Mayo Clinic Cancer Center

Evaluating the impact of 18F-DOPA-PET on radiotherapy planning for newly diagnosed gliomas

Study Chairs: Nadia N. Laack, MD[1]
Debra H. Brinkmann, PhD[1]
Mayo Clinic
200 First Street SW
Rochester, MN 55905
507/284-2511
507/284-5280 (FAX)

Study Co chairs: [redacted]

Statistician: [redacted]

[1]Department of Radiation Oncology, Mayo Clinic Rochester
[2]Department of Radiology, Nuclear Medicine Program, Mayo Clinic Rochester
[3]Department of Radiology, Neuroradiology, Mayo Clinic Rochester
[4]Department of Radiology, Mayo Clinic Arizona
[5]Department of Health Sciences Research, Biomedical Statistics and Informatics, Mayo Clinic Rochester

√Study contributor(s) not responsible for patient care.

Document History	Effective Date
Activation	December 12, 2013
Addendum 1	January 23, 2014
Addendum 2	February 14, 2014
Addendum 3	March 10, 2014
Addendum 4	August 18, 2014
Addendum 5	November 20, 2014
Addendum 6	April 20, 2015
Addendum 7	August 21, 2015
Addendum 8	April 27, 2017
Addendum 9	March 15, 2018

Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Phone: [redacted] E-mail: [redacted]
Forms completion and submission	[redacted] Phone: [redacted] Email: [redacted]
Protocol document, consent form, regulatory issues	See Protocol Catalog for current RPS assignment: [redacted]
Serious Adverse Events	[redacted] Phone: [redacted] E-mail: [redacted]

*No waivers of eligibility per NCI

Table of Contents

EVALUATING THE IMPACT OF 18F-DOPA-PET ON RADIOTHERAPY PLANNING FOR NEWLY DIAGNOSED GLIOMAS **1**

PROTOCOL RESOURCES **2**

TABLE OF CONTENTS **3**

SCHEMA **4**

1.0 BACKGROUND 5
2.0 GOALS 14
3.0 PATIENT ELIGIBILITY 15
4.0 TEST SCHEDULE 17
5.0 GROUPING FACTORS: 18
6.0 REGISTRATION/RANDOMIZATION PROCEDURES 18
7.0 PROTOCOL TREATMENT 20
8.0 DOSAGE MODIFICATION BASED ON ADVERSE EVENTS 25
9.0 ANCILLARY TREATMENT/SUPPORTIVE CARE: NONE 25
10.0 ADVERSE EVENT (AE) REPORTING AND MONITORING 25
11.0 EVALUATION CRITERIA 31
12.0 DESCRIPTIVE FACTORS 35
13.0 FOLLOW–UP DECISION AT EVALUATION OF PATIENT 35
14.0 BODY FLUID BIOSPECIMENS - NONE 36
15.0 DRUG INFORMATION 36
16.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY 37
17.0 PATHOLOGY CONSIDERATIONS/TISSUE BIOSPECIMENS: N/A 46
18.0 RECORDS AND DATA COLLECTION PROCEDURES 47
19.0 BUDGET 49
20.0 REFERENCES 50

APPENDIX I ECOG PERFORMANCE STATUS **54**

APPENDIX II FOLSTEIN MINI MENTAL STATE EXAMINATION (MMSE) **55**

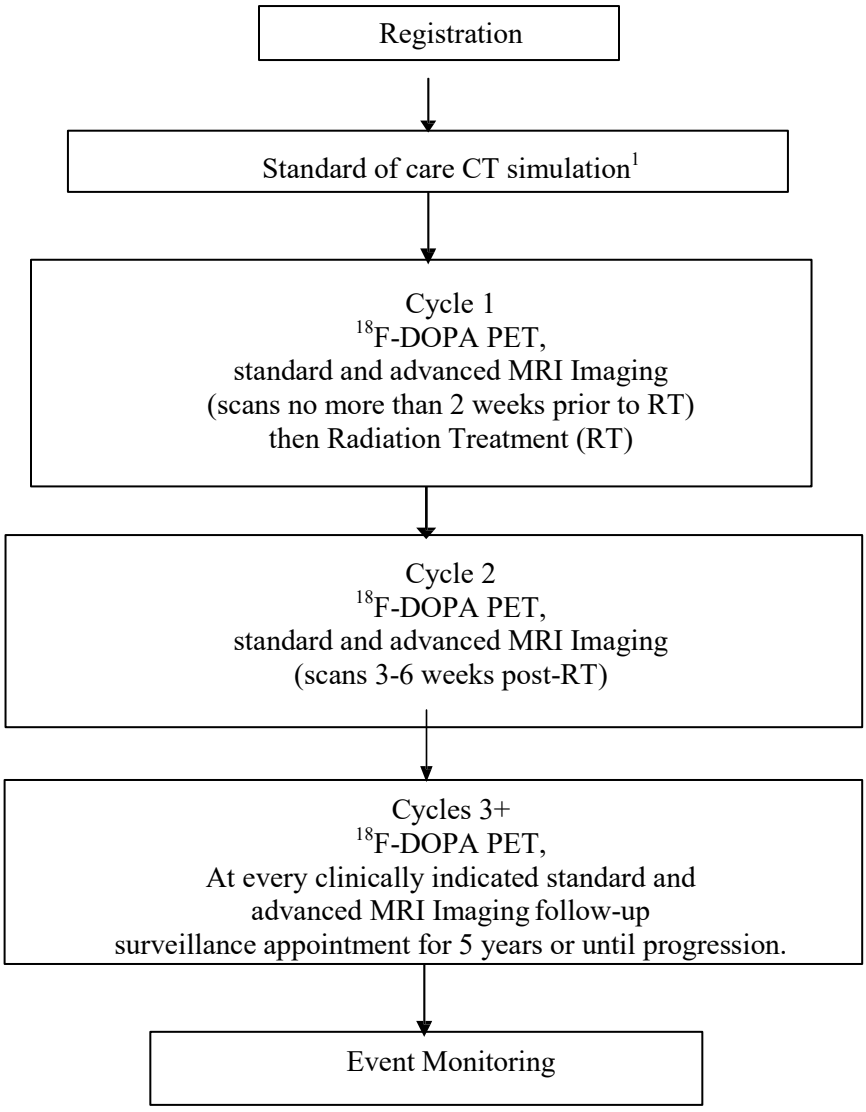
APPENDIX III PATIENT INFORMATION SHEET **58**

APPENDIX IV MDASI - BT **59**

APPENDIX V CONTOURING CNS AND H/N **61**

APPENDIX VI IMAGING GUIDELINES **63**

Schema



[1]CTsimulation can be done prior to or after registration

1.0 Background

1.1 Conventional imaging is inadequate to differentiate high- and low-grade gliomas and normal tissue:

Image-guided techniques have assumed a central role in maximizing the therapeutic benefit of first-line multi-modal treatment for gliomas. However there are significant deficiencies associated with conventional contrast enhanced magnetic resonance imaging (CE-MRI), the current standard of care for image-guided radiotherapy (RT) of brain tumors. MRI findings typically include a heterogeneous area of CE solid tumor surrounded by a large area of vasogenic edema. CE on T1-weighted images is used to identify regions of highest tumor density/grade or malignant potential for radiotherapy planning. However, approximately one-third of high-grade gliomas demonstrate no contrast enhancement (NCE), while benign tumors, such as pilocytic astrocytomas, infection, demyelination, and treatment effect commonly enhance [1]. Although used to define the extent of tumor infiltration relative to normal neuro-anatomic structures, abnormal T2/FLAIR signal is known to contain both regions of non-tumoral vasogenic edema and non-uniform tumor infiltration [2, 3]. Recent spectroscopic data suggest that the infiltration of tumor cells is not necessarily uniform with some areas of T2 change more likely to be edema and other areas more likely to have tumor infiltration [3]. Furthermore, tumor infiltration has been found to extend beyond areas that demonstrate abnormal T2/FLAIR or enhancement [4]. There is a critical need to incorporate imaging-based techniques to guide therapy that address these deficiencies of CE-MRI. Molecular imaging techniques provide visual information about biological processes and have the potential to improve the accuracy of RT tumor delineation and image-guided dose escalation, which impact the overall course of treatment and prognosis for brain tumor patients.

1.2 Amino acid PET tracer ^{18}F-DOPA PET appears promising for gliomas:

In contrast to the most commonly used tracer 18-Fluoro-deoxyglucose (^{18}F-FDG), which is taken up in both the tumor and normal brain glucose-metabolizing tissues, amino acid PET tracers such as 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (^{18}F-DOPA), show a high uptake in tumor tissue and low uptake in normal brain tissue [5-7]. ^{18}F-DOPA transport is independent of the blood-brain barrier breakdown, allowing uptake to occur in both enhancing and non-enhancing tumor with CE-MRI. Limited studies evaluating the sensitivity of ^{18}F-DOPA indicated that although FDG PET demonstrated a higher absolute standard uptake value (SUV) compared with 18F-DOPA, the sensitivity for detection of low- or high-grade tumors was 96% for 18F-DOPA versus 61% for 18F-FDG [6, 8]. The most studied amino acid tracer is 11C-methionine (11C-MET PET) [9]. Discrepancies of high 11C-MET PET uptake extending up to 4.5 cm beyond the CE region on CE-MRI for glioma patients have been reported [10], with high MET uptake also reported extending beyond the abnormal T2 signal area [10]. Several studies have indicated MET-PET altered resection planning for a majority of both low- and high-grade gliomas [11, 12]. A comparison of the performance of 18F-DOPA with 11C-MET concluded that 18F-DOPA provided equivalent visual and quantitative SUV information when imaging cerebral lesions [13]. The short physical half-life of 11C limits the ability to image patients at a facility without a cyclotron. Therefore, labeling an amino acid tracer with 18F would increase the physical half-life and increase the feasibility of multi-institutional use. Unfortunately, labeling methionine with ^{18}F is not chemically feasible. The sensitivity for differentiating tumor from normal brain, compelling literature evidence for amino acid tracers to detect additional tumor beyond conventional CE-MRI,

and the feasibility of multi-institutional use all substantiate the need to further investigate the value of ^{18}F-DOPA PET in the clinical management of gliomas.

1.3 ^{18}F-DOPA-PET for gross and clinical target volume delineation

Manual delineation of target volumes based on the PET data using different window-level settings and lookup tables is highly operator-dependent and subject to large inter-observer variability [14-25]. Several image segmentation approaches have been developed and used in the clinical setting, such as thresholding, region growing, edge detection, deformable models, clustering, and many more [15-24, 26-41]. A study by Grosu *et al*. demonstrated a reduction in interobserver variability defining the gross tumor volume (GTV) with agreement in more than 80% of the outlined volume from 1 in 5 patients to 5 in 10 patients with the inclusion of MET-PET [25]. Reports in the literature have demonstrated the significant volume delineation differences between MRI alone and MET- PET/MRI fusion. A study by Matsuo *et al*. concluded that based on 19 patients with 95 brain metastases, for GTV-MRI volumes greater than 0.5 mL, the GTV-MET-PET volumes were larger, and that a 2 mm margin outside the GTV-MRI significantly improved coverage of the GTV-PET [42]. A study by Grosu *et al*. found that of 39 patients undergoing radiation therapy planning for malignant gliomas after surgical resection, 74% had a MET-PET tumor volume (up to 4.5 cm) larger than the contrast-enhanced T1-weighted MRI-defined volume [10]. Also shown, for 18 patients who underwent both T2-weighted MRI and MET- PET, there was a 50% increase in MET uptake extended beyond the abnormal T2 signal area. Given the studies that demonstrate the significance of ^{11}C-MET PET to adequately delineate tumor volume, using ^{18}F-DOPA-PET as a surrogate is anticipated to play an important role in the planning of radiation treatment of gliomas.

1.4 Re-visiting dose escalation incorporating biological imaging-based treatment volumes:

Previous studies have clearly defined the role for RT in controlling high grade gliomas [43]. Previous dose escalation studies without chemotherapy up to 90 Gy to a 0.5 cm PTV margin from the contrast-enhancing lesion did not alter the median survival benefit, with treatment failures within the high dose RT IMRT fields remaining at over 90%, although no significant treatment toxicities occurred [44, 45]. In 2004, a randomized phase III trial reported improved median and 2-year survival in GBM patients treated with concomitant and adjuvant temozolomide (TMZ) and conformal RT with 60 Gy in 30 fractions [46]. Unfortunately, subsequent studies not only reported patterns of failure within the high dose (60 Gy) treatment field in over 90% of patients with GBM, but also showed an increase in distant failures [47, 48]. A dose escalation retrospective analysis with TMZ did not show a survival benefit or a reduction of in-field failures, but did show tolerable doses up to 78 Gy with only 8% experiencing RTOG grade 3 acute CNS toxicity and 0% grade 4 [49]. While these results appear to be discouraging, we believe they highlight the deficiencies of conventional imaging modalities in RT treatment planning. To date, the MRI CE lesion plus resection cavity have been used to define the dose escalation volume. However, a recent imaging study with the amino acid tracer, ^{11}C MET PET, revealed tracer uptake outside the high-dose region defined by CE-MRI was correlated with non-central recurrences [50]. Another recent study showed that dose escalation to the MRI CE lesion of up to 75 Gy in 30 fractions decreased central recurrences, and did not cause radiation necrosis or any late CNS toxicities [51]. These studies suggest that re-visiting dose escalation strategies by incorporating biological

imaging-based treatment volumes in the era of 3D-conformal and intensity modulated RT with added radiosensitizing chemotherapy (TMZ) could reveal improved patient outcomes without added acute or late toxicities. We will evaluate the impact of integrating molecular imaging into RT for guidance of tumor delineation and dose escalation. We expect that dose escalation of the combined ^{18}F-DOPA PET uptake and CE-MRI volumes with adjuvant TMZ will lead to a reduction in both in-field and central failures, and improve patient outcomes without additional acute or late toxicities.

1.5 Advanced MRI for tumor delineation and assessment of recurrence:

Advanced MRI techniques, including Perfusion MRI (pMRI) and Diffusion Tensor Imaging (DTI), provide physiologic information that complements anatomical information from CE-MRI [52-56]. The pMRI method employs dynamic susceptibility contrast-enhanced (DSC) MRI and rapid bolus injection of gadolinium-based (Gd) contrast agent to measure relative cerebral blood volume (rCBV) as an estimate of tissue microvasculature [52-54]. Based on inherent differences in microvasculature, relCBV has been used to distinguish high-grade and low-grade components of non-enhancing and enhancing gliomas at the time of surgical biopsy [57, 58] and to distinguish high-grade glioma recurrence from pseudoprogression and radiation necrosis [59, 60].

Diffusion Tensor Imaging (DTI) is based on the use of multi-directional magnetic gradients to detect Brownian diffusion of tissue water, which is directionally specific in the brain, due to white matter tracts [55, 56]. Preliminary studies comparing DTI with CE-MRI indicate that DTI can more accurately distinguish tumor margins and tumor infiltration along white matter tracts [61, 62].

These advanced MRI techniques for differentiating tumor extent and grade are sensitive to the contrast administration technique, acquisition protocol, and method of additional post-processing [63-66]. However, use of these advanced techniques in oncology has been reported, suggesting they may differentiate regions of tumor into various degrees of aggressiveness, provide information about tumor infiltration and predict treatment efficacy [57, 58, 61, 62]. Accordingly, in addition to each PET scan acquired for this study, pMRI and DTI data will be acquired and compared with 18F-DOPA PET in for impact on RT planning and for differentiation of tumor recurrence from pseudo-progression during follow-up imaging.

1.6 Preliminary Data

^{18}F-FDOPA-PET has been in production at Mayo Clinic Rochester since 2001, used to image Parkinson's patients to study the ^{18}F-FDOPA uptake in the caudate nucleus and putamen. More recently we have been using ^{18}F-FDOPA-PET to image gliomas prior to neurosurgery on our open IRB-approved pilot study (MC1078), where the trajectory of the biopsy will be planned per the co-registered PET and MR images, targeting the maximum PET uptake as well as any discordant regions, e.g. MR-enhancing but no PET uptake. Below are some preliminary findings from the first subset of patients accrued to the pilot study.

Preliminary results – ^{18}F-DOPA PET identifies high-grade disease beyond conventional MRI: In our pilot study, 9 patients had an ^{18}F-DOPA PET/CT scan prior to stereotactic resection or biopsy. The PET scan was rigidly registered to the T1-weighted scan using MIM Maestro™ (MIM Software Inc., Cleveland, OH). The registered PET

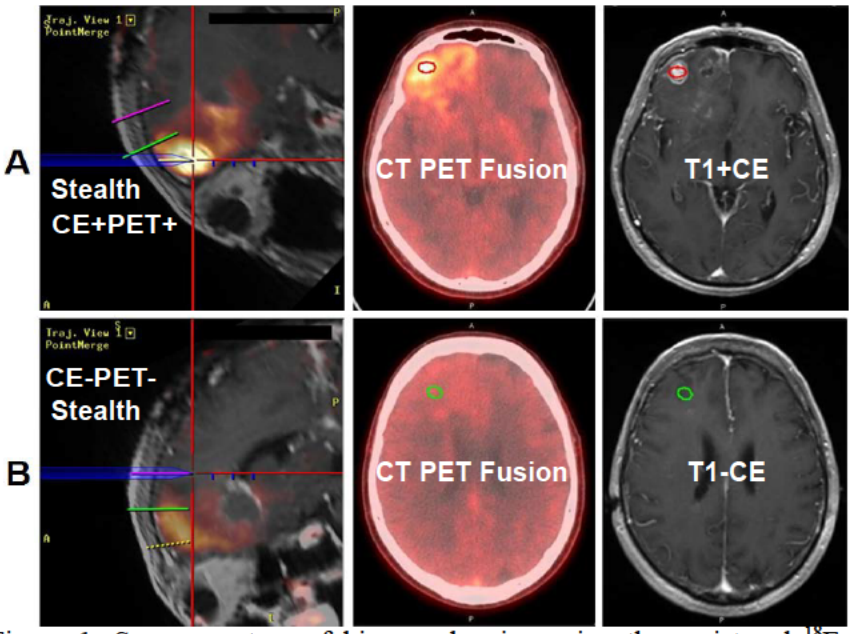


Figure 1: Screen capture of biopsy planning using the registered ^{18}F-DOPA PET and T1-CE MRI in the Stealth™ Neuronavigation System for blue needle locations (Left), CT-PET Fusion (Middle), and T1-MRI (Right) at (A) CE+PET+ (red circle) and (B) CE-PET- (green circle).

images were transferred to the Stealth Station™ Neuronavigation System (Medtronic Sofamor Danek, Memphis, TN) and 1 to 3 stereotactic biopsy locations were planned based on the PET SUV_{max} and other locations of PET and MRI discordance (Figure 1). Of 21 stereotactic biopsy specimens graded by [redacted], 16 were found to be high-grade. Of the HGG specimens, 81% were obtained from regions of elevated ^{18}F-DOPA uptake, while T1-CE was present for only 38% of those samples. The overall accuracy in the detection of HGG and LGG was higher for ^{18}F-DOPA PET than MRI. It is clear that substantial regions of pathology-confirmed high-grade disease are not visualized with conventional MRI. In this protocol, we will compare delineated volumes of high density / high grade disease for RT planning between standard of care MR only and integrated ^{18}F- DOPA PET. In addition we will compare differences in the impact of ^{18}F-DOPA PET with pMRI and DTI for RT planning.

Preliminary results – High ^{18}F-DOPA PET uptake correlates with high grade disease: Figure 2 highlights an example which was NCE on MRI, but clearly visible with PET and was pathologically-confirmed as high-grade disease. In our pilot study, stereotactic biopsies at various locations were targeted to evaluate the relationship between SUV and grade. Coordinates corresponding to each biopsy specimen stored within the neurosurgical Stealth Station™ software were translated into the coordinate space of each image set. A 5 mm radius region of interest (ROI) was created around each coordinate point within MIM Maestro™ to account for the biopsy sample size as well as uncertainties in the physical biopsy volume and stereotactic biopsy coordinates, for determining SUV para-meters. When stratified into grade, a correlation was found between SUV_{max} and tumor grade across samples ($p = 0.0005$) (Figure 3), with a significant difference found between grade II and grade IV disease ($p = 0.008$), and between grade III and grade IV ($p = 0.024$), but no difference between grade II and grade III ($p = 0.174$). These results are in agreement with previous studies using ^{18}F-DOPA PET with non-spatially accurate samples [67], which found correlations between all three grades in newly diagnosed patients. We anticipate a larger sample of grade II biopsies is needed to show a difference between grades II and III. The ability of SUV_{max} to predict grade in astrocytoma patients could be valuable in

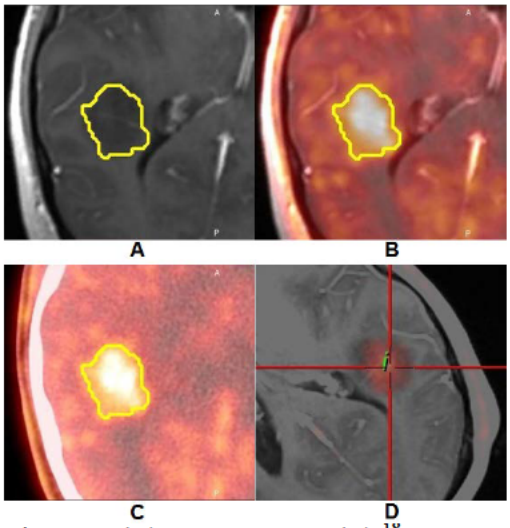


Figure 2: (A) T1-NCE MR, (B) ^{18}F-DOPA PET-MR fusion, (C) ^{18}F-DOPA PET-CT fusion, (D) uptake targeted for biopsy in Stealth Station™

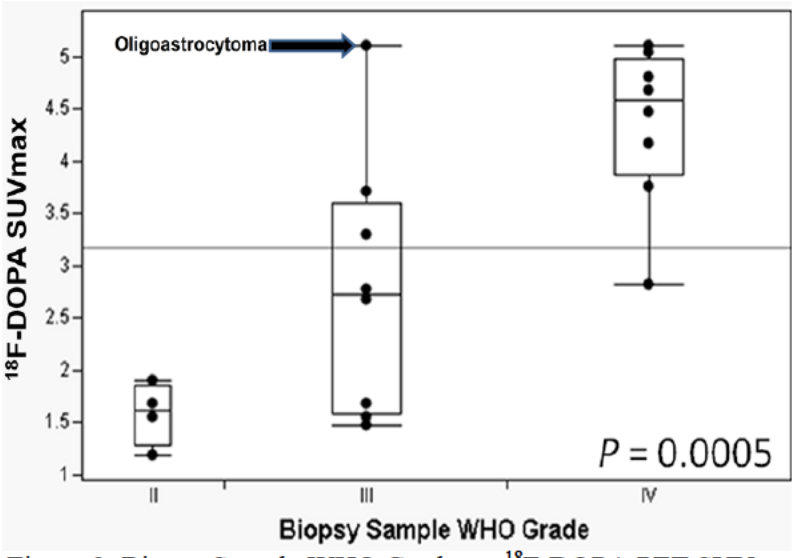


Figure 3: Biopsy Sample WHO Grade vs. ^{18}F-DOPA PET SUV_{max}

stereotactic biopsy planning, especially in NCE tumors. We will be evaluating correlations between image-guided, spatially accurate tissue samples across a range of SUVs over a large cohort in concurrent trial (MC#TBD).

Preliminary results – ^{18}F-DOPA PET correlations with cellularity, proliferation index and thresholds: MRI CE is targeted during neurosurgical planning and RT delineation of the boost dose volume based on the presumption that this region contains the highest density of tumor and/or highest grade disease. Histopathological markers of cellularity and Ki-67 proliferative index were analyzed for the 20 positive biopsy samples, and assessed with SUV_{mean}. SUV_{mean} was chosen for correlation as it is more representative of the entire cellular area used in calculations of both cellularity and Ki-67 compared to a single value at SUV_{max}. Our results show that both cellularity ($p = 0.03$) and proliferative activity ($p < 0.001$) significantly correlate with ^{18}F-DOPA PET SUV_{mean}. This is evident in Figure 4 comparing SUV_{mean} with stained nuclei for 3 samples from the same patient. These Ki-67 results agree with previous ^{18}F-DOPA PET correlations between Ki-67 and SUV_{mean} ($p = 0.001$) in newly diagnosed gliomas [67].

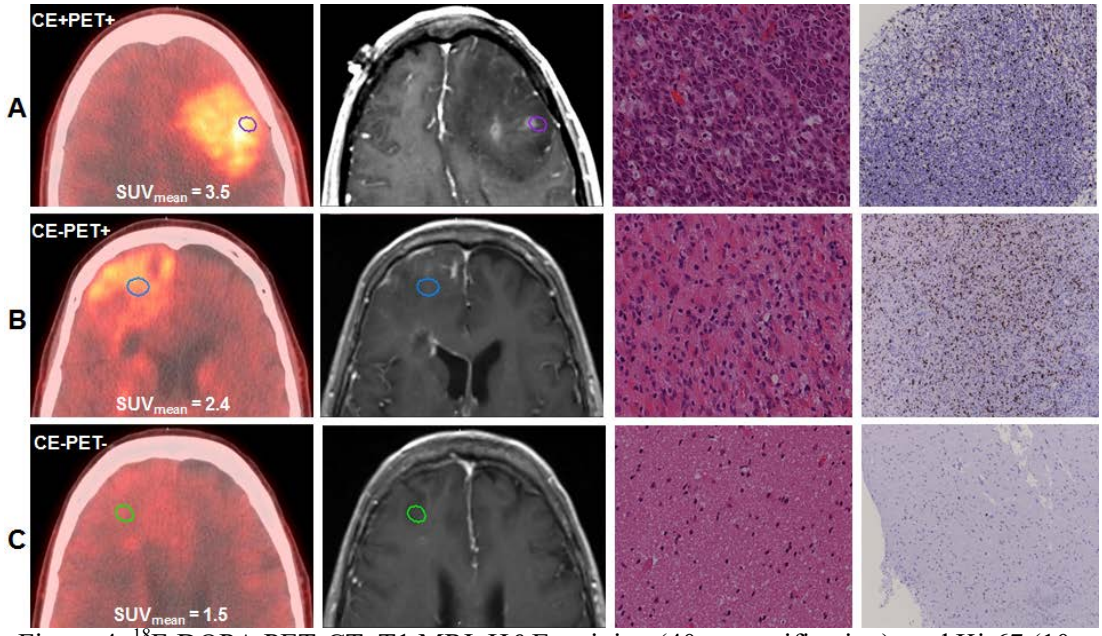


Figure 4: ^{18}F-DOPA PET-CT, T1 MRI, H&E staining (40x magnification), and Ki-67 (10x magnification) staining (from left to right) for biopsy samples located in (A) CE+PET+ (purple), (B) CE-PET+ (blue), and (C) CE-PET- (green).

^{18}F-DOPA PET thresholds were computed based on ratios of SUV_{max} of the tumor to SUV_{mean} of the contralateral normal brain tissue (T/N) to facilitate future delineation of high density regions from the entire ^{18}F-DOPA

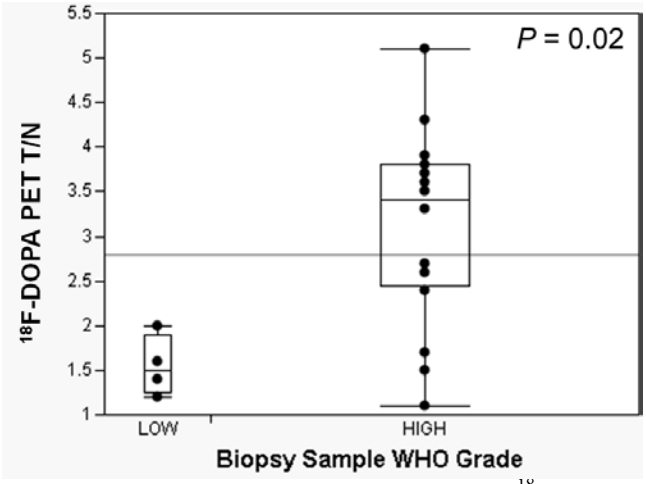


Figure 5: Biopsy sample grade vs. ratios of ^{18}F-DOPA PET tumor SUV_{max} to SUV_{mean} of the contralateral normal brain tissue (T/N), excluding oligodendroglioma samples.

uptake volume. For the 20 pathology-positive biopsy samples, a T/N of 1.2-2.0 and 1.1-5.1 was calculated for LGG and HGG samples, respectively. A strong correlation ($p < 0.05$) was found between T/N and grade stratification with a statistically significant difference ($p = 0.02$) comparing the T/N for HGG versus LGG (Figure 5). Given the overlap in the T/N range for high- and low-grade disease, a T/N > 2.0 could be used to define "high-grade" disease components within the PET contours drawn by Nuclear Medicine physician [redacted] for each patient. This threshold is consistent with a previous study by Chen *et al*, in which an average T/N of 2.5 ± 0.73 was found as the diagnostic threshold for high-grade brain tumors imaged with ^{18}F-DOPA PET, using non-spatially accurate samples [6].

Preliminary results – potential impact of ^{18}F-DOPA PET for neurosurgical resection and RT planning: Utilizing the T/N > 2.0 derived from our pilot tissue correlations, areas of high grade/high density disease were identified on each pre-operative PET scan and compared against CE volumes contoured by our experienced neuroradiologist [redacted]. For the 6 patients with visible CE, the total volume with a PET T/N > 2.0 outside the CE volume ranged from 15 - 81%), with high PET activity disease extending 0.5-3.5 cm beyond the CE lesion (Figure 6). For RT of HGG, typically a 1-2 cm uniform expansion is placed around the resection cavity and any residual CE to define the high density volume to receive a higher boost dose of radiation. However, extension of high grade/high density disease seen in our pilot data suggests that standard target delineation

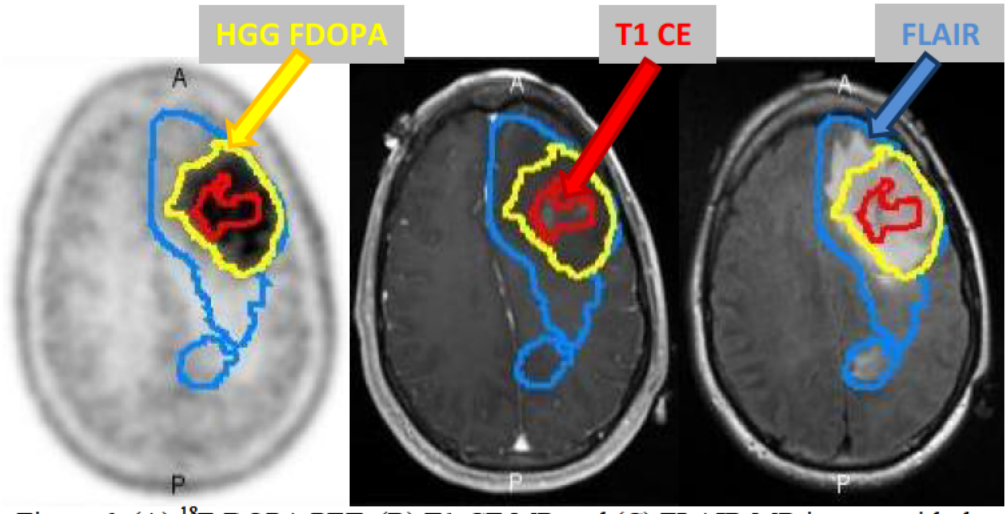


Figure 6: (A) ^{18}F-DOPA PET, (B) T1-CE MR and (C) FLAIR MR images with the PET-defined T/N >2.0 volume in yellow, and the CE and FLAIR volumes (red and blue, respectively), defined by our expert neuroradiologist.

with CE-T1 images are not sufficient to ensure adequate targeting of the region of highest density disease for either resection or RT. For NCE HGG cases where the standard of practice high-dose radiation target is defined as the entire T2 signal abnormality, our pilot data suggests ^{18}F-DOPA could be used to differentiate regions of metabolically active disease to more selectively target RT boost dose volumes. After applying a 1 cm expansion to the high grade/high density disease volume derived from the T/N > 2.0 threshold for the NCE HGG patients, a significant portion of T2-defined target (42 – 89%) did not have PET avid disease as defined by ^{18}F-DOPA PET (Figure 7). No reported studies have investigated ^{18}F-DOPA PET for RT target delineation or for dose

escalation guidance. We will integrate ^{18}F-DOPA PET utilizing biopsy-validated thresholds into RT planning to evaluate the impact of PET integration on RT volumes (tentatively de-fined as 2.0 for differentiating LGG from HGG components and 1.3 for tumor extent per our preliminary data to date – see Figure 5 – to be updated after pilot study accrual is complete, prior to beginning this study. We will also utilize biopsy-validated thresholds to guide dose escalation, and will compare subsequent patterns of failure and outcomes against those for patients treated using current clinical standard of care. In a concurrent study, we will use image-guided biopsy correlations from a larger cohort to accurately define a T/N threshold to delineate high grade/ high density from low grade/ low density gliomas.

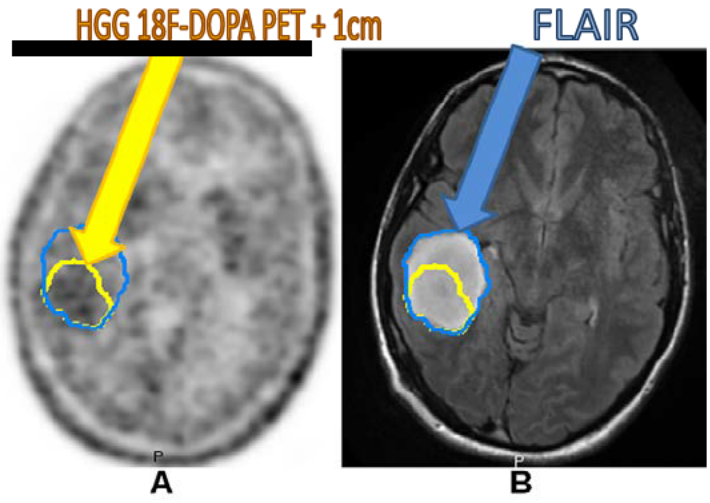


Figure 7: (A) ^{18}F-DOPA PET and (B) FLAIR MR images from a patient with NCE, with PET-defined volume of T/N >2.0 + 1cm expansion in yellow, and the FLAIR volume in blue

Advanced techniques used in pMRI and DTI also show promise for better differentiation of high density tumor and post-treatment radiation effect from true tumor progression compared to CE-MR. No reported studies have performed a head-to-head comparison of ^{18}F-DOPA PET with state-of-the-art perfusion and diffusion MR. [redacted] has extensive experience with the use of state-of-the-art MR for gliomas, and has demonstrated the direct impact of both acquisition and post-processing on determining relative cerebral blood volume (relCBV) threshold values for distinguishing tumor from post-treatment radiation effect [68]. Differences in RT volumes identified using biopsy-validated thresholds as highly aggressive disease comparing ^{18}F-DOPA uptake and relCBV from pMRI as well as differences in RT volumes identified using biopsy-validated thresholds as tumor extent comparing ^{18}F-DOPA uptake and diffusion maps from DTI will be evaluated.

In summary, ^{18}F-DOPA PET metabolic imaging demonstrates significant correlation with histopathologic markers of grade and cellularity. Our data suggest that biopsy-validated ^{18}F-DOPA PET thresholds may reliably delineate areas of high-grade astrocytoma not otherwise recognized with standard MRI. Our results suggest that ^{18}F-DOPA PET may more accurately identify regions of higher grade disease in patients with astrocytomas and will have utility in guiding radiotherapy targeting. Future incorporation of ^{18}F-DOPA PET into clinical practice for radiation therapy planning will evaluate the influence of ^{18}F-DOPA PET on local control and survival outcomes.

1.7 Adverse event assessment

Based on preliminary data of ^{18}F-DOPA trials in glioma patients at Mayo Clinic, no adverse events related to the agent have been reported. As of 09Jun2015, 82 glioma patients have received at least one injection and a total of 174 injections have been administered. Although, the most likely adverse event would be allergic reaction to the agent, no such reaction has been seen to date. If allergic reaction were to occur, it would happen shortly after injection of the agent. Based on our data, we are reducing the observation time required post-injection from one hour to the duration the patient is in the PET suite for dosing and imaging (approximately 15-20 minutes). This change will reduce the time the patients must wait after their scans are completed and will not compromise patient safety (based on no adverse events seen in the five years this agent has been studied in glioma patients).

1.8 Rationale for Addendum 8:

Addendum 8 was required to solve several issues. The first solution is to no longer enroll Grade-III patients. The enrollment of Grade-III patients was proceeding slower than expected; therefore the anticipated sample size at the end of the study would no longer be sufficient for many of the Grade-III related endpoints. The second solution is to redefine our endpoint based on the Grade-IV MGMT un-methylated patients. This is necessary due to the markedly different progression free survival depending on MGMT methylation status, and the change in distribution of MGMT status for patients accrued to this study due to the competing study A071102, a large cooperative group study opened by the Alliance which is/was enrolling only Grade-IV MGMT Methylated patients. During the period (8/1/2015-1/25/2017) only three Grade-IV MGMT Methylated patients were enrolled to this study compared to 14 Grade-IV MGMT un-methylated patients. Third, we added the option to deliver the radiation in our regional Radiation Oncology sites which have matched treatment machines and share the same beam model in our treatment planning system. All of the advanced imaging and treatment planning must still take place in Rochester, but this will be more convenient for patients who live closer to one of our regional sites. We have had several patients who were interested in this study but chose not to participate because the did not want to come to Rochester for their daily radiation treatments.

2.0 Goals

2.1 Primary

Compare confirmed-progression free survival at 6 months for Grade IV MGMT un-methylated glioma patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients, including those treated on North Central Cancer Treatment Group (NCCTG) clinical trials.

2.2 Secondary

2.21 Compare progression free survival at 12 months for Grade III patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients, including those on NCCTG clinical trials**.**

2.22 Compare patient overall survival after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients, including those on NCCTG clinical trials.

2.23 Evaluate quality of life after radiotherapy treatment targeting dose escalated volumes defined to include high^{18}F-DOPA PET uptake.

2.24 Determine acute and late effect toxicity after radiotherapy treatment targeting dose escalated volumes defined to include high^{18}F-DOPA PET uptake.

2.25 Compare confirmed-progression free survival at 12 months for Grade IV MGMT Methylated patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients, including those on NCCTG clinical trials**.**

2.26 Compare confirmed-progession free survival in grade IV MGMT un-methylated patients with similar historical controls from Mayo Clinic Rochester patients, including those on NCCTG clinical trials.

2.27 Compare confirmed-progession free survival in grade IV MGMT methylated patients with similar historical controls from Mayo Clinic Rochester patients, including those on NCCTG clinical trials.

2.3 Correlative Research

2.31 Compare RT treatment volumes defined by MR only with RT treatment volumes defined with both PET and MR information for Grade IV glioma patients.

2.32 Compare timing of accurate identification of progression defined by ^{18}F- DOPA PET, pMRI and conventional MRI for Grade IV glioma patients.

2.33 Compare patterns of failure after radiation therapy targeting volumes defined with target volumes designed to with both ^{18}F-DOPA PET and conventional MR image information with patterns of failure for historical controls from Mayo Clinic Rochester patients, including those on NCCTG clinical trials**.**

2.34 Compare RT treatment volumes defined by MR only with RT treatment volumes defined with both PET and MR information for Grade III glioma patients.

2.35 Evaluate intra- and inter-observer variability with vs. without the addition of ^{18}F-DOPA PET uptake for radiotherapy target volume delineation**.**

2.36 Compare timing of accurate identification of progression defined by ^{18}F-DOPA PET, pMRI and conventional MRI for Grade III glioma patients.

2.37 Compare predictive capabilities of ^{18}F-DOPA PET, pMRI and DTI for localization of recurrences for patients treated with ^{18}F-DOPA PET-guided RT dose escalation.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histologically confirmed newly diagnosed grade IV malignant glioma.
Note: as of addendum 8, Grade III patients are no longer being enrolled.

3.13 CT simulation, immobilization, MRI and PET imaging, treatment planning, and all follow-up MRI and PET scans to be performed at Mayo Clinic Rochester.
Note: The actual radiation therapy treatments and follow-up other than imaging can be performed at Mayo Clinic Rochester, Northfield, LaCrosse, Mankato, Eau Claire, or Albert Lea.

3.14 Provide written informed consent.

3.15 Ability to complete questionnaire(s) by themselves or with assistance.

3.2 Exclusion Criteria

3.21 Patients diagnosed with anaplastic oligodendroglioma

3.22 Unable to undergo MRI scans with contrast (e.g. cardiac pacemaker, defibrillator, kidney failure).

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	Active Monitoring			
					Until PD or patient refusal
	≤21 days prior to registration	Cycle 1 Pre-RT Scans	Cycle 1 RT	Cycle 2 Post RT Scans ≤42[5] days after RT	At every clinically indicated follow-up MR scan (end of each new cycle)
Physical exam, wt, ECOG PS	X				
Neuro history and exam	X			X	X
MMSE[4]		X[12]		X	X
CT simulation for radiotherapy planning	X[8,9]				
Pregnancy test		X[1,R]		X[1,R]	X[1,R]
^{18}F-DOPA-PET[R]		X[8]		X	X[3]
MRI with contrast/ RANO Assessment		X[6,8]		X	X[3]
Advanced MRI		X[7,8]		X	X[3]
^{18}F-DOPA adverse event assessment		X[2]		X[2]	X[2]
Adverse event assessment[11] (See Section 10.3)	X		X[10]	X	X
QOL assessment[4]		X[12]		X	X
Concurrent Steroids and Anticonvulsants		X[12]		X	X
MGMT Methylation Status	X[13]				

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. For any post-RT ^{18}F-DOPA injection, the patient will not undergo the ^{18}F-DOPA PET scan and will instead move to event monitoring.
2. ^{18}F-DOPA post-injection assessment: done approximately 15-20 minutes post injection of ^{18}F-DOPA and if AE observed a second AE assessment is required ≤24 hours post injection.
3. All follow-up serial imaging after initial treatment until progression up to 5 years. Note a typical grade IV follow-up schedule will include follow-up scans every 2 months for the first year after

radiation therapy, every 3 months for the second year, every 4 months for the third year, every 6 months after that. The actual timing of the follow-up scans for an individual patient will be per the clinician's discretion, e.g. if the clinician suspects possible progression, they may schedule more frequent follow-up imaging. While it is extremely unlikely (as current time to progression is 6 to 9 months), if a grade IV patient did not progress for 5 years, they may have up to 16 follow-up visits.

4. Patient will complete a maximum of 6 post-baseline QOL/MMSE evaluations
5. Post RT scans to occur 3 to 6 weeks after RT is complete, to coordinate with first follow-up appointment
6. Pre-treatment measurement
7. For patients who have had a 3T glioma protocol MR scan post-operatively at this institution prior to consenting for this study, research funds will be used to repeat the advanced MR scans prior to RT for this study.
8. Must be done ≤14 days prior to start of RT
9. CT simulation can be done prior to or after registration.
10. Max grade of Adverse Events experienced during RT to be recorded at the end of RT.
11. To be assessed by Radiation Oncologist at baseline and during RT, and Medical Oncologist for Cycle 2 and subsequent cycles.
12. Baseline MMSE, QOL, Concurrent Steroids and Anticonvulsants assessments can occur prior to registration and are to be completed prior to the first ^{18}F-DOPA injection.
13. MGMT Testing Results can be submitted at any time prior to, or after, registration.

R Research funded (see Section 19.0)

5.0 Grouping Factors:

Group 1: Grade IV patients vs.

Group 2: Grade III glioma patients: Note: as of addendum 8, Grade III patients are no longer being enrolled.

6.0 Registration/Randomization Procedures

6.1 To Register a Patient

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site.

If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page[redacted] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office[redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.

- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 IRB Approval

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.3 Verification prior to registration

Prior to accepting the registration, the remote registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 Radiation therapy on this protocol must be performed at Mayo Clinic Rochester, Northfield, LaCrosse, Mankato, Eau Claire, or Albert Lea under the supervision of a radiation oncologist.

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

6.6 Patients may be registered by the treating physician or healthcare provider.

6.7 Patient questionnaire booklet is available on site; copies are not acceptable for this submission.

7.0 Protocol Treatment

7.1 CT simulation

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

7.2 PET Scanning

7.21 Timing of PET scanning:
PET scans will be acquired prior to and after completion of radiotherapy. The PET scan to be used for radiation treatment planning should be acquired no more than 14 days prior to beginning radiation treatments. The post-RT PET scan should be acquired 3-6 weeks after completing radiation treatments, to correspond with the first follow-up appointment. Follow-up PET scans will also be acquired at each clinically indicated appointment per the standard of care follow-up regimen at Mayo Clinic Rochester until progression (up to 5 years).

7.22 Patient preparation for PET scan:
A negative urine pregnancy test must be done ≤48 hours prior to each ^{18}F-DOPA injection for women of child-bearing potential only. For a positive pregnancy test prior to any post-RT ^{18}F-DOPA injection, the patient will not undergo the ^{18}F-DOPA PET scan and will instead move to event monitoring.

Patients will be instructed to follow a four hour food fast prior to the ^{18}F-DOPA PET scan. 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 ^{18}F-DOPA PET:
A total of 5.0 $\pm$ 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 3D PET acquisition will be acquired for no more than 30 minutes. 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.

7.3 Advanced MRI Scanning

7.31 Screening for advanced MR eligibility:
The subject will undergo MRI screening for contraindications to scanning and contrast agent administration as per routine clinical protocol at Mayo Clinic.

7.32 Timing of advanced MR scanning:
Advanced 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, 3 to 6 weeks after completing radiation treatments (corresponding with the first follow-up appointment), and for all follow-up serial imaging after final RT treatment until progression (up to 5 years). The estimated

additional time of advanced MRI (Perfusion MRI and Diffusion Tensor Imaging) will be approximately 10 minutes).

7.33 Perfusion MRI:
The pMRI DSC acquisition will be acquired as per standard perfusion DSC clinical protocol of the Radiology Department at Mayo Clinic. The DSC acquisition time is approximately 3 minutes.

The single dose of Gd-based contrast agent gadobutrol (Gadavist) (0.10 mmol/kg) to be administered for each MR exam is current standard of care for the Radiology Department at Mayo Clinic. Recent literature has linked the development of a conditional called Nephrogenic Systemic Fibrosis (NSF) with administration and dosage of Gd-based contrast agents in patients with renal failure or insufficiency. Per standard of care at Mayo Clinic, we will screen all patients for renal failure/insufficiency to ensure normal renal function. There have been no reports in the literature of the occurrence of NSF in patients with normal renal function [62, 69].

7.34 Diffusion MRI:
DTI data will be acquired as per standard DTI clinical protocol of the Radiology Department at Mayo Clinic.

7.4 Radiation Treatment

7.41 Target delineation:

Following informed consent and co-registration of the PET and MRI datasets with the planning CT acquired during the standard of care CT simulation appointment, the radiation oncologist will define the target volumes to use for radiation treatment planning. The pre-RT ^{18}F-DOPA PET scan and standard of care MRI will be co-registered with the treatment planning CT.

Target delineation will be based both on MRI and PET imaging, defining each gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV) and associated dose as in **Table 1.** The MR criteria used in the definition of GTV5100_MR and GTV6000_MR will be identical to the historical standard of care at Mayo Clinic and NCCTG, but volumes encompassing both low and high signal PET disease (GTV5100_PET) and only high signal PET disease (GTV6000_PET) will also be included in the treatment volumes. GTV5100_MR, GTV5100_PET, GTV6000_MR and GTV6000_PET will be expanded by 1 cm to accommodate sub-clinical disease spread, modified per MD discretion as needed (see Figure 8). These CTVs will then be combined for each dose level, and CTV5100 and CTV6000 will be expanded by 0.3 cm to accommodate random setup uncertainty. These expansion values and doses being delivered to PTV5100 and PTV6000 conform to the Mayo standard of care and are the same expansion definitions used in NCCTG clinical trials N0177, N057K, N0874 and N0877.

Beyond these standard treatment doses, we plan to boost the MR- and PET-defined high density disease (GTV7600=GTV6000) with no expansion for sub-clinical disease to a total dose of 76 Gy. Boost volumes will be based on post-operative ^{18}F-DOPA imaging. For patients that also were included on the corresponding neurosurgical trial (MC1373), post-operative ^{18}F-DOPA will be required for any patients that have undergone any surgical procedure other than biopsy only.

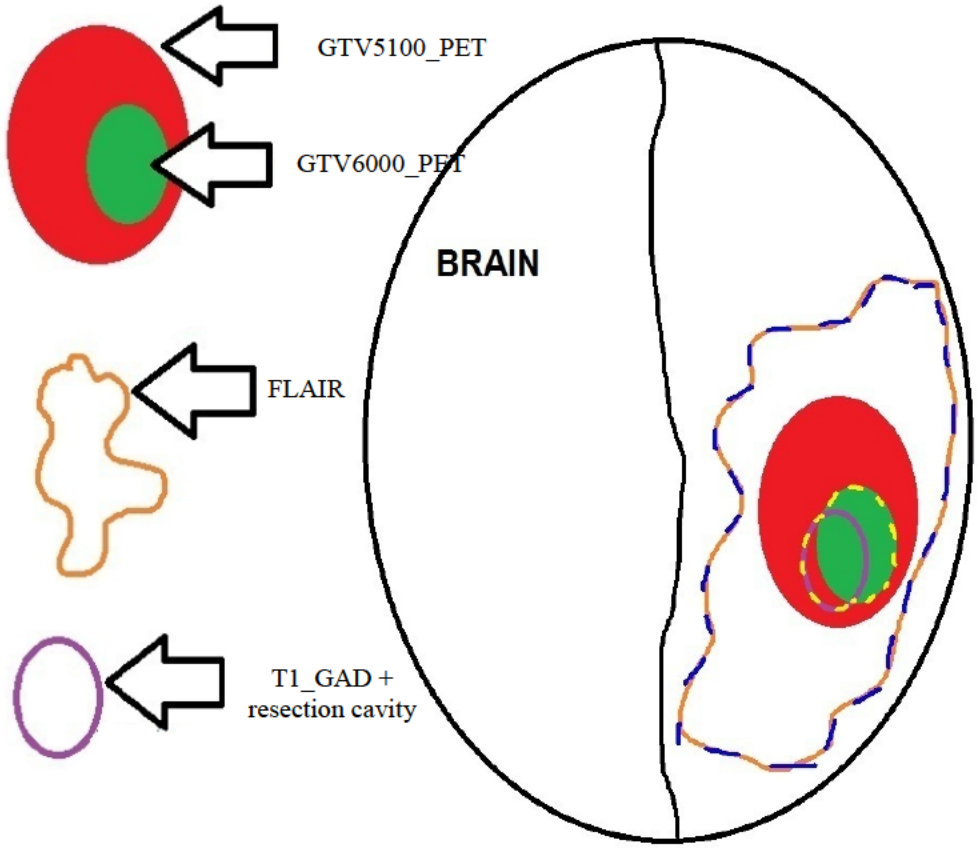
Delineation of normal structures should follow the "Contouring CNS and Head and Neck" in **Appendix V**.

Table 1. Target delineation for MRI and PET Imaging

Dose	GTV/CTV/PTV definition:	GTV_MR definition:	GTV_PET definition:
51 Gy	GTV5100 = GTV5100_MR + GTV5100_PET CTV5100_MR = GTV5100_MR + 1 cm (modified as needed) CTV5100_PET = GTV5100_PET + 1 cm (modified as needed) CTV5100 = CTV5100_MR + CTV5100_PET PTV5100 = CTV5100 + 0.3 cm	GTV5100_MR = Boolean (T1_GAD ± FLAIR) ± T1_Cavity	GTV5100_PET = gold_PET
60 Gy	GTV6000 = GTV6000_MR + GTV6000_PET CTV6000_MR = GTV6000_MR + 1 cm (modified as needed) CTV6000_PET = GTV6000_PET + 1 cm (modified as needed) CTV6000 = CTV6000_MR + CTV6000_PET PTV6000 = CTV6000 + 0.3 cm	GTV6000_MR = Boolean (T1_GAD ± T1_Cavity)	GTV6000_PET = Boolean (HGG Threshold and gold_PET)
76 Gy	GTV7600 = GTV7600_MR + GTV7600_PET CTV7600_MR = GTV7600_MR + 0 cm CTV7600_PET = GTV7600_PET + 0 cm CTV7600 = CTV7600_MR + CTV7600_PET PTV7600 = CTV7600 + 0.3 cm	GTV7600_MR = GTV6000_MR	GTV7600_PET = GTV6000_PET

Table 1: Radiotherapy doses and definitions of the volumes to be targeted with those doses, with the gold_PET contour reviewed and approved by either [redacted] or [redacted], and the HGG Threshold contour derived from a tumor to normal brain ratio (T/N)>2.0 determined initially from preliminary studies (Figure 5).

7.42 Treatment planning and delivery:
Patients will receive intensity modulated RT delivered over 30 fractions with either photons or protons per MD discretion, with concurrent and adjuvant TMZ.



GTV5100= 51Gy (in blue dashes) CTV5100= GTV5100 + 1cm PTV5100= CTV5100 + 0.3cm GTV6000= 60Gy (in yellow dashes) CTV6000= GTV6000 + 1cm PTV6000= CTV6000 + 0.3cm GTV7600= 76Gy (in yellow dashes) CTV7600= GTV7600 + 0cm PTV7600= CTV7600 + 0.3cm	GTV5100_MR= Boolean (T1_GAD + FLAIR) + T1_Cavity GTV5100_PET= gold_PET GTV5100= Boolean (GTV5100_MR + GTV5100_PET) GTV6000_MR= Boolean (T1_GAD + T1 Cavity) GTV6000_PET= Boolean (HGG_threshold **and** gold_PET) GTV6000= Boolean (GTV6000_MR + GTV6000_PET) GTV7600= GTV6000
CTV5100_MR=GTV5100_MR + 1CM (modified as needed) CTV5100_PET=GTV5100_PET + 1CM (modified as needed) CTV5100= GTV5100 + 1cm, then Boolean (CTV5100 **and** brain) or CTV5100_MR + CTV5100_PET CTV6000_MR=GTV6000_MR + 1CM (modified as needed) CTV6000_PET=GTV6000_PET + 1CM (modified as needed) CTV6000= GTV6000 + 1cm, then Boolean (CTV6000 **and** brain) or CTV6000_MR + CTV6000_PET CTV7600= GTV7600 + 0 cm, then Boolean (CTV7600 **and** brain)	PTV5100 = CTV5100 + 0.3cm PTV6000 = CTV6000 + 0.3cm PTV7600 = CTV7600 + 0.3cm *Need to evaluate T1_GAD volume outside FLAIR and determine if real or to exclude *Need to evaluate inclusion or exclusion of small GTV6000_PET volume at a considerable distance from bulk T1_GAD and bulk GTV6000_PET *Need to make sure GTV6000_PET does not exceed GTV5100_PET *Need to make sure all CTVs are inside the brain tissue contour *Need to evaluate inclusion or exclusion of small PTV volumes at a considerable distance from bulk CTV volumes

Figure 8: Depiction and details for generating GTV, CTV and PTV volumes

7.5 Follow-up protocol

7.51 Response Assessment:
Post-treatment tumor recurrence will be monitored through follow-up imaging, using standard of care MRI to assess tumor response based on the Response Assessment in Neuro-Oncology (RANO) Working Group criteria until progression of disease (up to 5 years) [70].

7.52 Patterns of Failure:
For those 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 the recurrence volume (RecVol) that falls within the 95% isodose line of the boost dose from the delivered RT plan and classifying each recurrence as either 'central' (>95%), 'in field' (80 - 95%), 'marginal' (20 - <80%), or 'distant' (<20%).

7.53 Follow-up Imaging:
Once the full course of radiotherapy is complete, an ^{18}F-DOPA-PET scan will be obtained in addition to the standard of care MRI along with state-of-the-art pMRI and DTI sequences, to use as a baseline for follow-up imaging. ^{18}F-DOPA PET imaging has been demonstrated to differentiate recurrence from pseudo-progression [6, 9]. Accordingly, at every standard of care glioma follow-up imaging regimen appointment scheduled at Mayo Clinic Rochester until progression (up to 5 years), in addition to standard of care MRI, an ^{18}F-FDOPA-PET scan as well as perfusion MRI and DTI sequences will be obtained. pMRI and DTI sequences will be compared against ^{18}F-DOPA PET data to evaluate earliest accurate differentiation of tumor progression versus treatment response.

7.54 Outcomes:
Outcomes for patients treated prospectively with the addition of ^{18}F-DOPA PET image-guided dose escalation will be determined and compared against patients treated at Mayo Clinic on NCCTG trials as described in Sections 7.41 and 16.11.

7.55 Acute and Late Toxicity Monitoring:
Using the dose escalation approach described above, previous studies have successfully dose escalated to 76 – 80 Gy without significant increases in acute or late adverse effects [51]. Nonetheless, both acute (available at http://ctep.cancer.gov) and late [71] toxicity will be monitored continuously as each patient is accrued and follow-up data are accumulated, and the PTV3 dose level will be adjusted if necessary.

7.6 Quality of life – patient reported outcome:
Quality of life (QOL) will be compared to high-grade glioma patients treated on previous Radiation Therapy Oncology Group (RTOG) protocols. QOL and cognitive function will be evaluated with the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) and Mini-Mental Status Exam (MMSE) questionnaires. 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 Adverse Event Characteristics

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).

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using a copy of the CTCAE v4.0. Next, determine whether the event is expected or unexpected (refer to Sections 10.2 and 15.0) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) or as part of the routinely reported clinical data. Important: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

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

10.2 Expected vs. Unexpected

- 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" means any adverse experience that is neither identified in nature, severity, or frequency of risk, in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

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. Post therapy ^{18}F-DOPA scans will have pre-existing conditions documented prior to ^{18}F-DOPA injection in order delineate causality for pre and post ^{18}F-DOPA AEs.

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

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to PET scanning and ^{18}F-DOPA injection
Probable - The adverse event *is likely related* to 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 PET scanning and ^{18}F-DOPA A injection
Unrelated - The adverse event *is clearly NOT related* to PET scanning and ^{18}F-DOPA injection

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

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

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.
- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators. See Section 10.6.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch.

- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.4 Expedited Reporting Requirements for IND/IDE Agents

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

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 [redacted]

Mayo Clinic Cancer Center (MCCC) Institutions:

Provide copies of all serious events, regardless of drug relatedness to: [redacted] (^{18}FDOPA IND sponsor) at [redacted], and [redacted]. These emails will be managed by the SAE, IND and Safety Reporting Coordinators.

10.41 **Special** Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. 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.**

PET scanning, PET tracer injection and dose escalation 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 or radiotherapy will be graded and reported in this protocol. All other 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.

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 disorders	Rash maculo-papular	≤Grade 3

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

10.51 Persistent or Significant Disabilities/Incapacities

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 at any time following treatment with an 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

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

The reporting period for radiation dose escalation for this study is 30 days.

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.

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.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE 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 outlined in each protocol.

10.54 Second Malignancy

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.

10.6 Required Routine Reporting

Adverse events related to PET scanning and PET tracer injection to be graded if detected during observation post injection, or if noted within 24-hour post PET tracer injection per the CTCAE v4.0 grading. Adverse events related to dose escalation will be graded at baseline, assessed during RT and reported at the end of RT, and during every clinically indicated MR follow-up during Active Monitoring until progression.

Category (CTCAE SOC)	Adverse event/Symptoms	Baseline	Post injection assessment[1]	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	

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

10.61 Additional instructions:
Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.611 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.612 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.613 Grade 5 AEs (Deaths) (See Section 10.52)

10.62 Late Occurring Adverse Events:

Refer to the instructions below and in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule – see Section 4.0).

Toxicity will be monitored continuously as each patient is accrued and follow-up data are accumulated. Acute radiation therapy and chemotherapy toxicities will be graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (available at http://ctep.cancer.gov). Late toxicities will be reported using the RTOG/EORTC late toxicity criteria [71].

11.0 Evaluation Criteria

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 5 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 [70]. 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

Measurable disease is 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

Patients with non-measurable disease cannot have a partial response. The best response possible is stable disease.

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
     - Because of the difficulty determining pseudoprogression from progression, and bevacizumab can be used to treat either progression or radiation-related treatment changes, treatment with bevacizumab alone does not qualify as progression. Clinical progression is determined by treating oncologist or initiation of systemic salvage regimens other than bevacizumab.
   - Cannot be considered Pseudoprogression
3. Patients with possible PsP should initially be given the Objective Status of Preliminary Progression.
   - 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 measurements. 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

12.1 Corticosteroid therapy at study entry: Yes (specify dose) vs. no

12.2 Histologic type of primary tumor: Oligodendroglioma vs. oligoastrocytoma vs astrocytoma vs other, specify

12.3 Histologic grade of primary tumor: 3 vs. 4

12.4 ECOG PS (see Appendix I): 0 vs. 1 vs. 2 vs. 3

12.5 Neurologic deficit: Yes vs. no

12.6 History of seizures: Yes vs. no

12.7 Prior surgical resection or biopsy: Yes vs. no

12.8 Age ≤70 vs. >70

12.9a MGMT: Methylated vs. Unmethylated vs. Not available

12.9b Family history of brain tumor: Yes vs. no
If yes, check all that apply:
_____Father/Mother
_____Brother/Sister
_____Child
_____Other (list:_____)

13.0 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.

13.2 On-study material and the End of Active Treatment/Cancel Notification Form must be submitted for patients who *cancel* participation prior to the start of pre-RT PET. These

materials must be provided to the MCCC Operations office. All data up to the point of going off study must be submitted to the MCCC Operations Office. No additional follow-up will be necessary.

13.3 Those patients who will *not* receive ^{18}F-DOPA PET image-guided dose escalation radiation treatment *or* who will receive radiation treatment elsewhere (other than specifically listed in section 6.4) will move to Event Monitoring phase.

13.4 Patients remain on study and continue to receive ^{18}F-DOPA PET scans at each clinically indicated MR scan until all of the following are confirmed / complete (up to 5 years or patient refusal):

- Radiological progression by central review per RANO criteria
- Clinical progression identified by the treating oncologist
  - Because of the difficulty determining pseudoprogression from progression, and bevacizumab can be used to treat either progression or radiation-related treatment changes, treatment with bevacizumab alone does not qualify as progression. Clinical progression is determined by treating oncologist or initiation of systemic salvage regimens other than bevacizumab.
- It is more than 3 months since radiation treatments have been completed, to ensure the radiological evidence is tumor progression versus treatment response
- Note: the ^{18}F-DOPA PET scan (study imaging) during the patient visit at the time the above three conditions are met is highly desired and the patient is to be encouraged to complete it even if it is scheduled after the patient has been informed they have progressive disease.

13.5 Patients who develop Confirmed PD (both clinical and radiologic progression) or withdraw from further ^{18}F-DOPA PET scans will go to the event-monitoring phase per Section 18.0.

14.0 Body Fluid Biospecimens - None.

15.0 Drug Information

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 [72]. ^{18}F-DOPA-PET is currently in production at this institution, and is used to image Parkinson's patients to study the ^{18}F-DOPA uptake in the caudate nucleus and putamen.

16.0 Statistical Considerations and Methodology

16.1 Study Overview:

This is a one-stage Simon's Optimal Phase-II study [73] with an interim analysis that will compare confirmed-progression free survival at 6 months (CPFS6) for Grade IV MGMT un-methylated glioma patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients treated on NCCTG clinical trials. To determine if the integration of ^{18}F-DOPA imaging into a dose escalation strategy for RT/TMZ therapy significantly improves tumor control, we will analyze confirmed-progression free survival for patients treated with PET-guided dose escalation and will compare against historical controls for Grade IV MGMT un-methylated patients treated at Mayo Clinic either with standard of care RT+TMZ then TMZ-alone or on the NCCTG clinical trials N057K or N0874. These trials have completed accrual. These trials all use identical MRI-based definitions of $GTV1_{MR}$ and $GTV2_{MR}$, and the same CTV and PTV expansions as the proposed study (Section 7.0, Table 1). On all trials, PTV1 and PTV2 were treated to 50 Gy and 60 Gy respectively, and radiation was delivered with concomitant TMZ (75 mg/m^2/day x 6 weeks) and subsequently adjuvant TMZ (150-200 mg/m^2 days 1-5 x 6 cycles). Progression-free survival was a secondary endpoint in all these trials, and each specified the same MR imaging follow-up regimen as the proposed study. Moreover, all patients had both acute and late toxicities recorded at each of their pre-defined follow-up and treatment visits. All of the treatment dosimetry and MR imaging is archived within the Mayo Clinic electronic medical record, which will facilitate greatly our planned analysis of patterns of failure.

16.11 The primary endpoint of this trial is the proportion of Grade IV MGMT un-methylated patients that experience confirmed-progression-free survival at 6 months (CPFS6) based on our hypothesis that the combination of more accurate delineation of high density tumor by ^{18}F-DOPA PET combined with dose escalation will improve overall tumor control. One of our neuro-radiologists, [redacted] or [redacted], will review all cases to define the date of radiographic progression, with analysis of historical controls falling under IRB #12-004263. With the close imaging follow-up mandated on all these clinical trials, we will be able to robustly evaluate progression. Both Grade III and IV glioma patients will be enrolled on this clinical trial, however Grade III astrocytomas are relatively rare and not commonly studied in NCCTG or Mayo Clinic trials. At the time of Addendum 8, there exists an Alliance clinical trial lead by a Mayo Clinic Principal Investigator enrolling Grade IV MGMT methylated patients. Enrollment of Grade IV MGMT methylated patients has been reduced compared to the expected rate. Therefore, as of Addendum 8, only the Grade IV MGMT un-methylated patients will be included in the statistical analysis described below. All Grade IV MGMT un-methylated patients meeting eligibility criteria who have signed a consent form and who have begun treatment with ^{18}F-DOPA PET image-guided dose escalation RT will be evaluable for the endpoint.

16.2 Statistical Design

16.21 Decision Rules

An endpoint-evaluable patient is defined to be a patient that is treated with ^{18}F-DOPA PET image-guided dose escalation RT. The primary endpoint is the proportion of grade-IV MGMT un-methylated patients treated with ^{18}F-DOPA PET image-guided dose escalation RT who are alive and do not have confirmed - progression within 6 months from the time of craniotomy. A success will be a patient who is alive and does not have confirmed-progression within 6 months from the time of craniotomy. At Mayo Clinic, the 81 Grade IV MGMT un-methylated patients accrued to the two trials listed above, combined with the 14 similar patients not treated on clinical trials had a combined rate of CPFS6 of 59.3%. These patients were newly diagnosed grade-IV MGMT un-methylated patients treated with 3D-conformal or IMRT with TMZ. Therefore the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 60%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen would be 72.5%. The following Simon's Optimum design requires 45 grade-IV MGMT un-methylated patients to test the null hypothesis that the proportion of successes is at most 60% with an overall significance level (alpha) of 0.20, and a power of 80% to detect a true success proportion of 72.5%.

16.211 Stage 1: If 15 or fewer successes are observed in the first 25 grade-IV MGMT un-methylated evaluable patients that have been followed for at least 6 months, we will consider this regimen to be ineffective in this patient population. If 16 or more successes are observed in the first 25 evaluable patients we will continue accrual and results will wait until the final analysis.

16.212 Stage 2: After 45 evaluable grade-IV MGMT un-methylated patients are accrued to this study and followed for at least 6 months, if 30 or more successes are observed in the first 45 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

16.213 Over Accrual: If more than the target number of Grade-IV MGMT un-methylated patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.214 Note: We will not suspend accrual between stages to allow the first 25 patients to become evaluable, unless undue toxicity is observed.

16.22 Sample Size

The two-stage design to be utilized is fully described in Section 16.21. A minimum of 25 and a maximum of 45 Grade-IV MGMT un-methylated evaluable patients will be accrued to this phase-II study unless undue toxicity is encountered. We anticipate accruing an additional 5 Grade-IV MGMT un-methylated patients to account for ineligibility, cancellation, major treatment violation, or other reasons. We also anticipate accruing a total of 25 Grade-IV MGMT methylated, 12 Grade-IV patients with unknown MGMT status, and 6 grade-III patients. Maximum projected accrual is therefore 87 grade–IV patients and 6 grade-III patients. We anticipate pre-registering 150 patients to register these 93 patients necessary for the study design.

16.23 Accrual Time and Study Duration

Based on institutional experience, we deliver RT on average to 48 Grade IV glioma patients annually, of which about 60% are MGMT un-methylated. Our plan to accrue 14 Grade IV MGMT un-methylated patients per year is based on including about 50% our Grade IV MGMT un-methylated glioma population, which is readily achievable. We plan to accrue patients for Years 1-5.5, leaving the last 6 months of Year 6 for remaining follow-up and analysis. Therefore, the overall study duration is expected to be 72 months.

16.24 Power and Significance Levels

Assuming the number of successes is binomially distributed, the significance level is 0.20 and the 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.

If the true success proportion is ...	**0.55**	**0.60**	**0.65**	**0.70**	**0.725**	**0.75**
then the probability of declaring that the regimen warrants further studies is ...	0.065	0.195	0.425	0.692	0.804	0.889
and the probability of stopping at stage 1 is ...	0.758	0.575	0.370	0.189	0.122	0.071

16.25 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.

16.3 Analysis Plan

The analysis for this trial will commence at the planned timepoints (see 16.2) and at the time the patients have become evaluable for the primary endpoint. Such decision will be made by the Statistician and Study chair, in accord with the Cancer Center Statistics (CCS) Standard Operating procedures, availability of data for secondary endpoints, and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via a manuscript, abstract, or presentation format is when 45 patients have either had confirmed-progression or been followed for at least 6 months. Subgroup analysis will be included for this primary endpoint to assess known prognostic factors such as performance status at baseline and age. Additionally, while no expected difference is anticipated, subset analysis will also be conducted for the primary endpoint to assess if there was any difference in patients treated via photons vs. protons.

16.31 Primary Endpoint:

16.311 Definition: The primary endpoint of this trial is the proportion of Grade-IV MGMT un-methylated patients that experience confirmed-progression-free survival at 6 months from the time of craniotomy. All Grade IV MGMT un-methylated patients meeting eligibility criteria who have signed a consent form and who have begun RT treatment will be evaluable for the endpoint. All eligible patients will be followed until death or a maximum of 5 years. Time to confirmed-progression is defined as the time from initial surgery to the earliest date documenting confirmed-progression. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor

progression at the time of death. 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.

16.312 Estimation: The proportion of CPFS6 successes and associated 95% confidence intervals will be estimated using Kaplan-Meier analysis methods.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence limits.

16.32 Definitions and Analyses of Secondary Endpoints

Subgroup analysis will be included as appropriate for these secondary endpoints to assess known prognostic factors such as performance status and age at baseline. Additionally, subset analysis will also be conducted for the primary endpoint to assess whether there was any difference in patients treated via photons vs. protons. To control for multiple testing the false discovery rate (FDR) [75], which is the expected proportion of false discoveries amongst the rejected hypotheses, will be used at a 0.05 level.

16.321 Compare progression free survival at 12 months for Grade III patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients, including those on clinical trials.

While both Grade III and IV glioma patients will be enrolled on this clinical trial, Grade III astrocytomas are relatively rare and not commonly studied in NCCTG or Mayo Clinic trials. Grade III patients are included in our prospective dose-escalation trial given their overall poor prognosis and the often limited contrast enhancement observed in these tumors. The target definitions will be similar to those described in section 7.0, Table 1. The progression-free survival at 12 months will be compared to historical controls treated at Mayo Clinic. Given the small numbers of patients with Grade III glioma anticipated (4 endpoint-evaluable patients as of 2/16/2017) on this prospective trial; this analysis will be hypothesis generating. The proportion of successes will be estimated by the number of successes divided by the total number of Grade-III evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (1987).

16.322 Confirmed-Progression Free Survival

We will analyze the confirmed-progression free survival time to event data combined with the confirmed-progression free survival data from the Mayo Clinic patients treated either with standard of care RT+TMZ then TMZ-alone or on studies N057K or N0874. These Mayo Clinic patients will be considered to be a control group. The distributions of confirmed-progression free survival times and comparisons between these two groups will be estimated using the method of Kaplan-Meier

[76]. Time to disease progression is defined as the time from initial surgery to the earliest date documenting confirmed-progression. If a patient dies without documentation of disease progression, the patient will be considered to have had tumor progression at the time of death. 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. This analysis will be conducted split by MGMT-methylation status of the patients and historical control.

16.323 Overall Survival

Compare patient outcomes including overall survival after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients. As described above for confirmed-progression free survival, we will analyze both historical control patients and our prospective dose escalation patients for overall survival. Survival time is defined as the time from initial surgery to death due to any cause. The distributions of survival times and comparisons between these two groups will be estimated using the method of Kaplan-Meier [76].

16.324 Quality of Life

Evaluate quality of life after radiotherapy treatment targeting dose escalated volumes defined to include high^{18}F-DOPA PET uptake. Quality of life (QOL) will be compared to high-grade glioma patients treated on previous North Central Cancer Treatment Group protocols. QOL and cognitive function will be evaluated with the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) and Mini-Mental Status Exam (MMSE) questionnaires at baseline and at each MRI evaluation up to 6 evaluations 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. The main QOL analysis will be the change from baseline to first subsequent MRI timepoint in the overall score from the MDASI-BT. All other QOL analysis will be exploratory and may include change percent from baseline to all timepoints using t-tests and generalized linear models to test for changes at each time point and non-zero slope respectfully.

16.325 Adverse Events

Determine acute and late effect toxicity after radiotherapy treatment targeting dose escalated volumes defined to include high^{18}F-DOPA PET uptake. The rate of acute and late treatment-related toxicities for newly diagnosed high-grade glioma patients treated with ^{18}F-DOPA PET image-guided dose escalation will be determined, with acute RT toxicities graded using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (available at http://ctep.cancer.gov), and late toxicities reported using the RTOG/EORTC late toxicity criteria [71]. Patients will be considered evaluable for adverse events if they receive ^{18}F-DOPA PET or ^{18}F-DOPA PET image-guided dose escalation RT.

16.326 Compare confirmed-progression free survival at 12 months for Grade IV MGMT-methylated patients after radiation therapy targeting volumes designed with both ^{18}F-DOPA PET and conventional MR image information with historical controls from Mayo Clinic Rochester patients, including those on clinical trials.

16.33 Correlative Research

In addition to the 45 evaluable Grade-IV MGMT Un-methylated patients, these correlative research endpoints will use the combined information from all of the evaluable grade-IV patients. As of 2/16/2017 this sample size will include at least 22 endpoint-evaluable patients with Grade-IV MGMT methylated status and 5 endpoint-evaluable patients with unknown MGMT status. Therefore the minimum sample size for these correlative endpoints is 72 patients. Subgroup analysis will be included as appropriate for these correlative endpoints to assess known prognostic factors such as MGMT and age. To control for multiple testing the false discovery rate (FDR) [75], which is the expected proportion of false discoveries amongst the rejected hypotheses, will be used at a 0.05 level.

16.331 Compare RT treatment volumes defined by MR only with RT treatment volumes defined with both PET and MR information for Grade IV glioma patients.

To assess the impact of integrating PET on target definition, the treating radiation oncologists (Dr. N. Laack, [redacted]) will first define the treatment volumes for $GTV1_{MR}$ and $GTV2_{MR}$ using the MR images while blinded to the PET study. Then the PET contours, using gold standard volumes generated by Drs. Hunt or Lowe for $GTV1_{PET}$ and T/N ratio of >2.0 for $GTV2_{PET}$, will be reviewed by the treating radiation oncologist and expanded as described above. The volume of overlap and non-overlap between the GTV1 and 2 defined by MR and that defined by PET will be calculated. Similarly, the MR-only defined volumes will be compared against the volumes defined with the combination of MR and PET planning. 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 MR only and treatment volumes defined with both PET and MR information. The analysis of volumes from the combined 72 Grade IV patients will have 90% power to detect differences in volumes with an effect size of 0.39 using a paired t-test with a 0.05 two-sided significance level. Alternate metrics for comparison will also be assessed, including spatial overlap, distance, correlations and 3D shape comparisons.

16.332 Compare timing of accurate identification of progression defined by ^{18}F-DOPA PET, pMRI and conventional MRI for Grade IV glioma patients.

Both ^{18}F-DOPA PET imaging [6, 9] and pMRI [54] have been shown to differentiate recurrence from pseudo-progression better than conventional MR imaging. There are several reasons why we anticipate ^{18}F-DOPA PET imaging will identify HGG progression earlier than pMRI, and may more accurately differentiate progression from pseudo-progression. As pMRI is based on angiogenesis, it is possible that ^{18}F-DOPA may detect additional separate or complimentary tumor segments

that aren't particularly angiogenic, and could therefore be missed with pMRI. Also, per our preliminary data, ^{18}F-DOPA appears to successfully detect tumor in non-enhancing tissue. pMRI has not been used to characterize tumor in the non-enhancing segment, so there is no historical data to compare ^{18}F-DOPA and pMRI for this tumor segment. For each confirmed incidence of progression per conventional MRI we will review follow-up imaging acquired with PET and pMRI prior to the confirmed progression to determine which modality correctly identified progression earliest. We will compare ^{18}F-DOPA PET with our recently published pMRI-Fractional Tumor Burden method to differentiate regional tumor progression from radiation necrosis and pseudoprogression [68]. To compare the progression identification timing we will calculate the percentage of time each modality was earlier than conventional MRI. With a sample size of 72, if the observed percentage earlier than conventional MRI is 30% for either modality, a two-sided 95.0% confidence interval for a single proportion using the large sample normal approximation will be ±10.6%. Progression identification timing will also be compared using Kaplan-Meier methods and paired t-tests to determine if differences exist between the modalities.

16.333 Compare patterns of failure after radiation therapy targeting volumes defined with target volumes designed to with both ^{18}F-DOPA PET and conventional MR image information with patterns of failure for historical controls from Mayo Clinic Rochester patients**.** As described above for confirmed-progression free survival, we will analyze both historical control patients and our prospective dose escalation patients. Imaging archived for the cohort of Mayo Clinic patients used as historical controls for confirmed-progression free survival will be assessed for patterns of failure, to compare with patterns of failure determined for patients treated with ^{18}F-DOPA PET image-guided dose escalation. As noted above, one of our neuro-radiologists, [redacted] or [redacted], will review all cases to define the date of radiographic progression. The relevant image set will be fused with our treatment planning scan and then the radiologist will contour the region of progression blinded to the dose distribution contour. A volumetric analysis then can be performed to define the doses delivered to the absolute and relative volume of the region where the recurrence is defined. With the close imaging follow-up mandated on clinical trials and for our standard of care, we will be able to robustly evaluate the patterns of failure relative to dose delivered to those regions. Chi-square tests of proportions will be used to test for differences in the proportions of patients with central, in-field, marginal, or distant failures between the patients on this study and historical controls.

16.334 Compare RT treatment volumes defined by MR only with RT treatment volumes defined with both PET and MR information for Grade III glioma patients. 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 MR only and treatment volumes defined with both PET and MR information.

16.335 Evaluate intra- and inter-observer variability with vs. without the addition of ^{18}F-DOPA PET uptake for radiotherapy target volume delineation. Potential for reduction in inter- and intra-observer variability for RT target delineation with the addition of PET in conjunction with biopsy-validated threshold guidance will be evaluated through volume comparisons of target volumes delineated with MR alone and MR in combination with PET information by our radiation oncologists (Drs. Laack, Sarkaria and Yan) as well as gold standard volumes generated by Drs. Morris or Kaufmann for MRI and Drs. Hunt or Lowe for PET. The concordance correlation coefficient will be used to measure agreement between volumes generated with each method, as well as to evaluate inter-observer variability, where variability associated with MR will serve as the standard for comparison.

Several tools commercially available for semi-automated PET contouring will be investigated for consistency with the biopsy-validated thresholds, to standardize the method of ^{18}F-DOPA PET integration into RT delineation, reducing operator error and subjectivity commonly associated with manual delineation of target volumes utilizing PET data. The variation of PET volumes defined with different segmentation techniques will be evaluated, including manual visual delineation, SUV-based delineation using an isocontour of SUV = 2.5, fixed threshold techniques ranging from 40-80% of the maximum signal intensity in the primary tumor, adaptive threshold delineation using the source-to-background ration (SBR) technique, and the PET Edge gradient technique in the MIM software package.

16.336 Compare timing of accurate identification of progression defined by ^{18}F-DOPA PET, pMRI and conventional MRI for Grade III glioma patients. In addition to Grade IV patients analyzed above, progression identification will also be made for the Grade III patients and analysis will include determination of any differences between Grade IV and III patients. Progression identification timing will be compared using Kaplan-Meier methods and paired t-tests to determine if differences exist between the modalities. An exploratory analysis of DTI for detecting invasive non-enhancing tumor recurrence will also be performed.

16.337 Compare predictive capabilities of ^{18}F-DOPA PET, pMRI and DTI for localization of recurrences for patients treated with ^{18}F-DOPA PET-guided RT dose escalation. Predictive capabilities of ^{18}F-DOPA PET, pMRI and DTI for localization of recurrences for patients treated with ^{18}F-DOPA PET-guided RT dose escalation will be compared by identifying the recurrence volume with each modality and correlating with identification of aggressive disease in the pre-RT planning images.

16.4 Data and Safety Monitoring Plan:

16.41 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.

16.42 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 15.0), and there have been no allergic reactions in all patients accrued to date to the pilot study (MC1078), no reactions are anticipated. As such, at any point in the enrollment process after 10 or more patients have been enrolled, if more than 10% of these patients enrolled are unable to complete PET scanning due to allergic reactions to the tracer, 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 DMC.

There have been no reports in the literature of the occurrence of NSF in patients with normal renal function [62, 69]. 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 [62, 69]. 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 DMC.

Using the dose escalation approach described in Section 7, previous studies have successfully dose escalated to 76 – 80 Gy without significant increases in acute or late adverse effects [51]. Nonetheless, both acute (available at http://ctep.cancer.gov) and late [71] toxicity will be monitored continuously as each patient is accrued and follow-up data are accumulated. As such, at any point in the enrollment process after 10 or more patients have been enrolled, if more than 10% of these patients enrolled experience any of the following adverse events considered to be at least possibly related to treatment, enrollment will be suspended so the details of each episode can be examined and a trial recommendation will be formulated and presented to the MCCC DMC, adjusting the PTV3 escalated dose level if necessary.

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

16.5 Results Reporting on ClinicalTrials.gov:

16.51 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 60 months after the study opens to accrual.

16.52 Definition of Primary-Endpoint Completion Date (PCD): The PCD is the date at which the last confirmed-progression free patient has been followed for 6 months.

16.6 Inclusion of Women and Minorities

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

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:

	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	3	4	7
Not Hispanic or Latino	35	51	86
Ethnic Category: Total of all subjects	38	55	93
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	1	1	2
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	1	1
White	35	51	86
Racial Category: Total of all subjects	38	55	93

17.0 Pathology Considerations/Tissue Biospecimens: N/A

18.0 Records and Data Collection Procedures

18.1 Submission Timetables

18.11 Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study Form	≤2 weeks after registration
Baseline Adverse Event Form	
MMSE Form	
Patient Questionnaire Booklet[3]	
Patient Questionnaire Booklet Compliance Form[2]	
End of Active Treatment/Cancel Notification Form[1]	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy
Concurrent Steroid and Anticonvulsant Treatment Form	≤4 weeks after start of RT

1 Submit if withdrawal/refusal prior to radiotherapy treatment occurs.
2 This form must be completed **only** if the QOL booklet contains absolutely **NO** patient provided assessment information.
3 Patient questionnaire booklet **must** be used; copies are not acceptable for this submission.

18.12 Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)			
	≤4 weeks after each evaluation during RT treatment	≤1 week after each ^{18}F-DOPA-PET scan	≤6 months after end of RT treatment[5]	≤6 months after every clinically indicated MR scan[5]
Pre-RT Measurement Form			X	
Imaging Form		X		X
End of Active Treatment/Cancel Notification Form			X	
Adverse Event Form (Post Injection of ^{18}F-DOPA)		X[7]		
Radiation Therapy Adverse Event Form (Toxicity)	X[1]			X[2]
Concurrent Steroid and Anticonvulsant Treatment			X	X
Radiation Therapy Reporting			X[3]	
Active Monitoring Measurement			X	X[6]
Patient Questionnaire Booklet[9]			X[4]	X[4]
MMSE			X[4]	X[4]
Patient Questionnaire Booklet Compliance Form[8]				
ADR/AER (see Section 10.0)	At each occurrence			

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 Patient will complete a maximum of 6 post-RT QOL evaluations
5 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).
6 See Section 4 for time of assessments.
7 Done approximately 15-20 minutes post injection of 18F-DOPA after scan is completed and if AE observed a second AE assessment is required ≤24 hours post injection.
8 This form must be completed only if the QOL booklet contains absolutely NO patient provided assessment information.
9 Patient questionnaire booklet must be used; copies are not acceptable for this submission.

18.13 Follow-up Material(s)

CRF	Event Monitoring Phase[1]		
	q. yearly for 5 years	At PD	Death
Event Monitoring Form	X	X	X
CD/DVD Radiology Imaging		X[2]	

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. If patient leaves Mayo Clinic, please obtain imaging in DICOM format from local MD. The study will pay for costs associated with providing copies of the imaging to Mayo Clinic. See Appendix VI for details. Imaging CDs (MRI) must be de-identified. The surface of the CD should be labeled with MC1374, the patient's Mayo Clinic identification number (or initials (L, F, M) and birth date) and the scan date only.
   Mail CDs to: Mayo Clinic, Attn: QAS Study MC1374, [redacted] Rochester, MN [redacted].

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded:
Pregnancy test for women of childbearing potential only, FDOPA, PET scan, additional limited 3T MR scan for advanced imaging prior to radiotherapy when not clinically indicated (i.e. for patients who have had a post-operative 3T glioma MR scan at this institution); and costs incurred for providing copies of imaging from local MD.

19.3 Other budget concerns: None.

20.0 References

1. Mihara, F., et al., *Non-enhancing supratentorial malignant astrocytomas: MR features and possible mechanisms.* Radiation medicine, 1995. **13**(1): p. 11-17.
2. Schomas, D.A., et al., *Intracranial low-grade gliomas in adults: 30-year experience with long-term follow-up at Mayo Clinic.* Neuro-oncology, 2009. **11**(4): p. 437-45.
3. Grosu, A.L., et al., *Implications of IMT-SPECT for postoperative radiotherapy planning in patients with gliomas.* International journal of radiation oncology, biology, physics, 2002. **54**(3): p. 842-54.
4. Kelly, P.J., et al., *Imaging-based stereotaxic serial biopsies in untreated intracranial glial neoplasms.* Journal of neurosurgery, 1987. **66**(6): p. 865-74.
5. Wong, T.Z., G.J. van der Westhuizen, and R.E. Coleman, *Positron emission tomography imaging of brain tumors.* Neuroimaging clinics of North America, 2002. **12**(4): p. 615-26.
6. Chen, W., et al., *18F-FDOPA PET imaging of brain tumors: comparison study with 18F-FDG PET and evaluation of diagnostic accuracy.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2006. **47**(6): p. 904-11.
7. Ledezma, C.J., et al., *18F-FDOPA PET/MRI fusion in patients with primary/recurrent gliomas: initial experience.* European journal of radiology, 2009. **71**(2): p. 242-8.
8. Hustinx, R., et al., *Can the standardized uptake value characterize primary brain tumors on FDG-PET?* European journal of nuclear medicine, 1999. **26**(11): p. 1501-9.
9. Chen, W., *Clinical applications of PET in brain tumors.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2007. **48**(9): p. 1468-81.
10. Grosu, A.L., et al., *L-(methyl-11C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy.* International journal of radiation oncology, biology, physics, 2005. **63**(1): p. 64-74.
11. Pirotte, B., et al., *Integrated positron emission tomography and magnetic resonance imaging-guided resection of brain tumors: a report of 103 consecutive procedures.* Journal of neurosurgery, 2006. **104**(2): p. 238-53.
12. Pirotte, B., et al., *Integration of [11C]methionine-positron emission tomographic and magnetic resonance imaging for image-guided surgical resection of infiltrative low-grade brain tumors in children.* Neurosurgery, 2005. **57**(1 Suppl): p. 128-39; discussion 128-39.
13. Becherer, A., et al., *Brain tumour imaging with PET: a comparison between [18F]fluorodopa and [11C]methionine.* European journal of nuclear medicine and molecular imaging, 2003. **30**(11): p. 1561-7.
14. Hong, R., et al., *Correlation of PET standard uptake value and CT window-level thresholds for target delineation in CT-based radiation treatment planning.* International journal of radiation oncology, biology, physics, 2007. **67**(3): p. 720-6.
15. Yaremko, B., et al., *Thresholding in PET images of static and moving targets.* Physics in medicine and biology, 2005. **50**(24): p. 5969-82.
16. van Baardwijk, A., et al., *PET-CT-based auto-contouring in non-small-cell lung cancer correlates with pathology and reduces interobserver variability in the delineation of the primary tumor and involved nodal volumes.* International journal of radiation oncology, biology, physics, 2007. **68**(3): p. 771-8.
17. Weber, D.C., et al., *[(18)F]Fluoroethyltyrosine- positron emission tomography-guided radiotherapy for high-grade glioma.* Radiation oncology, 2008. **3**: p. 44.
18. Breen, S.L., et al., *Intraobserver and interobserver variability in GTV delineation on FDG-PET-CT images of head and neck cancers.* International journal of radiation oncology, biology, physics, 2007. **68**(3): p. 763-70.
19. Bosmans, G., et al., *Intra-patient variability of tumor volume and tumor motion during conventionally fractionated radiotherapy for locally advanced non-small-cell lung cancer: a*

prospective clinical study. International journal of radiation oncology, biology, physics, 2006. **66**(3): p. 748-53.
20. Davis, J.B., et al., *Assessment of 18F PET signals for automatic target volume definition in radiotherapy treatment planning.* Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 2006. **80**(1): p. 43-50.
21. Wong, C.Y., P. Mahajan, and D. Yan, *Dynamic threshold for radiation target volume by PET/CT.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2007. **48**(5): p. 849; author reply 847.
22. van Dalen, J.A., et al., *A novel iterative method for lesion delineation and volumetric quantification with FDG PET.* Nuclear medicine communications, 2007. **28**(6): p. 485-93.
23. Aristophanous, M., et al., *A Gaussian mixture model for definition of lung tumor volumes in positron emission tomography.* Medical physics, 2007. **34**(11): p. 4223-35.
24. Schaefer, A., et al., *A contrast-oriented algorithm for FDG-PET-based delineation of tumour volumes for the radiotherapy of lung cancer: derivation from phantom measurements and validation in patient data.* European journal of nuclear medicine and molecular imaging, 2008. **35**(11): p. 1989-99.
25. Grosu, A.L., et al., *11C-methionine PET improves the target volume delineation of meningiomas treated with stereotactic fractionated radiotherapy.* International journal of radiation oncology, biology, physics, 2006. **66**(2): p. 339-44.
26. Greco, C., et al., *Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC).* Lung cancer, 2007. **57**(2): p. 125-34.
27. van Baardwijk, A., et al., *The current status of FDG-PET in tumour volume definition in radiotherapy treatment planning.* Cancer treatment reviews, 2006. **32**(4): p. 245-60.
28. A., B. and Z. H., *Image segmentation techniques in nuclear medicine imaging*, in *Quantitative Analysis of Nuclear Medicine Images*, H. Zaidi, Editor. 2006, Springer: New York. p. 308-357.
29. Ciernik, I.F., et al., *Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study.* International journal of radiation oncology, biology, physics, 2003. **57**(3): p. 853-63.
30. Nestle, U., et al., *Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2005. **46**(8): p. 1342-8.
31. Vees, H., et al., *Assessment of various strategies for 18F-FET PET-guided delineation of target volumes in high-grade glioma patients.* European journal of nuclear medicine and molecular imaging, 2009. **36**(2): p. 182-93.
32. Erdi, Y.E., et al., *Segmentation of lung lesion volume by adaptive positron emission tomography image thresholding.* Cancer, 1997. **80**(12 Suppl): p. 2505-9.
33. Daisne, J.F., et al., *Tri-dimensional automatic segmentation of PET volumes based on measured source-to-background ratios: influence of reconstruction algorithms.* Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology, 2003. **69**(3): p. 247-50.
34. Drever, L., et al., *Iterative threshold segmentation for PET target volume delineation.* Medical physics, 2007. **34**(4): p. 1253-65.
35. Schinagl, D.A., et al., *Comparison of five segmentation tools for 18F-fluoro-deoxy-glucose-positron emission tomography-based target volume definition in head and neck cancer.* International journal of radiation oncology, biology, physics, 2007. **69**(4): p. 1282-9.
36. Hatt, M., et al., *Fuzzy hidden Markov chains segmentation for volume determination and quantitation in PET.* Physics in medicine and biology, 2007. **52**(12): p. 3467-91.
37. Montgomery, D.W., A. Amira, and H. Zaidi, *Fully automated segmentation of oncological PET volumes using a combined multiscale and statistical model.* Medical physics, 2007. **34**(2): p. 722-36.

38. Drever, L., et al., *A local contrast based approach to threshold segmentation for PET target volume delineation.* Medical physics, 2006. **33**(6): p. 1583-94.
39. Biehl, K.J., et al., *18F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate?* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2006. **47**(11): p. 1808-12.
40. Jentzen, W., et al., *Segmentation of PET volumes by iterative image thresholding.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2007. **48**(1): p. 108-14.
41. Ciernik, I.F., et al., *Automated functional image-guided radiation treatment planning for rectal cancer.* International journal of radiation oncology, biology, physics, 2005. **62**(3): p. 893-900.
42. Matsuo, M., et al., *Target definition by C11-methionine-PET for the radiotherapy of brain metastases.* International journal of radiation oncology, biology, physics, 2009. **74**(3): p. 714-22.
43. Walker, M.D., et al., *Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas. A cooperative clinical trial.* Journal of neurosurgery, 1978. **49**(3): p. 333-43.
44. Lee, S.W., et al., *Patterns of failure following high-dose 3-D conformal radiotherapy for high-grade astrocytomas: a quantitative dosimetric study.* International journal of radiation oncology, biology, physics, 1999. **43**(1): p. 79-88.
45. Chan, J.L., et al., *Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2002. **20**(6): p. 1635-42.
46. Stupp, R., et al., *Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma.* The New England journal of medicine, 2005. **352**(10): p. 987-96.
47. Minniti, G., et al., *Patterns of failure and comparison of different target volume delineations in patients with glioblastoma treated with conformal radiotherapy plus concomitant and adjuvant temozolomide.* Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, 2010. **97**(3): p. 377-81.
48. Dobelbower, M.C., et al., *Patterns of failure for glioblastoma multiforme following concurrent radiation and temozolomide.* Journal of medical imaging and radiation oncology, 2011. **55**(1): p. 77-81.
49. Watkins, J.M., et al., *High-dose radiotherapy to 78 Gy with or without temozolomide for high grade gliomas.* Journal of neuro-oncology, 2009. **93**(3): p. 343-8.
50. Lee, I.H., et al., *Association of 11C-methionine PET uptake with site of failure after concurrent temozolomide and radiation for primary glioblastoma multiforme.* International journal of radiation oncology, biology, physics, 2009. **73**(2): p. 479-85.
51. Tsien, C.I., et al., *Concurrent temozolomide and dose-escalated intensity-modulated radiation therapy in newly diagnosed glioblastoma.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2012. **18**(1): p. 273-9.
52. Rosen, B.R., et al., *Perfusion imaging with NMR contrast agents.* Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 1990. **14**(2): p. 249-65.
53. Pathak, A.P., et al., *MR-derived cerebral blood volume maps: issues regarding histological validation and assessment of tumor angiogenesis.* Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 2001. **46**(4): p. 735-47.
54. Hu, L.S., et al., *Correlations between perfusion MR imaging cerebral blood volume, microvessel quantification, and clinical outcome using stereotactic analysis in recurrent high-grade glioma.* AJNR. American journal of neuroradiology, 2012. **33**(1): p. 69-76.
55. Price, S.J., et al., *Improved delineation of glioma margins and regions of infiltration with the use of diffusion tensor imaging: an image-guided biopsy study.* AJNR. American journal of neuroradiology, 2006. **27**(9): p. 1969-74.

56. Stadlbauer, A., et al., *Diffusion tensor imaging and optimized fiber tracking in glioma patients: Histopathologic evaluation of tumor-invaded white matter structures.* NeuroImage, 2007. **34**(3): p. 949-56.
57. Weber, M.A., et al., *Biopsy targeting gliomas: do functional imaging techniques identify similar target areas?* Investigative radiology, 2010. **45**(12): p. 755-68.
58. Hu, L.S., et al., *Relative cerebral blood volume values to differentiate high-grade glioma recurrence from posttreatment radiation effect: direct correlation between image-guided tissue histopathology and localized dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging measurements.* AJNR. American journal of neuroradiology, 2009. **30**(3): p. 552-8.
59. Barajas, R.F., Jr., et al., *Differentiation of recurrent glioblastoma multiforme from radiation necrosis after external beam radiation therapy with dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging.* Radiology, 2009. **253**(2): p. 486-96.
60. Boxerman, J.L., K.M. Schmainda, and R.M. Weisskoff, *Relative cerebral blood volume maps corrected for contrast agent extravasation significantly correlate with glioma tumor grade, whereas uncorrected maps do not.* AJNR. American journal of neuroradiology, 2006. **27**(4): p. 859-67.
61. Stadlbauer, A., et al., *Fiber density mapping of gliomas: histopathologic evaluation of a diffusion-tensor imaging data processing method.* Radiology, 2010. **257**(3): p. 846-53.
62. Wang, Y., et al., *Incidence of nephrogenic systemic fibrosis after adoption of restrictive gadolinium-based contrast agent guidelines.* Radiology, 2011. **260**(1): p. 105-11.
63. Donahue, K.M., et al., *Utility of simultaneously acquired gradient-echo and spin-echo cerebral blood volume and morphology maps in brain tumor patients.* Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine, 2000. **43**(6): p. 845-53.
64. Kassner, A., et al., *Abnormalities of the contrast re-circulation phase in cerebral tumors demonstrated using dynamic susceptibility contrast-enhanced imaging: a possible marker of vascular tortuosity.* Journal of magnetic resonance imaging : JMRI, 2000. **11**(2): p. 103-13.
65. Hu, L.S., et al., *Optimized preload leakage-correction methods to improve the diagnostic accuracy of dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging in posttreatment gliomas.* AJNR. American journal of neuroradiology, 2010. **31**(1): p. 40-8.
66. Paulson, E.S. and K.M. Schmainda, *Comparison of dynamic susceptibility-weighted contrast-enhanced MR methods: recommendations for measuring relative cerebral blood volume in brain tumors.* Radiology, 2008. **249**(2): p. 601-13.
67. Fueger, B.J., et al., *Correlation of 6-18F-fluoro-L-dopa PET uptake with proliferation and tumor grade in newly diagnosed and recurrent gliomas.* Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 2010. **51**(10): p. 1532-8.
68. Hu, L.S., et al., *Reevaluating the imaging definition of tumor progression: perfusion MRI quantifies recurrent glioblastoma tumor fraction, pseudoprogression, and radiation necrosis to predict survival.* Neuro-oncology, 2012. **14**(7): p. 919-30.
69. Altun, E., et al., *Nephrogenic systemic fibrosis: change in incidence following a switch in gadolinium agents and adoption of a gadolinium policy--report from two U.S. universities.* Radiology, 2009. **253**(3): p. 689-96.
70. Wen, P.Y., et al., *Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2010. **28**(11): p. 1963-72.
71. Cox, J.D., J. Stetz, and T.F. Pajak, *Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).* International journal of radiation oncology, biology, physics, 1995. **31**(5): p. 1341-6.
72. Chevalme, Y.M., et al., *FDOPA-(18F): A PET radiopharmaceutical recently registered for diagnostic use in countries of the European union.* Brazilian Archives of Biology and Technology, 2007. **50**: p. 77-90.

Appendix I ECOG PERFORMANCE STATUS

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 Folstein Mini Mental State Examination (MMSE)

INTRODUCTION

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

The MMSE begins with a graded assessment of orientation to place and time, for which a maximum of 10 points is possible. This is followed by testing two aspects of memory. The first is the immediate recall for three objects presented orally, followed by a serial sevens task which is interposed to assess attention, concentration, and calculation, and also to prevent the individual from rehearsing the three objects previously learned. A maximum of 21 points may be obtained on this section of the test.

The final section surveys aphasia and apraxia by testing functions of naming, repetition, understanding a three-stage command, reading, writing and copying a drawing. There are a maximum of 9 points which may be obtained on this section, for a total possible MMSE score of 30 points.

MMSE SECTIONS

Detailed instructions are included here. A brief form for recording and scoring MMSE answers follows.

Orientation. Ask the patient for the date. Then ask for parts omitted (e.g., "Can you also tell me what season it is?"). Give one point for each correct response.

Ask in turn, "Can you tell me the name of this hospital? town? count? (and so on)". Give one point for each correct response.

Registration. Ask the patient if you may test his/her memory. Then name three unrelated objects, clearly and slowly, about a second for each. After you have said all three, ask the patient to repeat them. This first repetition determines the score. Score one point for each repeated object (0 – 3). If the patient does not repeat all three objects, the tester should repeat the objects (up to a maximum of six times) until the patient can say all three. In cases where a patient cannot learn all three objects in six trials, recall (see below) cannot be meaningfully tested.

When registration is complete, tell the patient, "Try to remember them because I will ask for them in a little while."

Attention and Calculation. Ask the patient to begin with 100 and count backwards by seven. Stop after five subtractions (93, 86, 79,72, 65). Score the total number of correct answers. If the patient will not perform this task, ask him or her to spell the word "WORLD" backwards. The score is the number of letters in correct order (e.g., DLROW – five, DLORW – three).

Recall. Ask the patient if he/she can remember the names of the three objects learned in the Registration section. Give one point for each correct answer.

Language. There are six operations in this section.

Naming. Show the patient a wrist watch and ask him/her what it is. Repeat for a pencil. Give one point for each correct naming (0 – 2).

Repetition. Have the patient repeat, "No, ifs, ands, or buts". All only one trial. Given one point for a completely correct repetition.

Three-Stage Command. Place a piece of blank paper in front of the patient and say; "Take this paper in your right hand. Fold the paper in half. Put the paper on the floor". Give one point for each correctly performed command.

Reading. Show the patient the page with the sentence "Close your eyes" (page 2). Ask the patient to read it and do what it says. Since this is not a memory task, the tester may prompt the reader to "do what it says" after the reader reads the sentence. Score one point if the patient actually closes his or her eyes.

Writing. Give the patient the page with the word sentence (page 3) and ask him/her to write a sentence for you. Do not dictate a sentence; it is to be written spontaneously. The sentence should contain a subject and a verb, and should make sense. Ignore minor spelling or minor grammatical errors when scoring. Score one point for a correct sentence.

Copying. Show the patient the page with the intersecting pentagons (page 4). Ask the patient to copy it exactly as it is. Give one point if all sides are preserved and if the intersecting sides from a four sided figure (i.e., ten sides and ten angles).

SPECIAL CONSIDERATIONS

The examination is conducted so as to minimize stress for the patient. Errors are not indicated to the subjects and, in general, mistakes are not corrected. Refusals are considered to be errors after a minimum of encouragement. Individuals with peripheral impairment such as blindness or restriction of the hands due to arthritis or other peripheral disorders are scored the number correct out of the possible items they could answer given their other non cognitive impairments. Please note these exceptions on the MMSE and the cover sheet. It is important not to allow your administration of this test to be affected by your perception of <u>why</u> the patient may have responded incorrectly or not at all. That is, the examination should be conducted without the examiner modifying the scoring by assumptions of whether or not the individual was motivated, paying attention, or could understand. For the purpose of the exam, the score indicates a failed performance, not necessarily a failed performance under all conceivable circumstances.

Spencer MP and Folstein MF. The Mini-Mental State Examination. In: PA Keller and LG Ritt (Eds), Innovations in Clinical Practice: A Source Book.

Vol. 4. Sarasota, FL: Professional Resource Exchange, Inc., 1985, 307-308.

Folstein Mini Mental State Examination (MMSE)

Place Label Here
Protocol Number _____
Patient ID # _____
Patient Initials _____
Date (mm/dd/yyyy) _____

_____/5 What is the: (year) (season) (date) (day) (month)?

_____/5 Where are we: (state) (county) (town) (building) (floor)?

_____/3 Learn: "apple, table, penny." _____ # of trials

_____/5 Subtract serial 7's: (100, 93, 86, 79, 72); or spell "WORLD" backwards

_____/3 Recall: "apple, table, penny."

_____/2 Name: "pencil and watch."

_____/1 Repeat: "no ifs, ands or buts."

_____/3 "Take this paper in your right hand, fold it in half, and put it on the floor."

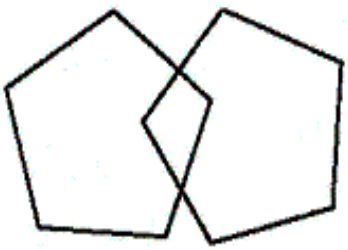
_____/1 Read and obey: "Close your eyes."

_____/1 Write a sentence on the back of this card.

_____/1 Copy the design on the back of this card

_____/30 Total (abnormal if <24; if <8th grade, then <21 is considered abnormal.)

Close your eyes.



Appendix III PATIENT INFORMATION SHEET

Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains questions for the MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT):

2. Directions on how to complete the questions are written on the top of the first set of questions.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

Appendix IV MDASI - BT

Date: _____ **Institution:** _____

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

Participant Number: _____

M. D. 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 fill in the circle below 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 feeling 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?	○	○	○	○	○	○	○	○	○	○	○

Page 1 of 2

MDASI-BT - 2006

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**:

	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 V Contouring CNS and H/N

ARIA Atlas Patient is Contours, Head (000-11-19-2013)

1) Brain: For patients receiving craniospinal or otherwise requiring treatment of CSF, window-level should be adjusted to bone windows to ensure brain contour includes entire CSF space/meninges as well as cribiform plate. For intraparenchymal tumors, it may be appropriate to use window-level on CT or MRI that allows visualization of brain parenchyma and contour actual brain parenchyma which may allow greater skin sparing for superficial targets.
2) Brain stem: (based on QUANTEC definition) Use CT/MRI sagittal image to define axial slice for the foramen magnum (usually one slice above dens) and cranially to include midbrain (ending inferior to the optic tracts/thalami).
3) Cochlea: Use CT bone window for contouring. Use a 6mm brush and deposit circular structure in the bone anterior to the internal auditory canal including the apical and basal turns of the cochlea. Usually on 2-3 axial slices. Alternatively, contour this volume using the free hand tool.
4) Cord: rostral; start on the slice inferior to brain stem and continue caudally to the end of the data set or to the end of the "region of interest depending on whether the full cord visualized on CT being in the denominator will impact your dvh evaluation. The standard should be to contour the cord 2 cm distal or proximal to the PTV whichever applies. In this case contouring was stopped at the upper chest for no particular reason as this study goes down through the thorax.
5) External auditory canal (middle ear and eustachian tube): Use CT bone window to contour boney portion of external auditory canal, middle ear (malleus, incus and stapes) and eustachian tube. Use Acquisition W/L to contour fleshy portion of external auditory canal from the inferior to the superior aspect of tragus.
6) Eyes: This is most easily done in GE prior to exporting to Eclipse where an automated tool contours the Eyes and the lenses. In Eclipse contour the globe on the CT data set and check on any MR data set. IF discordant use CT data set.
7) Hippocampus: Based on RTOG guidelines, contour the subgranular zone on T1-weighted SPGR MRI. Begin contouring at the most caudal (inferior) extent of the crescentic-shaped floor of the temporal horn of the lateral ventricle and contour the hypointense grey matter located medial to the CSF hypointensity, not the white, bright white matter. The emergence of the uncal recess of the temporal horn defines the anterior boundary of the hippocampus. The medial boundary of the hippocampus becomes defined by the medial edge of the uncal recess. Postero-cranially, the medial boundary of the hippocampus is defined by the lateral edge of the quadrageminal cistern which is the CSF containing space lateral to the pons. The hippocampal tail remains posterior to the thalamus as it curves medially toward the splenium of the corpus callosum and is still medially located relative to the lateral ventricle. Terminate hippocampal contours at the point where the T1-hypointense structure no longer borders the atrium of the lateral ventricle. At this point, the crux of the fornix emerges anteriorly and the splenium of the corpus callosum can be visualized posteriorly. If MRI is not available, a reasonable approximation can be drawn using an 8mm brush and contouring along the medial edge of the lateral ventricles from the temporal horn to posterior splenium of corpus callosum.
8) Hippocampus PRV: 3mm expansion of hippocampus contour
9) Hypothalamus. Follow pituitary stalk as it travels posterior to the chiasm. Posteromedial to the optic radiations are the mammillary bodies. Beginning one slice rostral to mammillary bodies, contour a cuboidal shaped structure that forms the walls of the third ventricle. Hypothalamus terminates antero-rostrally at the fornix

10) Lacrimal gland: the lacrimal gland is located between the lateral orbital rim and the globe, beginning at the most superior and lateral aspect of the globe and extending inferiorly to the level of the lens or lateral rectus muscle.

11) Lens: contour on CT data set (or use auto contour in GE prior to exporting to Eclipse).

12) Mastoid: Use CT bone window for contouring. Include all of the visible air cells.

13) Midbrain: begin contouring just above the pons structure (see above) and contour cephalad until the level of the ventricular system is reached. Check this on the CT so that partial volume averaging on the MRI doesn't have contour extending to where the ventricular space exists on the CT data but not quite present on the MR data set.

14) Nasal cavity: Inferiorly, start at the most inferior portion of the maxillary sinuses and first image of the boney hard palate, just above the alveolar ridge of the maxilla and mucosa of the hard palate. Going superiorly, include the nasal tip, ala, vestibule and columella anteriorly, the maxillary sinuses laterally and the septum and sphenoid sinuses posteriorly. Continue superiorly to include the ethmoid sinuses and stop at the opening to the frontal sinuses. You can include the frontal sinuses in nasal cavity/paranasal sinus cases in which it would be appropriate to spare it. In most head and neck cases, the frontal sinuses will be out of the treatment volume.

15) Optic Radiations: Approximately 1 cm long just posterolateral to the chiasm. Best seen on a FLAIR or T2 MR data set. Check against CT to ensure fusion there is accurate. Adjust on CT data set if needed.

16) Optic chiasm. A stubby chromosome shape using a 0.3 or 0.4 mm drawing sphere. It can be located behind or anterior to the stalk. Coronal view of CT/MR is helpful as the typical MR fused for H/N brain is not sliced thin enough to pick it up accurately and it exists on multiple axial images due to its oblique course. This can be minimized when needed by simulating the patient with 17-20 degrees of chin extension (that rotates the plane of imaging into the plane of the course of the ON to the chiasm.

17) Optic nerve: using a 0.3 or 0.4 mm sphere tool, contour from back of eye to chiasm. It is helpful to do chiasm first. The nerve should transit the optic canal seen on the CT data set. (see chiasm for optimizing this structure re head position for simulation). Double check the Orbital portion on the CT as this portion can move a great deal. When critical, instruct the patient to look straight ahead during simulation and MR and treatment.

18) Pituitary: using the FLAIR (to avoid contouring CSF) and the T1con fused data sets. Contour the gland just distal to the stalk. Do not contour the stalk itself. Check by moving to CT data set to see that structure lies in the fossa between the post clinoids and the medial edge of the sphenoid bone.

19) Retina: use a 3 mm static sphere contour the back of the eye. To determine ant extent draw a line in the long axis of the eye, then draw a perpendicular line that bisects the posterior edge of lens. That can serve as a surrogate for the ora serrata (which can be visualized on MRI if more accuracy is needed).

20) Semi-circular canals: Use CT bone widow for contouring. If you include the entire bone posterior to the internal auditory canal you will include the vestibule, superior semi-circular canal, lateral/horizontal semi-circular canal, posterior semi-circular canal and vestibular aqueduct.

21) Skin: standard skin definition is 5mm rind on body. However, in the head, deep skin border is limited by skull. 3mm is often a closer approximation of skin in the scalp. If 5mm is used, bones should be removed from skin volume.

Appendix VI IMAGING GUIDELINES

3.0 T Generic Protocol

Coil	Multi channel head coil (receive-only)

SERIES 1	3 plane localizer

SERIES 2	T1 Flair		
Pulse Sequence	Spin Echo	TE	9.3
		TI	890-930
Orientation	Sag Oblique		
TR (ms)	2200 - 2950		
Averages	1		
FOV Read (mm)	240	Dimension	2D
FOV Phase (mm)	240	Matrix	384/256
Slice Thickness (mm)	5.0		
Slice Gap (mm)	1		
Phase Enc. Dir.	A>>P		

Comments: Cover Brain scanning Left to Right
Angle slices to the patient's anatomy

SERIES 3	DTI (Diffusion Tensor)				
Pulse Sequence	Spin Echo EPI	TE1	109	Number of b-values	2
				b-value 1	0
Orientation	Axial Obl			b-value 2	1000
TR	5600-8000	Fat Suppr.	Fat sat	Diff. Directions	25-30
Averages	2				
FOV Read (mm)	230				
FOV Phase (mm)	230				
Slice Thickness (mm)	4.0	Matrix	128/128		
slice Gap (mm)	0				
Phase Enc. Dir.	A>>P				

Comments: Cover Brain scanning Inferior to Superior.
Scan parallel to the inferior tips of the Corpus Callosum as seen on the Sagittal
Angle slices to the patient's anatomy as seen on all 3 planes.

SERIES 4	T2 Flair		
Pulse Sequence	Spin Echo	TE	145-147
		TI	2250-2600
Orientation	Axial	Fat Suppr.	Fat sat.
TR	9200-11000		
Averages	1		
FOV Read (mm)	220		
FOV Phase (mm)	220	Dimension	2D
		Matrix	256/192
Slice Thickness (mm)	4.0		
Slice Gap (mm)	0		
Phase Enc. Dir.	R>>L		

Comments: Cover Brain scanning inferior to superior
Scan parallel to the inferior tips of the corpus callosum as seen on the sagittal.
Angle slices to the patient's anatomy

SERIES 5	MPRAGE (or equivalent)		
Pulse Sequence	Gradient Echo	TE	3.2-3.34
		TI	900
Orientation	Axial		
Slices per Slab	176-200		
TR	2200		
Averages	1		
FOV Read (mm)	220	Dimension	3D
FOV Phase (mm)	220	Matrix	256/256
Slice Thickness (mm)	1.0		
Phase Enc. Dir.	R>>L		

Comments Cover Brain scanning inferior to superior
Scan parallel to the inferior tips of the corpus callosum as seen on the sagittal.
Angle slices to the patient's anatomy

Administration of Gadolinium Contrast

SERIES 6	Perfusion	Flip Angle	60
Pulse Sequence	Gradient Echo	TE	20-25
Orientation	Axial	Fat Suppr.	Fat sat.
TR	1500		
Averages	1		
FOV Read (mm)	230		
FOV Phase (mm)	230	Matrix	96/128
Slice Thickness (mm)	5		
Slice Gap (mm)	0		
Phase Enc. Dir.	A>>P		

Comments
Inject contrast 1 minute after administration of contrast

SERIES 7	T2-weighted		
Pulse Sequence	Spin Echo	TE	102
Orientation	Axial	Fat Suppr.	Fat sat.
TR	3000-6000		
Averages	2		
FOV Read (mm)	220	Dimension	2D
FOV Phase (mm)	220	Matrix	256/256
Slice Thickness (mm)	4.0		
slice Gap (mm)	0		
Phase Enc. Dir.	R>>L		

Comments Cover Brain scanning inferior to superior
Scan parallel to the inferior tips of the corpus callosum as seen on the sagittal.
Angle slices to the patient's anatomy

SERIES 8	T1 Volumetric		
Pulse Sequence	Spin Echo	TE	minimum (full echo)
Orientation	Sagittal	Fat Suppr.	Fat sat.
Slices per Slab	200-224		
TR	600		
Averages	0.5-1.0		
		Dimension	3D
FOV Read (mm)	220	Matrix	256/256
FOV Phase (mm)	100%		
Slice Thickness (mm)	0.75-1.0		
Phase Enc. Dir.	A>>P		

Comments Cover Brain scanning Left to Right
Angle slices to the patient's anatomy as seen on all 3 planes.
Reformat Straight Cor & Ax Obl

1.5 T Generic protocols

Coil: Multi channel head coil (receive-only)

SERIES 1	3 plane localizer

SERIES 2	T1		
Pulse Sequence	Spin Echo	TE (ms)	9.5
Orientation	Sag Oblique		
TR (ms)	400 - 700		
Averages	1		
FOV Read (mm)	220	Dimension	2D
FOV Phase (mm)	220	Matrix	256/192
Slice Thickness (mm)	5 0		
Slice Gap (mm)	1		
Phase Enc. Dir.	A>>P		
Comments	Cover Brain scanning Left to Right Angle slices to the patient's anatomy		

SERIES 3	DWI		
Pulse Sequence	Spin Echo EPI	TE	82
Orientation	Axial Obl		
TR	5500	Fat Suppr.	Yes
Averages	4		
FOV Read (mm)	260	Diffusion	B Value=1000
FOV Phase (mm)	260		Diff Dir=All
Slice Thickness	4 0	Matrix	128/128
Slice Gap (mm)	0		
Phase Enc. Dir.	A>>P		
Comments	Cover Brain scanning Inferior to Superior.		

SERIES 4	T2 Flair		
Pulse Sequence	Spin Echo	TE	147
		TI	2250
Orientation	Axial		
TR	9500-11000		
Averages	1		
FOV Read (mm)	220		
FOV Phase (mm)	220	Dimension	2D
		Matrix	256/192
Slice Thickness	4 0		
Slice Gap (mm)	0		
Phase Enc. Dir.	R>>L		
Comments	Cover Brain scanning inferior to superior Scan parallel to the inferior tips of the corpus callosum as seen on the sagittal. Angle slices to the patient's anatomy		

Administration of Gadolinium Contrast

SERIES 5	Perfusion		
Pulse Sequence	Gradient Echo	TE	25-50
Orientation	Axial	Fat Suppr.	Fat sat.
Groups	1		
TR	1700-2000		
Averages	1		
FOV Read (mm)	220	Dimension	2D
FOV Phase (mm)	220	Matrix	96/128
Slice Thickness	5		
slice Gap (mm)	0		
Phase Enc. Dir.	A>>P		

Comments
Inject contrast 1 minute after administra ion of contrast

SERIES 6	T2-weighted		
Pulse Sequence	Spin Echo	TE	103
Orientation	Axial		
TR	4000		
Averages	1		
FOV Read (mm)	220	Dimension	2D
FOV Phase (mm)	220	Matrix	256/256
Slice Thickness	4 0		
Slice Gap (mm)	0		
Phase Enc. Dir.	R>>L		

Comments Cover Brain scanning inferior to superior
Scan parallel to the inferior tips of the corpus callosum as seen on the sagittal.
Angle slices to the patient's anatomy

SERIES 7	T1		
Pulse Sequence	Spin Echo	TE	Minimum (full echo)
Orientation	Axial		
TR	400-700		
Averages	2		
		Dimension	2D
FOV Read (mm)	220	Bandwidth (Hz/pixel)	630
FOV Phase (mm)	220		
Slice Thickness	4		
slice Gap (mm)	0		
Phase Enc. Dir.	R>>L		

Comments Cover Brain scanning Left to Right
Angle slices to the patient's anatomy as seen on all 3 planes.
Reformat Straight Cor & Ax Obl

SERIES 8	T1		
Pulse Sequence	Spin Echo	TE	7.6
Orientation	Coronal		
TR	400-700		
Averages	2		
FOV Read (mm)	180	Dimension	2D
FOV Phase (mm)	180	Matrix	320/224
Slice Thickness	4 0		
Slice Gap (mm)	1 0		
Phase Enc. Dir.	R>>L		

Comments Cover Brain scanning inferior to superior
Scan parallel to the inferior tips of the corpus callosum as seen on the sagittal.
Angle slices to the patient's anatomy