Oncology workstation.

7.253 The following MRI sequences will be obtained: Sagittal T1 FLAIR, Axial DWI, Axial T2 FLAIR, Axial BRAVO ARC, Gad Axial T2, Gad Sagittal Cube T1.

7.3 MRI Scanning

7.31 Patients requiring a separate diagnostic MRI

Patients undergoing PET/CT will require a separate diagnostic MRI. Patients undergoing PET/MRI may omit this step, as diagnostic-quality images will be obtained with PET/MRI.

7.32 Screening for MR eligibility

The subject will undergo MRI screening for contraindications to scanning and contrast agent administration as per routine clinical protocol at Mayo Clinic.

7.33 Timing of MR scanning

MRI will be acquired at the time of the standard CE-MRI examination on a 3.0 Tesla field strength scanner, no more than 14 days prior to beginning radiation treatments

Note: Standard treatment planning protocols will be used at the discretion of the radiation oncologist and radiologist, including T1-post contrast and T2 FLAIR sequences at a minimum

7.4 Comparison of volumes

To examine volumes delineated using ^{18}F-DOPA-PET and MRI, the union, intersection and discordant regions of PET and MR volumes will be quantified. For patients with PET uptake outside of the MR volume, the percentage of PET uptake encompassed by several different margins beyond the MR defined volume will be determined, and the maximal distance (in millimeters) between the margin of the MR volume and the margin encompassing 100% of the PET uptake will be quantified. Both PET T/N ratio >2.0 and T/N ratio > 1.5 will be used to define the PET volume.

7.41 Exploratory analysis for other T/N thresholds and SUV levels will be investigated

7.5 Radiation therapy

7.51 Target delineation

Following informed consent and co-registration of PET and MRI datasets with the planning CT acquired during standard CT simulation, the radiation oncologist will define the target volumes to use for radiation treatment planning.

7.52 Target delineation will be based on MRI and PET imaging, defining a gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) as defined below. In the event that gross disease is multifocal on MRI or FDOPA-PET, contours do not need to be contiguous.

7.5121 GTV_MRI = standard of care MRI contrast enhancement
7.5122 GTV_PET = high signal PET disease
7.5123 GTV_high = boolean of GTV_MRI and GTV_PET
7.5124 CTV_high = GTV_high
7.5125 PTV_high = CTV_high with a 0-2 mm expansion, based on the radiation oncologist's clinical judgment

7.53 Treatment planning and delivery

The prescription dose will be 35 Gy delivered in 10 fractions of 3.5 Gy each. Treatments will be delivered daily except weekends and holidays.

7.531 For PTV_high volumes less than 75 cc, a dose of 40 Gy in 10 fractions is allowed

7.532 Target coverage and normal tissue constraints are outlined below

	Constraints Goals			Highest Priority Constraints		
Structure	**DVH Endpoint**	**Constraint**	**Priority**	**DVH Endpoint**	**Constraint**	**Priority**

CTV_high	D95%[%]	>=100%	2	D95%[%]	>=95%	1
	-	-	-	CV95%[cc]	<0.5cc	1
	V110%		Report	-	-	-
PTV_high	D95%[%]	>=99%	2	D95%[%]	>=95%	1
	-	-	-	CV95%[cc]	<0.5 cc	1
	V110%		Report	-	-	-
Brain-ptv	-	-	-	V36Gy	<0.1 cc	1
	V31Gy[cc]	<1 cc	2	-	-	-
	V28Gy[cc]	<5 cc	2	-	-	-
	-	-	-	D0.03cc	<35 Gy	1
Optic_chiasm_PRV	D0.03cc	<20 Gy	2	D0.03cc	<25 Gy	1
Optic_chiasm	-	-	-	Dmax	-	Report
Optic_nerve_l_PRV	D0.03cc	<20 Gy	2	D0.03cc	<25 Gy	1
Optic_nerve_l	-	-	-	Dmax	-	Report
Optic_nerve_r_PRV	D0.03cc	<20 Gy	2	D0.03cc	<25 Gy	1
Optic_nerve_r	-	-	-	Dmax	-	Report
Brainstem	D0.03cc	<24 Gy	2	D0.03cc	<30 Gy	1
Cord	-	-	-	Dmax	-	Report
Lens_r	D0.03cc	<4 Gy	2	-	-	-
Lens_l	D0.03cc	<4 Gy	2	-	-	-
Eye_r	Mean	≤20 Gy	2	-	-	-
	D0.03cc	<35 Gy	2	-	-	-
Eye_l	Mean	≤20 Gy	2	-	-	-
	D0.03cc	<35 Gy	2	-	-	-
Parotid_r	Mean	<16 Gy	2	-	-	-
Parotid_l	Mean	<16 Gy	2	-	-	-
Cochlea_r	D0.03cc	<35 Gy	2	-	-	-
	Mean	<20 Gy	2	-	-	-
Cochlea_l	D0.03cc	<35 Gy	2	-	-	-
	Mean	<20 Gy	2	-	-	-
Hippocampus_l	Mean	≤20 Gy	2	-	-	-
Hippocampus_r	Mean	≤20 Gy	2	-	-	-

7.54 Brain constraints were determined using the cumulative normal tissue dose($NTD_{cumulative}$) constraint of 100 Gy in 2 Gy fractions (assuming $\alpha/\beta=2$ for late brain toxicity) reported by Mayer et al. to minimize the risk of radiation necrosis.[30] Assuming the brain received a previous dose of 60 Gy in 30 fractions, keeping the dose less than or equal to 31 Gy will result in an $NTD_{cumulative}$ of 99.5 Gy.

7.55 If the patient previously received less than 60 Gy in 2 Gy equivalent fractions, the brain constraint can be relaxed as to keep the $NTD_{cumulative}$ below 100 Gy.

7.56 Plans created using proton therapy will utilize robust optimization as per the departmental standard. No PTV will be needed for these patients.

7.57 ExacTrac or PAIS will be used for image guidance

7.58 Plan deviations

	Deviation	
	Minor	Major
Target volumes	CTV_high D95% between 90% and 95%	CTV_high D95% <90%
Volume	CTV or PTV margins larger than allowed in the protocol	Contoured GTV does not include imaging-visible tumor
Organs at Risk	Will be assessed at the time of data review	Will be assessed at the time of data review

7.6 Concurrent chemotherapy

Concurrent chemotherapy will not be required by the protocol. However, retrospective data of Mayo Clinic patients receiving reirradiation revealed a significantly lower risk of radionecrosis when bevacizumab was administered concurrently. Thus, we recommend use of concurrent bevacizumab with radiotherapy when possible.

7.7 Follow-up protocol

7.71 Follow-up imaging

Once radiation treatment planning is complete, additional ^{18}F-DOPA-PET scans will not be required. Standard of care MRI scans will be used for follow-up imaging.

7.8 Response assessment

Post-treatment tumor recurrence will be monitored with follow-up MRI imaging to assess tumor response based on RANO Working Group criteria until progression or death (or up to 2 years)

7.9 Patterns of failure

For patients who recur, follow-up imaging at progression will be co-registered with pre-treatment imaging in MIM Maestro™ and patterns of failure will be analyzed in the Eclipse treatment planning software (Varian Medical Systems, Palo Alto, CA) by determining the portion of recurrence volume (RecVol) that falls within the 95% isodose line of the PTV from the reirradiation plan.

7.91 Failures will be documented as ‘central’ relative to the treatment volume if >95% of the recurrence volume is within the 95% isodose line,‘in field’ (80-95%), ‘marginal’ (20-80%), or ‘distant’ (<20%).

7.92 Failures will be documented as 'central' relative to the T1-CE MRI if >95% of the recurrence volume is within the T1-CE volume, 'in field' (80-95%),'marginal' (20-80%), or 'distant' (<20%).

7.93 Failures will be documented as 'central' relative to the ^{18}F-DOPA-PET avidity if >95% of the recurrence volume is within the PET volume (defined as T/N > 2.0), 'in field' (80-95%), 'marginal' (20-80%), or 'distant' (<20%).

7.931 Exploratory analysis for T2 FLAIR volumes, other T/N thresholds and SUV levels and their relationship with sites of failure will be investigated

7.10 Reoperation rates

Patients undergoing repeat surgical intervention will have the date of the procedure, operative intervention performed, and pathologic findings recorded

7.11 Outcomes

Outcomes for patients treated prospectively with the addition of ^{18}F-DOPA-PET image-guided radiotherapy will be determined based on comparison with historical controls in the published literature.[24-29, 33-36]

7.12 Acute and late toxicity monitoring

Using the standard doses, target volumes and constraints described above, previous studies have reported minimal acute or late toxicity.[24-27, 30]

7.13 Quality of life

Quality of life (QOL) and cognitive function will be evaluated with the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) and the Brief Fatigue Index (BFI). Every patient will be asked to complete the whole form packet at baseline and at each MRI evaluation for a maximum of 6 evaluations. These time points are selected to capture the quality of life profile and correlate findings with radiologic and clinical progression as well as time points used on prior studies to allow historical comparisons.

8.0 Dosage Modification Based on Adverse Events

If a patient develops an allergic reaction during injection of ^{18}F-DOPA, the patient is not to receive any additional tracer and will not undergo PET imaging and will go off study.'

9.0 Ancillary Treatment/Supportive Care:

None

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions/^{18}F-DOPA

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.
Serious Adverse Event - Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.
All adverse events that do not meet any of the criteria for serious, should be regarded as **non-serious adverse events**.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)- Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.
- Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically

significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events/^{18}**F-DOPA**

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.21 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.25).

Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4 and 10.6. All expected AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.22 Assessment of Attribution/**^{18} F-DOPA**

Patients will be observed for adverse events for approximately 15-20 minutes post ^{18}F-DOPA injection by the Nuclear Medicine health professionals administering the scan. If AE is observed a second AE assessment is required < 24 hours post injection which will be performed by study staff.

10.221 When assessing whether an adverse event is related to the ^{18}FDOPA injection, the following attribution categories are utilized:

PET adverse events
Definite - The adverse event is clearly related to the PET scanning and ^{18}F-DOPA injection
Probable - The adverse event is likely related to the PET scanning and ^{18}F-DOPA injection
Possible - The adverse event may be related to PET scanning and ^{18}F-DOPA injection
Unlikely - The adverse event is doubtfully related to the PET scanning and ^{18}F-DOPA injection
Unrelated - The adverse event is clearly NOT related to the PET scanning and ^{18}F-DOPA injection

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the agent and the adverse event.

10.3 Expected vs. Unexpected/ **^{18}F-DOPA**

- The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific adverse event information provided in section 15.0 of the protocol.

NOTE: "Unexpected adverse experiences" mean any adverse experience that is neither identified in nature, severity, or frequency of risk, in the information neither provided for IRB review nor mentioned in the consent form.

10.4 Expedited Reporting Requirements for IND/IDE Agents/ **^{18}F-DOPA**

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour, 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.41 of the protocol.

Expedited AE reporting timelines are defined as:
- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period. **For ^{18}FDOPA, 10 radioactive half-lives is 18.3 hours or 1 whole day.**

Effective Date: May 5, 2011

NOTE: Use paper Adverse Event Expedited Report- Single Agent to report SAEs.

Provide copies of all serious events, regardless of drug relatedness, along with the Event Reporting cover sheet to:

Dr. Brian Mullan (^{18}FDOPA IND 61300 sponsor) at bmullan@mayo.edu , and Lori Lutzke (Nuclear Medicine Clinical Research Coordinator/IND Coordinator) at Lutzke.Lori@mayo.edu. These email notifications will be managed by the SAE, IND, and Safety Reporting Coordinators.

10.41 Special Situations for Expedited Reporting/**^{18}F-DOPA**

Exceptions to Expedited Reporting: ^{18}F-DOPA
An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting Requirements**: Hospitalizations for reasons deemed to be disease related will not be reported.**

System Organ Class (SOC)	Adverse event/symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Immune system disorders	Allergic Reaction	≤ Grade 3
Nervous system disorders	Vasovagal reaction	≤ Grade 3
Injury, poisoning and procedural complications	Bruising	≤ Grade 3
Skin and subcutaneous tissue disorder	Rash maculo-papular	≤ Grade 3

PET scanning, PET tracer injections are the only procedures unique to this study. All other aspects of radiation therapy and follow-up are part of standard brain cancer treatment. Consequently, only adverse events *possibly*, *probably*, or *definitely* related to ^{18}F-DOPA PET administration will be graded and reported to the IRB.

Report any clinically important increase in the rate of a serious suspected adverse reaction over that which is listed in the protocol or investigator brochure as an expedited.

Report an expected event that is greater in severity or specificity than expected as an expedited event.

10.5 Other Required Reporting/ **^{18}F-DOPA**

10.51 Persistent or Significant Disabilities/Incapacities / **^{18}F-DOPA**

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur up to 24 hours post injection following administration

of the investigational agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.52 Death/**^{18}F-DOPA**

The reporting period for ^{18}F-DOPA for this study is 1 day.

Any death occurring within 1 day after ^{18}F-DOPA agent was last administered or within 30 days of the last radiation dose, regardless of attribution requires expedited reporting within 24 hours.

Any death occurring greater than 1 day after the last ^{18}F-DOPA agent was administered with an attribution of possible, probable, or definite requires expedited reporting within 24 hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)" under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.6 Reporting of Serious Adverse Events and Unanticipated Problems/ **^{18}F-DOPA**

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

10.61 Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.62 Investigator Reporting: Notifying the Mayo IRB/**^{18}F-DOPA:**
The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration

(FDA) in early 2007 and are respectively entitled “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” and “Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection.”

10.621 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.622 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs. Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject’s name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed (if applicable). For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.7 ^{18}F-DOPA adverse events to be graded prior to and post ^{18}F-DOPA scan per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Post injection assessment[1]
Immune system disorders	Allergic reaction		X
Nervous system disorders	Vasovagal reaction		X
Injury poisoning and procedural complications	Bruising	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X
Renal and urinary disorders	Acute kidney injury		X

1. This assessment should occur approximately 15-20 minutes post injection (after scan is completed)

10.71 Submit via appropriate *reporting mechanisms (i.e., paper or electronic)* the following AEs experienced by a patient and not specified in Section 10.4:

10.711 Grade 2 AEs deemed possibly, probably, or definitely related to the ^{18} F-DOPA PET scan.

10.712 Grade 3 and 4 AEs regardless of attribution to the ^{18} F-DOPA PET scan.

10.713 Grade 5 AEs (Death)

10.714 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure

10.715 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.8 Recording Adverse Events/**Radiation Therapy**

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.81 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to Radiation Therapy. With this information, determine whether the event must be reported as an expedited report (see Section 10.9).

Expedited and routine reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4 and 10.6. All expected AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

10.82 Assessment of Attribution

10.821 Patients will be regularly evaluated by a radiation oncology health professional per standard clinical practice throughout their course of external beam radiation therapy.

10.822 When assessing whether an adverse event is related to Radiation Therapy, the following attribution categories are utilized:

RT adverse events
Definite- The adverse event *is clearly related* to RT
Probable- The adverse event is *likely related* to RT
Possible- The adverse event *may be related* to RT
Unlikely- The adverse event is *doubtfully related* to RT
Unrelated- The adverse event *is clearly NOT related* to RT

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the treatment and the adverse event.

10.9 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriate action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

10.91 Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.10 Radiation Therapy adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	During Treatment	Active Monitoring
General disorders and administration site conditions	Fatigue	X		X
Immune system disorders	Allergic reaction		X	
Nervous system disorders	Central nervous system necrosis			X
Nervous system disorders	Vasovagal reaction		X	
Injury poisoning and procedural complications	Bruising	X	X	
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X	

10.101 Submit via appropriate *reporting mechanisms (i.e., paper or electronic)* the following AEs experienced by a patient.

10.1011 Grade 2 AEs deemed possibly, probably, or definitely related to the Radiation Therapy

10.1012 Grade 3 and 4 AEs regardless of attribution to Radiation Therapy

10.1013 Grade 5 AEs (Death)

10.1014 Any death within 30 days of the patient's last treatment or procedure regardless of attribution to the study treatment or procedure

10.1015 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.11 Special Situations for Expedited Reporting**/Radiation Therapy**

Exceptions to Expedited Reporting/Radiation Therapy

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting

Requirements**: Hospitalizations for reasons deemed to be disease related will not be reported.**

System Organ Class (SOC)	Adverse event/symptoms	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administration site conditions	Fatigue	≤ Grade 3
Immune system disorders	Allergic Reaction	≤ Grade 3
Nervous system disorders	Central nervous system necrosis	≤ Grade 3
Nervous system disorders	Vasovagal reaction	≤ Grade 3
Injury, poisoning and procedural complications	Bruising	≤ Grade 3
Skin and subcutaneous tissue disorder	Rash maculo-papular	≤ Grade 3

All aspects of radiation therapy and follow-up are part of standard brain cancer treatment. All toxicities associated with other components of conventional brain cancer treatment (e.g. hematological events resulting from chemotherapy) will not be graded or reported as part of this protocol.

Report any clinically important increase in the rate of a serious suspected adverse reaction over that which is listed in the protocol or investigator brochure as an expedited.

Report an expected event that is greater in severity or specificity than expected as an expedited event.

10.12 Death/ **Radiation Therapy**

The reporting period for radiation therapy for this study is 30 days.

Any death occurring greater than 30 days after the last radiation dose was administered with an attribution of possible, probable, or definite requires expedited reporting within 24 hours.

Reportable categories of Death

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as Grade 5 “Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)” under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes

suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.121 Second Malignancy/ **Radiation Therapy**

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy).
Second malignancies require ONLY routine reporting.
All secondary malignancies that occur following treatment will be reported.
Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms.

10.122 Second Malignancy**/ Radiation Therapy**

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.13 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.131 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10.7 "Monitoring and Auditing"). Medical monitoring will include a regular assessment of the number and type of serious adverse events. "Any serious adverse events will be followed up by the sentinel event reporting procedure"

10.132 Internal Data and Safety Monitoring Board

The trial will be reviewed by the Cancer Center Auditing area on a bi-annual or yearly basis dependent on random study selection to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

11.0 Treatment Evaluation

11.1 Measurement of Effect

Tumor response will be assessed, using contrast and non-contrast brain magnetic resonance imaging (MRI) with assessment based on the RANO criteria, until progression of disease (up to 2 years).

11.2 Definitions:

Response and progression will be evaluated in this study using the international criteria proposed by the Response Assessment in Neuro-Oncology (RANO) Working Group.[14]

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

11.21 Measurable Disease

Defined as bi-dimensionally contrast-enhancing lesions with clearly-defined margins by MRI with two perpendicular diameters of at least 10 mm, visible on 2 or more axial slices which are preferably at most 5 mm apart with 0 mm skip.

In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity is problematic. In general, such lesions should be considered non-measurable unless there is a nodular component measuring at least 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

11.22 Non-measurable Disease

This is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters <10 mm.

11.23 Target Lesions

All measurable lesions up to a maximum of five lesions should be identified as target lesions and recorded and measured (sum of the products of the perpendicular diameters) at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repeated measurements by imaging techniques. Occasionally, the largest lesions may not be suitable for reproducible measurements and the next largest lesions which can be measured reproducibly should be selected.

11.24 Non-target Lesions

For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered non-target lesions and should also be recorded. Rarely, unequivocal progression of a non-target lesion requiring discontinuation of therapy, or development of a new contrast-enhancing lesion may occur even in the setting of stable disease (SD) or partial response (PR) in the target lesions. These changes would qualify as progression. Non-target lesions also include measurable lesions that exceed the maximum number of 5. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

11.3 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. Baseline evaluations should ideally be performed within 21 days before the beginning of treatment. These techniques should be performed with cuts of 4 mm or less in slice thickness contiguously. The MRIs will be evaluated both locally and centrally by a core lab.

11.4 Response Criteria

11.41 Evaluation of Target Lesions

11.411 Complete Response (CR): Requires all of the following:

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
- No new lesions
- Stable or improved non-enhancing (T2/FLAIR) lesions
- Patients must be off corticosteroids
- Stable or improved clinically
- Patients with non-measurable disease cannot have a complete response. The best response possible is stable disease.

11.412 Partial Response (PR): Requires all of the following:

- ≥50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks
- No progression of non-measurable disease
- No new lesions
- Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan
- The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of the baseline scan
- Stable or improved clinically

11.413 Stable Disease (SD): Requires all of the following:

- Does not qualify for complete response, partial response, or progression
- Minimum 4 weeks duration
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose
- Stable clinically

11.414 Progression: Defined by any of the following:

- ≥25% increase in the sum of products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids
- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects)
- Any new lesion
- Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the investigator but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to co-morbid events.
- Failure to return for evaluation due to death or deteriorating condition
- Clear progression of non-measurable disease

11.415 Pseudoprogression (PsP): All of the following must be true:

- Progression of contrast enhancing lesions and or T2/FLAIR is restricted to the initial radiation therapy volume.
- There are no new enhancing lesions outside of the initial radiation therapy volume.
- Patients are stable or improved clinically.
- PsP may be diagnosed at any time during therapy (beyond the typical 12 week window defined by RANO).

11.416 Summary of the RANO Response Criteria Table

	CR	PR	SD	PD[1,2]	Preliminary PD/PsP[3]
T1-Gd +	None	≥50% decrease	<50% decrease-<25% increase	≥25% increase*	Any increase is restricted to initial RT Volume
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase*	Any increase is restricted to initial RT Volume
New Lesion	None	None	None	Present*	None
Corticosteroids	None	Stable or decrease	Stable or decrease	**NA**	Stable or decrease
Clinical Status	Stable or improved	Stable or improved	Stable or improved	Worsened*	Stable or improved
Requirement for Response	All	All	All	Any*	All

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease, PsP = Pseudoprogression

NA - Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

1. RANO Progression occurs when any of the criteria with * are present.
2. Confirmed PD requires all of the following If not all criteria are met then Preliminary PD
   - More than 3 months post RT
   - Radiologic progression by central review by RANO criteria
   - Clinical progression as determined by treating Oncologist
   - Cannot be considered Pseudoprogression
3. Patients with possible PsP should initially be given the Objective Status of Preliminary Progression. Once PsP or Progression is confirmed, the Objective Status can be changed accordingly. If Progressive Disease is subsequently confirmed, the Objective Status is to be recorded for the current cycle as PD (confirmed) and the back-dated date of the progressive disease (from the cycle with the initial Preliminary PD) is to be used as the date of progressive disease which is documented via the Event Monitoring Form. If progressive disease is not confirmed the Objective Status for the current cycle can be documented as SD, PR, or CR as appropriate using the baseline scan measurement as the baseline for comparison with the current measurement. The Objective Status for the cycle initially documented as Preliminary PD can be changed to PsP.

11.417 Confirmatory Measurement/Duration of Response

11.4171 Confirmation:
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat

assessments that should be performed 4 weeks after the criteria for response are first met.

11.4172 Duration of Overall Response:
The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

11.4173 Duration of Stable Disease:
Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

12.0 Descriptive Factors

- Corticosteroid therapy at study entry: yes (specify dose) vs no
- Histologic grade of primary tumor: 3 vs 4
- Histologic type of primary tumor: oligodendroglioma vs oligoastrocytoma vs astrocytoma vs other (specify)
- ECOG PS (see Appendix I): 0 vs 1 vs 2 vs 3
- Neurologic deficit: yes (specify) vs no
- History of seizures: yes (specify last seizure) vs no
- Prior surgical resection or biopsy: yes vs no
- Age:<=70 vs >70
- MGMT: methylated vs unmethlated vs not available
- IDH status: mutated vs wild type vs not available
- 1p/19q status: single deleted vs codeleted vs not available
- Time since last RT course: <6 months vs 6-12 months vs >12 months
- Salvage chemotherapy: yes (specify agents, dates treated) vs no

13.0 Treatment/Follow-up Decision at Evaluation of Patient

13.1 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient will go off study.

- If the patient received MR and PET for radiotherapy planning, all data up until the point of confirmation of ineligibility must be submitted.
- If the patient never received pre-RT PET, on-study material must be submitted. No additional follow up is necessary.

13.2 Those patients who will not receive any radiation treatment or who will receive radiation treatment elsewhere (not at Mayo Clinic) will be considered non-evaluable for the study endpoint and move to Event Monitoring phase per Section 18.0.

13.3 Patients who are CR, PR, REGR, or SD will continue to obtain MRI scans at each clinically indicated follow-up for up to 2 years from registration.

13.4 Patients who develop PD or withdraw from further follow-up scans will go to the event-monitoring phase per Section 18.0.

14.0 Body Fluid Biospecimens: None

15.0 Drug Information

^{18}F-DOPA is an investigational PET tracer utilized for the study under a Mayo physician-sponsor IND #61300 held by Dr. Brian P. Mullan in the division of Nuclear Medicine. The ^{18}F-DOPA is produced in the Mayo Clinic PET Radiochemistry Facility using Good Manufacturing Practice as defined by 21 CFR Part 212.

The literature reports no deleterious effect was revealed in toxicity testing of ^{18}F-DOPA-PET, and concludes the toxicological safety of the product is guaranteed given the toxicity data of the various potential impurities. ^{18}F-DOPA-PET is currently in production at this institution, and is used to image malignant gliomas for research studies MC 1373 (IRB 13-005102) and MC 1374 (IRB 13-005106).

16.0 Statistical Considerations and Methodology

16.1 Study Overview

This is a single-arm, single-stage phase II Simon's Optimum study with an analysis that will compare progression-free survival (PFS) at 3 months for recurrent glioma patients after radiotherapy targeting volumes designed with both ^{18}F-DOPA-PET and MRI information with historical controls.

16.11 The primary endpoint of this trial is the proportion of patients that experience progression-free survival at 3 months based on our hypothesis that the combination of more accurate target delineation of high-grade glioma by ^{18}F-DOPA-PET will improve overall tumor control.

16.2 Statistical Design

16.21 Decision Rules

The primary endpoint of this trial is the proportion of patients treated with ^{18}F-DOPA-PET guided radiotherapy who are alive and have not progressed within 3 months. A success will be a patient who is alive and without evidence of progressive disease within 3 months from registration. Median PFS after bevacizumab failure ranges between 1-2 months.[17, 34] Thus, the largest success proportion where the proposed treatment would be considered ineffective in this population is 20%. The following Simon's Optimum design uses 20 patients to test the null hypothesis that the proportion of successes is at most 20% with an overall significance level (alpha) of 0.186, and a power of 85.9% to detect a true success proportion of 40%.

16.22 After 10 evaluable patients are accrued to this study and followed for at least 3 months, if 2 or more successes are alive and progression-free at 3 months, the results will wait until conclusion of the study. If 1 or fewer patients are alive without evidence of progression at 3 months, the study will be stopped and the treatment will be deemed ineffective in this population.

16.23 After 20 evaluable patients are accrued to this study and followed for at least 3 months, if 6 or more successes are observed we may recommend further testing of this regimen in subsequent studies in this patient population.

16.24 We will not suspend accrual between stages to allow the first 20 patients to become evaluable, unless undue toxicity is observed.

16.3 Sample Size

The design to be utilized is fully described in section 0. A maximum of 20 evaluable patients will be accrued to this pilot study unless undue toxicity is

encountered. We anticipate accruing an additional 2 patients to account for ineligibility, cancellation, major treatment violation or other reasons. Maximum projected accrual is therefore 22 patients. We anticipate screening 30 patients to register a total of 22 patients necessary for study design.

16.4 Accrual Time and Study Duration

Based on institutional experience, we deliver RT to an average of 25 recurrent glioma patients annually. Our plan to accrue 10 patients per year is based on including less than 50% of our recurrent glioma RT population, which is readily achievable. We plan to accrue patients for years 1-2, leaving years 3-4 for follow-up and analysis. Therefore, the overall study duration is expected to be 48 months.

16.5 Power and Significance Levels

Assuming the number of successes is binomially distributed, the significance level is 0.186 and probability of declaring that this regimen warrants further studies (i.e. statistical power) under various success proportions and the probability of stopping accrual after the first stage can be tabulated as a function of the true success proportion as shown in the following table.

16.6 Other considerations:

Adverse events and patterns or failure observed in this study as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.7 Analysis plan

The analysis for this trial will commence at the planned time points (see Section 4.0) and at the time patients have become evaluable for the primary endpoint. Such decisions will be made by the statistician and the study chair, in accord with the Cancer Center Statistics (CCS) Standard Operating Procedures, availability of data for secondary endpoints, and level of data maturity. The earliest date anticipated in which results will be available for manuscript, abstract or presentation format is when 20 patients have either progressed or been followed for at least 3 months. Subgroup analyses will be included for this primary endpoint to assess known prognostic factors such as MGMT status, age, and time from prior RT to reirradiation.

16.71 Primary Endpoint:

16.711 Definition: the primary endpoint of this trial is proportion of patients experiencing progression-free survival at 3 months. All patients meeting eligibility criteria who have a signed consent form on record and who have begun ^{18}F-DOPA-guided reirradiation treatment at Mayo Clinic will be evaluable for the endpoint. All eligible patients will be followed until death or a maximum of 4 years. Time to disease progression is defined as the time from study registration to the earliest date documenting disease progression. If a patient dies without evidence of disease

progression, the patient will be censored on the last date the tumor was evaluated. If a patient is declared to be a major treatment violation, the patient will be censored on the date the treatment violation was declared to have occurred. In the case of a patient starting treatment and then never returning for any evaluation, the patient will be censored for progression on the last day of therapy.

16.712 Estimation: the proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.[37]

16.713 Over Accrual: if more than the target number of patients are accrued, the additional patients will not be used for evaluation of stopping rules or in any decision making process. The will be included in the final point estimates and confidence limits.

16.8 Definitions and Analysis of Secondary and Correlative Endpoints

Subgroup analyses will be included as appropriate for these secondary endpoints to assess known prognostic factors.

16.81 Overall Survival: compare overall survival (OS) at 12 months for patients after radiation therapy targeting volumes designed using ^{18}F-DOPA in addition to MRI contrast enhancement with historical controls. Survival time will be determined from the time of initial diagnosis to death from any cause. Survival from reirradiation will be determined from the time of study registration to the time of death from any cause. The distributions of the survival time will be estimated using the Kaplan-Meier method.[38]

16.82 Volumetric Comparison: to differences in the ^{18}F-DOPA-PET avid region with abnormalities on MRI, the treating radiation oncologists will first define treatment volumes for GTV_MRI using the T1-post contrast MRI scans while blinded to the PET study. A volume named T2_FLAIR_NCET will be defined by outlining T2 hyperintensity on T2 FLAIR MRI sequences. Then the PET study will be fused with the contouring software to allow automated contouring of GTV_PET defined by the T/N ratio > 2.0 (and T/N > 1.5). These contours will be reviewed by the treating radiation oncologist and then expanded as noted above. The volume of overlap and non-overlap between the GTV_MRI, T2_FLAIR_NCET and GTV_PET will be calculated. Paired t-test statistical analysis will be performed to determine if any differences exist and the level of statistical significance between treatment volumes defined by MRI only and the treatment volumes defined by both PET and MRI. The analysis of volumes from 20 patients will have 80% power to detect differences in volumes with an effect size of 0.63 using a pared t-test with 0.05 two-sided significance level. Alternate metrics for comparison will also be assessed including spatial overlap, distance, correlations, and 3D shape comparisons.

16.83 Patterns of Failure: observe patterns of failure after reirradiation using ^{18}F-DOPA-PET to guide treatment volumes. The MRI scan indicating progressive disease will be fused with our treatment planning scan and the region of progression will be contoured by an investigator blinded to the GTV_MRI, T2_FLAIR_NCET, GTV_PET, PTV_high, and isodose lines. A volumetric analysis will then be performed to define the doses delivered to the absolute and relative volume of the region where recurrence is defined.

16.84 Adverse Events: determine acute and late toxicity after radiotherapy treatment using ^{18}F-DOPA-PET to delineate treatment volumes. The rate of acute and late treatment-related toxicities for recurrent high-grade glioma patients treated with ^{18}F-DOPA-PET image-guided radiotherapy will be determined, with acute RT toxicities graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (available at http://ctep.cancer.gov), and late toxicities reported using RTOG/EORTC late toxicity criteria.[39]

16.85 Reoperation Rates: determine the rate of reoperation for patients undergoing reirradiation for recurrent high-grade gliomas treated using ^{18}F-DOPA-PET guided volumes. When available, pathologic information detailing the presence of necrosis and/or tumor progression will be recorded.

16.86 Quality of Life: estimate quality of life (QOL) after radiotherapy using ^{18}F-DOPA-PET to establish treatment volumes. QOL will be evaluated using the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) and fatigue will be evaluated using the MD Anderson Brief Fatigue Inventory. These questionnaires will be administered at baseline and at each MRI evaluation up to 6 total evaluations to capture quality of life and correlate findings with clinical and radiographic progression. Analysis will include change percent from baseline using t-tests and generalized linear models to test for changes at each time point and non-zero slope.

16.9 Data Safety Monitoring Plan

The Study Chairs and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety and Monitoring Board (DSMB) is responsible for reviewing the accrual and safety for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.91 **Adverse Event Stopping Rules:** As no reactions to ^{18}F-DOPA have been reported within the institution, toxicity testing reported in the literature revealed no deleterious effects (section 0), and there have been no allergic reactions in all

patients accrued to date on multiple studies MC1078, MC1373, and MC1374, no reactions are anticipated. As such, if either of the two scenarios below occur, enrollment will be suspended so that details of each episode can be examined and a trial recommendation will be formulated and presented to the MCCC DSMB:

- At any point during the AE evaluation of the first 9 AE-evaluable patients, one or more patients is unable to complete PET scanning due to allergic reactions to the tracer.

Or, after 10 or more patients are evaluable for AEs, more than 10% of these patients are unable to complete PET scanning due to allergic reactions to the tracer.

There have been no reports in the literature of the occurrence of nephrogenic systemic fibrosis (NSF) in patients with normal renal function. Additionally, we will use the contrast agent gadobenate dimeglumine, which has been shown to have a high safety profile (lower incidence of NSF in patients with renal failure/insufficiency) compared with many other available Gd-based contrast agents. Therefore no reactions are anticipated. As such, if at any time a patient develops NSF enrollment will be suspended so that details of the episode can be examined and a trial recommendation will be formulated and presented to the MCCC DSMB.

Using the radiation treatment dosing, fractionation and normal tissue constraints outlined in Section 7 have been performed in several studies without significant adverse effects. While radiation-induced brain necrosis is rare, a cumulative normal brain dose of < 100 Gy in 2 Gy equivalents has been suggested as a constraint to minimize the risk of necrosis.[30] Two large studies reported no grade 3 or higher toxicity and no radionecrosis using the same dosing and fractionation as our protocol.[26, 27] In fact, studies using larger fraction sizes (5 Gy/fraction) reported very low rates of radionecrosis when keeping reirradiation doses under 40 Gy.[28, 29] However, tumor progression is expected in the majority of patients and commonly results in severe neurologic symptoms near the end of life. Both acute (available at http://ctep.cancer.gov) and late [39] toxicity will be monitored continuously as each patient is accrued and follow-up data are accumulated. If at any time, 1) 3 or more of the first 9 AE-evaluable patients; or, 2) after 10 or more patients are AE-evaluable, more than 30% experience any of the following adverse effects considered to be at least possibly related to radiation treatment up to and including the three-month timepoint; enrollment will be suspended so the details of each episode may be examined and a trial recommendation will be formulated and presented to the MCCC DSMB, adjusting the dose, fraction size or volumes as needed.

- Grade 3 or 4 irreversible CNS toxicity
- Grade 4 non-hematologic, non-CNS toxicity
- Any Grade 5 toxicity

16.10 Results Reporting on ClinicalTrials.gov

Initial estimated Primary Completion Date: At study activation, this study will have been registered within the www.ClinicTrials.gov (CT.gov) website. The Primary and Secondary endpoints along with other required information for this study will be reported on CT.gov. For purposes of timing of the CT.gov results reporting, the initial estimated completion date of the primary endpoint of this study is 27 months after the study opens to accrual.

16.101 Definition of Primary-Endpoint Completion Date (PCD): The PCD is the date at which the last progression free patient has been followed for 3 months.

16.11 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

16.111 There is no information currently available regarding differential effects of this regimen in subsets defined by gender, race or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences based on gender and racial groupings, the sample size is not increased in order to provide additional power for such subset analyses. Based on prior studies involving similar disease, we expect about 7% of patients will be classified as minorities by race and about 40% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	8	12	20
Ethnic Category: Total of all subjects	9	13	22
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	8	12	20
Racial Category: Total of all subjects	9	13	22

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Bio specimens:
None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Active-Monitoring Phase (Baseline)** (Compliance with Test Schedule Section 4.0)
Demographics	≤2 weeks after registration
Institutional Contacts	
Eligibility Checklist	
On-Study Form	
Initial Tumor Form	
Baseline Adverse Event Form FDOPA Pre-injection	
MD Anderson Symptom Inventory-Brain Tumor (MDASI) Questionnaire (Baseline)	
Brief Fatigue Inventory Questionnaire (Baseline)	
Concomitant Medications	
Off Treatment[1]	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Consent Withdrawal (if applicable)	

1. Submit if withdrawal/refusal prior to RT occurs

Test Schedule Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)			
	≤ 1 week after ^{18}F-DOPA-PET scan	≤ 4 weeks after each evaluation during RT	≤ 6 months after end of RT[5]	≤ 6 months after every clinically indicated MR scan[5]
Radiation Therapy Reporting Form			X[3]	
Adverse Event Form	X	X[1]	X	X
Post ^{18}FDOPA Injection	X[6]			
Patient Status: Clinical Follow-Up/Observation		X	X	X[2]
MD Anderson Symptom Inventory-Brain Tumor (MDASI) Questionnaire	X	X	X	X

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)			
	≤ 1 week after ^{18}F-DOPA-PET scan	≤ 4 weeks after each evaluation during RT	≤ 6 months after end of RT[5]	≤ 6 months after every clinically indicated MR scan[5]
Brief Fatigue Inventory Questionnaire	X	X	X	X
Adverse Events : Late Toxicities			X	X
Concomitant Medications	X	X	X	X
Notification/ Hospitalizations	At each occurrence			
Off Treatment	Submit ≤2 weeks after registration if withdrawal/refusal occurs after receiving therapy			
Consent Withdrawal				

1. Acute toxicity will be assessed during standard of care monitoring by the radiotherapy team during the course of treatment.
2. Late toxicity will be assessed during standard of care appointments. To be submitted ≤2 weeks after each clinically indicated MR scan.
3. This form should be completed **after** the radiation is completed.
4. Timeframes for submission purposefully large as they do not affect patient care i.e. the data being collected is for investigational use only and no patient decisions will be made with it, which allows us to batch the data for analysis by the study team (e.g. for Radiation Oncologist and Radiologists to contour volumes on image data).
5. See Section 4 for time of assessments.
6. Done approximately 15-20 minutes post injection of ^{18}F-DOPA after scan is completed and if AE observed a second AE assessment is required <24 hours post injection which is performed by study staff.

Follow-up Material(s)

CRF	Event Monitoring Phase[1]		
	Yearly for 2 years	At PD	Death
Adverse Events: Late Toxicities	X	X	
Patient Status: Survival Status Follow-up/ Event Monitoring	X	X	X

1. If a patient is still alive 2 years after registration, no further follow-up is required.

18.2 Data Handling and Record Keeping

18.21 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

(This information is contained within the Mayo IRB Informed Consent Template Section 14)

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

18.22 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Source documents are kept in a secure location.

18.23 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained.

18.24 Data Management

All data will be entered into electronic case report forms (eCRF's) through the Medidata Rave system. Case report forms will be automatically rolled out based on a predetermined, and visit based schedule to improve study staff workflow and data quality. Data will be exported nightly to a secure FTP for analysis and reporting.

18.25 Data Quality Assurance and Clarification Process

Each eCRF will contain edit checks and custom functions to ensure the highest possible data quality. Only necessary eCRFs will be available for data entry to reduce the possibility of erroneous entry. The edit checks and custom functions on the eCRFs will trigger queries requesting the attention of appropriate study staff. The fields will be marked in pink to allow study staff to quickly identify the data fields that require attention or actions. Additionally, secure email notifications will be sent for adverse event tracking and monitoring

18.26 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports for;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"

19.0 Study Finances

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be funded by research.

19.21 ^{18}F-DOPA-PET scan

19.3 Conflict of Interest

Any study team member who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor-investigator prior to participation in this study.

20.0 Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study and approval from the principal investigators must be obtained before any information can be used or passed on to a third party.

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Appendix I

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.
From http://www.ecog.org/general/perf_stat.html

Appendix II

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

MD Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours.*** Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking (finding the words)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Appendix II

Date: _____ **Institution:** _____

Participant Initials: _____ **Hospital Chart #:** _____

Participant Number: _____

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern (diarrhea or constipation)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

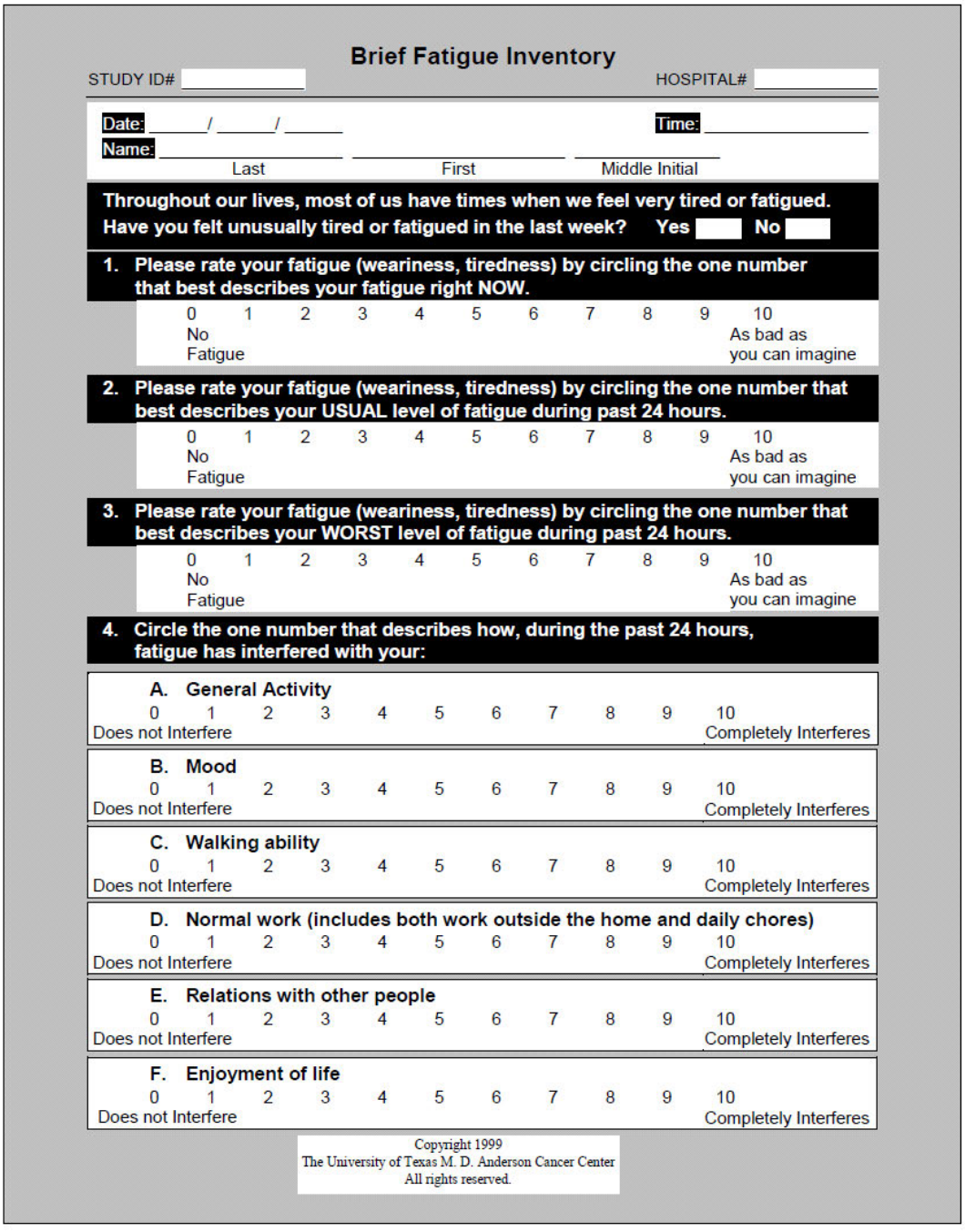
Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items ***in the last 24 hours***? Please select a number from 0 (symptoms have not interfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

MDASI-BT - 2006

Appendix III



Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL# _____

Date: ____/____/____ Time: _____

Name: _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General Activity
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

BFI - English - Formatted March 19, 2008